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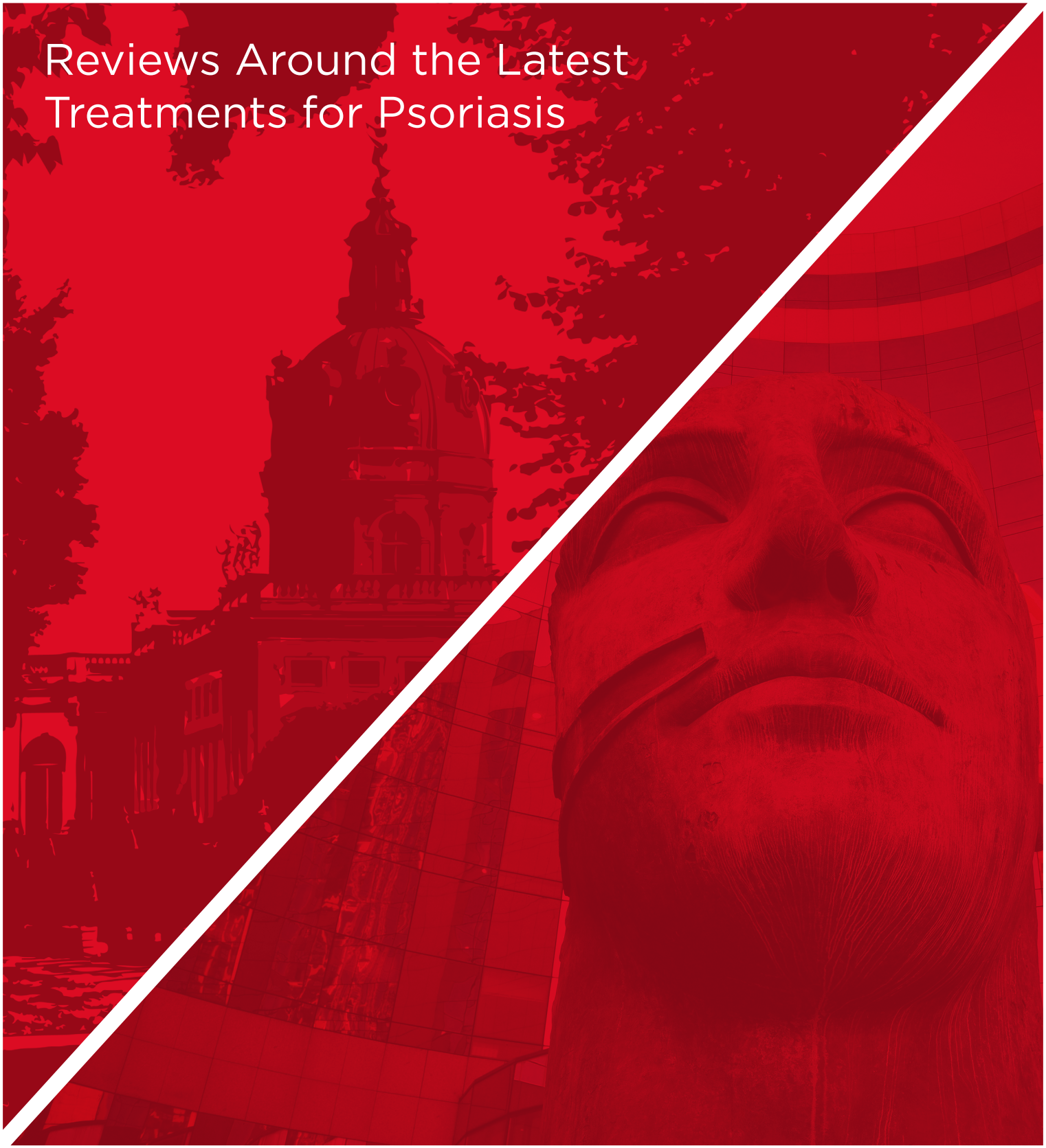
Reviews Around the Latest Treatments for Psoriasis



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IL-23 Inhibition in Psoriasis: Changing the Present, Shaping the Future

This symposium took place on 13th September 2018, as part of the 27th European Academy of Dermatology and Venereology (EADV) Congress in Paris, France

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Meeting Summary

This symposium took place at the 27th European Academy of Dermatology and Venereology (EADV) Congress. The session examined the latest data for contemporary therapeutic agents in psoriasis, focussing on IL-23 inhibitors as the most recently approved class of therapies, and provided perspectives on the implications of these data for clinical practice. With a wide array of potential treatment options now available for psoriasis, the symposium initially explored remaining areas of unmet treatment need, highlighting correct and timely diagnosis, effective management of comorbidities, undertreatment, and real-world data as key aspects requiring further improvement. The speakers subsequently reviewed the current evidence for the latest therapeutic strategies in psoriasis, concentrating on the therapeutic attributes that are considered most desirable for an 'ideal' agent, including efficacy for psoriasis and related comorbidities, durability of effect, improvement in quality of life, safety, and convenience. In this context, the rationale for selective IL-23 inhibition was examined, with the faculty highlighting how this approach differs from IL-17 inhibitors, at both the mechanistic and clinical levels. In addition, the session called attention to areas of ongoing investigation where there may be opportunities for the latest therapies to

provide further patient benefit, with focus on the potential for novel, less frequent dosing intervals with IL-23 inhibitors.

Introduction

Professor Kristian Reich

Despite recent advances, there remains substantial unmet need in the treatment of psoriasis and further progress is required. IL-23 inhibitors represent the latest class of therapies to emerge, adding to already available agents, which include TNF inhibitors, IL-12/23 inhibitors, and IL-17 inhibitors. Given the spectrum of potential treatment options available, it is important to understand the role and importance of each class of agent in the therapeutic armamentarium.

Are There Still Unmet Needs in the Evolving Psoriasis Treatment Landscape?

Professor Richard Warren

Psoriasis is a serious global problem, as acknowledged by the World Health Organization (WHO) in their recent Global Report on Psoriasis, issued in 2016.[1] Worldwide, 125 million patients are affected by psoriasis,[2] approximately 14 million of whom reside in Europe.[3] Key areas of unmet medical needs in psoriasis relate to correct and timely diagnosis, effective management of comorbidities, addressing undertreatment, overcoming the challenges posed by psoriasis occurring in difficult-to-treat areas, and the lack of real-world patient data with newer therapeutic agents.[1,4-6]

Improving the management of psoriasis requires early diagnosis, timely referral, and correct assessment of disease severity.[1] Patient and physician perceptions of psoriasis severity may differ,[1] as illustrated by evidence from the Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey.[4] In the MAPP survey, 22% of patients who had ≤3 palm lesions considered their psoriasis to be severe,[4] which is likely to differ from the physician-perceived severity of such cases of psoriasis. The lack of concordance between patient and physician-perceived severity indicates a need for improved methods for assessing severity in the clinic. Beyond the severity of psoriasis, it is also important to consider the presence of comorbidities when selecting an appropriate therapeutic strategy. Psoriatic arthritis, hypertension, depression, Type 2 diabetes mellitus, obesity, and hyperlipidaemia are all common comorbidities in patients with psoriasis.[7,8] In addition, Crohn's disease is genetically linked with psoriasis and represents a further potential comorbidity.[9] Taken together, the physical and psychological impact of psoriasis and associated comorbidities may have a cumulative impact on patients' lives over time, particularly for those patients who are less adept at coping with their condition, ultimately altering patients' life choices and impacting the course of their lives.[10,11] This concept is known as 'cumulative life-course impairment' and highlights a need for early and effective treatment of psoriasis and related comorbidities.[10,11]

With regard to treatment standards and the unmet need in psoriasis, the recently conducted 'Clear About Psoriasis' survey of >8,000 patients with moderate-to-severe psoriasis from 31 countries indicated that a large number of patients remain dissatisfied with their psoriasis treatment.[12] Within this study, 57% of patients reported having not achieved clear or almost clear skin with their current treatment regimen.[12] While 56% of patients reported that they were 'satisfied' with their treatment, 24% were 'uncertain' and 20% were 'dissatisfied', with the majority of dissatisfied patients (89%) not achieving clear or almost clear skin.[12] Such dissatisfaction may be linked with undertreatment; in the MAPP survey, nearly 40% of patients with >10 palm lesions were receiving no treatment, and only 11% of those patients were receiving oral or biologic therapy.[4] Among the audience members at this symposium, the majority considered undertreatment to be a bigger unmet need for patients with psoriasis than delayed (or incorrect) diagnosis. The challenge of undertreatment may be related to the high proportion of

patients who are affected by psoriasis in difficult-to-treat areas, such as the scalp, face, nails, genitals, intertriginous areas, palms, and soles.[6] These psoriasis subtypes may disproportionately impact patients' quality of life, while simultaneously not meeting the criteria for access to the most effective therapies if assessed using thresholds such as body surface area affected of >10%, leading to undertreatment.[6] Furthermore, treatment of such subtypes may require a tailored therapeutic strategy, as agents commonly used for psoriasis are not always suitable or effective in treating psoriasis affecting these specific areas.[6]

Over 70% of attendees at the symposium indicated that long-term real-world data have greater influence on their prescribing decisions than robust Phase III data from clinical trials. The representativeness of clinical trials to real-world clinical practice is therefore key and has been explored in several analyses.[5,13] In the UK, when data from the British Association of Dermatologists Biologic Interventions Register (BADBIR) registry were analysed, it was found that just over half (53%) of patients were considered to meet the enrolment criteria for the Phase III licensing studies for etanercept, adalimumab, or ustekinumab.[5] Around one-third of patients (32%) had insufficient baseline data to allow analysis or missing data, and the remainder were considered ineligible (15%).[5] Among the ineligible group, there were more elderly patients (aged ≥70 years) than in the eligible group and patients tended to have higher BMI, more comorbidities, and experienced smaller reductions in Psoriasis Area Severity Index (PASI) with treatment.[5] Crucially, a higher rate of serious adverse events was observed in the ineligible patient group when treated with etanercept, adalimumab, or ustekinumab than in those patients considered eligible for the clinical trials.[5] When interpreting clinical trial results, it is therefore critical to consider how representative the trial is of the real-world patient population; there is a need to improve under-representation of real-world patient subsets within clinical studies.

In summary, there are still numerous unmet medical needs affecting patients with psoriasis. Future efforts need to focus on encouraging earlier diagnosis of psoriasis and associated comorbidities, curtailing undertreatment, and addressing the under-representation of real-world patient subsets in clinical studies.

What is the Best Target for Psoriasis: IL-23 Versus IL-17A?

Doctor Andrew Blauvelt

While methotrexate and phototherapy formed the backbone of early management of psoriasis, recent decades have seen revolutionary changes in treatment, first with the emergence of TNF inhibitors, and more recently with IL-12/23, IL-17, and IL-23 inhibitors.[14] The emergence of each class of new treatment option has reflected an evolving understanding of the pathogenesis of psoriasis, which is now understood to be primarily an immunologic disease mediated by dysfunction in regulation of the IL-23/Th17 axis.[15-17] A key benefit of specifically targeting the IL-23/Th17 pathway is that although the pathway is involved in mucocutaneous immune defences,[18] it is not involved in systemic immunity.[19]

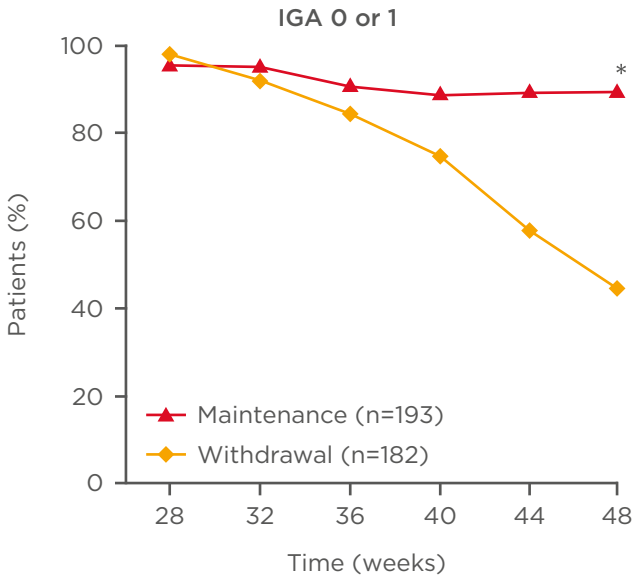

Figure 1: Investigator's Global Assessment 0 or 1 response rate among patients withdrawn from or maintaining guselkumab therapy following an initial response† in the VOYAGE 2 trial.

*p<0.001; †≥90% improvement in Psoriasis Area Severity Index after 28 weeks' guselkumab treatment.

Adapted from Reich et al.[25]

Modern treatment options provide the opportunity to inhibit this pathway at various stages, including at upstream (e.g., IL-23 inhibitors), intermediate (e.g., IL-17 inhibitors), or downstream points (e.g., IL-17 receptor antagonists).[16,17] Physicians are now faced with the challenge of determining whether to select an inhibitor targeting IL-23 or IL-17 as the therapeutic strategy for their patients.

Focussing first on treatment efficacy, primary endpoint data from pivotal clinical trials in moderate-to-severe psoriasis with biologic agents targeting IL-17 indicated PASI 75 response rates of 77–82% at Week 12 with the IL-17A inhibitor secukinumab (300 mg),[20] 87–90% at Week 12 with the IL-17A inhibitor ixekizumab (80 mg; every 2 weeks),[21] and 85–86% at Week 12 for the IL-17 receptor agonist brodalumab (210 mg; every 2 weeks).[22] In similar studies with IL-23 inhibitors, PASI 75 response rates of 61–64% were observed at Week 12 with tildrakizumab (100 mg),[23] with rates of 86–91% seen at Week 16 with guselkumab (100 mg).[24,25] Although the current lack of head-to-head clinical trials between IL-17 and IL-23 inhibitors limits the possibility of drawing robust conclusions about the comparative efficacy of these agents, ongoing studies are being conducted to address this question, including the ECLIPSE study,[26] which will directly compare the efficacy of guselkumab with secukinumab.

Given the chronic nature of psoriasis, it is important that therapeutic agents have durable efficacy. Sustained PASI response rates over time have been demonstrated with up to 5 years' treatment with secukinumab,[27] with up to 3 years' treatment with ixekizumab,[28] and with up to 2 years' treatment with guselkumab.[29] In addition, it is interesting to note that the efficacy of guselkumab appears to be sustained for a substantial duration of time after withdrawal of therapy.[25] In the VOYAGE 2 study,[25] patients who had received 28 weeks' guselkumab treatment and achieved PASI 90 were randomised to continued guselkumab therapy or withdrawal (placebo). Although PASI 90 and Investigator's Global Assessment 0 or 1 (cleared or minimal) response rates at Week 48 were significantly greater in those receiving continued guselkumab therapy versus those who were withdrawn from therapy ($p<0.001$), 37% of patients in the withdrawal arm still had a PASI 90 response at Week 48 (28 weeks after the last guselkumab dose), and >40% had Investigator's Global Assessment 0 or 1 responses (Figure 1).[25]

A previous study has explored the potential for prolonged efficacy to enable dosing-interval extension using the IL-12/23 inhibitor ustekinumab.[30] In this study, patients with moderate-to-severe psoriasis responding (Physician's Global Assessment [PGA] of 0 or 1) to 28 weeks' ustekinumab treatment were randomised to either dosing every 12 weeks (in line with the recommended dosing regimen) or to a response-based dosing regimen, with a variable dosing interval ranging from every 12 weeks for those who lost response at Week 32 to every 24 weeks for those who maintained response at Week 40.[30] This study found that in some patients, dosing can successfully be extended to every 6 months, with higher PGA 0 or 1, PASI 75, and PASI 90 response rates observed from Week 40–112 in patients in the subgroup who received 24-week dosing from Week 40 compared with those receiving more frequent dosing.[30] Taken together, the results of the these studies of IL-12/23 inhibition with ustekinumab and selective IL-23 inhibition with guselkumab suggest that upstream inhibition of the IL-23/Th17 axis may be linked with sustained pharmacodynamic effects after the drug has been eliminated from the body. Given that Th17 cells are known to be dependent on IL-23 for cell survival, this result may indicate that IL-23 inhibition leads to death of pathogenic skin-resident memory Th17 cells, potentially leading to more prolonged disease control.[31]

Psoriatic arthritis is prevalent among patients with psoriasis,[7] and it is therefore important to consider the efficacy of potential psoriasis treatment options on this comorbidity. Both secukinumab and ixekizumab have been approved in the European Union (EU) and the USA for the treatment of psoriatic arthritis.[32-35] In Phase III trials in patients with psoriatic arthritis, these IL-17 inhibitors have been shown to significantly improve American College of Rheumatology (ACR) 20 response rates compared with placebo over 24 weeks.[36-39] With regard to the efficacy of IL-23 inhibitors in patients with psoriatic arthritis, Phase II data have recently been published for guselkumab

that showed significantly greater ACR 20 response rates at Week 24 versus placebo,[40] with similar response rates to those seen in the previous studies with IL-17 inhibitors. These encouraging early data for guselkumab require verification in larger Phase III studies, which are currently ongoing.[41,42]

Safety is a critical factor when evaluating potential treatment options for psoriasis, given a likely need for long-term treatment. Agents directly targeting IL-17 or its receptor (e.g., secukinumab, ixekizumab, and brodalumab) are considered to be generally well-tolerated;[43] however, consistent with the known role of the IL-17 pathway in resistance to mucocutaneous infections, such agents are associated with mucocutaneous candidiasis infections.[32,33,44] In addition, exacerbations of Crohn's disease have been seen in clinical studies with secukinumab,[32] and cases of new onset or exacerbated Crohn's disease and ulcerative colitis have been reported with ixekizumab.[33] It has been hypothesised that IL-17 may play a protective role in the gastrointestinal tract, and therefore IL-17 inhibition may block this protective action, predisposing some patients to the development or exacerbation of inflammatory bowel diseases.[45] Agents inhibiting IL-23 (e.g., ustekinumab, guselkumab, and tildrakizumab) are also considered to be generally well-tolerated[43] but have not been reported to be associated with candidiasis or inflammatory bowel disease.[46-48] Furthermore, ustekinumab is in fact indicated for the treatment of Crohn's disease.[47] In this context, it is important to note that not all IL-17A-producing cells are regulated by IL-23, including in the gut.[49] These IL-23-independent pathways may allow for continued protective IL-17A production during IL-23 inhibition.[49]

An additional consideration when selecting the therapeutic regimen for psoriasis is the required frequency of dosing, which is an aspect in which IL-17 and IL-23 inhibitors differ. While IL-17 inhibitors require dosing every 2–4 weeks,[32,33,44] IL-12/23 and IL-23 inhibitors are dosed less frequently, typically every 8–12 weeks.[46-48]

In summary, while IL-17 and IL-23 inhibitors both represent highly efficacious and broadly well-tolerated classes of therapy for psoriasis,[43] differences exist between agents in durability, safety, and posology. It is also important to acknowledge that the therapeutic profiles of individual agents within each class may differ, likely driven by differences in antibody binding affinity, dose, dosing frequency, or other attributes.

