EMJ EUROPEAN MEDICAL JOURNAL

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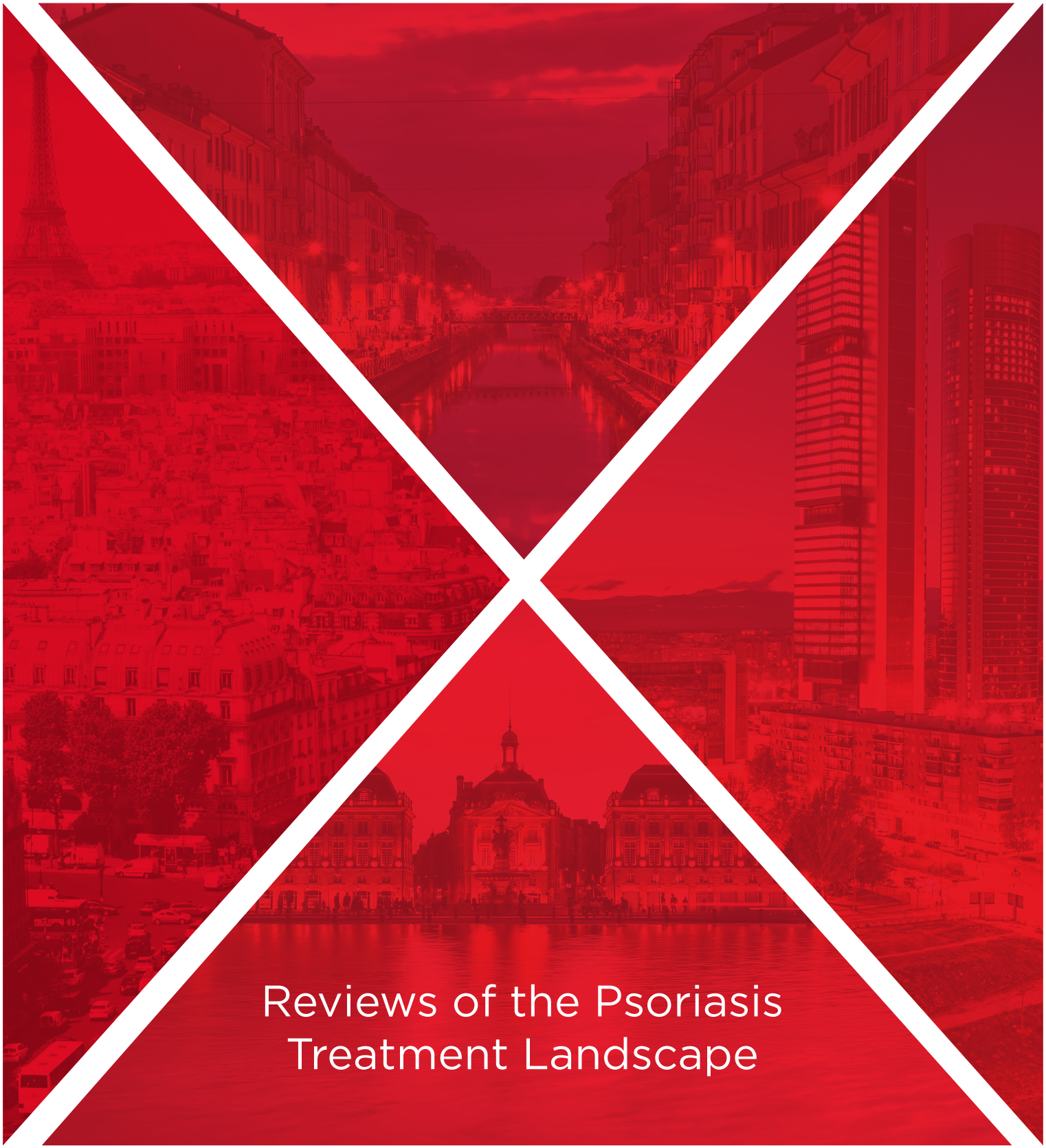

Reviews of the Psoriasis Treatment Landscape

Contents

Previously published content from EMJ Dermatology Supplements.

IL-23 Inhibition as a Key Component in Psoriasis Treatment is Here to Stay

This satellite symposium took place on April 25th 2019 as part of the 6th Congress of the Skin Inflammation & Psoriasis International Network (SPIN) in Paris, France

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Disclosure: Prof de Jong has received research grants for the independent research fund of the Department of Dermatology, Radboudumc, Nijmegen, the Netherlands, from AbbVie, Janssen, National Psoriasis Foundation USA, Pfizer promotion fund Rumc/SMK, VGZ, and ZonMw; and has acted as consultant and/or paid speaker for and/or participated in research sponsored by companies that manufacture drugs used for psoriasis treatment, including AbbVie, Almirall, Celgene, Janssen, Leo, Eli-Lilly, Novartis, and Pfizer.

Dr Pinter has worked as an investigator and/or speaker and/or advisor for AbbVie, Almirall-Hermal, Amgen, Biogen Idec, Boehringer-Ingelheim, Celgene, GSK, Eli-Lilly, Galderma, Hexal, Janssen, LEO-Pharma, CC2, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pascoe, Pfizer, Tigercat Pharma, Regeneron, Roche, Sandoz Biopharmaceuticals, Schering-Plough, and UCB.

Acknowledgements: Writing assistance provided by Janet Fricker.

Support: The symposium and publication of this article were sponsored by Janssen Immunology.

Citation: EMJ Dermatol. 2019;7[Suppl 5]:2-11.

Meeting Summary

Prof Elke de Jong focussed her presentation on data from randomised clinical trials (RCT) and real-world evidence (RWE) from psoriasis patient registries. Such data is complementary with RCT having high internal validity but low external validity, and RWE having low internal validity but high external validity. She reviewed the predictors for stopping psoriasis biological treatment of high BMI and female sex and predictors for continuing treatment as concurrent psoriatic arthritis.

Current unmet needs in psoriasis that demonstrate the requirement for additional treatments include patients experiencing psoriasis for roughly 20 years before being prescribed biologics, prevention of damage (e.g., psoriatic arthritis), achieving sustained effectiveness or cure, developing better patient-reported outcome measures, and better treatment of specific psoriatic areas (scalp, face, nails, and genitalia).

Dr Andreas Pinter reviewed the role played by IL-23, IL-17A, and IL-22 in psoriasis, and new agents including ustekinumab blocking both IL-12 and IL-23; guselkumab, tildrakizumab, and risankizumab blocking IL-23; and brodalumab blocking IL-17A.

He explored VOYAGE 1 data that showed that the IL-23 inhibitor guselkumab maintained Psoriasis Area and Severity Index (PASI) 90 response through Week 156 in >80% of patients. Furthermore, VOYAGE 2 results showed PASI 90 response was maintained in >50% of patients 6 months after guselkumab withdrawal.

He demonstrated how re-treatment with guselkumab led to a high PASI 90 response in patients who lost PASI 90 response after withdrawal of treatment. Data from the VOYAGE 1 study further showed that guselkumab produced statistically significant improvements in scalp and palmar plantar scores over adalimumab, and comparable nail scores to adalimumab.

Data from the UltIMMa-1 and ULtIMMa-2 studies showed that IL-23 inhibition with risankizumab produced better quality of life scores than with ustekinumab. Additionally, the ECLIPSE trial showed that IL-23 inhibition with guselkumab produced higher PASI 90 response rates than IL-17 inhibition with secukinumab at Week 48.

From Registry to Practice: Real-World Evidence and Unmet Needs in Psoriasis

Professor Elke de Jong

Photographic images from the Canadian Photographer François Brunelle's Doppelganger Project (involving unrelated look-alikes who can be mistaken for twins) demonstrates how even though people may appear outwardly the same they can be very different inside.[1] The same principle holds for patients enrolled in RCT and registries. Although the two groups can appear superficially the same, those in trials represent a more controlled population while those in registries also include patients who have one or multiple comorbidities or who are older.[2]

PASI scores are commonly used to assess lesion severity and the area affected by psoriasis. Relative PASI scores, which indicate a percent reduction compared to baseline, are commonly used in randomised clinical trials to illustrate the efficacy of a treatment i.e., PASI 90 represents a 90% reduction of the PASI score compared to the beginning of the trial.[3] In the randomised clinical VOYAGE 2 trial, PASI responses for guselkumab were rapid, with >80% of guselkumab patients achieving PASI 75 at Week 24, >70% achieving PASI 90, and >40% achieving PASI 100.[4] In contrast, patients in the BioCAPTURE registry (involving a greater diversity of patients with older people, children, and patients with psoriatic arthritis or diabetes) found it harder to achieve PASI 75, PASI 90, and PASI 100 scores, and mean PASI was used as an outcome measure.[5]

Registries involving large numbers of patients (e.g., PSOLAR, ESPIRIT, and SERENA) have been used to generate safety data. Registries can also explore effectiveness, cost-effectiveness, drug survival, predictors of outcome (e.g., sex, BMI, or age), and biomarkers. Through quality of life and treatment satisfaction data (using Dermatology Life Quality Index [DLQI], 36-Item Short Form Health Survey, and Treatment Satisfaction Questionnaire for Medication [TSQM]), registries reveal the 'patient voice' and explore unmet needs and dose reductions.

A systematic overview of 14 long-term psoriasis patient registries revealed that registries most frequently consider effectiveness/efficacy/outcomes (9 registries), followed by baseline descriptions (8 registries), and safety (7 registries).[6] Subjects less frequently addressed included treatment patterns (2 registries), drug survival (4 registries), predictor analyses (4 registries), and registry descriptions (5 registries). Furthermore, the overview showed the most common outcome measure instrument used was PASI, followed by DLQI.[6]

Data derived from RCT and RWE are complementary, with both included in guidelines. RCT have high internal validity (in which the analysis is well done) but low external validity (data may not transfer to broader patient groups). In contrast, RWE has low internal validity (because of lack of randomisation) but high external validity (i.e., the data is applicable to clinical practice).[7] Insights from registries show effectiveness is reached in daily practice, but with higher doses than in trials, or in combination with other psoriasis therapies.[8] Regarding effectiveness, registries

show switching between biologics is safe and effective but dosage increases and combinations with other systemic treatments might be needed (opinion of the speaker). Regarding safety, psoriasis treatments are safer than expected, with patients stopping because of side effects less often than the lack of efficacy. Furthermore, strict laboratory controls have proved less necessary than expected, leading to the adjustment of guidelines (opinion of the speaker). For patient-reported outcomes, registries reveal patient quality of life increases substantially on biologics as does treatment satisfaction measured on the TSQM.[9]

For psoriasis, the proportion of patients on a drug decreases (from the lack of efficacy, side effects, or patients lost to follow-up), until around 2 years when less than half of the original cohort are still on the drug (information provided by the speaker). However, unpublished data from the BioCAPTURE registry exploring treatment durations up to 12.5 years revealed that ustekinumab had the highest drug survival, with adalimumab in second place, and etanercept in third.[5] Drug survival of biologics for psoriasis represents a composite measure taking into consideration effectiveness and safety as well as physician and patient behaviour. The BioCAPTURE registry revealed that the most frequent reason for stopping treatment was its sub-effectiveness, rather than its side effects.[10]

A meta-analysis of RWE, including 37 studies involving 32,631 subjects, demonstrated that ustekinumab had the highest 4-year drug survival, dropping from 82% at Year 1 to 56% at Year 4.[11] This is compared to etanercept, dropping from 66% at Year 1 to 41% at Year 4, adalimumab from 69% at Year 1 to 47% at Year 4, and infliximab from 61% at Year 1 to 42% at Year 4.[11] For etanercept, low drug survival was largely attributable to sub-effectiveness, while for infliximab it was largely because of side effects, allowing clinicians to use such data for treatment choices.[11]

A literature review, involving 16 cohort studies including 32,194 patients, found that biological treatment discontinuation was predicted by obesity (hazard ratio [HR]: 1.21; 95% confidence interval [CI]: 1.10–1.32) and female sex (HR: 1.22; 95% CI: 1.07–1.38), while persistence was predicted by psoriatic arthritis (HR: 0.83; 95% CI: 0.80-0.86).[12] In summary, predictors for stopping biologic treatments are a high BMI[10,12] and female sex,[10,12] and a predictor for continuing is psoriatic arthritis.[12] Furthermore, an observational cohort study assessing drug survival of second-line biologics found female sex, multiple comorbidities, concomitant cyclosporine, and high PASI at switching to second-line biologics all predict discontinuation.[13]

Biomarkers can predict treatment response,[14] toxicity, or progression (opinion of the speaker). A known factor is that psoriasis is a marker for psoriatic arthritis,[15] with patients developing psoriatic arthritis 10 years after the onset of psoriasis.[16] One recent study suggested allele *HLA-Cw6* represents a predictor of ustekinumab efficacy,[14] but a confounder is that *HLA-Cw6* negative patients can also show good ustekinumab responses. In the future, biomarker profiles might predict whether patients would benefit most from adalimumab, etanercept, or ustekinumab.

A study introducing the 'happy' drug survival concept combined drug survival with dermatological quality of life measures for 186 patients taking adalimumab, etanercept, or ustekinumab (with happy defined as DLQI ≤5; unhappy defined as DLQI >5).[17] At baseline, 73% of patients were considered unhappy, and 27% happy (happy:unhappy ratio 1:27); while at 1 year, 79% of patients reported being happy on their drug (happy:unhappy ratio 3.7:1.0).[17]

Current unmet needs in psoriasis that demonstrate the requirement for additional treatments include patients experiencing psoriasis for 18–20 years before being prescribed biologics,[18] prevention of damage (e.g., psoriatic arthritis), achieving sustained effectiveness or cure, developing better patient-reported outcome measures, and better treatment of specific psoriatic areas (scalp, face, nails, genitalia) (opinion of the speaker).

Regarding damage prevention, psoriasis remains the best marker for psoriatic arthritis,[15] demonstrating the need for early detection through screening and rheumatology referrals for early treatment. Young adults represent the population with the greatest number of new patients,[19] with psoriasis onset often coinciding with life events such as studying and finding a job or partner. Questions remain around whether patients should be over-treated or under-

treated, with updosing effective in some patients (depending on BMI and other factors) (opinion of the speaker).

