Translating Knowledge of IL-23 Targeting into New Solutions for Psoriasis Treatment

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Chairperson: Jo Lambert[1]

Speakers: Jo Lambert,[1] Stefano Piaserico,[2] Marc Radtke[3]

1. Ghent University, Ghent, Belgium
2. University of Padova, Padova, Italy
3. University Medical Centre of Hamburg, Hamburg, Germany

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Meeting Summary

Following a brief introduction by Prof Lambert, the symposium started with an in-depth review of the current unmet needs in the clinical management of psoriasis, provided by Prof Radtke, who also reported on the multiple and cumulative negative effects of the condition on patients' health, activity engagement, family relationships, and overall quality of life (QoL). Prof Radtke went on to describe the factors contributing to the burden of psoriasis, other than disease severity, and highlighted the importance of taking a holistic approach to the management of the condition that takes into consideration the individual patient's expectations and needs. Prof Lambert continued the symposium with an overview of the core pathways involved in disease pathogenesis in relation to the development of novel targeted immunotherapies.

Prof Lambert reviewed the current clinical paradigms for the treatment of psoriasis, including targeted biological therapies, such as TNF-α inhibitors and newer agents acting on IL-17 and IL-23, which research shows may represent a more effective approach to the treatment of psoriasis and other autoimmune inflammatory disorders. The latest Phase III clinical trial data on therapies selectively targeting the upstream cytokine IL-23 were then presented by Dr Piaserico, with a focus on the monoclonal antibodies guselkumab, risankizumab, and tildrakizumab, and their potential to achieve consistent rates of skin clearance long-term, with the added benefit of prolonged dose intervals and intermittent treatment in some patients.

Burden of Psoriasis at Individual and Societal Levels

Professor Marc Radtke

The last decade has been one of the most exciting for dermatologists managing patients with psoriasis, and this has been largely due to the significant progress of targeted treatments. The key question is how to exploit these achievements to minimise the disease burden on individuals and society. Frequently underdiagnosed and undertreated,[1,2] psoriasis is a chronic, systemic inflammatory, autoimmune skin disease characterised by a relapsing-remitting course,[3,4] which is associated with multiple comorbidities.[2] Although psoriasis can occur at any age, the highest prevalence is among people aged 50–80 years, and the majority of patients face >40 years of life with the disease.[5] In children, prevalence rates increase from infancy to adulthood with each year of age.[5,6] The average lifetime period with psoriasis in this population is >60 years.[5]

Crucially, the effects of psoriasis on the skin are only the tip of the iceberg. Genetic and environmental factors can lead to systemic inflammation, an important contributor to the pathogenesis of cardiovascular and metabolic comorbidities;[5] therefore, psoriasis is often associated with atherosclerosis, psoriatic arthritis, obesity, diabetes, and hypertension.[5,7] The psychological component of psoriasis also needs to be considered; an estimated 77% of patients experience stigmatisation related to their condition and 30% suffer from depression.[5] Additionally, patients with psoriasis experience lower QoL as well as reduced work productivity and associated economic loss.[7]

As described by Kimball et al.,[8] the overall negative effects of psoriasis accumulate over time, resulting in impaired QoL, including a feeling of lost opportunities and unfulfilled potential. This concept is known as the Cumulative Life Course Impairment (CLCI) of psoriasis.[8] Understanding the patients' perspective is crucial to identifying those who are more vulnerable to cumulative impairment, improving CLCI prevention, and optimising treatment and allocation of healthcare resources.

Most psoriasis patients report the need to be healed of skin defects, free of itching, comfortable appearing in public, and able to lead a normal working life.[5] Patients also report a substantial burden in terms of the impact of psoriasis on health-related QoL (HRQoL). This is illustrated in a conceptual model developed by Narayanan et al.[9] using data from a study of patients with moderate-to-severe psoriasis in France, Germany, Italy, Spain, the UK, Brazil, Canada, and the USA.