Are We Thinking Long Enough? Applying Clinical Evidence to Practice

Professor Kristian Reich

Plaque-type psoriasis is driven by the interaction between the immune system and the epidermis. In the initial 'feed-forward' response, dendritic cells activate T cells via IL-23 release, which in turn release mediators, such as IL-17, that activate keratinocytes and stimulate keratinocyte proliferation, ultimately leading to psoriatic plaque formation.[16] Once keratinocytes are activated, they release further mediators that signal back to the immune system, such as IL-8 which attracts neutrophils to the skin,[16] creating a vicious circle with both feed-forward and feed-back responses between the immune system and skin.

In clinical studies in patients with psoriasis, high response rates have been observed with IL-17A inhibitors. With secukinumab, an average PASI 90 response rate of 75% was observed after 24 weeks' treatment across the FIXTURE, CLEAR, and PRIME clinical studies, and a similar proportion of patients (75%) achieved absolute PASI scores ≤2.[50] Response rates at Week 24 with secukinumab in these studies were higher than those seen with etanercept (PASI 90: 40%; PASI ≤2: 38%) or ustekinumab (PASI 90: 61%; PASI ≤2: 61%).[50] Similarly, ixekizumab has demonstrated greater clinical efficacy in terms of PASI 90 and PASI ≤2 response rates at Week 24 (83% and 84%, respectively) compared with ustekinumab (59% and 62%, respectively; $p<0.01$).[51] Taken together, these data suggest that IL-17A inhibitors provide greater response rates than ustekinumab. Ustekinumab is a monoclonal antibody that binds to the p40 subunit common to both IL-12 and IL-23, thereby inhibiting receptor binding and suppressing both the IL-12-mediated Th1 pathway and the

IL-23-mediated Th17 pathway.[47] In contrast, the IL-23-specific inhibitors, such as guselkumab, bind to the p19 subunit of IL-23, providing the opportunity for selective blockade of IL-23-mediated pathways.[16,46]

Pivotal clinical studies of guselkumab in patients with psoriasis include the VOYAGE 1 and 2 trials.[24,25] In VOYAGE 1, patients receiving guselkumab achieved a PASI 90 response rate of 80% after 24 weeks' treatment, with superior response rates to adalimumab (53%; p<0.001) (Figure 2).[24]

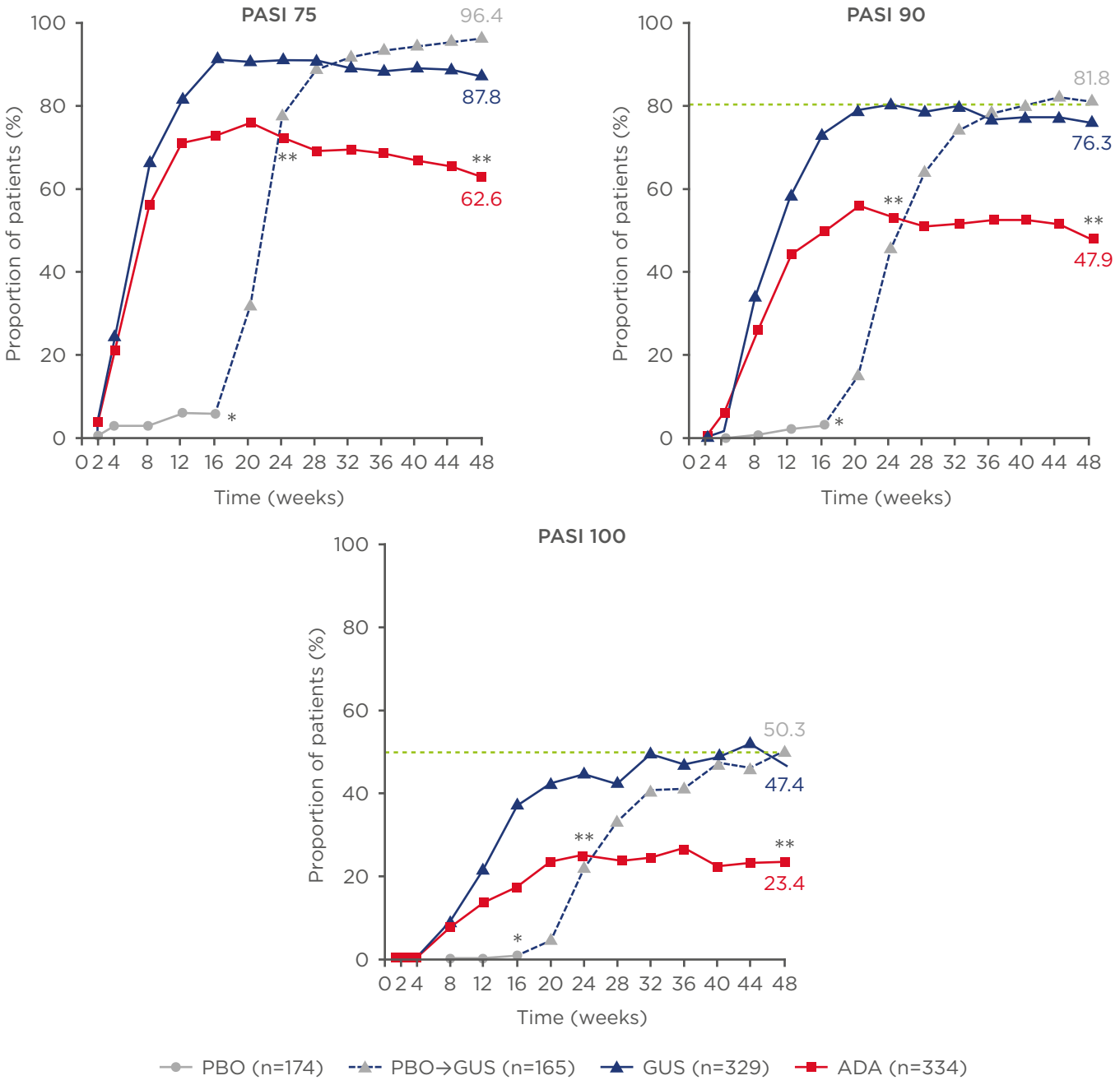

Figure 2: Psoriasis Area Severity Index response rates over time with placebo, guselkumab, and adalimumab in the VOYAGE 1 trial.

Data are from a non-responder imputation analysis. Patients in the placebo group switched to guselkumab treatment from Week 16 onwards.

*p<0.001 for GUS versus PBO; **p<0.001 for GUS versus ADA.

ADA: adalimumab; GUS: guselkumab; PASI: Psoriasis Area Severity Index; PBO: placebo.

Adapted from Blauvelt et al.[24]

Notably, at the end of the 1-year study, almost half (47%) of patients in the guselkumab group achieved PASI 100, indicating clearance of psoriasis, compared with 23% of adalimumab-treated patients (p<0.001).[24]

The high rate of complete resolution of psoriasis with guselkumab may be important in the context of durability of efficacy and potential extension of the dosing interval, particularly given that a previous study with ustekinumab identified achievement of PGA 0 (cleared disease) as a predictor of ability to successfully extend the dosing interval while maintaining response.[30] As mentioned in the previous presentation, VOYAGE 2 explored the efficacy of guselkumab after withdrawal, with patients responding to 28 weeks' guselkumab therapy randomised to either withdrawal of therapy or continued guselkumab.[25] In those patients withdrawn from guselkumab, the estimated median time to loss of PASI 90 response was >3 months (15 weeks).[25] However, this evidence alone does not imply that patients with well-controlled psoriasis achieving PASI 90 with guselkumab can be withdrawn from therapy or switched to less frequent dosing in clinical practice; further data are required.

As highlighted earlier, many patients present with psoriasis involving the nails, hands, or feet.[6] In the VOYAGE 2 study, among the subgroup of patients with hand/foot (hf) psoriasis, 77% of guselkumab-treated patients achieved a hf-PGA of 0 or 1 with a ≥2-grade improvement at Week 16, a significantly greater proportion than those receiving placebo (14%; p<0.001) and numerically more than those receiving adalimumab (71.4%).[25,52] At Week 24, a significantly greater proportion of patients in the guselkumab group achieved the hf-PGA endpoint (82%) compared with adalimumab (66%; p=0.046),[25,52] consistent with the previously discussed superiority of guselkumab over adalimumab for plaque psoriasis. In contrast, in those patients with fingernail involvement, no significant difference was seen between guselkumab and adalimumab in fingernail-PGA 0 or 1 response rates, which were significantly greater with guselkumab versus placebo at Week 16 (52% versus 15%, respectively) but not significantly different versus adalimumab at Week 24 (63% versus 67%, respectively; p=0.376).[52] These results may indicate that the pathogenic contribution of TNF-α and IL-23 varies between different subtypes of psoriasis.

Given the impact of psoriasis on patients' daily lives, including their psychological wellbeing, it is important to evaluate the effectiveness of treatment on patient-reported outcomes. In VOYAGE 2, among those patients with Hospital Anxiety and Depression Scale (HADS) scores indicating anxiety (HADS-A ≥8) or depression (HADS-D ≥8) at baseline, guselkumab was associated with greater improvements in anxiety and depression compared with adalimumab, as indicated by higher rates of patients achieving HADS-A <8 (58% versus 43%, respectively; p=0.028) or HADS-D <8 (60% and 46%, respectively; p=0.079).[53] Improvements in anxiety and depression were correlated with improvements in psoriasis (assessed via PASI scores).[53] More broadly, the clinical benefits of guselkumab appear to translate into improvements in quality of life, with significantly more patients achieving Dermatology Life Quality Index of 0 or 1 with guselkumab versus adalimumab at both Week 24 (61% and 40%, respectively; p<0.001) and Week 48 (63% and 39%, respectively; p<0.001) in the VOYAGE 1 study.[24] At Week 52 in the VOYAGE 1 study, patients receiving adalimumab were switched to guselkumab; by Week 100, the proportion of patients achieving Dermatology Life Quality Index of 0 or 1 was similar in those switched from adalimumab to guselkumab (74%) compared with those who had received 2-years' guselkumab (71%).[29]

With regard to the safety profile of guselkumab, a pooled analysis of the VOYAGE 1 and 2 studies, including 1,221 patients, indicated a low incidence of serious infections (1.06 infections per 100 patient years [including Week 0–100 data from patients randomised to guselkumab and those who crossed-over to receive guselkumab]).[29] Similarly, the rates of malignancy and major adverse cardiovascular events were very low (both 0.38 events per 100 patient years).[29]

In summary, IL-23 inhibitors are an important component of the treatment repertoire for psoriasis. Such therapies demonstrate high levels of therapeutic efficacy, are well tolerated, and have durable responses that allow long injection intervals,[24,25] which may have the potential to be extended further in the future.

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From Evolution to Revolution: IL-23 in the Treatment of Psoriasis Patients

This symposium took place on 14th September 2018, as part of the 27th European Academy of Dermatology and Venereology (EADV) Congress in Paris, France

Chairpeople: James Krueger,[1] Lluís Puig[2]

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Meeting Summary

This symposium, which took place during the 2018 meeting of the European Academy of Dermatology and Venereology (EADV) in Paris, France, provided an overview of the IL-23 revolution in psoriasis, with a specific focus on psoriasis pathogenesis and its relation to potential treatment targets and the development of novel targeted immune therapies. The session focussed on the discovery and development of IL-12 and IL-23-targeted therapies for psoriasis, the role of IL-23 in disease control, and the implications of recent data for clinical practice.

An increasing number of potential treatment options are becoming available for psoriasis, and the differential effect of these agents on various signalling pathways has facilitated a greater understanding of the molecular mechanisms driving disease progression. The symposium initially explored the central role of IL-23 in psoriasis, the mode of action of the monoclonal antibody (mAb) guselkumab in targeting this heterodimeric cytokine, and the parameters associated

with a maintenance of response in patients with psoriasis undergoing treatment. The speakers subsequently reviewed current data relevant to the blockade of IL-23 versus dual blockade of IL-12/23, or blockade of the downstream effector IL-17, and the relative effects of these different strategies in psoriasis at the molecular and cellular levels. The concept of 'disease memory' in psoriasis was also explored, with an examination of recent data of patients with long-lasting remission, and disease models and future investigations discussed.

Introduction

Dermatologists need to understand the unmet needs in the management of psoriasis and how current data from recently approved or pipeline compounds can help address these needs in clinical practice. This symposium aimed to promote an understanding of psoriasis pathogenesis and its relation to the development of novel targeted immune therapies. The presenters discussed how treatment strategies could be used to optimise long-term patient outcomes and addressed the concept of potential disease modification effects of targeted therapies in psoriasis.

The Road of Discovery: IL-12 and IL-23-Targeted Therapies in the Treatment of Immune-Mediated Inflammatory Diseases

Doctor Ernesto Muñoz-Elías

The proposed model for the immunopathology of psoriasis was, until recently, based on an equal contribution of IL-12 and IL-23 when produced by activated macrophages and dendritic cells. In this model, IL-12 activates Th1 cells and IL-23 activates both Th17 and Th22 cells, which leads to the proliferation of keratinocytes, production of multiple proinflammatory cytokines, increased inflammation, and the formation of psoriatic plaques. However, accumulating data from various sources suggest that the most important driver of pathogenesis in psoriasis is IL-23 rather than IL-12.[1] For example, gene expression data show psoriasis lesions have raised expression levels of genes encoding IL-23 (p19, a unique subunit of IL-23, and p40, a subunit of both IL-23 and IL-12) compared with a gene encoding a subunit associated with IL-12 only (the p35 subunit).[2] In addition, clinical data showed that the blockade of IFN-γ (primarily a downstream cytokine of IL-12) with anti-IFN-γ was not efficacious in treating psoriasis.[3,4] Furthermore, in a knockout mouse model in which IL-12 was silenced, IL-12 was shown to have a protective role in psoriasis-like disease.[5] Molecular data show that the first-in-class mAb guselkumab, which binds specifically to the p19 subunit of IL-23, blocks IL-23 signalling while having no effect on IL-12 signalling.[6] The downstream production of IL-17 by IL-17-expressing CD8+ T (Tc17) cells, when blocked by a mAb with specificity for IL-17A, such as secukinumab or ixekizumab, precludes the keratinocyte activation that is characteristic of psoriasis.[7] Ongoing studies are evaluating the possible effects of IL-23 in multiple immune cell types.

Data from clinical studies are being evaluated to gain insights into the effect of guselkumab on cytokines downstream of IL-23. Response to guselkumab has been examined in patients with moderate-to-severe psoriasis in the Phase III VOYAGE 1 and 2 trials. In the VOYAGE 1 study[8] (N=837), patients receiving guselkumab achieved a Psoriasis Area Severity Index (PASI) 90 response rate of 76.3% after 48 weeks of treatment, with superior response rates to adalimumab (47.9%; $p<0.001$). Guselkumab significantly reduced the levels of key serum effector cytokines, including IL-17A, IL-17F, and IL-22, in the IL-23 pathway at 48 weeks compared with adalimumab.[9] The psoriasis transcriptome of patients from VOYAGE 1 was also analysed. Following treatment with guselkumab, an improvement was observed at 4 weeks, 24 weeks, and 48 weeks, and at the 24 and 48-week timepoints, the profile resembled that of non-lesional skin.[9] Improvement of the psoriasis transcriptome was more prominent in patients treated with guselkumab than adalimumab. When evaluating multiple gene sets relevant to inflammation, similar results were observed.[10] One limitation of whole skin biopsy gene expression analysis is that it does not

allow for the characterisation of a drug's effect on immune cell numbers or phenotypes. Therefore, methods have been developed that allow the dissociation of skin biopsies into single cell suspensions that can then be analysed by flow cytometry for surface and intracellular protein expression. Skin-resident T cells isolated from biopsy samples have been examined, showing that epidermal T memory cells are pathogenic producers of IL-17A, IL-17F, TNF-α, and IL-22.[11] Fluorescence-activated cell sorting analysis of skin immune cells represents a new approach for understanding drug effects on skin tissue immune cells and is being incorporated into ongoing studies.

Maintenance of clinical response (PASI 90) after withdrawal of guselkumab has been evaluated in the VOYAGE 2 study,[12] in which patients who had received 20 weeks of guselkumab treatment and achieved PASI 90 at 28 weeks were randomised to receive continued guselkumab or switch to placebo. PASI 90 response rates at Week 48 were significantly greater in those receiving continued guselkumab therapy versus those who were withdrawn from therapy ($p<0.001$); however, 36.8% of patients in the withdrawal arm maintained a PASI 90 response at Week 48 (28 weeks after the last guselkumab dose). Compared with maintained response, loss of response (PASI <75) among patients in the withdrawal arm was associated with significantly increased levels of serum IL-17A, IL-17F, and IL-22 at Week 48.[13] Conversely, parameters associated with maintenance of PASI 90 following guselkumab withdrawal included a shorter duration of disease, lower BMI, and lower IL-17F at baseline, as well as complete skin clearance and higher guselkumab concentration at Week 28.[14] Further models of single and combined parameters and biomarkers are being investigated to better understand response to guselkumab and the mechanisms behind its action.

In conclusion, the data discussed support the hypothesis that IL-23 is a central driver of psoriasis. Studies show that blockade of IL-23 with guselkumab is associated with a clinical response, a normalisation of the psoriasis transcriptome, and a reduction in inflammatory cytokines of the IL-23/IL-17 pathway, such as IL-17A, IL-17F, and IL-22.

The Role of IL-23: From Disease Control to Disease Remission

Doctor Lluís Puig

Since the 1980s, it has been recognised that T cells are implicated in psoriatic disease, but the role of IL-23 only began to gain prominence in 2004.[15] In the current model of psoriasis pathophysiology, environmental stress causes keratinocytes to produce primary cytokines that activate antigen-presenting cells (usually dendritic cells), which then produce IL-23. In turn, via the IL-23 receptor (IL-23R) expressed on their surfaces, Th17 cells are stimulated to produce IL-17, which leads to the release of various cytokines that promote local keratinocyte activation, epidermal remodelling, and psoriatic plaque formation.[15] Therefore, the main rationale for blocking IL-23 in psoriasis treatment is to prevent the IL-23/Th17-mediated 'feed-forward' mechanism, which self-amplifies the inflammatory response in keratocytes of psoriatic skin.[7] Hence, blockade of the upstream regulator (IL-23) rather than the effector (IL-17) cytokine may be a more effective approach to psoriasis control. This question is currently being addressed in clinical trials involving a range of mAb that block either IL-23 or IL-17, with the latter group requiring a relatively high frequency of dosing in maintenance treatment to be effective.

Another possible advantage of IL-23 blockade is that the effects are not limited to targeting Th17. For example, the effects of IL-23 on regulatory T cells may promote differentiation into Th17 cells,[16] as well as affecting cell types known to be present in the skin, such as mast cells, which may be stimulated to promote extracellular trap formation and degranulation, and neutrophils.[17] As discussed, a localised disease memory, in the form of epidermal Th22 and Tc17 cells, can form in cases of clinically healed psoriasis. In this setting, epidermal CD8+ T cells are activated and a proportion become enriched in tissue that has healed, including those that express IL-23R as well as cutaneous lymphocyte-associated antigen, CCR6, and CD103.[11] These CD8+ T cells respond to *ex vivo* stimulation by producing IL-17A, while epidermal CD4+ T cells respond

by producing IL-22 for as long as 6 years following TNF-α inhibition.[11] These pathways have the potential to be modified by agents that target IL-23.