The controlled dose reduction (CONDOR) study is currently randomising 120 patients with stable plaque psoriasis and low disease activity in combination with good dermatological quality of life included in BioCAPTURE network hospitals taking adalimumab, etanercept, or ustekinumab to either usual care or tight controlled biologics dose reduction.[20] Preliminary results (unpublished) showed that >50% of patients who underwent dose reductions experienced 'good effects without serious adverse events or an increase in psoriasis activity', suggesting dose reduction to be possible.

The BioCAPTURE registry, involving 700 patients in a Netherlands network of 3 academic centres and 14 regional hospitals, is exploring the unmet needs of psoriasis patients.[21] In a recent, unpublished analysis focussing on patients who started a biologic (etanercept, adalimumab, ustekinumab, secukinumab, ixekizumab, guselkumab, brodalumab, or apremilast) between 2017 and 2018 (involving 219 treatment episodes) looked at PASI, quality of life, and TSQM. Results at 1 year showed that the mean PASI was 4. Furthermore, results showed that after 6 months, 35.2% of patients had PASI 75, and 21.7% had PASI 90; while after 1 year, 35.1% of patients had PASI 75 and 10.8% PASI 90. These far from ideal results may be because of patients having to stop biologic administration due to infections and other comorbidities.

In the same study, the mean DLQI 12 months after starting a biologic is around 5. TSQM is divided into four domains: at 1 year, the mean TSQM for effectiveness was 69.6; for side effects it was 93.1; for convenience it was 77.8; and for global satisfaction it was 76.5. All domains fall short of the ideal result of 100, with the greatest room for improvement in effectiveness. The BioCAPTURE registry demonstrates that psoriasis clearance is not yet a reality for most patients.

The sentiment that therapies may not be good for all patients and of the need to choose between different therapies was highlighted by the recent US National Psoriasis Foundation (NPF) magazine cover headline "One size does not fit all".

From Trial to Practice: Key Trial Data and Long-Term IL-23 Inhibition Doctor

Doctor Andreas Pinter

Understanding of psoriasis pathophysiology has evolved from hyperproliferation of skin cells (prior to 1980) and involvement of T cells (1982), to recognition of IL-23 (including the p19 and p40 subunits) and IL-17 as the most important cytokines in classic plaque psoriasis.[23] However, there have been delays between the understanding of cytokine involvement to development of psoriasis treatments, with the first selective IL-23 (p19) blocker approved in 2017,[24] and trials ongoing for p19 subunit inhibitors.[25]

IL-23 plays a central role in psoriasis pathogenesis, with dendritic cell-derived IL-23 and downstream helper T cells products (including IL-17A and IL-22) considered to be important.[26] Treatment possibilities include ustekinumab blocking both IL-12 and IL-23; guselkumab, tildrakizumab, and risankizumab blocking IL-23; and brodalumab blocking IL-17A. Questions remain around whether these treatments are a good choice for patients and whether their results are comparable.

For psoriasis, treatment goals have evolved from achieving PASI 50 with conventional therapy to PASI 75 with first-generation biologics (anti-IL-12/23 antibodies and anti-TNF antibodies), to PASI 90 plus Physician's Global Assessment with second-generation biologics (anti-IL-17A antibodies), to long-lasting clear skin with third-generation (anti-IL-23 antibodies) (opinion of the speaker).

Dr Pinter shared a case of a 57-year-old woman from his clinic who had experienced psoriasis from the age of 5 years (whose grandmother also had psoriasis). The patient, whose previous therapies included extensive topical therapy, fumaric ester acid, methotrexate, cyclosporine, psoralen and ultraviolet A (PUVA), apremilast, and adalimumab, was treated with guselkumab. In March 2018, prior to guselkumab, she had a PASI of 29 and body surface area (BSA) involvement of 42%. In April 2018, 4 weeks after starting guselkumab, her PASI was 9 and BSA involvement was 36%; in July 2018, 16 weeks after initiating treatment, her PASI was 0 and BSA involvement was 0%.

In the reSURFACE 1 trial data for tildrakizumab (a high-affinity, humanised IgG1 k antibody targeting IL-23 p19), at Week 12 the PASI 75 response treatment goal was achieved in 62% of patients taking tildrakizumab 200 mg, 64% taking tildrakizumab 100 mg, and 6% taking placebo ($p<0.0001$ for comparisons of both tildrakizumab groups versus placebo).[25] Furthermore, by Week 28, PASI 75 response was achieved in 77% taking tildrakizumab 100 mg and 79% taking tildrakizumab 200 mg. At Week 12, PASI 90 was achieved in 35% taking tildrakizumab 100 mg, 35% taking tildrakizumab 200 mg, and 3% taking placebo. By Week 28, 49% of patients taking tildrakizumab 100 mg and 57% taking tildrakizumab 200 mg achieved PASI 90.[25]

In the VOYAGE 1 study, patients with moderate-to-severe psoriasis were randomised to guselkumab 100 mg (Weeks 0 and 4, then every 8 weeks; n=329), placebo then switch to guselkumab (with guselkumab 100 mg at Weeks 16, 20, then every 8 weeks; n=174), or adalimumab (every other week; n=334). Results at Week 48 showed that PASI 75 was achieved in 96.4% of patients receiving placebo then switching to guselkumab, 87.8% receiving guselkumab, and 62.6% receiving adalimumab; PASI 90 was achieved in 81.8% receiving placebo then switching to guselkumab, 76.3% receiving guselkumab, and 47.9% receiving adalimumab; and PASI 100 was achieved in 50.3% receiving placebo then switching to guselkumab, 47.4% receiving guselkumab, and 23.4% receiving adalimumab.[27]

The UltIMMa-1 study of risankizumab (a humanised IgG1 monoclonal antibody binding to the p19 subunit of IL-23) found that at Week 52, PASI 90 was achieved in 82% of patients randomised to risankizumab, 78% randomised to placebo then switching to risankizumab, and 44% randomised to ustekinumab.[28] At 52 weeks, the ULtIMMa-2 study found that PASI 90 was achieved in 85% of patients randomised to placebo then switching to risankizumab, 81% to risankizumab, and 51% to ustekinumab.[28]

The VOYAGE 1 study showed PASI 90 response was maintained through Week 156 in >80% of patients treated with guselkumab, and that PASI 100 response was maintained through to Week 156 in >50% of patients treated with guselkumab.[29]

Further analysis of VOYAGE 1, showed that at Week 52, 49.1% of patients receiving guselkumab had a PASI score of 0 and 64.3% had a score ≤1; at Week 100, 51.1% had a PASI score of 0 and 68.8% a score ≤1; and at Week 156, 50.8% of patients had a PASI score of 0 and 68.4% had a score ≤1.[30]

In the VOYAGE 2 study, patients were randomised to guselkumab 100 mg (Weeks 0 and 4, then every 8 weeks; n=496), placebo then switching to guselkumab (placebo Weeks 0, 4, and 12, then guselkumab at Weeks 16 and 20; n=248), or adalimumab (80 mg at Week 0, then 40 mg at Week 1, and every 2 weeks through to Week 23; n=248). At Week 28, guselkumab PASI ≥90 responders were re-randomised to guselkumab (n=193) or placebo (n=182), with guselkumab after loss of response. Furthermore, placebo then switching to guselkumab responders and adalimumab responders received placebo, then guselkumab after loss of response, and non-responders received guselkumab.[4] Results for guselkumab-treated patients re-randomised at Week 28 (receiving their last injection at Week 20) showed that a PASI 90 response was maintained in >50% of patients 6 months after guselkumab withdrawal.[4] The ability to maintain PASI 90 some months after coming off treatment is a finding that is unique to the newer generation of p19 IL-23 blockers (opinion of the speaker).

Stopping and restarting therapy is far from ideal because the practice increases the risk of developing neutralising antidrug antibodies.[31] A study exploring VOYAGE 2 patients who lost response after guselkumab withdrawal found that the majority regained PASI 90 response 6 months after re-treatment (PASI 90 was achieved in 20.0% of patients at 1 month and 87.6% at 6 months).[32]

An analysis of VOYAGE 2 showed at 48 weeks following guselkumab withdrawal, parameters predicting PASI 90 maintenance were lower than baseline IL-17F and shorter disease durations. The analysis further found that 6 months after withdrawal, parameters associated with PASI 90 maintenance were lower BMI at baseline, complete skin clearance at Week 28, and higher guselkumab concentrations at Week 28.[33]

One analysis using VOYAGE 1 data to explore specific body regions found that at Week 24, 84.5% of patients receiving guselkumab showed

improvements in scalp scores versus 69.2% receiving adalimumab (p<0.001), 49.8% receiving guselkumab showed improvements in nail scores versus 49.4% receiving adalimumab (not significant), and 78.9% receiving guselkumab showed improvements in palmar plantar scores versus 56.8% receiving adalimumab (p<0.0001).[27] While adalimumab has been considered the first choice for nail involvement, it is noteworthy that guselkumab achieves the same effects (opinion of the speaker).

A second case from Dr Pinter's practice was presented: a 50-year-old male psoriasis patient with moderate palmoplantar involvement whose previous therapies included high-potency topical steroids, PUVA, re-PUVA, methotrexate, and secukinumab. In March 2018, prior to starting guselkumab, the Patient's Psoriasis Global Assessment (PPGA) was 3, but in May 2018 (after 2 months guselkumab) his PPGA was 0, demonstrating complete clearance of palmoplantar involvement.

PASI scores can be hard to understand, with patients more interested in the Psoriasis Symptom and Sign Diary, which numerically rates, from 0–10, five symptom items (itch, pain, stinging, burning, and skin tightness) and six patient-observable signs (skin dryness, crackling, scaling, shedding or flaking, redness, and bleeding),[34] and the DLQI, a 10-item questionnaire assessing six different aspects affecting disease specific health-related quality of life.[35]

In VOYAGE 1, the proportion of patients taking guselkumab achieving symptom-free status for Weeks 76 and 156 were 49.0% and 50.0%, respectively, for itch; 77.0% and 75.5% for pain; 76.9% and 74.7% for stinging symptoms; 79.0% and 76.0% for burning sensation; and 61.4% and 59.5% for skin tightness.[36] Results for observable sign items showed the proportion who were sign-free for Weeks 76 and 156 were 39.5% and 40.8%, respectively, for skin dryness; 72.6% and 69.9 % for cracking; 53.0% and 52.1% for scaling; 56.4% and 51.1% for shedding or flaking; 54.5 % and 54.0% for redness; and 87.7% and 87.8% for bleeding.[36]

An analysis of UltIMMa-1 and UltIMMa-2 studies in patients with moderate-to-severe chronic plaque psoriasis found that at Week 16, the percentage of patients achieving DLQI scores 0 or 1 for risankizumab was 66% in UltIMMa-1 and 67% for UltIMMa-2, for ustekinumab was 43% for UltIMMa-1 and 46% for UltIMMa-2, and for placebo was 8% for UltIMMa-1 and 4% for UltIMMa-2.[28]

At Week 52, DLQI scores 0 or 1 were achieved for 75% of patients taking risankizumab in UltIMMa-1 and 71% taking risankizumab in UltIMMa-2, for ustekinumab was 47% in UltIMMa-1 and 44% in UltIMMa-2, and for placebo then switching to risankizumab was 62% in UltIMMa-1 and 68% in UltIMMa-2.[28] Such results demonstrated risankizumab delivered better DLQI 0/1 than ustekinumab.[28] Furthermore, the frequency of treatment-emergent adverse events in UltMMa-1 and UltIMMa-2 trials were similar across risankizumab, placebo, ustekinumab, and placebo then switching to risankizumab.[28] Such data provide reassurance of no new safety signals for the next generation of selective IL-23 blockers.

In the ECLIPSE trial, 1,048 patients with severe plaque psoriasis were randomised to receive either guselkumab (subcutaneous injection at baseline, Weeks 4 and 12, then once every 8 weeks [n=534]) or a pair of 150 mg secukinumab (300 mg dose total) subcutaneous injections (at baseline, Weeks 1–4, then once every 4 weeks [n=514]).[37]

Results showed that at Week 48, 84.5% of patients treated with guselkumab achieved PASI 90 compared to 70.0% of those treated with secukinumab (p<0.001). The treatment difference was 14.2%.

For secondary endpoints of PASI 75 response at Week 12 and Week 48, guselkumab demonstrated non-inferiority when compared with secukinumab (84.6% versus 80.2%; p<0.001). Due to the 'hierarchical' analysis, the subsequent five secondary endpoints could not be answered with a p-value. Regarding adverse events, 77.9% of patients receiving guselkumab reported at least one adverse event versus 81.6% receiving secukinumab, and serious adverse events occurred in 6.2% receiving guselkumab versus 7.2% receiving secukinumab.

Audience Questions

The first audience question concerned whether it was possible to extract information regarding

age, sex, and comorbidities from registries to inform individual treatments for patients. Prof de Jong answered that individualised predictors were currently unavailable, but that in the future it might be possible to set individualised patient goals by using questionnaires to identify the outcomes people wanted.

The second question commented on the complacency of prescribers 'happy' with PASI 5 results, adding that such results were because of reluctance among patients and prescribers to switch treatments. Prof de Jong felt that the reluctance was due to the uncertainty surrounding new treatments, with the setting of treatment goals enabling people to switch. Dr Pinter added that prescribers should consider switching patients with PASI 4.

Considering the question of how to choose between different IL-23 inhibitors, Dr Pinter said that some were prescribed every 8 weeks and others every 12 weeks. There will be a need, he added, for registry data to explore how patients who had been pre-treated with other medications fare on guselkumab.

