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Review of
EADV 2016
Vienna, Austria

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DERMATOLOGY

Editorial Board

Dermatology

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Welcome

Welcome to *EMJ Dermatology 4.1*, presenting all the latest efforts being made to challenge and improve our understanding of the developments in the dermatology field. Inside, we have a detailed review of this year's European Academy of Dermatology and Venereology (EADV) Congress, which took place in the beautiful city of Vienna, Austria. We present a host of abstract reviews presented at the congress, peer-reviewed articles, and a series of captivating interviews from our renowned Editorial Board.

This year's congress was fascinating as ever, bringing to light an array of new findings; we have chosen a select few of the best and most relevant research presentations from the congress, including calls for better safeguards for Europe's outdoor workers as well as in the tattoo and sunbed industries. Psoriasis was also a hot topic this year, with global action plans being developed to take the skin disease more seriously because of the negative consequences for its sufferers.

As always, we bring you a wide selection of peer-reviewed articles, including an examination of the immunopathogenesis of leprosy as a model for T cell anergy by Nath and a review of the reconstructive options available for defects of the nose following skin cancer by Jarayajan. Korkmaz and Kartal assess the skin manifestations associated with the zoonotic infection brucellosis with particular consideration of developing countries in which the disease is still prevalent.

An overview of the treatment of Stevens–Johnson syndrome and toxic epidermal necrolysis, two of the most concerning drug reactions in children, is provided by del Pozzo-Magaña and Lazo-Langner. They argue that, despite the variety of treatment currently available, there remains an inadequate amount of evidence to properly establish its safety and efficacy due to the complexities of performing such trials. Karadağ and Özlü assess the role of toll-like receptors and antimicrobial peptides in the pathogenesis of acne vulgaris, arguing that both play a crucial role in its development, while Szmurło and Kucharska focus their paper on the pathogenesis of acne vulgaris in the context of diet and dietary supplements. Finally, Reginatto and Silva provide a synopsis of skin conditions in neonates.

We hope you enjoy reading this edition of *EMJ Dermatology* and that the information provided may be used for your own benefit in everyday practice. Next year's EADV congress will be held in Geneva, Switzerland; we hope to see you there and look forward to reporting on another year of impressive progress.

Spencer Gore

Director, European Medical Journal

European Medical Journal Dermatology is published once a year.
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Front cover and contents photograph: Vienna, Austria, home of EADV 2016.

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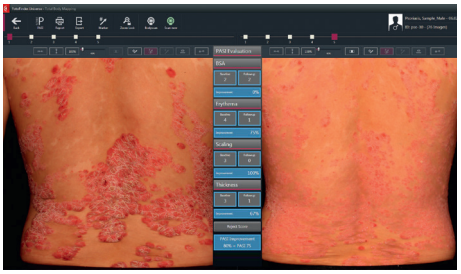

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Foreword

Prof Lawrence F. Eichenfield

Professor of Dermatology and Pediatrics, Chief, Pediatric and Adolescent Dermatology, and Vice Chair, Department of Dermatology, University of California, San Diego, and Rady Children's Hospital, San Diego, California, USA.

Dear Colleagues,

I am delighted to welcome you to *EMJ Dermatology 4.1*, highlighting current developments in dermatological medicine with extensive coverage of the 25th European Academy of Dermatology and Venereology (EADV) Congress, hosted in the 'city of music', Vienna, Austria.

The EADV 2016 Congress played host to professionals esteemed within their field, allowing expansive networking between clinicians and researchers, both well-established and rising stars alike, over the course of 5 consecutive days. Attendees also had the ideal platform for the presentation and discussion of innovative investigations. Building on the continuous growth of the event, this year participants were given ample opportunity to tailor their experience to best suit their professional needs. *EMJ Dermatology 4.1* provides an extensive overview both for those wishing to revisit the event and for those who were unable to attend.

This edition's selection of peer-reviewed articles span a spectrum of disease areas and research topics, including surgical procedures, neonatal and paediatric dermatological conditions, immunological mechanisms, and developments in the treatment of acne. A thriving area of research at present, the role of immunological mechanisms in the pathogenesis of both acne vulgaris and leprosy, are discussed in detail by Özlü and Karadağ in the Editor's Pick, and by Nath, respectively. In a timely article considering the rising incidence of both non-melanoma skin cancer and melanoma globally, Jayarajan provides an overview for clinicians on the various surgical routes available for cutaneous reconstruction of the nose following cancer resection. Reginatto and Silva categorise the most common neonatal findings presented within paediatric dermatological care including birth marks, lesions, and malformations. Bringing to light one of the most alarming presentations within dermatology-related practice, Del Pozzo-Magaña and Lazo-Langner analyse currently available therapeutic options for both Stevens-Johnson syndrome and toxic epidermal necrolysis, conditions that develop as a result of adverse drug reactions. Additionally, Korkmaz and Doyuk Kartal describe the rare cutaneous manifestations associated with zoonotic brucellosis infection, endemic within developing countries across the globe and finally, Szmurło and Kucharska describe the benefit of oral supplementation, particularly that of omega-3 fatty acids, antioxidants, and probiotics, in acne vulgaris management.

I hope that you will enjoy reading the works presented in the eJournal and that you find the contents, including the coverage of this year's EADV Congress, both stimulating and insightful.

Kind regards,

Lawrence F. Eichenfield

Professor of Dermatology and Pediatrics, Chief, Pediatric and Adolescent Dermatology, and Vice Chair, Department of Dermatology, University of California, San Diego, and Rady Children's Hospital, San Diego, California, USA.

Exclusive Interviews on Dermatology

(Click on video clip to view)

Congress Review - EADV 2016

An interview with Prof Torello M. Lotti at the 2016 EADV Congress

Changing the Treatment Landscape of Metastatic Melanoma

Axel Hauschild

Updating the Treatment Algorithm for Metastatic Melanoma

Axel Hauschild

An interview with Prof Chris Griffiths at the 2016 EADV Congress

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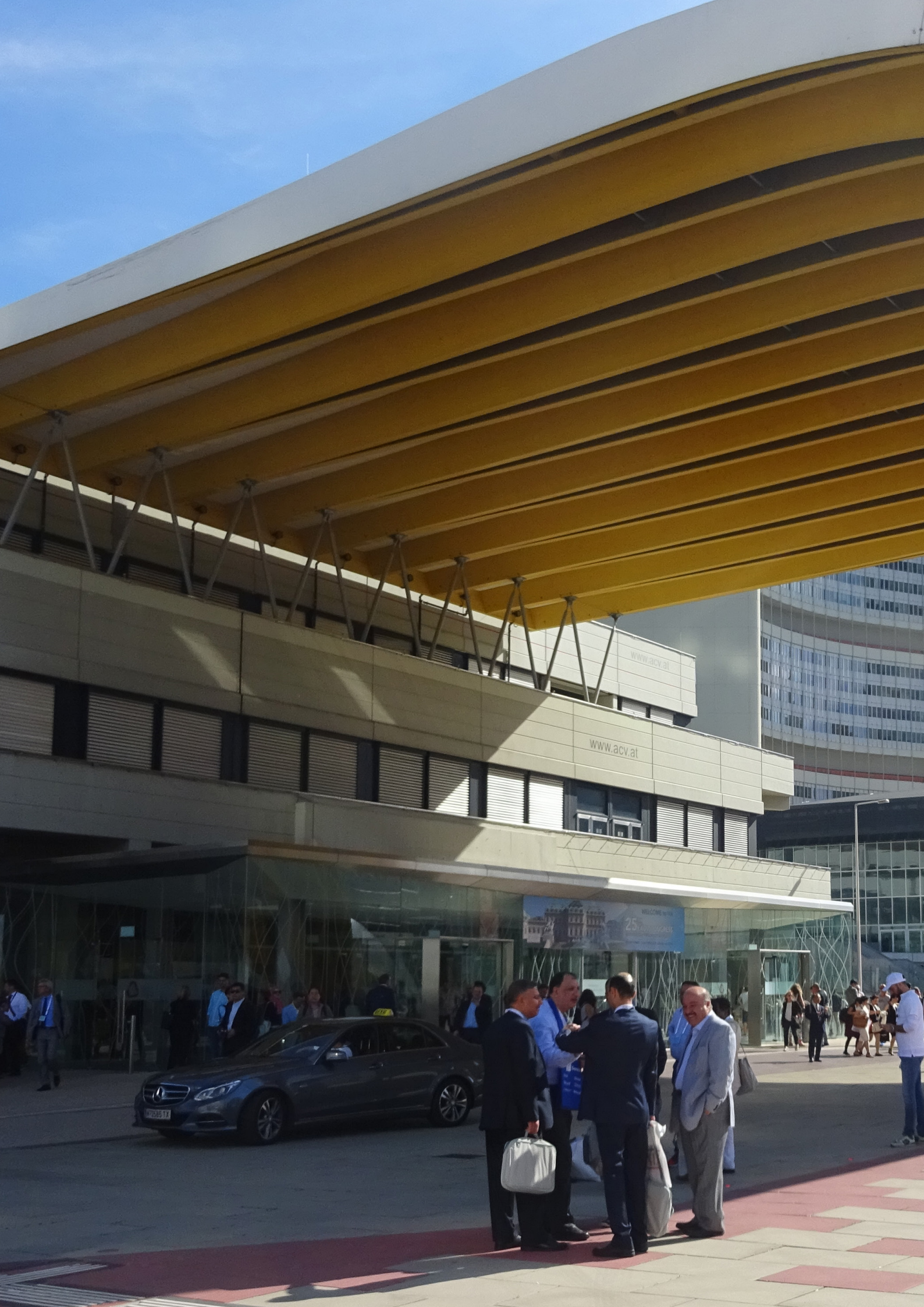
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EADV ANNUAL CONGRESS 2016

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Welcome to the *European Medical Journal* review of the 25th Annual Meeting of the European Academy of Dermatology and Venereology Congress

This year's EADV Congress took place in Vienna, Austria, with a record number of 11,320 attendees. Coined as the 'city of dreams' because it was the home of psychoanalyst Sigmund Freud, Vienna was a spectacular setting for Europe's largest dermatology and venereology meeting. More than 700 speakers were invited to present and there were 180 thought-provoking sessions, featuring contributors from over 30 countries.

Speaking at the opening ceremony, the President of the EADV Prof Erwin Tschachler said: "This Congress offers to all a collegial, collaborative, and congenial setting in which experts, participants, and speakers alike can share their knowledge and learn from one another. Painstakingly designed, this year's scientific programme has been built from the success of last year, employing varying levels of teaching that enable participants to optimise their session selections and best meet their professional needs. Great care was taken to ensure that we bring both cutting edge speakers, lecturers, and scientists, as well as rising stars in the widest range of relevant topics."

Genetics was a core theme of the scientific programme, with 2 days of lectures detailing everything clinicians need to know about both basic skin diseases with classical genetics and the growing understanding of the biological coding underlying complex diseases including psoriasis and atopic dermatitis. Further highlights of the congress included 2 half-day tracks covering dermatology and important diseases from the Americas and diseases in dark skin, which were presented by key speakers from Africa and India.

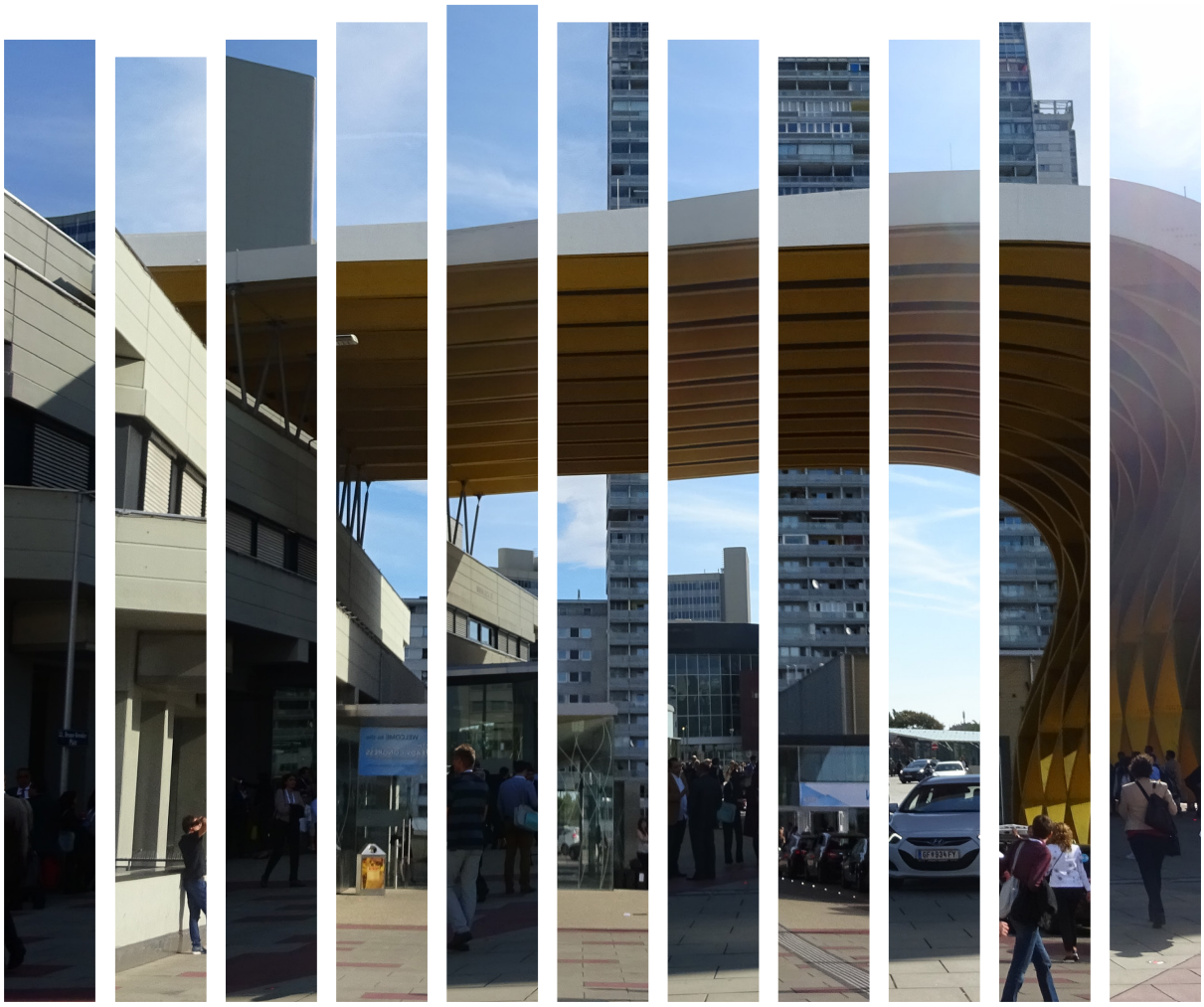
The President's symposium featured a brand new element this year, with the addition of an interactive aspect that enabled the audience to use their smartphones and tablets to send questions directly to the speakers and make comments. These audience responses were projected onto a screen in real time, as were answers provided by the audience to questions raised by the speakers. Building on its success in Copenhagen, Aesthetic Sunday made a return, putting aesthetics and cosmetic dermatology in the foreground of proceedings. The sessions focussed on a variety of topics including dermocosmetics,

aesthetic lasers, and aesthetic surgery, with renowned specialists detailing the very latest advances.

This year's congress saw a change in the leadership of the EADV. Dr Michael Reusch took over as Secretary General, with the previous holder of the post, Prof Carle Paul, elected President-Elect. Also, Prof Erwin Tschachler's term as President ended, and Prof Luca Borradori was installed as President of the EADV until 2018. After assuming his duties as President, Prof Luca Borradori outlined his vision for his term, saying: "My goal for the next 2 years is for the EADV to consolidate its role as a successful educational promoter and effective policy advocate in our changing world, as well as, together with Ms Nancy Induni, to optimise the organisational structure of the EADV and its operation model."

> "This Congress offers to all a collegial, collaborative, and congenial setting in which experts, participants, and speakers alike can share their knowledge and learn from one another."

In this issue of *EMJ Dermatology*, we present some of the key features of the EADV Congress 2016, with a review of the most impactful research from the congress and summaries of some of the presentations made this year. We hope this gives you an insight into the latest in the field of dermatology and will be of use in your practice in the future. The 26th edition of the EADV Congress is set to take place next year in Geneva, Switzerland, in September 2017, and we are already looking forward to this next instalment with much anticipation.



EADV 2016 Revealed: Interaction and Innovation

INAUGURATING the 25th aggregation of dermatology and venereology specialists from Europe and beyond, Prof Erwin Tschachler, EADV President, spoke of both interaction and innovation as congress itinerary highlights. As noted by a EADV press release dated 28th September 2016, Prof Tschachler explained that: "It is my honour and pleasure to welcome you in my hometown and [I] hope that together, we can use the Congress to advance excellence in clinical care, research, education, and training in the field of dermatology and venereology in Europe."

> "...[I] hope that together, we can use the Congress to advance excellence in clinical care, research, education, and training in the field of dermatology and venereology in Europe."

Directly from the frontier of genetic research, EADV saw 32 of the most auspicious clinician-geneticists provide a comprehensive cross-section of this innovative field of dermatology. With a focus on the genetics of a variety of skin diseases, the lectures provided a real opportunity for all delegates to learn more about this aspect of dermatology. Over 2 days, EADV offered delegates a whirlwind tour of the genetic landscape, covering everything from basic to complex skin disease genetics and the implications of this fast-paced field for real-world practice and treatment.

Vienna

Founded in 1987, this non-profit organisation has long stood as an advocate for both patients and specialists. Honouring this dedication, EADV 2016 for the first time hosted a policy roundtable press conference, engaging delegates in their impressive work on behalf of the public and healthcare professionals. The emerging key issues included skin cancer risk for outdoor workers, health policies concerning sunbed use, and advocacy of tattoo regulations and awareness. A spotlight on the World Health Organization (WHO) resolution on psoriasis proved to be a highlight of the discussion.

The congress design was imbued with innovation; from start to finish, digital audience and presenter interaction was facilitated. The president's highly anticipated symposium covered important topics including the use of biologics with psoriasis patients, teaching green flags to general practitioners, and new global challenges for dermatology. "We sure expect a highly interactive, and above all, interesting discussion between the panellists and the attendees," Prof Tschachler anticipated.

Dermatology Deemed First Medical Discipline to Develop Immunotherapy Against Solid Cancer

SURVIVAL of patients with metastatic diseases has, for the first time, remarkably improved following immunotherapy of solid cancers, according to a EADV press release dated 4th October 2016. This provides considerable hope for those with advanced and metastatic melanomas as well as for the field of oncology more generally.

In Europe and Northern America, melanomas are among the eight most frequently fatal cancers. However, there are two key aspects which divide melanomas from other types of cancer. Firstly, the risk of death from melanoma is strongly affected by differences in tumour size on the order of millimetres as opposed to centimetres, and secondly, metastatic melanomas have an electively low sensitivity to conventional chemotherapy. As of yet, no clinical trial involving either chemotherapy or immune-chemotherapy has shown to significantly lengthen patient survival rates.

> It was found that immunotherapies with antibodies aimed against a molecule, programmed death 1, can provide help for >50% of patients for ≥2 years providing they have low metastatic burden and a strong immune system.

Networks of signalling molecules are able to inform cells how to thrive within healthy environments, and subsequently, further research discovered signalling events able to initiate the development of benign pigment cells to melanomas. As a result, drugs that are able to act specifically for melanoma therapy were developed but were only able to provide a short-term solution. New investigations into these signalling events have now led to the creation of more effective combination therapies able to help patients for ≥3 years. However, metastases generally return quite quickly following such therapies if treatment is interrupted.

Publicly-funded research has led to the development of immunotherapy treatments for metastatic melanoma. The retrospective study, including hundreds of patients receiving immunotherapy, presented the vital necessity of beginning immunotherapy for metastatic melanoma at the earliest stage possible. It was found that immunotherapies with antibodies aimed against a molecule, programmed death 1, can provide help for >50% of patients for ≥2 years providing they have low metastatic burden and a strong immune system.

This discovery has important implications for dermatologists: after primary excision, melanoma patients must have numerous follow-up investigations to enable the detection of metastatic disease at the earliest stage possible; dermatologists must learn to carry out targeted therapies and immunotherapies as well as how to treat associated immune-mediated side effects. If there is a single recurrent metastasis, excision is still vital.

Health of Europe's Outdoor Workers at Risk

NON-MELANOMA skin cancer risk has been proven to at least double after just 5 years of outdoor work compared with those who work indoors. This is according to a EADV press release dated 30th September 2016.

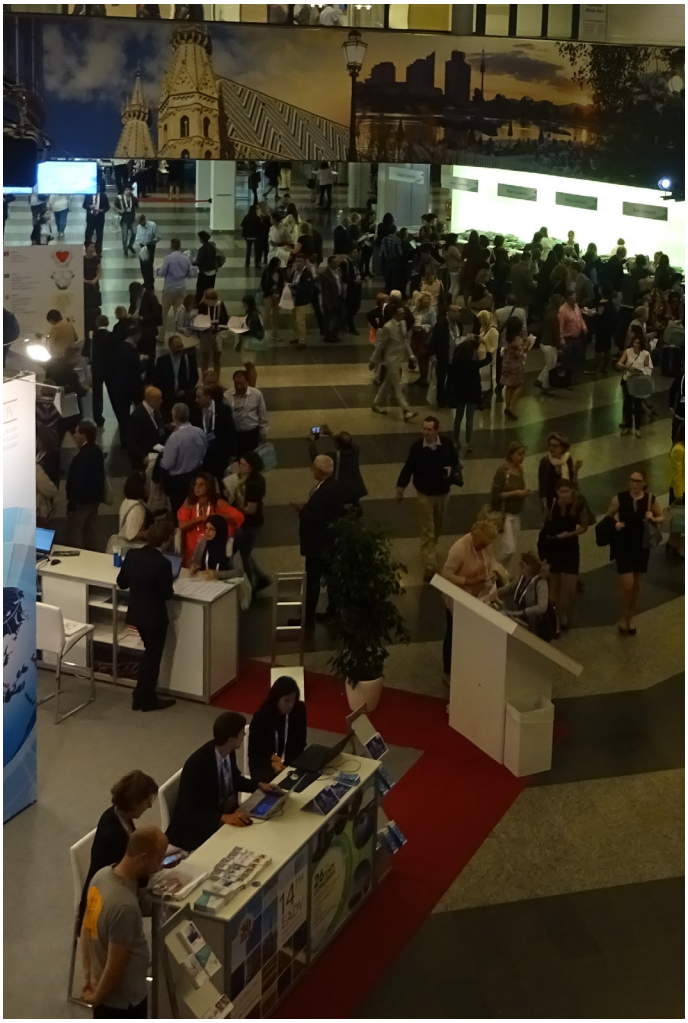
> "...with a workforce of approximately 14.5 million occupied for at least 75% of their work time outdoors, in Europe alone, attention to the invisible risk of UV exposure to develop occupational skin cancer has been vastly neglected."

Among those who work outdoors in Europe, it is reported that health literacy levels are far poorer than among those who work indoors. Prof Swen Malte John, Chairman of the Department, Dermatology, Environmental Medicine, Health Theory, University of Osnabrück, Osnabrück, Germany, commented: "The effects of recreational solar ultraviolet (UV) radiation inducing skin cancer are largely recognised, and numerous national campaigns have been launched over the past decades as a response to this fact. However, with a workforce of approximately 14.5 million occupied for at least 75% of their work time outdoors, in Europe alone, attention to the invisible risk of UV exposure to develop occupational skin cancer has been vastly neglected."

Last April, the EADV instigated a global call to action aimed at encouraging policy makers, employers, workers' organisations, and physicians to help protect outdoor workers from solar UV radiation-induced skin cancer. Prof John noted: "Employers rarely undertake health surveillance, seldom introduce organisational changes at the worksite, and

provide poor or no instructions on adequate sun protection. Yet, what seems to make a difference to sun-safe behaviour is perception of workplace support, including proper safety and health regulations."

Among the 24 health and safety directives of the European Commission which aim to protect workers from a whole host of problems, one in particular is currently under review: the artificial optical radiation directive, which aims to limit the amount of exposure workers' skin and eyes have to artificial optical radiation. This directive however, fails to address the issue of workers' exposure to natural UV radiation. Prof John stated: "Awareness-raising campaigns addressing the general population seem to bear results: people's knowledge on solar UV radiation risks and on their sun protection behaviour has increased. Why then shouldn't this be possible for occupational skin cancer?" Consequently, the EADV is currently working towards including solar UV radiation within this directive in the hope of protecting outdoor workers.



11,320 attendees

Sentinel Node Biopsy for Melanoma Patients Discussed During Plenary Lecture

THE LEADING ROLE that should be played by dermatologists as primary caregivers for melanoma patients, especially with reference to the sentinel lymph node biopsy (SLNB), was a core theme of the plenary lecture at this year's EADV Congress. The lecture was presented on 29th September 2016 by Dr Timothy Johnson, Lewis and Lillian Becker Professor of Dermatology, University of Michigan, Ann Arbor, Michigan, USA, and in a EADV press release.

> "The next time you are in the moment with that patient with melanoma, you should view them through the eyes of many specialties, and with the most contemporary knowledge base."

While the field of melanoma spans several specialties, patients typically first look to their dermatologist for guidance and information, including on the subject of SLNB. In medical practice, accurate staging of melanoma is the key factor driving the course of treatment and the range of treatment options available to the patient. Speaking about current global practice guidelines, Dr Johnson stated: "The staging accuracy of sentinel node biopsy

is not argued anymore. There is a small likelihood of identifiable distant disease if the SLNB is negative." He noted that the majority of patients did not require consideration for SLNB, although those with a Breslow depth ≥1 mm or from 0.75–0.99 mm with higher-risk factors should be considered.

SLNB results will enable clinicians to determine the need for adjuvant therapy, as well as the type of adjuvant therapy required. It is expected that in the future, more effective adjuvant therapy will remove the necessity for completion lymph node dissection after a positive SLNB result. Although it is thought that in the near future sentinel lymph node staging is likely to become more relevant and frequent, within our lifetime it is probable that few (if any) SLNBs will be carried out once true precision medicine has been developed.

Finally, Dr Johnson discussed the importance of taking a holistic approach to treating patients with melanoma, in order to reflect the wide range of specialties it covers. He commented: "The next time you are in the moment with that patient with melanoma, you should view them through the eyes of many specialties, and with the most contemporary knowledge base."

'Tanorexia': A Health Concern for Sunbed Users

SUNBEDS have been a hot topic at this year's EADV Congress, according to a EADV press release dated 30th September 2016. The overwhelming concern, alluded to by Dr Mariano Suppa, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium, was the greatly increased risk of skin cancer development from sunbed use and the 'fashionable' aspect of the product.

> “Indeed, it has been suggested that addictive sunbed use should be regarded as a type of substance-related disorder.”

As it stands, individual exposure is higher in both Northern and Western Europe in comparison to the USA and Australia, in both adults (42%) and adolescents (24%). “It has been reported that over 3,400 melanoma cases are attributed to sunbed use every year in Europe and that the risk of melanoma is significantly increased for subjects ever exposed to sunbeds, particularly over the age of 35,” explained Dr Suppa. It has been estimated that 429,927 cases of skin cancer are attributable to indoor tanning annually, in comparison to 362,941 cases of smoking-related lung cancer.

Over 30 countries

The psychological wellbeing of individuals who engage in sunbed use is another cause for concern, with suggestions that there are certain addictive qualities about it. “Indeed, it has been suggested that addictive sunbed use should be regarded as a type of substance-related disorder,” emphasised Dr Suppa. American studies have supported this, linking sunbed use to anxiety, depression, and substance abuse, indicating that some of those who use sunbeds possibly suffer from psychological stress.

Currently there are no specific European Union (EU) regulations regarding sunbeds. It does, however, fall under the Low Voltage Directive (2014/35/EU) which ensures the safety of electrical consumer products. Over the last 20 years more and more countries have initiated the development of legislation aimed at reducing sunbed use, including special taxes, lower amounts of UVB output, and age restrictions. Dr Suppa commented on the positivity of such steps, pointing out that: “There are some indications that restrictions in sunbed use may succeed in reducing prevalence of use and, eventually, associated risks.”

For now, Dr Suppa will turn his attention to the manufacturers, concluding with the statement that: “Our first goal is to make the sunbeds industry admit that they are selling a product that can cause skin cancer and enhance addictive behaviours. To this matter, the parallelism with [the] tobacco smoking industry is quite interesting.”

Global Action Plan for Tackling Psoriasis in Development

PSORIASIS is not merely a skin disease, states a recent resolution by the World Health Organization (WHO), but it also has many other negative consequences. The subsequently published WHO report recommends 20 actions and practical solutions to control and reduce the harm of this disease. To analyse the significance of the resolution and the report to dermatological practice, Ms Sophie Andersson, Executive Director, International Federation of Psoriasis Associations (IFPA), was invited to this year’s EADV Congress to talk about the group’s significance, as well as to explain the aims of the IFPA following the publication of the report.

The resolution stated that psoriasis, aside from being a skin condition, is a "chronic, non-communicable, painful, disfiguring, and disabling disease for which there is no cure." Ms Andersson expanded on this in a EADV press release dated 30th September 2016, emphasising that psoriasis is a systemic disease that has high physical, mental, emotional, social, and economic implications for patients, with an increased risk of associated comorbidities such as cardiovascular disease. "Even though the disease itself is rarely fatal for the patient, the comorbidities might [be]," she explained.

The WHO's Global Action Plan for the Prevention and Control of Non-Communicable Diseases (NCDs) for 2013–2020 was also discussed by Ms Andersson during her presentation. Within the plan itself, there are four main recognised NCDs (cardiovascular diseases, diabetes, respiratory diseases, and cancer), and four main prevention areas are focussed upon (healthy diet, exercise, alcohol, and tobacco). It was noted by Ms Anderson that at least two of the NCDs overlap with psoriasis-associated comorbidities. She then described how the IFPA plans to focus its efforts on early scanning to detect psoriasis, as well as on the four prevention areas, in order to achieve improved diagnoses and treatments for patients.

> "Even though the disease itself is rarely fatal for the patient, the comorbidities might [be]."

Finally, Ms Anderson spoke about the IFPA's strategic goals over the next few years, informing the audience of the upcoming meeting at the United Nations (UN) in 2018 to revise the Global Action Plan. It was also made clear that the IFPA is actively seeking to expand the scope of the proposed plan, working to achieve a global psoriasis coalition which will include patient associations, healthcare professionals, pharmaceutical companies, medical associations, and policy makers to assist in this effort.

Legislation Progress to Target Tattoo Ink Toxicity

TATTOO ink constituents should be better regulated stressed Dr Christa De Cuyper, Dermatologist, Sint-Jin General Hospital, Bruges, Belgium, and founding member of the European Society on Tattoo and Pigment Research (ESTP). This is according to a press release dated 30th September from this year's EADV Congress, held in Copenhagen, Denmark.

Tattoo inks are developed, manufactured, and sourced largely from the USA, Europe, and Asian/Chinese markets. Selected by artists

individually, the substances used to make each dye are not uniformly controlled, resulting in a differential chemical profile across companies. The popularity of tattoos is increasing, particularly among those aged 18–24 years old, and dermatologists are becoming increasingly concerned with the broad range of adverse reactions and complications presented within their practice. Both tattoos and permanent make-up involve the dispersal of coloured pigments, additives, and often unintentional particulates, under the epidermis and into the underlying dermis of clients, presenting the ideal environment for infections and allergic reaction development.

> “We need a positive list of safe pigments and ingredients. Tattoo inks should at least meet the same standards as cosmetic products.”

Speaking at last year’s event, Dr Cuyper emphasised: “We need a positive list of safe pigments and ingredients. Tattoo inks should at least meet the same standards as cosmetic products.” After the success of EADV’s custom cartoon video highlighting the importance of the topic in June, Dr Cuyper returned to this year’s congress to explain recent developments, namely by the European Commission (EC), who have now requested that the European Chemicals Agency (ECHA) implement a potential restriction of tattoo products within their REACH (registration, evaluation, authorisation, and restriction of chemical substances) framework.

More than 700 speakers

Based on a proposed strategy from the final Report on the Safety of Tattoos and Permanent Make-Up, published in 2015, the ECHA now have a year to obtain the necessary chemical profiles and manufacturing information from companies before a final decision is made. Dr Cuyper commented: “The interested parties now await the conclusion of the ECHA on whether chemicals used in tattoo inks will come under REACH with some anxiety. Indeed, if the decision is positive, there is a very high risk that many current inks will ultimately be considered unsafe.”

The Future of Dermatology: Can You Imagine?

VISUALISATION of the possibilities within dermatology was the overarching theme in the opening lecture to this year’s EADV Congress in Vienna, Austria. Prof Alfred Vendl and Dr Stephen Katz presented their thoughts on the current status of dermatological research.

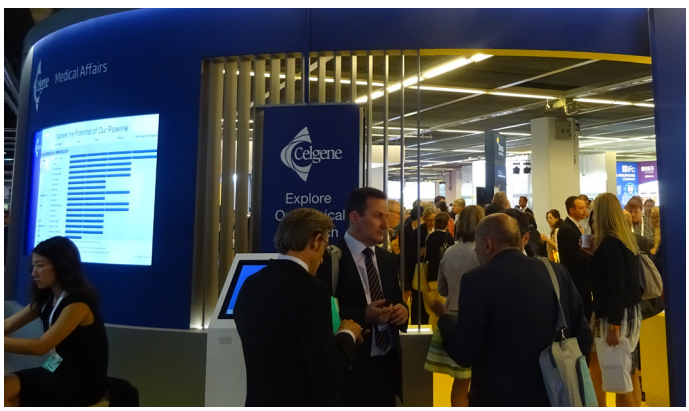
> “If we glean anything from the tremendous advances of the past decade, one can only imagine what the future holds for us and our patients who have skin diseases.”

Dr Stephen Katz began the lecture by summarising the extraordinary achievements of dermatologists across the world in the past 10–15 years of research. As Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) at the National Institutes of Health (NIH), as well as having extensive experience training the most distinguished immune-dermatologists across the world, Dr Katz is uniquely placed to reflect on the successes of his colleagues in the field. In a EADV press release dated 29th September 2016, he commented: "If we glean anything from the tremendous advances of the past decade, one can only imagine what the future holds for us and our patients who have skin diseases."

Dr Katz also emphasised the importance of research into rare diseases: "Research on rare diseases has tremendous potential to improve the lives of affected individuals. It also substantially advances our understanding of fundamental biology, and therefore often provides insights that can be applied to other diseases that affect larger numbers of people." It is this basic biology, explained Dr Katz, that has allowed us to view diseases such as psoriasis, atopic dermatitis, and metastatic melanoma in a completely new light.

Following on from this, Prof Vendl, Technical University of Vienna, Vienna, Austria, played clips from his award-winning film 'Planet You'. The visualisation of the human body as a planet, inhabited by a vast population of microcreatures, allowed the audience a glimpse into the normally invisible world of the human body. Prof Vendl, who has achieved success within the worlds of both medicine and film-making, explained the importance of multimedia resources such as this, which was created using high-resolution microscopic techniques: "[These] phenomena are outside of the limits of human perception when being too small, too big, too fast, too slow, or outside the visible part of the electromagnetic wavelength spectrum. The average human is host to almost 4 pounds of alien creatures that inhabit every nook and cranny of our body."

180 thought-provoking sessions



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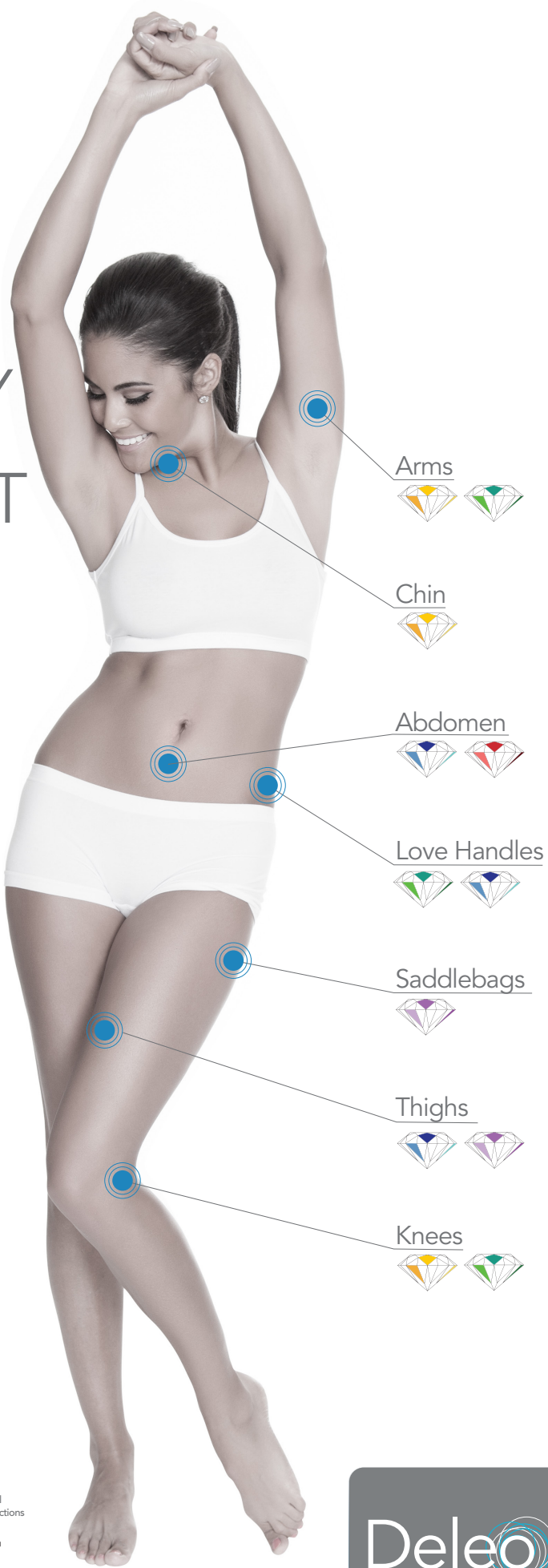

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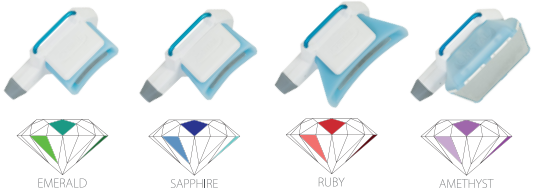

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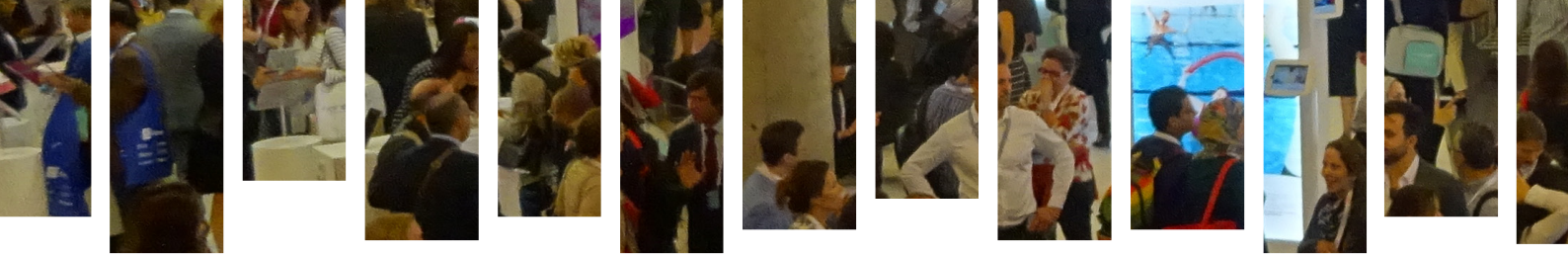


Torello Lotti

Professor and Chair of Dermatology, University of Rome 'Guglielmo Marconi', Rome, Italy; President, Executive Scientific Committee, Vitiligo Research Foundation; President, World Health Academy Dermatology; Past-President, International Society of Dermatology, Italian Society of Dermatology, European Society for Cosmetic and Aesthetic Dermatology.

Q: What first inspired you to specialise in dermatology?

A: The medical discipline can be considered a vocation to which I felt a call at a young age, long before the termination of pre-university studies. I always had a great and sincere interest in the medical sciences, in particular in dermatology which has created bias in my studies since high school, and an innate dedication to healing and healthcare through a traditional approach but with special consideration of the possible innovative ways, especially those aspects not clearly evident or taken for granted by the traditional therapies.

Q: What advances within your field do you value as being the most important since you started your career?

A: My specialisation in dermatology is based mainly on my studies of neuropeptides, plasminogen activators in autoimmune dermatosis and lichen planus, clinical features, and treatment of psoriasis with regard to biologics. The research that I have conducted and am still developing is on vitiligo and new opinion poll methods for the prevention of skin cancer as well as on psychosomatic factors in dermatological diseases and new treatments for vitiligo. Particular interest was developed in respect to hair diseases (alopecia) and of the sebaceous gland (acne).

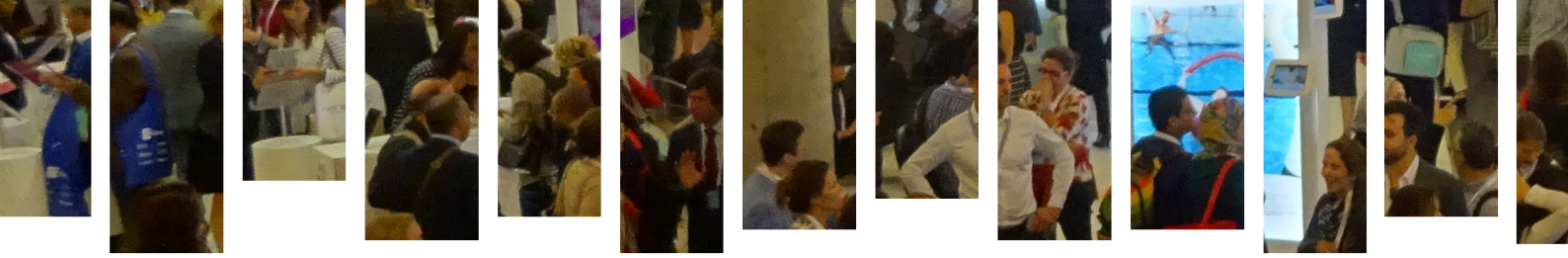
Q: Can you please provide us with some brief details about your current research interests? What do you hope to achieve in these?