Other clinical advantages of blocking IL-23 include differential impacts on the bowel mucosa important for inflammatory bowel disease (IBD), a reduced risk of candidiasis or other opportunistic infection versus the risk with blockade of IL-17, and potential impacts on neoplasm formation. In the gut, unlike other tissues such as the skin, IL-17 promotes homeostasis and tissue repair rather than driving pathogenic inflammation; nevertheless, it is clear that antibodies targeting IL-23 ameliorate IBD. Data from a mouse model of IL-17A-producing gut cells suggest that the activity of these cells is independent of IL-23, implying that antibodies against IL-23 would not impair IL-17 production by innate lymphocytes. These data help to explain the observation that targeting IL-17 is ineffective in IBD.[18] In opportunistic infections of the mucosa caused by *Candida albicans*, IL-17 signalling is key to immunity and absence of the IL-17 receptor (IL-17R) in mice or humans leads to chronic infection;[19] therefore, blockade of IL-23 may represent an alternative therapeutic strategy. More generally, the marked redundancy seen in pathways involved in the IL-effector response to a wide range of pathogens suggests that IL-12/23 blockade should not have a significant impact on signalling, implying a favourable safety profile for IL-23 targeted agents (Figure 1).[20]

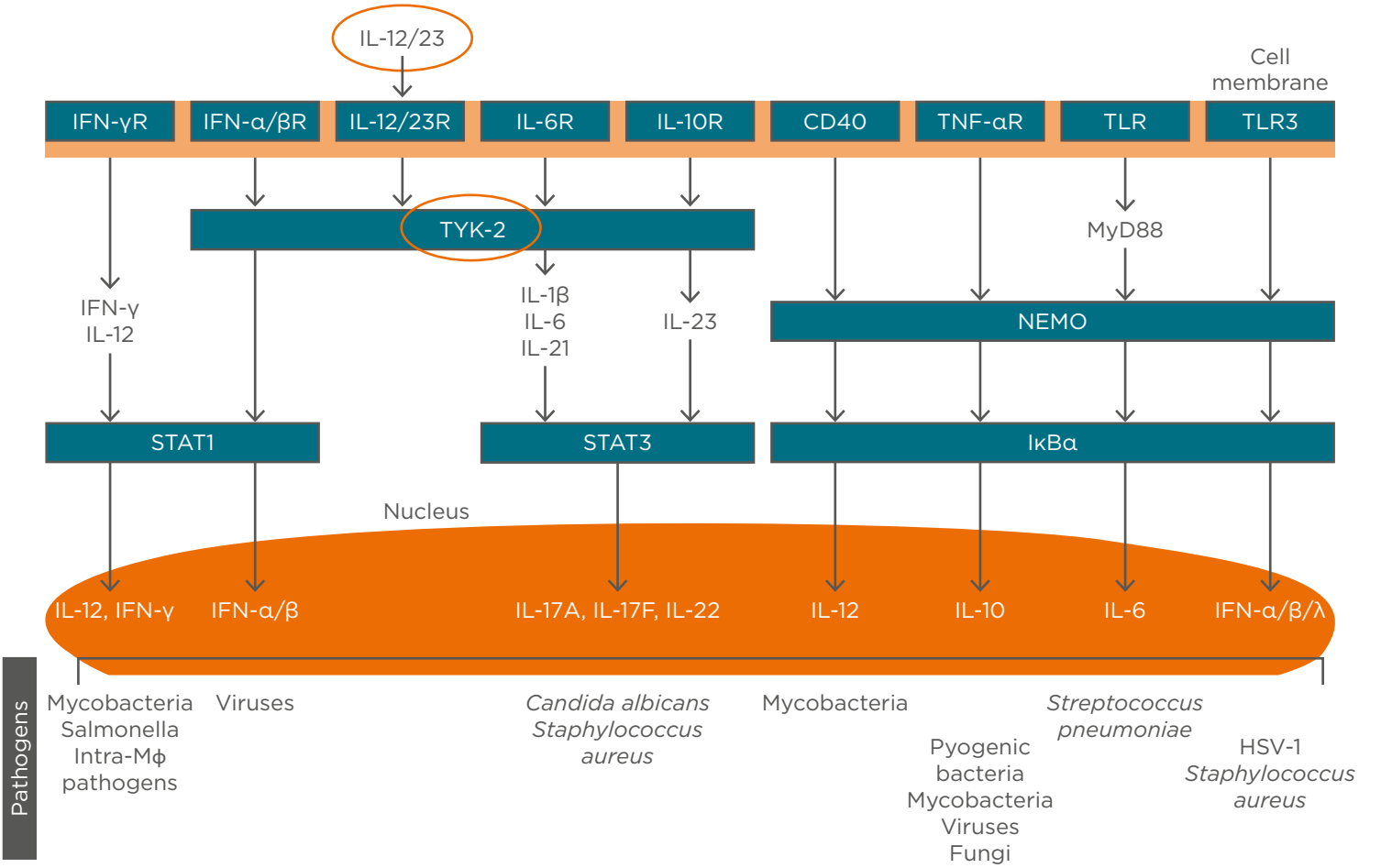

Figure 1: The role of cytokines in the pathogenesis of psoriasis and immune defence against infectious agents, showing redundancy in pathways downstream of IL-12/23 in Th cells that may favour the targeting of regulatory, rather than effector, cytokine blockade in the avoidance of infection.

HSV: herpes simplex virus; NEMO: NFκB essential modulator; R: receptor; TLR: toll-like receptor; TYK: tyrosine kinase.

Adapted from Blauvelt et al.[20]

Finally, in immune surveillance, IL-12 acts on lymphoid cells, such as natural killer cells and CD8+ cytotoxic T lymphocytes, which then produce IFN-γ and prevent tumour initiation, growth, and metastasis. In mouse tumour models, there is evidence for various activities of IL-23 in disease: as a tumour suppressor in ultraviolet-induced skin cancer, as an inducer (when overexpressed) of *de novo* intestinal tumours, and as a target for eliminating residual tumour cells from occult tumours.[6] Ultimately, head-to-head clinical trials will determine the extent of the advantages in blocking IL-23 versus IL-17A. Several such clinical trials are currently ongoing in patients with psoriasis.

Cellular and Molecular Changes in Response to Selective IL-23 Versus Dual IL-12/23 Blockade in Psoriatic Skin

Professor James Krueger

The two founding members of the IL-12 cytokine family, IL-12 and IL-23, share a common p40 subunit but are distinguished by their unique p35 and p19 subunits and their predominant downstream activity of IFN-γ or IL-17 activation, respectively.[6] The accepted disease model in psoriasis was, until less than a decade ago, one of inflammatory dendritic cells stimulating keratinocytes to produce a range of multiple cytokines, chemokines, and other inflammatory molecular and cellular effects that resulted in lesion formation, plus feedback and perpetuation of this reaction.[21] However, with the more recent availability of specific antibodies to p40 (e.g., ustekinumab) and p19 (e.g., guselkumab), the pathogenic axis was more specifically recognised as IL-23/IL-17, and the respective clinical effects of these differentially targeted mAb have generated much discussion and research interest.

As noted earlier in the symposium, data from head-to-head studies of guselkumab and ustekinumab are lacking. However, biopsy data comparisons have been made using samples from individuals treated in separate clinical trials of the two agents: the Phase III ACCEPT (T12)[22] study, combining patients treated with high-dose guselkumab 100 mg and 300 mg, and the Phase I study,[23] in which patients were treated with ustekinumab 90 mg. The two patient cohorts shared similar characteristics, with comparable baseline demographics, disease characteristics, and skin histopathology, and all the samples were fed into identical analyses.[24] Expression analyses indicated that >2,900 gene transcripts were upregulated in psoriasis lesion tissue, but in 'recovered' tissue 12 weeks post-treatment, a higher rate of renormalised (i.e., modulated ≤2-fold) transcripts was seen in those treated with guselkumab (77%) versus ustekinumab (45%) (unpublished data). Also, 75% of transcripts returned to a baseline level ≥75% of normal with guselkumab treatment, versus only 27% with ustekinumab. A 'molecular scar' can be identified at Week 12 of treatment versus baseline, in which the transcriptome recovers to 17% of its previous value with guselkumab, versus 58% with ustekinumab. After both 1 and 12 weeks of treatment, the neutralisation of activity of relevant transcriptomic genes following high-dose guselkumab was significantly more extensive than that with ustekinumab (unpublished data). These data were further supported in a real-time PCR analysis of the *DEFB4* and *LCN2* gene products, showing that these IL-17-responsive antimicrobial proteins recovered to a greater extent with guselkumab versus ustekinumab.[24] Histological staining of tissue using markers for keratin 16, T cells, dendritic cells, and other markers also demonstrated 12-week recovery with ustekinumab. These observations prompt the question of the relative potency of guselkumab and ustekinumab, and data show that, across a range of assays, there is a 2–14-fold difference in potency in favour of guselkumab.[24]

There are several factors that could contribute to the superiority of guselkumab over ustekinumab in neutralising psoriasis-related gene expression. In a mouse model of IL-17-mediated inflammatory activity in skin, knockout of the IL-12 subunit p40 resulted in inflammation, thin skin, and a doubling in transepidermal water loss.[5] Therefore, IL-12 may counter-regulate the IL-23/Th17 axis, which is critical for sustaining psoriasis. In addition, there is complexity within the IL-12 family of cytokines, and gene expression data reveal a possible role for other, less well-characterised members. As well as

changes in the levels of various members of the IL-12 family, such as K16, IL-17A, p19, and p40, psoriasis is also associated with raised IL-27 (unpublished data). IL-27 is composed of the subunits p28 and Ebi3 (named for homology to an Epstein–Barr virus gene),[25] neither of which are targeted by guselkumab or ustekinumab. As the IL-12 cytokine family is promiscuous and protein subunits of the family can combine with different partners to activate other pathways, Ebi3 could pair with p19 to form IL-39.[25] In a mouse model of lupus, IL-39 drives inflammation, including neutrophil activation,[26] and although a native human IL-39 has not been identified, the subunits are both elevated in psoriasis cells (unpublished data). Moreover, p40 can pair with p28 to form IL-Y,[7] which has anti-inflammatory activities; therefore, it is possible that some of the benefits of blocking IL-12 and IL-23 activity could be reduced by downregulating beneficial IL-Y activity. Furthermore, there may be functional plasticity in the Th17 lineage, such that removal of IL-23 from pathogenic T cells can convert them to non-pathogenic, regulatory T cells.[27] Any or all of these effects may play a role and require further investigation. In summary, although molecular data have shown very clear differential effects of guselkumab and ustekinumab on the transcriptome of psoriasis-associated cells, other potential cytokine activities in psoriasis still require full characterisation.

Disease Modification in Psoriasis: Fantasy or Reality?

Doctor Curdin Conrad

In patients with psoriasis receiving anti-IL-23 treatment, a positive response to continuous treatment can be very long-lasting. A high rate of freedom from disease has been seen with continuous guselkumab treatment in the Phase III VOYAGE studies[8,12] and with risankizumab in a Phase II study.[28] This clinical benefit is beyond that anticipated based on the half-life of the drugs and raises the possibility that, by some mechanism, a form of disease modification has resulted from treatment. Such a mechanism may involve activated T cell migration to the lymph nodes, where they perform a central memory function and/or reside in the skin for a long period. As noted, evidence for the latter originates from disease memory in clinically healed skin, which shows relatively high levels of IL-17-producing T cells.[29] It has been proposed that, following successful treatment, the *in situ* activation of epidermal T cells resident in psoriatic skin can lead to IL-17A production, resulting in recruitment of further inflammatory T cells from the blood and subsequent clinical relapse.[12] This suggests that, to have any long-term disease-modifying effect, skin-resident memory T cells should be targeted.

In psoriasis, Th17 and Tc17 cells coproduce IL-17A and other cytokines, with their expansion dependent on IL-23.[30,31] The physiological function of these cells is thought to be protection from extracellular pathogen attack (Figure 1); however, overexpression in autoimmune disease is also common.[30] It is clear that to achieve a response to psoriasis treatment, a reduction of IL-17 levels is necessary,[32] and with the array of targeted agents available (e.g., TNF inhibitors, IL-12/23 or IL-23 inhibitors, IL-17A or IL-17R inhibitors) there are many methods to achieve this. Relapse following discontinuation of IL-17R blockade generally occurs within a few weeks,[33] suggesting that blockade of IL-17 rather than its receptor may be a more efficacious long-term approach. In Crohn's disease, in which IL-17 is highly expressed, expectations for anti-IL-17 treatment were not fulfilled; indeed, cases of aggravated IBD following anti-IL-17 treatment were observed.[30,34] One explanation for this is the existence of two types of IL-17-producing cells: pathogenic Th17 cells and non-pathogenic Th17 cells that also produce IL-10 (which also provide a beneficial barrier and pathogen defence function) independent of IL-23 signalling.[35] Only the former are blocked by IL-23 targeting.

How can we effectively assess the effects on IL-17 and IL-22-producing skin-resident memory T cells present in non-lesional tissue? Following treatment discontinuation, psoriasis tends to revert to its baseline severity.[11] In a recent study of secukinumab treatment discontinuation, gene expression analysis of non-lesional skin in patients who did not relapse showed a robust, durable effect 1 year after stopping therapy.[36] This may be due to the removal of memory T cells from non-lesional skin. From hypotheses

about any long-term effects on these cells, it has been suggested that targeting IL-23 may be beneficial in preventing Th17/Tc17 cells from becoming pathogenic. In addition, single nucleotide polymorphisms in *IL-23R* are associated with autoimmune disease, including psoriasis, and IL-23R is preferentially expressed in these skin cells in psoriasis patients. Possibilities for purging memory T cells include antibody-dependent cell-mediated cytotoxicity or lack of stimulus through IL-23R, though evidence for any of the available drugs exerting either mechanism in non-lesional skin is lacking. In conclusion, multiple observations suggest disease modification in patients with psoriasis receiving anti-IL-23 treatment: a clinical effect beyond drug half-life and biological half-life of the treatment, possible effects on skin-resident memory T cells that mediate disease memory, and the effect of blocking only pathogenic (not non-pathogenic) Th17 cells.

WATCH THE FULL SYMPOSIUM ONLINE ←

https://www.youtube.com/watch?v=jW9kpRu4ccI

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Emerging Insights in the Treatment of Psoriasis and Psoriatic Arthritis

These posters were presented at the 5th World Psoriasis & Psoriatic Arthritis Conference 2018, held from 27th–30th June in Stockholm, Sweden

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Overview

Guselkumab is a monoclonal antibody targeting IL-23 that is approved for the treatment of patients with moderate-to-severe plaque psoriasis. Two of the posters reviewed in this article provide new insights into the clinical efficacy of guselkumab in patients with plaque psoriasis from the VOYAGE trials, firstly among those previously failing to respond to adalimumab and secondly in the setting of drug withdrawal and subsequent retreatment. In addition, data from a study reporting 56-week results from a Phase IIa study exploring the efficacy and safety of guselkumab in patients with psoriatic arthritis (PsA) are reviewed. The article concludes with a summary of the results of a survey highlighting the potential importance of evaluating gastrointestinal (GI) signs and symptoms during the management of patients with psoriasis.

Clinical Response After Guselkumab Treatment Among Adalimumab PASI 90 Non-Responders: Results from the VOYAGE 1 and 2 Trials (Poster P042)

Professor Christopher E.M. Griffiths

Guselkumab is a fully human monoclonal antibody that selectively binds to the p19 subunit of IL-23, thereby inhibiting interaction with the IL-23 receptor and preventing downstream release of proinflammatory mediators.[1,2] Guselkumab is approved in the USA and Europe for the treatment of adults with moderate-to-severe plaque psoriasis.[1,2] The pivotal clinical trial programme for guselkumab in patients with plaque psoriasis included two Phase III, double-blind, placebo and adalimumab-controlled studies, VOYAGE 1 and 2.[3,4] The analysis presented in this article was conducted to evaluate clinical response and patient-reported outcomes among those patients who initially received adalimumab and failed to achieve Psoriasis Area Severity Index (PASI) 90 responses in VOYAGE 1 and 2 and were subsequently switched to guselkumab. In addition, the safety of the crossover to guselkumab was explored.

As this analysis focussed on the patients in VOYAGE 1 and 2 who were initially randomised to adalimumab, those initially randomised to placebo or guselkumab are not discussed herein.

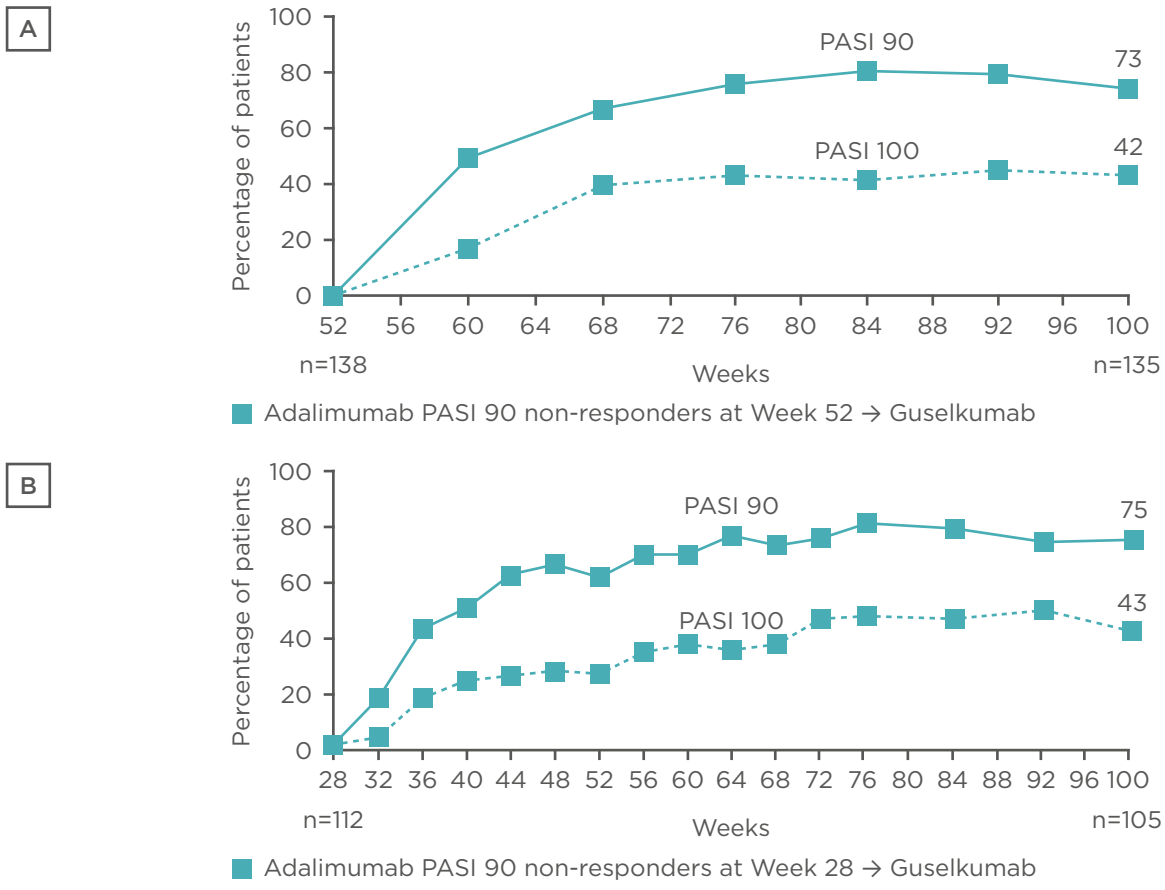

Figure 1: Proportion of PASI 90 and 100 responders among adalimumab PASI 90 non-responders who crossed over to guselkumab at Week 52 in VOYAGE 1 (A) and at Week 28 in VOYAGE 2 (B).