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Date of preparation: August 2019
CP-120821

IL-23 Inhibition in Psoriasis: A Novel Approach to Convenient, Consistent Clearance

This sponsored symposium took place on 12th June 2019 in Milan, Italy, as part of the 24th World Congress of Dermatology (WCD), 2019

Chairperson: Kristian Reich[1]

Speakers: Bruce Strober,[2] Curdin Conrad[3]

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Disclosure: Prof Reich has been an advisor and/or paid speaker and/or participated in clinical trials for AbbVie, Affibody, Almirall, Amgen, Avillion, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Centocor, Covagen, Forward Pharma, Fresenius Medical Care, Galapagos, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, Leo, Lilly, Medac, Merck Sharp & Dohme, Novartis, Miltenyi Biotec, Ocean Pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Sun Pharma, Takeda, UCB, Valeant, and Xenoport. Prof Strober has been an advisor and/or participated in clinical trials for AbbVie, Almirall, Amgen, Arena, Boehringer Ingelheim, Bristol-Myers-Squibb, Celgene, Dermavant, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Janssen, Leo, Medac, Meiji Seika Pharma, Menlo Therapeutics, Merck, Novartis, Ortho Dermatologics/Valeant, Pfizer, Regeneron, Sanofi-Genzyme, Sebela Pharmaceuticals, Sienna, Sirtris, Sun Pharma, and UCB. He is Scientific Director of CORRONA Psoriasis Registry; and AbbVie and Janssen have supported the University of Connecticut Fellowship Program. Prof Conrad has been a consultant and/or paid speaker and/or principal investigator in clinical trials for: AbbVie, Actelion, Amgen, Almirall, Celgene, Eli Lilly, Galderma, Janssen-Cilag, Leo Pharma, MSD, Novartis, Pfizer, and UCB.

Acknowledgements: Writing assistance was provided by Helen Saul.

Support: The symposium and this article were funded by Janssen.

Disclaimer: Investigational compounds and off-label uses of therapies were discussed in this session. Bimekizumab is an investigational compound which has not received marketing approval; guselkumab has not been licenced for the treatment of psoriatic arthritis.

Citation: EMJ Dermatol. 2019;7[Suppl 7]:2-11.

Meeting Summary

Prof Reich outlined our latest understanding of relevant psoriasis pathophysiology. Psoriasis was believed to be a skin disease mediated by T helper cell 1 (Th1 cell) 20 years ago; it has now been shown to be driven by Th17 cells, which are stimulated by a number of proinflammatory cytokines, among which IL-23 is overexpressed. Characteristics of the individual antibodies determine clinical properties. IL-23 inhibitors have long injection intervals, and inhibit more regulatory than effector cytokines.

Prof Strober reviewed key clinical data on IL-23 inhibitors including that from VOYAGE 1 and 2, NAVIGATE, and ECLIPSE for guselkumab; reSURFACE 1 and 2 for tildrakizumab; and ultIMMa-1/2

and IMMvent for risankizumab. Taken together, the many comparator studies suggest that the IL-23 inhibitors deliver robust and long-lasting efficacy, with long treatment intervals and with relative safety; there are few contraindications to use an IL-23 inhibitor. Prof Strober said he believes that, over time, this class will replace ustekinumab and become the first-line therapeutic approach in psoriasis.

Prof Conrad gave an overview of patients' needs and the drug, patient, and disease-related factors to be considered when choosing a therapy from the increasing numbers available. He stressed that no single agent or class is appropriate for all patients and that, in many instances, traditional anti-TNF are being superseded in terms of both efficacy and safety by newer drugs. Data on some disease-related factors, e.g., the presence of psoriatic arthritis, however, support the use of anti-TNF. Prof Conrad outlined his considerations regarding drug choice for patients with conditions such as pregnancy, inflammatory bowel disease (IBD), latent tuberculosis (TB), or hepatitis B virus (HBV).

Introduction

With increasing treatment options in psoriasis (e.g., TNF inhibitors, IL-12/IL-23 inhibitor ustekinumab, IL-17 inhibitors, and now IL-23 inhibitors), treatment strategies have become increasingly complex. This symposium aimed to help physicians manage this complexity and consider how advances in treatment can be used in the clinic to ensure that individual patients are offered the most appropriate therapy.

Navigating the Complex Waters of Psoriasis Treatment: Assessing the Best Target

Professor Kristian Reich

For many years, psoriasis was considered to be a skin disease mediated by Th1 cells.[1] TNF is a signature cytokine of the Th1 response, and therefore anti-TNF therapies, such as etanercept,[2] infliximab,[3] and adalimumab,[4] were introduced in the early 2000s. Ustekinumab,[5] which inhibits both IL-12 and IL-23, was introduced in 2009. The IL-17 blockers secukinumab,[6] ixekizumab,[7] and brodalumab[8] (anti-IL-17R) came next, followed by IL-23 inhibitors guselkumab,[9] in 2017, and more recently, tildrakizumab[10] and risankizumab.[11]

Patients have individual patterns of psoriasis and disease domains or manifestations include the scalp, palmar-plantar, pustular versus nonpustular, nail disease, psoriatic arthritis, and pericardial disease. Specific cytokine pathways may contribute differentially to various disease domains; this may influence the choice of therapy.

The pathophysiology of psoriasis involves epidermal hyperproliferation, abnormal differentiation of epidermal keratinocytes, and decreased keratinocyte apoptosis, all contributing to a thickening of the epidermis. An influx of immune cells, particularly T cells, is the main driver of psoriasis pathophysiology. Histological samples have shown that the T cells and dendritic cells sit in direct proximity in the skin;[12] they work in tandem and the so-called cross-talk between them is the focus of research interest in psoriasis. Immunologic cells, including the dendritic cells, release an 'educational' cytokine which activates T cells and leads to the development of Th1 and/or Th17 cells. Ten years ago, it was believed that IL-12 stimulated the overexpression of Th1 cells in psoriasis;[13] now it is believed that overexpression of the Th17 pathway, stimulated by IL-23, is the key driver in this disease.

Th17 cells release cytokines such as IL-17, which activate keratinocytes and initiate the epidermal pathology in psoriasis.[14] Once activated, keratinocytes are themselves an active source of cytokine mediators that then signal back and modulate the immune system. Epidermally-derived cytokines such as IL-19, IL-1β, IL-36, and IL-17C are relevant targets for agents in development or future drugs. The system is modulated via feed-forward and feed-backward responses.

This simplified upstream/downstream model (Figure 1) demonstrates that dendritic cells produce TNF-α that, acting synergistically with IL-17, activates keratinocytes. The dendritic cells also produce IL-23 that, in turn, activates neutrophils and T cells to produce IL-17. The model does not, however, explain the potential downside of inhibiting IL-17. In some patients, IL-17 inhibition

leads to exacerbation of IBD. This unexpected clinical finding led to the new understanding that Th17 cells may be pathogenic or nonpathogenic. Healthy skin has nonpathogenic Th17 cells that produce physiological IL-17 and protect against candida infection in the absence of IL-23. In the presence of IL-23, pathogenic Th17 cells overproduce IL-17.[15,16] IL-17 inhibitors are only given to patients with elevated IL-17 levels to normalise them, but over-suppression may increase the risk of candida infections. This is not seen with IL-23 inhibition.

This type of therapeutic molecule (e.g., human monoclonal antibodies [adalimumab] or polyethylene glycol PEGylated human fragment antigen-binding region [certolizumab][17]) may have distinguishing properties in the clinic. The mechanism by which agents inhibit IL-17 also influences its clinical properties. Secukinumab and ixekizumab inhibit both the IL-17A homodimer and the IL-17A/F heterodimer. Bimekizumab, currently in development, inhibits IL-17A and IL-17F as well as the IL-17A/F heterodimer. Brodalumab has a wider effect, blocking its receptor, and thereby the signalling for IL-17A, IL-17F, IL-17E, and IL-17C.[18]

Selective targeting of IL-23 varies according to the agent. The IL-23 receptor is comprised of subunits p40 and p19: the IL-12 receptor of p35 and p40 subunits. Ustekinumab binds to p40, thereby inhibiting both IL-23 and IL-12. The IL-23 inhibitors guselkumab, tildrakizumab, and risankizumab selectively target the p19 subunit and inhibit IL-23, but not IL-12. IL-12 is now thought to have anti-inflammatory properties in psoriasis, playing a role in defence against intracellular pathogens, and inhibiting IL-23 alone has been shown to be preferable to inhibiting IL-12/IL-23.[19]

Differences between drugs in terms of pharmacokinetics, dose, immunogenicity, affinity, potency, and specificity are characteristic of the antibodies themselves; three antibodies with the same target may have different properties in practice. There are also class effects; the long injection intervals (every 8 or 12 weeks) with IL-23 inhibitors may be due to the drugs' upstream effect (Figure 1), inhibiting an educational rather than an effector cytokine. Response rates are high and stable with this class of drug.

One reason why psoriasis can reappear once therapy is stopped could be that an inflammatory memory develops if the disease has been uncontrolled over time. Researchers have found that treatment with the IL-17A inhibitor secukinumab reduced counts of the so-called resident memory T cells,[20] which carry the inflammatory memory. IL-23 inhibitors may have an even greater effect than IL-17 inhibitors on the resident memory T cells, but currently this is unproven. It has been shown that patients responding to guselkumab lose response only slowly if the drug is discontinued,[21] and a proportion maintain response for a prolonged period without further treatment.

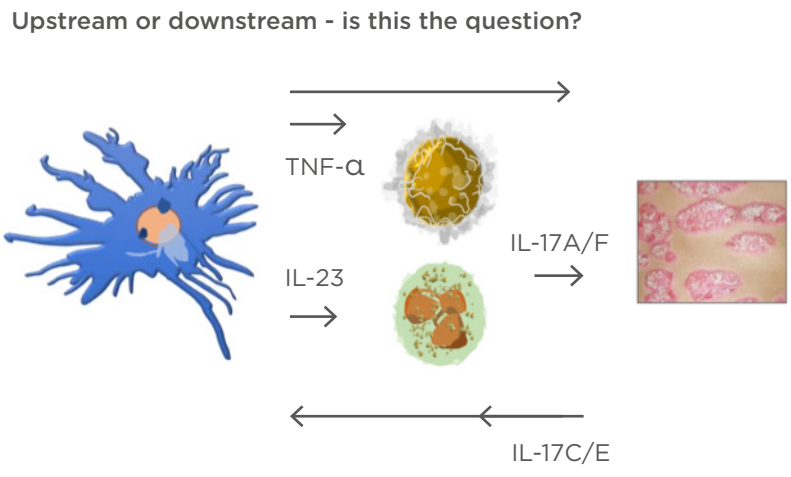

Figure 1: A simplified model demonstrating the importance of activation of dendritic cells in the epidermis.

Patients responding to guselkumab at Week 20 were randomised to continue treatment (n=193) or to receive placebo (n=182). Six months later, at Week 48, more than one third of the patients (36.8%) in the placebo arm continued to have a Psoriasis Area Severity Index (PASI) 90 response[21,22] without being on active treatment. This observation needs to be explored further.

Clinical and biological markers associated with long-term maintenance of PASI 90 response following withdrawal of guselkumab[23] include a range of factors such as lower BMI (p<0.001), PASI 100 response at Week 28 (p<0.005), and a shorter disease duration (p<0.005).[23] Prof Reich said that allowing a patient's disease to remain uncontrolled may reduce the chance of him/her ever becoming disease-free while not on active treatment.

What Do the Data Say? Evidence-Based Decision Making for Psoriasis Treatment

Professor Bruce Strober

In 2009, the approval of ustekinumab, which inhibits IL-12/IL-23, represented a significant advance in psoriasis therapy. The PHOENIX 1 study found that of 255 patients given 45 mg ustekinumab, 41.6% achieved PASI 90, compared to 2.0% on placebo (p<0.0001).[24] In 2017, the specific IL-23 inhibitor guselkumab was compared with the anti-TNF-α agent adalimumab in the VOYAGE 1 study.[25] Patients with moderate-to-severe psoriasis received placebo (n=174), guselkumab (n=329; 100 mg at Weeks 0 and 4 then q8w), or adalimumab (n=334; 80 mg Week 0, 40 mg Week 1, then 40 mg q2w). At Week 16, 73.3% of the guselkumab arm had achieved PASI 90, and this was maintained, with 76.3% of the group still having PASI 90 at Week 48. This compared to 49.7% of the adalimumab arm with PASI 90 at Week 16, dropping to 47.9% at Week 48.

Rates of PASI 90 in the guselkumab arm were approximately equivalent to rates of PASI 75 in the adalimumab arm.[25] Prof Strober said this comparison puts the efficacy of guselkumab into perspective. Rates of PASI 100 in the guselkumab arm were approximately double those in the adalimumab arm (37.4% versus 17.1% at Week 16; 47.4% versus 23.4% at Week 48);[25] patients had almost a one in two chance of having totally clear skin after a year of guselkumab therapy.

At Week 52, adalimumab nonresponders (failure to achieve PASI 90) in VOYAGE 1 were switched to guselkumab.[26] At Week 100, 73% had achieved PASI 90 and 42% had achieved PASI 100,[26] findings replicated in VOYAGE 2. The therapy switch turned inadequate responders into responders, Prof Strober said.

The NAVIGATE study[27] included patients who did not achieve an Investigator's Global Assessment (IGA) score of 0/1 after 2 doses ustekinumab (n=135). At Week 16, they were switched to guselkumab; those who were switched derived significant benefit over those were maintained on ustekinumab (n=133). Greater proportions achieved IGA 0/1 and at least a two-grade improvement at Week 28 (31.1% versus 14.3%; p=0.001) and at Week 52 (36.3% versus 17.3%; p<0.001).[27]

In the Phase III ECLIPSE trial,[28] guselkumab and secukinumab were compared head-to-head. In the guselkumab arm (n=534), a 100 mg dose was given at Weeks 0, 4, 12, then q8w. In the secukinumab arm (n=514), a 300 mg dose was given at Weeks 0, 1, 2, 3, 4, then q4w. Initially, at Week 12, patients in the secukinumab arm were more likely to have a PASI 90 response (76.1% secukinumab patients versus 69.1% guselkumab patients). But over time, the situation reversed and at Week 48, the PASI 90 rates confirmed the superiority of guselkumab over secukinumab (70.0% secukinumab patients versus 84.5% guselkumab patients; p<0.001).[28] The study used the conservative, nonresponder imputation (NRI) approach. Prof Strober said that the guselkumab arm showed a stable PASI 90 response rate, whereas the rate in the secukinumab arm declined slightly, implying that the gap between the arms may widen over time.

Tildrakizumab is another approved IL-23 inhibitor which specifically blocks the p19 subunit, however data from the reSURFACE trial[29] suggests lower efficacy than is seen with guselkumab. The trial compared tildrakizumab with placebo or etanercept; at Week 12, 61% of patients receiving 100 mg tildrakizumab, and 66% of those receiving 200 mg tildrakizumab, had achieved a

PASI 75 response. By Week 28, 74% patients on either tildrakizumab dose had achieved PASI 75 response. A PASI 90 response was achieved by 37% of patients on the lower dose and 39% of patients on the higher dose at Week 12. By Week 28, these figures were 56% and 58%, respectively. A PASI 100 response was achieved by 12% of patients on either dose at Week 12, and by 23% and 27% in the 100 mg and 200 mg groups, respectively, at Week 28.