A: Low-dose medicine (LDM), a medical approach (born from the fusion of the most recent knowledge in the fields of molecular biology, psychoneuroendocrine immunology, and nano-concentrations research and is founded on the use of biological signalling molecules that control and guide the homeostatic functions in order to restore the physiological homeostasis) based on the use of nano-concentrations of cytokines (in the range of pg/mL), can be administered orally in order to achieve a systemic effect. The availability of LDMs containing nano-concentrations (in the range of pg/mL), sequentially kinetic-activated (a pharmaceutical productive technique codified and standardised by GUNA Laboratories, Milan, Italy) cytokines, and growth factors represents a unique opportunity for the study of an innovative immunological therapeutic approach for vitiligo treatment.

Q: As a current and former President of several international societies, what are the main challenges in ensuring that strategies and approaches are consistent across borders to combat dermatological conditions?

A: As former president of the International Society of Dermatology (ISD), my impression of the current status and progress of the con-division of new interactions and multidisciplinary research and therapy is that it is positively and geometrically improving and growing, in both interest and results among the international scientific community. The goal should be to share knowledge and new achievements among professionals in an ever fluid environment of availability of interaction between different countries.

> "Innovation, technology, and organisation are increasingly and explicitly recognised as an absolute necessity of any health system."



Q: What are the main differences between the way in which dermatological care is provided in Italy and the rest of Europe? What lessons can be learnt from the Italian experience?

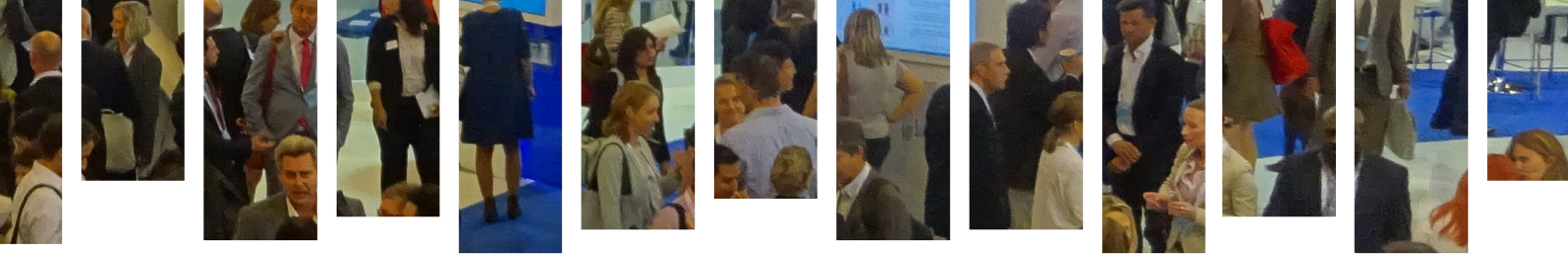
A: Innovation, technology, and organisation are increasingly and explicitly recognised as an absolute necessity of any health system. If there is strong empirical evidence that a new technology (in the broadest sense: diagnostic procedures, medications, operations, organisational structure, etc.) provides some benefit to the patient (for direct effects on health in terms of effectiveness and/or safety, or as a reduction or removal of some inconvenience in access or use of health services), it must be considered for early introduction in practice so that it becomes a necessary part of the ordinary operation of the health system. A health system that is not ready to acquire the technological and organisational innovations that the advancement of knowledge provides disappoints its recipients and demoralises its operators. The objective of facilitating the introduction of innovation in the healthcare system must in fact be pursued in a judicious and selective manner. The instruments of governance are based on rigorous scientific evidence of the effectiveness of new technologies, the assessment of cost-effectiveness ratios, and the assessment of their impact in the specific organisational contexts. In other words, the health technology assessment and implementation of guidelines for their proper use. Access, clinical transferability, and economic sustainability of the technological innovations represent the most critical elements of Italian health policies and welfare systems, as in all countries.

Q: You are a key member in numerous dermatology societies. What development(s) are you proudest to currently be working on?

A: LDM represents a new therapeutic approach based on the integration of the most recent knowledge in the fields of molecular biology, psychoneuroendocrine immunology, and nano-concentrations pharmacology research. LDM approach, based on oral systemic administration of low-dose signalling molecules (cytokines, growth factors, hormones, and neuropeptides), represents the cutting-edge therapeutic tool for preservation and/or restoration of psychoneuroendocrine immunology homeostatic equilibrium, a pivotal point in guaranteeing the best physiological conditions of skin and body. The presence of a state of chronic subacute systemic inflammation is the basis of both the physiological processes of ageing (inflammaging) and the onset of chronic diseases such as diabetes, obesity, and cardiovascular disease (low-grade chronic inflammation). In healthy conditions, the slow progress of inflammaging leads to physiological deterioration of biological functions in advanced age. Conversely the presence of chronic diseases results in a constant state of low-grade chronic inflammation and thus earlier onset of the ageing process and reduced lifespan. Prevention and therapy of low-grade chronic inflammation, in accordance with the principles of LDM, represent a modern approach to facilitate the natural process of physiological ageing.

Q: You are Chair of the Executive Scientific Committee of the Vitiligo Research Foundation which has changed the lives of nearly 100 million vitiligo sufferers and their families. Why did you choose to focus on vitiligo? What are the most notable developments that have been made from this?

A: Vitiligo is an acquired and progressive hypomelanotic disease that manifests as circumscribed depigmented patches on the skin. The aetiology of vitiligo remains unclear but recent experimental data underline the interactions between melanocytes and other typical skin cells, particularly keratinocytes. Our previous results indicate that keratinocytes from perilesional skin show the features of damaged cells. Sirtuins such as SIRT1 are well-known modulators of lifespan in many species that have a role in gene repression, metabolic control, apoptosis and cell survival, DNA repair, development, inflammation, neuroprotection, and healthy ageing. In literature there is no evidence for SIRT1 signalling in vitiligo or its possible involvement in the disease progression. Biopsies were taken from the perilesional skin



of 16 patients suffering from non-segmental vitiligo and SIRT1 signalling was investigated in these cells. For the first time, a new SIRT1/Akt signalling pathway, also known as protein kinase B/mitogen-activated protein kinase (MAPK), has been revealed in vitiligo. SIRT1 regulates the MAPK pathway via Akt-apoptosis signal-regulating kinase-1 and downregulates proapoptotic molecules, leading to decreased oxidative stress and apoptotic cell death in perilesional vitiligo keratinocytes. We therefore propose SIRT1 activation as a novel way of protecting perilesional vitiligo keratinocytes from damage.

Q: In your experience, do you believe people disregard their symptoms due to a lack of awareness of what they could signify and how it could be an indicator of other health problems? How can we increase such awareness in the general population in the future?

A: Brain–body influences are bidirectional and skin should be considered as an active neuro-immunoendocrine interface, where effector molecules act as common words used in a dynamic dialogue between brain, immune system, and skin. It has been widely demonstrated that stimuli received in the skin can influence the immune, endocrine, and nervous systems at both a local and central level. In the past, much work has been devoted to psychosomatic dermatology (or psychodermatology) by well-known pioneers. In recent years, the molecular mechanism by which neuropeptides link the neural–immune–endocrine axis has been receiving increasing attention. Functional dysregulation of neuropeptides has been associated with pathologic cutaneous conditions, such as psoriasis and atopic dermatitis, and the current understanding of the bidirectional loops between the immunoendocrine system and the central and autonomic nervous systems may clarify the pathophysiology of these diseases, thus providing potential targets for therapeutic interventions.

Q: What advice do you have for those starting out in the field of dermatology?

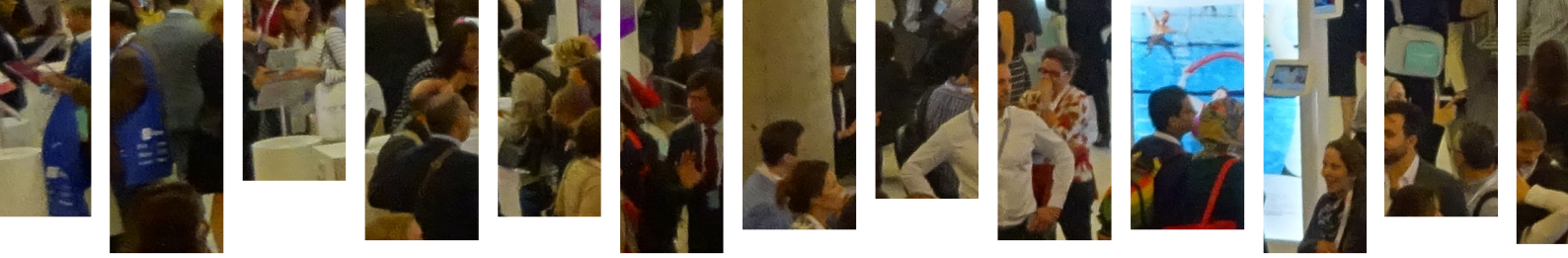
A: Specialisation in dermatology involves aesthetic involvement as well as medical, so the attention paid to the patient in need of treatment may target not only purely the physical aspect of the problem but often, and in some cases overwhelmingly, the appearance as a reflection of a mental and physical situation to be solved at various levels of therapeutic depth. My advice to doctors who are starting in this specialisation is to search for the true reason for the disease in a multidisciplinary approach, involving psychoneuroendocrine immunology and physiological aspects of dermatology.

Lawrence F. Eichenfield

Professor of Dermatology and Pediatrics, Chief, Pediatric and Adolescent Dermatology, and Vice Chair, Department of Dermatology, University of California, San Diego; Rady Children's Hospital, San Diego, California, USA.

The EMJ team recently caught up with Prof Lawrence Eichenfield, a paediatric dermatology specialist and distinguished member of the *EMJ Dermatology* Editorial Board, at the recent EADV Congress. Set in the beautiful surroundings of Vienna, Austria, the Californian professor was in good spirits as he discussed with us the importance of this annual event to the field of dermatology, provided advice for current medical students, and gave his views on the exciting progress being made across the field.

Prof Eichenfield began by providing a sense of the sheer size and scale of the event, expressing the practical difficulties of attending all the sessions that he would like to: "Like anyone, it is quite difficult because one of the good problems of the meeting is that there are many excellent sessions



occurring at the same time, so I will generally try to mix and match between topic areas that I want to attend and try to discern if there is new information that is coming, and/or to get a chance to hear experts that I know previously have given state-of-the-art presentations."

There are many reasons why events such as the EADV Congress are so vital to medical professionals like Prof Eichenfield. One is the unique networking and discussion opportunities that arise on such occasions among like-minded professionals from around the globe. He explained that: "Congresses are partially successful because they allow us to catch up with other people personally during the meetings," while commending "the mixture of new information and distilled clinical information, along with [giving] the chance to see colleagues and/or meet in certain organisational meetings or research meetings etc. occurring at the same time. This is what makes these meetings very efficient venues."

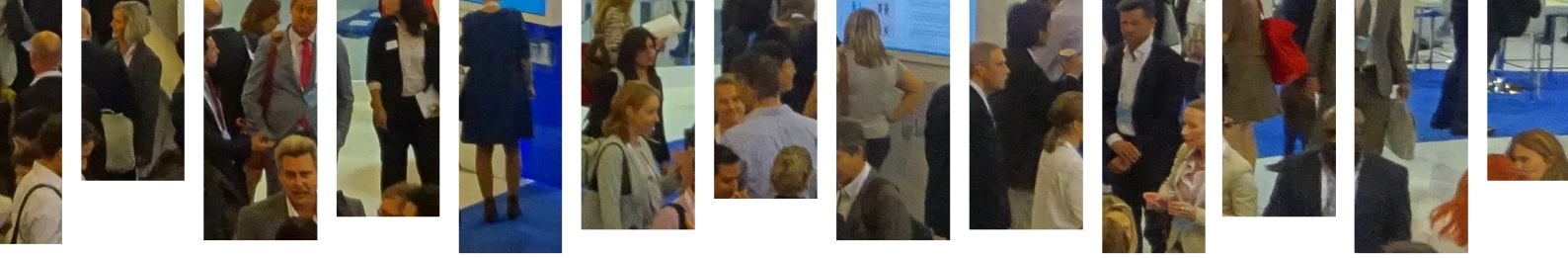
Another factor is, of course, the huge amount of information on display at events such as this; in particular, the need for practitioners to receive the very latest updates on new treatments for their patients is often best met during such occasions. "I think that the major congresses internationally, probably are more important than they have ever been for all concerned," stated the pre-eminent professor. "They become incredibly important events for industry as they are laying out their new information and looking at the information as it has been laid out by other people. And it is really the primary place at which information on new medications that have been in clinical trials are released to healthcare practitioners. So they are probably more important than ever in terms of being communication devices and in the time frame of new drugs being pushed out to healthcare practitioners to be able to use them."

As well as attending a range of fascinating talks and presentations, Prof Eichenfield also spoke at length about the role of chairing sessions at the EADV Congress, and the different insights and challenges that this often allows. "The advantage is that it keeps you sitting in one place for a few hours, which is good!" he quipped. "When you are a Chair, you will hear some talks you probably would never have chosen to hear but you can still learn from them, so that is one of the pleasures of doing that. And then of course, you are usually forced to be a very careful listener because often there aren't questions from the audience and it is your job to come up with good questions, so that is a good intellectual process."

Yet another important role of international congresses is the invaluable experience that they give medical students as they continue to learn about the field. "I think that it is very useful for medical students to be involved," said Prof Eichenfield. "They tend to be very wide-eyed and excited, and that is fine, but it also starts to give them experience in recognising the differences between presentations that may be really new information and presentations that are distillations of both clinical exposure and data, and as medical students they should be excited and confused at that wealth of information because they are still grappling to figure out what diseases are and how to treat them. But they also should learn that part of the learning process is to understand the way the knowledge of disease and its treatment is going to change tremendously during their time period."

Prof Eichenfield also provided some tips about how aspiring medical students can get the most out of their time at events such as EADV: "Try to plan where you think you should be, and the more junior you are the more important it is to grab someone who is more senior, and just say 'hey, what do you think will be the best stuff to see today or tomorrow', because many times the people with a lot of experience will be really helpful."

We asked Prof Eichenfield about his thoughts on the progression and future advances in dermatology, both in terms of his own areas of expertise and that of the field in general. There is certainly plenty to excite the specialist in paediatric dermatology regarding his line of work: "So with inflammatory skin disease, the translation of new biologics and small molecules into paediatrics after adult studies is something that will be highly



intriguing, because the major question is can you mediate the cause of the disease by early intervention? So if I treat paediatric atopic dermatitis with new systemic agents, can I induce children into early remission or essentially free them of their disease, or not? These are the very major questions I get very excited about."

We were delighted to hear that Prof Eichenfield anticipates lots of exciting new research emerging in the coming years which is likely to significantly enhance patient care in the future. These should be prevalent at future EADV congresses. "I think that the hot areas of research will include the inflammatory skin diseases, new therapies coming down in acne, as well as the continued analysis of biologic therapy, particularly looking at long-term improvements in health and/or any safety issues in relation to psoriatic agents," he mused.

Overall, we were left in little doubt that there will be many research updates to look forward to within the field over the months and years ahead: "There is a lot of change happening in the field scientifically, both in terms of the translations of new genetic information towards diseases and new biological agents and small molecules, and so we are at the edge of this tremendous revolution in many of our diseases," added Prof Eichenfield.

We enjoyed our thought-provoking discussion with the amiable Prof Eichenfield, and look forward to him continuing his invaluable work as an Editorial Board member for *EMJ Dermatology*, as we seek to continue improving our dermatology-related content.

Branka Marinovic

Professor and Head, Department of Dermatology and Venereology, University Hospital Center Zagreb, University of Zagreb School of Medicine, Zagreb, Croatia; President, Croatian Dermatovenereological Society of the Croatian Medical Association (Zagreb Branch); Member of the Board of Directors, European Academy of Dermatology and Venereology.

Q: What led you to pursue a career in dermatology and venereology?

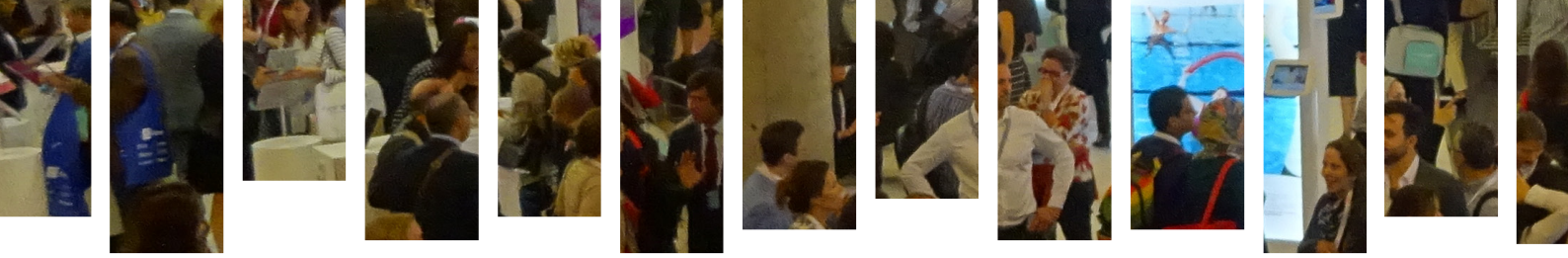
A: It was partly by chance as at the time I started my residency, dermatology and venereology was not so attractive and prosperous as it is today. During my residency I realised how diverse the field was and how much potential it offered for different fields of clinical and laboratory work. Then I discovered the world of blistering diseases which is still my main field of interest.

Q: Since beginning your career, what have been the biggest developments in treating venereal dermatological conditions?

A: Of course, the biggest advances have been made in the field of human papilloma virus (HPV), especially with the introduction of different vaccines. So I would say that the biggest developments have been made in the prevention of dermatological conditions.

Q: As a board director of the European Academy of Dermatology and Venereology (EADV), you have an important role within an influential association. What has been the EADV's biggest achievement in advancing excellence in the field of dermatology and venereology during your involvement as a member and as a board director?

A: My first improved insight into the functioning of the EADV was when I was appointed the Secretary General of the EADV Spring Symposium that was held in Cavtat, Croatia, in 2010. As a member of the board and as a member of different committees within the EADV, I can say that the biggest achievements have been made in the scientific programme of symposia and congresses.



After a few years of hard work and after the time participants needed to adapt to the new form, the final result has been a big success. The programme is divided into training and educational forums, reviews and updates, and an expert forum, so everybody can find something for him/herself. The EADV is also investing time and money in fostering courses organised on many different topics for residents as well as for specialists. A few years ago EADV opened a call for different projects. There is still room for improvement. I am honoured that the members of the board elected me as their representative in the Executive Committee of the EADV and I hope that there, I will have the opportunity to contribute to the development of the academy.

Q: How do events such as the EADV congress help your clinical practice?

A: As mentioned previously, the current scientific programme is organised on three levels: a training and educational forum (mostly for residents and young dermatologists), reviews and updates, and an expert forum. There are also four to eight parallel tracks with up-to-date topics that are important for our everyday practice. Finally, the so-called 'aesthetic Sunday' with topics covering only this part of our field.

Q: One of the EADV's aims is to act as an advocate and educator of patients with cutaneous or venereal diseases. In what ways does the EADV act as an advocate for patients, and how does it educate patients with a particular condition?

A: The EADV works a great deal to make better connections with different patient organisations. Since the congress in Copenhagen in 2015, a so-called 'patients' village' has been organised where different patient organisations can present themselves and have the opportunity to contact dermatovenereologists. There are also board members that are appointed to improve this contact with patient organisations.

Q: Do governments do enough to enhance public policy related to venereal dermatological conditions, in your opinion? How could this be further improved?

A: The answer to this question varies from country to country. In Croatia many actions were taken to encourage parents to vaccinate their children for HPV and the result was not the greatest. I would say that there is still a stigma on patients with venereal diseases and that much more could be done in the field of education and prevention.

Q: What do you anticipate will be the 'next big thing' in dermatology? How would this change your practice?

A: We are expecting the next big thing to be either developmental drugs or gene therapy for some rare dermatological diseases. This could be a big step forward for these patients.

Q: What research are you currently undertaking and how do you hope it will develop?

A: At the moment we are waiting for the assessment of a few projects, one of them is the European Reference Network (ERN) for rare skin diseases in which our department is participating. There are also a few clinical studies in the field of atopic dermatitis, pemphigus vulgaris, and psoriasis in which we are also taking part.

Q: What advice do you have for anyone interested in pursuing a career in dermatology or venereology?

A: This is such a broad field of medicine, from classical clinical dermatology, dermatosurgery, venereology, and medical cosmetology that encompasses such a range of laboratory work that everybody can find a niche for his/her interests.

"We are expecting the next big thing to be either developmental drugs or gene therapy for some rare dermatological diseases. This could be a big step forward for these patients."

USEFUL PHOTOPROTECTION IN DERMATOLOGICAL PRACTICE

This symposium took place on 30th September 2016 as a part of the European Academy of Dermatology and Venereology (EADV) Congress 2016 in Vienna, Austria

Chairperson

Franz Trautinger[1]

Speakers

Thierry Passeron,[2] Dominique Moyal[3]

1. Karl Landsteiner Institute of Dermatological Research, St. Pölten, Austria

2. Department of Dermatology, University Hospital of Nice, Nice, France

3. La Roche-Posay Dermatological Laboratories, Asnières, France

Disclosure: Prof Trautinger has acted as consultant/advisor to AbbVie, Angelini, BMS, Eli Lilly, Galderma, Leo, MSD, Novartis, Roche, and Sanofi; received speaker's honoraria from BMS, Galderma, Hollister, Leo, MSD, Novartis, and Roche; and received research grants from AbbVie, Angelini, and Roche. Prof Passeron has been an advisor/consultant for AbbVie, Galderma, ISIS Pharma, Janssen, La Roche-Posay, Lancôme, Novartis, Pfizer, SVR, and Symrise; was a speaker for Abbvie, Beiersdorf, Bioderma, Galderma, GSK, ISIS Pharma, Janssen, La Roche-Posay, Lancôme, Leo Pharma, MSD, Novartis, Pfizer, SVR, Syneron, and Vichy; and received clinical research grant from Beiersdorf, Bioderma, DELEO, Galderma, Lancôme, MSD, and Syneron. Dr Moyal is a full-time employee of La Roche-Posay Dermatological Laboratories (Asnières, France).

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MEETING SUMMARY

The main objectives of this symposium were to explore the effect of light on individuals with hyperpigmentation disorders and acne, present the latest clinical research on the importance of photoprotection, and discuss the role of adapted photoprotection to improve patient adherence. Prof Passeron introduced the topic of hyperpigmentation by providing a brief background of pigmentary disorders and the mechanisms involved in ultraviolet (UV)B-induced pigmentation and the physiology of UVA pigmentation, and describing the latest findings from clinical studies that compared the effects of visible light and UVB on pigmentation and melasma. Dr Moyal presented the latest research on sun protection to prevent hyperpigmentation, focussing on the need for products to contain very high-level and well-balanced protection against UVA and UVB light, and discussed adherence, as well as how formulations can be adapted to meet patient needs by skin type, texture preference, and climatic requirements. Dr Moyal also presented the latest research on post-inflammatory hyperpigmentation (PIH) as a long-lasting sequela of acne, photoprotection to prevent drug-induced phototoxicity, and whether adapted dermocosmetics and photoprotection can be used to prevent acne outbreaks. Prof Trautinger provided an overview of the epidemiology, physiology, and interaction with light and presented studies regarding the effect that sunlight has on acne severity. Prof Trautinger also discussed why photoprotection is important for patients with acne, focussing on the phototoxic side effects of conventional acne treatment.

Photoprotection Needs for Patients with Hyperpigmentation Disorders

Professor Thierry Passeron

Pigmentary disorders affect ≤60% of the population, depending on the country and studies.[1-3] It is one of the most frequent dermatological conditions across all phototypes[1-3] (Fitzpatrick skin type determined by constitutional colour and exposure to UV radiation), with an impact on quality of life.[4,5] Pigmentary disorders are more prevalent in dark-skinned individuals but can be observed in all phototypes.[1-3] Accurate diagnosis is necessary to select the correct treatment and to assign effective photoprotection.

The colour of skin is determined by pigments, in particular: melanins, haemoglobin, and carotenoids. Melanins are composed of two main subtypes: eumelanins (photoprotective) and pheomelanins (not photoprotective and promote oxidative stress). When diagnosing a pigmentary disorder, it is important to determine whether it is vascular, owing to xeroderma, ochronosis, dyskeratosis, chromhidrosis, heavy metal deposition, exogenous pigments, or melanin hyperpigmentation.

More than 170 genes are involved in the control of human skin pigmentation. Exposure to UV light, particularly UVB, stimulates keratinocytes and activates downstream pathways that lead to an increase in melanin hormone production. The most important pathway is the alpha-melanocyte-stimulating hormone (α-MSH) pathway. UVA light pigmentation differs from that of UVB in that it does not confer a photoprotective effect.[6] UVA light induces immediate pigment darkening, persistent pigment darkening, and delayed tanning;[7] it has a deeper skin penetration compared with UVB (penetrates to the dermis and fibroblasts); and is known to cause oxidative stress.[8] Photoprotection should have a UVA/UVB balance to prevent relapse of melasma.[9] UVA is also suspected to play a key role in the late occurrence of actinic lentigines.

Studies of visible light exposure have demonstrated the role of visible light in skin ageing by a mechanism, at least in part, that involves inflammatory cytokines, the production of reactive oxygen species, and the activation of matrix metalloproteinases.[10,11] However, it is the effect of visible light on hyperpigmentation that is of interest. Mahmoud et al.[12] carried out a study of the effect of visible light compared with UVA radiation on healthy volunteers with phototypes IV and VI and demonstrated that visible light caused more intense and prolonged pigmentation than UVA1 radiation in darker phototypes (IV and VI) but had no effect on fairer phototypes (II).

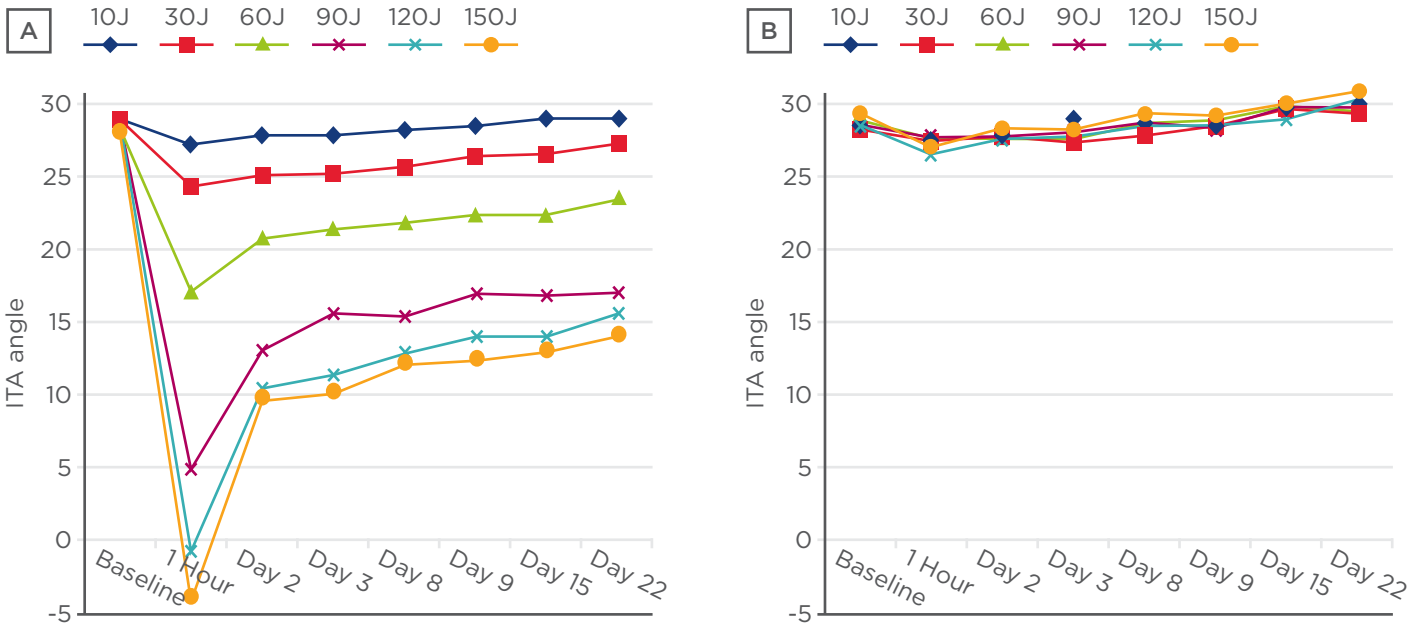

Figure 1: The effect of two wavelengths of visible light at multiple doses on individual typology angle, measured at time intervals after exposure.
A) 415 nm; B) 630 nm.
ITA: individual typology angle.

Table 1: Pigmentation protection factor determination.

Product	SPF	UVAPF	Ratio SPF/UVAPF	PPF
A	30	15	2.0	18.9
B	30	9	3.3	9.0
C	50	21	2.4	58.9
D	50	13	3.8	22.3

PPF: pigmentation protection factor; SPF: sun protection factor; UVAPF: ultraviolet A protection factor.

A randomised controlled study of the pro-pigmenting effect of visible light at two distinct wavelengths (415 nm [blue-violet] and 630 nm [red]) in healthy volunteers with phototypes III and IV, demonstrated an increasing pigmentary effect with blue light and no pigmentary effect with red light (Figure 1).[13] Results were determined by colourimetric measurements at 1 hour, 2 days, 8 days, 9 days, 15 days, and 22 days after exposure. Pigmentation was sustained for 22 days after exposure; therefore, to assess whether exposure had a long-term effect, volunteers were assessed at 3 months after exposure to reveal if pigmentation was present. Blue light was compared with UVB, which demonstrated pigmentation at 15 days after exposure to both wavelengths; however, 3 months after exposure, pigmentation was observed in those exposed to blue light but not to UVB. Histology revealed hypermelanosis with UVB and blue light, no significant melanocyte proliferation for blue light, and significantly higher keratinocyte necrosis, number of melanophages, and p53 activation in UVB exposure compared with blue light. Therefore, it can be concluded that the mechanism of pigmentation induced by visible light differs from the p53-induced mechanism of UVB pigmentation.

A prospective randomised study by Boukari et al.[14] compared the effectiveness of UVA/UVB sun protection with UVA/UVB plus shorter wavelength visible light sun protection for the prevention of melasma relapse. Patients with melasma were assessed during 6 months of summer sun exposure and it was determined that fewer melasma relapses occurred in the group that used UVA/UVB plus shorter wavelength visible light protection than in those who used UVA/UVB protection. These clinical studies demonstrate the effects of visible light on pigmentation and on melasma. However, the impact of visible light on other pigmentary disorders is yet to be explored and is a topic for future research.

Towards a Broader Sun Protection for Patients with Hyperpigmentation Disorders

Doctor Dominique Moyal

Prevention of Pigmentation Induced by Ultraviolet A Light

Pigmentation is induced by UVA, UVB, and visible light, and effective sun protection should offer high-level and broad protection from UVA and UVB as a priority. In a comparative study, the effectiveness of products with the same sun protection factor (SPF) and a different UVA protection factor (UVAPF) was explored in a population of individuals with phototypes III and IV. The pigmentation protection factor was determined for each product. The UV source was representative of an average daily sun emission, with a higher UVA/UVB irradiance ratio compared with the UV source used for SPF determination (zenithal conditions).[15] Patients were assessed 7 days after UV exposure (the time at which pigmentation is stable). Results demonstrated that, for the same SPF level, only products with a high UVAPF, a well-balanced UVA/UVB protection, and a SPF/UVAPF ratio <3 could prevent sun exposure-induced pigmentation (Table 1).

The effectiveness of sun protection (Anthelios, SPF50+, UVAPF28, SPF/UVAPF=2.1) for the prevention of recurrence of melasma was studied in a trial of 185 pregnant women in Morocco.[9] In women with phototypes II–V, 15% had a history of melasma, 6% presented with melasma at the start of the study, and 29% had facial PIH. Patients were monitored for the duration of their pregnancy with dermatological examination, Wood's light examination, and colourimetric measurements at the beginning of pregnancy and at 3, 6, and 8 or 9 months. At the end of the study, five new

cases (2.7%) of melasma were observed, compared to previous studies that demonstrated a 53% occurrence.[16] At 6 months, clinical improvement was observed in 8 of the 12 patients affected by pre-existing melasma. Colourimetric measurements at 8–9 months revealed that 21% of patients had darker skin, 10% had identical skin colouration, and 69% had lighter skin than at enrolment. Overall, the occurrence of melasma decreased (preventative efficacy) and pre-existing melasma intensity was reduced (curative efficacy).

To confirm the results in another population, a study was carried out in 217 pregnant women in Korea with phototypes III and IV, using an Anthelios sunscreen (SPF50+, UVAPF30, SPF/UVAPF=2) for sun protection.[17] Patients were followed up throughout pregnancy using colourimetric assessment, Melanin Index (Mexameter®, Courage + Khazaka Electronic, Cologne, Germany) and Melasma Area and Sensitivity Index (MASI) on the forehead, chin, and right and left malar. At the end of the study, 1% of women developed melasma with mild severity (MASI between 1.2 and 2.7) confirmed by colourimetric measurements. Overall, across the two studies it was confirmed that sun protection with high UVB and UVA broad protection (SPF/UVAPF=2) has preventative effectiveness against melasma.

It is known that UVA induces pigmentation through an oxidative mechanism, and to assess the value of using an antioxidant complex to prevent UVA-induced pigmentation a study of 20 individuals with phototypes III and IV was carried out. Patients were exposed to a single dose of long UVA at 50 J/cm^2 on a non-treated area and on a treated area; the results, assessed using colourimetric measurements 24 hours after exposure, revealed significantly lower pigmentation induced by UVA on areas treated with antioxidant complex compared with untreated areas.

Prevention of Pigmentation Induced by Visible Light

Short wavelength visible light is known to cause pigmentation, and currently the only way to prevent visible light-induced pigmentation is by use of pigments such as iron oxides. To test the effectiveness of sun protection containing iron oxides, a trial comparing sun protection SPF60, SPF/UVAPF ≤2 with and without iron oxides was carried out. Ten patients with phototype IV (n=8) or V (n=2) were enrolled, each product was applied to a test zone, and one zone was untreated. Patients were exposed to visible light (400–700 nm) 30 minutes after application of sun protection, at doses ranging from 20–640 J/cm^2. On Day 7, visual assessments and colourimetric measurements were carried out. Results revealed that pigmentation was significant but very low at visible light doses of ≤160 J/cm^2; 160 J/cm^2 was the minimal pigmenting dose. Test zones that were untreated demonstrated a high level of pigmentation (approximately -4 delta luminance at a visible light dose of 640 J/cm^2), likewise test zones treated with sun protection and without iron oxides showed no difference with the untreated zones. Pigmentation of the test zones treated with sun protection containing iron oxides was significantly lower than its comparators.

Adapted Sun Protection for Improved Adherence

Sun protection strategies and formulations can only offer the expected protection if applied regularly in accordance with product recommendations. In a recent article[18] it was shown that cosmetic elegance is the most important feature for consumers when considering sun protection, and should therefore be considered in the context of adherence, particularly for those who must use sun protection daily. Cosmetic elegance refers to a pleasant texture and easy-to-use formulation, which many high-level UVA/UVB products do not have. Adaptive formulations that are tailored to different skin types (such as oily or dry skin), different preferences and needs in texture (such as cream or ultra-light fluid), and different climatic conditions are necessary.

Photoprotection Needs for Patients with Acne

Professor Franz Trautinger

Overview of Acne

Acne is an inflammatory condition that is common in individuals aged 15–17 years old. In most people acne is relatively mild, however 15–20% develop moderate-to-severe acne. Acne is initially self-healing yet in a percentage of people it will continue into adult life.[19] The pathophysiology of acne is well characterised despite the lack of an appropriate animal model, and is generally caused by the combination of inflammation, keratinisation of keratinocytes in the upper hair follicle, increased

sebum production, and infection and colonisation with *Propionibacterium acnes*.[20] When considering the interaction of electromagnetic radiation, whether it be UV, visible light, or infrared, and acne, it is important to think about whether there is a physical reaction and how deep it penetrates into the skin to interact with pilosebaceous units. UVA in particular can penetrate the deeper areas of the dermis and interact with pilosebaceous units. UVB can reach the epidermis and interact with keratinocytes and the upper area of the dermis.

Is Sunlight and Ultraviolet Light Good for Acne and Can it be Used as Treatment?

A popular misconception is that sunlight and UV light are good for acne and can be used as a treatment. In a study by Cafri et al.,[21] college students were asked the reasons they used tanning beds, and a large number used them to treat acne. However, older studies, such as that by Gfesser and Worret,[22] failed to demonstrate any significant variance between acne aggravation in the summer or winter months. A more recent study by Pascoe and Kimball[23] surveyed doctors regarding the number of patient visits for almost-clear and moderate/severe acne throughout a year. Results revealed a minor seasonal effect, with a slightly higher percentage of patients presenting with severe acne in the winter months; however, the methods had many confounding factors (such as the number of visits was recorded instead of the number of patients).

Phototherapy for the treatment of acne has been studied in numerous trials with small patient numbers,[24,25] and, although the evidence is poor, there seems to be no benefit from broad-band and monochromatic visible, UV, or infrared sources alone. There is some benefit if a photosensitiser is added, so photodynamic therapy with 5-aminolevulinic acid or methyl aminolevulinate might have an effect. However, when compared with conventional acne treatment, there is no superiority.[24]

Why Recommend Photoprotection for Acne?

Photoprotection should be recommended for patients with acne for three main reasons: to prevent skin cancer and photoageing, as in the general population; to protect patients with acne from the negative effects of treatment-associated photosensitivity, and to prevent long-lasting PIH.

Acne treatment conventionally includes topical and systemic retinoids, topical benzoyl peroxide (BPO), and systemic tetracyclines. Studies to assess the phototoxic effects of systemic retinoids have failed to demonstrate a photosensitising effect,[26] which differs from experience in daily practice, and data on topical retinoids and BPO are limited. However, the package inserts and product characteristics recommend photoprotection.[27-29]

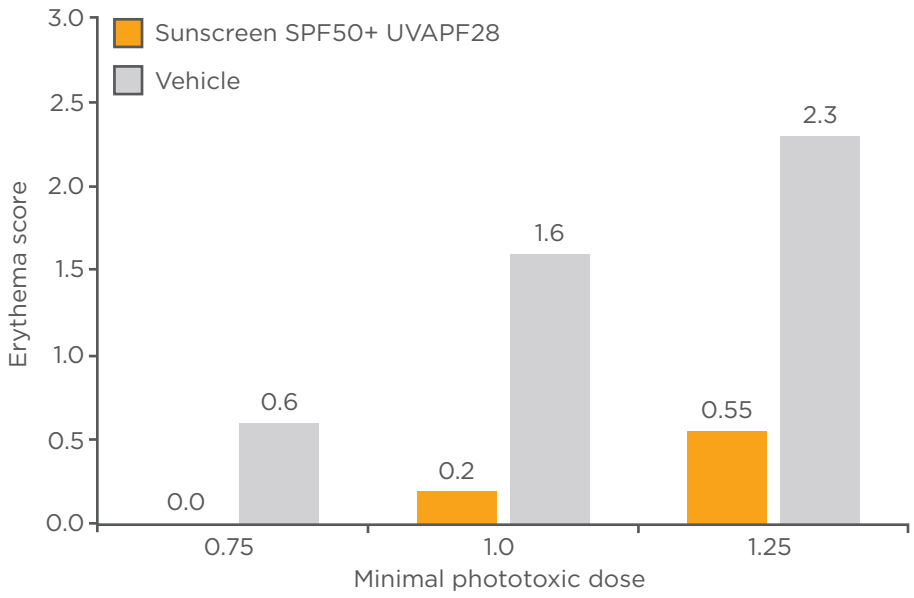

Figure 2: Erythema score after exposure to ultraviolet A radiation in patients treated with tetracycline, using a sunscreen SPF50+ UVAPF28 or vehicle product.

SPF: sun protection factor; UVAPF: ultraviolet A protection factor.

Systemic tetracyclines, most commonly doxycycline, are known to cause photosensitisation in ≤20% of patients,[30-32] depending on the environment and behaviour of the patient. A study by Hasan et al.[33] demonstrated doxycycline degradation with increasing exposure to UVA radiation, and Duteil et al.[34] provided evidence that broad-spectrum photoprotection against UVA is especially important in protecting patients from phototoxic skin rash. Photoprotection is necessary to prevent PIH in all patient populations, particularly in individuals with darker skin in whom incidence can be ≤65% and treatment is unsatisfactory.[35]

In conclusion, all patients with acne should be counselled regarding appropriate photoprotection, and common myths surrounding acne treatment with sunlight should be addressed. Patients should be advised to avoid sunbathing and tanning beds, encouraged to wear protective clothing such as hats, and advised to wear broad-spectrum photoprotection, especially when photosensitising treatment is prescribed. Acne treatment, if topical, should be applied first, followed by photoprotection. The level of SPF should be based on the individual's skin type, geographic location, and type of leisure activity. Patients should also undergo regular assessment of their acne and use of photoprotection should be reaffirmed.