Analyses were performed using non-responder imputation through to Week 72 for Figure 1B and using observed data after applying treatment failure rules for Figure 1A and for Week 76–100 for Figure 1B.

PASI: Psoriasis Area Severity Index; →: crossover.

In VOYAGE 1, 334 patients were initially randomised to adalimumab 80 mg subcutaneously at Week 0, followed by 40 mg at Week 1 and 40 mg every 2 weeks thereafter through to Week 47.[3] All adalimumab-treated patients switched to guselkumab 100 mg at Week 52 and continued to receive guselkumab every 8 weeks until Week 100. The present analysis focussed on the 138 adalimumab-treated patients who were PASI 90 non-responders at Week 52. A similar initial adalimumab treatment regimen was used in VOYAGE 2 (n=248),[4] with the exception that patients were switched to guselkumab 100 mg at Week 28. Patients subsequently received a second guselkumab dose at Week 32 and then every 8 weeks until Week 100. In VOYAGE 2, 112 adalimumab-treated patients were PASI 90 non-responders at Week 28 and were included in this analysis.

The results of the analysis revealed a robust clinical response associated with switching to guselkumab among adalimumab-treated patients who had initially failed to achieve PASI 90 at Week 52 and 28 in VOYAGE 1 and 2, respectively. At Week 100, after ~1 year of guselkumab treatment following adalimumab non-response, 73% and 42% of patients achieved a PASI 90 and 100 response, respectively, in the VOYAGE 1 trial (Figure 1A). Similarly, in VOYAGE 2, 75% and 43% of adalimumab non-responders had PASI 90 and 100 responses at Week 100, respectively, ~1.5 years after switching to guselkumab (Figure 1B).[4] Improvements were also noted in the proportion of patients achieving an Investigator's Global Assessment (IGA) score of 0 or 1 (cleared or minimal) after crossing over to guselkumab. By Week 100, 79% and 81% of adalimumab PASI 90 non-responders who switched to guselkumab had achieved IGA scores of 0 or 1 in VOYAGE 1 and 2, respectively.

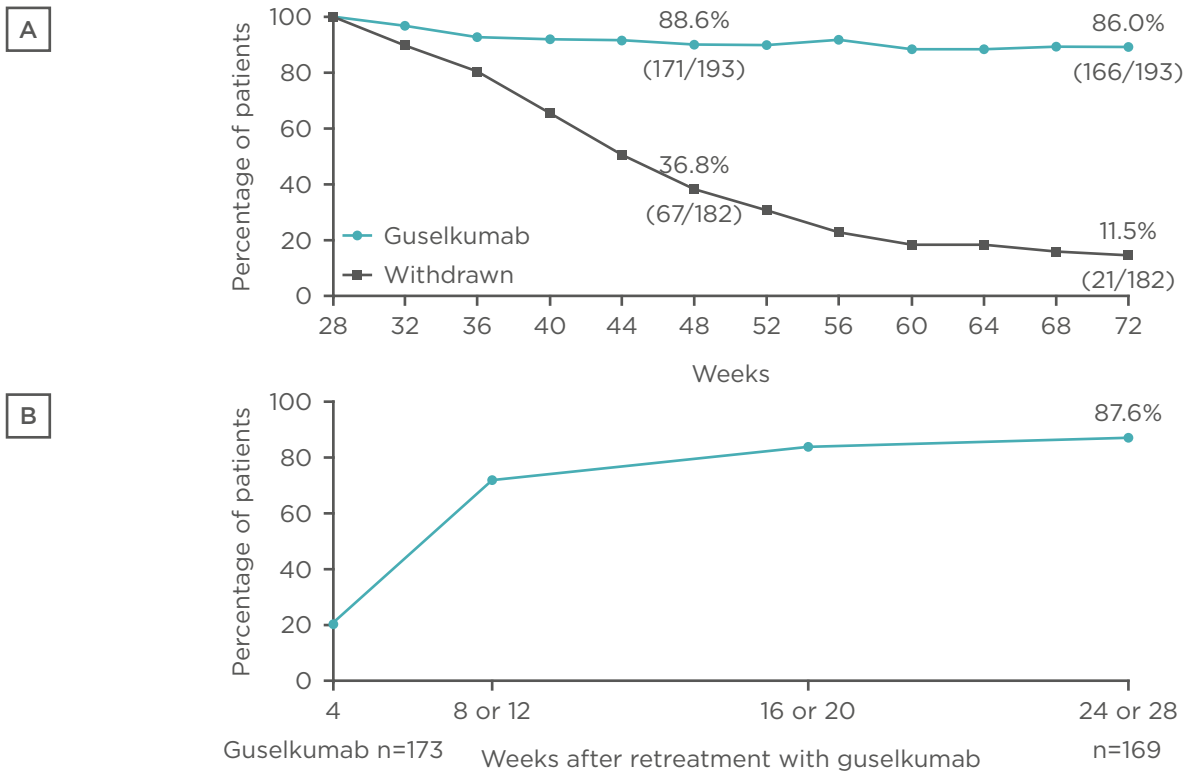

Figure 2: A) PASI 90 response among patients who were originally randomised to guselkumab, achieved a PASI 90 response at Week 28, and were subsequently randomised to withdrawal or continued guselkumab. B) Recapture of PASI 90 response following retreatment with guselkumab among patients randomised to withdrawal at Week 28.

Analysis performed with non-responder imputation for Figure 2A.

PASI: Psoriasis Area Severity Index.

To further explore the impact of switching from adalimumab to guselkumab on patients, effects on health-related quality of life were analysed using the Dermatology Life Quality Index (DLQI) Score and patient-reported psoriasis symptoms and signs were assessed using the Psoriasis Signs and Symptoms Diary (PSSD). Adalimumab PASI 90 non-responders who switched to guselkumab achieved improvements in DLQI in both VOYAGE 1 and 2; the proportion of patients achieving DLQI scores of 0 or 1 increased from 25% to 75% from Week 48 to 100 in VOYAGE 1 and from 14% to 65% from Week 28 to 100 in VOYAGE 2. Improvements were also observed in the proportions of adalimumab PASI 90 non-responders achieving PSSD symptoms or signs scores of 0 following crossover to guselkumab. By Week 100 in VOYAGE 1, 33% of patients had achieved a PSSD symptom score of 0 and 19% had achieved a PSSD sign score of 0. In VOYAGE 2, 33% and 18% of patients achieved PSSD symptom and sign scores of 0, respectively.

No new safety signals were observed following crossover to guselkumab in adalimumab-treated patients, with the safety profile consistent with the overall guselkumab safety data previously reported from VOYAGE 1 and 2.[5] Among the pooled population of patients in VOYAGE 1 and 2 (data through Week 100), rates of serious adverse events (AE) per 100 patient years in those treated with adalimumab (prior to guselkumab) and in those who crossed over to guselkumab were 7.77 and 4.44, respectively. Similarly, there was no notable elevation in the incidence of AE of interest with crossover to guselkumab: for adalimumab (prior to guselkumab) and adalimumab crossover to guselkumab groups, the incidence rates per 100 patient years were 1.8 and 0.0 for serious infections, respectively, 0.4 and 0.2 for major adverse cardiovascular events, respectively, 0.4 and 0.8 for non-melanoma skin cancer, respectively, and 0.4 in both groups for malignancy excluding non-melanoma skin cancer.

In summary, this analysis of data from the VOYAGE 1 and 2 studies established that, among adalimumab PASI 90 non-responders, switching to guselkumab provided robust levels of clinical response, enhanced health-related quality of life, and improved psoriasis signs and symptoms.

Long-Term Efficacy of Guselkumab Treatment After Drug Withdrawal and Retreatment in Patients with Moderate-to-Severe Plaque Psoriasis: Results from VOYAGE 2 (Poster P049)

Professor Kenneth Gordon

The VOYAGE 2 study[4] was a Phase III, double-blind trial that investigated the efficacy and safety of guselkumab compared with adalimumab in patients with moderate-to-severe psoriasis. Following the initial 28-week active comparator period, the study design of VOYAGE 2 included a withdrawal and retreatment period that explored the comparative clinical efficacy and safety of continued guselkumab therapy versus withdrawal and retreatment upon relapse. Given that discontinuation of biologics, and in some instances retreatment, is a relatively common occurrence in patients with psoriasis,[6] it is important to understand the impact of such events on clinical efficacy and safety. The study presented here reports the long-term results from the withdrawal and retreatment phase of VOYAGE 2.

In VOYAGE 2, 375 patients who were originally randomised to guselkumab 100 mg (at Week 0 and 4, and every 8 weeks thereafter) and achieved PASI 90 response at Week 28 were rerandomised to withdrawal (n=182) or continued guselkumab (n=193).[4] Patients in the withdrawal group initially received placebo but were retreated with guselkumab upon loss of ≥50% of the PASI improvement achieved at Week 28; all patients who did not require retreatment were switched back to guselkumab at the Week 72 timepoint.

Patients who were randomised to receive continuous guselkumab therapy following a PASI 90 response at Week 28 typically maintained PASI 90 responses, with a PASI 90 response rate of 86% observed at Week 72 (Figure 2A). In contrast, PASI 90 response rates gradually declined in the group randomised to withdrawal following initial guselkumab PASI 90 response at Week 28, by Week 48, 37% of

patients in the withdrawal group had PASI 90 response, and only 12% maintained PASI 90 response at Week 72. Among those patients in the withdrawal group who were retreated with guselkumab following loss of ≥50% of the PASI improvement achieved at Week 28, PASI 90 responses were recaptured in 88% of patients within 6 months of starting retreatment (Figure 2B).

The observed maintenance of PASI 90 response at Week 48 among approximately one-third of patients withdrawn from guselkumab in VOYAGE 2 has previously been reported to be associated with sustained suppression of serum cytokines, including IL-17A, IL-17F, and IL-22.[7] Conversely, loss of response (PASI <75) is associated with increases in serum levels of these cytokines.[7] For example, in those with loss of response, serum levels of IL-17A were significantly elevated from Week 28 levels (the time of withdrawal) at Week 40, 44, and 48 ($p<0.01$), and were significantly greater at Week 44 and 48 than the levels seen in those with maintained responses ($p<0.05$).

In addition to PASI response, the present study incorporated assessment of the effects of guselkumab withdrawal (and subsequent retreatment as needed) versus maintenance therapy on health-related quality of life using the DLQI score. Among those patients who had a PASI 90 response at Week 28, the proportion of patients achieving DLQI scores of 0 or 1 was maintained in the guselkumab maintenance group from Week 28 (70%) to Week 48 (69%) and increased to 80% by Week 100. In those who were randomised to withdrawal at Week 28, the proportion of patients with DLQI 0 or 1 scores decreased substantially after the switch to placebo, falling from 67% at Week 28 to 32% at Week 48. Retreatment with guselkumab in the withdrawal group led to recapture of the lost DLQI 0 or 1 response, with 68% of patients in the withdrawal group acheving DLQI 0 or 1 scores by the Week 100 timepoint. All withdrawal group patients reverted to guselkumab from Week 72 onwards.

In terms of safety and tolerability, no safety signals were observed with withdrawal and retreatment with guselkumab. The incidence of AE from Week 28–72 was similar in both the continued guselkumab and withdrawal groups, with 61% and 59% of patients per group experiencing ≥1 AE, respectively. Incidences of infections were similar in both maintenance and withdrawal groups (41% of patients in both) from Week 28–72, and there were no cases of tuberculosis, opportunistic infection, or serious hypersensitivity reactions. In those patients who were withdrawn from guselkumab, prior to retreatment with guselkumab there were two events of psoriasis rebound (≥125% increase in PASI score from baseline at any time during withdrawal) and no AE related to other forms of psoriasis.

In conclusion, the results of this long-term assessment of the efficacy of guselkumab treatment after withdrawal and retreatment following response at Week 28 provide several insights into guselkumab-based therapy. Firstly, the analysis demonstrated that continued treatment with guselkumab following PASI 90 response is associated with superior efficacy compared with treatment interruption, in terms of both maintenance of PASI 90 response over time and sustaining improvements in health-related quality of life. In contrast, guselkumab withdrawal leads to gradual declines in both of these variables. Maintenance of PASI 90 response after drug withdrawal was associated with continued suppression of IL-17A, IL-17F, and IL-22. Retreatment with 6 months' guselkumab after withdrawal led to the recapture of PASI 90 response in the majority of patients, and there were no safety concerns identified among those initially withdrawn and subsequently retreated.

Efficacy and Safety Results of Guselkumab in Patients with Active Psoriatic Arthritis over 56 Weeks (Poster P119)

Professor Wolf-Henning Boehncke

Guselkumab is approved for the treatment of moderate-to-severe plaque psoriasis[1,2] and is currently being evaluated in patients with PsA. PsA is a common comorbidity that has been estimated to affect approximately one in five patients with psoriasis,[8] and significantly impairs patients' physical function and ability to

work.[9] This poster describes the results from a randomised, double-blind, placebo-controlled, Phase IIa trial of guselkumab in PsA through Week 56.[10]

Eligible patients for this study included adults with active PsA, ≥3 tender and ≥3 swollen joint counts, and ≥3% body surface area affected by plaque psoriasis. In addition, patients were required to have previously experienced an inadequate response to current standard-of-care treatment, including non-biologic disease-modifying antirheumatic drugs, oral corticosteroids, or non-steroidal anti-inflammatory drugs. Prior exposure to an anti-TNF agent was permitted but limited to 20% of the enrolled population. Eligible patients were randomised 2:1 to receive guselkumab 100 mg subcutaneously or placebo at Week 0, 4, and every 8 weeks thereafter, until Week 44. Patients were subsequently followed-up until Week 56. At Week 16, those patients who achieved <5% improvement from baseline in swollen and tender joint counts were able to switch to open-label ustekinumab. The placebo-controlled period ended at Week 24, at which point placebo-treated patients were switched to guselkumab therapy until Week 44.

In total, 149 patients were randomised, with 49 receiving placebo and 100 receiving guselkumab. Baseline demographics and American College of Rheumatology (ACR) component measures were generally similar between the two groups. Twenty-seven patients switched to ustekinumab at Week 16 (placebo group: n=17; guselkumab group: n=10). Among those initially randomised to guselkumab, 84 patients completed the 56-week study. Twenty-nine patients randomised to placebo switched to guselkumab at Week 24, of whom 28 completed the remainder of the study.

The proportion of patients achieving a 20% improvement in ACR criteria (ACR 20) at Week 24 (the primary endpoint) was significantly greater with guselkumab (58% of patients) compared with placebo (18.4%; p<0.001). Significantly greater ACR 20 response rates were observed with guselkumab versus placebo at the first assessment timepoint (Week 4; p<0.001) and were sustained throughout the 24-week placebo-controlled period (p<0.05 to p<0.001). Among the group continuing guselkumab therapy after Week 24, ACR 20 responses rates were maintained, with 61% of patients achieving ACR 20 at Week 56. In addition, guselkumab therapy was associated with significantly greater response rates than placebo in terms of ACR 50 (34% versus 10%, respectively; p=0.002) and ACR 70 (14% versus 2%, respectively; p=0.023 [post-hoc analysis]) at Week 24, with response rates maintained to Week 56.

Improvements in ACR criteria with guselkumab were complemented by reductions in the severity of psoriasis, with significantly greater PASI 75, 90, and 100 response rates with guselkumab versus placebo at Week 24 (all p<0.001). In addition, the proportions of patients with unresolved enthesitis or dactylitis were significantly reduced in the guselkumab group versus placebo at Week 24 (p<0.05). Patient-reported health-related quality of life measures were significantly improved with guselkumab relative to placebo at Week 24, including when assessed via the Health Assessment Questionnaire (HAQ-DI) and the 36-item Short Form Health Survey (SF-36) physical and mental component scores (all p<0.01). At Week 24, a significantly greater proportion of patients achieved minimal disease activity with guselkumab than placebo (23% versus 2%, respectively; p=0.001). PASI response rates, enthesitis and dactylitis resolution rates, health-related quality of life scores, and minimal disease activity rate were generally well maintained to the end of the study with continued guselkumab therapy.

Guselkumab was well-tolerated over the 56-week study, with no injection site reactions reported among the 750 guselkumab injections administered. Through Week 24, incidences of AE and infections were comparable between the guselkumab and placebo groups (AE: 36% and 33%, respectively; infections: 16% and 20%, respectively). Longer guselkumab exposure through Week 56 did not lead to a disproportionate increase in the incidence of AE or infections. Serious AE were reported by six patients (6.0%) through Week 56 in the guselkumab group and two patients (2.0%) discontinued due to AE (leukopenia/neutropenia and pneumonia, respectively). A single malignancy (basal cell carcinoma) was reported by one patient (0.8%) who received

guselkumab. Neutropenia was reported in four guselkumab-treated patients through Week 24 (three cases of Common Terminology Criteria for Adverse Events [CTCAE] Grade 2, which resolved spontaneously, and one case of CTCAE Grade 3, in whom guselkumab was discontinued and neutropenia resolved without treatment). There were no infections reported in the patients developing neutropenia, and no additional cases with Grade ≥2 occurred after Week 24. Increases in alanine transaminase/aspartate transaminase were generally comparable between guselkumab and placebo groups. There were no deaths, opportunistic infections, cases of active tuberculosis, or anaphylactic reactions.

In summary, the study demonstrated significant improvements in joint symptoms, physical function, psoriasis, enthesitis, dactylitis, and quality of life with guselkumab in patients with active PsA, with efficacy well-maintained through Week 56. Furthermore, guselkumab was well tolerated over the course of approximately 1 year of exposure.

Gastrointestinal Symptoms are Common in U.S. Patients with Moderate-to-Severe Psoriasis (Poster P112)

Professor Steven Feldman

Patients with plaque psoriasis are at increased risk of developing inflammatory bowel disease (IBD), with the risk increasing with higher degrees of psoriasis severity.[11] Such concordance in disease incidence may arise from shared genetic susceptibilities and common inflammatory pathogenic pathways.[12] Understanding the frequency of GI symptoms in patients with psoriasis is important, as the presence of GI disease could impact which treatments are chosen. This survey study was conducted to evaluate the prevalence of GI signs and symptoms among patients with plaque psoriasis.