The model shows how physical symptoms, such as pain and itching, impact the patient's HRQoL through negative effects on mental health (e.g., stress and poor self-image), activity engagement (e.g., avoidance of hobbies and changing careers), social life (e.g., avoidance of contact with other people), and family relationships (e.g., perceived lack of support).[9] Factors such as stress and infections can aggravate symptoms and further reduce QoL. However, the latter can improve with effective treatments and avoidance of symptom triggers.[9]

Clearly, disease severity is not the only determinant of the multifaceted clinical, individual, and economic burden of psoriasis. This view is further supported by the results of a survey of dermatologists (n=524) and their patients (n=3,821) that indicates that physical and psychological comorbidities as well as type of itch and lesion site all contribute to the overall burden of psoriasis.[7] The mean±standard

deviation Psoriasis Area Severity Index (PASI) of the surveyed patients was 6.4±7.0. However, having anxiety or depression significantly increased the likelihood of experiencing skin pain (adjusted odds ratio [OR]: 1.52; 95% confidence interval [CI]: 1.16–1.96) and itch (adjusted OR: 2.09; 95% CI: 1.68–2.61). The presence of itch increased the likelihood of experiencing skin pain (adjusted OR: 1.76; 95% CI: 1.43–2.17), worsening QoL (p<0.01), and increased percentage of overall work impairment (17%; 95% CI: 2%–34%).[7]

Furthermore, compared with patients with skin lesions affecting only nonvisible body areas, those with lesions in both visible and nonvisible body areas were more likely to have skin pain (p<0.0001), worsening QoL (p<0.01), and decreased adjusted mean EuroQol-5D (EQ-5D) utility weight.[7] Similarly, patients with lesions in both sensitive (the face, scalp, and genitals) and nonsensitive (including the torso, arms, and legs) areas were more likely to have skin pain (p<0.0001), worsening QoL (p<0.01), and decreased adjusted mean EuroQol-5D (EQ-5D) utility weight than patients with lesions in nonsensitive areas only.[7]

The correlation between site of psoriatic lesions and psychological comorbidities has been investigated in detail by Łakuta et al.[10] They reported the strongest association for experiences of stigmatisation and presence of skin lesions on the arms and hands (r=0.34; p<0.0001) and chest (r=0.33; p<0.0001), whereas depressive symptoms were found to be significantly related to lesions on the head and neck (r=0.28; p<0.0001), genitals (r=0.25; p<0.0001), and upper back (r=0.25; p<0.0001).[10]

Other research has identified a link between psoriasis and sexual dysfunction. This affects 22.6–71.3% of patients, according to a systematic review by Molina-Leyva et al.[11] The same review established that the risk of sexual dysfunction is higher in patients with genital lesions.[11] Therefore, evaluating the presence of the latter, as well as the presence of sexual dysfunction, is important in order to determine disease severity when making treatment decisions.

Understanding patients' expectations is also crucial, as these do not always necessarily align with those of doctors.[5] The psoriasis treatment landscape has evolved considerably over the last 15 years, and current therapies achieve improvements in PASI score of up to 90–100%, corresponding to near-complete or complete resolution.[12,13] It is important not to focus exclusively on these targets but to consider also what matters to patients in terms of their QoL goals.

Pathophysiology of Psoriasis and Implications for Treatment

Professor Jo Lambert

Etanercept, the TNF receptor protein, is a widely-used systemic treatment for chronic, moderate-to-severe plaque psoriasis. Its clinical efficacy has been linked of the downregulation of the IL-17 pathway, suggesting that downstream suppression of Th17 cells is an essential response to TNF inhibitors.[14]

The IL-17 pathway plays a prominent role in the pathophysiology of psoriasis, contributing to the clinical manifestations of the disease.[15] Among the new therapies that have been developed to target this pathway, the human monoclonal antibody, ustekinumab, inhibits both IL-12 and IL-23, and, unlike TNF inhibitors, does not increase the risk of malignancy.[16] Ustekinumab also has the highest drug survival period, a measure of the time a patient remains on a certain therapeutic agent. A prospective, observational cohort study using data from the British Association of Dermatologists Biologic Interventions Register (BADBIR), compared with patients on the TNF inhibitor adalimumab, those receiving ustekinumab had an increased likelihood of remaining on therapy (hazard ratio [HR]: 0.48; 95% CI: 0.37–0.62), whereas those receiving etanercept or infliximab were more likely to discontinue therapy (HR: 1.63; 95% CI: 1.45–1.84 and HR: 1.56; 95% CI: 1.16–2.09, respectively).[17]

However, ustekinumab is not effective in some patients. Langley et al.[18] demonstrated, in the Phase III NAVIGATE trial, that these patients may become responders when switched to a therapy exclusively targeting the IL-23 pathway. Patients (n=871) with moderate-to-severe psoriasis were administered a 45 or 90 mg

ustekinumab dose at Week 0 and 4. At Week 16, 268 subjects with inadequate response were randomised (double-blind) to receive 100 mg guselkumab (an anti-IL-23 monoclonal antibody) or to continue the ustekinumab regimen. Compared with the randomised ustekinumab group, more patients on guselkumab achieved PASI 90 (51.1% versus 24.1%; p<0.001, respectively) and PASI 100 (20.0% versus 7.5%; p=0.003, respectively) at Week 52.[18]