Towards Adapted Sun Protection for Patients with Acne

Doctor Dominique Moyal

Tetracyclines and systemic retinoids as treatment for acne have been demonstrated to induce phototoxicity. Therefore, several clinical studies have been carried out to prove that sun protection can prevent such side effects. A study of 35 patients with acne treated with doxycycline or lymecycline compared the efficacy of the Anthelios sunscreen SPF50+ UVAPF28 with the vehicle (the excipient of the sunscreen, i.e. all ingredients except the UV filters) to prevent tetracycline-induced phototoxicity.[34] Patients were exposed to UVA radiation on their backs, and the minimal phototoxic dose for each individual was determined. Patients were exposed to UVA doses of 0.75, 1.0, and 1.25 minimal phototoxic dose on areas treated with sunscreen or vehicle product, and assessed 24 and 48 hours after exposure for clinical signs of erythema and colourimetric measurements. Visual scoring (Figure 2) and colourimetric assessment revealed that minimal erythema appeared in areas treated with the sunscreen versus the vehicle product (differential colourimetric redness score of 1.5 versus 4.3, respectively, at 1.0 minimal phototoxic dose). A second study explored the effectiveness of a sunscreen SPF60+ for the prevention of phototoxicity in 26 patients with severe acne treated with isotretinoin. Patients' acne was evaluated using the Cook Index (0–9 scale)[36] at the start of the study and at the end of the summer season (4 months later). At the end of the season, the intensity of acne was reduced (mean Cook Index score: 2.6) compared with the start of the study (mean Cook Index score: 7.1) with no adverse effects. These results demonstrated that the use of effective sun protection was beneficial in avoiding the side effects of isotretinoin.

PIH is a common sequela of acne and can be long-lasting. An observational study carried out in >5,000 patients with acne (phototypes II [47%] and III [39%]) across 11 countries found that 76% of patients had residual colour marks that were erythematous, pigmentary, or both. A second observational study of 3,800 patients with acne was carried out and included patients with darker skin (phototype II: 40%, phototype III: 41%, phototype IV: 12%). It was determined that residual erythematous, pigmentary, or combined marks were present in 74% of patients. To explore whether there is a link between severity of acne and PIH, patients were stratified into mild acne and moderate acne groups and assessed for residual marks. More patients with moderate acne had residual marks (81.9%) than those with mild acne (57.5%). The results confirmed that PIH was common in patients with acne, especially in individuals with severe acne and with darker skin, and that photoprotection is important in preventing intensified pigmentation after sun exposure.

To explore whether adapted dermocosmetics and photoprotection can be used during the summer to avoid acne outbreaks, 337 patients who were at the end of local or systemic medical treatment were evaluated for acne outbreaks and severity. Patients with phototypes II–IV were included and prescribed an anti-acne dermocosmetic (Effaclar DUO+) and a sunscreen with SPF30 and UVAPF25 developed for oily skin (Anthelios AC) for 90 days during the summer. Acne evaluation was carried out at the start of the study and 90 days after beginning treatment. At baseline, 70% of patients

had no or almost no lesions, 21% had low-level acne, and 9% had moderate acne, and at Day 90, 81% of patients had no or almost no lesions, 17% had low-level acne, and 3% had moderate acne, which corresponded with a significant decrease in acne severity (overall, 45% experienced a decrease in acne severity, 45% experienced no change, and 10% an increase).

In conclusion, PIH is often associated with acne and UVA has an important role in increasing hyperpigmentation, and photoprotection can potentially offset and prevent dermatological side effects of acne treatments. Acne can worsen with sun exposure, and prescription of photoprotection to and adherence from patients is insufficient. Photoprotection should provide high-level protection from UVA and UVB radiation, be non-comedogenic, and textures should be adapted to the needs of the patient.

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WILL BIOSIMILARS CHANGE THE TREATMENT PARADIGM IN PSORIASIS?

This symposium took place on 29th September 2016 as a part of the European Academy of Dermatology and Venereology (EADV) Congress in Vienna, Austria

Chairperson

Matthias Augustin[1]

Speakers

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MEETING SUMMARY

Prof Augustin opened the meeting and reviewed the use of systemic treatments recommended for moderate-to-severe psoriasis. Data indicating a lack of access to biologic treatments were presented, and barriers to the use of biologics, including both patient and physician-related cost, were discussed. The opportunity for improved access to biologic treatment options, portrayed by the availability of biosimilars, and the potential to improve healthcare for patients with psoriasis was presented.

Dr Schiestl explained that the demonstration of biosimilarity for regulatory requirements is based on the totality of evidence generated from analytical, non-clinical, and clinical data. The physicochemical and biological assessments performed for comparison of the proposed biosimilar and the originator molecule, using state-of-the-art technology, are most sensitive. Comparative, analytical, and functional testing therefore represent the major part of the comparability exercise, proving that the biosimilar and originator product contain essentially the same active substance. After demonstration of similarity at an analytical and functional level, suitable comparative pharmacodynamics (PDs) and/or pharmacokinetics (PKs) and/or safety studies in animal models are performed. Comparative clinical PKs/PDs and safety is assessed in healthy volunteers as an essential part of the clinical development programme. A final confirmatory Phase III clinical study is conducted in a sensitive patient population to confirm similar safety and efficacy of the biosimilar compared to the originator molecule.

Dr Gerdes explained why psoriasis is a sensitive and robust indication for confirming clinical efficacy of a biosimilar. He presented data from the EGALITY confirmatory study of the etanercept biosimilar

(GP2015) in patients with moderate-to-severe psoriasis to compare safety and efficacy, and provided data on multiple switches between the originator etanercept (ETN) and the biosimilar. The trial confirmed the clinical equivalence of the efficacy and safety of GP2015 with ETN; no new safety signals were observed. Switching between the originator and biosimilar had no effect on safety or efficacy over the 52-week study.

The Evolving Role of Systemic Therapy in Psoriasis

Professor Matthias Augustin

Psoriasis is a key disease for dermatologists, with a prevalence in Europe of 2.5% (approximately 15 million people), with 20–25% of these having severe disease. Recent European and World Health Organization (WHO) reports[1,2] have recommended that patients should have early, comprehensive treatment, and have highlighted costs limiting access to biologics as the main barrier. Healthcare systems also affect access to biologics for psoriasis. The European Dermatology Survey found that the prescription of systemic psoriasis treatment by dermatologists varies between countries and in some European countries biologic treatments can only be prescribed by hospitals. Around half of European countries have fixed budgets for prescribing biologics in psoriasis, and two-thirds require additional approval of the clinician's prescription. The importance of treatment access is demonstrated by the significant link between lack of access to multiple systemic treatments and reduced treatment success.[3]

Over the last decade, systemic biologic therapies for psoriasis have become widespread, with new biologics and biosimilars of existing biologics anticipated within the next few years. The challenge for dermatologists is how best to use this abundance of new treatments. The patient needs which dermatologists are addressing are wider than simply improvements in skin conditions, as measured by the Psoriasis Area and Severity Index (PASI).[4] Current European guidelines[5,6] recommend several systemic biologic treatments for moderate-to-severe psoriasis, as well as conventional systemic therapies and ultraviolet (UV) treatment, but there is currently no clear guidance on which systemic therapy to use first, nor on switching biologics. The selection of a systemic treatment for psoriasis should take into account the clinical criteria, the drug characteristics, the patient characteristics, and the regulatory requirements (including national healthcare system regulations). Treatment goals for moderate-to-severe psoriasis have been defined, and the European consensus is that the ultimate goal of any treatment is the complete clearance of lesions.[7] However, while the complete clearance of lesions (PASI score 90–100) is a good indicator of drug performance, the most patient-relevant endpoints are actually PASI 50, 75, and 90 scores.[8] Early intervention with systemic treatment provides benefit in terms of minimising increases in morbidity and patient suffering, and in minimising associated costs.[9] The long-term safety of treatment is also a key factor as psoriasis is a lifelong disease. Data from pharmacovigilance registries are essential for patient safety, as patients in the real world can have different rates of adverse events to those selected for clinical trials.[10] Data from the PsoBest registry show that the rate of serious adverse events is similar between conventional systemic treatments for psoriasis and biologics.[11]

Despite the guidelines and evidence for both benefit and long-term safety, many patients with severe disease still do not get access to systemic therapy.[12] These barriers to guideline-compliant psoriasis care come from patients, physicians, and external factors. Patients are unaware of the benefits of systemic therapies and have misconceptions of the risks, whilst physicians can lack knowledge of the guidelines or have a fear of legal liability in the case of adverse outcomes. External factors such as poor healthcare infrastructure, low budgets, or lack of training may also prevent guideline-compliant psoriasis care.[13] Recommendations have been made to overcome these barriers, and these include acknowledging the financial implications of treating a complex disease such as severe psoriasis.[13]

The increasing number of biologics and biosimilars in the market and in development provides the opportunity to overcome the cost barrier in accessing systemic treatment for psoriasis. The use of biosimilars has been shown to reduce healthcare costs,[14] and the estimated cost savings achieved by use of an ETN biosimilar instead of ETN (between 2016 and 2020) could provide the opportunity to fund treatment for an additional 3,100 patients in the UK or 17,310 patients in Germany.[15]

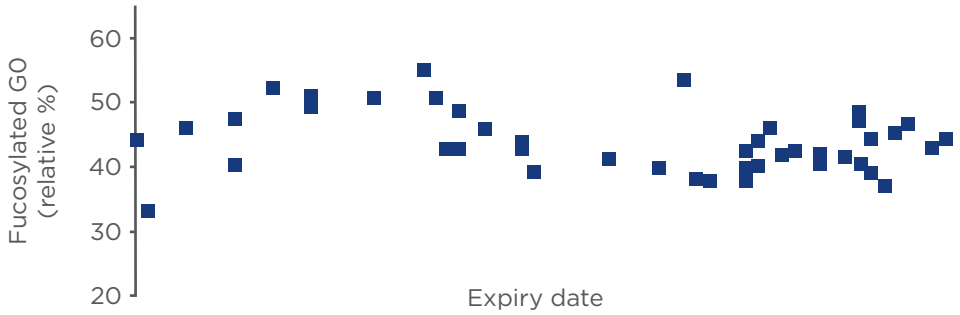

Figure 1: Variability of major glycan variants in commercially available monoclonal antibody.[22]

Therefore, improved access and lower costs of systemic therapy have the potential to allow innovation in the treatment paradigm for patients with psoriasis, as well as enabling a more patient-centred approach to treatment.[16-18]

In summary, biologic treatments have changed the landscape of psoriasis care and provide added value. There is clear evidence for starting systemic treatment early, but with the variety of effective systemic treatment options for moderate-to-severe psoriasis there is no clear evidence about optimum treatment pathways or long-term management. Choices for systemic treatment take into account clinical characteristics of the patient's psoriasis, drug properties, and patient preferences. There is a large body of evidence generated by real-world safety data of systemic biologic treatments for psoriasis, but other barriers to their use exist. Removing these barriers will involve creating awareness of the evidence for their benefits, disseminating expert knowledge of their use, optimising prices, and making use of the potential of biosimilars.

Analytical Comparison as the Foundation of Biosimilarity

Doctor Martin Schiestl

Despite biosimilars having been approved for use within Europe for the past 10 years, there is still a lack of awareness regarding their development. The essential point is the paradigm shift involved; in contrast to the development of an originator where the major goal is to determine the clinical efficacy and safety, the major goal in biosimilar development is to demonstrate that the biosimilar and originator are structurally and functionally comparable. Analytical methods provide the most sensitive tools to establish head-to-head comparability and thus provide the foundation of biosimilar development.[19] Tailored head-to-head non-clinical and clinical studies are focussed on identifying any differences between the originator and the biosimilar, if they exist, rather than re-establishing the clinical efficacy and safety *de novo*, which has already been demonstrated by clinical studies of the originator. In Europe and the USA, the term 'biosimilar' is strictly defined as a biologic product (usually a successor to a biologic that has lost exclusivity) that has been approved via a stringent regulatory pathway. An approved biosimilar matches the reference biologic, and patients and physicians can expect the same safety and efficacy profile.[20]

An approved biosimilar must match its reference biologic structurally. The amino acid sequence has to be identical and the folding that results in the three-dimensional structure (the secondary, tertiary, and quaternary structure of the protein) must be indistinguishable from the originator.[21] Post-translational modifications of the protein such as glycation, which are highly variable in nature, must contain identical structures in comparable amounts. Differences in these are only acceptable if it can be demonstrated that they do not lead to any clinically relevant effects.[21] A degree of variability is natural in glycated proteins, and batch-to-batch variability in glycation can readily be measured in commercially available complex biological products e.g. monoclonal antibodies (Figure 1). Changes in the manufacturing process, such as implementation of a new purification method or a change in manufacturing site, may also cause minor but measurable changes in the glycation or the purity profile of a biologic.[22] These changes are stringently controlled by regulators and are only approved if they do not lead to clinically meaningful differences.

Companies may change manufacturing processes for originator biologics many times after approval,[23] and these changes are well understood and tightly controlled by health authorities. The scientific principles in regulating those manufacturing changes are described by internationally accepted guidelines.[24] Biosimilar regulation is in fact based on experience with the regulation of manufacturing process changes of originator products.

Analytical comparison of molecules sets the foundation for extrapolation of indication for biosimilars. Extrapolation follows the concept that the same molecule will behave the same way as the original molecule in all indications and patient populations. If the totality of the evidence (structural, functional, and PK analyses, and clinical data in at least one sensitive indication) demonstrates that the biosimilar and reference product are highly similar, then extrapolation from one molecule to the other is scientifically justified; i.e. the biosimilar can be safely used in all indications approved for the originator.[21,25] Extrapolation to all the originator indications is not based simply on the clinical data alone for a biosimilar in one tested indication, but includes all the analytical data demonstrating that the molecules are structurally and functionally the same.[26] Therefore, it can be expected that both will behave the same way in all the indications tested for the originator. It should be noted that extrapolation for biosimilars is not granted automatically but is evaluated for each indication individually based on the totality of evidence.[20,21]

The concept of extrapolation is not new; it is also applied when the manufacturing processes of originator medicines are changed. For example, if changes in glycation of an originator molecule following manufacturing process changes were identified, the company is required to demonstrate that the changes do not lead to clinically meaningful differences and therefore patients and physicians can expect the same safety and efficacy. If the modified process is approved as producing a highly similar product under the same label, it can be extrapolated to all approved indications.[22]

Current analytical tools are extremely powerful and able to detect very small variations in molecular structure and function. When demonstrating whether a biosimilar matches the originator in all relevant structural and functional attributes, typically >40 methodologies are used to analyse >100 different attributes.[27] Ideally, attributes are measured by more than one method. Using the development of the ETN biosimilar GP2015 as an example, the primary structure was tested by peptide mapping and mass spectrometry, and was shown to be 100% identical in amino acid sequence to ETN samples sourced in Europe and the USA.[28] X-ray crystallography confirmed that the higher order structure of GP2015 was indistinguishable from ETN sourced from Europe and the USA. Similar biological activity in neutralising tumour necrosis factor-α (TNF-α) was confirmed in a TNF-α reporter gene assay.[29] Structurally and functionally, and considering the batch to batch variability, GP2015 is indistinguishable from ETN and can therefore be expected to have the same clinical activity in all indications approved for the originator.

In conclusion, biosimilarity is established through stringent regulatory licensing pathways based on analytical data and complemented by preclinical and clinical studies confirming structural and functional similarity. Physicians and patients can expect the same clinical efficacy and safety profile for the biosimilar as for its originator. Extrapolation is evaluated for each indication based on the totality of evidence of structural, functional, preclinical, and clinical data. This concept has also been successfully used for originator products following manufacturing process changes. The safety and efficacy of biosimilars has been confirmed by over 10 years' experience with biosimilar products on the European market.

Demonstrating Clinical Equivalence: Results of the EGALITY Trial

Doctor Sascha Gerdes

In biosimilar development, clinical studies are required to confirm the equivalent efficacy of the biosimilar and its originator. Clinical studies to confirm biosimilarity need a sensitive population, a well-defined primary endpoint, and an adequate study duration to allow detection of small differences in efficacy, safety, and immunogenicity, should there be any. Plaque-type psoriasis fulfils all of these criteria. The response, in terms of reduction in skin lesions, is rapid and easy to assess. PASI and Physicians' Global Assessment (PGA)-based endpoints are well-established and consistent.[30] The treatment effect size compared to placebo is large, and the dosing for ETN in psoriasis is within the linear range of the dose-response curve.[6,31]

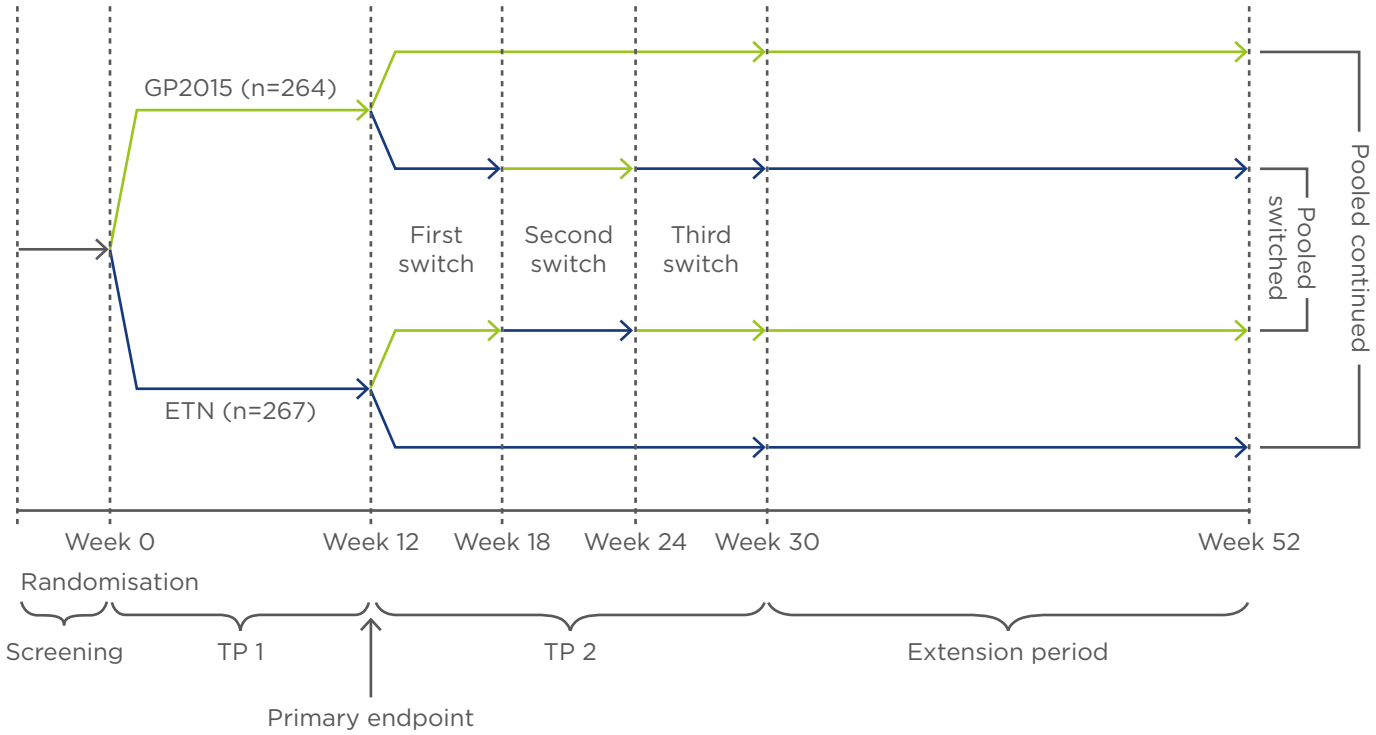

Figure 2: Study design of EGALITY.[34]
Randomised, double-blind, Phase III confirmatory study of the etanercept biosimilar GP2015 and ETN.
ETN: originator etanercept; GP2015: ETN biosimilar; TP: Treatment Period.

In psoriasis, biologics are usually used as monotherapy, in contrast to indications such as rheumatoid arthritis where co-medication with immunosuppressive drugs is common and drug interactions may occur.[32,33]

EGALITY is a randomised, double-blind, Phase III confirmatory study conducted in patients with moderate-to-severe psoriasis to compare efficacy, safety, and immunogenicity of GP2015 with ETN. The study also provides data on multiple switches between the originator and the biosimilar, which is relevant for clinical practice.[34] The primary endpoint is equivalence of PASI 75 response rates at Week 12 and the main secondary endpoint is equivalence of the mean percent change in PASI score from baseline to Week 12. The study was conducted in 74 dermatology centres in 11 European countries and South Africa. Overall, 531 patients were randomised 1:1 to 50 mg GP2015 or ETN twice weekly (subcutaneous regimen) for 12 weeks (Treatment Period [TP] 1). Patients who reached a PASI 50 response at Week 12 compared with baseline were re-randomised to receive either continuous treatment with ETN or GP2015, or treatment that involved three treatment switches between GP2015 and ETN at 6-week intervals until Week 30 (TP 2), after which they continued on their current treatment until Week 52 (Extension Period) (Figure 2).

Eligible patients were male or female adults with active but clinically stable chronic plaque-type psoriasis diagnosed at least 6 months prior to enrolment, with ≥10% of the body surface area affected, a PASI score of ≥10, and an Investigators' Global Assessment (IGA) score of ≥3. These patients had to have previously received phototherapy or systemic therapy for psoriasis, or have been candidates for such therapy.[34] Patients were excluded if they had other forms of psoriasis, in case of ongoing use of protocol-prohibited psoriasis treatments such as topical corticosteroids or UV therapy, or in case of previous exposure to ETN. Baseline characteristics were similar between the study arms. The mean age was approximately 42 years and BMI was 28.6 kg/m^2 in the GP2015 group and 28.5 kg/m^2 in the ETN group. The baseline PASI score was quite high, with a mean value of 22.5 in both groups.

PASI 75 (describing a 75% improvement compared with baseline) response rates were equivalent at Week 12, and were achieved by 73.4% of patients receiving GP2015 and 75.7% of patients receiving ETN in the per-protocol set (PPS).[34]

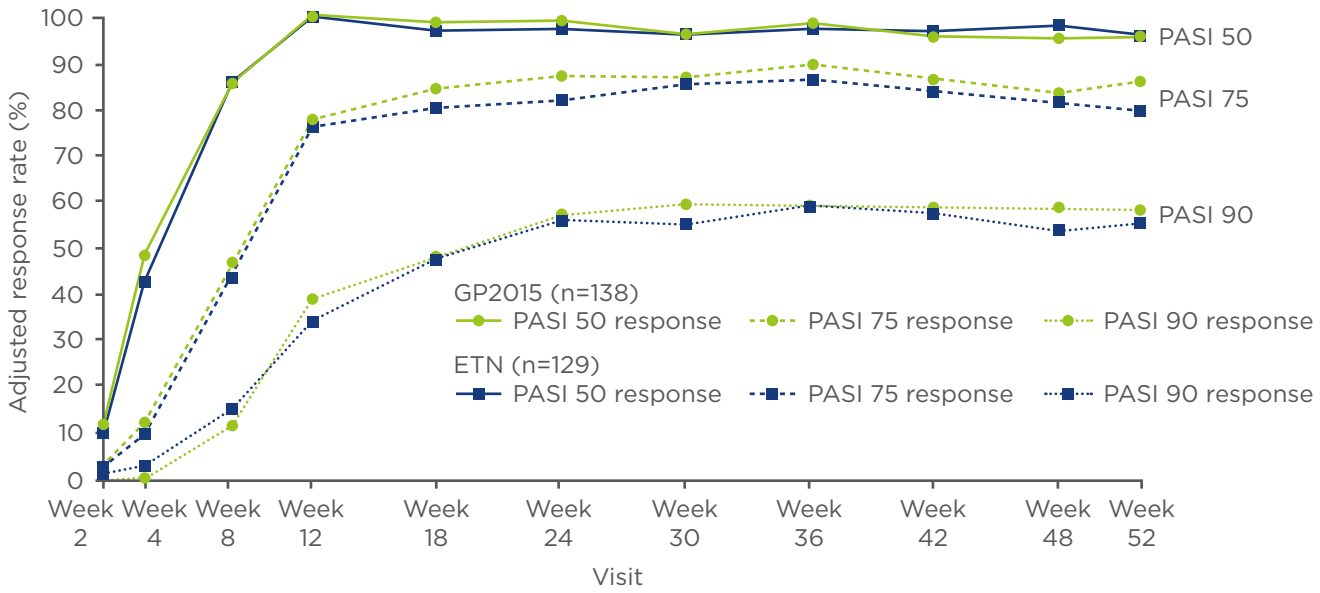

Figure 3: PASI response rates for continued GP2015 and ETN treatment groups from baseline to Week 52 in the overall per-protocol set.[34]

ETN: originator etanercept; GP2015: ETN biosimilar; PASI: Psoriasis Area and Severity Index.

Overall, PASI response rates (PASI 50, 75, and 90) were highly similar over the first 12 weeks of the trial. The mean percentage change in PASI score from baseline to Week 12 was equivalent between the GP2015 and ETN-treated PPS groups; the least square means difference between the two groups was -0.64% for the mixed-model repeated measures and -0.88% for the averaged treatment effect. The 95% confidence intervals were within the pre-specified margin range (15% to -15%). The PPS was used for the PASI response rates instead of the intent-to-treat or last observation carried forward approach used in pivotal trials testing for superiority, because the PPS is considered the more sensitive population in equivalence or non-inferiority trials. Similar improvements in IGA and Dermatology Life Quality Index (DLQI) scores were achieved in both treatment arms.[34]

Up to Week 52, PASI response rates were comparable between the groups who continued GP2015 or ETN treatment without switching (Figure 3). There was no impact of treatment switches on PASI response up to Week 52 when pooled data from all patients who underwent repeated switches between GP2015 and ETN were compared with pooled data from all patients who continued treatment without switching. Immunogenicity was low and in line with previously reported rates for ETN; five patients, all in the ETN group, developed anti-drug antibodies (ADAs) in the period up to Week 12, and one further patient who switched from ETN to GP2015 developed ADAs in the extension period up to Week 52. All ADAs were non-neutralising, transient, and low in titre.

The safety profiles of GP2015 and ETN were similar over the 52 weeks and were not affected by treatment switching (Table 1). There was no discernible pattern in treatment-emergent adverse events of special interest, such as rash (none with GP2015 versus one with ETN), neoplasms (five with GP2015 versus one with ETN), neutropenia (two with GP2015 versus none with ETN), or infections (eight with GP2015 versus three with ETN).[34]

The EGALITY study confirmed equivalence in the efficacy of GP2015 and ETN in patients with moderate-to-severe, chronic, plaque-type psoriasis by meeting all the primary and secondary endpoints. The safety profiles of GP2015 and ETN were comparable, and no new or unexpected safety issues with GP2015 or ETN were reported. The incidence of ADAs was low. Switching treatments did not impact efficacy, safety, or immunogenicity. These findings provide clinical confirmation of similarity between GP2015 and ETN and contribute to the totality of evidence, confirming that GP2015 is an adequate ETN biosimilar.

Table 1: Patients with treatment-emergent adverse events in the study groups over the 52-week trial period.[34]

Patients, n (%)	Continued GP2015 (n=164)	Continued ETN (n=171)	Pooled continued (n=335)	Pooled switched (n=196)
≥1 TEAE	98 (59.8)	98 (57.3)	196 (58.5)	118 (60.2)
≥1 SAE	7 (4.3)	7 (4.1)	14 (4.2)	12 (6.1)
≥1 treatment-related TEAE	34 (20.7)	33 (19.3)	67 (20.0)	42 (21.4)
≥1 severe TEAE	7 (4.3)	8 (4.7)	15 (4.5)	8 (4.1)
≥1 treatment-related SAE	0	1 (0.6)	1 (0.3)	1 (0.5)
Discontinuation due to TEAE	11 (6.7)	8 (4.7)	19 (5.7)	7 (3.6)
Study drug interrupted due to TEAE	9 (5.5)	17 (9.9)	26 (7.8)	8 (4.1)
≥1 AE of special interest	18 (11.0)	8 (4.7)	26 (7.8)	16 (8.2)
Deaths	0	1 (0.6)*	1 (0.3)*	0

*Cardiopulmonary failure, considered by investigator to be unrelated to study drug.
TEAE: treatment-emergent adverse events; SAE: severe adverse events; AE: adverse events; GP2015: ETN biosimilar; ETN: originator etanercept.

Question and Answer Session

Q: Is the triple switch in EGALITY sufficient to get an interchangeability approval on the label in the USA and Europe?

Dr Gerdes replied that the triple-switch study design was unique to this study, and whereas a single switch in a study was probably not sufficient to address whether switching affects safety or efficacy, the triple switch in EGALITY had clearly shown that it did not impact efficacy.

Q: Do the manufacturers of originator biologics have more scope for improvements in functionality resulting from manufacturing process changes than manufacturers of biosimilars?

Dr Schiestl replied that for the originator, the goal was still to keep the same safety and efficacy profile. Regulatory agencies will only approve a manufacturing process if the safety and efficacy stay the same. If the manufacturing process changes the molecule such that clinically meaningful differences occur, then the company has to do additional trials for safety and efficacy, and the molecule will be approved with a different name and label with its own safety data.

Click here to view the full symposium.

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QUALITY OF CARE: THE CHALLENGES, THE SOLUTIONS

This symposium took place on the 29th September 2016 as a part of the European Academy of Dermatology and Venereology (EADV) Congress in Vienna, Austria

Chairperson

Kim Papp[1]

Speakers

Christos C. Zouboulis,[2] Hilary Thomas[3]

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MEETING SUMMARY

Psoriatic arthritis (PsA) and hidradenitis suppurativa (HS) are both immune-mediated diseases with common cellular and cytokine pathways involved in their pathogenesis.[1] Both are characterised by chronic and systemic inflammation and both involve elevated levels of the cytokines tumour necrosis factor-α (TNF-α), interleukin-17, and interleukin-23.[1-5] PsA and HS are associated with substantial unmet needs and are sub-optimally managed. This educational session discussed ways to improve the quality of care and patient outcomes in PsA and HS.

Dr Kim Papp opened the symposium with an overview of the current unmet needs in PsA and HS and the key barriers to improving the management of both diseases. Prof Hilary Thomas discussed the Quantum initiative and how it could assist dermatologists in the treatment of PsA and HS. Dr Papp and Prof Christos C. Zouboulis then discussed the challenges of achieving optimal management in PsA and HS, as well as the solutions.

Unmet Needs in Psoriatic Arthritis and Hidradenitis Suppurativa

Doctor Kim Papp

In his overview, Dr Papp pointed to misdiagnosis, delays in diagnosis, the lack of awareness among physicians and patients of either condition,[6] and undertreatment of patients as the main unmet needs in PsA and HS. He also cited the lack of evidence-based treatment and guidelines as a barrier to effective disease management in HS. Both PsA and HS are associated with a high prevalence of

comorbidities such as cardiovascular comorbidities and impaired quality of life, where patients' physical function and ability to work and socialise are adversely affected. The financial burden associated with both diseases is substantial both to the patient, due to lost productivity arising from impaired physical function, and to the healthcare system, in which patients fail to receive optimal treatment due to misdiagnosis. Thus, there are hospitalisations and vast amounts of resources expended for inappropriate treatments over time. Dr Papp observed, based on the literature and his own experience, that some patients have symptoms for up to 10–15 years before they receive a diagnosis for HS.

How Quantum Can Help Dermatologists

Professor Hilary Thomas

The goal of the AbbVie Quantum initiative is to improve quality of care and, ultimately, patient outcomes, through the following:

- Raising awareness of the current challenges in identification and management
- Increasing levels of active patient participation in the management of disease
- Reducing the level of misdiagnosis and delays in diagnosis
- Promoting dialogue between centres of care to enable sharing of good practices
- Encouraging greater collaboration between specialties
- Delivering consistent care across geographic regions and hospitals

KPMG has supported AbbVie for the past 2 years in the development of Quantum across a range of therapeutic areas, including PsA and HS. The Quantum reports capture key learning on best-in-class care from selected centres, and are then disseminated for the purpose of sharing those insights and promoting improvement in the quality of care.

The process of developing and disseminating Quantum reports comprises four phases:

1) Selecting and engaging centres: In the first phase, KPMG selects and engages centres worldwide to cover a broad spectrum of healthcare systems and patient demographics. Centres of particular interest are those with individuals or groups of individuals who are experts in the field under investigation.

2) Learning from the centres: In the second phase, KPMG seeks to interview the full range of stakeholders involved in the management of the disease. Typically, KPMG would speak with as many healthcare professionals and staff at the selected centres as possible, from specialists and general practitioners to nurses, social workers, and pharmacists, to gain a first-hand understanding of the key challenges they face and the interventions that have been put in place to address them. The outreach is also extended to patients and patient associations to enhance KPMG's understanding of the personal impact of current standards of care.

3) Synthesising the findings in a global report on good practice: In the third phase, these findings are synthesised first into a centre-specific report on good practice and then into a global report drawing out the main themes and conclusions on good practice from the various centres.

4) Sharing the report and facilitating peer learning: In the fourth phase, the report is shared with the wider scientific, medical, and patient communities with the aim of helping other centres achieve best-in-class care and improvement in outcomes.

The KPMG report on PsA, entitled 'Improvement in the Management of Psoriatic Arthritis', was the result of visits to seven centres in the USA, Canada, UK, Germany, South Africa, Hong Kong, and Argentina.[7] The report was reviewed and validated by the Group for Research and Assessment of Psoriasis and Psoriasis Arthritis (GRAPPA) and was presented at their Annual Meeting in Miami, Florida, USA, in July 2016.

The KPMG report on HS, entitled 'Guiding Principles in Hidradenitis Suppurativa Care', captures the insights gained from visits to eight centres in Western Europe, Canada, and the Middle East.[8] It has been reviewed and validated by Prof Zouboulis as President of the European Hidradenitis Suppurativa Foundation (EHSF) in 2016.

Prof Thomas believed that Quantum would help reduce the rates of misdiagnosis and delays in diagnosis in PsA and HS as well as encourage increased collaboration between specialties. She underscored the fact that one of the themes that had emerged from her work was the importance of care networks. She pointed to Canada as an example of a vast country with widely distributed population centres where community networks have given patients greater access to care,

reducing their need to travel distances ≤200 miles each way to receive treatment in a major urban centre. Furthermore, Prof Thomas expected care networks to help raise the level of patient involvement in their own disease management, increase dialogue and the sharing of good practices between centres, and contribute to the delivery of consistent care across geographic regions and hospitals.

In Prof Thomas' view, the Quantum initiative is helpful to dermatologists in the following ways:

- Provides insights on the management of PsA and HS from leading specialist reference centres, secondary and tertiary care centres, and community clinics
- Maps the common challenges in the management of PsA and HS
- Provides insights on how challenges are addressed in specialist centres
- Provides guidance on the implementation of solutions to common clinical challenges in a wider group of clinics across the network, and where appropriate, across communities

Achieving Optimal Management of Psoriatic Arthritis: The Challenges and the Solutions

Doctor Kim Papp

The patient pathway in PsA comprises four stages:

- Pre-diagnosis (patient experiences symptoms)
- Referral and diagnosis (patient receives a referral to a dermatologist or rheumatologist and receives a diagnosis)
- Treatment initiation and management (patient begins treatment)
- Follow-up (long-term management with regular monitoring)

The challenges associated with each phase and their solutions are described in Table 1.[7]

Table 1: Patient pathway in psoriatic arthritis: challenges and solutions.[7]

Phase	Challenges	Solutions
Phase 1: Pre-diagnosis	Limited awareness of PsA among HCPs and patients	• Increase education of GPs and dermatologists • Attend educational meetings, particularly those run by rheumatologists • Participate in or establish combined clinics (which ensure a close working relationship between dermatologists and rheumatologists) • Use/help to develop educational tools about the signs and symptoms of PsA • Use questionnaires e.g. PASE • Educate patients • Educate patients and their families about early symptom detection and the long-term consequences of PsA • Encourage patients to educate themselves • Provision of educational materials at doctor's office and referral to patient association groups • Encourage patients to communicate about their skin and joint symptoms by asking probing questions
Phase 2: Referral and diagnosis	Lack of screening	• Use screening tools to regularly screen patients with psoriasis for signs and symptoms of PsA: - PASE - ToPAS - PEST
	Delayed referrals	• Patients should be referred to a rheumatologist as soon as PsA is suspected • Referral forms for GPs to improve the quality and speed of referrals • Self-referral scheme • Outreach activities • Networks and referral pathways • Close collaboration between GPs/dermatologists and rheumatologists • Novel referral pathways can improve efficiency e.g. self-referral scheme
	Challenges with differential diagnosis	• When diagnosis is not straightforward, a multidisciplinary approach may be required (e.g. rheumatologists, dermatologists, orthopaedics) • Combined dermatology–rheumatology clinics can be useful • Use diagnostic equipment such as X-ray and ultrasound

Table 1 continued.

Phase	Challenges	Solutions
Phase 3: Treatment initiation and management	Siloed approach to care in secondary, tertiary, and community centres	• Improved co-ordination of dermatology and rheumatology services • Combined clinics • Multidisciplinary team meetings • Informal communication and knowledge sharing • Develop networks and relationships between community-based centres • Use technology (teleconferences and online connectivity platforms) and face-to-face meetings
	Gaps in clinical management	• Use protocols and treatment algorithms, e.g. GRAPPA or EULAR • Use a treat-to-target approach • Uncertainty on measures of disease activity
	Challenges associated with the use of biologics	• Enrolment of patients into clinical trials • Development of relationships with commissioners; may help create alternate care pathways and improved reimbursement **Personal approach** • Use tools available more creatively e.g. prednisone is not ideal but can be effective
	Lack of patient centricity	• Improved communication between HCPs and patients, and engagement of patients in their care • Development/use of educational programmes for patients • Educate patients on disease, treatment options, and their risks and benefits • Patient education by the medical office staff
Phase 4: Follow-up	Inadequate treatment of comorbidities	• Educate HCPs on the impact of PsA on daily life, comorbidities and the long-term outcomes of PsA • Patients should be educated on the risk of developing comorbidities, particularly the cardiovascular risk • Nurse-led clinics for monitoring patient comorbidities
	Lack of regular follow-up	• Regularly monitor patients • Psychological, social, and physical impact of the disease could also be monitored; use a validated tool • Use databases and electronic medical records • Educate patients on the need for regular assessments

EULAR: European League Against Rheumatism; GP: general practitioner; GRAPPA: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; HCP: healthcare professional; PASE: Psoriatic Arthritis Screening and Evaluation; PEST: Psoriasis Epidemiology Screening Tool; PsA: psoriatic arthritis; ToPAS: Toronto Psoriatic Arthritis Screening.

Achieving Optimal Management of Hidradenitis Suppurativa: The Challenges and the Solutions

Professor Christos C. Zouboulis

Low clinician awareness of HS is the leading cause of delayed diagnosis, misdiagnosis, and lack of or misdirected referrals in HS, and it represents the principal challenge to achieving improvement in HS management and outcomes.[8] These challenges are present at each stage of HS management (presentation of first symptoms, diagnosis, referral to a dermatologist or rheumatologist, initiation of treatment, long-term follow-up, and ongoing care).[8] The challenges faced at each of these stages of HS management, along with their solutions, are outlined in Table 2.

Professional scientific associations that are relevant to HS include the EHSF, which has published diagnostic criteria for HS as well as the European and evidence-based guidelines for the treatment of HS, and the World Union of Wound Healing Societies (WUWHS), which has issued a position document on HS entitled 'Understanding Hidradenitis Suppurativa'.[9] AbbVie indirectly supports the HS Alliance, whose mission is to generate clear and credible guidance on the treatment and management of HS through the development of evidence statements. Initiatives sponsored by AbbVie include 'What's Your

Sore Spot?', a patient-focussed website with information about HS;[10] and EIDON (Expertise in Delivering Optimal Care in HS), a medical education programme aimed at improving HS management through the establishment of a European network of specialist reference centres and sharing of best practices between the centres.

Table 2: Patient management in hidradenitis suppurativa: challenges and solutions.[8]

Stage of management	Challenges	Solutions
First symptoms	Delayed presentation to clinicians/ dermatologists	• Public awareness campaign • To raise awareness of HS amongst undiagnosed patients, as well as the general public • HS awareness training • Training for primary and secondary clinicians to improve their understanding of HS
Diagnosis	Delays in diagnosis or misdiagnosis	• HS awareness training • Training for primary and secondary clinicians to improve their understanding of HS • HS training for nurses • Training for nurses to equip them to recognise HS and provide appropriate care • Patient association, running awareness campaigns • Campaigns targeted at the medical community
Referral	Lack of or misdirected referrals	• HS training for clinicians • Training for primary and secondary clinicians to improve their understanding of HS • Jointly agreed referral criteria • Referral criteria drawn up by collaborating clinicians to create a clear and standardised agreement on what triggers referrals
Treatment	Difficulty in accurately identifying disease extent	• Ultrasound • Ultrasound images can be used to accurately determine disease extent • CO_2 laser surgery • Patients requiring surgery can have their diseased tissue vaporised in thick layers so that clinicians can see where the healthy tissue starts and minimise removal
	Multiple patient needs and comorbidities	• Multidisciplinary team • Clinicians and support services should work collaboratively to provide treatment that addresses the entirety of patients' needs
	Low patient adherence to treatment plans	• Jointly developed treatment plans • Practitioners explain treatment decisions to patients and address patient preferences wherever possible when initially making the decisions • Patient education • Sessions can be held to educate patients and to provide a platform to share experiences and concerns • Multidisciplinary team offering lifestyle support • Patients supported by practitioners in effecting lifestyle changes that might positively affect their symptoms
Follow-up and ongoing care	Clinician capacity affected by follow-up demand	• Nursing support • Specialist wound care nurses or general dermatology nurses can provide support by assisting in the treatment of follow-up wound care • Follow-up care in the community • Patients requiring follow-up care for flares or wound management supported in community settings rather than at a hospital or medical centre
	Physical, psychological, and financial strain on patients	• Patient association • Formed, either independently or with the support of centre staff; may work at a public or government level • Multidisciplinary team offering psychological support • Patients offered assistance in dealing with the psychological effect of HS • Patient care meetings

Table 2 continued.

Stage of management	Challenges	Solutions
Follow-up and ongoing care	Physical, psychological, and financial strain on patients	• Regular meetings held with staff and patient representatives to discuss patient care optimisation • Hyperbaric chamber therapy • Patients attend a set number of sessions in a hyperbaric chamber after surgery
	Professional siloes (lack of support)	• Global network • Centres, clinicians, and patients link to each other via virtual networks to provide global support optimising local activity

HS: hidradenitis suppurativa.