An electronic survey was undertaken in the USA using an online opt-in patient panel/database, with data collected from January 2017 to February 2017. Patients with self-reported moderate-to-severe plaque psoriasis and healthy controls were eligible for inclusion in the survey, with psoriasis patients categorised into two subgroups: those with recent (within 4 months) exposure to biologic therapy (the PsO^{RT} group) and those without such exposure (the PsO group). Patients were evaluated for GI signs and symptoms consistent with IBD, and the frequency and severity of such symptoms were compared across groups. Patients with a diagnosis of IBD, irritable bowel syndrome, or other GI disorders with symptoms overlapping with IBD were excluded from the analysis. To further explore the impact of psoriasis on IBD risk, CalproQuest scores were calculated; CalproQuest scores have recently been proposed as a potential tool for identifying patients who have elevated faecal calprotectin levels and increased risk of IBD.[13] The CalproQuest score is calculated from an IBD symptom questionnaire consisting of eight criteria (e.g., 'Does the patient report a bloody stool?'), with results considered positive if ≥2 major criteria, or one major and two minor criteria, are met.[13]

In total, 915 patients with self-reported moderate-to-severe plaque psoriasis (450 of whom had recent biologic exposure) were enrolled in the survey, along with 1,411 healthy controls. Demographics were broadly comparable between groups, although patients in the plaque psoriasis cohort were on average younger than those in the healthy control group. Among those with psoriasis, almost all patients had a disease duration >1 year, and 39% and 21% reported having had psoriasis for >10 years in the PsO and PsO^{RT} groups, respectively. Substantially more patients in the PsO^{RT} group (35%) had been hospitalised within the last year for psoriasis versus the PsO group (3% of patients).

GI signs and symptoms were more common among those in the PsO and PsO^{RT} groups compared with healthy controls for all variables assessed, including stomach pain, feeling full or bloated, diarrhoea, mucus in the stool, and blood in the stool (Table 1). A significantly lower incidence of stomach pain, a full or bloated sensation, and diarrhoea were reported in those without versus with recent exposure to biologic. Incidences of mucus or blood in the stool were numerically, but not significantly, lower among PsO versus PsO^{RT} patients.

Table 1: Gastrointestinal signs and symptoms among patients with psoriasis and healthy controls.

	PsO	PsO^{RT}	HC
Number of patients, n	465	450	1,411
GI signs and symptoms			
Stomach pain	20.6% p=0.002 vs. HC p=0.002 vs. PsO^{RT}	36.9% p=0.002 vs. HC	10.5%
Full or bloated	37.2% p=0.002 vs. HC p=0.002 vs. PsO^{RT}	48.4% p=0.002 vs. HC	25.3%
Diarrhoea	16.3% p=0.023 vs. HC p=0.002 vs. PsO^{RT}	29.3% p=0.002 vs. HC	12.2%
Mucus in stool	4.5% p=0.020 vs. HC p=0.317 vs. PsO^{RT}	6.0% p=0.002 vs. HC	2.4%
Blood in stool	4.3% p=0.004 vs. HC p=0.390 vs. PsO^{RT}	5.6% p=0.002 vs. HC	1.9%

*Within last 4 months.

GI: gastrointestinal; HC: healthy controls; PsO: psoriasis patients without recent biologic exposure; PsORT: psoriasis patients with recent biologic exposure.

Calculation of CalproQuest scores indicated a significantly greater proportion of patients with a positive CalproQuest result among the PsO group (10%) versus the healthy controls (6%; p=0.005). The greatest incidence of positive CalproQuest scores occurred among the PsO^{RT} group, with positive results for one in five patients (20%; p=0.002 versus both the PsO and healthy volunteer groups).

Although the cause of higher frequency of GI symptoms in those with recent biologic exposure was not assessed, one possible explanation is that patients with recent biologic exposure may have worse psoriasis, and that worse psoriasis has a greater association with IBD. Another possibility is that some agents used to treat moderate-to-severe psoriasis are associated with increased risk of IBD (in particular, IL-17 blockers) or simply GI intolerance (apremilast).

In summary, the present survey highlights that GI signs and symptoms are common in patients with moderate-to-severe plaque psoriasis, and occur at a higher incidence than seen in healthy controls. As such, it is important for healthcare professionals involved in the care of patients with psoriasis to consider assessing and monitoring GI signs and symptoms to identify patients who may be at risk of developing IBD.

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Efficacy, Sustainability, and Patient-Reported Outcomes of Guselkumab to Treat Plaque Psoriasis in the Post-Approval Setting

These posters were presented at the 27th European Academy of Dermatology and Venereology (EADV) Congress, held from 12th–16th September in Paris, France

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Overview

Plaque psoriasis is an autoimmune condition characterised by the development of red, dry, scaly skin lesions that cause irritation and pain for patients. It is a disabling and disfiguring condition and, alongside the physical effects, is associated with psychological comorbidities, including anxiety and depression.[1] Combined effects of the condition are known to affect productivity at work, with increased rates of absenteeism.

Novel targeted therapies have the potential to transform treatment in this field. Adalimumab is a monoclonal antibody that inhibits TNF and has been approved in Europe since 2007 for the treatment of patients with moderate-to-severe chronic plaque psoriasis who are eligible for systemic therapy or phototherapy. Guselkumab is a novel IL-23-blocking monoclonal antibody that has been approved for use in the same indication as adalimumab in Europe since 2017. Personalised treatment is becoming more common and the delivery of therapeutics is a changing landscape, with a shift towards patients administering their own medication through novel devices.

This article reviews four posters displayed at the European Academy of Dermatology and Venereology (EADV) Congress 2018 that present results demonstrating the efficacy of guselkumab compared to adalimumab for the treatment of psoriasis, as measured by a range of outcomes, a favourable drug delivery system, and a higher drug survival rate overall.

Drug Survival is Superior Among Patients Treated with Guselkumab Compared to Adalimumab in the VOYAGE 1 Trial (Poster P1937)

Doctor David Pariser

Drug survival, defined as the probability that a patient will remain on a given therapy, is an important measure of the success of a therapeutic, especially in chronic conditions. Drug survival demonstrates the long-term tolerability and efficacy of an agent indicated in a condition and can show favourability over other therapies in head-to-head trials to measure treatment sustainability.

A post-hoc analysis of data collected in the VOYAGE 1 study was carried out to determine drug survival of guselkumab compared with the active comparator adalimumab.[2] In VOYAGE 1, patients were randomised 1:1 to guselkumab (n=329) or adalimumab (n=334). Baseline demographic characteristics were comparable between the groups. Primary analyses of discontinuation for any reason up to 48 weeks of treatment were performed. Specific reasons for discontinuation were tabulated and a comparison of demographic and disease characteristics of patients discontinuing each treatment was carried out. Kaplan–Meier plots were produced to compare drug survival of guselkumab and adalimumab. The hazard ratio for risk of discontinuation of guselkumab versus adalimumab was calculated using Cox modelling. Secondary analyses were carried out, including evaluation of worsening disease or lack of treatment efficacy and adverse events.

Primary analyses compared baseline demographic characteristics of patients discontinuing the study drug. In the adalimumab group, patients discontinuing treatment had a higher median baseline body weight than those in the guselkumab arm (97.7 kg versus 84.9 kg, respectively). Other demographic and disease characteristics were comparable between discontinuing patients in both groups. Higher body weight has been associated with lower efficacy for a number of biologic agents, and this association has been reported to be more pronounced for adalimumab compared with guselkumab.[2] This may be reflective of differences in immunogenicity or other factors affecting the serum levels of each drug and, therefore, its biologic availability and efficacy.

Guselkumab showed a superior drug survival rate compared with adalimumab at 48 weeks of treatment. Fifty-two (15.6%) patients in the adalimumab group discontinued the agent for any reason, compared with 28 (8.5%) patients in the guselkumab group. This difference in failure rate was statistically significant (p=0.0053) and the hazard ratio of 1.88 for discontinuing adalimumab versus guselkumab (95% confidence interval [CI]: 1.19–2.98; p=0.0070) was also statistically significant. It was suggested that the greater efficacy seen with guselkumab largely accounted for its superior drug survival compared with adalimumab.

Secondary analyses revealed that lack of efficacy or worsening of psoriasis was the most frequent reason for cessation of adalimumab, with 17 (5.1%) patients discontinuing as a result, compared to 3 (0.9%) patients in the guselkumab group (hazard ratio: 5.714 [95% CI: 1.675–19.500; Cox model p=0.0054]). For patients discontinuing treatment for reasons other than lack of efficacy or worsening psoriasis, drug survival was similar in the two groups; guselkumab had a survival rate of 97.0% compared to 98.2% with adalimumab (p=0.2790).

Overall, drug survival was superior for the guselkumab group compared with the adalimumab group at Week 48 in the VOYAGE 1 study. Drug survival can be assessed using data from clinical trials with an active comparator arm, as is the case in this analysis, but it should be noted that analysis of real-world data from drug registries in the post-approval setting is required to confirm these conclusions.

Association Between Improvements in Patient-Reported Outcomes and Absolute Psoriasis Area Severity Index Score: Results from VOYAGE 2 (Poster P1944)

Professor Stephen Tyring

VOYAGE 2, a double-blind, placebo and active comparator-controlled study, investigated

the association between changes in patient-reported outcomes (PRO) and Psoriasis Area Severity Index (PASI) scores in patients with moderate-to-severe plaque psoriasis.[3] A number of PRO measures were used to assess health-related quality of life (HRQoL).

Patients (N=992) were randomised 2:1:1 to one of three treatment groups, receiving either 100 mg guselkumab via subcutaneous injection at Weeks 0, 4, 12, and 20 (n=496); placebo at Weeks 0, 4, and 12, followed by 100 mg guselkumab via subcutaneous injection at Weeks 16 and 20 (n=248); or adalimumab via subcutaneous injection, 80 mg at Week 0, 40 mg at Week 1, and then 40 mg every 2 weeks through to Week 23 (n=248). PRO measures were assessed using three questionnaires and results were stratified by five thresholds, defined according to absolute PASI score: 0, >0–<1, ≥1–≤3, >3–≤5, and >5.

The Dermatology Life Quality Index (DLQI) assesses HRQoL with 10 dermatologic disease-specific questions, producing a combined total score from 0–30. A score <1 indicates no impact of disease on a patient's daily QoL. In VOYAGE 2, there was a statistically significant association between lower PASI scores and proportions of patients with a DLQI score of 0 or 1 at Weeks 16 and 24 ($p<0.0001$ for both timepoints).

The Hospital Anxiety and Depression Scale (HADS) has two subscales, one for anxiety and one for depression, each producing a score ranging from 0–32. A score <8 on each respective subscale indicates no anxiety or depression. Both anxiety and depression scores correlated with PASI score in VOYAGE 2. For example, associations between HADS anxiety score at both Week 16 ($r=0.20$) and Week 24 ($r=0.16$) were statistically significant ($p<0.0001$ for both). Similarly, a statistically significant correlation between HADS depression score and PASI score was found at both Week 16 ($r=0.27$) and Week 24 ($r=0.22$) ($p=<0.0001$ for both).

Finally, the Medical Outcomes Study 36-Item Short Form (SF-36) derives mental and physical component summary scores, ranging from 0–100, from eight multi-item scales. A score ≥50 is indicative of normal HRQoL. Mental component scores ≥50 were significantly correlated with lower PASI scores at both Week 16 ($r=0.29$) and Week 24 ($r=0.25$) ($p<0.0001$ for both). Scores ≥50 in the physical component also showed a relationship with PASI assessment at Week 16 ($r=0.40$) and Week 24 ($r=0.30$) ($p<0.0001$ for both).

Improvement in absolute PASI score was strongly associated with improvement in HRQoL in all PRO measures that were investigated, showing statistically significant correlations in every measure used.

Association of Absenteeism and Presenteeism with Anxiety and Depression in Patients with Moderate-to-Severe Psoriasis and Improvement After Treatment: Results from the VOYAGE 2 Trial (Poster P1921)

Doctor Kristian Reich

Analysis of the effect of psoriasis on productivity, absenteeism, and presenteeism was also carried out using data from the VOYAGE 2 study.[4] Alongside physical manifestations of the condition, psoriasis is associated with psychological comorbidities and either or both can affect productivity, absenteeism, and presenteeism. The methodology of VOYAGE 2 up to Week 24 is described in the previous section. At Week 28, patients receiving guselkumab 100 mg subcutaneous injection at Weeks 0, 4, 12, and 20 who achieved ≥90% improvement in PASI were re-randomised to guselkumab 100 mg every 8 weeks or placebo. Responding patients who received placebo at Weeks 0, 4, and 12 and guselkumab 100 mg subcutaneous injection at Weeks 16 and 20 received placebo at Week 28; non-responders in this group continued guselkumab treatment. Patients who had been receiving treatment with adalimumab subcutaneous injections were given placebo at Week 28 if they had responded to treatment or crossed to guselkumab therapy. One hundred and ninety-three patients were randomised to guselkumab at Week 28. In all groups, patients received guselkumab upon loss of response on placebo.

Absenteeism and presenteeism data through to Week 48 of the study were presented. Absenteeism was reported using the DLQI question: 'Over the last week, has your skin prevented you from working or studying? [Yes=3]. If No, how much has your skin been a problem at work or at school? [A lot=2, A little=1, Not at all=0].' A score for presenteeism was derived from responses to the following domain from the Work Limitations Questionnaire: time management, physical demands, mental–interpersonal demands, and output demands. HADS responses were used to evaluate the impact of depression and anxiety on productivity.

At baseline in all treatment arms, 22.9% of study participants reported that their skin had prevented them from working or studying, according to their response to the DLQI question; patients who had anxiety or depression at baseline were more likely to report this outcome (43.2%) than those who did not (17.1%). Patients in active employment had HADS scores that correlated with productivity evaluation based on their responses to the Work Limitations Questionnaire domains (HADS anxiety: r=0.59; HADS depression: r=0.64; p<0.001 for both).

Guselkumab was shown to be an effective treatment in terms of work-related disease impact. At Week 24, 82% of patients treated with guselkumab who had scored 3 on the DLQI domain question at baseline now reported a score of 0, compared to 50% of patients treated with adalimumab (p<0.001). With further follow-up to Week 48, 83% of guselkumab patients had reduced their DLQI score from 3 at baseline to 0. Patients who were randomised to guselkumab treatment at Week 28 showed an improvement in absenteeism and presenteeism up to Week 48.

The improvement in presenteeism at Week 24 was significantly greater in the guselkumab group compared to the adalimumab group, in three out of the four domains. The mean percentage improvements for guselkumab and adalimumab, respectively, were 38% versus 21% in physical demands, 42% versus 22% in mental–interpersonal demands, and 40% versus 16% in output demands. A sustained improvement in presenteeism was seen at longer-term follow-up at Week 48. Mean improvements from baseline were 46% in physical demands, 37% in time management, 49% in mental–interpersonal demands, and 49% in output demands.

Guselkumab demonstrated an advantage over adalimumab in patients both with and without anxiety and depression when measured by the DLQI domain absenteeism question. In patients treated with guselkumab, 73.5% of study participants with anxiety or depression who scored 3 on the DLQI assessment at baseline reported a score of 0 at Week 24, compared to 38.7% of patients treated with adalimumab (p=0.002). For patients without depression or anxiety, 88.9% of patients scoring 3 in the DLQI assessment at baseline had improved to a score of 0 at Week 24 when treated with guselkumab, compared to 64.0% of patients treated with adalimumab (p=0.006). The odds ratio for patients treated with guselkumab achieving a score of 0 on the DLQI assessment at Week 24 was 2.85 (95% CI: 1.83–4.46) compared to patients receiving adalimumab (p<0.0001).

In conclusion, anxiety and depression have significant impacts on productivity at work, affecting absenteeism rates, productivity, and presenteeism in patients with moderate-to-severe psoriasis. Treatment with guselkumab demonstrated significantly better outcomes for patients in absenteeism and presenteeism domains compared to treatment with adalimumab.

Evaluation of the Usability and Acceptability of a Novel, Patient-Controlled Injection Device for the Treatment of Moderate-to-Severe Psoriasis: Results from the Phase III ORION Study (Poster P1898)

Doctor Laura Ferris

The Phase III ORION study is a multicentre, randomised, double-blind, placebo-controlled study of guselkumab in patients with moderate-to-severe psoriasis. At baseline, 78 patients were randomised to placebo (n=16) or guselkumab (n=62).[5] All study agents were administered

using a manually-operated, patient-controlled, disposable device that delivered the contents of a pre-filled syringe via subcutaneous injection. The device included an automatically locking safety guard to shield the needle and prevent accidental needle stick injury. This poster presented results of patient-reported satisfaction with the self-injection device, including its ease of use and their experience of psoriasis after initiating treatment delivered in this way, along with assessment of correct use of the device by an objective observer.

Objective usability of the device was assessed at Week 0 through a three-step Observer Injection Checklist that reported on the patients' removal of the device cap, positioning of the device, and completion of the injection. Patient-rated acceptability was assessed post-injection at Weeks 0, 4, and 12 using a Self-Injection Assessment Questionnaire (SIAQ) consisting of six domains (feeling about self-injections, self-image, self-confidence, pain and skin reactions during or after injections, ease of use of the injection device, and satisfaction with self-injection) (Table 1). The domains 'feeling about self-injection,' 'self-confidence,' and 'satisfaction with self-injection' were also scored pre-injection at Week 0. The SIAQ used a semantic Likert-type scoring method and responses were transformed into scores of 0–10 (worst to best). A three-question patient rating system was also used to assess speed of injection, handle design of the device, and ease of identifying completion of the injection.

Patients in both groups were primarily successful in the Observer Injection Checklist assessment for device-related problems associated with the injection at Week 0, with 98.7% (77 out of 78) of patients observed to have successful, problem-free injections. One patient in the guselkumab group used the device improperly. This indicates favourable usability, as assessed objectively.

Scores for the three SIAQ domains assessed prior to the first injection, 'feeling about self-injection,' 'self-confidence,' and 'satisfaction with self-injection,' ranged from 6.59–8.23 and showed a tendency to remain high or increase at assessment post-injection at Week 0 and at Week 12. In the self-confidence domain, mean SIAQ score in the placebo group was 6.35 at Week 0 pre-injection, increasing to 8.21 at Week 12. Patients treated with guselkumab had mean scores of 6.67 at Week 0 pre-injection and 8.48 at Week 12. This indicated an increase in self-confidence over time when using the patient-controlled injection device.

Similarly, SIAQ scores for 'satisfaction with self-injection' increased from pre-injection at Week 0 to Week 12. In the placebo group, the mean score at pre-injection was 6.33, increasing to 9.26 at Week 12, compared to 6.65 and 9.64, respectively, for patients treated with guselkumab.

Table 1: Summary of score changes in six patient-reported Self-Injection Assessment Questionnaire domains measured in the ORION Study.