Risankizumab is the third IL-23 inhibitor approved in moderate-to-severe psoriasis. In the ultIMMa-1 trial,[30] 75.3% patients receiving risankizumab achieved a PASI 90 response at Week 16, rising to 81.9% at Week 52. In the comparator group, 42.0% of those receiving ustekinumab achieved a PASI 90 response at Week 16,[30] rising to 44.0% at Week 52. Some loss of response between injections was seen in the ustekinumab group, while the response with risankizumab remained stable between injection intervals. Integrated data from ultIMMa-1 and ultIMMa-2[30] showed that 88.4% of risankizumab patients who achieved PASI 90 at Week 16 retained the response at Week 52 compared to 73.3% receiving ustekinumab ($p<0.001$).

The IMMvent study[31] compared risankizumab with adalimumab. At Week 16, patients randomised to risankizumab continued with this treatment; those on adalimumab with a PASI 90 response continued with adalimumab. However, nonresponders to adalimumab (PASI <50) were switched to risankizumab; those with intermediate response (PASI 50–<90) were rerandomised to either adalimumab or risankizumab. At Week 44, 76% of those who received risankizumab throughout the study had PASI 90 response. Among the intermediate responders who switched therapy, 66% achieved PASI 90 compared to 61% among nonresponders who switched. Of those rerandomised to adalimumab, 21% had PASI 90 at Week 44. This suggests that patients can be successfully switched from adalimumab to risankizumab, but those with an initial intermediate or nonresponse to adalimumab may be harder to treat.

The IL-23 inhibitors have a reassuring safety profile with few notable differences between the various agents. None are associated with serious infections, major adverse cardiac events, malignancy, or death. Patients in the guselkumab arm of VOYAGE 1 and VOYAGE 2 were followed for 156 weeks and no clear discrepancy was found in serious infections, malignancies excluding nonmelanoma skin cancers, major adverse cardiac events, or deaths.[32,33] The safety profile of tildrakizumab is again reassuring. The higher dose of tildrakizumab was not associated with more infections than the lower dose, and there appeared to be a large therapeutic window within the limits of the doses used in moderate-to-severe psoriasis.

Data from the ultIMMa trials[30] suggest risankizumab has a similar safety profile; upper respiratory tract infections account for most of the infections that occur more frequently.[30] Analysis of pooled clinical trial data found a slight increase in fungal infections, predominantly superficial tinea infections, and a few cases of herpes zoster which did not necessitate discontinuation of treatment.[34]

Studies on the three IL-23/p19 inhibitors have included patients who tested positive for latent TB prior to entry and were allowed to receive prophylaxis with standard local regimens. There were almost no cases of reactivation of TB.[9-11] None of the 105 patients with latent TB receiving guselkumab developed active disease: nor of the 103 receiving risankizumab. One patient developed TB while receiving tildrakizumab, but of the 55 with latent disease receiving prophylaxis, none developed active TB.

In conclusion, IL-23 inhibitors deliver robust and long-lasting efficacy even where dosing is infrequent and variable. In fact, patients can miss a dose by up to 3 weeks and still maintain the response. Taken together, the many comparator studies suggest that the IL-23 inhibitors provide better efficacy and equivalent safety to ustekinumab. Over time, this class is likely to replace ustekinumab and become the first-line therapeutic approach in psoriasis. The efficacy of IL-23 inhibitors is yet to be determined in both treating psoriatic arthritis and reducing systemic inflammation. Because there are few contraindications to the use of IL-23 inhibitors, patients with IBD, multiple sclerosis, liver disease, or heart disease may all be considered for these drugs.

Patient Profiling in Daily Practice: Which Drug for Which Patient?

Professor Curdin Conrad

There are >10 approved biological therapies for psoriasis which makes choosing the optimal therapy a complex decision. As an example, a recent publication[35] demonstrated the potential importance of the choice of first biologic. Of patients with moderate-to-severe psoriasis who received the IL-17 inhibitor secukinumab as first-line therapy, approximately 80% were still taking the drug after 3 years. This figure fell to approximately 50% among those receiving secukinumab as the second-line biologic, and to approximately 30% among those receiving the treatment after two or more previous biologics.

There are no current guidelines stating which drug should be given to which patient. In making a choice, drug-related factors include efficacy, safety, and convenience which in turn affects compliance. Patient-related factors include age, sex, child-bearing potential, demand, or expectation. Disease-related factors include disease activity and course, the phenotype (whether there is nail psoriasis, palmoplantar psoriasis, or psoriatic arthritis), the severity and impact of the disease, and comorbidities. Taken together, these factors feed into drug survival; no single treatment is effective and appropriate for all patients.

On drug efficacy, as has been described, an early meta-analysis[36] showed ustekinumab to be more efficacious than the anti-TNF therapies adalimumab and etanercept. The IL-17 inhibitors, approved in 2015, were associated with significantly higher response rates than ustekinumab;[37] the introduction of IL-23 specific inhibitors was associated with still higher PASI responses and high levels of maintained efficacy.[28]

Regarding safety, meta-analyses show no major differences between anti-TNF therapies and anti-IL- 12/23.[38,39] Real-life data suggests however that anti-TNF therapies have a higher risk of serious infections,[40] and that patients on ustekinumab are less likely to withdraw from treatment due to adverse events.[41] Notwithstanding specific circumstances, anti-TNF therapies are being superseded in terms of both efficacy and safety by the newer drugs.

On drug survival, approximately 50% patients withdraw from anti-TNF therapy within 3 years; drug survival is significantly higher with ustekinumab than with adalimumab, infliximab, or etanercept.[42] Whilst still a matter of debate, drug survival rates with IL-17 inhibitors probably lie between the range of ustekinumab and other anti-TNF responses; there is no conclusion yet on this aspect for guselkumab or the other IL-23 inhibitors, but research is ongoing.

In a patient with no comorbidities, ustekinumab, IL-17 inhibitors, and IL-23 inhibitors are all safe options, but comorbidities can drive the choice of drug (Table 1). For example, where a patient has severe psoriatic arthritis, robust data supports the use of the anti-TNF as the gold standard. The anti-IL-17 therapies would be second choice, and ustekinumab and the IL-23 inhibitors third. This does not mean that all patients with psoriatic arthritis should be treated with an anti-TNF; a patient with mild psoriatic arthritis and severe psoriasis could be appropriately treated with one of the other therapies.

The development of IL-17A inhibitor secukinumab as a treatment for IBD was stopped because of lack of efficacy and higher rates of adverse events compared to placebo;[43] new onset IBD and aggravation of existing disease was reported. As described by Prof Reich, this led to the description of pathogenic and nonpathogenic Th17 cells[44] and new understanding that suppression of IL-17 can lead to aggravation of IBD. For a patient with a family or personal history of IBD, the first choice of psoriasis therapy would be an anti-TNF or ustekinumab, which are indicated in Crohn's disease. Studies on IL-23 inhibitors are still ongoing, but this class of drug is likely to have a beneficial effect on IBD as well. Etanercept is not effective in IBD but will not exacerbate the condition; IL-17 inhibitors should be used only with caution in these patients.

Risk of TB reactivation is a specific class effect of the anti-TNF therapies;[45] therefore, ustekinumab, IL-17 inhibitors, and IL-23 inhibitors are all preferable to anti-TNF for a patient with latent TB. The necessity of TB screens might no longer be obligatory in the future when prescribing drugs other than anti-TNF. In a patient with acute infection with HBV, biologic treatment should be avoided before antiviral therapy is initiated.

Table 1: Treatment choices in psoriasis with comorbidity.

In case of...	Therapy			
Lupus, paradoxical psoriasis	Ustekinumab	Anti-IL-23	Anti-IL-17	Anti-TNF
Multiple sclerosis	Anti-IL-17	Ustekinumab	Anti-IL-23	Anti-TNF
Congestive heart failure (NYHA3/4)	Ustekinumab	Anti-IL-17	Anti-IL-23	Anti-TNF
Uveitis	Anti-TNF			
Overweight	Ustekinumab	Infliximab	Anti-IL-23	
Malcompliance	Ustekinumab	Infliximab	Anti-IL-23	
Psoriatic arthritis	Anti-TNF	Anti-IL-17	Ustekinumab	Anti-IL-23
IBD	Anti-TNF	Ustekinumab	Anti-IL-23	Anti-TNF
Latent tuberculosis	Ustekinumab	Anti-IL-17	Anti-IL-23	Anti-TNF
Hepatitis B	Ustekinumab	Anti-IL-17	Anti-IL-23	Anti-TNF
Childbearing potential	Certolizumab			
Children	Etanercept	Adalimumab	Ustekinumab	

A suggested scheme for treatment choice in psoriasis patients with comorbidities. The colours show the order of preference: dark green for the first-choice therapy, followed by paler green, then pink. Dark pink indicates that therapies would normally be avoided for patients with these comorbidities.

Anti-TNF: Anti-tumour necrosis factor; IBD: inflammatory bowel disease; IL: interleukin; NYHA: New York Heart Association.

Where the infection is occult, reactivation can occur with ustekinumab or IL-17 inhibitors but only in patients who test positive for hepatitis B surface antigen or DNA-detected HBV.[46,47] With that caveat, ustekinumab, anti-IL-17, and anti-IL-23 are safe choices in patients with a history

of HBV infections, whereas HBV reactivation has been shown for anti-TNF treated patients.

Paradoxical psoriasis and lupus or lupus-like syndrome have been shown to be a class effect of anti-TNF drugs,[48] and there is ongoing discussion on whether anti-TNF approaches increase the risk of demyelinating disorders and lymphoma.

Discontinuation of treatment during pregnancy is often the preferred approach; however, a study on pregnant women treated with certolizumab pegol found, at the time of birth, that women had expected levels of the drug in blood samples; the infants had minimal or no detectable levels.[49] The study concluded there was a lack of placental transfer of certolizumab pegol during pregnancy; this drug would therefore be preferable to others in pregnant women if psoriasis treatment is necessary.

In European children, adalimumab[4] has been indicated since 2015 for those of ≥4 years of age; etanercept[2] since 2004 for those of ≥6 years of age; and ustekinumab[5] since 2015 for those of ≥12 years of age. Etanercept is the first-choice therapy in children because of long experience, and also because etanercept can be stopped after initial treatment and restarted, which is particularly useful as the disease course can alter during adolescence.

For the future, research is ongoing into biomarkers, which will predict a patient's response. HLA CW6 predicts better response to ustekinumab. Drug levels of adalimumab measured as early as Week 1 may predict response; the BSTOP Study Group/PSORT Consortium found that after a single injection of 80 mg adalimumab, blood levels ≥7 µg/mL suggests 80% probability of achieving PASI 75 response and 51% probability of achieving PASI 90 response.[50] Blood levels <3 µg/mL indicate that treatment response will be low. While this is useful clinical information, Prof Conrad said the ideal is to find biomarkers to drive decisions prior to initiation of treatment.

Summarising this message, he said that there is not a single biologic agent or class which can be used to treat all patients. All classes have unique benefits and limitations depending on drug-related, patient-related, or disease-related factors.

Conclusion

Prof Reich concluded the symposium by stating that the introduction of IL-23 inhibitors has broadened the therapeutic armamentarium in psoriasis, to the extent that many patients on IL-23 inhibitors have a PASI 100 response after a year. The IL-23 inhibitors give high levels of response, seem to be extremely safe, and instill stable responses in patients. Great things have clearly been achieved in the treatment of psoriasis.

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Date of preparation: August 2019
CP-120824

Pathways to Silencing Psoriasis: Remission or Cure?

This symposium took place on Friday 20th September 2019, as part of the 49th Annual European Society for Dermatological Research (ESDR) meeting in Bordeaux, France

Chairpeople: Jo Lambert,[1] Jörg Prinz[2]

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Disclosure: Prof Prinz has been a consultant, speaker, or advisory board member for Almirall, Janssen-Cilag, Novartis, and Pfizer. Dr Lambert has received unrestricted grants from AbbVie, Celgene, Eli Lilly, Janssen-Cilag, LEO Pharma, and Novartis; has been a speaker for Pfizer, AbbVie, and Janssen-Cilag; and has been a consultant for AbbVie, Celgene, Eli Lilly, Janssen-Cilag, LEO Pharma, and Novartis. Dr Paul has a consulting agreement with AbbVie, Almirall, Amgen, Astellas, Celgene, GSK, Lilly, Janssen-Cilag, Leo Pharma, Pierre Fabre, Novartis, Pfizer, and Sanofi/Regeneron; and has received research grants from Astellas, Abbvie, Janssen-Cilag, Lilly, Novartis, and Pierre Fabre.

Acknowledgements: Medical writing assistance was provided by Megan Breuer, Excerpta Medica, Amsterdam, the Netherlands.

Support: The symposium and the publication of this article were funded by Janssen. The views and opinions expressed are those of the speakers and not necessarily of Janssen.

Citation: EMJ Dermatol. 2019;7[Suppl 9]:2-8.

Meeting Summary

The symposium "Pathways to silencing psoriasis: Remission or Cure?" took place during the 2019 European Society for Dermatological Research (ESDR) annual congress in Bordeaux, France. The presentations reviewed the role of the IL-23 pathway in psoriasis pathogenesis and other immune-mediated inflammatory diseases (IMID), underlined the importance of assessing and treating comorbidities in patients with psoriasis, and concluded with a glimpse into the future of psoriasis management, examining whether drug-free remission from disease is a viable goal for future treatment plans.

After defining and giving some examples of familial and poly-autoimmunity, Prof Jörg Prinz described the common pathways shared by several IMID. The involvement of the IL-23/Th(c)17 pathway in the pathogenesis of various IMID may represent opportunities for future therapeutic targets and treatment strategies.

The importance of holistic treatment in psoriasis management was illustrated by Prof Jo Lambert, who showed the audience how psoriasis can be linked to several different comorbidities, all of which should be addressed when making treatment decisions. Proper assessments and informed treatment choices could help patients with psoriasis achieve better clinical outcomes and help improve their long-term health expectations.