Table 3: Proposed action plan for psoriatic arthritis and hidradenitis suppurativa.

The goal	The plan
1) Use a screening tool	**Who:** All dermatologists in the department **What:** Use PEST (or another questionnaire) **How:** Complete printed questionnaires **When:** On patients' first visit
2) Increase HS awareness	**Who:** All dermatologists in the department **What:** Attend awareness training courses **How:** Complete course and follow-up **When:** Within the next 6 months
3) Increase patient understanding of PsA/HS	**Who:** Patients **What:** Improve awareness/understanding of disease **How:** Sharing of patient information leaflets; making sure patients know where they can find more information **When:** Straight away

HS: hidradenitis suppurativa; PEST: Psoriasis Epidemiology Screening Tool; PsA: psoriatic arthritis.

Discussion: Practical Solutions in Psoriatic Arthritis and Hidradenitis Suppurativa

Doctor Kim Papp

Symposium participants were asked to propose high-impact short-term (≤6 months) action plans for PsA and HS that would be simple to implement. Table 3 shows an example of a proposed action plan.

As highlighted in this symposium, PsA and HS are associated with substantial unmet needs including delayed diagnoses or misdiagnoses, lack of or misdirected referrals and undertreatment of patients. Low clinician awareness is the leading cause of delayed diagnoses and misdiagnoses. Therefore, increasing healthcare professionals' education and awareness is critical for improving the management of, and outcomes in, both diseases.

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VALUE IN PSORIASIS CARE: FROM PATIENTS TO PAYERS

This symposium took place on 25th April 2016 as part of the Psoriasis Excellence Program for European Dermatologists in Hamburg, Germany, in collaboration with the Universitatsklinikum Hamburg-Eppendorf, the Hamburg Center for Health Economics, and the Regionale Psoriasisnetze in Deutschland

Chairpersons

Matthias Augustin,[1] Marc Radtke[1]

Speakers

Matthias Augustin,[1] Marc Radtke,[1] Diamant Thaci,[2] Kristian Reich,[3] Ulrich Mrowietz[4]

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MEETING SUMMARY

The symposium explored new approaches to optimising the value of psoriasis management from the perspective of physicians, patients, and healthcare systems, drawing on research and evidence from real world clinical practice. The value in improving the management of psoriasis means boosting the efficacy of patient management, improving the power of outcomes measurement, raising the quality of care, and working more effectively with payers.

Many patients with moderate-to-severe psoriasis do not currently receive high quality care and are often undertreated, with many not receiving systemic therapy despite this being recommended by evidence-based guidelines. Reasons for not initiating or maintaining systemic therapy included long-term safety concerns, convenience of use, and cost, even though psoriasis can result in irreversible cumulative life impairment.

The growing recognition that psoriasis is a systemic inflammatory disorder that is associated with a wide range of comorbidities, including obesity, cardiovascular disease, diabetes, hypertension, and depression, underlines the need for systematic evaluation and treatment of comorbidities and the use of systemic treatment. Setting and implementing treatment goals is considered essential for driving up the value of psoriasis care. These should include measures that matter most to patients, taking into account the impact of psoriasis on their quality of life, including involvement of visible areas and nails, pruritus, and recalcitrant plaques, in addition to objective measures such as their Psoriasis Area Severity Index (PASI) score. Comprehensive management of psoriasis should provide treatment or referral to relevant specialists working in an integrated way across a networked service.

Improving Value in Psoriasis Management

Professor Matthias Augustin

"Improving the value of psoriasis management means optimising the efficacy of patient management, improving the power of outcomes measurement, increasing the quality of care, and working more effectively with payers," suggested Prof Augustin as he opened the symposium. He suggested that measuring values of psoriasis management is often limited to a narrow focus on cost containment. "But healthcare organisations are starting to see improvement in value for patients as a key goal in shaping their strategies," he said.

Important issues in improving psoriasis management include improving communication with patients, optimising long-term management of psoriasis, keeping up-to-date with new treatment strategies, best practice and guidelines, managing comorbidities, and demonstrating value in healthcare, Prof Augustin proposed. He pointed to the Global Report on Psoriasis[1] published recently by the World Health Organization (WHO), which sets out the need for improved psoriasis care based on the epidemiology and burden of the disease.

The WHO report[1] warned that psoriasis causes great physical, emotional, and social burdens, significantly impairing patient's quality of life. It noted that too many people suffer needlessly from psoriasis due to an incorrect or delayed diagnosis, inadequate treatment options, and insufficient access to care. Recommendations included ensuring that patients with psoriasis have access to comprehensive, individually adapted treatment, including treatment of comorbidities, based on a model of people-centred and integrated health services.

Prof Augustin reported on the first European Dermatology Health Care Survey[2] which is collecting data on dermatological care in 38 European countries. Results so far reveal wide variations in how psoriasis is currently managed in different countries, such as the percentage of dermatologists prescribing systemic drugs ranging from <5% in Cyprus to 100% in several countries, including Austria and Norway. Of the countries taking part in the survey, 18 had national psoriasis guidelines yet 14 did not.

Barriers to Guideline-Based Treatment

Professor Matthias Augustin

Considering the factors that limit provision of psoriasis care according to guidelines, Prof Augustin suggested three main barriers (Figure 1):[3]

- Physician factors: Lack of knowledge by physicians is a common problem in psoriasis care, particularly regarding the complexity of comorbidities, in addition to lack of awareness of guidelines, treatment goals, and limited interdisciplinary co-operation
- Patient factors: Many people have limited knowledge about psoriasis or treatment options and adherence to treatment is often poor, primarily due to concerns about treatment risks and side effects
- External factors: There are wide variations in psoriasis healthcare and implementation of

guidelines and training, in addition to poor health infrastructure and the failure of health systems to fund good quality care

How to Improve the Value of Psoriasis Care

Professor Matthias Augustin

A key step in improving the value of psoriasis care is to set treatment goals and support physicians, patients, and healthcare systems in achieving these. The recent European consensus on treatment goals for moderate-to-severe psoriasis[4] recommended using two measures to assess the impact of treatment: the change of PASI score from baseline until evaluation and the absolute Dermatology Life Quality Index (DLQI). The consensus advised that after induction and during maintenance therapy, treatment can be continued if the reduction in PASI score is ≥75%. Treatment should be modified if the improvement in PASI score is <50%. Where the therapeutic response improves by ≥50% but <75%, therapy should be modified if DLQI is >5 but continued if DLQI is ≤5. "Implementation of treatment goals in the management of psoriasis will improve patient care and reduce the problem of undertreatment," suggested Prof Augustin.

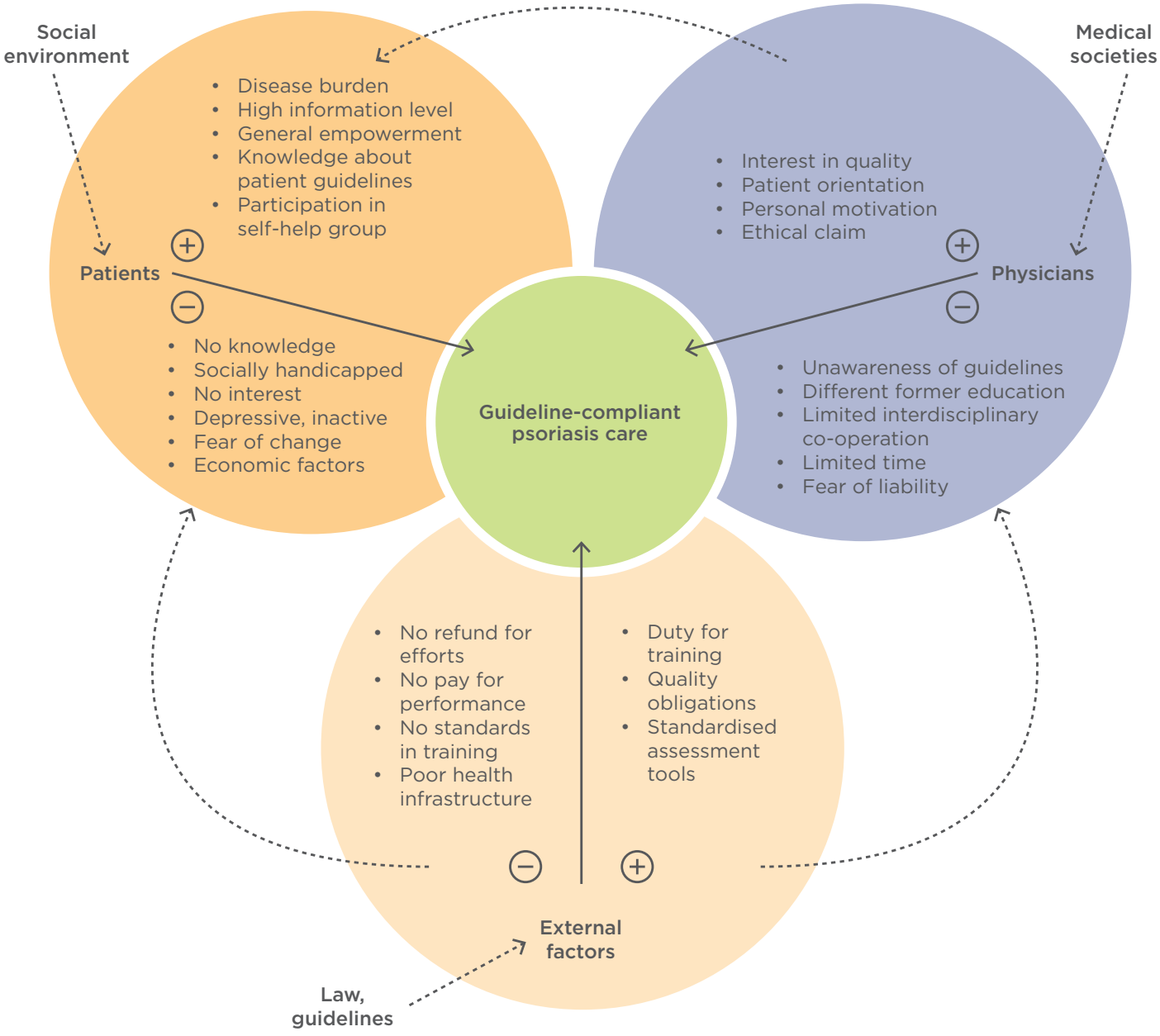

Figure 1: Barriers to guideline-compliant psoriasis care.
Adapted from Eissing et al. 2015.[3]

He added: "It is essential that the patient's perspective, as measured by their quality of life, drives treatment decisions." The annual national conference on healthcare for psoriasis in Germany agreed the following goals for 2010–2015:[5]

- Patients with psoriasis have a good quality of life
- Psoriatic arthritis will be detected and treated early
- Comorbidities in patients with psoriasis will be detected and treated early
- Children with psoriasis are treated early and have a good quality of life

Treatment goals should include measures that matter most to patients, he suggested, taking account the impact on their lives with involvement of visible areas and nails, pruritus, and recalcitrant plaques, in addition to objective measures such as their PASI score.

Monitoring has shown that quality indicators for psoriasis care have improved markedly over the last 10 years and regional variations have been reduced.[6] "A co-ordinated nationwide psoriasis programme based on goal orientation can contribute to better quality of care and optimised outcomes," concluded Prof Augustin.[7]

Measuring Value in Psoriasis Care: Physician and Patient Perspectives

Professor Marc Radtke

Physicians' and patients' perspectives on psoriasis and its management have changed dramatically over the past decade and it is essential that the value of care for both groups is measured as part of optimising quality, argued Prof Radtke. He noted that inpatient treatment was common in 2004, with patients typically remaining in hospital for 1–2 months each year. Treatments were generally topical, with different treatments being used on an intermittent basis, rotating different options. Comorbidities were considered coincidental rather than part of a systemic disease.

Nowadays the inflammatory nature of psoriasis is clearly understood, systemic treatment has become a standard in most countries, and healthcare provision is comprehensive. "The time to achieve control of the disease is much shorter than in the past and treatment encompasses a holistic approach in an interdisciplinary setting," Prof Radtke suggested. Recent surveys have revealed the gap between physicians' perceptions of factors contributing to the severity of psoriasis and what most bothers patients. Patients reported that the most bothersome skin symptom was pruritus (itching) (38%)[8] while a survey of 391 dermatologists working in Europe and North America found that only 7% selected itching as the most important factor contributing to patients' quality of life.[9]

From the physicians' perspective the expectations for treatment have changed as new treatments have become available, with increased expectation for higher rates of skin clearance than in the past. The survey[9] found their top attributes for ideal therapy focussed on safety, with 36.6% wanting therapy with no increased risk of serious infection or cancer and 17.4% desiring therapy with a manageable tolerability profile. The top unmet needs were improved efficacy (35.5%) and improved long-term safety (33.5%).

In terms of treatment expectations Prof Radtke suggested that efficacy, as assessed by clinical improvement measured by the percentage reduction of skin lesions on the PASI score, is of central importance to physicians. He noted that a network meta-analysis of randomised controlled trials[10] showed that the efficacy of different therapies in moderate-to-severe psoriasis differed considerably. He noted that maintenance of efficacy with no loss over time was also important to physicians, together with efficacy on retreatment, if this is required. "Long-term efficacy is increasingly important. We expect long-term disease control with psoriasis treatment," he noted, adding that there are significant differences between different therapies in sustained efficacy over time.[11]

What Matters to Patients?

Professor Marc Radtke

"It is also essential to assess the outcomes of psoriasis care according to patients' needs," Prof Radtke told the symposium. He noted that some of the currently used measures for assessing psoriasis, including the DLQI and PASI, are often insufficient to accurately monitor disease severity in individual patients. "Optimising treatment in practice includes the patient perspective," he argued, recommending that subjective

assessment at the patient level should be included in assessment of treatment effects.[12]

The patient benefit index assesses a patient's needs with a questionnaire before psoriasis therapy and measures the patient's benefits after treatment. Patients are asked questions about their expectations of treatment that include those related to PASI scores, such as recovery from skin lesions, but also questions that go far beyond this, including how important they rank being free of itching and being able to sleep better. Prof Radtke said it was also important to consider the time needed for psoriasis treatment as this has been shown to be the major predictor of quality of life in patients with psoriasis.[13] Prof Radtke concluded that greater use of patient-reported outcomes is essential in improving the value of psoriasis care. He suggested that these should measure the impact of the disease and its treatment at the individual patient level, using condition-specific measures that take into account the considerable psychosocial and emotional impact of living with psoriasis.

Recognising That Psoriasis is a Systemic Disease

Professor Diamant Thaci

"Psoriasis is a complex systemic disease," said Prof Thaci. "In the past we perceived psoriasis as only a skin disease. But it is not just about keratinocytes. We now recognise it is a T cell-driven disease involving multiple cytokines," he told the symposium. The underlying systemic inflammation occurring in patients with psoriasis is associated with a wide range of comorbidities, including diabetes and cardiovascular disease. "Systemic biologics demonstrate the importance of tumour necrosis factor-α (TNF-α) and other cytokines in psoriasis," he pointed out, adding that inflammation is the underlying process.

Hyperinsulinaemia (an increase in insulin levels)[14] is linked with insulin resistance and the Boehncke et al. study[15] has demonstrated that insulin resistance was correlated with the severity of psoriasis. A more recent study teased out the inter-relationships between obesity, psoriasis, and psoriatic arthritis, demonstrating that obesity increases the risk of both psoriasis and psoriatic arthritis as well as increasing insulin resistance, diabetes, dyslipidaemia, and metabolic syndrome, which are in turn also increased by psoriasis.[16]

The systemic abnormalities associated with psoriasis start in childhood. A recent study[17] showed that obese children with psoriasis had higher total serum cholesterol, low-density lipoprotein cholesterol and triglycerides than children of similar BMI without psoriasis. They also had higher levels of alanine aminotransferase.

A systemic review and meta-analysis[18] demonstrated that the risk of having diabetes mellitus increased with the severity of psoriasis. Patients with mild psoriasis had a 53% higher risk of diabetes than people without psoriasis (odds ratio [OR]: 1.53) and those with moderate-to-severe psoriasis had a 97% higher risk of diabetes (OR: 1.97). "The more severe the psoriasis, the more inflammation and this increased the risk of diabetes," Prof Thaci suggested.

Potential Impact of Current Therapies on Comorbidity

Professor Diamant Thaci

It is important to consider the potential impact of psoriasis therapy on comorbidities, advised Prof Thaci. He noted that the Medical Board of the National Psoriasis Foundation (NPF) found the following after reviewing the literature:[19]

- Phototherapy: has no major cardiovascular impact and may reduce levels of pro-inflammatory cytokines
- Acitretin: can increase serum lipids and triglycerides but has not been shown to increase cardiovascular risk
- Cyclosporine A: can increase blood pressure, serum triglycerides, and total cholesterol
- Methotrexate: is generally associated with a decreased risk of cardiovascular disease morbidity and mortality
- Among the biologics, data for TNF-α inhibitors suggest an overall reduction in cardiovascular events; most data on short-term ustekinumab use suggest no effect on major adverse cardiovascular events, although some authorities remain concerned

"Currently there is not enough evidence to recommend therapies for psoriasis based solely on cardiovascular impact," said Prof Thaci. "Longer-term studies are needed on this."

Looking to the future, Prof Thaci predicted that moderate-to-severe psoriasis will be treated

systemically to ensure optimal impact, recognising the systemic nature of the underlying disease process. "Psoriasis is a systemic disease, which means systemic treatment is needed," he told the symposium, adding that treatment should be tailored much more to meet patients' needs. He suggested that optimised management of psoriasis clinics, providing an integrated approach to the evaluation and management of patients' comorbidities, is important to improve the value to patients and health systems.

Therapies: Optimising Value to Patients

Professor Kristian Reich

"There is no excuse for not treating psoriasis effectively with the growing range of options now available," suggested Prof Reich. He noted that options in systemic therapy for psoriasis are available or in development for a growing range of targets including: anti-TNF-α agents (etanercept, infliximab, adalimumab, plus golimumab and certolizumab, currently used for psoriatic arthritis); anti-interleukin (IL)-12/23p40 (ustekinumab); anti-IL-17A (secukinumab plus ixekizumab in Phase III trials); anti-IL-23p19 (tildrakizumab, guselkumab, and BI 655066 in Phase III development) and PDE4 inhibitors (apremilast).

In terms of selecting psoriasis therapies Reich proposed two options:

1. Strive for the Best Efficacy

Research shows that patients' expectations of therapy are met more completely by psoriasis therapies achieving higher PASI scores.[20] Real-world data from the German Registry showed little difference in patients' quality of life between treatments achieving PASI scores of 90 and 100, but there was a major difference between those scoring 75 compared to those scoring 90, Prof Reich reported. "So you could say, 'the higher the PASI score the better'," he suggested. "We have enormously effective drugs achieving high PASI scores. But how are these drugs being used by dermatologists to make patients' lives better?" he asked.

A real world survey of patient perspectives in the management of psoriasis, the Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) Survey, called nearly 140,000 households in Western countries selected at random and identified 3,426 patients to ask about their treatment. Over one-third (37%) of the 168 patients with psoriasis affecting >10 palm-sized areas of their body were currently on no treatment for their condition. Just over half (52%) were on topical treatment only, while 5% were on oral plus topical therapy, and 5% were on a biologic plus topical therapy.[8] "There is a massive problem with undertreatment. Although we have effective therapies many patients with psoriasis are not receiving them," said Prof Reich. "Striving for the best is not what is happening as far as many patients are concerned." Itching was the most important factor contributing to the severity of their psoriasis, given by 38% of patients taking part in the survey. This was followed by the location and size of skin lesions (17%), scales (11%), and flaking (10%).[8] "We have tended to overlook the importance of itching to patients in the past," said Prof Reich.

Considering potential reasons for the undertreatment of psoriasis, Prof Reich suggested that factors include: the perception of psoriasis by both physicians and patients; lack of experience in managing psoriasis among some physicians; fear of side effects with treatment by physicians and patients; reimbursement issues, particularly for more expensive therapies; and convenience of use, with some treatments requiring blood tests.

2. Broad use of Appropriate Systemic Therapies

Broad use of systemic therapies for psoriasis requires drugs that achieve a good balance between efficacy and safety. Large molecule biologic therapies, such as those acting on IL-6 or TNF-α, disrupt extracellular communication between a variety of cells including macrophages and keratinocytes.[21] "However, more recently developed drugs such as apremilast act at the level of intracellular signal transduction," Prof Reich noted, adding that this may potentially improve the balance between therapeutic benefits and side effects.

Summing up, he suggested: "Different patients require different treatment options depending on their individual risk factors, disease profile, and personal preferences." In his personal view he recommended that phototherapy be used as induction therapy, followed by conventional systemic therapies such as methotrexate where appropriate. He proposed that the phosphodiesterase-4 inhibitor apremilast is considered as a second-line therapy in patients

with moderate stable disease with limited disease burden, with or without psoriatic arthritis, and in those with particular safety concerns. The use of biologics, including adalimumab, ustekinumab, and secukinumab should be used based on individual patient profile.

"Treatment goals must include measures that matter most to patients," Prof Reich proposed. These should take account of the impact on their lives of involvement of visible areas and nails, pruritus, and recalcitrant plaques, in addition to objective measures such as their PASI score. "To understand patient benefit, we have to ask the patient," he concluded.

Managing Comorbidity: Providing Integrated Care

Professor Ulrich Mrowietz

Psoriasis is associated with a range of other non-dermatological conditions, generally referred to as psoriasis comorbidity (Figure 2), explained Prof Mrowietz. "This is not just a disease of the skin. It is a complex condition," he told the meeting. "The major implication of psoriasis being associated with other conditions is the now widely accepted concept of psoriasis as a systemic inflammatory disease."[22]

Obesity is the most important comorbidity in psoriasis.[23] Obesity is also a risk factor for the disease. Studies have shown that having a BMI >30 kg/m^2 doubles the risk of developing psoriasis and is an independent risk factor for the disease across different ethnic groups.[24] Prof Mrowietz noted that obesity also reduces the response to psoriasis treatment, with a large Italian study showing that obese patients did not respond as well to systemic treatment as lean patients did.[25] In addition, obesity is associated with psoriatic arthritis; patients with a BMI <25kg/m^2 in young adulthood have a 75% chance of not having psoriatic arthritis compared with only a 35% chance of being free from psoriatic arthritis in those with a BMI >30.[26]

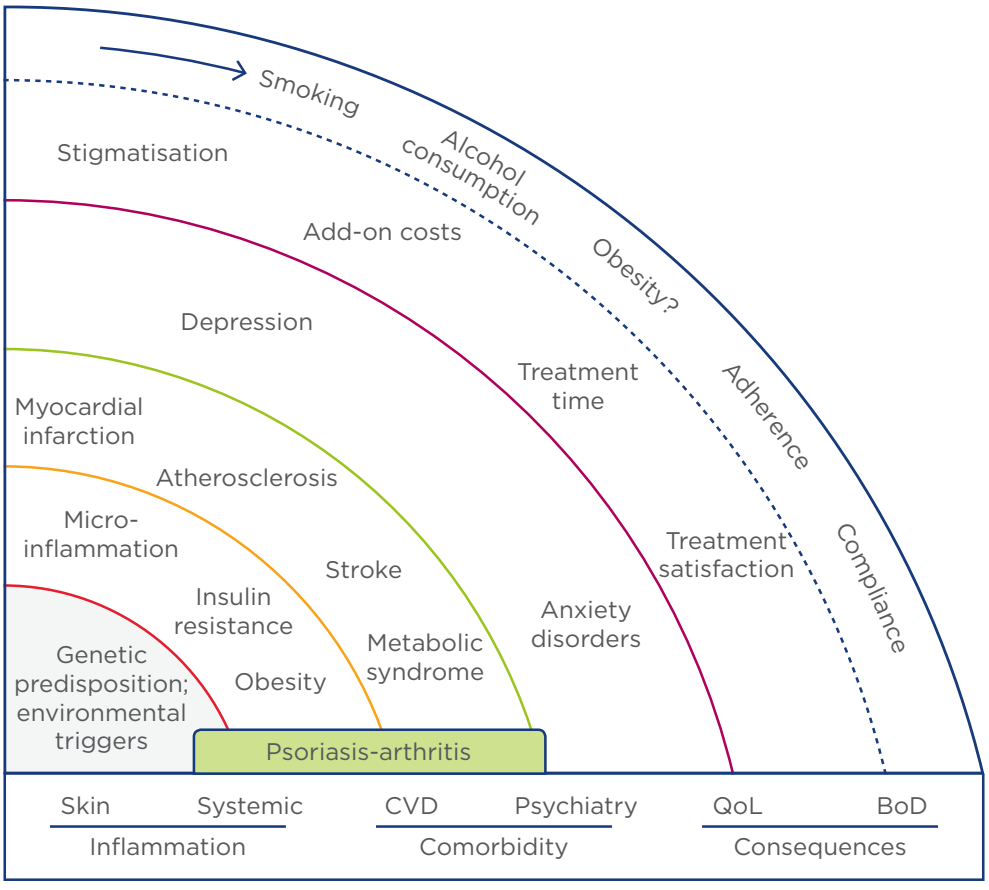

Figure 2: The spheres of psoriasis disease.
CVD: cardiovascular disease; QoL: quality of life; BoD: burden of disease.
Adapted from Mrowietz et al. 2014.[23]

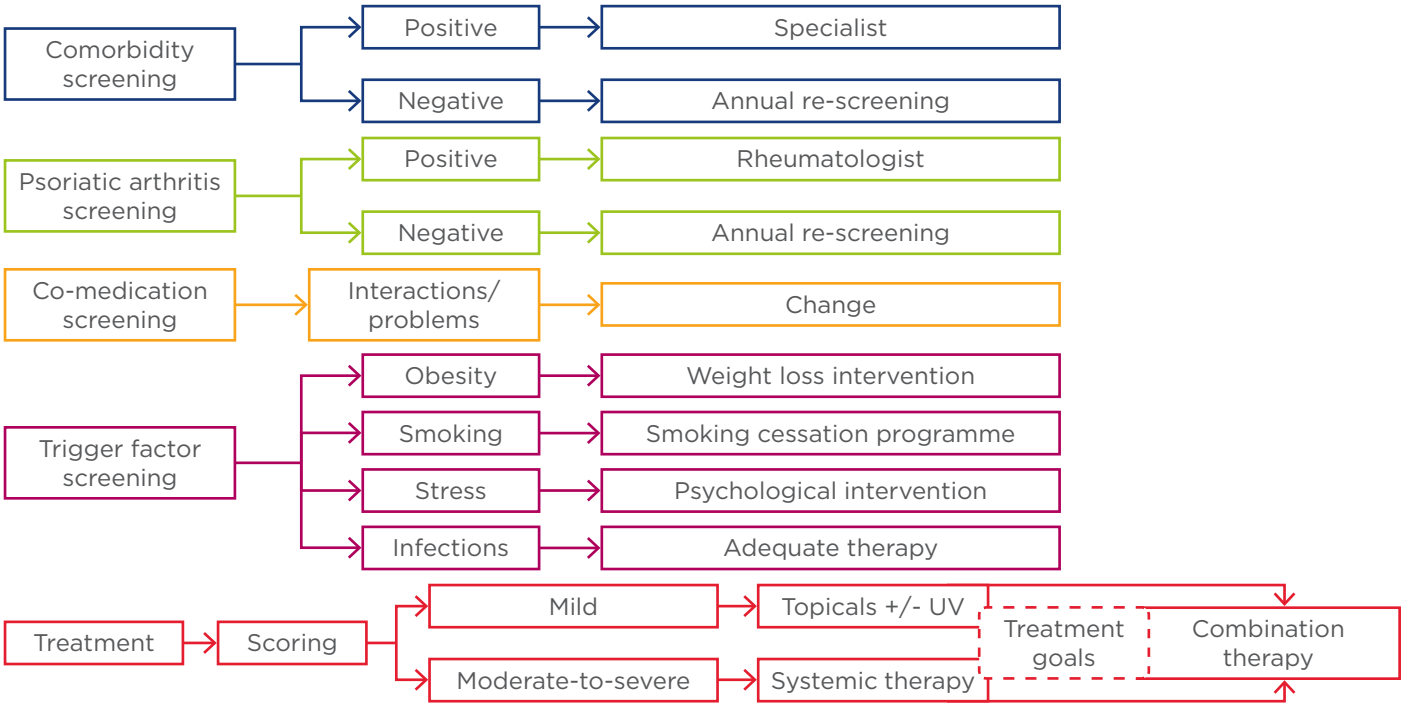

Figure 3: Integrated concept of psoriasis management.
UV: ultraviolet.
Adapted from Mrowietz et al. 2014.[23]

Why is obesity so important in psoriasis? Prof Mrowietz explained that fat cells increase in number and size with weight gain, which leads to increased production of the chemokine MCP-1. This recruits inflammatory macrophages which produce TNF-α and IL-6. The change in metabolic profile with obesity produces hormones such as leptin, resulting in insulin resistance. "The result is constant micro-inflammation throughout the whole body," Prof Mrowietz told delegates. He reported intriguing research suggesting that increased levels of inflammatory cytokines such as TNF-α and IL-6 in the central nervous system can cause depression,[27] noting that increased rates of anxiety and depression occur in both children and adults with psoriasis.

Metabolic syndrome is another important condition commonly associated with psoriasis and with the subsequent or parallel development of atherosclerosis implicated in cardiovascular complications including myocardial infarction (MI) and stroke.[28] Patients with psoriasis have an increased risk of MI compared to people without psoriasis, and those who have had a MI have an increased risk of a second event.

Effective management of psoriasis includes screening patients for comorbidities and providing treatment or referral to relevant specialists working in an integrated way across a networked service. Prof Mrowietz suggested: "It is essential to identify associated conditions such as obesity, and lifestyle factors including smoking and alcohol consumption, which can exacerbate psoriasis. Patients should be encouraged to join weight loss and smoking cessation programmes." A retrospective analysis of psoriasis patients undergoing bariatric surgery for obesity showed that 70% achieved remission within 6 months.[29] "Weight loss is a very meaningful intervention," he said.

Systemic anti-inflammatory drugs have been shown to reduce the risk of cardiovascular events in patients with psoriasis. One study has shown that the risk of MI was reduced with TNF-α inhibitors compared to treatment with topical agents.[30] Five-year follow-up of a Danish nationwide cohort showed that methotrexate was associated with significantly lower rates of cardiovascular events (hazard ratio [HR]: 0.53) and there was a comparable protective effect with biological drugs (HR: 0.58) compared to other anti-psoriatic therapies including cyclosporine (HR: 1.06) and retinoids (HR: 1.80).[31]

Prof Mroweitz noted that effective treatment of cardiovascular risk factors including diabetes, dyslipidaemia, and hypertension are also important. "This underlines the need for a multidisciplinary approach to managing patients with psoriasis," he pointed out. He recommended that all patients with moderate-to-severe psoriasis be screened regularly for risk factors including blood pressure, lipids, BMI, glucose metabolism, and depression.[32] "Risk screening must be holistic, using a comprehensive screening tool," he said.

Summing up, Prof Mrowietz said that comorbidity is an important facet of psoriasis, with a wide range of commonly occurring comorbidities, including cardiovascular disease, depression, and anxiety. "Screening for comorbidities and effective management is essential for improving the care of patients with psoriasis," he concluded. An integrated approach (Figure 3), involving co-operation between different disciplines and centres of excellence working effectively with networks of psoriasis centres, is essential to improving the management of psoriasis.

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SCHNITZLER SYNDROME: A REVIEW

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Schnitzler syndrome (SS) and other auto-inflammatory syndromes in which interleukin-1b plays an important role were trending topics at the 25th EADV Congress which took place in Vienna, Austria.

SS is a rare disorder regarded as the paradigm of an acquired auto-inflammatory syndrome later in life. It was first described in 1972 by the French dermatologist Liliane Schnitzler and since then ≤200 patients have been reported. The diagnostic criteria were updated in 2013 by Lipsker and collaborators. The diagnosis of SS is defined as a combination of two major criteria, including a chronic urticarial rash and an immunoglobulin M or immunoglobulin G gammopathy, as well as some additional minor criteria. Minor criteria include: recurrent fever, leucocytosis and/or elevated C-reactive protein, objective signs of abnormal bone remodelling, and a neutrophilic infiltrate on skin biopsy. The gammopathy is commonly monoclonal and of uncertain significance, defined as <10 g/L. However, the most harmful complication is the evolution into an authentic lymphoplasmacytic malignancy which, according to data described in the literature, occurs in at least 15% of patients.

Conventional therapies including antihistamines, anti-inflammatory drugs, steroids, immunosuppressive drugs, and immunomodulating agents are usually ineffective, providing only a partial improvement of symptoms. In recent years, anakinra (an interleukin-1-receptor antagonist) has proved effective in treatment of SS as well as in cryopyrin-associated auto-inflammatory syndromes. The origin of this disorder remains obscure, although some theories of activating mutations in the gene *NLRP3* have been proposed.

LENTIGO MALIGNA TREATMENT: THE SURGICAL APPROACH

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Although not without certain controversy, lentigo maligna is currently considered a type of melanoma *in situ* with an undetermined lifetime risk of progressing into invasive melanoma. It appears mostly in the elderly on chronically sun exposed areas, particularly on skin with severe cumulative sun damage. The progression to invasive melanoma may occur within a few months to many decades after the appearance but unfortunately the timing is unpredictable. Accordingly, this is a type of lesion that should be treated.

The treatment of lentigo maligna represents a challenge. This is because it often presents on the face as a large lesion with an ill-defined border, with tumour cells extending sometimes >1 cm beyond the clinically obvious disease and subtle pathologic findings. Furthermore, ≤20% of the cases with an initial biopsy of melanoma *in situ* show invasive disease after complete excision.

In order to deal with the aforementioned issues, surgery is the treatment of choice for lentigo maligna, particularly with surgical modalities that allow the pathologic examination of 100% of the lateral margins. These modalities include Mohs surgery with either frozen or paraffin sections and staged excision, and their variants ('spaghetti technique', Johnson square procedure, or contoured technique). With these modalities the cure rate is high with recurrence rates <5% at 5 years (conventional surgery shows a recurrence rate of 7–20%). Interestingly, with these modalities it has been demonstrated that the usual margin of 0.5 cm

of surrounding healthy skin is not appropriate for lentigo maligna. Instead, a margin of ≥1 cm should be used in most of the cases and this should be even larger in recurrent tumours with an ill-defined border, or previously treated with non-surgical modalities (i.e. cryotherapy, electrocoagulation, laser, depigmenting creams). On the other hand, the complete excision of the tumour allows evaluation of the whole lesion and therefore detection of the invasive component when it is present.

The use of dermoscopy and *in vivo* reflectance confocal microscopy significantly reduces the number of stages and overall timing of the surgical procedure, obtaining free margins after one stage in ≤85% of the patients. Recently, a hyperspectral imaging system has been shown to be useful for the same purpose. Concerning histological assessment of the margins, besides the haematoxylin-eosin stain, the use of immunohistochemistry is strongly recommended and the most valuable histopathological marker is microphthalmia-associated transcription factor which, with a nuclear staining, is particularly helpful for quantifying the number of intraepidermal melanocytes.

When surgery is not feasible due to short life-expectancy, comorbidities, or very complicated surgery; observation, radiotherapy, or medical treatments can be considered. In such cases however, biopsy mapping or non-invasive image techniques (i.e. confocal microscopy) are highly recommended in order to rule out an invasive tumour.

KERATINOCYTE SKIN CANCER: A BIOLOGICAL AND MORPHOLOGICAL CONTINUUM

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Keratinocyte skin cancer (basal cell carcinoma, actinic keratosis [AK], and squamous cell carcinoma [SCC]) is the most common cancer in Caucasians. Among these, squamous cell neoplasia carries the highest mortality rates, with locoregional and distant metastasis mortality rates of 4–8%. Cutaneous SCC derives from AK in the context of severely sun-damaged skin. In areas of chronic sun damage (face, scalp, dorsum of the hands) in fair skinned individuals, multiple actinic keratoses may develop and become visible, ranging from a few to numerous red, scaly lesions, that in histopathology show a variable degree of keratinocyte atypia. Moreover, the presence of dyskeratotic keratinocytes has been documented in skin of a normal appearance, giving rise to the concept of 'field cancerisation', a body area with a variable degree of keratinocyte dysplasia and a higher risk of development of invasive squamous neoplasia.

In this context, AK and SCC are considered a biological and morphological continuum. The risk of developing invasive SCC rises with immunosuppression; the most common example is the high degree of SCC in transplanted patients. The total number of AKs is also a risk factor for the development of SCC; the higher the number of AKs the higher the risk of SCC. However, not all AKs progress into SCC. AKs may go through one of the following pathways: stability, regression, or progression. Much work has focussed in recent years on finding morphological markers of the progression risk of AKs.

A histopathological grading system of AKs has been developed, parallel to the grading of squamous neoplasia of the cervix (CIN I, II, and III). AK I presents keratinocyte atypia located at the basal epidermal layer only, while AK III shows full thickness keratinocyte atypia, being essentially *in situ* SCC. A clinical grading of AKs has also been proposed. The clinical grading is based on the degree of hyperkeratosis, with Grade 1 being more felt than seen and Grade 3 presenting a thick hyperkeratotic surface. A dermoscopic classification

system, parallel to the clinical classification system, was recently described.

However, the clinico-dermatological classification was demonstrated to rarely correspond to the histopathological classification. Thus, when we speak about clinical Grade 3 this does not mean that this lesion is histopathologically AK III. Moreover, a very recent study suggested that the linear progression model underlying the histopathological classification system is probably not valid in all cases. In another recent study the authors histopathologically examined a series of SCC and evaluated the type of AK present at the border of the lesions. In the majority of cases, adjacent to invasive SCC the authors found AK I. The authors concluded that the progression from AK I to III and then to invasive SCC, might not be inevitable in a high number of cases. Further studies are needed to validate these findings and to explore the mechanisms of progression of AKs into invasive SCC.

EPIDEMIOLOGICAL TRENDS AND RISK FACTORS OF NON-MELANOMA SKIN CANCERS

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Skin cancer is the most common type of cancer in Caucasians, with an increasing incidence worldwide. Under the broad term of 'non-melanoma skin cancer' (NMSC) we include all the malignant neoplasms that may potentially involve the skin. However, from an epidemiological point of view, when we talk about NMSC we are in practice referring to basal and squamous cell carcinoma (BCC and SCC, respectively), as they account for 99% of cases.

Even though the incidence of NMSCs is about 20-times higher than that of melanoma, there are significant limitations in their epidemiology. The chief reason for this is that national cancer registries do not consider NMSCs in their records, firstly because of the burden imposed in ascertaining the large number of cases and secondly because of the relatively low mortality rate. However despite their low mortality rate, keratinocyte carcinomas are characterised by significant morbidity and a remarkable economic burden. A rough estimation of global incidence rates show that Australia has the highest (>1,000 [2,448 in 2011], per 100,000 person-years), followed by North America (450 per 100,000 person-years in 2010), and Europe (129.3 in men and 90.8 in women per 100,000 person-years).

Possible reasons for the recorded increase in the incidence rate of NMSCs include recreational and occupational ultraviolet (UV) over-exposure, especially in Western countries. Furthermore, given the predilection of keratinocyte carcinomas in the elderly, increased longevity results in higher rates.

With respect to the economic burden as estimated in Australia and the USA, NMSCs represent one of the most costly types of cancer. As shown for BCC, hospital settings are more expensive compared to physician-based treatment settings, with imiquimod and 5-flurorouracil being the cheapest therapeutic options. Based on this, we assume that development of therapeutic strategies easily applied in physician-based settings may reduce the overall economic cost.

Personal risk factors for NMSCs include older age, male sex, light skin phototype, and previous history of a NMSC. In addition, specific genodermatoses, immunosuppression, arsenic exposure, and history of irradiation, burns, or chronic dermatoses also increase the risk of NMSCs.

Solar exposure is the main environmental risk factor. Cumulative sun exposure linearly increases the risk for SCC, while excessive/intermittent

sun exposure and sunburn in childhood and adolescence is responsible for the development of BCC. Cumulative evidence confirming that outdoor workers are at higher risk for keratinocyte carcinomas led to the recognition of SCC and multiple actinic keratoses as a new occupational disease in many European countries.

Worrisome epidemiologic data suggest a substantial increase of BCC among younger women. This is in line with indoor tanning habits, which despite the numerous campaigns concerning its carcinogenic effect, remain very popular among female adolescents. Given that this is a modifiable risk factor, we should consider stricter regulations and more efficient public-education campaigns.

In the context of high prevalence and increasing incidence of NMSC, prevention policies should be one of our priorities. Primary prevention includes interventions for modification of sun exposure behaviour, namely reduction of sun exposure, use of adequate UV-light protection, and deterrence of indoor tanning. Secondary prevention aims to detect NMSCs early and provide adequate treatment. Interventions that serve as secondary prevention include: screening of high-risk populations, skin self-examination with the assistance of a partner, and physicians' surveillance. A total body skin examination and the use of dermatoscopy is highly recommended as both result in the early detection of NMSCs.

E-NAIL: MEDICAL

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Most nail diseases can be diagnosed by clinical examination. A correct evaluation of the patient is therefore mandatory, together with their clinical history. The examination must look at the feet and hands, where shape and skin should be evaluated, and sometimes the skin at other sites. All nails should be looked at, even if the patient presents with a disease involving one digit. Nail evaluation must include the nail plate and the periungual tissues, including the distal pulp, and should involve moving the digit in order to look at it frontally, laterally, and from below. Touching the digit will allow perception of its temperature and show the presence of pain. Nail clippers and a dermatoscope should be to hand to allow correct study of the different features. The fingernails should be looked at with the hand resting on a flat surface and the digits spread. The toenails should be looked at with the patient seated and the feet parallel and resting flat, in order to appreciate the morphology of the feet and the way in which they stay in the shoes. Examination of the skin can be necessary to confirm the diagnosis of specific disorders, especially a dermatological nail disease.