SIAQ domain	Stable or increase in mean score	
Week 0 (Pre) to Week 12 (Post)	**Guselkumab**	**Placebo**
Feeling about self-injections	✓	×
Self-confidence	✓	✓
Satisfaction with self-injection	✓	✓
Week 0 (Post) to Week 12 (Post)		
Self-image	✓	✓
Pain and skin reactions during or after the injection	✓	✓
Ease of use of the self-injection device	✓	✓

SIAQ: Self-Injection Assessment Questionnaire.

Adapted from Ferris et al.[5]

Mean SIAQ scores for 'feeling about self-injection' decreased from 8.18 at pre-injection (Week 0) to 7.50 at Week 12 in the placebo group and increased slightly from 8.23 to 8.45 in the guselkumab group. Additionally, SIAQ scores only measured post-injection (at Weeks 0, 4, and 23) were favourable across all treatment domains and at all timepoints, suggesting that the patient-controlled delivery device was well-accepted by study participants. Median self-image scores remained at 10 from Week 0 to Week 12 in both placebo and guselkumab groups.

SIAQ reports of pain and skin reactions during or after the injection were relatively uncommon. A median score of 10, indicating no pain or skin reaction at all, was reported at all timepoints throughout the study. Mean scores also remained stable; in the placebo group, the mean score was 9.86 at Week 0, 9.77 at Week 4, and 9.89 at Week 12. In the guselkumab group, these were 9.82, 9.75, and 9.83, respectively, indicating that the injection device was well tolerated by users operating it correctly. SIAQ scores for the ease of use of the self-injection device remained consistent at the three timepoints measured in both groups. For the total study population (N=78), the mean ease of use was 8.81 at Week 0, 9.19 at Week 4, and 9.24 at Week 12.

Following the first injection at Week 0, study participants from across the treatment groups said that the injection device was easy or very easy to use; 94.9% of patients were either satisfied or very satisfied with the current method of medication administration. Results from the three-question patient questionnaire indicated that the injection device was well tolerated and well received by patients. Across both treatment groups (n=75), 97.3% of study participants either agreed or strongly agreed with the statements 'I liked being able to inject the medication at a speed that was comfortable for me' and 'The design of the handle made the device easy to use'; furthermore, 94.7% of patients agreed or strongly agreed that they were able to easily tell when the injection was finished.

Although this study did not compare the use of the self-injection device to other drug delivery systems, the results confirmed that the patient-controlled device was well tolerated and accepted by study participants, who had a favourable experience when using it, and showed an association between using the device and successful, problem-free injections.

Conclusion

Guselkumab has been assessed in the post-approval setting for the treatment of plaque psoriasis and a number of reporting measures, including safety and efficacy, usability, and PRO, have been used to determine its suitability. Guselkumab has been evaluated against adalimumab as a treatment for plaque psoriasis in active comparator studies, with generally favourable outcomes.

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INTERLEUKIN-23 IN PSORIASIS: INTEGRATING NEW THERAPIES IN THE CURRENT TREATMENT LANDSCAPE

This symposium took place on 14th September 2017 as a part of the 26th European Academy of Dermatology and Venereology (EADV) congress in Geneva, Switzerland

Chairperson

Kristian Reich[1]

Speakers

Kristian Reich,[1] Andrew Blauvelt,[2] Giampiero Girolomoni[3]

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Disclaimer: This report contains information on drug treatments that are not currently approved for use in Europe. Interleukin-23 (p19) inhibitors risankizumab and tildrakizumab are not approved for the treatment of psoriasis or psoriatic arthritis in Europe.

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MEETING SUMMARY

Prof Reich welcomed delegates to the satellite symposium and explained that the aims of the meeting were to introduce the clinical role of targeted interleukin (IL)-23 therapies in psoriasis, show why IL-23 therapy is effective against psoriasis, show how it works in patients by illustrating emerging clinical trial data, and, finally, describe how the IL-23 inhibitors can be used to address unmet clinical needs in patients with psoriasis. Dr Blauvelt started the meeting by providing an update on the current understanding of the immunology of cytokine pathways in psoriasis. Prof Reich then gave an overview of the clinical value of IL-23 inhibitors as novel targeted treatments for psoriasis, summarising data from pivotal clinical trials that have been carried out to support the introduction of these treatments into the clinical armamentarium. Finally, Prof Girolomoni reviewed the indications for biologic therapies and discussed how IL-23 inhibitors can be integrated into the current therapeutic environment. The satellite symposium concluded with a lively question and answer session.

An Immunologic Understanding of Cytokine Pathways in Psoriasis

Doctor Andrew Blauvelt

Psoriasis has a highly complex pathophysiology driven by increased T helper (Th) cell activity resulting in inflammation, overproduction and activation of keratinocytes, and the formation of psoriasis plaques. IL-23 is a key upstream regulatory cytokine in psoriasis pathogenesis. Produced by antigen-presenting dendritic cells, the normal function of IL-23 is to stimulate differentiation, activation, proliferation, and survival of Th17 cells. Specialised Th17 cells are normally involved in the adaptive response utilised in mucocutaneous defence against infection by extracellular organisms such as *Candida albicans* or *Staphylococcus aureus*, which may also play a role in pathogenesis of psoriasis (Figure 1).[1-4] IL-23 is composed of two molecular subunits, p19 and p40; blockade of IL-23 can be achieved by targeting either subunit, but only p19 subunit inhibition specifically blocks the IL-23 cytokine. Ustekinumab, a biologic therapy for psoriasis and psoriatic arthritis, is an inhibitor of p40, and results in the blockade of IL-12 as well as IL-23. The focus of current clinical research has been the specific inhibition of IL-23 via more targeted inhibition of the p19 subunit alone. In patients with psoriasis, overproduction of IL-23 occurs in the upper dermis, leading to excessive Th17 cell accumulation and overproduction of IL-17A and IL-22. This leads to keratinocyte proliferation and activation, pro-inflammatory cytokine production (e.g., tumour necrosis factor [TNF]-α), and neutrophil accumulation.

Psoriasis is associated with genetic polymorphisms in the *p19* and *p40* subunit genes of IL-23, as well as in *IL-23R*, a gene that encodes for a subunit of the IL-23 receptor present on the cell surface of Th17 cells.[5] A defect in *IL-23R* has been shown to be protective against the development of psoriasis by impairing IL-23-induced Th17 effector responses in humans.[6] Importantly, IL-17A, produced by Th17 cells and other cell types, is a downstream effector cytokine in psoriasis pathogenesis. There is evidence from animal studies, as well as human tissue studies, that blockade of IL-17 prevents the development of IL-23-mediated epidermal thickening and psoriasis-like disease.[7] In contrast, the inhibition of IL-23 provides upstream inhibition of pathologic processes.

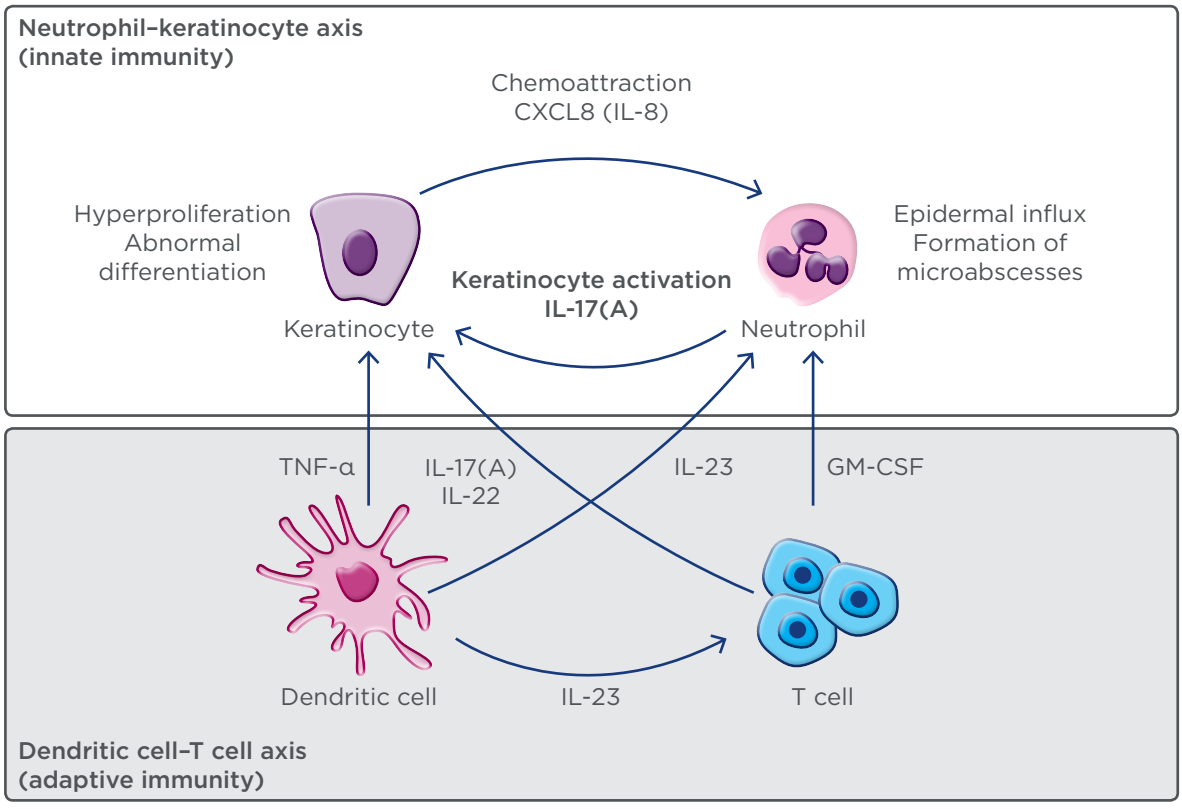

Figure 1: Model of psoriasis pathogenesis.[2]

GM-CSF: granulocyte-macrophage colony-stimulating factor; IL: interleukin; TNF: tumour necrosis factor.

Blocking different targets in the immunopathogenic pathways involved in psoriasis has varying effects. Inhibition of the pathologic process with a broad immunosuppressant drug, such as methotrexate, is associated with more safety concerns and is less effective than more targeted inhibition of key cytokines such as IL-23 and IL-17A. Similarly, the mechanism of action of targeted inhibition of cytokine pathways has implications for safety and dosing. For example, loss of IL-17A activity is associated with the development of chronic mucocutaneous candidiasis in both mice and humans. Although there are currently no supporting scientific studies, it has been hypothesised that IL-23 blockade does not block all downstream IL-17 production (i.e., some residual IL-17A production remains from non-Th17 cells in the skin and gut); therefore, this may explain why IL-23 blockade may not lead to candidiasis or inflammatory bowel disease. To date, clinical evidence from studies of IL-23 inhibitors has shown no increase in the incidence of serious infections, reactivation of tuberculosis infection, hepatitis B, candidiasis, or inflammatory bowel disease. Blocking upstream targets, such as IL-23, is also associated with a need for less frequent dosing, since clinical efficacy of IL-23 inhibitors in psoriasis persists longer than serum drug levels. It is possible that IL-23 inhibition may cause the death of Th17 cells, which are dependent on IL-23 for cell survival, and thus could lead to prolonged disease control. Such considerations are based upon the basic understanding of the IL-23/Th17 immunologic pathway but require detailed tissue studies in humans to confirm.

The Clinical Value of Interleukin-23 Inhibitors

Professor Kristian Reich

Several IL-23 inhibitors are in clinical development, including guselkumab. It is the first IL-23 inhibitor to be approved for the treatment of patients with moderate-to-severe plaque psoriasis in the USA and is in Phase II evaluation for use in psoriatic arthritis. Other IL-23 inhibitors in clinical development include tildrakizumab and risankizumab, which are in Phase III, and mirikizumab, in Phase II.

Clinical Evidence: Guselkumab

The efficacy and safety of guselkumab has been evaluated in two recently published pivotal randomised, double-blind, placebo and active-controlled Phase III trials: VOYAGE 1[8] and VOYAGE 2.[9] In VOYAGE 1, guselkumab was compared with adalimumab and placebo over a 1-year active comparator period, followed by a 4-year follow-up.[8] The study included 837 patients, of whom 174 were initially randomised to placebo, 329 to guselkumab, and 334 to adalimumab. Co-primary endpoints included the proportions of patients achieving an Investigator Global Assessment (IGA) score of cleared or minimal disease (IGA 0 or 1), and ≥90% improvement in Psoriasis Area Severity Index (PASI 90) at Week 16 in the guselkumab group compared with placebo. The baseline patient characteristics were those of a typical psoriasis population: mean BMI of 30, mean overall PASI of 22, mean dermatology quality of life (QoL) index of 14, and a long duration of disease (mean: 18 years). Compared with placebo, a significantly higher percentage of patients on guselkumab achieved an IGA 0 or 1 (85.1% versus 6.9%, respectively; $p<0.001$) and PASI 90 (73.3% versus 2.9%, respectively; $p<0.001$). The response to guselkumab was rapid and the proportion of patients achieving PASI 100 at Week 16 was significantly higher for guselkumab than placebo ($p<0.001$). Responses to guselkumab were also significantly better than to adalimumab in the proportion of patients achieving IGA 0 or 1, PASI 90, and PASI 100. High level clinical responses were sustained to Week 48 (Figure 2).[8] Guselkumab was effective in improving the scalp and nail manifestations of psoriasis, although the improvements compared with adalimumab were attenuated.[8] Unpublished long-term data show that responses to guselkumab were sustained for up to 2 years, demonstrating excellent longevity of the therapeutic response.

A high level of treatment response has been shown to correlate with improved patient QoL. The Phase III clinical data from VOYAGE 1 show that the higher level of clinical efficacy in terms of PASI 90/100 response reported for guselkumab compared with adalimumab translates into significant and sustained improvements in QoL, as evidenced by higher Dermatology Life Quality Index (DLQI) scores.[8]

VOYAGE 2 had a similar design to VOYAGE 1, but included a period of randomised withdrawal (Weeks 24–28) followed by re-treatment or treatment switch (PASI 90 non-responders) through to Week 48.[9] Co-primary endpoints were the same as in VOYAGE 1.

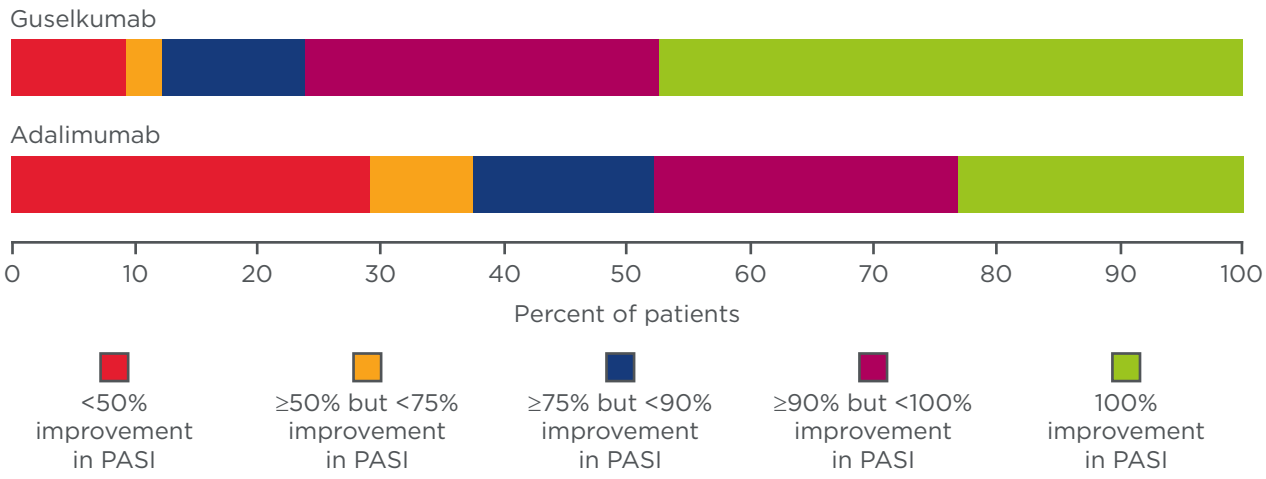

Figure 2: Distribution of psoriasis treatment responses (improvement in Psoriasis Area Severity Index) at Week 48 in the VOYAGE 1 trial.[8]
PASI: Psoriasis Area Severity Index.

A total of 992 patients were randomised in a 2:1:1 ratio to guselkumab (496 patients), placebo (248 patients), and adalimumab (248 patients). Efficacy results were very similar to those of VOYAGE 1; clinical responses were observed early in the treatment period and, at Week 16, significantly higher proportions of patients achieved IGA 0 or 1, PASI 90, and PASI 100 compared with either placebo or adalimumab ($p<0.001$ for all comparisons with guselkumab).[9] VOYAGE 2 also evaluated the effect of withdrawal of active treatment and demonstrated that the therapeutic efficacy of guselkumab was sustained after treatment was stopped. The mean time to loss of PASI 90 response was 15.0 weeks in the guselkumab-treated patients compared with 8.6 weeks in adalimumab-treated patients. In addition, 66% of patients who did not achieve a PASI 90 response to adalimumab achieved PASI 90 after switching to guselkumab at Week 28.[9]

The Phase III VOYAGE 1 and 2 safety data showed that guselkumab has a comparable safety profile to adalimumab with no new safety signals reported, resulting in a favourable risk:benefit profile. The incidence of overall infection, serious infections, and infections requiring antibiotic treatment were similar in guselkumab and adalimumab-treated patients.[8,9]

Clinical Experience with Other Interleukin-23 Inhibitors

Risankizumab is an IL-23 inhibitor that is in Phase II/III of clinical development. Data from a comparative clinical trial of risankizumab versus ustekinumab showed that in patients treated with risankizumab (dosed at Weeks 0, 4, and 16), 50% of patients maintained a PASI 90 response at Week 48; i.e., 32 weeks after the last risankizumab dose.[10] These data provide further evidence of the sustainable effect of IL-23 inhibition in psoriasis, as seen in VOYAGE 2 with guselkumab. The immunological impact of targeted upstream IL-23 inhibition in the immunopathology of psoriasis requires further study to better understand this effect on the underlying disease process.

Another IL-23 in Phase III development is tildrakizumab. Data from the placebo-controlled reSURFACE 1 Part 1 trial[11] show that although a significantly higher percentage of patients treated with tildrakizumab achieve PASI 75, PASI 90, and PASI 100 compared with placebo, the proportions of patients with PASI 90 and PASI 100 responses were lower than those reported for guselkumab or risankizumab.[8-11] However, the proportion of patients achieving PASI 90 and PASI 100 improved at 28 weeks,[11] suggesting that the time to treatment response may be longer with tildrakizumab; head-to-head comparisons are needed to better understand the efficacy of tildrakizumab.

IL-23 inhibitors also represent a promising new treatment option for patients with psoriatic arthritis. Guselkumab is the first anti-IL-23 biologic to demonstrate efficacy in psoriatic arthritis. Clinically significant effects on American College of Rheumatology (ACR) 20, ACR50, and ACR70 scores, enthesitis, and dactylitis at 24 weeks have

been reported in a Phase II trial.[12] In summary, in patients with moderate or severe psoriasis, IL-23 inhibitors are associated with high levels of clinical response, stable long-term responses that extend beyond serum drug levels, convenient injection intervals, and no safety concerns to date compared with other biologic treatments.