Reducing treatment burden for patients, and the possibility of achieving and maintaining drug-free remission, was discussed by Prof Carle Paul, who underlined the importance of examining several important predictive biomarkers of treatment response. Early, intensive treatment and disease modification could result in long-term remission of severe psoriasis and further decrease the treatment burden for patients.

The Role of IL-23 in the Pathogenesis of Psoriasis: A Common Pathway in Immune-Mediated Inflammatory Diseases

Professor Jörg Prinz

Psoriasis occurs more frequently alongside other IMID, indicating common pathogenetic pathways. Many of these IMID show familial accumulation as a sign of a strong genetic predisposition. These phenomena have long been known as poly-autoimmunity and familial autoimmunity.[1] Poly-autoimmunity refers to the persistence of multiple IMID in the same patient. Patients with one IMID are therefore susceptible to developing other IMID.[1] Shared clinical and immunological characteristics of these IMID owing to overlapping aetiological factors reflect shared pathogenic pathways that may result in similar responses to the same therapeutic treatment.[1]

IMID are generally defined as a group of common and highly disabling chronic immune-mediated inflammatory conditions, characterised by a dysregulation of normal immune responses that lead to inflammation in the target organs and systemic effects. Over 80 IMID have been defined thus far, and their estimated current prevalence in Western society is approximately 5–7%.[2,3] The most relevant IMID include rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis, Crohn's disease (CD), ulcerative colitis (UC), systemic lupus erythematosus (SLE), Type I diabetes mellitus, and multiple sclerosis (MS).[4]

IMID have complex genetic predispositions, and outside the major histocompatibility complex regions, each IMID shows >80 risk variants; however, the presence of genetic overlaps between IMID indicates possible similarities in pathogenetic pathways.[4] For example, cross-trait analyses of multiple IMID have revealed that several of the diseases share several gene loci.[5,6] Up to 85% of associated variants may be shared between different IMID, offering a glimpse into disease biology and directing common treatment approaches.[5,6] Shared loci can have a concordant effect on disease manifestation, implying a shared risk of the disease, or a discordant effect, meaning that one locus indicates a disease risk factor despite having a protective function for a different disease.[5,7] Importantly, concordant and discordant association of gene variants for psoriasis, AS, SLE, CD, UC, RA, MS, and coeliac disease are all related to the IL-23 and T helper (Th)1/Th17 pathways.[5,7]

Previous *in vivo* studies have indicated that the IL-23/17 pathways are involved in autoimmunity. Mice lacking IL-23, or displaying loss of IL-23 function, lack expression of IL-17-producing T cells and are resistant to developing several types of autoimmune diseases, including experimental autoimmune encephalitis and collagen-induced arthritis.[8-10] Loss of function *IL23R* mutations in humans protect from psoriasis and psoriatic arthritis, CD, and AS. Thus, IL-23 and Th17 cells are implicated in the pathogenesis of various human autoimmune diseases. Accordingly, neutralising IL-23 specifically downregulates pathogenic Th/c17-cell activation and is highly effective in the treatment of psoriatic arthritis, AS, CD, UC, and SLE.[4,8-10]

In psoriasis, IL-23 maintains activation of the pathogenic T cell response, stimulating keratinocyte proliferation.[11,12] Blockade of the IL-23 pathway in patients with psoriasis is an effective and sustainable treatment, and efficacy appears to increase as interference with the IL-23/Th(c)17 axis becomes more targeted.[13-21] For example, recent results from the ECLIPSE clinical trial showed that treatment with guselkumab, an IL-23p19 inhibitor, resulted in superior long-term efficacy at 48 weeks based on Psoriasis Area Severity Index (PASI) 90 compared with secukinumab, an IL-17A inhibitor.[22] Guselkumab treatment resulted in sustained PASI 90 scores over 48 weeks in 84.0% of patients, compared

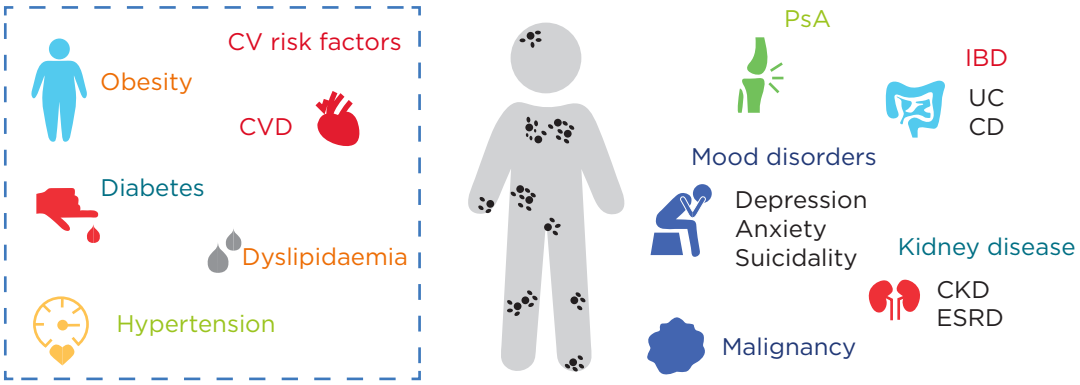

Figure 1: Psoriasis is associated with increased risk of serious comorbidities.

Comorbidities and risk factors associated with psoriasis.

CD: Crohn's disease; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; ESRD: end-stage renal disease; IBD: inflammatory bowel disease; PsA: psoriatic arthritis; UC: ulcerative colitis.

Adapted from Takeshita et al.[25] and World Health Organization.[27]

with 70.0% of patients receiving secukinumab.[22] Similarly, results from the VOYAGE 2 trial showed that 88.6% of patients receiving guselkumab maintained PASI 90 responses at 48 weeks. Many patients showed a sustained effect of IL-23 blockade beyond discontinuation of the drug: 28 weeks after responders had been rerandomised to placebo, 62.0% still showed PASI 75, 36.8% PASI 90, and 19.0% were still free of disease.[23]

In conclusion, IMID are chronic inflammatory diseases with complex genetic predispositions. Shared genetic factors provide important insights into disease biology. Interfering with the IL-23/Th(c)17 pathway provides control over various IMID associated with IL-23, resulting in novel treatment perspectives for diseases such as psoriasis, psoriatic arthritis, AS, UC, CD, and SLE. Thus, the shared genetic predispositions and disease pathways provide possible mechanistic links among IMID and represent valid and important therapeutic targets.

Optimising Psoriasis Care of Patients with Comorbidity

Professor Jo Lambert

Comorbidities associated with psoriasis can be classified into categories such as classic, emerging, lifestyle-related, or treatment-related, and can include such afflictions as cardiovascular disease, mood disorders, psoriatic arthritis, inflammatory bowel disease, malignancies, and kidney disease.[24,25] Furthermore, cardiovascular disease is the leading cause of death in patients with psoriasis (Figure 1).[25-27]

The importance of a multidisciplinary approach to psoriasis management emphasises the value of treating beyond the target of optimal skin care.[28] Traditional screening methods include medical history, clinical exams, blood tests, and questionnaires, with defined cut-offs for specialist referrals, and use guidelines for age-appropriate cancer screening.[25,29,30] Optimal treatment strategies rely on dermatologists' awareness of psoriasis-related comorbidities, because the type of comorbidity can define later treatment decisions.[31]

Optimal treatment strategies should not only focus on the patient's condition, but also address the patient's needs and improve patient value.[32] Patient value is particularly important, because there currently seems to be a disconnect between patient-perceived and medically-perceived disease severity.[33-35] A proposed novel approach to psoriasis management includes addressing the issue of undertreatment, taking an integrated approach to known health issues, screening for other psoriasis-related comorbidities, referring adequately, and paying more attention to the

psychosocial and lifestyle-associated factors to ensure a full cycle of care for patients.[33]

Treatment decisions are ultimately the shared decision of the healthcare provider and the patient and should occur simultaneously while monitoring for comorbidities.[36] The goals of treatment, therefore, should be to improve outcomes for the patient and improve patient and clinician experience, while keeping costs to a minimum.[37] In the future, payment processes may move to a more 'bundled payment' plan for patients for psoriasis, shifting from fee-for-service practices to value-based reimbursement plans. The total payer cost would therefore focus on meaningful clinical outcomes for the patient and longitudinal, rather than acute, care programmes.[32]

The need to treat patients holistically and encourage them to adopt lifestyle changes to reduce the risk of other comorbidities is an important factor in psoriasis management; treatment choices can also have a substantial impact on psoriasis-related comorbidities and patient quality of life. In a recent study, patients treated with guselkumab showed significant improvements in general health-related quality of life, as well as significant decreases in anxiety and depression symptoms after 24 and 100 weeks of treatment.[38,39] Another study, in a population of psoriasis patients at risk of coronary artery disease, showed how treatment with secukinumab may have a positive effect on cardiovascular health.[40] Inhibition of the IL-12/23 pathway with ustekinumab has also been shown to transiently reduce aortic vascular inflammation in patients with psoriasis.[41] Furthermore, comorbidities can also have an impact on the effectiveness of treatment. Results from a recent study showed that obesity can negatively impact treatment responses to anti-TNF agents.[42]

In conclusion, the importance of comorbidities in psoriasis management should not be underestimated. Taking these factors into consideration could result in better treatment outcomes for patients, and help patients improve their long-term health expectations.

Future of Psoriasis: Can Lasting Improvement be Achieved in Psoriasis Care?

Professor Carle Paul

Though many steps have been made in the past to improve psoriasis treatment, psoriasis management should focus on the need to decrease the treatment burden for patients, and to help patients achieve both long-term clearance and remission of psoriasis. Results from recent studies have shown that newer biologic therapies have resulted in increased efficacy in patients with psoriasis.[43] Data from the BADBIR Registry and DERMBIO studies show that IL-12/23 inhibition results in higher levels of drug persistence and drug survival, compared with anti-TNF alpha or anti-IL-17 therapies.[44,45] Furthermore, data from the PSOLAR study shows that drug persistence with ustekinumab was higher when given either as first, second, or third-line treatment, compared with infliximab, adalimumab, or etanercept.[46]

However, the data from real-life clinical practice does not always mirror clinical trial results, reflecting the need for a holistic approach to psoriasis and comorbidity management, and recognition of the fact that adherence to long-term treatment represents a challenge for some patients. Therefore, the PSTELLAR study aimed to examine the effect of dosing interval extension beyond 12 weeks on the efficacy of ustekinumab in subjects with moderate-to-severe plaque-type psoriasis.[47] An assessment of Physician's Global Assessment (PGA) scores showed that a subset of patients was able to maintain clearance while receiving a dose every 24 weeks,[48] indicating that a decrease of treatment burden for patients can be achieved, while still effectively maintaining a clinical effect.

Furthermore, studies with guselkumab show that >85% of patients maintained PASI 90 scores, and almost 60% of patients maintained PASI 100 scores 28 weeks after treatment cessation.[23] Results from the VOYAGE-2 study led to the identification of important predictors for drug-free remission, including shorter disease duration and lower level of serum IL-17F (Figure 2), but also PASI 100 achievement at Week 28; Investigator's Global Assessment (IGA) 0 achievement at Week 28; and higher blood guselkumab concentration at Week 28. The greatest amount of predictive power for drug-free remission of psoriasis was obtained using a model combining disease duration, IGA 0 response, and guselkumab concentration at Week 28.[49]

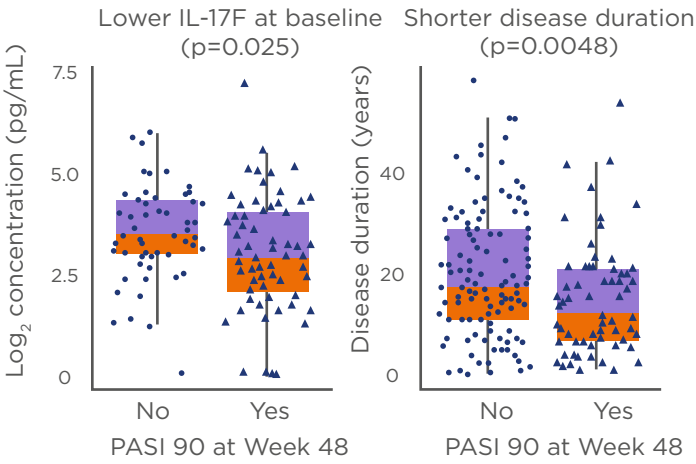

Figure 2: Predictors of drug-free remission after withdrawal from treatment with guselkumab.

PASI: Psoriasis Area Severity Index.

Adapted from Liu et al.[49]

The GUIDE study will examine further maintenance treatment strategies with guselkumab by comparing several patient populations, including patients with short versus long disease duration and those with biomarkers identified as predictors of drug-free remission in the VOYAGE 2.[50]

For several reasons, the goal of obtaining remission in psoriasis represents a substantial hurdle for dermatologists. Epidermal Th22 and Tc17 cells can form localised 'disease memory' in clinically healed psoriasis plaques, and can produce cytokines associated with lesion formation, leading to relapses.[51] Triggering of IL-17A resident memory T cells can also result in tissue-specific disease responses, and relapse, in previously resolved plaques.[52] However, early, intensive treatment and modification of the longterm disease course may result in the remission of severe psoriasis.[53] Disease modification may offer the possibility to decrease, or discontinue, biologic treatment if the patient shows complete psoriasis clearance and no psoriatic arthritis development, has a normal body weight, and has recent onset of psoriasis.[53] In Prof Paul's opinion, current evidence appears to indicate that IL-23 inhibitors may lend themselves more easily to treatment reduction, or cessation of treatment, compared with TNF agonists and IL-17 antagonists.

In conclusion, numerous therapeutic options have helped to drastically improve psoriatic care, but the possibility to lower the burden of treatment for the patients should be evaluated in prospective clinical trials. The possibility of achieving long-term disease remission is being assessed in targeted populations and may represent opportunities for disease control beyond symptom management alone.