Examining the patient's clinical history is mandatory for the diagnosis of some diseases, where details on course or modality of onset are strongly suggestive. Clinical assessment can involve a combination of invasive and non-invasive examination techniques that are easy to perform and facilitate diagnosis. The tools needed for a correct nail examination are easily available in any dermatological office: nail clippers, dermatoscope, curettes, petri dishes or a paper envelope for mycological samples, and tools for nail biopsy. Other diagnostic examinations, such as X-ray and ultrasonography, are not expensive and can be performed in any hospital. In contrast, it is not easy to obtain a magnetic resonance imaging (MRI) of a distal digit, as several radiological centres do not have an MRI machine with small dedicated surface coils. When dealing with chronic nail disorders, which need periodic evaluation, it is advisable to take photographs of the disease at any follow-up visit, in order to better monitor its evolution and response to therapy. In some nail diseases dermoscopic examination provides the diagnosis, even though in the majority of cases it only permits a better visualisation of features already visible with the naked eye. As with any other examination, nail dermoscopy requires a good knowledge of nail

anatomy and physiology and the pathogenesis of nail diseases; we have to know which part of the nail we have to look at! Mycology is mandatory to confirm the clinical diagnosis of onychomycosis, as the choice of treatment can be influenced by the type of fungus. It is also necessary to rule out distal subungual onychomycosis in nails with dystrophies from other causes, i.e. trauma or psoriasis. A nail biopsy is required in all cases of suspected nail tumour and in inflammatory conditions where the clinical features are not sufficient for diagnosis. It is very cheap, quick, and easy to obtain in any hospital.

EFFICACY OF INTRAVENOUS GLUTATHIONE VERSUS PLACEBO FOR SKIN TONE LIGHTENING

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INTRODUCTION

Fair complexion is considered a sign of beauty in South Asia. Glutathione is being increasingly used as a new therapy for skin lightening. Glutathione is an antioxidant that is naturally synthesised in the body and is found in many foods. Oral absorption is not reliable because of degradation by enzymes in the digestive tract. Topical application of glutathione is not absorbed by the skin cells; however, intravenous glutathione delivers directly into the systemic circulation.

OBJECTIVE

To evaluate the efficacy and possible side effects of intravenous glutathione used for skin tone lightening.

MATERIALS AND METHODS

The prospective, controlled, randomised study was conducted by the Department of Dermatology, City Hospital Multan, Multan, Pakistan, from January 2014–August 2015. The study was conducted on 50 patients, but only 32 patients completed the study. All patients were females aged 25–47 years old. The 32 patients were treated in two groups (A and B). In Group A, 16 patients were given intravenous glutathione and vitamin C.

Table 1: Side effects.

Side effects	Patients (n)
Sensation of warmth during injection	11
Abdominal cramps	10
Deranged liver function tests	8
Feeling of heart sinking	7
Diarrhoea	4
Paraesthesia	4
Dizziness	3
Anaphylactic shock	1
Vomiting	1

Patients in Group B were given intravenous normal saline as placebo. In Group A, eight patients, who had deranged liver function tests, and one patient, who developed anaphylactic shock, were excluded from the study along with their controls from Group B. All side effects reported during the study are listed in Table 1. Final results were concluded in only those patients who completed the study. The Taylor Hyperpigmentation Scale was used to measure skin tone. Change of even a single shade was considered significant. Two body sites, which were non-exposed to sunlight, were measured with Taylor Hyperpigmentation cards. The skin tone of the upper inner arm below the axilla and upper-outer thigh of all patients was noted. Injections of GSH Detox Forte 1,200 mg (aqua, glutathione 1,200 mg, ascorbic acid, hydrolysed collagen 35 mg, and sodium chloride) were given twice a week for a period of 6 weeks, totalling 12 injections. Liver function tests and complete blood counts were checked every 2 weeks. The effectiveness and side effects were assessed at the end of therapy and at 2, 4, and 6 months after cessation of treatment.

RESULTS

For efficacy of treatment, a test for two proportions showed a p-value=0.031, reaching significance. This means that the proportions for these two groups are not the same and the proportion (of effect) for Group A is greater than that of Group B. The time period to assess the effectiveness of the drug was 6 months after stopping treatment. Two-way ANOVA for response versus time and treatment proved that time (with p-value=0.054) is significant i.e. with the passage of time, treatments lost their effect.

CONCLUSION

Glutathione is ineffective for skin tone lightening and incurs a number of side effects. Furthermore, treatment loses its efficacy with time.

MOBILE TELEDERMATOLOGY USING WHATSAPP SMARTPHONE APPLICATION: A PROSPECTIVE STUDY OF DIAGNOSTIC ACCURACY

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Teledermatology (TD) is the use of telecommunications technology to convey patients' clinical information and images to a remotely situated consultant. Current technology also allows a rapid link between doctors and patients which might eventually affect our concept of traditional dermatological practice. The development of smartphones with integrated digital cameras has given rise to a demand from our patients to consult with their doctors through the WhatsApp smartphone application (WhatsApp Inc., Mountain View, California, USA).

Therefore, we conducted a study that simulated a real-life clinical setting using patients' mobile phones to transmit clinical history and images through WhatsApp. Photographs of 74 patients who agreed to participate in this study were taken by patients themselves with their own mobile phone (Group 1). Additionally, the attending resident obtained standardised pictures by using her mobile phone under controlled conditions (Group 2). The digital images and a brief history were then forwarded to a dermatologist with 6 years of experience and she viewed all images on her mobile phone (iPhone 6®, Apple Inc., Cupertino, California, USA).

In both groups, the observer was able to make the correct diagnosis in 66 (86.6%) cases and between these groups, the diagnostic concordance was 97% ($p<0.001$, $\kappa=0.77$). In Group 1, in 69 (90.8%) cases

the observer referred the patient for a face-to-face consultation, whereas in Group 2, 63 (82.9%) cases were referred (p=0.003, κ=0.318). The two most common reasons for referral for a face-to-face consultation were the need for additional information and the need to run tests.

Our results showed that TD with WhatsApp reached a high level of diagnostic accuracy and concordance. New technologies can be accepted as reliable enough for preliminary diagnosis and could be used in the management of patients with dermatological conditions. At the European Academy of Dermatology and Venereology (EADV) Congress 2016 the advantages and disadvantages of using WhatsApp in TD were discussed.

Table 1: Summary of the advantages and disadvantages of using WhatsApp in teledermatology practice.

Advantages	Disadvantages
Expands access to dermatologists enabling direct interaction between consultants and patients	Requires a smartphone with an internet connection
May improve patient satisfaction	Requires high quality images and camera resolution varies between smartphone models
Interferes less with routine daily workflow	Maintenance of patients' privacy and data security would need to be solved
Compared to video images, it has higher resolution quality	May be less convenient for physicians practicing in different time zones
Easy to repeat consultation if any information is missing or any additional data are needed	
Can be used for consultation, direct care, and follow-up	

SHARING DERMATOLOGY EXPERTISE: CURRENT PRACTICE

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SUMMARY

Historically, sharing knowledge between medical peers has always played an essential role in improving healthcare. Established channels through which medical expertise is exchanged include publication in medical books or journals and presentations at (inter)national medical society meetings. However, there is a significant time delay between writing a scientific medical report and subsequent presentation at a conference or publication in a medical journal. As a result, medical specialists have found faster channels to share their knowledge through electronic communication tools such as email and phone-based messaging services. For this reason, alternative electronic-based messaging applications are being developed such as, 'Figure 1' (Figure 1 Inc., 2014, Ontario, Canada), 'Siilo' (Siilo, Amsterdam, Netherlands), and 'Doximity' (Doximity, Inc., San Francisco, California, USA), claiming more secure communication between healthcare providers.

According to the 2015 edition of the Dutch yearly national report on eHealth, supported by the Royal Dutch Medical Association (KNMG), there is a clear need for improved secure health information exchange services among medical specialists. Sharing medical expertise in order to get the most up-to-date answers to complex clinical dermatological questions in an efficient and secure

way would be of definitive value to both clinicians and patients. Statistics show that ~75% of medical specialists are already exchanging patient-related clinical information electronically, while being worried about the safety of sharing data through non-secured email and messaging services. Simultaneously, it remains difficult to find the right world-renowned medical expert to provide the most up-to-date answers to queries.

Sharing medical expertise should be safe, efficient, and convenient for busy medical specialists juggling priorities during a working day in the hospital. For this reason, a new, secured, and innovative peer-peer online application is currently being developed by the authors. The application will be free of charge and aimed at searching, finding, and directly contacting the right world-renowned dermatology experts in order to get answers to challenging clinical cases. A pilot version of this new concept will be launched in the Netherlands in 2017.

It would be beneficial for both clinicians and their patients if worldwide healthcare could further improve by sharing medical expertise for patients suffering from challenging skin diseases.

A NEW COMBINATION TREATMENT FOR SCALP ALOPECIA AREATA

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BACKGROUND

The incidence of alopecia areata (AA) has been increasing over the last few years. This condition affects 0.1–0.2% of people, occurring in both men and women. AA occurs in people who are apparently healthy and have no existing skin disorders. It usually appears smooth with bald skin spots (spot baldness) and may lead to broken hair known as 'short stubs'. Different regimens are already in practice including local irritants such as capsicum lotion, topical steroids, oral immunosuppressants, and oral and injectable steroids. Hair regrowth results are variable, with the hair being either uniform or bush-like, and recurrence is very common. This paper aims to present a study of a relatively new combination procedure to treat AA. In our study we combined high negative pressure microdermabrasion (MD) with intralesional steroids (ILST), and compared this with ILST alone.

METHODS

MD can result in:

- Very effective and controlled irritation of the scalp (contact immunotherapy)
- Cleansing of plugged follicular canals
- Assistance in the uniform distribution of injected ILST
- Improvement in blood flow (indirectly helping immunotherapy)

During each treatment session MD was carried out followed by ILST. MD was performed with aluminium oxide crystals using a specially designed handpiece (made in Pakistan) that had a wide hole at its tip suctioning almost a 1 cm square chunk of skin and shot a crystal jet in a fan-like movement, abrading a fine layer of skin. This was followed by application of 0.02 cc of undiluted ILST to an approximately 2-inch square area of AA on the scalp.

Our study criteria included patients from 5–50 years old of both sexes with only non-scarring alopecia, and excluded patients with unhealthy skin on the scalp (due to eczema, fungus, or other infections), scarring alopecia, diabetics, and if pregnant. We carried out a study of 80 patients; 60 patients had a combination of MD plus ILST, and 20 patients had ILST alone. The study period started in 2011 and continued to-date. Each patient had six sessions every 15–20 days. Pre and post-treatment photographs were taken.

RESULTS

With our combination treatment (MD+ILST) all patients had remarkable improvement in symptoms, and hair growth was usually obvious after the third or fourth session. There was usually enough growth in 4–6 sessions. The regrowth of hair was fast, full, and very uniform. With ILST alone, the growth was slower, less uniform, bush-like, unevenly distributed, with areas of no-grow.

We proposed the following criteria for evaluating the results:

- Complete response (80–100%): all patches full, uniform, fast growth, and no recurrence before 6 months
- Partial response (50–80%): most patches had enough growth, but the growth was not full, was less uniform, and there was recurrence in <6 months
- No response (<50%): hair growth was not optimum and new lesions continued

Our results of MD+ILST of the scalp for the 80 patients were:

- Complete response in 60 patients (75%)
- Partial response in 16 patients (20%)
- No response in 4 patients (5%)

CONCLUSION

Our results indicate that MD+ILST is a safe and very effective treatment for AA. MD produced controlled irritation of bald skin, suctioned follicular plugs, improved blood flow, and enabled uniform distribution of ILST. The ILST also provided immunosuppression. The recurrence rate was approximately 30% and of these patients, 40% had recurrence after 4–6 months of stopping treatment and another 40% after 6–12 months. An estimated 10% have had some recurrence every 1–2 years during the last 4 years, and another 10% recovered partially but did not recover on all patches.

FIBROMYALGIA AND DYNIAS: IS THERE AN ASSOCIATION?

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Chronic pain syndromes are a real concern in many medical fields. Rheumatologists, gastroenterologists, gynaecologists, and urologists all treat patients with fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome (IBS), and interstitial cystitis; we as dermatologists attend dynias patients. Some studies are investigating possible relationships among them. Vulvodynia has been found among fibromyalgia, interstitial cystitis, and IBS patients but other dynias have not yet been explored.

Our main objective was to study the presence of dynias and other chronic pain syndromes among fibromyalgia patients. We performed an observational prospective study on a sample of 30 female patients with fibromyalgia who were diagnosed and followed up with at the rheumatology department at our hospital. We found that 33% of our patients suffered from orodynia: 27% in the tongue, and 26% in the lips. Of the patients, 56% had scalp pain associated with fibromyalgia. To our knowledge, no previous studies have pointed out this association.

Among our patients, we discovered that the younger the patient at the moment of diagnosis, the higher the presence of orodynia. Of the patients, 24% had vulvodynia. The conclusion drawn from these results indicate that it is worth investigating dynias among fibromyalgia patients.

In addition, our patients with fibromyalgia and IBS showed higher anxiety scores in the Hospital Anxiety

and Depression Scale questionnaire. The patients with anxiety showed higher levels of alexithymia: difficulties expressing feelings, isolation tendencies, and superficiality in interpersonal relationships. Alexithymia was found in 57% of our patients, and proved to be related with working activity. There were lower levels of alexithymia among those not currently working and higher levels among patients who were working or who had previously worked but had now retired.

RADIOFREQUENCY FOR SKIN TIGHTENING AND FAT REDUCTION OF THE LEGS

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Radiofrequency (RF) is one of the most frequently used energies in medicine, particularly in aesthetic medicine. However, its selective application is a novel approach. In cases when the treated area appears to be more resistant to dieting and sport, this is the desired method as it can be very effective. The energy is selectively delivered to the adipose tissue through a contactless applicator and then transformed into heat. This selectiveness relies on the impedance difference between fat and other tissues, led by the absence and presence of water, respectively. The aim of this process is to provoke the apoptosis of fat cells.

The opportunity to research this novel approach for selective application of RF, especially in areas that are resistant to sport and dieting, were among my main incentives for undertaking this study. As a specialist in aesthetics medicine, I hoped to design and conduct a study evaluating the effectiveness of selective RF therapy for thigh circumference reduction as well as improving the overall appearance of the thigh area.

The assessment included baseline and 2-week post-treatment measurements of thigh circumference and digital photographing of the treated area. All data were obtained in an equal manner in order for any possible bias to be minimised. As RF is known for its long-lasting effect, a 2-week post-treatment assessment was planned.

All patients from the active group (n=40) received the therapy once a week over a 4-week period, with each one having equal initial power settings that could be adjusted to the patients' subjective heat perception afterwards. Another 10 patients served as a control group without treatment.

The results obtained during the study demonstrated a scientifically significant difference between the baseline and 2-week post-treatment circumference measurements in the active group whilst the results were not statistically significant in the control group. Similar results confirmed the theory of the apoptosis process led by RF application and its effect on circumference reduction. Except for the mathematical evaluation of the circumference values, the photograph assessment showed overall clinical appearance improvement and a smooth, natural transition from the treated to the non-treated areas of the thighs was observed.

These results suggest that selective application of RF energy is a beneficial method for circumference reduction and appearance, especially in areas resistant to dieting and sport, with possibilities for further investigation into the longevity of these outcomes.

HELICOBACTER PYLORI INFECTION IN PATIENTS WITH CHRONIC URTICARIA AND DYSPEPSIA: EXPERIENCE FROM A DEVELOPING COUNTRY

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Objective: To determine *Helicobacter pylori* infection using stool antigen assays and *H. pylori* immunoglobulin M (IgM) antibodies in patients with chronic urticaria and dyspepsia.

Study design: This was a descriptive, cross-sectional study.

Materials and methods: The sampling of cases was done using a non-probability purposive sampling technique at the Department of Dermatology and Pathology, Fauji Foundation Hospital, Rawalpindi, Pakistan, from May 2014–April 2015. A total of 87 patients diagnosed with chronic urticaria with symptoms of gastritis were tested for *H. pylori* infection using the monoclonal *H. pylori* faecal antigen assay (Biotec, Spain) and serological test (IgM antibodies). Patients infected with *H. pylori* were given a triple regimen comprising omeprazole 20 mg, amoxicillin 1,000 mg, and clarithromycin 500 mg twice daily for 10 days. *H. pylori* eradication was assessed by monoclonal faecal antigen assay after 4 weeks. Beneficial effect was determined by subjective response to treatment and improvement in urticarial symptoms using the Chronic Urticaria Quality of Life Questionnaire, while objective response to treatment was judged by need for antihistamine medication post-eradication.

Results: Stool antigen was positive for *H. pylori* in 59.77% (n=52) and IgM antibodies were present in 72.41% (n=63) of patients with chronic urticaria and dyspepsia. After antibacterial therapy, there were 40 stool samples which were negative (n=52), and among them the remission of urticaria and dyspepsia was observed in 39 patients (75%). There were 50 of 63 (79.37%) *H. pylori* IgM-positive patients who responded to triple regimen therapy when eradication was considered by objective improvement in urticaria and gastritis symptoms (Table 1). However, when stool antigen and serum IgM were considered simultaneously there was 80% (52 of 65 patients) remission response post-treatment. There was significant association (i.e. a Chi square p-value of <0.05) between the presence of *H. pylori* and the response to eradication regimen (28.68, p=0.0001).

Table 1: Diagnosis and response to treatment of patients with *Helicobacter pylori* infection associated with gastritis and urticaria (N=87).

Helicobacter pylori detection procedure	Number of patients who showed positive results	Number of patients who responded* to treatment**
Stool antigen assay	52 (59.77%)	39 (75.00%)
IgM antibodies	63 (72.41%)	50 (79.37%)
Stool antigen and IgM antibodies	65 (74.71%)	52 (80.00%)

*Eradication response was considered as cure of the urticaria and gastritis symptoms.
**First-line triple regimen comprising omeprazole 20 mg, amoxicillin 1,000 mg, and clarithromycin 500 mg twice daily for 10 days; or second-line regimen comprising omeprazole 20 mg, amoxicillin 1,000 mg, and metronidazole 500 mg twice daily for another 7 days.
IgM: immunoglobulin M.

Table 2: Response to treatment.

	n	Subjective response to treatment (CU-Q2oL)			p-value	Confidence interval (95%)
		Pre-treatment (mean±SD)	Post-treatment (mean±SD)	Change (mean±SD)		
***Helicobacter pylori* eradication treatment given**	65	72.12±9.93	43.43±8.00	28.68±4.58	0.0001	28.65–28.72
Antihistamine treatment given	22	70.10±7.93	66.22±7.766	3.97±0.17	0.1	7.28–7.70

SD: standard deviation; CU-Q2oL: Chronic Urticaria Quality of Life Questionnaire.

The Chronic Urticaria Quality of Life Questionnaire for patients who received specific treatment also revealed improvement (p=0.0001), while patients without specific treatment revealed no change (p=0.1) (Table 2).

Conclusion: Chronic urticaria and dyspepsia are associated with *H. pylori* infections. The response of *H. pylori* eradication in infected patients of chronic urticaria is significant, and *H. pylori* detection should be included in the diagnostic work-up of all patients with chronic urticaria and dyspepsia. However, due to intermittent shedding of the micro-organism in faeces, if *H. pylori* stool antigen is declared negative before eradication treatment, patients with strong suspicion of *H. pylori* should receive a repeat test to be certain of the diagnosis.

The presence of this organism in such cases can be detected with confidence by using non-invasive, sensitive, specific, and cheaper techniques such as stool *H. pylori* antigen and serum *H. pylori* IgM antibodies. This is particularly true in developing counties where invasive techniques like gastric antral biopsy, rapid urease tests, and non-invasive urea breath tests are difficult to perform due to financial constraints.

EDITOR'S PICK

A chronic, multifactorial, inflammatory skin condition with extensive underlying mechanisms, the current therapeutic options for acne vulgaris (AV) are governed by strict regimes and acute side effects. Özlü and Karadağ focus on the role of the innate immune response in AV aetiopathogenesis, namely that of toll-like receptor activation and subsequent antimicrobial peptide release. The authors allude to the possibility of applying their findings for novel drug development, a promising advance in the field of dermatology for the improvement of quality of life in affected patients.

THE ROLE OF TOLL-LIKE RECEPTORS AND ANTIMICROBIAL PEPTIDES IN THE PATHOGENESIS OF ACNE VULGARIS

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ABSTRACT

Acne vulgaris (AV) is a chronic inflammatory disease of the pilosebaceous unit. AV has a multifactorial pathogenesis with specific roles played by the sebaceous glands, abnormal follicular hyperkeratinisation, inflammation, *Propionibacterium acnes*, hormonal factors, immune mediators, and genetic and environmental factors. Significant improvements have been made to elucidate acne pathogenesis, through developments in molecular biology, immunology, and genetic techniques. Toll-like receptors and antimicrobial peptides play significant roles in the host defense system against different pathogenic micro-organisms on the skin and these molecules induce several immunological responses. It is well known that toll-like receptors and antimicrobial peptides play important roles in AV pathogenesis and further understanding of these will contribute to improvements in treatment.

Keywords: Acne vulgaris (AV), antimicrobial peptides (AMPs), toll-like receptors (TLRs).

INTRODUCTION

Acne vulgaris (AV) is a multifactorial disorder of the pilosebaceous unit and can affect individuals of all ages, but is particularly common among adolescents. AV is not a life-threatening disease, but it can negatively affect the mood state during adolescence and hence may reduce quality of life. AV is a chronic inflammatory disease, with several factors playing roles in its development.[1] Increased sebum production, alteration of the quality of sebum lipids, regulation of cutaneous steroidogenesis, androgen activity, interaction with neuropeptides, exhibition of pro and anti-inflammatory properties, follicular hyperkeratinisation, and the proliferation of *Propionibacterium acnes* within the follicle may be listed among these factors.[2] Although acne is the most common skin disease, its pathophysiology is complex and incompletely understood.[3]

The increased sebum production is a major simultaneous event associated with the development of acne. Lipids produced by sebaceous glands have a variety of effects on signal transduction and are involved in biological pathways of acne. Moreover, fatty acids act as ligands of nuclear receptors. Sebaceous gland lipids have pro and anti-inflammatory properties. Furthermore, some hormones, such as androgens, control the sebaceous gland size and sebum secretion.[2]

Molecular components called pathogen-associated molecular patterns (PAMPs) that exist as part of micro-organisms are known to have a significant role in the protection of immunity. The cells of the immune system recognise the PAMP receptors through pattern recognition receptors (PRRs); toll-like receptors (TLRs) are a member of the PRR class and each TLR recognises a different PAMP region.[4] Activation of TLRs stimulates the production of antimicrobial effector molecules while inducing the signalling pathways that provide an increased adaptive response by facilitating the display of the costimulatory molecules and the release of cytokines at the same time. Moreover, TLRs activate the host's defence mechanisms that defend against foreign organisms.[5] Multiple cell types within the skin express TLRs. Keratinocytes and sebocytes of the epidermis were shown to contain functional TLRs.[4] AV lesions have been associated with increased TLR2 and TLR4 expression. Moreover, *P. acnes* induces the release of pro-inflammatory cytokines from the monocytes through the activation of TLR2.[5]

By activating antimicrobial pathways, TLR activation results in the release of antimicrobial peptides (AMPs).[6] AMPs consist of 10–50 amino acid residues and are positively-charged amphipathic molecules that are considered the natural antibiotics of the immune system. AMPs have several subtypes and various human epithelial tissues, including the epidermis, release them. AMPs produced in the skin to ensure elimination of micro-organisms protect the epithelium from microbial infections and colonisation. *P. acnes* colonisation, which increases in AV, is known to cause accumulation of inflammatory cells in the infected region, by increasing the release of chemokines from keratinocytes and mononuclear cells, as well as the secretion of human β-defensin (hBD)1 and hBD2.[7] Cathelicidins are known to affect the functions of TLRs. *P. acnes* causes induction of cathelicidin expression in the sebocytes.[8] The acne pathophysiology and the roles of TLRs and AMPs in acne pathogenesis are summarised in Figure 1. The present review focusses on the role and importance of TLRs and AMPs in AV aetiopathogenesis.

ACNE VULGARIS AND TOLL-LIKE RECEPTORS

The human epidermis represents the first defence barrier of the host. The host response against pathogens is characterised by two types of immunity: innate and adaptive. In addition to playing a role in recognition and elimination of the pathogens, innate immunity also contributes to the development of adaptive immunity.

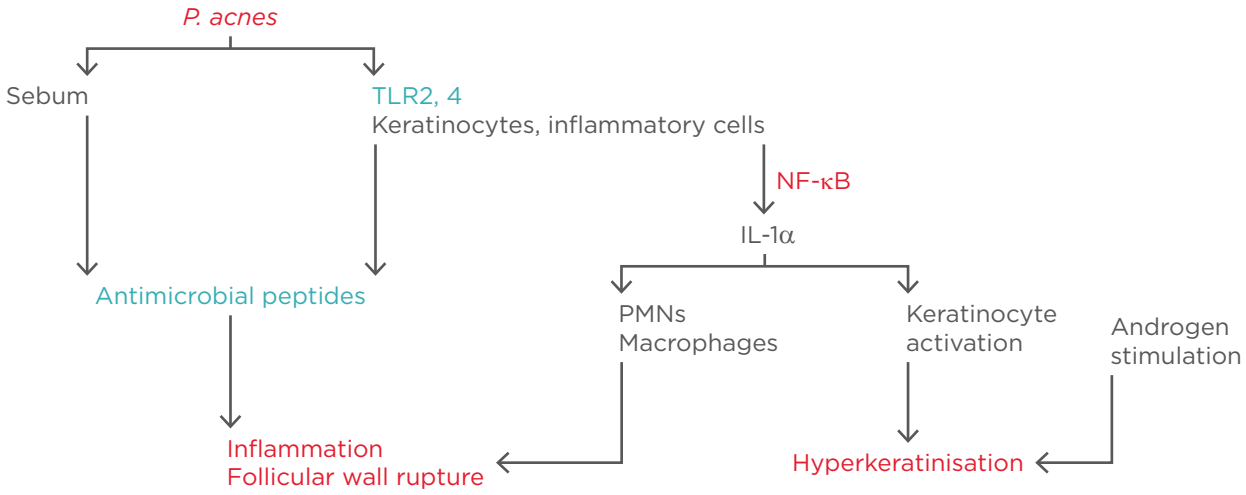

Figure 1: Acne pathophysiology and the roles of toll-like receptors and antimicrobial peptides in acne.
IL: interleukin; NF: nuclear factor; *P. acnes*: *Propionibacterium acnes*; PMNs: polymorphonuclear leukocytes; TLR: toll-like receptor.

It achieves these functions mainly through PRRs.[9] The mechanisms involved in the recognition of the pathogenic agents by the host's immune cells and generation of agent-specific immune responses have been investigated in more detail in recent years.[10] The receptors that exist on immune cells and are responsible for recognising the pathogens were first discovered in 1996 in *Drosophila melanogaster* flies and they were then called 'tolls'. Currently these molecules, which are interleukin (IL)-1-receptor-I homologues, are called TLRs.[11] TLRs are transmembrane proteins of the PRR protein family and act through their immunoadjuvant abilities and by activating cells that display antigens.[9] TLRs ensure the generation of a pathogen-specific immune response and this capability is genetically determined.[12] The discovery of TLRs significantly contributed to the understanding of the mechanisms underlying the generation of cellular and hormonal immune responses in host/pathogen interactions.[13]

A TLR increases the levels of costimulatory proteins ensuring a more effective stimulation of T cells by dendritic cells.[14] An innate immune response is primarily characterised by the functions of dendritic cells, monocytes, natural killer cells, lymphocytes, and epithelium cells; these cell types were all shown to express TLRs.[12] So far, 11 types of TLRs have been defined and other than TLR10, the ligands of all TLRs are known.[11] Multiple ligands have been identified for TLR2 and TLR4.[15] Among the TLRs expressed in human keratinocytes, TLR2 and TLR4 are particularly important. TLR4 acts as a signal receptor for the lipopolysaccharides in Gram-negative bacteria. TLR2 recognises molecules with different structures, such as lipoproteins, lipopeptides, peptidoglycan, lipoteichoic acid, lipoarabinomannan, glycolipids, and zymosan.[6] Additionally, TLR expression by cells is a dynamic process and certain ligands were shown to result in the activation of different TLR subtypes in different tissues.[16]

The studies investigating the roles of TLRs in AV are rather new. Kim et al.[17] suggested that the local inflammatory response in acne results from the effects of cytokines released from the $TLR2^+$ monocytes stimulated by *P. acnes*. In that study, $TLR2^+$ macrophages were identified in the acne lesions and around pilosebaceous units, and their numbers were shown to increase during the course of the disease.[17] Jugeau et al.[6] reported elevated TLR2 and TLR4 expression in the epidermal keratinocytes in superficial inflammatory acne. In their study, TLR2 levels in the epidermal keratinocytes were higher than TLR4 levels. Similarly, TLR2 distribution was found to be associated with keratinocyte maturation.[6]

Keratinocytes activated by different *P. acnes* extracts show increased TLR2 and TLR4 expression *in vivo*. Expression of acne matrix metalloproteinase-16 (MMP16), IL-8, and hBD2 was also shown to be enhanced in the keratinocytes stimulated through TLR2 and TLR4.[18] TLR2 and TLR4 are associated with the inflammatory reaction and tissue destruction in acne. These findings suggest that in the presence of inflammatory acne, *P. acnes* stimulates the keratinocytes and/or macrophages with the mediation of TLR.[15]

Chemokine and cytokine synthesis in human monocytes is induced by *P. acnes*-mediated TLR2 activation. TLR2-mediated pro-inflammatory cytokine release was suggested to worsen the disease course by causing inflammation and tissue destruction. There are also some studies arguing that TLR2 alone is sufficient for the activation of monocytes by *P. acnes*.[19]

In their study aiming to identify the role of *P. acnes* in inflammatory acne, Jugeau et al.[6] demonstrated increased TLR2 and TLR4 expression in the epidermis of acne lesions *in vivo*. In addition, TLR2 and TLR4 expression *in vitro* was shown to be enhanced after the incubation of keratinocyte cultures by bacterial fractions and a higher amount of MMP9 was released from the keratinocytes *in vitro*.[6] In another study, Selway et al.[20] investigated the role of TLR2 in acne pathogenesis and its contribution to comedogenesis by using immunohistochemistry and Western blotting methods in *ex vivo* sebaceous gland and primary keratinocyte cultures. They demonstrated TLR2 expression in basal keratinocytes, infundibular keratinocytes, and sebaceous glands, and found that TLR2 activation in human keratinocytes increased IL-1α release *in vitro*. The increase in TLR2 activation was also shown to stimulate hypercornification and comedogenesis in human sebaceous glands *ex vivo*.[20]

Previous studies have demonstrated that certain medications used in acne treatment can alter TLR expression.[21-26] Liu et al.[21] detected that all-trans retinoic acid treatment can reduce the expression of TLR2 and its co-receptor CD14 but does not lead to a significant change in the expression of TLR1 or TLR4. In a study performed by Tenaud

et al.[22] in patients with acne, TLR2 expression in the keratinocytes was shown to be reduced after 24 hours of incubation with adapalene. Similarly, Jarrousse et al.[23] demonstrated that zinc salts exert anti-inflammatory effects on acne by reducing the levels of TLR2.[23] Dispenza et al.[24] showed that the monocytes of patients with acne expressed more TLR2 and less TLR4 compared to healthy controls. Isotretinoin treatment, on the other hand, reduced TLR2 expression in the monocytes *in vivo* but did not alter TLR4 expression.[24] Lee et al.[25] evaluated the effect of magnesium ascorbyl phosphate on MMP9, TLR4, and AMP expression in sebocyte cultures by using reverse transcription-polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA) methods, and determined that magnesium ascorbyl phosphate treatment reduced MMP9, TLR4, and AMP expression. Jeong et al.[26] investigated the effects of topical aminolevulinic acid photodynamic therapy on the levels of TLR2 and TLR4 expression. In that study 5 out of 10 cases had enhanced TLR2 expression before photodynamic therapy, and it was reported that although TLR2 expression decreased after therapy in patients with enhanced TLR2 expression, no change was noted in patients with normal TLR2 immunoreactivity. Similarly, TLR4 expression was found to be elevated before therapy in 3 out of 10 patients and the levels of TLR4 expression decreased after therapy in these patients.[26]

Clinically, AV can present with different non-inflammatory and inflammatory lesions. In the biopsy samples obtained from AV lesions TLR2 expression was found to be extensive, particularly in the perifollicular region, and long-term disease was associated with an increased number of $TLR2^+$ cells.[27] Moreover, a positive correlation was found between the severity of AV lesions and concentration of TLR2-expressing cells.[28]

A limited number of studies have been performed to date to investigate how TLR expression varies between different types of AV lesions and the different regions of a lesion. Bakry et al.[29] examined 30 acne cases (involved and non-involved skin) and the normal skin biopsies of 30 healthy controls using immunohistochemical methods. In this study, there were significant differences between acne-involved skin and normal skin, and between acne-involved and non-involved skin, concerning TLR2 expression intensity in pilosebaceous units and dermal inflammatory infiltrates. TLR2 expression was shown to be more intense in the pilosebaceous units and dermal infiltrates regions of inflammatory and severe acne lesions.[29] In a previous study, we evaluated the levels of TLR2 and TLR4 expression in comedonal, papular, pustular, and nodular lesions of AV according to different regions of the lesion including the epidermis, site of inflammation, dermis, and skin appendages. We found that TLR2 expression was elevated in the papular and comedonal lesions compared to the nodular lesions in the epidermis region, and in the papular lesions compared to pustular lesions in the inflammation and dermis sites. Moreover, TLR4 expression was lower in the comedonal lesions than papular lesions in the dermis.[1] These findings suggest that the TLRs play important roles in the development of different clinical lesions of AV.

ACNE VULGARIS AND ANTIMICROBIAL PEPTIDES

The epidermis not only acts as a physical barrier against infectious agents, but it also quickly develops resistance mechanisms. This rapid response is regulated by certain low-molecular weight proteins called AMPs. AMPs are an important component of our innate immune system. AMPs are structures that both provide the baseline protection and also induce the development of the adaptive immune system. AMPs are recognised based on their cutaneous antimicrobial and immunomodulatory characteristics and inhibit bacterial, fungal, protozoal, and viral infections.[30] These proteins are considered to perform their antimicrobial functions by binding to the surface of microbes and forming pores on their cell membranes.[31] The AMP family consists of α and β-defensins, cathelicidins, S100 proteins, ribonucleases, and others.[30] These small endogenous cationic proteins are found in the keratinocytes, eccrine glands, mast cells, phagocytes, and sebocytes. In resting skin cells, so far it has been identified that β-defensins (hBD1, hBD2, hBD3), cathelicidin (LL37), psoriasin, and ribonucleases are all synthesised by the keratinocytes, while dermcidin is a molecule of the human sweat. AMP release may be induced by bacteria, bacterial products, TLRs, or pro-inflammatory cytokines.[31] In addition to their antimicrobial effects, AMPs are also significantly involved in inflammatory cell migration and cytokine release.[32] Due to their cationic characteristics they frequently act by inducing a negative charge on bacterial membranes.[30]

Several studies performed in recent years have indicated that AMPs play significant roles in the pathogenesis of chronic inflammatory skin disorders.[33] The regulation of the synthesis of innate and specific AMPs is known to be impaired in AV patients.[34] The roles of AMPs, particularly those including hBD and cathelicidin subgroups, have been extensively investigated in AV pathogenesis.[34,35] Defensins are a small AMP family, and are expressed in all human epithelial tissues.[7] Three subtypes of β-defensins have been identified thus far, hBD1, hBD2, and hBD3, and they were shown to be expressed by several epithelial cells.[36] β-defensin release increases in response to microbial or pro-inflammatory stimuli.[37] Typical fatty acids found in sebum, such as palmitic acid and oleic acid, were shown to increase the antimicrobial activity of the sebocytes against *P. acnes* by enhancing hBD2 expression.[38]

Chronnell et al.[34] evaluated hBD1 and hBD2 expression patterns in the pilosebaceous units of healthy individuals and AV patients and reported a marked increase in hBD1 and hBD2 expression in AV patients, particularly in the all suprabasal layers of the epidermis, the distal outer root sheath of the hair follicle, and the pilosebaceous duct. That study indicated a marked elevation in hBD1 and hBD2 expression in the skin with lesions. Moreover, maximum levels of hBD2 expression were revealed in the pustular lesions.[34] In another study, different *P. acnes* strains were treated by keratinocyte cultures and an increase was noted in hBD2 messenger RNA expression by certain *P. acnes* isolates, while some isolates were shown not to effect hBD2 expression. Moreover, *P. acnes*-mediated hBD2 elevation was found to be inhibited by anti-TLR2 and anti-TLR4 antibodies. This finding suggests that the *P. acnes*-mediated AMP release by keratinocytes is dependent on TLR2 and TLR4.[7] In a study investigating the levels of hBD1 and hBD2 expression in healthy human hair follicles and papular, pustular, and comedonal AV lesions and perilesional skin using immunohistochemical methods, Philpott[36] detected strong hBD1 and hBD2 immunoreactivity in the whole suprabasal epidermis, hair follicles, and the pilosebaceous canal. In contrast, hBD1 and hBD2 expression was absent in the proximal follicle section progressing to apoptotic regression. In addition to marked hBD2 expression, partial hBD1 expression was also detected particularly in the lesional and perilesional epithelium of the pustular lesions.[36]

Medications used for AV treatment can also alter AMP expression. In the *ex vivo* lipopolysaccharide-induced inflammatory skin explant model, Poiraud et al.[39] demonstrated increased hBD2 and psoriasin expression after zinc gluconate therapy but did not find any change in hBD4 expression. Harder et al.[40] evaluated the stimulation of *hBD1*, *hBD2*, *hBD3*, and *hBD4* gene expression in the keratinocytes and established that all-trans retinoic acid inhibited the pro-inflammatory cytokine-mediated expression of the *hBD2*, *hBD3*, and *hBD4* genes, but did not alter the expression of the *hBD1* gene. Borovaya et al.[41] evaluated the effects of isotretinoin treatment in AV on the levels of AMP expression using RT-PCR. They measured the levels of AMP expression before isotretinoin therapy, during therapy, and after 6 months of continuous therapy. Compared to the control group, expression of cathelicidin, hBD2, lactoferrin, lysozyme, psoriasin, koebnerisin, and ribonuclease-7 increased in pre-treatment patients with AV, while the expression of α-defensin-1 decreased. Moreover, the expression of cathelicidin, hBD2, lactoferrin, psoriasin, and koebnerisin decreased during isotretinoin therapy, and the expression of cathelicidin and koebnerisin reached normal levels after 6 months of therapy. On the other hand, increased lysozyme and ribonuclease-7 expression was not affected by isotretinoin therapy and the authors suggested that lysozyme and ribonuclease-7 have stronger antimicrobial than pro-inflammatory activity. The authors concluded that the expression levels of several AMPs can be altered in the presence of acne.[41]

Cathelicidins belong to the AMP family.[8] Wang et al.[35] reported that the first AMP described in reptiles was cathelicidin, and an AMP called cathelicidin-BF exists in the venom of *Bungarus fasciatus* snakes. In that study, experimental administration of cathelicidin-BF in topical gel form on rat tissues provided strong antibacterial and anti-inflammatory efficacy against *P. acnes*. Thus, the researchers suggested that the cathelicidins may represent an alternative therapeutic option for AV.[35]

In a previous study we evaluated the levels of hBD1 and cathelicidin expression in different AV lesions such as comedonal, papular, pustular, and nodular lesions, according to different regions of the lesion including the epidermis, site of inflammation, dermis, and skin appendages. We observed that in the epidermis, hBD1

expression was elevated in the comedonal lesions compared to the nodular lesions. On the other hand, cathelicidin expression was lower in the inflammation area in comedonal lesions.[1]

In addition to their antimicrobial effects, AMPs also show anti-inflammatory effects. McInturff et al.[42] demonstrated that granulysin-derived peptides, as well as showing antimicrobial effects, exert anti-inflammatory activity by inhibiting *P. acnes*-induced cytokine release.

CONCLUSIONS

In conclusion, the discovery of TLRs and AMPs introduced a new perspective to the investigations of the innate immune system. However, there is still a lot to elucidate about the biology of TLRs and AMPs. TLRs and AMPs play crucial roles in AV pathogenesis and extensive studies on this matter will increase the understanding of AV pathogenesis. Different therapeutic options targeting the regulation of the release of TLRs and AMPs may provide successful outcomes in AV treatment.

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STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS IN CHILDREN: A LITERATURE REVIEW OF CURRENT TREATMENTS

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ABSTRACT

Stevens-Johnson syndrome and toxic epidermal necrolysis are among the most concerning drug reactions affecting adults and children. Although the overall mortality has reduced substantially after the introduction of several strategies, such as prompt withdrawal of the causal drug and management of the patients in an intensive care or burn unit, these conditions continue to be associated with severe complications and a mortality rate of 1–4%. Currently, several treatment options including systemic corticosteroids, intravenous immunoglobulins, cyclosporine, tumour necrosis factor-α inhibitors, and plasmapheresis among others, have shown inconclusive benefits regarding their efficacy and safety in patients with these conditions. This review analyses the most recent literature regarding treatment options for paediatric patients with Stevens-Johnson syndrome and toxic epidermal necrolysis.

Keywords: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), adverse drug reactions, children, systemic corticosteroids, intravenous immunoglobulin (IVIg) therapy, cyclosporine (CsA), tumour necrosis factor-α (TNF-α) inhibitors.