The Current Landscape of Psoriasis Treatments: When and Where to Embed Emerging Therapeutic Options

Professor Giampiero Girolomoni

Despite the introduction of new biologic treatments, there are a number of unmet needs in the clinical management of moderate-to-severe psoriasis, including late or inadequate use of systemic treatment, poor tolerability or effectiveness of conventional therapy in many patients, and effective treatment of psoriasis in difficult areas (scalp, genitalia, and palmoplantar areas).[13,14] In addition, many current therapies (including biologics) lose optimal efficacy over time in a substantial proportion of patients. Severe psoriasis has a very significant impact on QoL, affecting the emotional,[15] socio-familial,[16] financial,[17] work,[18] and leisure[19] aspects of patients' daily lives. The systemic inflammation associated with severe psoriasis also puts patients at increased risk of metabolic disorders, such as Type 2 diabetes mellitus, non-alcoholic fatty liver disease, hypertension, and, ultimately, atherosclerosis and cardiovascular disease.[20]

Appropriate use of systemic therapy is very important, and treatment success requires the complete, or almost complete, clearance of psoriasis. Systemic therapy is indicated for patients with a PASI ≥10 or those with a PASI <10 who have involvement of the hands, scalp, face, nails, or palmoplantar or genital areas.[21] Other indications include a body surface area (BSA) involvement of ≥5%, either where there is resistance to topical therapy or where patients are reluctant to use it; a BSA <5% with disseminated lesions; a patient's subjective perception of disease severity (e.g., DLQI ≥10); active psoriatic arthritis; and psoriasis associated with severe symptoms (e.g., itch or burning) that are not controlled by topical therapies. Treatment goals should be agreed with patients after an informed discussion and re-evaluated after 3–4 months during treatment initiation and every 3–6 months during maintenance. The treatment efficacy goal that best correlates with disease remission and good patient satisfaction is an improvement in BSA of ≥90% (PASI 90); the targets for the maintenance phase are a minimum PASI of <1 or a BSA <1%, and a DLQI of <5.[21,22] If treatment goals are not met, therapy may be changed or another drug may be added to the treatment regimen.

Box 1: Key factors to be considered when choosing a biologic treatment.[21]

Patient characteristics

- Patient age, sex, body weight.
- Patient expectations.
- Comorbidities that may contraindicate or raise a caution on the use of selected biologics (e.g., latent tuberculosis, severe heart failure, personal history or strong family history of demyelinating disease or alopecia areata for TNF-α blockers, Crohn's disease for IL-17A inhibitors).
- Presence of concomitant diseases that may benefit from the same treatment (e.g., psoriatic arthritis, Crohn's disease, ulcerative colitis, pyoderma gangrenosum, uveitis, sarcoidosis, Behçet's disease, hidradenitis suppurativa for anti-TNF-α monoclonal antibodies; Crohn's disease for ustekinumab).

Disease characteristics

- Disease severity, activity, and stability.
- Skin areas involved.
- Severity of symptoms (e.g., pruritus).
- Disease and treatment history, rapid relapse after treatment withdrawal, intermittent or continuous disease activity.

Treatment-related considerations

- Drug availability.
- Overall efficacy (short and long-term) and the need for a rapid response.
- Tolerability and safety (including patient concerns over side effects).
- Need for flexible treatment (e.g., need for easy interruption or restart).
- Administration modality (oral, subcutaneous, intravenous; frequency of injections).

IL: interleukin; TNF: tumour necrosis factor.

A survey of the use of biologic therapy recently reported that many physicians also adjust either the dose or dose interval as a strategy to improve treatment response or maintain remission, even though this is an off-label approach and cannot be recommended.[23] Important factors to be considered when selecting a systemic psoriasis treatment include age, body weight, treatment availability, disease severity, comorbidities, and concomitant diseases (Box 1).[21,22]

There is limited evidence to indicate which factors, if any, influence treatment outcomes. Age and body weight can have an impact on treatment efficacy, as well as disease severity and disease manifestations such as psoriatic arthritis. A multicentre study reported that patients who were genotyped positive for *HLA-C*6* (generally younger patients) had a faster and greater response to treatment with the IL-23/IL-12 inhibitor ustekinumab.[24] A French study[25] recently reported that patients were more likely to be prescribed adalimumab than either etanercept or ustekinumab if they had severe psoriasis or if they had psoriatic arthritis. Younger patients (<30 years of age) and those who had positive screening for latent tuberculosis were more likely to receive ustekinumab than adalimumab. Patients with chronic obstructive pulmonary disease were also more likely to receive ustekinumab or etanercept than adalimumab, and there was a trend toward increased etanercept use in patients with cardiovascular comorbidities, metabolic syndrome, or a history of cancer. Systemic psoriasis treatments have distinct efficacy and safety profiles. Conventional systemic treatments such as methotrexate, cyclosporine, and dimethyl fumarate are associated with significant metabolic toxicity resulting in side effects (e.g., nausea, fatigue, headache, diarrhoea) and poor tolerability. TNF-α inhibitors have demonstrated greater tolerability compared with conventional therapy and are associated with longer drug survival times.[26] Ustekinumab has also been reported to have higher drug persistence rates and longer drug survival than the TNF-α inhibitors etanercept, infliximab, and adalimumab.[27]

To conclude, the choice of treatment for a patient with moderate-to-severe psoriasis should involve a holistic decision-making approach, encompassing disease, patient, and treatment characteristics.

Question and Answer Session

Q: Why has candidiasis been noted in patients treated with IL-17 inhibitors but not in the clinical trials with IL-23 inhibitors?

A: Dr Blauvelt replied that an IL-17 inhibitor blocks all production of IL-17 from all cell types (Th17, neutrophils, innate lymphoid cells), and therefore, as IL-17 has a defensive role in the skin and gut, elimination of IL-17 would be expected to result in skin infections or gut inflammation. With IL-23 inhibition, a large proportion of IL-17 production will be removed, but a small amount (˜10%) of IL-17 production is not under IL-23 control, and it is hypothesised that this residual IL-17 is sufficient to protect the skin from *Candida* infection and the gut mucosa from inflammation.

Q: If you have a patient who is treated with adalimumab and does not achieve a PASI 90 response, what is the best treatment strategy?

A: Dr Blauvelt replied that if a patient is clearly not responding to treatment, the drug needs to be switched. In a patient with inadequate response, however, the situation is more difficult, and you can consider either switching or adding another drug to the regimen, such as methotrexate. Prof Reich added that dose adjustment is also an option; with adalimumab the normal dose is administered every 2 weeks but can be changed to weekly dosing on label, although this will double the cost of treatment.

Q: Can achieving and maintaining remission in psoriasis impact patients' risk of cardiovascular disease?

A: Dr Blauvelt replied that there is an almost linear correlation between the level of systemic inflammation and the severity of psoriasis, and a patient with severe psoriasis is likely to have an increased risk of atherosclerosis and cardiovascular disease. Therefore, clearing psoriasis should improve cardiovascular risk by reducing inflammation. Some evidence is emerging to support this in the case of TNF-α inhibitors, but studies need to be carried out for IL-17 and IL-23 inhibitors.

Prof Reich added that, because atherosclerosis is an inflammatory process, treatment with an anti-inflammatory agent could reduce cardiovascular risk. If a psoriasis treatment could block pro-inflammatory cytokines in the heart vessels in

addition to reducing the skin inflammation, it would have an impact on cardiovascular risk. The picture is not yet clear, but data are emerging showing that IL-17 inhibition may have positive effects on markers of cardiovascular risk.

Q: Why are we seeing differences in clinical responses with guselkumab, tildrakizumab, and risankizumab when they all target the same key cytokine, IL-23?

A: Prof Reich replied that there are also reported differences in the response to different TNF-α inhibitors. Blocking the same target does not mean the clinical response will be exactly the same; there will be differences in affinity, immunogenicity, and other aspects. Dr Blauvelt added that the mechanism of action is not the only consideration for treatment response; the drug must be dosed at the correct level and at the right frequency, because these factors also influence efficacy.

Q: Do you think that treatment with guselkumab is disease-modifying?

A: Prof Reich replied that, at present, only very preliminary observations can be made in this regard. IL-23 inhibitors, as a class, have a clear sustained efficacy that persists months beyond their pharmacokinetics and provides a lasting clinical response for a substantial subgroup of patients. More data from biopsy studies are required before this can be described as disease modification, but it seems likely that research is taking us closer to disease modification in the future. Prof Girolomoni and Dr Blauvelt agreed with Prof Reich's views.

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FROM REGISTRY DATA TO REAL-LIFE EXPERIENCES: A HOLISTIC PERSPECTIVE OF PSORIASIS TREATMENT

This symposium took place on 15th September 2017 as a part of the 26th European Academy of Dermatology and Venereology (EADV) congress in Geneva, Switzerland

Chairperson

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MEETING SUMMARY

Registries provide very high-quality data on the persistence of different therapies in the real world and can be used to compare and guide therapeutic guidelines. Dr Warren gave an overview of the different types of registries that capture data on patients with psoriasis. Furthermore, he discussed findings from the British Association of Dermatologists Biological Interventions Register (BADBIR), the Psoriasis Longitudinal Assessment and Registry (PSOLAR), and the Danish Biologic Interventions Registry (DERMBIO) data that help to gain insight on how best to prescribe drugs in a clinical setting. Prof Puig and Prof Gniadecki presented cases encountered in clinical practice to illustrate how real-world data can support the clinical decision-making process. Throughout their presentations, Prof Puig and Prof Gniadecki engaged the audience in interactive discussion on how to improve patient monitoring and management of comorbidities, and addressed issues such as drug survival, safety, and economics.

Interpreting Long-Term Registry Data in the Treatment of Psoriasis

Doctor Richard Warren

The presentation compared registries used to capture data in patients with psoriasis, evaluated the differences between studies that use registry data, and provided insights into how registry data should be interpreted.

Real-world evidence (RWE) is used to evaluate the impact of treatments in a routine clinical setting. RWE can be obtained from various sources, including patient registries, existing electronic health records, routinely collected administrative

data, primary patient data collection, and/or population surveys. Registries can provide information about a disease and/or therapeutic strategies. Compared with randomised controlled trials (RCT), RWE offer many advantages. Of note, RCT are commonly driven by an efficacy endpoint and are seldom powered to look at safety either in detail or the long term. Furthermore, the professional support networks that exist within RCT are often not available in a real-world setting, which can impact outcomes including treatment adherence, persistence (the duration of time from initiation to discontinuation of therapy),[1] and efficacy.

There are currently three key styles of registries for psoriasis and psoriatic arthritis (PsA): pharmacovigilance registries, epidemiology or observational studies, and network registries. Examples of pharmacovigilance registries include BADBIR, the German Psoriasis Registry (PsoBest), DERMBIO, and PSOLAR. BADBIR is a prospective observational comparator registry for patients with moderate-to-severe psoriasis receiving biologics (n=8,424) or conventional systemic therapies (n=4,488) and collects data from 151 dermatology departments across the UK and Ireland. An early publication based on these data compared the baseline characteristics of the patients between two cohorts (biologics [n=5,065] and systemic therapies [n=3,334]).[2] The findings showed that patients who had psoriasis for a reasonable amount of time (mean disease duration: 23.0±12.6 years versus 19.0±13.4 years) and those receiving biologics compared with non-biologics were generally heavier (mean body weight: 90.3±21.5 kg versus 87.2±21.4 kg).[2] All patients demonstrated high Psoriasis Area Severity Index (PASI) scores (16.4±8.3 versus 15.5±7.9, respectively), which were reasonably well matched between the cohorts.[2] A 5-year follow-up allowed the assessment of treatment, disease activity, and adverse events (data not shown).[3]

PsoBest is a registry for patients with moderate-to-severe psoriasis, with and without arthritis, with a 5-year observation time and follow-up of every 3 months; patients from this registry were treatment-naïve receiving biologics or non-biologic systemic therapies. Patients receiving biologics in this registry had a significantly greater mean duration of disease compared with systemic therapy (21.9±14.1 years versus 16.9±0.0 years). All other baseline characteristics were well matched.[4,5] PsoBest provided additional value in that it collected data on the first-line systemic therapy Fumaderm®, and therefore may provide RWE on the use of fumerates in these patients.

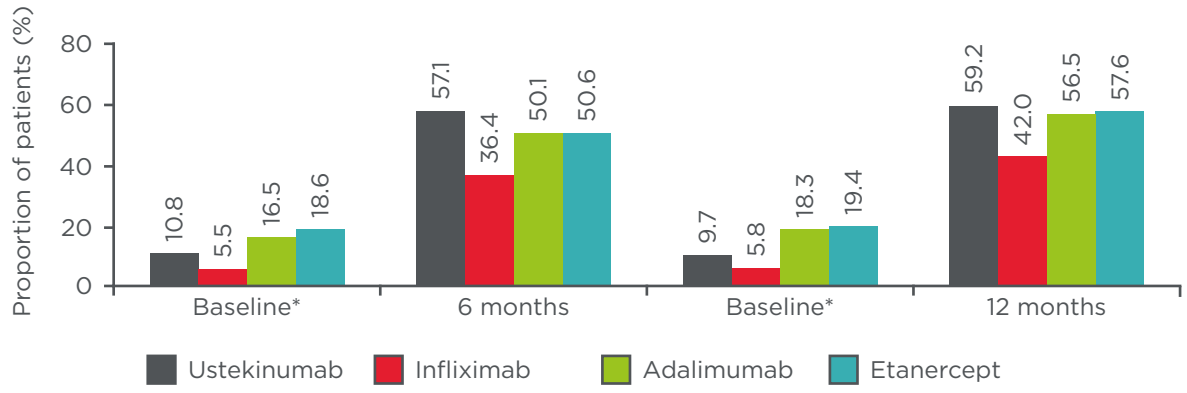

Figure 1: PSOLAR data. Proportion of patients with Physician's Global Assessment score of 0 (clear) or 1 (minimal) at 6 and 12 months.

Data were analysed from 2,076 users who initiated infliximab (n=116), adalimumab (n=662), etanercept (n=257), or ustekinumab (n=1,041) during PSOLAR participation. Only the first biologic started during registry participation was analysed. Of the participants, 80% had been exposed to a biologic prior to enrolment. Evaluations were limited to patients who had baseline data and continued their initiated therapy at their 6-month and/or 12-month visits.

*Baseline psoriasis severity was assessed at the closest visit before the first dose of the newly initiated biologic.

PGA: Physician's Global Assessment; PSOLAR: Psoriasis Longitudinal Assessment and Registry.

Adapted from Strober et al.[8]

DERMBIO is a registry for patients with psoriasis vulgaris receiving biologics (adalimumab [n=576]; etanercept [n=176]; infliximab [n=176]; ustekinumab [n=170]) with a 10-year data collection period.[6] Although this registry does not have a conventional therapy cohort, it provides other valuable RWE, for example, it shows that patients prescribed adalimumab, etanercept, or infliximab are more likely to have PsA compared with patients prescribed ustekinumab (38.1%, 39.6%, or 43.8% versus 14.1%, respectively).[6] Furthermore, patients prescribed the former three treatments are also more likely to be receiving concomitant methotrexate (21.9%, 22.5%, or 55.1% versus 12.4%, respectively).[6] Therefore, registries such as DERMBIO add value by helping to capture prescribing habits in a real-world setting.

PSOLAR is a registry for patients with moderate-to-severe psoriasis from 300 practices across North America, Latin America, and Europe. More patients in this registry receive biologics (ustekinumab, n=4,364; infliximab, n=1,394; or other biologics, n=4,251) compared with systemic therapies (n=2,804).[7] The value of this registry in providing RWE is highlighted in the vast patient numbers.

There are several key factors to consider when interpreting data obtained from registries: the size of the registry and/or whether the registry is powered to address the investigative question of interest. In addition, the external validity of the registry is important; for example, BADBIR collects data nationwide, indicating it is a reliable representation of the real-world setting in the UK and Ireland. Two other important factors of consideration are whether an *a priori* question was set and what adjustments have been performed.

Data from the PSOLAR registry in 2016 demonstrated that ustekinumab (n=1,041) was the most effective treatment compared with infliximab (n=116), adalimumab (n=662), and etanercept (n=257) over 12 months, measured by the proportion of patients with a Physician's Global Assessment (PGA) score of 0/1 (Figure 1).[8] Adjusted logistic regression analyses demonstrated that patients receiving tumour necrosis factor (TNF)-α inhibitors were significantly less likely to achieve a PGA score of 0/1 at 6 months compared with ustekinumab patients. Similar estimates were observed at 12 months, but only the infliximab versus ustekinumab data were significantly different.[8] In view of efficacy measures based on registry data, it is important to emphasise that PGA or PASI data are often missing. Accordingly, investigative efficacy questions may not always be possible or provide the full efficacy assessment. Consequently, drug persistence may be used.

Persistence is an important parameter in the measure of long-term therapeutic performance in a real-world setting[6] and arguably an appropriate surrogate for how successful a drug may be in a given population over time. Bio-CAPTURE,[9] a small registry based in the Netherlands collecting data across eight regional, non-academic centres, showed ustekinumab (n=66) to have the highest long-term drug survival compared with adalimumab (n=101; p=0.066) and etanercept (n=82; p=0.032) in 2011. A Japanese registry also demonstrated ustekinumab to have the highest long-term drug survival compared with infliximab (n=38) and adalimumab (n=59); both of which had a significance of $p<0.05$.[10] However, in view of earlier comments regarding registry size the small patient numbers in the registry would suggest these findings should be interpreted tentatively. Shortly after the Japanese and Dutch study data were released, data from the PSOLAR registry indicated ustekinumab to have the highest persistence compared with infliximab, etanercept, and adalimumab as a first, second, and third-line biologic.[11] Although taking into consideration that PSOLAR is a single company-sponsored registry, this conclusion may also be only tentatively accepted by the clinical community. BADBIR, however, corroborated these findings over a 3-year follow-up and overcomes concerns regarding patient numbers and single company-sponsored registries.[12] Altogether, the similar findings across different registries confirm the validity of the findings. Accordingly, these data support ustekinumab as the gold standard for psoriasis treatment in terms of persistence; however, recent RCT have indicated interleukin (IL)-17 inhibitors to be superior to ustekinumab.[13] If these findings translate into a real-world setting, IL-17 may be considered as a potential treatment over the coming years.

RWE from registry data have provided insights into the most common reasons for drug discontinuations. Data from BADBIR indicated ineffectiveness of therapy, particularly etanercept, and adverse events, particularly infliximab, to be the most common reasons for patients discontinuing biologics, while PSOLAR identified ineffectiveness to be the primary reason.[11] Data

from PsoBest suggest biologics to be associated with a high rate of serious infections compared with conventional systemic non-biologics.[5] In consideration of the factors discussed earlier when interpreting data from registries, PsoBest may not have been powered sufficiently to address investigative questions around serious infections. Both BADBIR and PSOLAR reported infections to be more common with infliximab use compared with other biologics. The current trend to use infliximab less often in real-world settings may be a reflection of the latter.