The findings suggest that IL-23 has a primary role in the regulation of inflammation and the pathophysiology of autoinflammatory diseases, including psoriasis.[19] Therefore, IL-23 may be a more appropriate target for the effective treatment of the condition than IL-17. Blocking IL-23 can lower the number of Th cells, resulting in the long-term reduction of cytokines, including IL-17. Conversely, when IL-17 is inhibited, the downstream production of cytokines such as IL-17A and IL-17F remains unaffected.[19]

Adequate targeting is important, because effective treatment can prevent negative outcomes, such as premature death. A prospective population-based cohort study by Noe et al.[20] found that untreated patients with physician-reported psoriasis body surface area (BSA) >10% (n=856) had increased mortality risk compared with the general population (adjusted HR: 1.68; 95% CI: 1.08–2.61).[20] This highlights the importance of clinicians being ambitious in treating psoriasis, by aiming to reduce BSA as much as possible: preferably to below 3%.

Inhibitors of the IL-17 pathway include guselkumab, risankizumab, tildrakizumab, secukinumab, ixekizumab, and brodalumab, all of which have a demonstrated good efficacy and safety profile, and are specific to psoriasis.[21] However, the aforementioned drugs are expensive and have limited long-term data. With the exception of secukinumab and ixekizumab, these newer biologics target IL-17F, which can halt the pathogenesis of psoriasis by preventing neutrophil influx and the expression of IL-8 and extracellular signal-regulated kinase (ERK)1/2 in keratinocytes.[22] As a downside, IL-17F inhibition can increase patient susceptibility to mucosal infections, particularly *Mycobacterium tuberculosis*.[23] In the AMAGINE-2 and AMAGINE-3 clinical trials, brodalumab demonstrated a faster onset of action compared with ustekinumab in patients with moderate-to-severe psoriasis.[24] However, brodalumab also inhibits IL-17E (otherwise known as IL-25),[25] which is thought to contribute to the establishment of physiological pregnancy[26] and to the prevention of fat accumulation in the liver.[27] Thus, potentially, brodalumab might not be appropriate for women of childbearing age with psoriasis and for patients with psoriasis in general, given the high prevalence of metabolic disease in this population.[28] Guselkumab, on the other hand, selectively targets the IL-23 subunit p19.[29] Specific IL-23 p19 blockade has been associated with improved and more sustained efficacy and safety as well as lower dosing frequency (every 8–12 weeks), compared with downstream targeting of cytokines of the IL-23/Th17 pathway,[19] resulting in long-term remissions that could potentially allow intermittent treatment.[30] In the clinical setting, PASI improvement from 28.8 to 1.8 has been observed with 6 months of therapy (two injections) of guselkumab.[31] Additionally, low dosing frequency may contribute to patient adherence.

Clearly, dermatologists have a wide range of more effective, newer biological therapies to choose from when it comes to managing psoriasis. But, since every patient is likely to have specific needs and expectations, it is important that they have an understanding of the mechanisms of action involved, in order to effectively personalise treatment. Active questioning of patients about comorbidities and lifestyle is also crucial.

Clinical Insights into Selective IL-23 Inhibitors

Doctor Stefano Piaserico

There is currently a need to raise the bar in psoriasis management. The focus of treating psoriasis should be on attaining long-term disease control to improve QoL and to reduce comorbidities and mortality. With regard to QoL specifically, a large body of evidence indicates that this improves as the patient's skin clears. This was the conclusion, for example, of a systematic review of randomised controlled trials evaluating biologics for moderate-to-severe psoriasis.[32] The analysis was based

on data from 22 treatment arms across 13 randomised controlled trials. It found a correlation between mean improvement in PASI and mean reduction in Dermatology Life Quality Index (DLQI) score (r^2=0.80, from baseline at Weeks 10–16), and the authors concluded that a ≥75% reduction in PASI can considerably improve QoL in patients treated with biologics.[32]