INTRODUCTION

Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are two uncommon but widely concerning conditions that affect both children and adults worldwide. Their overall annual incidence has been reported in 1–10 cases/1 million, of which 20% are paediatric cases.[1] Mortality rates in SJS range between 1% and 4%, whereas in TEN it increases to between 25% and 35%, being somewhat lower in children.[2] SJS/TEN represent entities in the same disease spectrum with different degrees of severity.[3,4] Recently Roujea[5] suggested denominating these conditions as epidermal necrolysis because both are characterised by skin and mucosal detachment due to keratinocyte apoptosis. SJS/TEN are mostly triggered by drugs such as anticonvulsants, allopurinol, sulfas, and antibiotics, and less frequently by infections such as mycoplasma pneumonia. However, other conditions have also been associated.[6] Although the precise pathogenesis of SJS/TEN remains uncertain, it is considered that specific agents (e.g. drugs, infection) elicit an immune-mediated cytotoxic reaction against keratinocytes, generating extensive apoptosis. The main cytotoxic molecules involved in its mechanism are granulysin, perforin/granzyme B, and Fas ligand.[7] More recently, the role of T helper 17 cells in the pathogenesis of SJS/TEN as enhancers of the immune response in affected patients has been proposed.[8] Additionally, several reports have shown a strong association among some HLA genes, with SJS/TEN incidence, as a result of specific drugs such as carbamazepine (HLA-B*58:02, HLA-A*31:01) and allopurinol (HLA-B*58:01).[5,9]

Clinically, the SJS/TEN spectrum is divided into three groups based on the body surface area (BSA) involved. SJS affects <10% of the BSA, while TEN affects >30%. SJS/TEN overlap refers to a skin

and mucosae involvement between 10% and 30% of BSA.[8] Patients may present a prodromal stage (fever, cough, sore throat, and general malaise) followed by skin and mucosal lesions. The skin lesions begin as erythematous macules with a possibility of developing rapidly into papules, vesicles, bullae, urticarial plaques, or confluent erythema and when the bullous lesions break, they leave large areas of denuded skin. Other lesions may have a peculiar appearance of 'flat atypical targets' differing from the typical target lesions of erythema multiforme (Table 1). At least two mucosae are always affected to a lesser or greater degree, and may present with erythema, oedema, sloughing, blistering, ulceration, and/or necrosis. Extensive loss of the epidermis layer leads to infections, electrolyte imbalance, and in some cases organ failure that could result in death.[10]

Although laboratory findings are not specific, several haematological or biochemical parameters can show abnormalities, including liver function and renal function tests.[1] Skin biopsies are very useful to rule out other entities (e.g. fixed drug eruption, Staphylococcal scalded skin syndrome, and other bullous diseases). They usually show varying degrees of vacuolisation of the basal membrane, including sub-epidermal blisters and keratinocyte apoptosis, possibly progressing to full-thickness necrosis. Sparse perivascular lymphoid infiltrate is also characteristically present.[10,11]

The severity of illness score for TEN patients (SCORTEN) was described by Bastuji-Garin et al.[3] The SCORTEN predicts the risk of death and evaluates different parameters at the time of hospital admission including: age >40 years, malignancy, heart rate >120/min, initial percentage of epidermal detachment >10%, blood urea >28 mg/dL, serum glucose >252 mg/dL, and serum bicarbonate <20 meq/L. The score ranges from 0 to 9; a score ≥5 is associated with a risk of death of 90%.[12] Long-term sequelae and recurrence may present in ≤47% of patients. Sequelae include post-inflammatory hypo/hyperpigmentation, scarring, uveitis, keratitis, corneal defects, blindness, sclerosing cholangitis, bronchiolitis obliterans, stridor, and venous thrombosis, among others. The prognosis depends on age, the percentage of BSA affected, and the associated comorbidities.[13] The treatment options more frequently used worldwide include intravenous immunoglobulin (IVIg) and systemic corticosteroids. Recently, cyclosporine (CsA) and tumour necrosis factor-α (TNF-α) inhibitors have also been explored in these conditions.[14-19] This manuscript reviews the recent literature regarding treatment options for the paediatric population.

TREATMENT UPDATE

Supportive Therapy

The initial management of SJS/TEN consists of the early withdrawal of the responsible drug and supportive therapy (ST) in an intensive care or burn unit, including fluid resuscitation, nutritional support, and the prevention of infections and sequelae.[4] Even though the overall mortality in patients with SJS/TEN has been reduced substantially thanks to advances in ST, a recent systematic review showed that patients receiving only ST took longer to achieve remission, had longer hospital stays, and presented more complications and deaths compared with patients treated with systemic therapy, such as systemic steroids or IVIg.[14]

Systemic Corticosteroids

Corticosteroids decrease the synthesis of pro-inflammatory molecules and inhibit prostaglandin and leukotriene production. These drugs also have anti-proliferative effects and impair monocyte and lymphocyte function. In theory, their mechanism of action could modify the uncontrolled immune response observed in patients with SJS/TEN though their role in the management of SJS/TEN patients remains questionable. For some authors, the use of systemic corticosteroids increased the risk of complications, infections, and hospital stays, and should thus be avoided.[20] On the other hand, others proclaim the benefits of steroid use in these conditions, such as a reduction in the duration of fever and skin eruption.[21] The multinational study EuroSCAR evaluated the role of corticosteroids in adults with SJS/TEN. The study found that prior use of corticosteroids in patients with SJS/TEN prolonged the period of disease progression but did not influence the disease severity or mortality.[22] While similar studies in paediatric patients have not yet been performed, we have recently published a systematic review evaluating the outcome of several treatment modalities for drug induced SJS/TEN in children, showing that patients with SJS receiving systemic corticosteroids (prednisone, prednisolone, or methylprednisolone) had a better outcome than patients receiving ST alone. Although in both groups the percentage of complications were similar (25%), the severity

was higher in the ST group (e.g. sepsis, death) compared with the corticosteroid group (e.g. scarring, hyperpigmentation, mild infections, bronchiolitis obliterans).[14]

More recently Finkelstein et al.[13] reported the outcome of 55 retrospective paediatric cases of SJS/TEN. They found that patients with no exposure to corticosteroids had a higher association with ocular sequelae than patients treated with these medications. Additionally, a retrospective study performed in Thailand reviewed 189 paediatric cases of SJS/TEN treated between 1979 and 2007, in which patients were divided into three groups depending on the period in which they were admitted to the hospital. Overall, 58% of the patients received treatment with systemic corticosteroids. The authors reported that the use of corticosteroids in their institution increased progressively from 18% to 64% to 87% (first, second, and third periods, respectively) due to the positive outcomes of these patients. Complications in the three groups reached 20% and included infections, eye sequelae, and hepatitis among others. Interestingly, and contrary to previous reports in the literature, the mortality decreased from 9% to 1.5%, this being lower during the last period precisely when more patients received steroids, although this could also have been associated with advances in supportive care in more recent years.[23]

Table 1: Clinical features of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Cutaneous lesions	Bullous EM	SJS	SJS/TEN overlap	TEN
Skin detachment	<10%	<10%	10–30%	>30%
Typical target lesion: Individual, <3 mm, well-defined border, regular round shape with three different zones	Yes	No	No	No
Raised atypical target lesion: Round, edematous, palpable, with only two zones and poorly defined borders	Yes	No	No	No
Flat atypical target lesion: Round, with only two zones, poorly defined borders, non-palpable, except when it has a central blister	No	Yes	Yes	Yes
Macula with/without blister: Non-palpable, erythematous/purpuric, irregular border, which may present a blister involving the full area of the lesion	No	Yes	Yes	Yes

EM: erythema multiforme; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis.
Modified from Bastuji-Garin et al.[3]

Table 2: Estimated cost of different treatment modalities for Stevens-Johnson syndrome/toxic epidermal necrolysis in the province of Ontario, Canada.

Drug	Posology	Dose for a 30 kg child	*Cost for one dose
Cyclosporine	3.0–6.0 mg/kg/dose	90–180 mg	4.00–10.00
Methylprednisolone	2.0 mg/kg/dose	60 mg	9.00
Etanercept (Enbrel®)	0.8 mg/kg/dose	24 mg	202.50
Infliximab (Remicade®)	5.0 mg/kg/dose	150 mg	790.00
Intravenous immunoglobulin	0.5–2.0 gr/kg/dose	15–60 gr	1,000–4,200

*Costs are current as of 2015 and expressed in Canadian dollars. They represent exclusively the cost of the drug/agent and do not include administration costs such as nursing. Costs may vary depending on the country and healthcare system.
Costs obtained from www.transfusionontario.org and www.health.gov.on.ca.

Ferrándiz-Pulido et al.[24] similarly reported a review of 14 paediatric cases of SJS/TEN of which 86% received treatment with systemic corticosteroids. The overall mortality rate in this study was 7%, but no deaths were reported in the corticosteroid group.[24] Despite the above data potentially suggesting the potential benefits of corticosteroids in paediatric patients with SJS/TEN, it is important to mention that there is no consensus regarding dose, type of corticosteroid given, and length of treatment for these patients, and in most of the studies these vary greatly.

Intravenous Immunoglobulin

IVIg consists of exogenous pooled human immunoglobulins, mainly IgG (IgG 1–4) and a minimal supply of IgA, IgE, and IgM antibodies, including autoantibodies against ubiquitous proteins such as Fas. The mechanism of action of IVIg is complex and still not completely understood, however its use in SJS/TEN has become popular following the *in vitro* demonstration by Viard et al.,[25] showing that IVIg can block the binding between apoptotic Fas ligand (CD95L) and its respective apoptotic receptor, located on the keratinocyte cell surface, responsible for the programmed cell death observed in patients with these conditions.[25] Initial data indicated that IVIg was superior to systemic corticosteroids in the management of severe drug reactions,[26] however further studies have shown contradictory results.[22,27] In 2008, the EuroSCAR study reported that adults with SJS/TEN treated with IVIg had no better outcomes compared with other treatment modalities (e.g. systemic corticosteroids, ST); moreover, the mortality was higher in this group.[28] However, some authors note that the IVIg group (EuroSCAR study) had a higher proportion of patients with TEN versus SJS, than other groups. They also suggest that many of these patients did not receive IVIg before Day 4 as recommended, that they were not admitted to a burn unit, and that they may have received sucrose-containing IVIg, which has been associated with renal toxicity.[29] Thus, several authors still consider that IVIg is the best treatment option for patients with SJS/TEN.

A recent survey performed among North American physicians with a special interest in patients with SJS/TEN showed that >70% of them preferred to use IVIg in patients with diagnosed TEN and >50% use IVIg in at least one form of SJS (SJS or SJS/TEN overlap).[19] On the other hand, our systematic review did not show a statistically significant difference in the outcome among patients who received systemic steroids versus IVIg.[14] More recently, Barron et al.[6] performed a meta-analysis with meta-regression of observational studies regarding IVIg in the treatment of SJS/TEN (both adults and children). They concluded that high doses (>2 g/kg) seemed to significantly decrease mortality in these patients, however other outcomes such as time of stay, sequelae, and other complications were not evaluated.[6] Finkelstein et al.[13] reported a retrospective study of 55 paediatric cases of SJS/TEN, in which 38% of the patients received IVIg as treatment (21% of them also received concomitant treatment with systemic corticosteroids). Interestingly, the group of patients treated with IVIg had a higher incidence of ocular complications.[13]

Despite literature showing that IVIg is relatively safe, it has an overall risk of adverse reactions of 10%, and although most of them are minor (mainly infusion reactions), serious adverse reactions like renal failure, aseptic meningitis, stroke, infection, haemolysis, deep venous thrombosis, and anaphylaxis have been reported.[30] Infusion reaction symptoms include headache, nausea, fever, vomiting, cough, malaise, myalgia, arthralgia, abdominal pain, flushing, urticarial lesions, and variations in heart rate/blood pressure.[31] Similarly to corticosteroids, guidelines regarding dosage and length of treatment vary widely among authors.[2] Finally, some authors consider that a combination of corticosteroids plus IVIg has a superior therapeutic effect and a reduced mortality associated in patients with SJS/TEN compared with any of these two medications alone, however evidence needs to be reviewed in more detail.[12,32,33]

Cyclosporine

CsA is a powerful immunosuppressive and immunomodulatory drug, used traditionally to prevent rejection of transplanted organs and other inflammatory or autoimmune conditions such as pemphigus, atopic dermatitis, and psoriasis, among others.[34] CsA targets mainly T cell-dependent immune mechanisms, which are implicated in transplant rejection and some forms of autoimmunity, through the inhibition of T helper cells and cytotoxic T cells. It also selectively blocks many immunoregulatory functions of activated T cells, thereby inhibiting the release of interleukin (IL)-3, IL-4, IL-5, interferon-γ, granulocyte monocyte colony stimulating factor, and TNF-α.[35]

The use of CsA in the treatment of SJS/TEN was first reported almost two decades ago. In 2000, Arévalo et al.[36] reported 11 adult patients treated with oral CsA twice daily (3 mg/kg/day) and then compared them with a historical series of patients (same institution) treated with either cyclophosphamide or different doses of corticosteroids. The authors found that the patients treated with CsA had an early time of arrest of disease progression and a shorter time of re-epithelialisation in comparison with the other patients.[36] Following this, other case series and case reports have also shown the potential benefit of CsA in the management of patients with SJS/TEN, although unfortunately, studies including children are scarce.[16,37,38] Aihara et al.[39] reported a case of a child with TEN treated successfully with IV CsA (1 mg/kg/day) and methylprednisolone (30 mg/kg/day), showing clinical and laboratory improvement in the first 24 hours after starting treatment. Valeyrie-Allanore et al.[40] performed an open trial of CsA in 29 patients with SJS/TEN, of which only 3 were <19 years old. All the patients were treated with oral CsA solution (through nasogastric tube) with an initial dose of 1.5 mg/kg twice daily for 10 days, with subsequent tapering until completing 1 month of treatment. The authors found that both mortality and the progression of detachment were lower than expected, and only a few patients presented complications (n=3) (leukoencephalopathy, neutropenia, and nosocomial pneumopathy). In two other patients, the dose was reduced early due to renal impairment.[40]

More recently Singh et al.[18] performed a retrospective comparison among 11 patients with SJS/TEN, treated with CsA, and patients treated with systemic corticosteroids for the same conditions. In this study, only two children were included (a 14-year-old and a 7-year-old). Overall the mean duration of re-epithelialisation was 14.5 days in the CsA group and 23.0 days for the corticosteroid group. The mean hospital stay was also lower in the CsA group (18 days) compared with the other (26 days). There was no mortality in the CsA groups and there were two mortalities in the group treated with corticosteroids.[18] Although the evidence suggesting that CsA could have a potential role in the management of paediatric patients with SJS/TEN is limited, the experience in other conditions such as atopic dermatitis and psoriasis may encourage other health professionals to develop better quality studies in the future and thus properly establish the use of CsA in the treatment of children with SJS/TEN.

Plasmapheresis and Haemoperfusion

Plasmapheresis and haemoperfusion are well-recognised procedures, characterised by the removal of toxic or pathological molecules from the blood potentially contributing to disease progression. Both procedures are currently used in children in the treatment of several inflammatory and/or immunological conditions, such as sepsis, Guillan-Barré, Henoch-Schönlein purpura, recalcitrant atopic dermatitis, and pemphigus vulgaris, among others.[41,42] Although the role of plasmapheresis/haemoperfusion in the treatment of paediatric SJS/TEN has not been well established, it can offer a potential benefit principally for patients with severe disease (mainly TEN) or those who have not responded to other treatments (corticosteroids and/or IVIg),[43] and is currently a Class III indication of the American Society for Apheresis (ASFA).[42] The mechanism by which plasmapheresis/haemoperfusion appear effective is by removing drugs and their metabolites, or immune complexes and inflammatory mediators that have been released and promote keratinocyte apoptosis, from the blood of the patient.[44]

The use of plasmapheresis in patients with TEN was initially reported in the 1980s and later, several authors also reported favourable outcomes, although these studies mainly included adults.[45] Subsequently, Chaidemenos et al.,[46] Egan et al.,[47] and Koštál et al.[48] published three independent case series including patients with TEN, which were successfully treated with plasmapheresis. However, only six paediatric patients were reported in these studies (two in each study).[14,48] More recently, Hinc-Kasprzyk et al.[43] reported a 4-year-old boy with late-stage TEN, who had previously failed systemic therapy with corticosteroids and IVIg, that was treated with plasmapheresis. The patient showed a remarkable improvement of his general condition only 2 days after the second plasmapheresis session.[43] Some of the disadvantages of plasmapheresis include its high cost and its risk of blood transfusion-related side effects, such as citrate effect, decrease in blood pressure, and allergic reactions.[44,48] Furthermore it is not widely available, particularly in resource-constrained environments.[49]

Haemoperfusion, on the other hand, does not seem to have the same limitations, as this requires less

costly equipment and is easier to perform compared to plasmapheresis.[44] Its success in the management of patients with sepsis has raised the interest of some authors to adapt this procedure as a new treatment option for patients with severe SJS/TEN. Wang et al.[44] reported in 2014 a series of seven paediatric patients with SJS/TEN treated satisfactorily with this procedure. All patients received a number of sessions, ranging from 3–5, and showed a rapid improvement of symptoms (fever or progression of the skin rash) after the first session. Patients' skin lesions healed after 7.0 days and the average length of hospital stay was 14.4 days. Some adverse reactions observed in these patients included hypotension and palpitations, and three patients developed femoral vein thrombosis which resolved with anticoagulant treatment.

Tumour Necrosis Factor-α Inhibitors

Biological agents specifically target mediators of inflammation by stimulating or suppressing particular components of the immune response. In children, TNF-α etanercept, infliximab, and rituximab are the most prevalent agents currently used to treat a wide variety of autoimmune and inflammatory conditions (psoriasis, atopic dermatitis, inflammatory bowel disease, juvenile arthritis).[50] Recent literature has showed high levels of TNF-α in skin biopsies of patients with TEN prompting several authors to use some of these agents in the management of patients with SJS/TEN.[51] In children, few reports have been published (three patients with infliximab and one with etanercept), and although the results seem encouraging, their use needs to be cautiously considered due to the potential side effects (increased risk of infections, haematological abnormalities, lymphoma, hepatotoxicity) and elevated costs compared with other treatment modalities (CsA or methylprednisolone) (Table 2).[50] Other drugs with similar anti-TNF-α properties, but with relatively low costs, include N-acetylcysteine and pentoxifylline. Few cases of paediatric patients with SJS/TEN being successfully treated with these agents have been reported thus far and unfortunately the literature regarding this topic remains limited.[10,14,52]

CONCLUSIONS

In spite of the current variety of treatment options reported in the literature regarding the management of SJS/TEN in children, there is not enough reliable evidence to establish their safety and efficacy, as randomised controlled trials are difficult to perform, mainly due to the rarity of this disease. However, better quality studies could be conducted in the future through international collaborative programmes or registries that establish standardisation of inclusion criteria, clinical and pathological information, outcome definitions, and treatment protocols based on expert consensus.

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SIGNIFICANCE OF DIET AND ORAL SUPPLEMENTATION IN ACNE VULGARIS

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ABSTRACT

Acne vulgaris is one of the most common skin diseases in the world. There are many factors involved in its pathogenesis. The dermatosis is characterised by seborrhoea and the formation of comedones, pustules, and papules and is very unpleasant for patients. Recent data have shown that there may be a connection between acne, diet, and dietary supplements. Researchers have found that milk and dairy products, high glycaemic load, and a diet low in omega-3 fatty acids can aggravate acne. On the other hand, there is also a hypothesis that oral supplementation can be beneficial. Supplements cited as beneficial are products containing omega-3 fatty acids, antioxidants, and probiotics. However, there are still many inaccuracies in this area of dermatology and further research is needed before any recommendations can be made.

Keywords: Acne vulgaris, diet, dietary supplements, omega-3 fatty acids, probiotics.

INTRODUCTION

Acne vulgaris is a common skin disease occurring most often during puberty. Its pathogenesis has multiple factors and is very complex. The dermatosis is characterised by seborrhoea and the formation of comedones, pustules, and papules in areas rich in sebaceous glands.[1,2] The variety of clinical acne is very wide. Patients may present with only a few blackheads or be afflicted with general skin involvement that consists of pustular deep lesions, abscesses, scarring and, though occurring rarely, can also involve the joints as in the case of acne fulminans. There are a few forms of acne vulgaris: acne comedonica, which is dominated by open and closed comedones; acne papulopustulosa, which is dominated by the inflammatory process; and acne conglobata, which is the most severe form of acne and is characterised by abscesses, fistulas, and scars.[3]

Acne vulgaris is one of the most common skin diseases in the world. It is more common in industrialised than less industrialised countries. For example, it does not often occur in Africa and usually affects those of Asian and Caucasian ethnicities.[4] Acne lesions are commonly present in almost all people at some period of their life. They might occur in prepubertal children (usually comedogenic), infants (usually disappear after 3 months), and most frequently in the early teenage years. This is because sebum secretion begins at that age and blackheads start to appear and can later turn into inflammatory lesions. Both women and men are affected by acne equally; however, a severe form often appears in men, probably due to the influence of hormones. Sometimes dermatosis can last until the fourth decade of life or even across an individual's lifetime.[5] In large studies performed in the USA, France, and the UK, acne is among the top three most common skin diseases in the general population.[5-7]

Acne vulgaris is a multifactorial dermatosis that can be caused by different factors such as increased production of sebum, the release of inflammatory mediators in the skin, hyperkeratosis, and colonisation by anaerobic *Propionibacterium acnes*.[8] Moreover, the factors contributing to the formation of acne also include genetic predispositions, hormonal abnormalities (androgens play a key role), immunological disorders,

psychological, environmental, and even iatrogenic factors.[9,10] It is believed that diet may play a role in the pathogenesis of acne vulgaris and some products may have an effect on the course of this dermatosis. Furthermore, there are some data that show the beneficial effect of oral supplementation in supporting the treatment of acne vulgaris.[11]

ACNE AND DIET

Studies on the influence of diet on acne vulgaris focus mainly on milk and dairy products, chocolate, glycaemic load of the diet, fatty acids, and antioxidants (zinc and vitamin A). It is thought that the comedogenic effects of milk and its products may be caused by their hormone content, which is produced by cows during pregnancy. Data show that the most comedogenic hormone is insulin-like growth factor 1 (IGF-1) which stimulates the pilosebaceous unit,[12] yet there is still no strong evidence that milk and dairy products aggravate acne. Also, chocolate has always been mentioned by patients as a factor that contributes to the exacerbation of acne but again there is a very limited amount of evidence that has confirmed its negative impact on the skin.[13] The next diet factor believed to influence acne is glycaemic load and glycaemic index of the diet. Data show that consumption of high glycaemic index products may participate in the pathogenesis of dermatosis; this is because consumption of such products leads to hyperinsulinaemia and insulin resistance. This in turn stimulates the secretion of androgens and causes an increased production of sebum.[13,14] Furthermore, hyperinsulinaemia affects the level of circulating IGF-1, directly affecting acne aggravation. There is a strong connection between a high glycaemic load diet and acne aggravation.[15-17] Whereas the association between insulin resistance is well known in females, especially those with polycystic ovary syndrome, this association has been poorly investigated in males and needs further research.[18] Dietary acids, especially the ratio of omega-6 to omega-3 fatty acids, are factors considered important due to their modulation of inflammatory mechanisms and antioxidants such as zinc and vitamin A, acting as anti-inflammatory factors by reducing the level of reactive oxygen species (ROS) that can be increased in acne patients.[19,20] This connection will be further described forthwith.

ACNE AND ORAL SUPPLEMENTATION

Omega-3 Fatty Acids

The idea of the beneficial effects of oral fatty acids supplementation on acne vulgaris originated from old epidemiological studies in which researchers found that populations consuming a diet rich in fish had significantly lower acne occurrence. This is supported by the fact that acne vulgaris is more common in Western countries.

Leukotriene B4 (LTB4) is a substance that regulates sebum production. Omega-3 fatty acids, and particularly eicosapentaenoic acid (EPA) derived from fish oils and γ-linolenic acid (GLA) derived from borage oil, inhibit the conversion of arachidonic acid into LTB4. Every pilosebaceous unit can produce pro-inflammatory substances, including LTB4, using substances that come from the decomposition of fat originating from the diet. Fish oil, especially EPA, can inhibit production of LTB4 and prevent inflammatory processes.[17,19] Omega-3 fatty acids can also lower IGF-1 levels. Furthermore, it has been shown that omega-3 fatty acid supplementation suppresses the production of tumour necrosis factor-α and interleukin-Iβ in healthy individuals. This all suggests that they may have a beneficial effect in the treatment of acne.[20,21]

Oral supplementation seems to be beneficial. A small study of five patients published in 2008 showed a reduced number of acne lesions among patients who consumed dietary supplements based on omega-3 fatty acids (which consisted of: EPA, selenium, zinc, and chromium). A study conducted by Rubin et al.[19] in Beverly Hills (Lasky Skin Center, California, USA) which examined the effect of a supplement containing EPA and antioxidants on five patients with mild-to-moderate acne for 2 months also demonstrated positive results. Inflammatory acne lesion count was significantly reduced in all patients. Moreover, Khayef et al.[21] examined healthy males with diagnosed mild-to-severe acne vulgaris. Patients were given three capsules of fish oil daily (930 mg EPA, 720 mg docosahexaenoic acid, and 174 mg docosapentaenoic acid each day) for 12 weeks. After the period of study researchers found improvement in 62% of patients.[19,21] Costa et al.[22] investigated the effects of oral fatty acids supplementation in acne patients. Patients were treated with antibiotics (lymecycline) (300 mg per day) and oral supplements (540 mg

of GLA, 1,200 mg of linoleic acid, and 510 mg of oleic acid per day). The whole course of therapy lasted 90 days. After the period of study researchers found that there were changes in patients' sebum composition, information that may be helpful in acne therapy.

GLA is commonly used in therapy for atopic dermatitis (AD), but its anti-inflammatory effects allowed researchers to conclude that it might also be helpful in acne therapy. Jung et al.[23] conducted a randomised double-blind prospective study of 45 acne patients. They were not pharmacologically treated for acne during the period of study. Researchers created three groups, and each group was given either omega-3 fatty acids (1,000 mg EPA and 1,000 mg docosahexaenoic acid daily), GLA (1,000 mg borage oil consisting 200 mg GLA daily), or placebo. The study lasted 10 weeks. At follow-up both the group taking omega-3 and the group taking GLA showed significant improvement compared with the placebo group. Although there are no specific recommendations for omega-3 fatty acid supplementation in acne vulgaris, there is strong evidence that it might reduce acne lesions; obtaining omega-3 fatty acid from a variety of dietary sources may be beneficial.

Antioxidants

Several emerging studies have shown that acne patients may be under increased local and systemic oxidative stress and have lowered blood levels of various antioxidant and anti-inflammatory nutrients.[24] This leads to higher levels of ROS produced by neutrophils. ROS participate in the inflammatory progression of acne. Normally they are removed by cellular antioxidants such as glucose-6-phosphate dehydrogenase and catalase. However, both enzymes are present in small quantities in patients with acne. It is therefore suggested that oxidative stress may be implicated in the origin of acne and that antioxidant supplements may be valuable adjuvants in acne treatment.[20]

For example, El-Akawi et al.[25] found lower levels of vitamins A and E among 200 age-matched acne patients compared with controls in a study conducted in 2006. They also found a correlation between serum levels of these vitamins and severity of acne. Furthermore, since selenium-dependent glutathione peroxidase enzyme activity is low in acne patients, it has been theorised that selenium would be of value. Indeed, low levels of blood selenium have been documented in acne patients. One study examined the effect of daily supplementation of selenium (400 mcg) and vitamin E (20 mg) for 12 weeks in acne. This combination led to improvements, especially in patients with low baseline glutathione peroxidase activity. Various studies over the last three decades have also shown that zinc levels are lower in acne patients than in controls and that oral and topical administration of zinc may be of therapeutic value. Another antioxidant that seems to be helpful in acne is the epigallocatechin-3-gallate polyphenol from green tea. It is believed that due to its well documented anti-inflammatory and antioxidant activity it can help acne patients. However, epigallocatechin-3-gallate has mainly been topically administered.[19] A study on hamsters has shown that catechins found in green tea inhibit sebum production[26] and that nobiletin, a flavonoid with antioxidant properties (found in the juice of *Citrus depressa*, popular in China and Japan) inhibits lipogenesis and proliferation of sebocytes and sebum production.[27] Resveratrol, a phytoalexin found in the skins of red grapes, red wine, peanuts, and mulberries may be another promising antioxidant therapy for acne. *In vitro*, it has been shown to have bactericidal activity against *P. acnes* and plays an important role in the pathogenesis of acne.[28]

One common acne therapy is oral isotretinoin administration. It is also well known to be associated with side effects such as dry skin, erythema, and desquamation. Fabbrocini et al.[29] investigated the effects of oral supplementation on reducing these side symptoms. Patients were given a supplement based on GLA, vitamin E, vitamin C, beta-carotene, coenzyme Q10, and *Vitis vitifera* twice a day. Patients treated with a dietary supplement and isotretinoin had fewer side effects than patients given only isotretinoin. Moreover, the group treated with supplements showed greater adherence to therapy.[29]

The studies mentioned above give credence to the theory of the positive role of antioxidants in acne therapy, but the effects of these substances over the course of this disease are not yet fully explored and are worth investigating.

Probiotics

The medical use of probiotics and prebiotics has become very common over the last few years. They act as immune modulators and have been

used in inflammatory skin conditions (mainly AD). Their role in acne however is not yet fully explored.

Probiotics are live micro-organisms that, when orally administered, may confer a health benefit on the host. They have been widely reported to be helpful in gastrointestinal disorders. The most commonly used probiotics are lactobacilli, bifidobacterium, and enterococci. Prebiotics on the other hand are non-digestible carbohydrates that stimulate the growth of probiotic bacteria in the intestine. The most common prebiotics are indigestible oligosaccharides.

The pathophysiology of acne involves excess sebum production, follicular hyperkeratinisation, *P. acnes* hypercolonisation, and inflammation, all of which can be increased with stress. Furthermore, they can alter the intestinal lining by encouraging bacterial overgrowth, stagnating intestinal transit time, and thereby compromising the intestinal barrier. The composition of intestinal microflora may also be disrupted by antibiotic therapies commonly used in acne, contributing to the fact that 54% of acne vulgaris patients have marked alterations of intestinal microflora and leading to the suggestion that oral probiotic and/or prebiotic supplementation may be helpful in acne treatment.[30]

One of the potential benefits that systemic probiotics supplementation may offer is the reduction of inflammation in acne. This is probably caused by the downregulation of gene expression related to the release of inflammatory cytokines and the recruitment of pathogenic CD8 T cells while activating regulatory T cells. Probiotics may also decrease sebum content leading to lower follicular colonisation by *P. acnes* and therefore decreased inflammation.[30]

A study conducted by Siver[31] showed an 80% clinical improvement in acne patients after oral supplementation of *Lactobacillus acidophilus* and *Lactobacillus bulgaricus*.[31] Another study (N=36) conducted by Kim et al.[32] showed statistically significant improvement in inflammatory lesion count, total lesion count, and clinical grade of acne after daily consumption of Lactobacillus for 12 weeks compared to fermented milk (placebo) consumption.[32] Although probiotic supplementation appears to be helpful in acne treatment, the connection between its supplements and acne occurrence still requires further research.

CONCLUSIONS

Acne vulgaris is a common skin disease and its symptoms are unpleasant for patients. Recent data show that oral supplements may be beneficial and can lead to decreased severity of the dermatosis. Most studies indicate that substances such as omega-3 fatty acids, antioxidants, and probiotics may help acne patients. However, this topic needs further research before any recommendations can be made.

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IMMUNOPATHOGENESIS OF LEPROSY: A MODEL FOR T CELL ANERGY

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ABSTRACT

Leprosy is a model disease for understanding human immune responses underlying diseases caused by intracellular pathogens, as well as providing valuable insights into autoimmune disorders and cancer. This review addresses the unresponsiveness/anergy of host T cells to the causative pathogen *Mycobacterium leprae* and describes both the adaptive and innate immune responses observed during the clinical course of the disease. Leprosy presents as a clinicopathological spectrum, with divergence in antigen-specific T cell responses and antibodies in patients at the two ends of the spectrum. Tuberculoid leprosy at one end presents with localised hypopigmented paucibacillary skin patches, and shows effective antigen-specific T cell responses and low antibodies. In contrast, lepromatous leprosy at the other end presents with generalised lesions with bacillary proliferation, abundant antibodies, and T cell unresponsiveness/anergy to *M. leprae*. Recent advances that may explain clinical divergence and T cell unresponsiveness/anergy associated with lepromatous leprosy include: cytokine dysregulation, T helper (Th)1, Th2 paradigm, Th17 cells, FOXP3$^+$ regulatory T cells, and pathogen-induced accessory cell subversion.

Keywords: Leprosy, regulatory T cells (Tregs) in leprosy, T helper (Th)17 in leprosy, leprosy reactions, T cell functions.

INTRODUCTION

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* which is non-cultivable by conventional methods. This ancient disease, seen less frequently in the developed world, is a public health concern in Asia[1] and Latin America. The genome of the pathogen is known[2] making it possible to now define antigens, examine their influence, and utilise specific antigens to dissect the immune basis of the disease, as well as develop diagnostics for early leprosy. Leprosy serves as a valuable model for gaining insights into human immune responses to infections, autoimmune disorders, and cancers.[3] Based on the host immune response, it presents in diverse forms, from localised to generalised disease in different individuals. The clinical manifestations of the disease are mainly characterised by involvement of skin and peripheral nerves. Leprosy has been classified into five types and represents a spectrum based on the host immunity, wherein polar stable forms of localised paucibacillary dermal patches are seen in tuberculoid leprosy (T-lep), and generalised lesions with bacilli are seen in lepromatous leprosy (L-lep). In between these polar forms are the less stable forms of borderline T-lep, borderline L-lep, and borderline-borderline leprosy.[4] Though many patients show a bland clinical course, 15–20% of patients develop leprosy reactions which are episodic, a cause of morbidity leading to peripheral nerve damage and requiring clinical intervention. They are classified into Type 1 or reversal reactions (RR) which present as inflammation of the local patches, mainly in borderline forms of leprosy and systemic Type 2 reactions or erythema nodosum leprosum (ENL), which present with fever, small reddish nodules scattered over the body, and joint pain in L-lep patients.[5] T cells are key to the elimination of intracellular pathogens as well as malignant cells.[3] Both escape T cell recognition by subverting innate and adaptive immune responses,

thereby resulting in T cell unresponsiveness/anergy. This review will focus mainly on the immune basis of the divergence seen between T-lep and L-lep forms, in both stable and reactional states (Figure 1).

The divergence between L-lep and T-lep patients lies in the former showing T cell unresponsiveness/anergy while mounting a good cytokine-dependent antibody response, whereas the latter shows the reverse pattern of immune responses. T cells are core to the protective immune response, evidenced by the existence of bacilli in L-lep patients. Moreover, T cell anergy is exquisitely antigen-specific and as such, patients mount responses to other bacteria including the related *Mycobacterium tuberculosis*. The antigen-specific anergy and the immunological basis for the clinical divergence associated with leprosy pose intriguing questions and have been investigated extensively in humans, as a suitable animal model is unavailable.[6,7]

DIVERGENCE IN ADAPTIVE IMMUNITY: T CELL RESPONSES

T-lep patients mount delayed-type hypersensitivity in skin tests and show *ex vivo* T cell responses to *M. leprae* antigens. Though integral or sonicated, *M. leprae* is not recognised by L-lep patients in skin tests or in *ex vivo* studies of peripheral blood cells;[6,7] certain peptides/antigenic determinants of *M. leprae* stimulate the T cells of L-lep patients.[6-9] Moreover, L-lep patients undergoing ENL reactions appear to recognise distinct peptides compared with the non-reaction group, both in cellular immune responses and antibody responses.[6,8] These findings indicate that L-lep patients have T cells that recognise some antigenic sites of the pathogen which may have been cryptic, and such T cells may emerge during alterations in clinical state, as in reactions akin to epitope spreading.

CYTOKINE DYSREGULATION

The divergence of cell-mediated and antibody-mediated responses in leprosy was due to different T helper (Th) subsets with divergent cytokine release. T-lep patients were reported to have a Th1 profile with interferon-γ (IFN-γ) and interleukin (IL)-2, whereas a Th2 profile with IL-4 and IL-10 was associated with L-lep,[6,7] thereby explaining the promotion of cell-mediated responses in the former and antibody responses in the latter. However, other studies including ours showed that this binary view may not provide a total explanation, as many T-lep and L-lep patients showed presence of a non-polarised Th0 subset of $CD4^+$ cells releasing both IFN-γ and IL-4.[10] It is of interest that during Type 2/ENL reactions, L-lep patients show a switch to a Th1 profile with IFN-γ production and low/absent IL-4 indicating cytokine dysregulation, which may lead to tissue damage.[11]

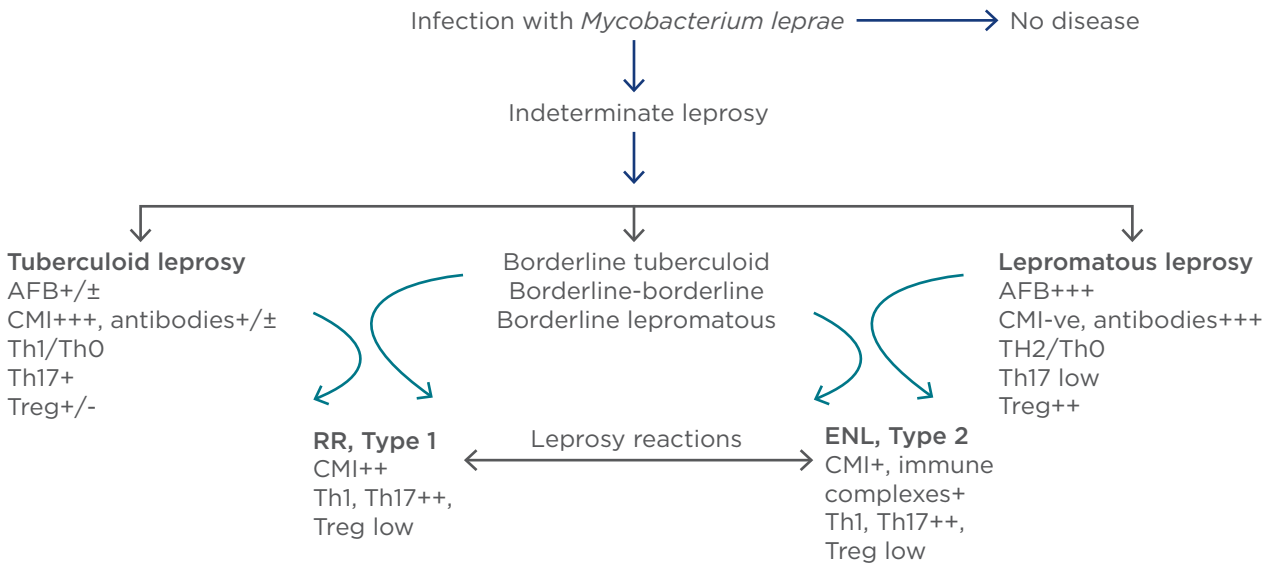

Figure 1: Clinicopathological classification of leprosy with significant immunological features under each leprosy type.

AFB: acid fast bacilli; CMI: cell mediated immunity; Th: T helper; Treg: T regulatory cells ($FOXP3^+$); ENL: erythema nodosum leprosum; RR: reversal reactions.

That the Th switch may be associated with dendritic cells (DCs) was indicated by *in vitro* studies of peripheral blood mononuclear cells (PBMCs).[12] Of clinical interest was the therapeutic potential shown by IFN-γ; L-lep patients given intramuscular IFN-γ showed rapid bacillary clearance in L-lep lesions compared with multidrug therapy alone.[13]

T HELPER 17 CELLS

Another CD4+ Th subset that shows divergence in leprosy is the Th17 population[14] associated with inflammation. The Th17 subset is highest in healthy contacts exposed to the diseases compared with patients, indicating its importance in innate immunity.[15,16] Moreover, T-lep patients showed higher expression of CD4+ Th17 cells than L-lep, both in stimulated PBMC and *in situ* skin lesions.[16,17] Th17 was associated with its signature transcription factor RORC. Though transcription factor STAT3 was expressed in similar amounts in both types of leprosy subjects, the difference was in its phosphorylation status, with only T-lep showing phosphorylated STAT3. IL-23 and IL-23 receptors, known to be important for the differentiation of Th17 cells, also showed a similar divergence in the leprosy types. That the Th17 was an effector cell was indicated by its association with CCR6, a chemokine receptor. Th17 cells appeared in the leprosy patients who showed non-polarised Th0 subset.[15] Therefore it would appear that Th17 plays a role in the immune responses to *M. leprae* infection and may be an alternate pathway for bacillary clearance both in the early and later stages of infection. The associated chemokines may help in its migration to lesional sites.

Both types of reactional leprosy patients showed an increase in Th17 cells in comparison to the non-reactional patients of the identical leprosy type, as attested by the presence of IL-17A and IL-17F in CD4+ cells.[18] There was a difference between the two reactions, in which the associated cytokine IL-21 showed an increase in ENL subjects and not in RR/Type 1 reaction subjects. In general, Type 1 reactions, seen more with borderline T-lep, showed higher expression of cytokines, cytokine receptors, and chemokines compared with ENL. The inflammation noted in lesions of leprosy reactions is not only due to IFN-γ of the Th1 subset but is also contributed to by IL-17, the signature cytokine of the Th17 subset. IL-17 is also detectable in the serum of healthy contacts and T-lep patients and may be useful as a surrogate marker for monitoring treatment response[19] and vaccine efficacy. IL-17 may also negatively regulate nerve growth factors and their receptors.[20] As these growth factors affect peripheral nerves, IL-17 may consequently contribute to the nerve damage characteristically associated with this disease. It is not clear whether Th17 cells reflect T cell plasticity or constitute a stable lineage as most studies on patients are undertaken at a single point during an ongoing clinical course. Thus, whether it is a rescue pathway or alternate defence mechanism needs further investigation.