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Date of Preparation: October 2019.
CP-120819

Date of preparation: October 2019
CP-120819

IL-23 Inhibition: From Pathophysiological Jungle to Clinical Clearance

This symposium took place on 10th October 2019, as part of the 28th Annual European Academy of Dermatology and Venereology (EADV) Congress in Madrid, Spain

Chairpeople: Kristian Reich,[1,2] Richard Warren[3]

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Disclosure: Prof Reich has been an advisor and/or paid speaker and/or clinical trial investigator for AbbVie, Affibody, Almirall, Amgen, Avillion, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Centocor, Covagen, Forward Pharma, Fresenius Medical Care, Galapagos, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, Leo, Lilly, Medac, Merck Sharp & Dohme, Novartis, Miltenyi Biotec, Ocean Pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Sun Pharma, Takeda, UCB, Valeant, and Xenoport. Prof Warren has been an investigator for AbbVie, Almirall, Amgen, Bristol-Myers Squibb, Eli Lilly, Janssen, Leo Pharma, Medac, Novartis, Pfizer, and UCB; and has been a speaker/consultant for AbbVie, Almirall, Amgen, Arena Pharmaceuticals, Avilion, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Janssen, Leo Pharma, Medac, Novartis, Pfizer, Sanofi, UCB, and Xenoport. Prof Kirby has received research support or been a principal investigator for clinical trials for AbbVie, Merck Sharpe & Dohme, Novartis, Pfizer, and UCB; has been a consultant for AbbVie, Celgene, Jansen, Lilly, Merck Sharpe & Dohme, Novartis, Pfizer, and UCB; has received honoraria from AbbVie, Celgene, Janssen, Lilly, Novartis, Pfizer, and UCB; and has been a scientific advisory board member for AbbVie, Celgene, Janssen, Lilly, Novartis, Pfizer, and UCB.

Acknowledgements: Medical writing assistance was provided by Megan Breuer of Excerpta Medica, Amsterdam, the Netherlands.

Support: The symposium and the publication of this article were funded by Janssen. The views and opinions expressed are those of the speakers and not necessarily of Janssen.

Citation: EMJ Dermatol. 2019;7[Suppl 10]:2-7.

Meeting Summary

The symposium "IL-23 Inhibition: From Pathophysiological Jungle to Clinical Clearance" took place during the 2019 annual European Academy of Dermatology and Venereology (EADV) congress in Madrid, Spain. The presentations gave an overview of how to navigate the complexities of the psoriasis treatment landscape, including updates on the newest developments in psoriasis, from pathophysiological considerations to clinical relevance, with a focus on how insights from recent trials can be applied in daily clinical practice.

Prof Reich discussed the pathophysiology of psoriasis and the scientific rationale for using different classes of biologics. It is likely that IL-17 and IL-23 have differential roles in psoriasis and psoriatic

arthritis (PsA) disease domains, and these different mechanistic roles translate into differences in clinical behaviour of respective inhibitors.

Analyses of clinical trial data, as presented by Prof Warren, show that treatment with IL-23 inhibitors results in high levels of efficacy that can be maintained for up to 3 years, with extended maintenance of 90% reduction in the Psoriasis Area and Severity Index (PASI) 90 responses after treatment withdrawal. Furthermore, the majority of patients report improvements in quality of life during treatment, with improved Dermatology Life Quality Index (DLQI) scores after 1 year of treatment. IL-23 inhibitors are a safe treatment option for patients with psoriasis, as evidenced by data produced by long-term extension and randomised clinical trials.

Prof Kirby shared his experiences managing patients with specific clinical challenges and comorbidities, such as PsA, obesity, cardiovascular diseases, psychological disorders, and inflammatory bowel disease (IBD). Current evidence indicates that IL-23 may be an attractive treatment target for disease and comorbidity management. A multidisciplinary approach to the management of psoriasis and its associated comorbidities is therefore recommended.

A Guide to Navigate Through the Jungle: Finding the Best Targets for Psoriasis

Professor Kristian Reich

Insights into psoriasis pathophysiology have led to the development and expansion of cytokine-targeted therapies. In the early and mid-2000s, the search for effective treatments led to the development of the first biologic treatments for psoriasis, including the anti-TNF therapies etanercept, infliximab, and adalimumab. More recent developments of the anti-IL treatments acting on the IL-23/12 (ustekinumab), IL-17 (secukinumab, ixekizumab), and IL-23 (guselkumab, tildrakizumab, risankizumab) pathways have shown that a more targeted approach may be the answer to more optimised psoriasis treatment; however, no single treatment is ideal for all patients with psoriasis.

The complicated evolution of the psoriasis disease model shows that feed-forward and feed-backward responses are both involved in the inflammatory process behind keratinocyte proliferation, driven mainly by T-cell activation (Figure 1).[1]

Closer examination of the IL-17 pathway reveals that several IL-17 ligand and receptor family members, including IL-17A, IL-17F, and IL-17C, are largely involved in the development of psoriatic lesions.[2] Furthermore, IL-17A is a main activator of abnormal epidermal function in TNF-primed keratinocytes.[3] This has led to the development of the IL-17 blockers secukinumab, ixekizumab, and bimekizumab, and the IL-17A receptor blocker brodalumab,[4] which show similar efficacy to other currently available treatments.[5-13]

The inflammatory nature of psoriasis means that patients may develop other comorbid diseases such as PsA. A mechanistic study of skin and joints showed that IL-17 and TNF-α activation not only increased the production of T cells and keratinocytes, but also increased the production of osteoprotegerin, a soluble decoy receptor for receptor activator of NFκB ligand, and osteoclast progenitor cells, which play a role in bone resorption.[14] An examination of the genetics underlying psoriasis development revealed the involvement of multiple loci, leading to abnormal cytokine responses, including IFN, NFκB, as well as IL-17 and IL-23 receptor signalling.[15]

Current models theorise that IL-23 can significantly activate pathogenic IL-17 production, but that IL-17 produced independently of IL-23 is physiologically normal. Therefore, IL-17 blockade may result in oversuppression of the IL-17 pathway in patients with psoriasis.[16,17] The differential effects of IL-17 and IL-23 show that blockade of IL-23 ameliorates colitis symptoms and improves epithelial barrier integrity in patients with IBD, while IL-17 blockade exacerbates disease symptoms, causing epithelial barrier breakdown and leaking of the lumen contents.[18]

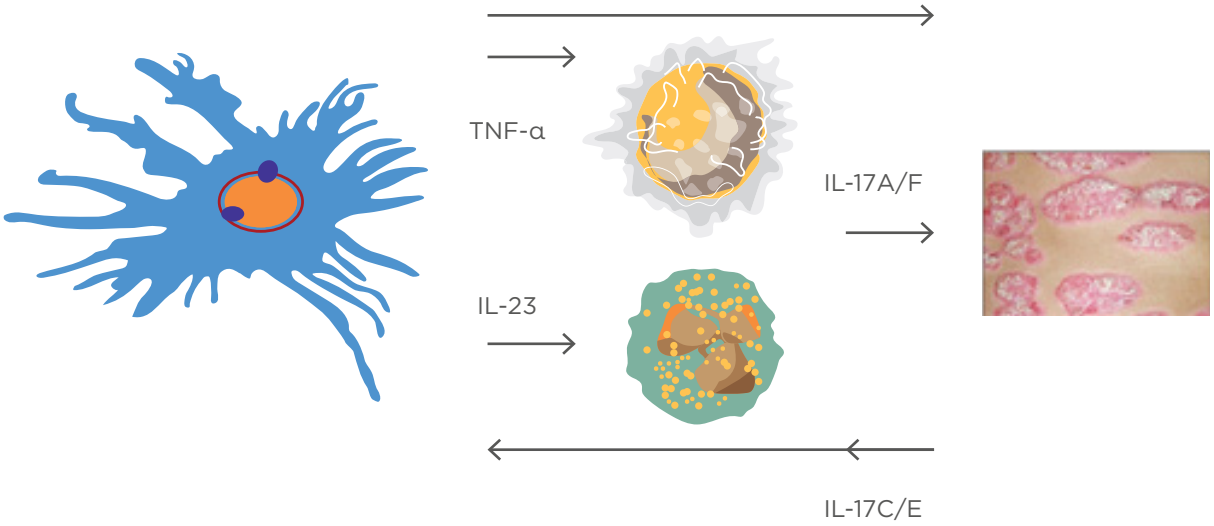

Figure 1: A very simplified version of the 'cytokine soup' model.

This model illustrates how dendritic cells, T-cell activation, and several feed-forward and feed-backward processes are involved in psoriasis development.

Images courtesy of Prof Kristian Reich.

Furthermore, patients with psoriasis have been shown to be at higher risk of developing IBD compared with healthy controls.[19] Psoriasis is also associated with the development of several comorbidities, including PsA, anxiety, and depression. Treatment with guselkumab, a human monoclonal antibody against the p19 subunit of IL-23, yielded greater improvements in anxiety and depression in patients with moderate-to-severe plaque psoriasis, compared with placebo or adalimumab treatment.[20]

One of the most pressing current challenges in the treatment of psoriasis is the achievement of disease remission, which is often hampered by 'disease memory', characterised by the presence of T cells with tissue-resident memory T cell (T_{RM}) phenotypes in clinically non-active psoriatic lesions.[21] These T_{RM} cells are capable of maintaining IL17 production and may be the main drivers behind disease recurrence.[21] However, data from the VOYAGE 2 study with guselkumab show that 86.0% of patients receiving guselkumab maintained a PASI 90 response from Week 28 to Week 72, compared with 11.5% of patients in the withdrawal group.[22] Furthermore, maintenance of a complete (PASI 100) response after drug withdrawal was associated with the continued suppression of IL-17A, IL-17F, and IL-22, reducing the levels of these cytokines to levels similar to controls.[22] These long-term responses may be linked to several markers, including shorter disease duration, lower baseline IL-17F levels, PASI 100, and Investigator's Global Assessment Score 0 responses at Week 28 of treatment, and higher guselkumab levels at Week 28 of treatment.[23]

In conclusion, IL-17A and IL-17F are the key activators of abnormal epidermal function in TNF-primed keratinocytes. IL-23 is the master cytokine, activating pathogenic Th17 activity and having possible effects on other cells in the pathway. It is likely that IL-17 and IL-23 have differential roles in psoriasis and PsA disease domains. These different mechanistic roles translate into differences in clinical behaviour of respective inhibitors.

Mapping Out the Evidence: What Do the Data Say?

Professor Richard Warren

Prior to the 1980s, it was believed that psoriasis was driven by dysregulation of keratinocyte hyperproliferation, after which, the role of T cells and the Th1/Th2 paradigm evolved.

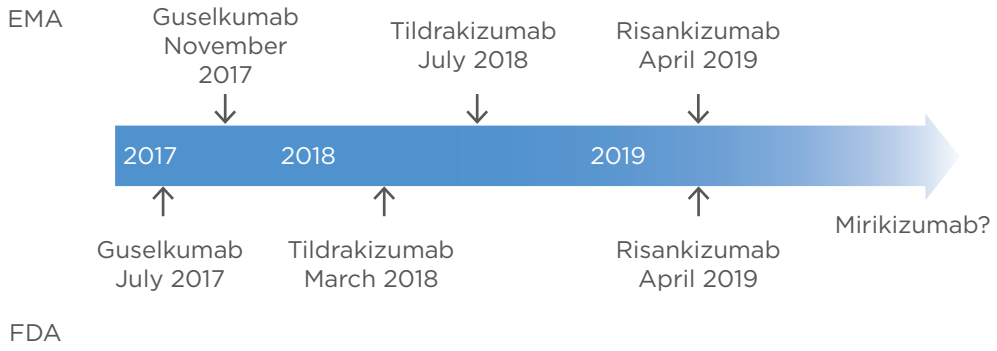

Figure 2: Approvals of IL-23 inhibitors in the EU (EMA) and the USA (FDA).

EMA: European Medicines Agency; EU: European Union; FDA: U.S. Food and Drug Administration.

The discovery of the IL-17 pathway led to insights into the involvement of the IL-12, IL-23, and IL-17 cytokines.[24] This opened the door for the development of inhibitors acting on these pathways, with increasing focus on IL-17A and the p40 and p19 subunits of IL-23.[24]

Several IL-23 inhibitors are currently available in the USA and the European Union (EU), including guselkumab, tildrakizumab, and risankizumab, with possible approval of mirikizumab in the next few years (Figure 2). Clinical trial data from the reSURFACE 1 and reSURFACE 2 studies show that IL-23 inhibition with tildrakizumab led to the maintenance of a 75% reduction in PASI (PASI 75) response in approximately 65% of patients at Week 12, and a PASI 90 response in almost 60% of patients at Week 28, compared with placebo and etanercept.[25] A similar proportion of tildrakizumab responders retained this response through Week 148 of treatment.[26]

Treatment efficacy and maintenance of response have been demonstrated in several studies. The results from the VOYAGE 1 and VOYAGE 2 clinical trials show that PASI 90 response was achieved in >70% of patients treated with guselkumab at Week 16, and maintained in 80% of patients at Week 48 and through Week 156.[27,28] These responses were also maintained in almost 50% of patients up to 6 months after withdrawal of guselkumab; 11.5% of patients still maintained a response 52 weeks after withdrawal.[22] The majority of patients regained a PASI 90 response following retreatment with guselkumab.[22] Data from the UltIMMa-1 and UltIMMa-2 trials further underline the role of the IL-23 pathway in psoriasis management; 75% of patients treated with risankizumab achieved a PASI 90 response at Week 16, and approximately 80% of patients achieved PASI 90 responses within the first year of treatment.[29] Furthermore, data from the IMMvent study showed that IL-23 inhibition with risankizumab led to a PASI 90 response in >70% of patients at Week 16 and Week 44.[30] Data from the IMMhance study showed that these responses were maintained in over 50% and in over 4% of static Physician's Global Assessment 0/1 responders through Weeks 52 and 104, respectively, after withdrawal from risankizumab at Week 16.[31]

Importantly, patient-reported outcomes on quality of life during treatment appear to mirror the clinical trial outcomes; patients receiving tildrakizumab reported improvements on the DLQI from baseline to Week 52, which correlated with improved PASI scores.[32] Furthermore, approximately 75% of patients treated with guselkumab have reported DLQI 0/1 scores that were improved and maintained from Week 76 to Week 156 of treatment.[28] Data from the UltIMMA-1 and UltIMMA-2 trials show that patients receiving risankizumab reported improved DLQI 0/1 scores at Weeks 16 and 52.[33]

The results of several studies also demonstrate the safety of IL-23 inhibitors, with no new or unexpected safety signals for tildrakizumab, no safety signals evident with continued use of guselkumab, and no new safety signals for risankizumab.[26,29,34]

But how does the efficacy of IL-23 inhibitors compare with that of IL-17 inhibitors in psoriasis management? In the ECLIPSE trial, the first head-to-head comparison of an IL-23 inhibitor (guselkumab) and an IL-17 inhibitor (secukinumab) showed that 84% of patients receiving guselkumab achieved the primary endpoint of a PASI 90 response at Week 48 of treatment compared with 70% of patients in the secukinumab group.[35] Both drugs showed a safety profile similar to their registrational trials.[35] However, the real test will be to see how long-term treatment with IL-23 inhibitors performs in real-world situations, though early data are promising.