Against this backdrop, it is worth considering that upstream blockage of the IL-23/Th 17 axis, by agents like guselkumab, risankizumab, and tildrakizumab (all acting on the p19 subunit of IL-23), has several advantages over mid or downstream inhibition. In the Phase III VOYAGE study, by Blauvelt et al.,[29] compared with patients on adalimumab (n=334), significantly more subjects on guselkumab (n=329) achieved PASI 90 at Week 16 (73.3% versus 49.7%), 24 (80.2% versus 53.0%), and 48 (76.3% versus 47.9%) (p<0.001 for all comparisons). Similarly, in two Phase III studies by Gordon et al.,[33] significantly more patients treated with risankizumab achieved PASI 90 compared with patients treated with ustekinumab or placebo.[33] Tildrakizumab demonstrated superiority versus etanercept in the Phase III trial reSURFACE 1 by Reich et al.,[34] with 73% of patients on tildrakizumab achieving PASI 75 at Week 28, compared with 54% of those on etanercept.[34] Guselkumab, risankizumab, and tildrakizumab also showed superior efficacy versus placebo, in the above studies.[29,33,34] Furthermore, treatment with guselkumab has been found to be effective at increasing absolute PASI response consistently during 2 years of treatment,[35] and improving the appearance of body areas that are especially difficult to treat, such as the scalp, hands, feet, and nails.[29]

From a practical viewpoint, it is worth noting that PASI responses are maintained after withdrawal of guselkumab in a high percentage of patients. For example, in the study by Reich et al.,[36] guselkumab-treated patients with moderate-to-severe psoriasis achieving ≥90% improvement in PASI score from baseline were randomised at Week 28 to either guselkumab (maintenance group) or placebo (withdrawal group). Through Week 48, 36.8% of patients in the withdrawal group sustained a PASI 90 response versus 88.6% of those in the maintenance group.[36] Research has also found that >70% of adalimumab PASI 90 non-responders achieved and maintained PASI 90 or 100 after switching to guselkumab.[37] Both guselkumab and risankizumab combine a high degree of efficacy with a favourable safety profile, with no new safety concerns, including serious infections or malignancies, compared with other agents.[29,33] Of note, Zhu et al.[38] found minimal anti-drug antibody development with guselkumab. Among patients with psoriasis who were treated with this IL-23 inhibitor (n=943), 8.6% (n=81) developed anti-drug antibody by Week 100. Only 4 (4.9%) of these patients had antibodies that could neutralise the bioactivity of guselkumab *in vitro*, corresponding to an overall incidence of neutralising antibodies of 0.4%.

Open Discussion

The last part of the symposium was an open discussion on the topics presented by the speakers. The following is a summary of the main points.

- Asked whether human data are available on the role of IL-17E in the establishment of physiological pregnancy, Prof Lambert clarified that the evidence to date comes from animal studies.
- It was highlighted that using a cascade model to illustrate the superiority of IL-23 inhibitors is not appropriate. A cascade model implies causation, which is not the case in the pathogenesis of psoriasis. A circular model would be more appropriate.
- There was scepticism regarding the effectiveness of exclusively targeting the IL-23 pathway, given that the pathogenesis of psoriasis is fairly heterogeneous and some patients may develop paradoxical side effects. It was noted that the efficacy data are certainly positive, but it was acknowledged that additional long-term safety studies are needed.
- It was generally agreed that ustekinumab will continue to play a major role in the management of psoriasis, largely due to the good safety profile, the long life of the medication, and the high patient adherence. However, it was pointed out that some patients may be underdosed at 45 mg.

- Members of the audience highlighted the need to establish the cost-effectiveness of individual drugs, and to identify biomarkers of response. There was the perception that avoiding overtreatment, by lowering doses and prolonging dose intervals in the right patients, will contribute to reducing costs in the future.
- It was asked why guselkumab, in particular, would be the perfect candidate for intermittent therapy. Dr Piaserico explained that guselkumab will likely be one of several medications allowing this, and noted that prolonging the dose interval, rather than stopping treatment altogether, would probably be a better approach in super responders.

Conclusion

Clinical paradigms for psoriasis management have evolved substantially in recent years. They include targeted biologic therapies, such as TNF-α inhibitors and newer agents that can target the upstream cytokine IL-23 or the downstream IL-17. Several sub-targets exist for the latter, including IL-17A and IL-17F, the targeting of which has advantages and disadvantages that may impact on treatment decisions. Selective blockage of the upstream cytokine IL-23 may be a more appropriate approach, according to the latest clinical trial data, potentially improving the management of psoriasis and other autoimmune inflammatory disorders. Although long-term safety data are needed, there is evidence to suggest that targeting IL-23 may provide several advantages, including consistent skin clearance long term, prolonged dose intervals, and intermittent treatment, enabling dermatologists to meet patients' individual needs and expectations more effectively.

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