FOXP3+ T REGULATORY CELLS

Another distinct lineage of T cells that has exciting implications for dampening inflammatory responses is the T regulatory cell (Treg), which has a CD4+CD25+ nuclear FOXP3+ phenotype and shares a similar differentiation pathway to Th17 cells, although they have opposite effects. They were first identified in murine models of autoimmune diseases[21] where they were shown to inhibit inflammatory responses. Since then, CD4+ Treg cells have been identified in humans,[22] in autoimmune diseases,[23] and in infectious diseases such as leishmaniasis[24] and tuberculosis.[25] Several types of Tregs have been described; some are natural Tregs derived from the thymus and act via contact with target cells.[26] Others are inducible and mediate inhibition through cytokines such as transforming growth factor-β (TGF-β) and IL-10 (induced Treg [iTreg]).[27] Transcription factor FOXP3 is thought to be the primary requirement for the suppressive function, though low and transient expression has been reported in activated human T cells with and without suppressor function. Though Tregs in mice express CD25 constitutively, in humans only those with $CD25^{hi}$ show suppressive function. Tregs revive the earlier concept of T suppressor cells in the 1970s and 1980s which was discarded when specific phenotypic markers could not be identified. The presence of T suppressor cells in L-lep patients was conflicting at that time. CD4+ or CD8+ populations of cells with inhibitory properties in *ex vivo* PBMCs derived from L-lep patients were reported by some[28] and refuted by others.[29]

The discovery of FOXP3+ Tregs has revived the quest for a cellular basis for the anergy noted in leprosy. Tregs have been shown by several studies to be enhanced in L-lep patients both in PBMCs

and in skin lesions.[17,30-34] Though unstimulated PBMCs in our study also showed an increase in $CD4^+$ Tregs, this was further enhanced by antigen stimulation, indicating recall responses. More importantly, TGF-β was associated only with $CD4^+$ and not $CD8^+$ cells. Furthermore, both $CD25^{hi}$ and $CD25^{low}$ cells showed divergence in the two types of leprosy with an increase in L-lep subjects. TGF-β required phosphorylation of the STAT5 transcription factor. Inflammatory cytokines IFN-γ or IL-17 were not detectable in $CD25^{hi}$ cells. It would appear therefore that Tregs play a significant role in L-lep and may downregulate antigen-specific T cell responses through TGF-β, and fall into the peripheral iTreg population. That TGF-β leads to facilitation and stability of FOXP3 through enhanced phosphorylation of SMAD3 and NFTAC was also shown in leprosy patients.[32] Some studies have implicated the increased interaction of nuclear FOXP3 with histone deacetylase and transcription regulation for the immune suppression noted with these cells.[33,34] This interaction downregulates gene expression of co-stimulatory CTLA-4, and may thereby inhibit T cell proliferation and cell-mediated immune responses to *M. leprae*. It has also been shown that macrophages infected with live *M. leprae* primed T cells towards $FOXP3^+$ Treg cell differentiation, and inhibited Th1 cytokines and $CD8^+$ cytotoxicity.[35]

Leprosy reactions in contrast showed a decrease in Treg cells which paralleled the increase in Th17 population.[18] Moreover, there was downregulation of intracellular TGF-β.[18,34] Most reports showed a reduction in Treg cells in patients with ENL reactions compared with non-reaction L-lep counterparts.[18,34] However, reports of patients with RR differed on the presence of Treg activity.[18,34] Recent evidence indicates that Th17 differentiation may be controlled by opposing roles of TGF-β and IL-6. Our studies indicated that monocyte-derived IL-6 may play a role in Th17 differentiation.[18] Thus, the inflammation associated with Th1 and Th17 cells in leprosy reactions may be due to the lowering of the dampening effects of iTreg cells.

Of interest is the finding that healthy contacts exposed to the disease had higher iTregs than those with T-lep, suggesting that early dampening of the immune responses may have a protective role.[18,35] However, this needs to be reconciled with the findings reported above of increased Th17 cells also seen in the healthy contacts of patients treated with chemotherapy.[16]

DIVERGENCE IN INNATE IMMUNITY AND SUBVERSION OF ACCESSORY CELLS BY MYCOBACTERIUM LEPRAE

Innate immunity is the first defence mechanism when a pathogen enters the host. Though there is overlap between the adaptive and innate immunity, several studies have shown differences in the latter which may contribute to the divergence in the clinical types of leprosy.[36] Macrophages and DCs play an important role in the recognition of the pathogen during innate immunity[37] as well as in triggering the adaptive immune system. The former has natural microbicidal ability that is further enhanced when primed by inflammatory cytokines such as IFN-γ and IL-17. *M. leprae* appears to subvert macrophage and Schwann cell functions in multiple ways. Foamy macrophages seen in skin lesions of L-lep inhibit bactericidal activity through phenolic glycolipid (PGE)2 of the pathogen, and have lipids that may provide a carbon source to promote mycobacterial proliferation.[38] Analysis of the *M. leprae* proteome shows the presence of fatty acid β-oxidation enzymes.[38] That lipid antigen may play a role was indicated in paucibacillary skin lesions of T-lep patients which showed enhanced CD1 proteins on $CD83^+$ DCs, whereas the bacilli-laden L-lep lesions showed an absence.[39]

Macrophages have opposing functions of both killing and promoting *M. leprae* proliferation in the two types of leprosy.[36,37] The M1 type of macrophages are pro-inflammatory and promote Th1 cytokine IFN-γ. On the other hand, M2 macrophages are anti-inflammatory, being associated with the Th2 cytokines IL-4, IL-10, and IL-13. L-lep monocytes were shown to be inhibitory for *in vitro* lymphoproliferation[29] through the release of factors such as PGE2, leukotrienes, and IL-10.[6] Live *M. leprae* infected macrophages of M2 type influenced Treg polarisation.[40] IL-10 and IL-15 are innate immune cytokines seen in leprosy lesions, with the former being associated with L-lep and the latter with T-lep. Though both cytokines enhance CD209 (C-type lectin) expression on monocytes, IL-10 promotes phagocytosis whereas IL-15 induces the vitamin D-dependent microbicidal pathway. The former pathway was prominent in the L-lep and the latter in the T-lep form of the disease.[37]

DCs are also key players in antigen presentation and play a major role in leprosy.[36,39] L-lep lesions have reduced DCs in skin lesions. B7-1, a co-stimulatory molecule, is reduced in L-lep lesions,[41] and

peripheral monocytes from L-lep patients fail to differentiate into CD1$^+$ DCs. It has been suggested that *M. leprae* interferes with DC differentiation, promotes host-derived oxidised phospholipids seen in the L-lep lesions,[38,42] and thus affects antigen presentation for effective T cell immunity.

Schwann cells are also host cells for *M. leprae* and appear to influence both innate and adaptive immune responses in leprosy. They have been implicated in the demyelination of peripheral nerves which is associated with this disease in the absence of immune cells,[43] by interacting with the PGE1 of *M. leprae*. Recent studies in a murine model have shown that *M. leprae* reprogrammes Schwann cells to a stage where they become migratory and promote the spread of infection directly or through recruited macrophages by releasing chemokines, cytokines, and growth factors.[44] Schwann cells have been shown to express CD209 and toll-like receptors (TLRs) in nerves of L-lep. Using Schwann cell lines, it was shown that CD209 and *M. leprae* binding was increased by Th2 cytokines IL-4 and IL-10, and not Th1 cytokine IFN-γ.[45]

Macrophages identify pathogens through pattern recognition receptors (PRRs) that recognise pathogen-associated molecular patterns present on the organisms. TLRs are PRRs on accessory cells which have been shown to interact with lipoproteins of mycobacteria and trigger host immune responses.[46] TLR2-TLR1 heterodimers lead to activation of macrophages, DCs, and *M. leprae* death.[47,48] They have also been observed in the Schwann cells of peripheral nerves. T-lep lesions show stronger expression of TLR1 and TLR2 compared to L-lep lesions.[48] Macrophage differentiation to DCs via NOD2 was dependent on IL-32, and showed improved antigen presentation to CD8$^+$ T cells.[49] Moreover, increased expression of nucleotide-binding oligomerisation domain containing protein 2 (NOD2) and IL-32 was seen in T-lep skin lesions. Major membrane protein II of the pathogen, a lipoprotein, triggered macrophages and DCs through TLR2;[47,50] such activation was enhanced by Th1 and inhibited by Th2 cytokines. Activation of TLR2/1 led to the production of inflammatory cytokine tumour necrosis factor-α as well as IL-12, promoting Th1 polarisation in the adaptive immune response.[48] TLR activation also results in granulocyte macrophage colony-stimulating factor (GM-CSF) release that expands DCs, releasing IL-15 which promotes macrophage differentiation.[48] TLR function in leprosy is regulated by cytokines. IFN-γ enhanced TLR1 expression, whereas IL-4 reduced TLR2 expression as well as cytokine release.[48] IL-10 on the other hand did not affect TLR2/1 expression but inhibited cytokine release. Phospholipids inhibited TLR2/1-induced IL-12, but not IL-10. TLR1, TLR2, and TLR4 have identified single nucleotide polymorphisms associated with the pathogenesis of leprosy, including protection against leprosy and Type 1 leprosy reactions.[51-53] Association of genes coding for host responses were reviewed recently.[53,54] DNA sensing via TLR9 was involved in ENL, in which the E6446 synthetic TLR9 antagonist inhibited pro-inflammatory cytokines.[55]

The antimicrobial effect of TLR engagement is independent of nitric oxide[50] and has been attributed to IL-15-dependent activation of vitamin D receptors with the induction of antimicrobial peptide cathelicidin.[37,55,56] Genes encoding the vitamin D pathway were differentially expressed in T-lep and L-lep lesions.[56] Moreover, miRNAs which have been shown to influence T cell differentiation, and activity of accessory cells has also been observed in leprosy. miRNA-21 seen in L-lep was shown to downregulate TLR2/1, upregulate IL-10, and inhibit vitamin D-dependent antimicrobial peptides.[57] *M. leprae* also upregulates expression of tryptophan aspartate coat protein (TACO) in macrophages[58] and downregulates TLR2-mediated signalling.[59] TACO has been shown in leprosy lesions as well as in *M. leprae* containing macrophages *in vitro*.

Another intracellular PRR present in macrophages is NOD2. Mycobacterial ligand binds to NOD2, resulting in activation and rapid differentiation of monocytes to CD1$^+$ DCs and requires IL-32. Such DCs are more efficient for priming CD8$^+$ T cells than the GM-CSF derived DCs. IL-32-secreting DCs are more prevalent among T-lep than L-lep patients.[37,49]

CONCLUSION

In summary, divergence in both innate and adaptive immune responses is notably distinct in restricted, compared to generalised, forms of leprosy. The innate immune cells may promote resistance or susceptibility to the disease, not only by confronting the pathogen but also by instructing an appropriate adaptive immune response. *M. leprae* escapes being killed by evading both types of host response in L-lep patients. The way in which it avoids or masks recognition, or promotes T cell plasticity to manoeuvre the immune response towards anergy, provides insights for understanding the pathogenesis of other infectious diseases as well as autoimmunity and cancers.

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RECONSTRUCTIVE OPTIONS FOR CUTANEOUS DEFECTS OF THE NOSE: A REVIEW

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ABSTRACT

Background: The face is the most common site affected by skin cancer in the body and of the facial skin it is the nose that bears the brunt of the attack.[1,2] Cancer resection results in the loss of a significant amount of tissue requiring replacement with either grafts or flaps in many cases. The expectation in nasal reconstruction, whether minor or major, is the restoration of symmetry, contour, colour match, and an overall pleasing result.

Objective: To review the various reconstructive options available for cutaneous defects of the nose following skin cancer resection and to describe outcomes associated with each.

Methods: A literature review was performed using PubMed, books, and websites. These were compiled to create a list of available options for the reconstruction of cutaneous defects on anatomical areas of the nose.

Results: Nasal reconstructive techniques have been evolving over centuries. With our advanced knowledge regarding blood supply and lessons learned from experiences, we have achieved a standard that offers excellent aesthetic results. The benefits and drawbacks of the common flaps are enunciated to provide a basis for decision making as to the best method to yield the optimum result in the reconstruction of cutaneous defects of the nose following resection of skin cancers.

Keywords: Skin cancer, nasal reconstruction, local flaps.

INTRODUCTION

The incidences of non-melanoma skin cancer and melanoma have been increasing over the past decades. Globally each year, there are 2–3 million recorded cases of non-melanoma skin cancer and 132,000 melanomas (as stated by the World Health Organization [WHO]).[3] A literature review compiling a list of available options for the reconstruction of cutaneous defects on anatomical areas of the nose was conducted using PubMed, books, and websites, in order to present the various reconstructive options available for cutaneous defects of the nose following skin cancer resection, and their outcomes.

BASAL CELL CARCINOMA

Basal cell carcinoma (BCC) is the most common type of skin cancer, with the sun-exposed areas of the head and neck the most frequently affected. This variety of cancer involves a slow growing tumour and metastasis is extremely rare. There are various effective topical and nonsurgical therapies available for low-risk BCCs. The factors influencing the prognosis of BCC are: tumour size, site, definition of clinical margins, histological subtype, features of aggression, recurrent lesions, and immunosuppression.[4]

Surgical Excision

Excision is widely used to treat both low and high-risk BCC, and is generally considered to have the lowest overall failure rate, based on the British Association of Dermatologists (BAD) guidelines. Surgical excision is a highly effective treatment for primary BCC with a recurrence rate of <2% reported 5 years following histologically complete excision in two different series.[5]

Mohs Micrographic Surgery

Pioneered by Frederic Mohs in the 1940s, this technique involves staged resection with immediate surgical margin examination.[6] This has the best cure rates; a retrospective review of 720 lesions gave an estimated 5-year cure rate of 98.8% for primary, and 93.3% for recurrent disease.[7]

Curettage and Cautery

This technique is also known as electrodessication. Curettage is a common form of treatment and is suitable for low-risk lesions.[8]

Cryosurgery

This method uses liquid nitrogen to cause deep destruction of BCC. Cryosurgery is most useful in the treatment of low-risk BCC[9] but also has a role in expert hands for high-risk lesions, especially following curettage.[10]

Topical Immunotherapy with Imiquimod

Topical imiquimod is approved by The European Medicines Agency (EMA) for the treatment of small BCC using the 5-times per week regimen for 6 weeks.[5]

Photodynamic Therapy

Topical photodynamic therapy using applied aminolevulinic acid or more recently methyl aminolevulinate, a more lipophilic methyl ester of aminolevulinic acid, is a good treatment for superficial BCC and a reasonable treatment for primary low-risk nodular BCC.

Radiotherapy

Radiotherapy (RT) is effective in the treatment of primary BCC[11] and can also be used in cases of recurrent BCC without previous RT.[12] In patients who are unwilling to have surgery or are unsuitable candidates for surgery, and have high-risk disease, RT is the treatment of choice.[11] RT is avoided, or used only with caution, in patients with basal cell nevus syndrome as it may promote the growth of new BCC.[13]

SQUAMOUS CELL CARCINOMA

This is the second most common form of skin cancer. It is locally invasive and has metastatic potential. Non-surgical therapies used include: topical imiquimod, intralesional interferon-α, intralesional 5-fluorouracil, and photodynamic therapy.

Surgical Excision

The standard treatment for squamous cell carcinoma (SCC) is surgical excision with predetermined margins. Well-defined tumours <2 cm are excised with a minimum 4 mm margin around the tumour, and high-risk lesions >2 cm in diameter are removed with a wider margin of ≥6 mm.[14] Surgery provides cure rates of 95%.[15]

Mohs Micrographic Surgery

This allows precise definition and excision of primary SCC but involves the long duration of the procedure, higher costs, and trained personnel, hence is considered only for areas where wide excision would result in significant functional impairment.

Curettage and Cautery

Small, slow-growing, well-differentiated SCC treated with this method show excellent cure rates in the hands of experienced physicians.[16]

Radiotherapy

RT can be considered as an alternative to surgery in inoperable SCC due to concomitant medical problems, a problematic location of SCC, or in the adjuvant setting.[17]

PRINCIPLES OF NASAL RECONSTRUCTION

The general principles for any reconstructive procedure apply to all nasal reconstruction procedures:

- Replace 'like with like'
- Consider aesthetic subunits
  - the nose consists of nine subunits: the dorsum, two lateral walls, two ala nasi, the tip, two soft triangles, and the columella
  - If the defect comprises >50% of the subunit, excising the remaining tissue and reconstructing the whole subunit gives an aesthetically pleasing result
- Compare all measurements with the opposite side to achieve symmetry
- Restore lining and support

The reconstructive methods available for simple cutaneous defects following tumour resection are considered based on the anatomical location.

SKIN GRAFTS AND LOCAL FLAPS

As the nose is the most prominent feature on the face, surgical management of skin cancer on the nose very often necessitates the need for reconstruction using either a skin graft or flap. Primary closure is possible only in very small defects on the dorsum and sidewalls of the nose.

Full Thickness Skin Grafts

Full thickness skin grafts taken from the post-auricular region or supraclavicular area provide the best match but are not suitable when the cartilage or bone is exposed, as the graft requires perichondrium or periosteum to be intact for 'take' of the graft to occur. It also does not provide the bulk needed to avoid contour defects. This is used as a common option due to ease of harvest of the graft, a good colour match of the skin, and the simplicity of the procedure. This procedure allows the retention of more characteristics of normal skin including colour, texture, and thickness, and undergoes less contraction while healing compared with split thickness grafts. For defects of the nose where both flap and graft repair may be technically possible, a flap is more likely to result in a superior cosmetic outcome.[18]

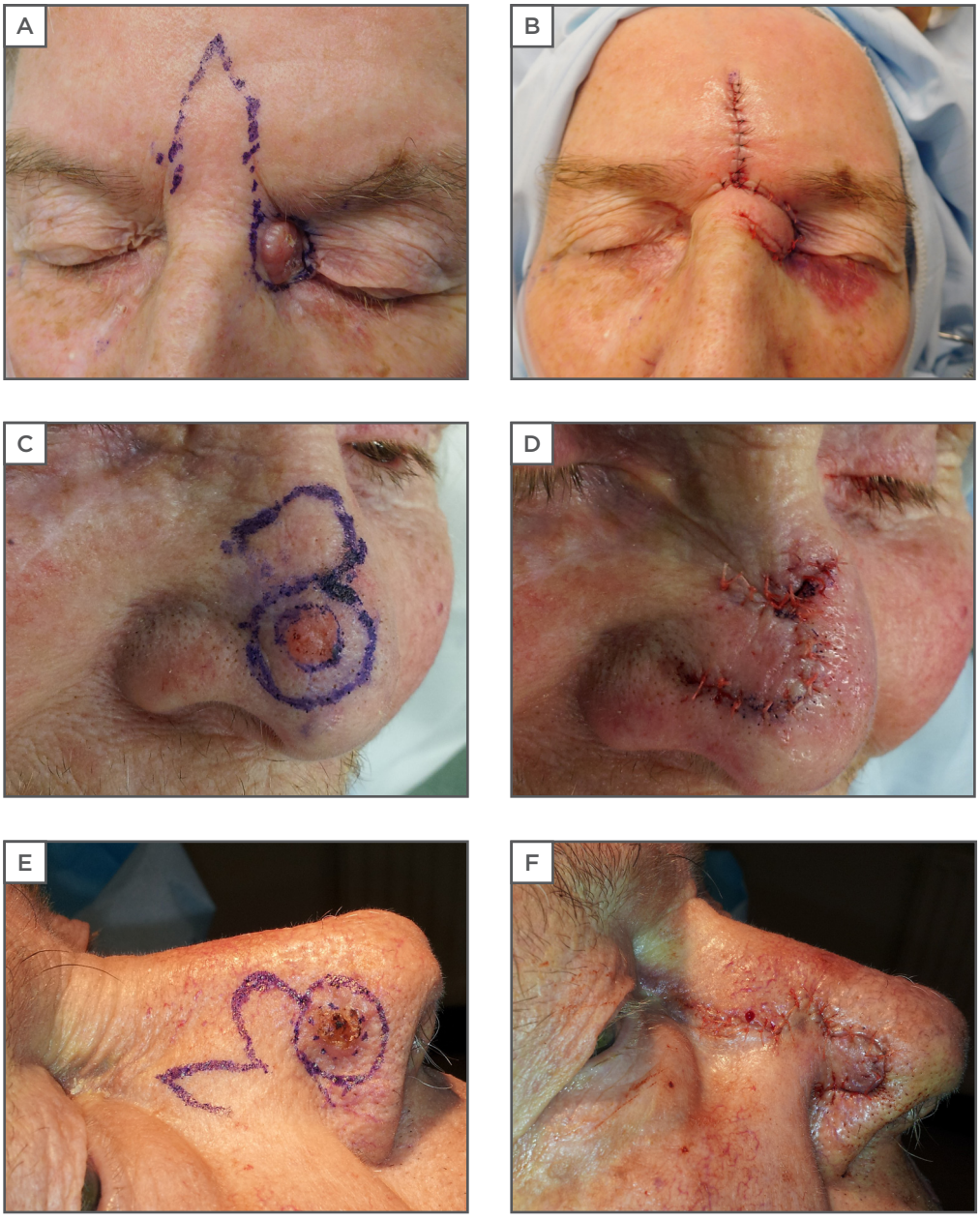

Figure 1: Glabella finger, bilobed, and banner flaps.
A, B) glabella finger flap; C, D) banner flap; E, F) bilobed flap.

Composite Skin Grafts

Composite skin grafts with superficial layers of subcutaneous tissue provide bulk for a better appearance. A composite graft from the helix including cartilage can be used for ala defect reconstruction. However, there are various simple flaps described in the literature that are as straightforward to do as a graft and provide a better appearance. Flaps are superior in terms of providing an accurate colour match and avoiding contour abnormalities.

The Local Flap

The various simple local flap options described in the literature for reconstruction of defects of the nose were reviewed. The earliest description of pedicled flaps for reconstruction of defects of the face and nose is by Sushruta in India in 600 BC.[19] In this account Sushruta described how a template was used to plan a flap for a defect. This is the earliest plastic surgical procedure recorded and hence Sushruta is called 'The Father of (Plastic) Surgery'.

The abundance of blood vessels on and around the nose provide the basis for the various flaps that can be used for reconstruction. The use of a flap follows the plastic surgical principle of replacing like with like. Local flaps are the most powerful reconstructive tools in the management of cutaneous nasal defects, providing a pleasing aesthetic outcome. In general, local flaps are used for reconstruction of nasal defects <1.5 cm in size. Park[20] describes defects >1.5 cm as large defects that are unlikely to be closed by simple local flaps. The donor site can be the nose itself, cheek, glabella, or forehead. Major and complex defects of the nose are beyond the scope of this discussion.

THE ROOT OF THE NOSE AND THE MEDIAL CANTHUS

The Glabellar Flap

The glabella is the area between the eyebrows where there is an adequate quantity of redundant skin to raise a flap and close the donor site directly. Usage of this skin was first described by von Grafe in 1818. The classic glabellar flap is a modification of a V-Y flap which is transposed into the defect; various modifications and variations have later been described. It can be transferred as a rotation flap, a transposition or an island flap, or through a combination of rotation and transposition. The author has noted that a transposition flap from the midline called a finger flap is the simplest to perform (Figure 1A, 1B). An island flap from this area with a subcutaneous pedicle does not have an added advantage and is more difficult to perform. The advantages of performing glabellar flaps include their robust blood supply and reliability to provide a good colour match. However, the thickness of the glabellar skin is more than that of the reconstructed area, causing it to look bulky. Additionally, there will be medial movement of the eyebrows as a result of direct closure.

A modification of the glabellar flap, termed the bipedicled flap, can be performed from this area based on either side and brought down to cover the defect and donor site closure by inferior advancement of the upper edge, described by Field.[21] A recent modification named the 'flap in flap technique' by Turgut et al.[22] involves an inverted V design with two flaps within; one transposed into the defect and the other advanced in a V-Y fashion.

LATERAL WALLS

The Note Flap

A note flap[23] is a very simple flap, ideal for this area; this is a straightforward triangular transposition flap. For a circular defect, two tangents are drawn parallel to the relaxed skin tension line. This provides four options for raising the note flap and the surgeon chooses the best option.

The Rhomboid Flap

The rhomboid flap is a very versatile flap which can be used in many parts of the body. It is suitable for most areas based on adjacent skin laxity. Limberg[24] first published the details of this flap and since then there have been various modifications published. Dufourmentel[25] modified the design in such a way that the pedicle width is widened. In the original Limberg design, the defect is converted into a rhomboid and the flap is designed as a parallelogram with angles of 120° and 60°; it is possible to raise four flaps from a single rhomboid (Figure 2A, 2B). The choice is made based on the area of maximum skin laxity and orientation of the skin tension lines. The defect from skin cancer excisions are usually circular. The rhomboid flap can be modified to close circular defects by mentally superimposing the rhombus onto the circle.[26] The main advantage of this technique is its versatility; the flap can be designed in various directions. However, it is a more complex

design and therefore there is wastage of the normal skin in trying to convert the circular defect to a rhomboid.

The Banner Flap

The banner flap is a transposition flap which can be used for small defects. Described by Masson and Mendelson,[27] the flap is designed by continuing the edge of the excision along a site of skin laxity on the nose (Figure 1C, 1D). According to the author, this is a very resourceful flap design for the nose and can be applied in different areas based on the direction of the skin laxity. It is extended slightly longer than needed and tapered down towards the end to facilitate closure. Elevation of the flap is carried out just above the nasal musculature, the flap trimmed to size, and inset. This is a simple flap that requires a simple technique however it is not suitable for the lower third of the nose as there is less tissue available. There is also a tendency for pin cushioning and dog ear formation.

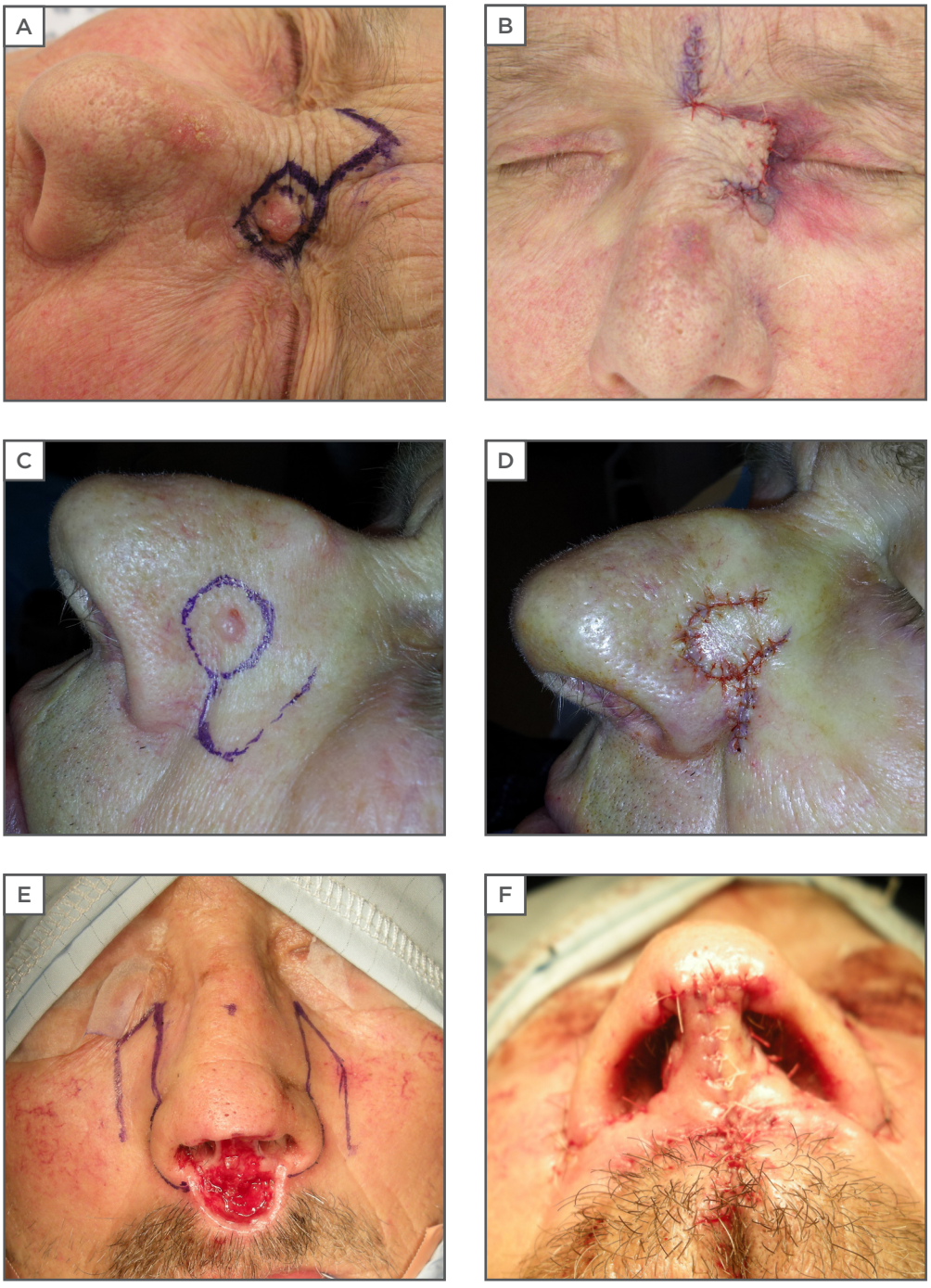

Figure 2: Rhomboid, nasolabial, and nasocheek flaps.
A, B) rhomboid flap; C, D) nasolabial flap; E, F) nasocheek flap.

The Bilobed Flap

This double transposition flap was first described by Esser in 1918.[28] Modification of the bilobed flap by Zitelli[29] made it an ingenuous technique for reconstruction of defects of the caudal aspect of the nose.[29] He reduced the pivotal angle from 180° to 90°, thus minimising donor site distortions which gives a good result (Figure 1E, 1F). Its use however is restricted by the site and size of the defect. Ideally these flaps are suited for small defects <1.5 cm on the distal third of the nose. The first flap is designed to be the same size as the defect at 45° to the defect and the second flap smaller than the defect at 45° to the first flap. The design can be modified according to the site of the defect as a 180° flap with the two flaps at 90° to each other. Wide undermining of both the donor and defect sites helps to avoid pin cushioning. A detailed description with pictures on the execution of this flap is given by Chu and Byrne.[30] This technique provides bulk in an area where skin and subcutaneous tissue is inherently thick and therefore its appropriate execution can give excellent results. It does carry several disadvantages including size limitation and distortion of the nasal tip, either elevation or notching, if used to reconstruct the extreme tip.

The Trilobed Flap

The trilobed flap[31] allows application of the principle of the bilobed flap for the reconstruction of defects of a wider range of sizes and locations. This technique is different from the bilobed flap in that it uses a third lobe. This tertiary flap is at 45° to the second flap and smaller.

The Dorsonasal Flap

The dorsonasal flap by Rieger[32] is a rotation advancement flap of dorsal and glabellar skin based superolaterally for defects of the middle and lower third of the nose (Figure 3A, 3B). It is elevated in a submuscular plane to protect the blood supply.

The Cheek Advancement Flap

These flaps are raised at the subdermal level and advanced to cover defects on a lateral aspect. This could cause a tenting effect on the medial cheek. The author uses a 5.0 polypropylene suture to anchor the dermis of the flap to the periosteum of the maxilla to maintain the contour of the nasocheek junction.

The Nasolabial Flap

This flap utilises the laxity of the nasolabial area to reconstruct defects of the side wall and lower third of the nose. The donor scar is easily hidden in the nasolabial fold. The colour match, proximity, and robust blood supply makes it a very appealing flap for reconstruction of nasal defects. Though it can be used for side wall, ala, and columella, it is best suited for the ala as the bulk recreates its natural shape. It can be designed as a transposition flap or as an island flap with subcutaneous pedicle. This is usually superiorly based (Figure 2C, 2D). When performed as a two-stage procedure, the pedicle division is usually done at 3 weeks.

The technique utilises the abundant tissue available adjacent to the nose where there is good vascularity. In addition, the donor site scar can be hidden in the nasolabial fold. However, it can cause distortion of the nasolabial sulcus and the bulk tissue can be excessive for side wall reconstruction. It has a tendency for trapdoor and pin cushioning and requires a staged procedure at times. Hair-bearing skin will be transferred to the nose if the flap is elevated low in male patients. The most common problem encountered by the author with the nasolabial flap initially has been the bulky appearance even for the ala; this has been solved by thinning the flap adequately at the time of harvest. It is safe to do so as this is a well vascularised flap.

THE ALA

The convexity and abundance of fibrofatty tissue in the ala nasi makes it a unique structure.

The Bilobed Flap

The bilobed flap can be used for reconstruction of small defects of the nasal ala.

The Nasolabial Flap

The ideal flap for ala reconstruction is the nasolabial flap as it can recreate the bulk and shape of the ala. Moreover, the tendency for pin cushioning delineates the ala subunit when used for whole subunit reconstruction. Though the ala has no cartilage, when reconstructing larger defects of the ala, a conchal cartilage graft is required as a framework to provide support and prevent collapse of the external nasal valve.

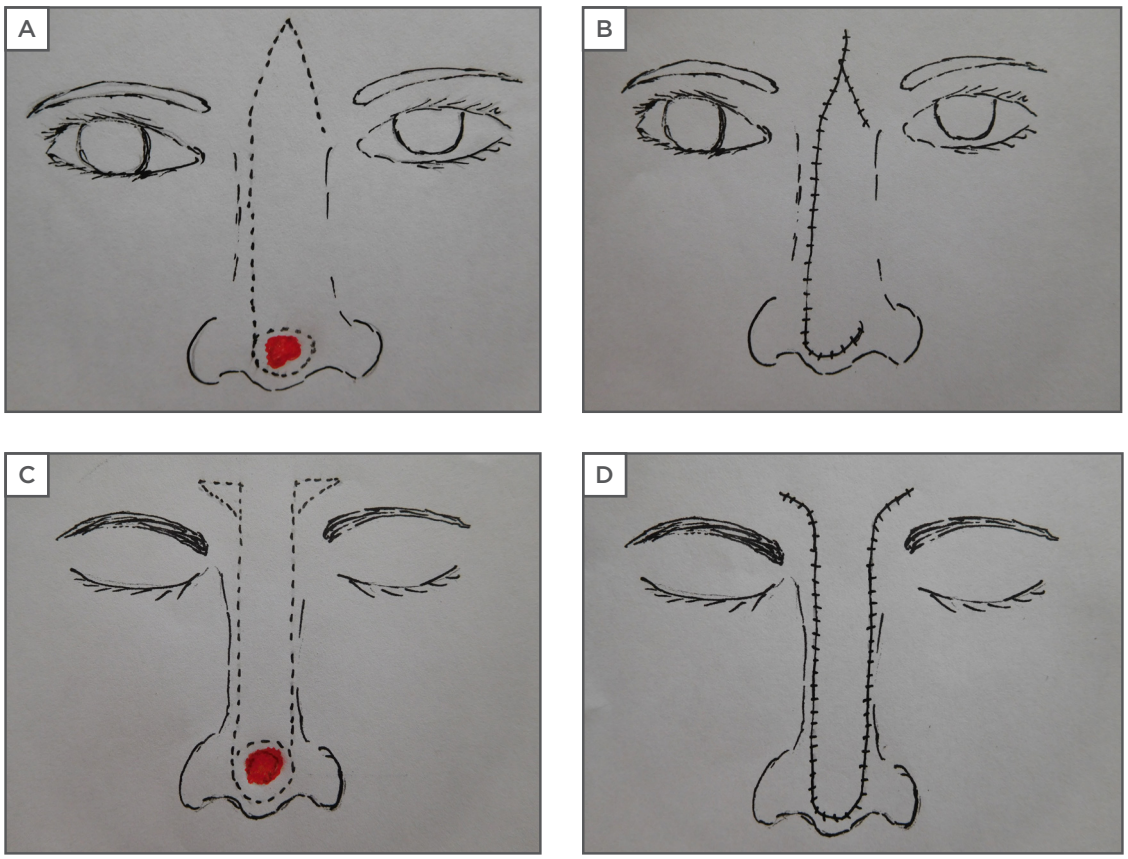

Figure 3: Dorsonasal and rintala flaps.
A, B) dorsonasal flap; C, D) rintala flap.

THE TIP AND SUPRATIP

The Banner and Bilobed Flaps

The banner flap and bilobed flap can be used for reconstruction of the tip. The bilobed flap is more suited for this region than the banner flap as the skin is thick and sebaceous, and transposition of a single flap can result in secondary distortion.

The Modified Nasalis Flap

The modified nasalis flap involves elevating bilateral transposition flaps from the lateral aspect of the defect on the tip.[33] An incision is made along the superior alar sulcus extending to the nasojugal fold and a back cut is then made in the nasojugal fold, parallel to the nasolabial fold. The flap is transposed in an anterior and caudal direction. This technique is a single-stage procedure and donor site scars are concealed, however alteration of the contour of the tip does occur.

The Rintala Flap

The rintala flap is a long advancement flap based on the mid forehead skin. Burrow's triangles (Figure 3C, 3D) are excised bilaterally lateral to the base of the flap.[34] A modification places the triangular resections above the medial canthus. Using this technique, like is replaced with like and the nasal skin itself is advanced, however, distal ischaemia and necrosis occur occasionally and the procedure does result in a slight shortening of the nose.

THE COLUMELLA

This is a complex area to reconstruct due to its position and anatomy.

The Nasolabial Flap

This requires a two-stage procedure for columella reconstruction as the position of the columella is distant to the donor area. Alternatively, a subcutaneous pedicle flap from the nasolabial area can be used but adds bulk in the route of transfer.

The Extended Abbe Flap

The extended abbe flap consists of an extension of the distal portion of the abbe flap over the chin

to create the neocolumella.[35] This is a two-stage procedure that can be used if the upper lip also requires reconstruction.

The Nasocheek Flap

The nasocheek flap, as described by Akbaş et al.,[36] utilises the skin of the nasojugal area to reconstruct the columella. This has the advantage that the thin and pliable skin of the nasojugal area allows good contouring. The addition of a strut of cartilage for columella support, as reported by the author (Figure 2E, 2F), gives an excellent result.[37] This is a simple, single-stage procedure with no donor site morbidity, however there can be collapse of the columella without cartilage support.

Elbaz' Flap

Tissue taken from the nostril edge based on the medial aspect; Elbaz' flap is useful in people with a broad nostril rim.[38]

The Forehead Flap

This flap is the workhorse for nasal reconstruction. This is called the 'Indian method' as the technique was practised by the Kumhar caste in India for nasal reconstruction as far back as 1,000 BC.[39,40] Even today, the forehead flap remains the gold standard for nasal reconstruction. A forehead flap is required when the defect is large, requires replacement of the support or lining, or is adversely located within the infratip or columella.[41] As this review is not on complex defects or complex procedures, details on the forehead flap are beyond the scope of this article.

CONCLUSION

There are several local flaps described for reconstruction of partial cutaneous defects of the nose. This article provides a review of some of the very useful and common surgical techniques used in the reconstruction of such defects. The decision on which flap to use depends on the site and size of the defect, skin type, sex, age, tobacco use, and surgeon's preference. Having a multitude of options in one's armamentarium helps to overcome the limitations associated with one or the other. Each case should be considered unique, and reconstruction tailored to fit the defect and patient expectations. The ultimate outcome of the procedure depends on careful assessment, accurate planning, and meticulous technique.

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THE MAIN NEONATAL DERMATOLOGICAL FINDINGS: A REVIEW

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ABSTRACT

Background: The neonatal period is a phase of adaptation during which several skin conditions can develop. Most of these findings characterise the newborn's skin, such as lanugo, erythema of the skin, and vernix caseous.

Objective: To describe the most common neonatal dermatological findings and classify them as transient neonatal skin conditions, congenital birthmarks, benign neonatal pustuloses, naevi lesions, and skin malformations.

Discussion: Skin changes are very common in neonates and span a vast range of conditions. This demonstrates the importance of good knowledge and awareness of newborn skin.

Keywords: Newborn (NB), skin diseases, neonatology, skin manifestations, neonatal dermatology.

INTRODUCTION

The neonatal period comprises the first 4 weeks of life. It is a period of adaptation during which several skin conditions can often occur, from temporary lesions caused by physiological responses, to others resulting from transient diseases, and some as markers of severe pathologies.[1-3] In their first days of life, newborn (NB) skin undergoes adaptation processes needed to accommodate the transition from the wet, aseptic, and homeostatic uterine environment to the dry atmosphere with temperature oscillation, surrounded by micro-organisms.[4] Some authors have studied the prevalence of dermatological findings on NB skin and how it differs among distinct racial groups.[5] It was found that >90% of NBs have some form of cutaneous manifestation and 84% have more than one single dermatological finding.[6,7]

NEWBORN SKIN CHARACTERISTICS

There are many important differences between adult, pre-term, post-term, and full-term skin (Table 1).[8,9] The functional difference between adult skin and that of NBs is due to the microstructure of the skin layers. The stratum corneum is thinner, the cohesion and adhesion of epidermal cells weaker, there is less melanin production, the pH of the skin is higher, and the skin surface area/weight is higher in NBs.[7,10,11] There is also major transepidermal water loss and a delay of the sudoral response which is believed to reflect the immaturity of the sympathetic nervous system. In the neonatal period, the most important function of the skin is thermoregulation and to act as a barrier against cutaneous infections.[12] The neonatal cutis is more likely to develop certain skin diseases, such as irritant contact dermatitis.[2,13]

NEONATAL DERMATOLOGICAL FINDINGS

The main dermatological findings in NBs include lesions that are benign, such as transient physiological dermatological phenomena, those from the neonatal period (vernix caseosa, lanugo, etc.), phenomena due to maternal hormonal status (gynaecomastia, genital hyperpigmentation), dermatological manifestation of systemic conditions, developmental anomalies, and neonatal vesicopustular lesions. For better didactic organisation, we have classified these as follows: physiological dermatological phenomena; phenomena due to hormonal status; dermatological

manifestations of systemic conditions; developmental anomalies; vascular anomalies; and neonatal vesicopustular lesions.