In conclusion, treatment with IL-23 inhibitors results in high levels of efficacy that can be maintained for up to 3 years, with extended maintenance of PASI 90 responses after treatment withdrawal. Furthermore, the majority of patients report improvements in quality of life during treatment, with DLQI scores of 0/1 after 1 year of treatment. IL-23 inhibitors are a safe treatment option for patients with psoriasis, based on randomised clinical trial data and long-term extension studies. In a head-to-head comparison study, guselkumab showed superior efficacy, compared with secukinumab, in the primary endpoint at Week 48.

Tips and Tricks for the Expedition: Beyond the Skin Surface

Professor Brian Kirby

Successful psoriasis management does not solely depend on the treatment of the skin manifestations of psoriasis, as the presence of several comorbidities, including PsA, obesity, IBD, cardiovascular complications, psychological disorders, and psoriasis in difficult-to-treat or high-impact areas all represent further treatment challenges for clinicians. However, data from several studies currently show that treatment with the IL-23 inhibitor guselkumab is effective in improving psoriasis of the hands, feet, and scalp, and palmoplantar pustulosis, compared with adalimumab and placebo, respectively.[36,37]

The role of psoriasis in the development of PsA has been examined in several studies, showing that psoriasis occurs in 6–48% of psoriasis patients,[38] with a probable prevalence of up to 30% in psoriasis patients and high percentages of underdiagnosis (Figure 3).[39,40] However, early diagnosis and treatment with disease-modifying drugs has a substantial impact on long-term morbidity.[41-43]

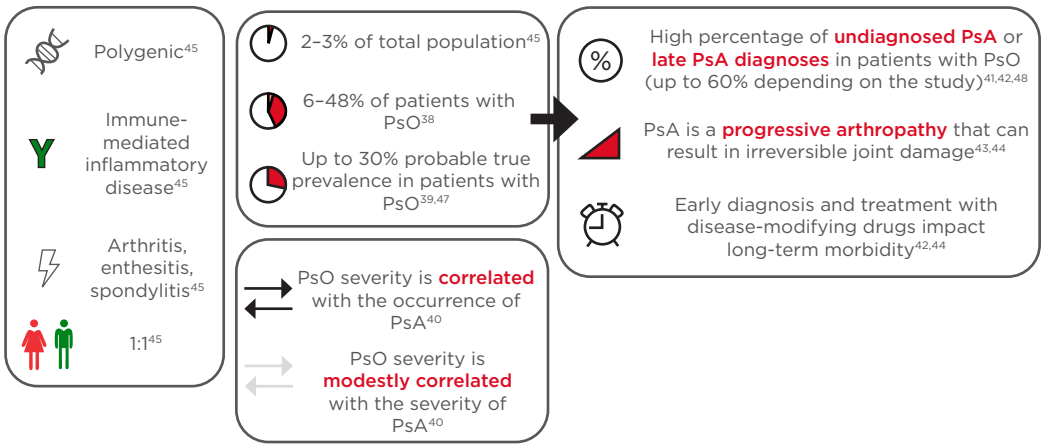

Figure 3: Psoriasis and psoriatic arthritis.

PsA is a polygenic, immune-mediated inflammatory disease, frequently occurring with arthritis, enthesitis, or spondylitis, with equal occurrence rates in males and females.[38-48]

PsA: psoriatic arthritis; PsO: psoriasis.

Therefore, dermatologists play a key role in the early diagnosis of psoriasis, and in the prevention of dactylitis, enthesitis, and joint destruction.[49] Current guidelines recommend consultations with other specialists when both psoriasis and PsA coexist, emphasising the importance of a multidisciplinary approach to disease management.[50,51] The use of questionnaires such as the Psoriasis Epidemiology Screening Tool (PEST) can help clinicians with diagnosis.[52,53] Regarding treatment, clinical trial results show that 58% of patients treated with the IL-23 inhibitor guselkumab achieved American College of Rheumatology (ACR) 20 scores at Week 24 of treatment compared with 18% of patients receiving placebo. Similarly, 79% of patients receiving guselkumab achieved PASI 75 scores at Week 24 of treatment compared with 13% of patients receiving placebo.[12]

The link between psoriasis and obesity can be explained by a dual-compartmental model of inflammation, as patients with psoriasis are at risk of increased BMI, and increased prevalence of obesity and metabolic syndrome. Conversely, patients with a high BMI or obesity are at high risk of psoriasis, with a risk of decreased efficacy of biologic treatment.[54-56] The results of the ECLIPSE study, in which patient weight was balanced between treatment groups, showed that guselkumab treatment resulted in a PASI 90 response in >80% of patients, across weight quartiles and BMI at Week 48.[57] Furthermore, the results of the VOYAGE 1 and VOYAGE 2 studies showed consistent maintenance of response across demographic subgroups in patients with psoriasis who were treated with guselkumab for up to 3 years.[58]

Psoriasis correlates with alcohol abuse, depression, anxiety, and cardiovascular disease, which can often be successfully managed by simultaneously treating both the skin condition and the psychological symptoms.[59,60] Patients treated with guselkumab have shown reductions in anxiety and depression over time, as measured by the Hospital Anxiety and Depression Scale-anxiety (HADS-A) and HADS-depression (HADS-D) scales.[20] Therefore, patients with psoriasis should always be screened for psychological comorbidities, including excessive alcohol use.

The significant association between psoriasis and IBD may be due to genetic abnormalities, immune dysfunction, systemic inflammation, or dysregulation of gut microbiota.[24,61,62] Targeting IBD with IL-23 inhibitors has shown promise in clinical trials; the results of the IM-UNITI trial show that induction and maintenance treatment with ustekinumab resulted in significant levels of clinical remission, clinical response, and glucocorticoid-free remission in patients with Crohn's disease at Week 44 of treatment.[63] Risankizumab treatment has also resulted in increased levels of CR100 and clinical remission in patients with Crohn's disease.[64]

In conclusion, patients with psoriasis are at higher risk of developing comorbidities such as PsA, obesity, cardiovascular diseases, psychological disorders, and IBD (Crohn's disease and ulcerative colitis). Current evidence indicates that IL-23 may be an attractive treatment target for disease and comorbidity management, and treatment of the skin condition often leads to improvements in associated comorbidities. A multidisciplinary approach in the management of psoriasis and its associated comorbidities is recommended.

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Date of preparation: November 2019
CP-125297

Latest Highlights from Guselkumab in Psoriasis from EADV 2019

These poster and oral presentations took place from 9–13th October 2019, as part of the 28th European Academy of Dermatology and Venereology (EADV) Congress in Madrid, Spain

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Disclosure: Prof Langley has served as principal investigator for and is on the scientific advisory board or served as a speaker for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Janssen, Leo, Lilly, Merck, Novartis, Pfizer, and UCB. Dr Armstrong has served as a research investigator and/or consultant to AbbVie, Janssen, Lilly, Leo, Novartis, UCB, Ortho Dermatologics, Dermira, Sanofi, Regeneron, BMS, Dermavant, and Modernizing Medicine. Dr Blauvelt has served as a scientific advisor and clinical study investigator for AbbVie, Aclaris, Akros, Allergan, Almirall, Allergan, Amgen, Arena, Athenex, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Dermavant, Dermire Inc., Eli Lilly and Company, FLX Bio, Forte, Galderma, Genetech/Roche, GlaxoSmithKline, Janssen, LEO Pharma, Meiji, Merck Sharp & Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron, Revance, Sandoz, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, UCB Pharma, Valeant, and Vidac; and as a paid speaker for AbbVie, Regeneron, and Sanofi Genzyme. Prof Reich has served as advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Affibody, Almirall, Amgen, Biogen Idec, Boehringer Ingelheim, Celgene, Covagen, Forward Pharma, Fresenius Medical Care, Galapagos, GlaxoSmithKline, Janssen Cilag, Kyowa Kirin, LEO Pharma, Lilly, Medac, Merck Sharp & Dohme, Miltenyi, Novartis, Ocean Pharma, Pfizer, Samsung Bioepis, Sanofi, Takeda, UCB Pharma, Valeant, XBiotech and Xenoport. Dr Muñoz-Elías is an employee of Janssen Research & Development LLC.

Support: The posters, presentations, and publication of this article were funded by Janssen. The views and opinions expressed are those of the speakers and not necessarily of Janssen.

Citation: EMJ Dermatol. 2019;7[Suppl 10]:10-16.

Presentation Summaries

Guselkumab was the first monoclonal antibody targeting the p19 subunit of IL-23 (IL-23p19) to be approved for the treatment of psoriasis. The registrational trials VOYAGE 1 and 2 established the efficacy and safety profile of guselkumab to Week 48 and demonstrated the superiority of guselkumab over placebo and adalimumab. A 5-year, open-label extension phase of both trials is currently ongoing. The poster and oral presentations reviewed here represent the latest data to emerge from the guselkumab

clinical trial programme in psoriasis, as presented at the 28th European Academy of Dermatology and Venereology (EADV) Congress. The ECLIPSE study was the first head-to-head trial between guselkumab and the IL-17A inhibitor secukinumab. Both agents were the first to be approved in their respective class with proven efficacy for the treatment of moderate-to-severe psoriasis but, until now, no direct comparisons were available to assist clinical decision making. Together with efficacy and safety, ECLIPSE also sought to understand the differential impact of IL-23 versus IL-17 inhibition on the immune profile of psoriatic skin and effector cytokines, providing insights into their respective mechanisms of action. Switching focus to the long term, the latest 3-year safety data from VOYAGE 1 and 2 are now available to accompany the established 3-year efficacy profile, providing unprecedented insights into the long-term response and tolerability of guselkumab for the treatment of psoriasis.

Overview of the ECLIPSE Study

The biologic era dawned in dermatology with the introduction of TNF antagonists. Since then, dermatologists have added the IL-12/23 p40 (subunit (IL-12/23p40) inhibitor ustekinumab to their armamentarium, and, more recently, monoclonal antibodies targeting IL-17, as well as IL-23.[1]

Comparator trials have established the superiority of IL-23 inhibition over TNF inhibition for treating psoriasis and demonstrated the favourable response rates attained by IL-17A inhibition and the selective inhibition of the IL-23 p19 subunit (IL-23/p19) compared with IL-12/23p40.[1]

The launch of novel IL-17A and IL-23p19 inhibitors has seen further evolution of the treatment paradigm with higher and more durable response rates, but until now no data were available to carry out meaningful comparisons of these latest targets and inform clinical decision making.[1]

ECLIPSE is the first head-to-head comparator trial of guselkumab and secukinumab, monoclonal antibodies that inhibit IL-23/p19 and IL-17A, respectively, in moderate-to-severe psoriasis. This randomised, Phase III trial was carried out in nine countries across Europe, North America, and Australia, and recruited adult patients with moderate-to-severe, plaque-type psoriasis who were candidates for systemic or phototherapy.[1]

In brief, patients were randomised 1:1 to receive 100 mg guselkumab (n=534) at Weeks 0, 4, and then every 8 weeks through Week 44, or 300 mg secukinumab (n=514) at Weeks 0, 1, 2, 3, 4, and then every 4 weeks through Week 44. Subjects in the guselkumab group also received placebo injections to mimic the secukinumab dosing schedule and maintain the double-blinding. Patients were followed up until Week 56, and the primary endpoint of the trial was the proportion of patients who achieved a response of Psoriasis Area and Severity Index (PASI) 90 at Week 48. This is a marked difference from prior comparator trials which have tended towards short-term outcomes.[1]

Consistent Responses to Guselkumab by Disease Region at Week 48 in the Treatment of Moderate to Severe Psoriasis: Results from the ECLIPSE Trial

Professor Richard G. Langley

This subgroup analysis of the ECLIPSE trial evaluated efficacy by body region components of PASI for patients who had a score >0 for the relevant component: specifically, head, trunk, upper extremities, and lower extremities. The baseline demographics and mean baseline PASI scores did not significantly differ between the two treatment groups in that the mean PASI score was 20, representing the moderate-to-severe disease experienced by the patient population.[2]

Guselkumab demonstrated superior efficacy at Week 48 with 84.5% (451/534) of patients achieving PASI 90 versus 70.0% (360/514) of patients in the secukinumab group (p<0.001). This represents a difference of almost 15 percentage points between the treatment groups. Furthermore, higher proportions of patients who received guselkumab reported improvements of ≥90% and 100% in PASI body region component

scores at Week 48 compared with those who received secukinumab. This was consistent for all regions measured; ≥90% PASI improvement in the guselkumab and secukinumab groups were reported by 85.0% versus 77.1% of patients for the head (Δ7.9), 86.7% versus 80.0% for the trunk (Δ6.7), 81.8% versus 66.9% for the upper extremities (Δ14.9), and 81.1% versus 66.9% for the lower extremities (Δ14.2), respectively. The proportion of patients with 100% improvement in PASI ranged from 74.9% and 61.4% (lower extremities) to 84.4% and 77.7% (trunk) in the guselkumab and secukinumab groups, respectively. Again, the greatest differences observed in 100% PASI improvement were observed between the upper and lower extremities (Δ16.2 and Δ13.5, respectively).[2]

The key safety findings were similar between treatment groups and consistent with those reported for their respective registrational trials. Of note, patients who received secukinumab experienced a higher rate of superficial *candida albicans* infections and tinea infections (5.7% and 4.5%, respectively), compared with those who received guselkumab (2.2% and 1.7%, respectively).[1,2]

Efficacy of Guselkumab versus Secukinumab in Patients with Moderate-to-Severe Plaque Psoriasis in Subgroups Defined by Previous Psoriasis Medication History: Results from the ECLIPSE Study