Physiological Dermatological Phenomena

These dermatological findings are found during the neonatal period itself and, most of the time, represent the neonate's skin. The main dermatological findings within this group are described below:

Lanugo

Lanugo occurs in approximately 40% of NBs.[14] It is a thin, soft layer of hair with little pigment and no medulla; it covers the NB skin and is more common and clearly seen in pre-terms. It is found on the dorsal trunk, shoulders, forehead, ears, and face of newborns. It should be considered in the differential diagnosis of congenital hypertrichosis lanuginose, a rare inherited disorder in which the lanugo is longer and darker.[12]

Vernix caseosa

This is an acidic lipid mantle produced by fetal sebaceous glands, composed of water (81%), lipids (19%), and protein (10%) naturally adhered to the NB skin.[15,16] Hydration of the skin tends to be higher in infants who remain with vernix caseosa and the pH and erythema of the skin tends to be lower than in neonates with their vernix removed. Its distribution across the NB skin depends on the gestational age, type of delivery, sex of the NB, race, and exposure to meconium. The majority of premature NBs lack this protective biofilm. In a previous study, maintaining or withdrawing the vernix caseosa using a bath showed no difference in the axillary temperature of the neonate.[17]

Erythema

Erythema is seen in around 19% of neonates.[14] It presents as bright red colouring all over the skin, usually seen within the first 24 hours of life. It occurs due to vasodilation of cutaneous capillaries, most likely caused by a decrease in sympathetic tone.[18]

Eyelid oedema

Observed in 17% of neonates within the first week of life, eyelid oedema occurs due to the increased pressure during birth, or due to the use of silver nitrate, and lasts 3–4 days.[14]

Milia

One of the most common transient skin conditions in neonates, milia presents in up to 30–50% of neonates. The milia consist of 1–2 mm yellow papules on the face, localised predominantly to the nose. It represents epidermal keratin cysts developing in connection with pilosebaceous follicles. When these cysts are seen on the palate, they are termed Epstein pearls and when on the alveolar margins, they are termed Bohn's nodules.[19] No treatment is required for neonatal milia as these spontaneously resolve within a few weeks. Extensive, persistent, and uncommon locations require attention, because this could be a manifestation of Marie Unna hereditary hypotrichosis, orofacial-digital syndrome Type I, Basan syndrome, or X-linked Bazex–Dupré–Christol disease.[20]

Desquamation

Desquamation is also a characteristic of NB skin and is one of the most common cutaneous findings in the neonatal period; it has been reported to occur in 12–65% of neonates.[14] Along with sebaceous hyperplasia, this shows a significant correlation with maturity; desquamation is more prevalent in post-terms and sebaceous hyperplasia in full-terms.[1]

Table 1: Findings of newborn skin compared to that of adults.

Barrier function	Weaker than that of adults
Hydration	The lowest level of hydration is seen at/soon after birth
TEWL	High values of TEWL are observed immediately after birth; TEWL values are higher in preterm infants compared to full-term
pH	The most alkaline at/soon after birth, ranging from 6.34–7.5
Sebum production	Vernix caseosa (*in utero*); low levels after birth until puberty
Blood flow	Capillaries fully developed at 14–17 weeks after birth

TEWL: transepidermal water loss.

Suction blisters

Suction blisters are induced by vigorous oral suction of a portion of the body while the baby is still in the uterus. They are observed in 0.5% of NBs and are characterised by oval blisters or erosions which mainly affect the back of the hands, fingers, forearms, and lips.[21] Other authors have reported that suction blisters account for approximately 4.5% of neonatal vesiculobullous injuries (Figure 1).[22]

Caput succedaneum

This is a localised swelling on the scalp of infants that occurs due to the pressure of delivery. It is related to venous congestion and oedema resulting from the pressure of the cervix and is more prevalent in NBs of prolonged vaginal delivery and primigravida.[7] Unlike with cephalhaematoma, caput succedaneum lesions often cross the midline and resolve spontaneously within 48 hours. Cephalhaematoma lesions do not cross the midline and are limited to a cranial bone (Figure 1).[21]

Mongolian spot or congenital dermal melanocytosis

A Mongolian spot or congenital dermal melanocytosis is a congenital birthmark with a collection of dermal melanocytes. It is clinically seen as a large macular lesion located over the lumbosacral area, buttocks, and occasionally the back, flanks, and shoulders of infants (Figure 1). It has been observed in 80–90% of black NBs, 91% of Asian children, 25% of NBs in Southern Brazil, and 20% of NBs within the USA.[12,23-27] Congenital dermal melanocytosis usually disappears at around 4 years of age, but may persist; it depends mainly on any destruction that occurs within the protective extracellular fibrous sheath that covers the dermal melanocytes, and due to growth factors, the regulation in melanocyte proliferation, and genetic factors.[5,28] Large and numerous congenital dermal melanocytosis lesions may be seen in lysosomal storage disorders, among them, Gangliosidosis Type 1 and Hunter and Hurler syndromes.[29] Large and persistent Mongolian spots can be seen in phakomatosis pigmentovascularis in association with vascular malformations.[30]

Cutis marmorata

This is a physiological change evidenced by reticulated patches caused by dilation of capillaries and venules. It usually appears when the infant is exposed to low temperatures and disappears with heating, corresponding to an overreaction to hypothermia. It can last minutes to hours, both in premature infants and full-term NBs. Physiological marmorata cutis should be distinguishable from cutis marmorata telangiectatica congenita (which is a persistent vascular anomaly due to capillary malformation) and from reticular livedo (which can be observed in infants with neonatal lupus).[12]

Harlequin colour change

Harlequin colour change is benign, uncommon, and often observed in pre-term infants.[27] It exhibits a sudden, brief change of skin colour, bordered on the midline, in which half of the body presents erythema and the other half pallor. Of unknown aetiology, this change in colour is believed to occur due to immaturity of the hypothalamic control of peripheral vascular tone.[31]

Miliaria

Miliaria rubra and crystalllina are both very common within the neonatal period and are caused by the obstruction of the exit of eccrine sweat from the gland ducts of the corneum stratum, with the subsequent retention of sweat. Miliaria rubra usually occurs in the second week of life and is characterised particularly by non-follicular erythematous papules, mainly in the intertriginous areas.[32]

Phenomena Due to Hormonal Status

Certain phenomena can occur mainly due to the passage of maternal and placental hormones. Most of the time, these are reversible.

Miniature puberty

Exhibiting changes that are similar during pregnancy and puberty, this may be observed as hyperpigmentation of the areola, the linea alba, and the external genitals. When this is accompanied by thickening and desquamation of the labia majora, with whitish or bloody discharge, it shows miniature puberty.[12]

Genital hyperpigmentation

Physiological melanic pigmentation fades away around the age of 2 years. It is seen in 19% of the NB population, and occurs at a higher rate in black skin.[14]

Neonatal acne

Facial inflammatory acne lesions, rash, and comedones can develop during the neonatal period.

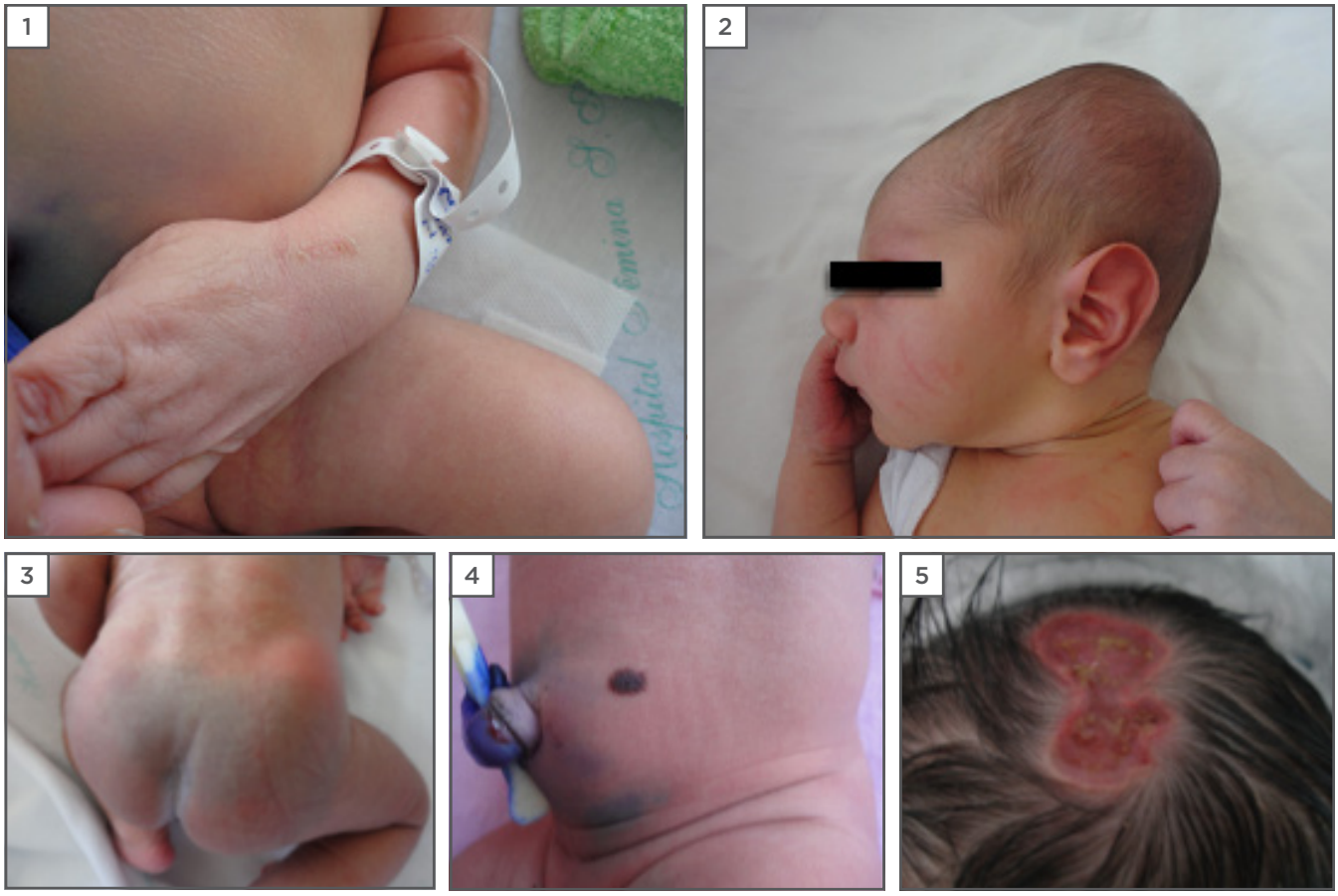

Figure 1: Paediatric dermatological findings presented at/shortly after birth.
1) Suction blisters on the hand; 2) caput succedaneaum; 3) Mongolian spot; 4) congenital naevus; 5) aplasia cutis congenita.

Hyperactivity of sebaceous glands and the stimulation of neonatal androgens are implicated in its pathogenesis.[33] There is controversy over what truly represents neonatal acne, and pustular-papular conditions, characteristically without comedones, such as benign cephalic pustulosis (BCP) are characteristic of the neonatal period.[34] Some authors consider BCP a neonatal acne variant caused by hypersensitivity to *Malassezia furfur*.[30,35] Despite being a transient injury of the neonatal period, in some cases it may be present through the first months of life.[21]

Sebaceous hyperplasia

Sebaceous hyperplasia is a physiological manifestation of the NB period with a prevalence of 35–42.6%.[24] It occurs in response to maternal androgen stimuli; this declines in the first trimester and only rises again during puberty.[36]

Dermatological Manifestations of Systemic Conditions

Jaundice

This occurs due to the immature liver's inability to process excess bilirubin. In the skin, it reveals as a yellowish hue. Neonatal jaundice can be observed in ≤60% of term and 80% of premature NBs; the peak of incidence is after the third day of life and its intensity decreases progressively. It is important to differentiate this condition from non-physiological causes of jaundice.[12]

Infections

Many skin disorders presenting at or soon after birth can mimic infectious diseases. Pustules on NB skin can indicate a congenital or non-congenital infection. The infection cannot be diagnosed on the cutaneous symptom itself; it depends on other signs such as muscular tone, hepatosplenomegaly, organ-specific deficit, and the general appearance of the NB.[37,38]

Developmental Anomalies

Some anomalies in development can occur in the skin and this is observed throughout the neonatal period. Usually, these involve the head, nose, pre-auricular region, cervix, or spine, some in more than one location. Those that occur in the midline, especially involving the head, the nose, and the spine, can be more severe because of possible connections to the central nervous system.[39]

Congenital melanocytic naevi

Congenital melanocytic naevi are a specific type of pigmentary lesion that consists of the proliferation of nested melanocytic cells or naevi cells of neural origin. Approximately 1% of NBs have a congenital melanocytic naevus;[31] American authors have reported an incidence of 2.4%.[24] The risk of evolution to neurocutaneous melanosis or melanoma depends on its location and size (Figure 1).[40]

Naevus sebaceous

Naevus sebaceous consists of an epidermal naevus whose main component is sebaceous glands. The sebaceous naevus is an uncommon birthmark, seen in 0.3% of NBs.[25] It is usually a single lesion, well defined, round, oval, or linear with a yellowish-pink colour, located on the scalp, face, or neck leather. There are three roots of these naevi: sebaceous glands stimulated by maternal androgen (at birth), those without a local stimulus, and sebaceous glands stimulated during puberty and gland enlargement.

Naevus achromicus or naevus depigmentosus

This presents as a hypopigmented spot, usually small and oval, but can also be extensive and follow the lines of Blaschko on the skin. These persist indefinitely and are more visible in the summer months and in patients with darker skin pigmentation.[12] A differential diagnosis must include conditions such as naevus anemicus, ash-leaf spots, and vitiligo.[41]

Cephalocoele

This condition involves the protrusion of intracranial structures through a defect in the skull and is due to abnormal separation of the neuroectoderma from the ectoderm in the beginning of pregnancy. Cephalocoele is clinically characterised by a bluish compressible mass, usually located in the occipital region.[39]

Dermoid cysts

Dermoid cysts are characterised by smooth nodules that are non-compressible, skin coloured, and usually located in the occipital region, nasal dorsum, and spinal cord. It can cause infection and/or meningitis if there is communication with the central nervous system.[39]

Aplasia cutis congenita

Aplasia cutis congentia presents as an absence or thinning of the epidermis, dermis, and subcutaneous tissue; it affects 3 in every 1,000 NBs.[39] It can be present as single or multiple lesions, alone or associated with other malformations, and most often affects the vertex of the scalp. According to clinical presentation, it can be divided into: aplasia cutis membranous, aplasia cutis irregular or stellate (usually non-membranous), aplasia cutis associated with embryonic alterations of internal organs, and aplasia with congenital absence of the skin (Figure 1).[12]

Amniotic constriction band

These are constricting rings that can affect the fingers, the extremities, and rarely, the cervical and trunk area; it is uncommon, occurring in 1 in 10,000 NBs.[39] It is generally sporadic, although familial cases have been reported. It is believed that this anomaly is the result of an early rupture of the amnion where the amniotic liquid is leaked, leading to introduction of the fetus within the chorionic cavity. The corium and the reabsorbed fluid stimulate the proliferation of mesodermal bands that compress the fetal structures.[28]

Accessory tragi

This is a small papule, skin coloured, and located in the pre-auricular region which may be unilateral or bilateral. In most cases, it is not associated with any other anomalies.[39]

Adnexal polyp

Adnexal polyps are congenital and benign neoformations, usually solitary, about 1 mm in diameter, skin-coloured or slightly darker; they are located around the nipples. These resolve spontaneously, usually within 4 weeks of birth.[42]

Ichthyosis

A rare genetic disorder of epidermal cornification, this is rarely associated with any other syndrome,

but could be a manifestation of Netherton syndrome or Refsum disease. Clinically seen as epidermal thickening, scaling, and cutaneous inflammation,[43,44] it can be preceded at birth as a collodion baby, referring to a membrane covering the NB skin with variable degrees of ichthyosiform erythroderma, with or without superficial blisters.[45] At birth the most common types are X-linked recessive ichthyosis, lamellar ichthyosis, and bullous congenital ichthyosiform erythroderma. The harlequin ichthyosis is the most rare and severe type of lamellar ichthyosis, with high mortality rates.[46]

Vascular Anomalies

Vascular anomalies can be classified into vascular tumours (benign, aggressive/borderline, and malignant) and vascular malformations including simple, combined, or major vessels, and those associated with other anomalies.[47]

Salmon patch or naevus simplex

This is the most common small cutaneous capillary malformation.[47] The salmon patch occurs in 70% of white NB skin and 59% of black NB skin, most often located on the glabella (angel kiss) and neck (stork bite).[5] A recent prospective study reported the presence of salmon patch in 83% of NBs within 48 hours of life.[21] It fades in the first 2 years, however it can persist in rare cases.[48]

Naevus flammeus or port wine stain

Naevus flammeus is also a cutaneous/mucosa capillary malformation and can be associated with an underlying syndrome such as Sturge–Weber. It occurs in about 3 in 1,000 individuals.[49]

Neonatal Vesicopustular Lesions

Neonatal vesicopustular lesions are described as non-infectious or sterile pustules presenting within the neonatal period. They are benign cutaneous findings, self-limited, asymptomatic, and only occur during this period of time.[37]

Erythema toxicum neonatorum

Erythema toxicum neonatorum (ETN) develops as small erythematous papules, sterile vesicles, and pustules affecting the trunk, the extremities, and the face. Lesions usually appear on the second day of life and regress in 5–14 days.[50,51] ETN can affect 30–70% of NBs, most of them born at term.[52] The frequency of ETN may increase with increasing gestational age.[53] Studies show that in full-term neonates its prevalence ranges from 30–50%, yet is only seen in 5% of pre-terms, with no statistically significant change in different races or sexes.[28] It has recently been highlighted that there is activation of immune cells within the ETN lesions, suggesting an inflammatory reaction to the skin's microbial colonisation at birth.[51] The Tzanck test, conducted on a pustule, revealed the presence of eosinophils. In a prospective study, ETN was observed in 25.3% of NBs and was more prevalent in males.[54] In 84.2% of allergic manifestations during the first 2 years of life, previous ETN or low pH was observed at birth; atopic dermatitis occurred in 85.7% of patients with previous ETN.[54]

Transient neonatal pustular melanosis

TNPM is presented at birth by flaccid and superficial pustules that break easily, forming a collaret scale and evolving into hyperpigmented macules of residual character. It occurs in 5% of black-skinned NBs and in <1% of white-skinned NBs.[32] All areas of the body can be affected, including the palm and soles. Hyperpigmented macules with vesicopustules are characteristic of TNPM.[55] Examination of the pustules using the Tzanck test showed the presence of polymorphonuclear neutrophils.[54]

Benign cephalic pustulosis

The cause of this neonatal skin colonisation by *Malassezia spp*. and the appearance of neonatal cephalic pustulosis in neonatal acne eruptions is uncertain. Authors have shown that colonisation increases significantly with the age of the neonate (5% in the first week, 30% from the second to the fourth weeks of life). Recent publications show that, although the skin colonisation increases after the first week of life, there was no correlation between cephalic pustulosis neonatal and *Malassezia spp*.[56]

CONCLUSION

The aim of this article was to provide a review of the main neonatal dermatological findings. NB skin is unique not only for its structure, but also its dynamics with the surrounding environment. Some of the knowledge about structural and physiological NB skin has changed over the years; we emphasise that the weaker barrier function is due to the immature cells and its cohesions. We reported some of the most common NB skin findings within the literature thus far by classifying them in a more didactical way. Earlier studies

reported different routes of pathogenesis from the ones we now see, such as with BCP and the *Malassezia spp*. With regard to this scenario, we have seen the evolution of neonatal dermatology, and we look forward with a hope to contribute new findings within this vast area.

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SKIN MANIFESTATIONS ASSOCIATED WITH BRUCELLOSIS

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ABSTRACT

Brucellosis is a zoonotic infectious disease of worldwide distribution and is still endemic in some developing countries. Brucellosis is a systemic disease in which any organ or system of the body can be involved. The most commonly affected systems are the locomotor, gastrointestinal, genitourinary, haematological, cardiovascular, respiratory, and central nervous systems. Cutaneous manifestations are rare in brucellosis and the lesions are not specific to the disease. Skin involvement is reported to range between 0.4% and 17.0% of the patients with brucellosis. The cutaneous manifestations in brucellosis are seen because of the direct inoculation of bacteria into the skin, hypersensitivity phenomena, deposition of immune complexes in the skin, and invasion of the skin via a haematogenous route of spread of the micro-organism. Papulonodular and maculopapular eruptions, and erythema nodosum-like lesions are the most frequently encountered cutaneous lesions in brucellosis. Brucellosis should be kept in mind by clinicians in the diagnosis of patients with complaints of fever and eruptions, especially in endemic regions.

Keywords: Brucellosis, cutaneous manifestations.

INTRODUCTION

Brucellosis is a zoonotic infectious disease of worldwide distribution, it is still endemic in some developing countries and it causes substantial morbidity in both human and animal populations. Major endemic areas are the Mediterranean Basin, Persian Gulf, Indian mainland, Mexico, and Central and South America.[1-4] The disease is also a major cause of public health problems and economic loss in many developing countries. *Brucella melitensis* infection causes a serious public health problem in bovines in some countries. A similar condition is observed in cattle with *Brucella suis* biovar 1 in South American countries.[4] Brucellosis commonly affects sheep, goats, cattle, water buffalo, and pigs, and it is transmitted directly or indirectly to humans from these animals. Among the Brucella species which are causative agents of disease in humans, *B. melitensis* leads to disease principally in sheep and goats, *Brucella abortus* in cattle and water buffalo, *B. suis* biovar 1–3 in pigs and *B. suis* biovar 4 in deer.[1,5] The principal pathogenic species of Brucella worldwide are *B. abortus*, *B. melitensis*, and *B. suis*. These three types of Brucella strains lead to great economic loss, usually by causing abortion in animals and they are also causative agents in most brucellosis cases in humans.

Brucella bacteria are found in urine, milk, placenta, and other animal bodily secretions.[1,5] Humans generally acquire the disease by consuming foods such as unpasteurised milk (e.g. cream, butter, ice cream), cheese, and undercooked meat from the infected animal. Humans may also acquire the disease through coming into conjunctival contact with secretions of infected animals via non-intact skin lesions in their hands and arms and inhalation of infected aerosols.[1,6-8]

Brucellosis is a systemic disease in which any organ or system of the body can be involved.[1,9] The most commonly affected systems are the locomotor, gastrointestinal, genitourinary, haematological, cardiovascular, respiratory, and central nervous systems.[10] Infection can be manifested by local or systemic symptoms. Localised infection can be seen in approximately 27.7–43.2% of patients. When localised infection is seen as a result of systemic infection, it can also be called a complication. It can be observed in acute, subacute, and chronic infections.[1,2,10-17] Skin involvement observed in patients with brucellosis was described in 1940.[18] Skin involvement is reported to range between 0.4% and 17.0%.[2,10,13,16-31] It is rare and the lesions are not specific to brucellosis.[19] Due to its non-specific nature and rarity, in this review we evaluate misdiagnosed skin involvement associated with brucellosis and raise awareness about this manifestation of brucellosis.

PATHOGENESIS

The cutaneous manifestations in brucellosis are seen because of direct inoculation of the bacteria into the skin, hypersensitivity phenomena, deposition of immune complexes in the skin, and invasion of the skin via a haematogenous route of spread of the micro-organism.[32] Skin lesions can be seen because of a direct effect of microbial replication, host response to bacteria, or interaction between them.[33] The invasion of skin via a haematogenous route of spread of Brucella bacteria is the most important underlying pathological mechanism of cutaneous lesions. Direct invasion of the skin by the bacteria reaching the skin through the haematogenous route and endotoxins released from the bacteria may explain the effect during the acute phase of the disease. Hypersensitivity phenomena, deposition of immune complexes in the skin, and granuloma formation may cause the cutaneous manifestations observed during the chronic phase of the disease.[18,19,34]

Table 1: Study abstracts of cutaneous manifestations associated with brucellosis.

Author	Patients with brucellosis (n)	Patients with skin lesion (n [%])	Cutaneous lesions (n [%])
Ariza et al.[18]	436	27 (6)	Disseminated 20 (71) papulonodular eruption Erythema nodosum-like lesions 3 (11) Diffuse maculopapular rash 3 (11) Extensive purpura 2 (7)
Artuz et al.[35]	50	6 (12)	Erythema 4 (66.6) nodosum-like lesions Diffuse maculopapular rash 2 (33.3)
Metin et al.[32]	103	14 (13.6)	Urticaria-like papules 5 (35.3) Erythema 3 (21.43) nodosum-like lesion Primary inoculation abscess 1 (7.14) Psoriasiform lesion 1 (7.14) Palmar erythema 1 (7.14) Urticaria-like papule + erythema nodosum-like lesion 1 (7.14) Malar eruption + psoriasiform lesion + livedo reticularis 1 (7.14) Malar 1 (7.14) eruption + eczematous lesion
Akcali et al.[37]	140	8 (5.71)	Maculopapular eruptions 2 (25) Erythema nodosum-like lesion 2 (25) Psoriasiform lesion 1 (12.5) Palmar erythema 1 (12.5) Malar eruption 1 (12.5) Palmar eczema 1 (12.5)
Turunc et al.[25]	447	8 (1.8)	Maculopapular eruptions 2 (28.5) Erythema nodosum-like lesion 1 (14.3) Psoriasiform lesion 1 (14.3) Palmar erythema 1 (14.3) Malar eruption 1 (14.3) Palmar eczema 1 (14.3)

Table 2: Summary of skin lesions associated with brucellosis.

Most frequent skin lesions associated with brucellosis
• Papulonodular lesions • Erythema nodosum-like lesions • Maculopapular eruptions • Petechiae, purpura • Contact urticaria
Rare skin lesions associated with brucellosis
• Vasculitic lesions • Subcutaneous abscesses • Chronic ulcerations • Liquefactive panniculitis • Recurrent epidermal cyst • Palmar erythema • Livedo reticularis

THE CUTANEOUS LESIONS OBSERVED DURING THE COURSE OF BRUCELLOSIS

There are a limited number of studies evaluating the cutaneous lesions associated with brucellosis. Relevant studies and the most frequently observed cutaneous lesions are shown in Table 1. When the studies performed were evaluated, it was seen that papulonodular and maculopapular eruptions and erythema nodosum-like lesions were the most frequently encountered cutaneous lesions in brucellosis and they were located on the trunk and lower extremities in most of the patients.[1,21,22,24,25,27,32,35,36] The cutaneous manifestations of brucellosis are summarised in Table 2.

DISSEMINATED PAPULONODULAR LESIONS

It has been observed that disseminated papulonodular lesions accounted for approximately 32% of the cases in the studies examining cutaneous manifestations in brucellosis.[18,25,32,35,37] Disseminated papulonodular lesions have a smooth surface, they are erythematous, and they are frequently seen on the upper trunk, shoulders, and thighs, and especially the lower legs. Skin lesions were non-pruritic with their sizes ranging from a few millimetres to >1 cm. There were central ulcerations in some lesions. Brucella bacteria were isolated from some cultures performed from papulonodular lesions. This suggests that these lesions were caused by the haematogenous route of spread of the micro-organism during the bacteremic phase of the disease. When disseminated papulonodular lesions were evaluated histologically, it was observed that there was an inflammatory process consisting of perivascular and periadnexial regions localised principally in the dermis and a granuloma structure. The same granulomatous findings were also discovered in erythema nodosum-like lesions, which were another frequently encountered lesion. It is believed that both lesions develop as a result of a similar pathogenetic mechanism.[18,38,39]

ERYTHEMA NODOSUM-LIKE LESIONS

Erythema nodosum-like lesions account for 25% of the cutaneous lesions associated with brucellosis. Erythema nodosum-like lesions develop due to hypersensitivity phenomena or involvement of the panniculus because of the haematogenous route of spread of the micro-organism. The cutaneous lesions associated with brucellosis are characterised by multiple erythematous nodules and located on the extensor surfaces of the lower legs. Lesions are usually painless. While these lesions are clinically similar to erythema nodosum, they are histologically different from the classical erythema nodosum. There is no deep dermal tissue inflammation or invasion of fat lobules in erythema nodosum. Additionally, plasma cells and necrosis seen in erythema nodosum-like lesions associated with brucellosis are not observed.[18,19,37,38]

MACULOPAPULAR ERUPTION

The pathogenesis of maculopapular eruption is not known. Although involvement is widespread in diffuse maculopapular eruption, the lower extremities are especially affected. There is no pruritus of the skin. While no previous drug use has been reported in most of the cases, drug reaction should be necessarily excluded in diffuse maculopapular eruption.[18,35]

VASCULITIC LESIONS

Vasculitic lesions associated with brucellosis were reported as case presentations (Figure 1).[40-50] Yrivarren and Lopez[41] described cryoglobulinaemia and cutaneous vasculitis in three patients with brucellosis. Hermida Lazcano et al.[42] reported a case with renal failure, cutaneous vasculitis, and peritonitis due to brucellosis and they concluded that the entire clinical picture (renal, hepatic, and cutaneous) was mediated and/or caused by cryoglobulins. Dizbay et al.[43]

determined hypocomplementaemia, increased levels of polyclonal immunoglobulins, positivity of rheumatoid factor, and perinuclear anti-neutrophil cytoplasmic antibodies in their patients with renal failure and leukocytoclastic vasculitis due to brucellosis; the authors stated that they thought that this picture was caused by mixed cryoglobulinaemia. In general, it is considered that immunological mechanisms play a role in the pathogenesis of these lesions.[32]

ALLERGIC LESIONS

A hypersensitivity reaction may also cause the cutaneous lesions observed in brucellosis. While the relationship between lesions and hypersensitive reactions could not be described exactly, cases of allergic vasculitis are reported.[46-48] Contact urticaria is an erythematous eruption observed in veterinary physicians and pet-sitters. Eruption begins with pruritus and erythema in the upper extremities within a few hours after exposure, sometimes face and neck may be involved, and the lesion improves approximately within 2 weeks.[38] Trunnell et al.[49] suggested that the pathogenetic mechanism causing contact urticaria could be an allergic hypersensitivity reaction.

OTHER LESIONS

Multiple cutaneous and subcutaneous abscesses and chronic ulcerations have been described in brucellosis patients with high occupational exposure risk.[50,51] Additionally, purpuric eruptions associated with coagulation disorders can also be seen in brucellosis patients.[18,52,53] Vaccination is effective in cattle. However, live animal vaccines may cause disease in humans.[4] Also, the occurrence of local reactions (swelling, redness, pain) and deep dermal nodules due to the Brucella toxin after accidental inoculation of the Brucella vaccine was reported.[54]

CLINICAL CHARACTERISTICS

The cutaneous lesions associated with brucellosis can be seen in every phase of the disease. In a study performed by Metin et al.,[32] 103 brucellosis cases were evaluated and skin involvement was determined in 14 (13.59%) of these patients. In this study, the cutaneous lesions occurred in chronic, acute, and subacute phases of the disease in 50.0%, 35.7%, and 14.2% of the patients, respectively. In a study performed by Akcali et al.,[37] 140 brucellosis cases were evaluated and skin involvement was determined in 8 (5.71%) of these patients.

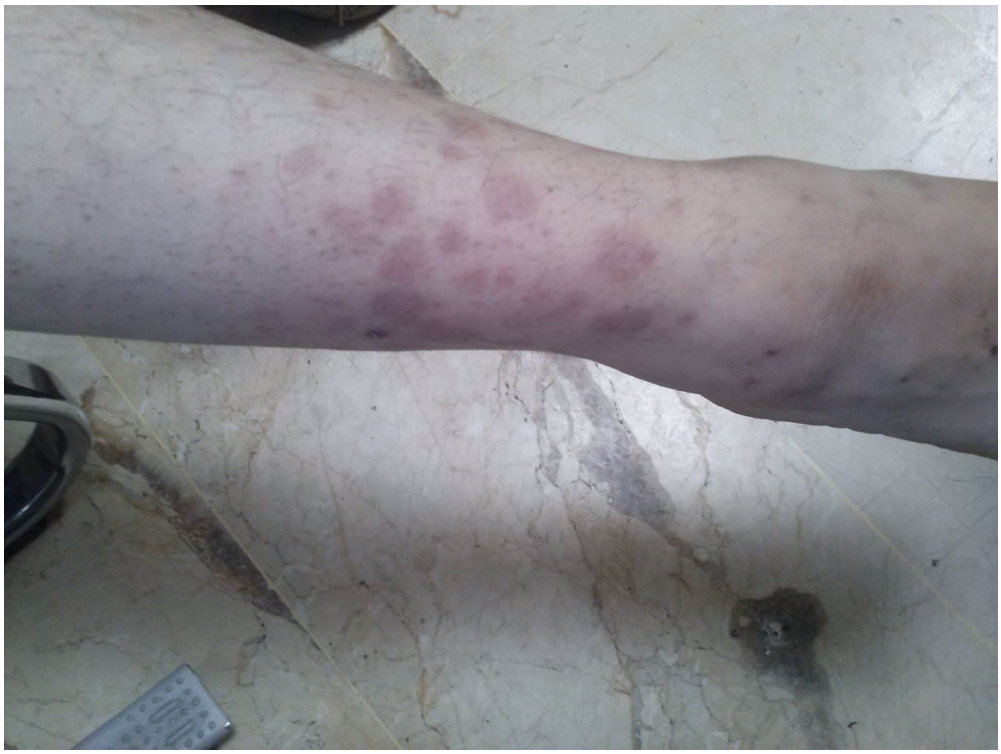

Figure 1: Non-blanchable maculopapular eruptions on the anterior parts of tibias in a patient with leukocytoclastic vasculitis and brucellosis.
Adapted from Korkmaz et al. 2016.[45]

In this study, the cutaneous lesions occurred in the acute phase of the disease in 62.5% of the patients. Skin lesion was observed in 27 (6%) of 436 brucellosis patients in a study performed by Ariza et al.[18] Skin lesion was observed in 24 patients at the initial period, in 4 at relapse, and in 1 both at the initial period and at relapse.[18] In a study performed by Buzgan et al.[10] evaluating 1,028 brucellosis cases, the rate of skin involvement was 2.4% and the rates of cutaneous lesions in acute, subacute, and chronic periods of the disease were 2.4%, 3.2%, and 2.1%, respectively. When the case presentations were evaluated, it was observed that the cutaneous lesions were usually determined in the acute phase of brucellosis.[38,42,44,54-56] Since cutaneous lesions observed in brucellosis are non-specific, the time of determination of the lesion may have varied in the studies performed.

When the studies related to the cutaneous lesions associated with brucellosis were evaluated, fever was observed in all cases except chronic patients.[25,44,45,55-58] Since systemic symptoms generally predominate in the patients with brucellosis and the cutaneous lesions regress with anti-brucellosis treatment, presentation to the dermatology clinics is rare. Since the cutaneous lesions are non-specific, it is difficult to diagnose some subacute and chronic cases.[18,32,35,38,54]

Therefore, brucellosis should be kept in mind in the differential diagnosis of cases of fever of unknown origin, especially in regions where brucellosis is endemic. When the brucellosis patients with and without cutaneous lesions were evaluated regarding systemic symptoms and clinical findings, no difference was determined.[18,32,35] When the patients with brucellosis were evaluated by sex, cutaneous lesions were more commonly seen in females.[18,32,37]

DIAGNOSIS

The definitive diagnosis of brucellosis requires the isolation of Brucella species from blood, bone marrow, or tissue samples. A culture should be performed from the affected area in the presence of focal complications. The Brucella bacterium grows slowly *in vitro* media. DNA amplification using polymerase chain reaction can be used in the blood and non-blood samples. Polymerase chain reaction is more sensitive than the culture irrespective of the stage of the disease; it can be used for identification of the bacterium in the tissue.[1,5,59]

The cutaneous lesions associated with brucellosis can be diagnosed histopathologically. Biopsy should be performed for all of the cutaneous lesions. Frequently there is a granulomatous structure in these lesions. The presence of plasma cells and necrosis in erythema nodosum-like lesions associated with brucellosis is beneficial for differential diagnosis from the classical erythema nodosum. However, histological changes may be insignificant in some patients and they can be observed as mild cell infiltration without a granulomatous structure.[18,38,54]

Since brucellosis is a multi-systemic infectious disease, it should be considered for the differential diagnosis of patients with rash and fever. However, skin involvement is generally not specific to brucellosis. This can be beneficial for the differential diagnosis of the lesions in the presence of non-specific complaints such as fever, fatigue, joint pain, and contact with animal tissues or consumption of non-pasteurised dairy products, especially in individuals living in endemic regions. It is necessary to increase awareness among clinicians and especially dermatologists in regions where the disease is endemic.

TREATMENT

There are two major treatment regimens for the treatment of uncomplicated brucellosis (without features such as spondylitis, neurobrucellosis, and endocarditis) in adult patients. The treatment regime of doxycycline (2x100 mg/day, 6 weeks) and streptomycin (1 g/day, 2–3 weeks) recommended by the World Health Organization (WHO) for combination treatment is used for the treatment of brucellosis. Another combination treatment recommended by the WHO is doxycycline (2x100 mg/day) and rifampicin (600–9,000 mg/day) for 6 weeks. *In vitro* efficacy of quinolones, especially ofloxacin and ciprofloxacin, is good. Although high relapse rates were observed with quinolone monotherapy, successful results were obtained with combination treatment; however, they were not first-line agents.[1,5] In the presence of focal involvements such as neurobrucellosis, endocarditis, and spondylitis, the period of treatment should be longer (at least 8–12 weeks) and combination treatment with at least three drugs is frequently recommended. In general, the type and period of treatment in other forms of localised infection is as in uncomplicated brucellosis cases.[1,5,60`]

Type and duration of treatment of brucellosis patients with cutaneous lesions is not different from classical treatment. It was observed that a regression occurred in the lesions within the first week after starting anti-Brucella treatment.[18,38,44,45,55,56] It was observed that this period of regression was as long as 1 month in some patients.[39] Classically, the period of regression was 6 weeks in the patients where the duration of treatment was indicated.[38,44,49,55-57]

CONCLUSION

Brucellosis is an important public health problem causing substantial morbidity in both human and animal populations. While skin involvement is rare in brucellosis, a patient with brucellosis may primarily present with cutaneous lesions. Cutaneous manifestations are not specific to brucellosis and the differential diagnosis can be made histopathologically. Brucellosis should be kept in mind in the differential diagnosis of patients with non-specific complaints of fever, weight loss, muscle, and joint pain who consume unpasteurised dairy products and engage in animal breeding in case of the presence of skin eruptions, especially in the endemic regions.

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UPCOMING EVENTS

The Austrian Society of Dermatology and Venereology (ÖGDV) Annual Meeting 2016

25th–27th November 2016

Vienna, Austria

A scientific and social highlight within the fields of dermatology and venereology, ÖGDV's annual meeting provides a hub for the discussion of interesting clinical case studies and therapeutic research results. Oral presentations, scientific posters, and lectures by esteemed award/scholarship beneficiaries will further your knowledge regarding recent innovations while also delivering the ideal setting for peer-to-peer discussion of updated clinical practice regimes.

Journées Dermatologiques de Paris 2016

6th–10th December 2016

Paris, France

The National Congress of the French Society of Dermatology (SFD) combines continuing medical education with the presentation of current papers, covering all areas of dermatology. Hot topic sessions will be voted for by attendees while the renowned 'international' session will play host to various foreign dermatological societies to provide international breadth. With over 100 Certified Medical Educator (CME) workshops and forums, this event is not to be missed.

20th European Dermatology Forum (EDF) Meeting 2017

19th–21st January 2017

Montreux, Switzerland

This annual calendar highlight provides both resources and constructive networking opportunities for key opinion leaders in dermatology. With an expansive programme of lectures spanning from innovative techniques to controversial practice, this event incorporates a vast amount of experience and provides a platform to better your professional skills. Hosted by the city of Montreux, this meeting will be located a stone's throw from Lake Geneva and situated at the foot of the Alps.

27th Annual Cutaneous Malignancy Update 2017

21st–22nd January 2017

Coronado, California, USA

Organised to highlight the necessity of clinician education as worldwide incidence of melanoma rises, Scripps Clinic's annual melanoma update provides lectures and interactive workshops from nationally recognised experts on the issue of dermatological cancers. Multidisciplinary efforts will ensure that attendees leave with a greater insight into the matter at hand. The training and information given at this workshop will enable early detection and personalised therapy to become routine in clinical practice.

19th IMCAS (International Master Course on Aging Science) World Congress 2017

26th–29th January 2017

Paris, France

Termed the 'gold standard' of medical aesthetic conferences and with an average of 6,500 participants, 500 guest speakers, and 200 exhibiting companies, dermatologists, practitioners, and plastic surgeons are cordially invited to take advantage of this event. Representing the theme of 'Redefining beauty: redefining learning' for 2017, presentations by expert speakers and >140 scientific sessions will delve deep into the aesthetic surgery and cosmetic dermatology field.

75th American Academy of Dermatology (AAD) Annual Meeting 2017

3rd–7th March 2017

Orlando, Florida, USA

Providing a platform for the advertisement of the best of dermatology, this event provides 5 days' worth of engaging sessions on topical matters, led by esteemed researchers from around the world. Taking place at the Orange County Convention Center, this conference will host clinicians, researchers, and next generation dermatologists alike. In addition, those presenting abstracts for poster or oral presentations will also be able to gain Maintenance of Certification (MOC) self-assessment credits.

49th German Society of Dermatology (DDG) Congress 2017

26th–29th April 2017

Berlin, Germany

Once again held within the spacious City-Cube Berlin exhibition hall, this congress is timetabled to focus on plenary sessions with esteemed speakers presenting novel research and issues encountered over the past year and will include bookable meeting rooms for working groups. Developments within the field of dermatology will be touched upon, with professional policies discussed and potentially updated. This annual meeting is both CME-certified and easily accessible.

26th European Academy of Dermatology and Venereology (EADV) Congress 2017

13th–17th September 2017

Geneva, Switzerland

Following the success of EADV 2016, Geneva, known as the 'smallest of big cities', will play host to next year's meeting. Founded in 1987, EADV conveys varying levels of education for both clinicians and researchers alike throughout their events, enabling attendees to optimise their session timetables and best meet their personal requirements. Invitations have been extended to cutting edge speakers, lecturers, and scientists, as well as rising stars across the field. EADV hosts the widest range of relevant topics for abstract and poster submissions ensuring you are provided with an in-depth overview of current events relevant to your field and applicable to future clinical practice. One of the biggest events on the dermatology calender, this is not to be missed.

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