Doctor Andrew Blauvelt

Dr Blauvelt and colleagues expanded the efficacy analysis of ECLIPSE by evaluating the response to guselkumab and secukinumab in subgroups of patients defined by their treatment history at baseline. Patients were grouped by those who had received prior phototherapy, non-biologic systemic therapy, or biologic therapy. Prior biologic therapies included TNF inhibitors, IL-12/-23 or IL-23 inhibitors, and IL-17 inhibitors, with the exclusion of patients who had received prior guselkumab and secukinumab.[3]

The psoriasis medication history was comparable between the two groups at baseline. The majority of patients had received prior topical agents, approximately half had undergone phototherapy, and just over half had received non-biologic systemics. Twenty-nine percent of patients had received prior biologic therapy, of which TNF inhibitors were the most common, followed by IL-17 inhibitors and IL-12/23 or IL-23 inhibitors. Finally, 37% were naïve to non-biologic systemic and biologic therapies.[3]

Treatment with guselkumab consistently resulted in numerically greater proportions of patients achieving PASI 90 and 100 at Week 48 compared with secukinumab, regardless of previous medication. In the guselkumab group, PASI 90 responses ranged from 73.3% in patients who had received prior IL-12/23 or IL-23 inhibitors to 85.5% in those who had received prior IL-17 inhibitors. This compared with 56.8% in patients who had received prior IL-12/23 or IL-23 inhibitors to 68.6% in those who had received prior phototherapy or non-biologic systemic therapy in the secukinumab group. There was a difference of 17 percentage points in PASI 90 response between treatments in the subgroup who had received prior biologics (81.4% in patients who received guselkumab versus 64.4% for those who received secukinumab). The greatest differences were noted in patients who had previously received TNF inhibitors (76.8% and 58.8% in the guselkumab and secukinumab groups, respectively; Δ18.0) and prior IL-17 inhibitors (85.5% and 68.1%, respectively; Δ17.4). The smallest difference occurred in patients who had received non-biologic systemic therapy (83.0% and 68.6% in the guselkumab and secukinumab groups, respectively; Δ14.3).[3]

A similar pattern was noted for PASI 100 responses, with the greatest difference occurring in the subgroup who had received prior TNF inhibitors (57.3% and 42.4% in the guselkumab and secukinumab groups, respectively; Δ15.0). The lowest differences in PASI 100 was observed in patients who had received prior phototherapy or IL-17 inhibitors (Δ9.0 and Δ7.2, respectively).[3]

An Investigator's Global Assessment (IGA) score of 0 followed the same trend, with consistently greater proportions of patients who received guselkumab achieving IGA 0 compared with those who received secukinumab. Approximately 60% of patients who received guselkumab

achieved IGA 0 regardless of psoriasis treatment history, compared with 40–52% of those who received secukinumab. The greatest differences were observed in those who had received prior IL-12/23 or IL-23 inhibitors (Δ16.9) and TNF inhibitors (Δ15.0).[3]

Guselkumab Demonstrates Greater Efficacy Compared to Secukinumab Across Body Weight Quartiles and Body Mass Index Categories: Week 48 Results from the ECLIPSE Trial

Doctor April Armstrong

It is known that patient body weight and BMI can impact the efficacy of fixed-dose biologics for psoriasis, to which Dr Armstrong led a further evaluation of the efficacy data from ECLIPSE with analysis of responses to guselkumab and secukinumab by body weight quartiles and BMI.[4]

There were no body weight criteria for enrolment into ECLIPSE and these post hoc analyses were carried out with the following baseline categories: body weight quartile 1 (Q1) ≤74 kg, Q2>74 to ≤87 kg, Q3>87 to ≤100 kg, and Q4>100 kg; and BMI normal (<25 kg/m^2), overweight (≥25 to <30 kg/m^2), and obese (≥30 kg/m^2). Patient numbers were roughly equal between each category for both treatment groups.[4]

The average baseline body weight was 89 kg and the average BMI was 30 for both treatment groups. Obesity was common, with 42% and 44% of patients recording a BMI ≥30 mg/kg^2 in the guselkumab and secukinumab groups, respectively.[4]

Week 48 PASI 90 and 100 response rates were consistently higher in the guselkumab group, regardless of baseline body weight quartile or BMI category, with the greatest numerical differences noted in the heaviest patient groups. PASI 90 response rates were >80.0% across all baseline categories in the guselkumab group and ≤89.1% in the Q2 subgroup. The greatest difference in PASI 90 by body weight quartile was observed in the Q4 group, with 82.1% and 61.3% response rates for guselkumab and secukinumab, respectively (Δ20.9). This pattern was repeated in the BMI analysis, with the greatest difference seen in the obese group (82.5% versus 65.3% for guselkumab versus secukinumab, respectively; Δ17.2). However, the smallest differences in PASI 90 response were not noted in the Q1 patients or those of normal BMI, but rather in the Q3 and overweight subgroups (Δ9.3 and Δ10.6, respectively). The greatest difference in PASI 100 response rate by BMI was also observed in the obese subgroup (Δ12.0), which was almost double the difference reported for the normal weight subgroup (Δ6.4). However, the trend did not continue for PASI 100 by body weight quartile, where the greatest difference was seen in the Q2 group (Δ14.6) with a difference of just 2.6 reported in the Q1 group.[4]

Similarly, the proportion of patients who achieved an IGA score of 0/1 or 0 at Week 48 was consistently higher in the guselkumab group compared with the secukinumab group, regardless of baseline body weight quartile or BMI. IGA 0/1 response rates to guselkumab ranged from 82.9% in Q4 to 89.9% in Q2, and again the greatest difference in response between treatment groups was observed in the Q4 subgroup (Δ20.0), with the smallest difference recorded in the Q3 subgroup (Δ2.7). Differences of 17.5 and 16.2 were demonstrated in IGA 0 response rates at Week 48 in the Q2 and Q4 subgroups, respectively, with the smallest difference in IGA 0 occurring in Q1 (Δ3.0). The pattern was repeated in the analysis by BMI where IGA 0/1 was achieved by 83.0–86.9% of patients who received guselkumab and 69.3–81.9% who received secukinumab. The greatest difference in response rates was again observed in the obese subgroup for IGA 0/1 and 0 with Δ13.7 and Δ13.9, respectively.[4]

Differential Impact of IL-23 vs IL-17 Blockade on Serum Cytokines, Gene Expression and Immune Cell Subtypes in Psoriatic Skin: Results from the ECLIPSE Study

Doctor Ernesto J. Muñoz-Elías

IL-23 is known to be a key driver of inflammation in psoriasis, in part through the proliferation of T cells that produce proinflammatory cytokines including IL-17A, IL-17F, IL-22, and TNF-α. Inhibition of IL-23 blocks downstream actions, including the production of proinflammatory cytokines and the suppression of regulatory T cell responses. The ECLIPSE study sought to examine the differential impact of IL-23 and IL-17 inhibition by guselkumab and secukinumab on cellular and molecular markers of the skin in patients with psoriasis.[5]

Dr Muñoz-Elías presented the results of this mechanistic series of sub-studies derived from skin biopsies and blood samples collected at Weeks 0, 4, and 24, as well as additional blood samples from Week 48.[5]

Pharmacodynamic Effects on Circulating Cytokines

Guselkumab resulted in a more rapid and greater reduction of serum IL-17F and IL-22 concentrations compared with secukinumab, which was sustained through Week 48 and reflects the driving role of IL-23 in downstream cytokine expression. IL-17F was significantly reduced from baseline by Week 4 in the guselkumab group; however, the same level of significance was not recorded until Week 24 in the secukinumab group. Although both treatments maintained a reduced concentration of serum IL-17F through Week 48, this was significantly lower in the guselkumab group compared with the secukinumab group ($p<0.05$ at all timepoints). Secukinumab did not significantly reduce the serum concentration of IL-22 from baseline, while guselkumab resulted in significantly lower IL-22 at Week 4 versus baseline, an influence maintained through Week 48 ($p<0.05$ for all timepoints).[5]

Gene Expression Analysis from Skin Biopsies

Changes in the gene expression within psoriatic skin were assessed via biopsies taken during treatment with guselkumab and secukinumab. Secukinumab was associated with faster normalisation of genes within the psoriatic transcriptome, with 46% of genes recording >75% improvement at Week 4, compared with 13% for guselkumab ($p<0.05$). However, by Week 24, the levels of normalisation were similar between the two groups (80% and 84% in the secukinumab and guselkumab groups, respectively). Furthermore, both guselkumab and secukinumab were associated with significant reductions in the gene expression of IL-17A, IL-17F, IL-22, and IL-23 in skin lesions at Weeks 4 and 24 versus baseline.[5]

A greater number of genes were normalised at Week 24 during treatment with guselkumab than secukinumab (383 and 124, respectively, were reported to undergo >50% improvement, with a >25% difference between treatments). Examination of IL-23 receptor expression demonstrated a differential between treatment groups, whereby the IL-23 receptor was significantly downregulated by guselkumab, but not secukinumab, at Week 24 ($p<0.05$ versus baseline).

It should be noted that this analysis was limited by the small numbers of biopsies available: 11 from the guselkumab group and 9 from the secukinumab group.[5]

Cellular Immunophenotyping from Skin Biopsies

Tissue resident memory T cells (TRM) have been previously implicated in the pathogenesis of psoriasis, with increased numbers identified in psoriatic skin and in 'cleared' skin following treatment with TNF inhibitors. Investigation of T cells at baseline indicated the increased presence of non-TRM CD4+ T cells and TRM CD8+ T cells in psoriatic lesions compared with non-lesional skin. Analysis of TRM by treatment group showed that treatment with guselkumab resulted in a greater reduction of CD8+ TRM in psoriatic lesions compared with secukinumab ($p<0.05$ at Weeks 4 and 24). Furthermore, the frequency of T-regulatory cells was maintained between Weeks 0 and 24 in patients treated

with guselkumab, while the equivalent cellular population was reduced in the secukinumab group ($p<0.05$). When combined, the ratio of T-regulatory cells to CD8+ TRM cells was higher in the guselkumab group which may lead to a more favourable immune microenvironment and supports the immunomodulatory effects of guselkumab.

Long-Term Safety of Guselkumab in Patients with Moderate to Severe Plaque Psoriasis: Integrated Data through Week 156 of the Phase 3 VOYAGE 1 and VOYAGE 2 Trials

Professor Kristian Reich

Both the VOYAGE 1 and 2 registrational trials for guselkumab in moderate-to-severe plaque psoriasis will extend to 5 years to assess the long-term efficacy and safety of guselkumab alongside endpoints of high clinical relevance. In this presentation, Prof Reich evaluated the pooled safety data from VOYAGE 1 and 2 to Year 3.[6]

VOYAGE 1 and 2 were both Phase III, randomised, double-blind, placebo and active comparator-controlled trials conducted in multiple locations globally. In brief, VOYAGE 1 randomised 837 patients to receive either guselkumab (100 mg at Weeks 0 and 4, then every 8 weeks), placebo to Week 16 followed by guselkumab (100 mg at Weeks 16 and 20, then every 8 weeks), or adalimumab (80 mg at Week 0, 40 mg at Week 1 and then every 2 weeks) to Week 48, at which point open-label extension with guselkumab was open to all patients through 5 years.[6,7] VOYAGE 2 followed the same initial randomisation as VOYAGE 1 (N=992), but at Week 28 patients were evaluated for PASI ≥90 and responders to guselkumab were randomised to continue 100 mg every 8 weeks or had treatment withdrawn following loss of response. Nonresponders continued to receive guselkumab every 8 weeks. Those in the placebo arm received their first dose of guselkumab at Week 16 and PASI ≥90 responders at Week 28 had treatment withdrawn, with retreatment upon loss of response and continued guselkumab for nonresponders. Finally, responders in the adalimumab arm had treatment withdrawn at Week 28 with guselkumab initiated following loss of response. Nonresponders to adalimumab were switched to guselkumab at Week 28. Open-label extension was open to all patients from Week 76 and is scheduled to continue through 5 years.[6,8]

Results from the double-blinded phase of VOYAGE 1 and 2 have demonstrated the superior efficacy of guselkumab compared with placebo and adalimumab.[7,8] Data from the open-label extension phase are now available through 3 years with maintained efficacy demonstrated through Week 156.[6]

The pooled safety analysis included 1,721 patients and was consistent with previous safety reports, revealing no new safety signals with guselkumab in the treatment of moderate-to-severe psoriasis through Week 156. There were a total of 3,222 patient years (PY) of follow-up in the guselkumab group (patients initially randomised to receive guselkumab and those who received placebo and later crossed over to guselkumab) and 4,244 PY of follow-up in the all guselkumab group, which also included patients initially randomised to adalimumab who crossed over to guselkumab. The incidence of adverse events leading to discontinuation at Week 156 was 1.71 and 1.61 per 100 PY of follow-up in the guselkumab and all guselkumab groups, respectively, which were similar to the rates observed at 100 weeks. The infection rate was 74.0 and 72.5 per 100 PY of follow-up, respectively, with a serious infection rate of 1.15 and 0.97, respectively. The incidence rates of patients experiencing at least one serious adverse event were 5.68 and 5.40 per 100 PY of follow-up in the guselkumab and all guselkumab groups, respectively, which was also similar to those reported at 100 weeks but higher than the Year 1 rate of 3.98/100 PY of follow-up (guselkumab group only reported). Incidence of malignancy and major adverse cardiovascular events remained consistent through Weeks 100 and 156 in both pooled groups.

Conclusions

In conclusion, the latest data from the guselkumab clinical trial programme provide clinically meaningful insights into the efficacy

and tolerability profile of this IL-23 inhibitor. Guselkumab demonstrated superior efficacy over secukinumab, with a 14.5% difference in PASI 90 between the treatment groups at Week 48. These data also establish that guselkumab showed consistently greater improvement in the different body region components, in addition to better response rates regardless of prior treatment history and baseline body weight quartiles and BMI categories. Furthermore, the safety of long-term guselkumab treatment has been confirmed through 3 years, with no new safety signals reported.

Looking at the specific mechanisms of IL-23 and IL-17 blockade, sub-studies within ECLIPSE provide evidence that support the central role of IL-23 in the pathogenesis of psoriasis and begin to dissect the differential molecular and cellular changes that take place following inhibition of these cytokines. Mechanisms behind the apparent immunomodulatory actions of guselkumab are now beginning to emerge which may begin to explain the durability of response associated with IL-23 inhibition.

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Date of preparation: November 2019
CP-126200