In conclusion, the data presented suggest that RWE based on registry data will be beneficial for long-term monitoring of adverse events and efficacy in psoriasis patients. Through future collaborations and publications of RWE, we will also continue to improve the wealth of information available in the field of dermatology.

Real-Life Experiences and Clinical Cases: An Interactive Discussion

Professor Lluís Puig and Professor Robert Gniadecki

As the need to provide a personalised treatment approach is becoming more important, the demand for real-world data to aid clinical decision-making in the treatment of psoriasis is increasing. Prof Puig and Prof Gniadecki presented patient cases to illustrate how real-world data can support clinical considerations such as patient adherence, comorbidities, drug survival, patient monitoring, safety, and economics.

Case 1: Association Between Psoriasis and Inflammatory Bowel Disease

A 25-year-old breastfeeding woman presented with mild psoriasis, which she had for the past 14 years, a PASI of 11.3 with no PsA, a history of intermittent abdominal pain, and occasional diarrhoea without blood in the stool. In light of these symptoms, clinical decision-making was centred around screening the patient for inflammatory bowel disease (IBD) or therapy with anti-IL-17 agents, which would likely exacerbate the IBD.

An analysis of data from DERMBIO, a Danish nationwide cohort study of 5.5 million patients,[14] found a psoriasis-associated increased risk of Crohn's disease and ulcerative colitis that was higher in severe psoriasis. Additionally, an increased risk of psoriasis in patients with IBD was also observed. However, of the 11,000 patients with Crohn's disease and the 30,000 patients with ulcerative colitis combined, only 82 had mild psoriasis and 54 had severe psoriasis, potentially explaining why clinicians rarely encounter this combination of conditions in practice.

Faecal calprotectin measurements are routinely used in the diagnosis and monitoring of patients with IBD; however, given the risk of obtaining false-positive results with this method,[15] the patient should ideally be referred to a gastroenterologist. The patient denied colonoscopy and referral to a gastroenterologist but noticed that her symptoms improved on a gluten-free diet. The patient was tested for coeliac disease and tested positive for anti-transglutaminase antibody. Although a meta-analysis comparing real-life data to registry data suggested an association between coeliac disease and psoriasis,[16] the link between a gluten-restricted diet and improvement in psoriasis is still lacking. Eventually, the patient was seen by a gastroenterologist who was unable to make a final diagnosis; after 3 months on a gluten-free diet, her psoriasis improved.

Case 2: Paradoxical Onset of Psoriatic Arthritis?

A 39-year-old man with psoriasis for the last 15 years, who was given methotrexate 15 mg on psoriasis flare, had to discontinue treatment after 2 months due to lack of efficacy and increased liver transaminases. The patient had a PASI of 10.6 before initiation of ustekinumab 90 mg (given at Week 0, Week 4, and then every 12 weeks). After 4 months of treatment, his PASI decreased to 1.2; however, after 11 months of treatment, the patient developed joint pain, three tender joints, one swollen joint, and occasional knee pain. No radiographic changes were detected and the patient was referred to a rheumatologist, who diagnosed possible PsA as a result of ustekinumab treatment. Clinical considerations for this patient included the potential for the joint pain being a treatment-related adverse event and impacted the decision to continue or discontinue treatment with ustekinumab.

A retrospective study assessing patients with psoriasis receiving biologic treatment found that 22 out of the 327 patients who met the inclusion criteria developed PsA during treatment: 6 (27.2%) patients who received etanercept therapy,

10 (45.4%) who received adalimumab, 4 (18.2%) who received ustekinumab, and 2 (9.2%) who received infliximab.[17] These results suggest that biologic therapy may not be sufficient to prevent the onset of articular involvement, and in most of the verified PsA cases, arthritis occurred in concomitance with severe cutaneous involvement.

Therefore, it is possible to develop PsA-like symptoms and signs on treatment with both TNF-blockers and ustekinumab, and a diagnosis of paradoxical arthritis was ruled out. In this instance, owing to a lack of history of joint pain, the inflammation status of the joint was determined, and the patient was given an intra-articular injection to allow the continuation of ustekinumab treatment, which ultimately improved the patient's skin.

Case 3: Dose Escalation

An obese 68-year-old man with a 30-year history of psoriasis, no PsA, mild hypertension, and a daily smoking habit, was previously treated with methotrexate and adalimumab but discontinued both due to lack of efficacy. The patient was started on adalimumab 40 mg every other week and had a good response (PASI 0–6) for 3 years. Upon psoriasis flaring up the dose was increased to 40 mg every week. As a result of these flare ups clinicians considered the options of continuing the patient on a higher dose, reverting to the standard dose of 40 mg every other week, or changing the biologic treatment entirely.

In an unpublished dose-escalation study by Gniadecki,[18] 1,256 patients receiving 40 mg adalimumab every other week achieved PASI ≥75 (64.1%), PASI ≥90 (40.3%), and PASI 100 (21.7%). The 349 (27.8%) patients who had a PASI <50 during Weeks 24 and 252 of the study were dose-escalated to 40 mg every week. Of these 349, 182 (52.1%) remained on every-week dosing and 167 (47.9%) achieved a PASI 75 response and were de-escalated to every other week. Later, 83 patients were re-escalated to every-week dosing, owing to a PASI <50 response (Figure 2).[18,19]

After escalation of adalimumab dosing to every week, approximately one-quarter of patients were able to successfully have their dose de-escalated and remained on every-other-week dosing for nearly 1 year without the need for dose re-escalation. Therefore, transient increase in the dosing frequency of adalimumab to every week improved responses to treatment and permitted long-term maintenance to be achieved.

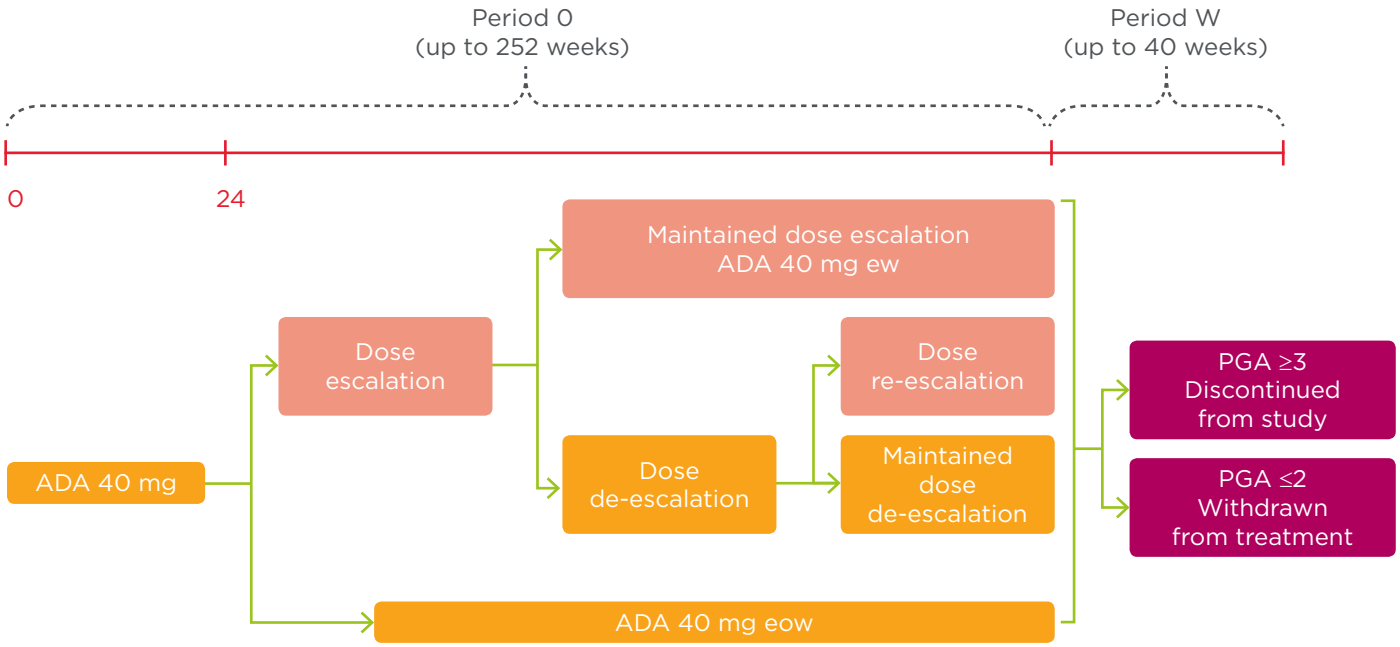

Figure 2: Dose escalation.
Adalimumab 40 mg every week can be considered in patients with inadequate response to adalimumab 40 mg every other week.
ADA: adalimumab; eow: every other week; ew: every week; PGA: Physician's Global Assessment.
Adapted from Gniadecki[18] and Gniadecki et al.[19]

Unmet Needs

There are a number of unmet needs in the clinical management of psoriasis. Focus on real-world practice needs to increase by moving away from population measures, such as PASI 75 and PASI 90, which are best suited to drug comparison in clinical trials, and moving towards individual measures (e.g., absolute PASI). Also, steps need to be taken to avoid inequality of care and ensure that access to treatment is improved for certain patient populations, such as elderly female patients with low educational and socioeconomic status.

PASI, the most frequently used clinical severity scale in clinical trials and drug approval, often depends on a 75% improvement in the baseline PASI score. In clinical trials, the mean baseline PASI is 20, whereas in real life it is closer to 12 or lower; therefore, the true success of psoriasis treatment seems to be under-represented. This discrepancy may relate to the way numerical values are assigned to the degree of body surface area involvement; thus, a better method to assess clinical improvement is needed.

Moreover, the relevance of baseline PASI diminishes with increasing duration of treatment, which implies that absolute PASI values are more appropriate to assess long-term response. Absolute PASI scores can be used where PASI 2 corresponds to a PASI 90, and a PASI 5 score, often considered the threshold for therapeutic adjustment or switching, corresponds to a PASI 75 or better response.[20]

Economics and Adherence

In the first year of treatment, some biologics carry a significant increase in their dose and, consequently, their cost. Therefore, it might be more sensible to switch to a drug that has a relatively small increment in the induction phase, rather than to others that might have a larger increment. Puig et al.[21] developed a decision tree with a 2-year time horizon to compare the cost consequence of biologic drugs for moderate-to-severe psoriasis from the perspective of the Spanish National Health System. Secukinumab monotherapy was found to be associated with the lowest cost per responder, followed by infliximab, and then ustekinumab.

Low adherence to therapies in psoriasis decreases treatment outcomes and increases total healthcare costs. Hsu and Gniadecki[22] surveyed patients' attitudes to treatment and measured adherence to biologics using the medication possession ratio index in a population of patients treated for psoriasis vulgaris. The medication possession ratio was calculated based on hospital records documenting the dispensing of biologics to patients, PASI, Dermatology Life Quality Index, presence of PsA, concomitant treatment, and cause for treatment discontinuation, all of which were obtained from DERMBIO. Patients' attitudes and beliefs were measured using the Medication Adherence Rating Scale. The authors found that adherence to biologics was very high, which is consistent with a positive attitude to treatment.

Factors Impacting Drug Survival

Biologic drug survival in psoriasis reflects long-term performance in real-life settings.[23] In economies where there is a need for sustainability, it is common practice to optimise the treatment dose by lengthening the dosing intervals for patients achieving PASI 90 and PASI 100. Sex, obesity, comorbidities, previous biologic exposure, and combination treatment are some of the variables that affect PASI response.[23] A retrospective, observational study on biologic drug survival in a real-life cohort of patients with moderate-to-severe chronic plaque psoriasis, found that cumulative probability of drug survival was lower in obese patients and significantly higher for ustekinumab than for any other biologic agent.[23] Multivariate analysis showed that obesity, etanercept treatment, and strict adherence to approved doses were associated with an increased probability of drug withdrawal, whereas ustekinumab treatment, and PASI 75 and PASI 90 responses at Week 16, prolonged drug survival.

Patients with Comorbidities

A 67-year-old male who has had psoriasis for 10 years, with no PsA, had a PASI of 16.4. The patient was obese, had unstable angina and hypertension, and eventually suffered a myocardial infarction. He had been subject to many treatments with no response; thus, the first treatment choice was an anti-TNF agent or methotrexate because both drugs are associated with a reduced rate of cardiovascular events. Cyclosporine should be avoided in this patient type due to the resulting increase in blood pressure and vascular resistance.

A 57-year-old woman with latent tuberculosis received adalimumab before starting on a efalizumab. After 22 months on adalimumab,

she presented with pneumonia. In elderly populations, and particularly vulnerable patients, a pneumococcal vaccine is prudent as these individuals are at a high risk of infection. A study by Dommasch et al.[24] examined the risks of infection and malignancy with the use of TNF antagonists in adult patients with psoriatic disease and found that there was a small increased risk of overall infection with the short-term use of TNF antagonists. Of reported infections, 97.6% were non-serious, and the large majority of these were upper respiratory tract infections.

A 67-year-old woman on infliximab acquired a left knee prosthesis infection, so her treatment was stopped. Following psoriasis relapse, she was started on ustekinumab and the infection was initially controlled with antibiotics. However, because her condition had become unstable and the prosthesis was replaced, a decision had to be made about the interruption of biologics prior to her operation. A study by Bakkour et al.[25] looked at the risk of postoperative complications in patients with psoriasis on biologic therapy undergoing surgical procedures. The authors reported that continuing biologic therapy in patients with psoriasis and PsA peri-operatively did not increase the risk of postoperative complications, and that interrupting biologic therapy peri-operatively significantly increased the risk of disease flare. There are currently very little data on the subject and for minor surgery. Some practitioners are stopping biologic therapy, which could have a detrimental effect on patients' psoriasis. However, for major surgery the risk of infection changes; therefore, stopping treatment should be considered and approached on a case-by-case basis.

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INTERLEUKIN-23 INHIBITION AS A STRATEGY TO TREAT IMMUNE-MEDIATED INFLAMMATORY DISEASES

This symposium took place on 1st December 2017 as part of the Psoriasis Gene to Clinic, 8th International Congress in London, UK

Speakers

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Disclosure: Prof Prinz is or has served as a consultant for Novartis, Pfizer, Janssen-Cilag, and Amgen, and has participated in speakers' bureaux meetings for Novartis, Pfizer, Abbott, Janssen-Cilag, MSD, and Amgen. Prof Danese is or has been a consultant, provided research support, or been a principal investigator, and participated in speakers' bureaux meetings for Abbvie, Allergan, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Hospira, Johnson & Johnson, Merck, MSD, Takeda, Mundipharma, Pfizer, Sandoz, Tigenix, UCB Pharma, and Vifor.

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MEETING SUMMARY

The satellite symposium comprised two short presentations aimed at providing an overview of the rationale for the use of interleukin (IL)-23 inhibition as a targeted strategy to treat immune-mediated inflammatory diseases. Presentations by Prof Prinz and Prof Danese focussed on psoriasis and inflammatory bowel disease, respectively, as examples of clinical indications in which the gene-to-clinic approach has led to the development and approval of biologic IL-23 inhibitors. In psoriasis the introduction of targeted anti-IL-17/IL-17 receptor A-chain (RA) and anti-IL-23 biologic therapies has provided a paradigm shift in the management of the disease, making complete clearance of disease a realistic aim for the first time. The use of IL-12/IL-23 inhibitors, such as ustekinumab, is now also possible in Crohn's disease (CD), providing another example of the successful translation of immunological targeting into clinical practice.

Interleukin-23 Inhibition as a Strategy to Treat Immune-Mediated Inflammatory Diseases: A Focus on Psoriasis

Professor Jörg Christoph Prinz

Effector T cells have evolved into different functional subsets, each with distinct physiological roles and signature cytokine profiles.[1-3] T helper 17 (Th17) cells are a functional lymphocyte subset that has developed to co-ordinate the immune response against bacterial and fungal infections and are characterised by the production of IL-17, IL-22, and interferon (IFN)-γ. As well as providing a key protective role in host immunity, Th17 can also have a pathogenic role in various autoimmune diseases, including systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, psoriasis, and inflammatory bowel disease (IBD).[3] Specific and targeted inhibition of Th17-mediated immune pathways has therefore emerged as a highly effective treatment approach for psoriasis and IBD, with a number of biologic agents being developed and licensed for these indications.

Differentiation of Th17 cells from naïve cluster of differentiation 4-positive (CD4+) T cells occurs in three distinct stages.[4] Upon activation of T cells, transforming growth factor-β and IL-6 establish early commitment to the Th17 lineage by activating signal transducer and activator of transcription 3 (STAT3), which induces the expression of IL-21.

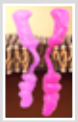
Cytokines	Source of cytokine	Receptor complexes	Expression of receptors
IL-17A IL-17F IL-17A/F heterodimer	• Th17 cells • NK T cells • CD8+ T cells • LTi cells • γδ T cells • NK cells • PMN cells (low concentration)	 IL-17RA IL-17RC	Ubiquitous (higher in haematopoietic tissues) Most human tissues (preferentially on nonhaematopoietic tissues)
IL-17C	Epithelial cells (trachea, colon, skin)	 IL-17RA IL-17RE	Ubiquitous (higher in haematopoitic tissues) Selectively induced in epithelia by bacterial, inflammatory stimuli
IL-17E	• Th2 cells • NK T cells • Alveolar MΦ • PMN cells (lower concentration)	 IL-17RA IL-17RB	Ubiquitous (higher in haematopoietic tissues) Th2 cells, Th9 cells, fibroblasts, basophils, endocrine cells, kidney cells, and liver cells

Figure 1: Spectrum of targets for interleukin-17A and interleukin-17RA antibodies.[5-8]
IL: interleukin; LTi: lymphoid tissue inducer; MΦ: macrophages; NK: natural killer; PMN: polymorphonuclear leukocyte; R: receptor; Th: T helper.

Autocrine signalling by IL-21 then promotes STAT3-dependent expression of the master transcription factor for Th17 differentiation, retinoic acid receptor-related orphan receptor gamma t (RORγt), leading to the production and expression of IL-17A and the IL-23 receptor. This allows IL-23 to bind to and exert its effects on previously committed Th17 cells, stabilising the phenotype and expansion of Th17 cells, which secrete the effector cytokines IL-17A, IL-17F, IL-21, IL-22, and IL-26. The development of biologic agents that target the Th17 pathways has used several approaches. One approach is to inhibit the Th17 effector response, either by inhibiting the production of IL-17A/IL-17F using anti-IL-17 antibodies or by inhibiting the signalling of IL-17A/F through the blockade of the IL-17 receptor alpha chain. More recently, an alternative strategy has emerged: the inhibition of IL-23 using anti-IL-23 antibodies to interfere with the stabilisation and expansion of Th17 cells.

The IL-17 family consists of six cytokines (IL-17A–F), which signal through a family of heterodimeric IL-17 receptor complexes, i.e., receptors composed of two different chains. Receptors for IL-17A, IL-17F, IL-17C, and IL-17E are composed of the IL-17RA chain and one of three different other chains to form a functional receptor unit. The IL-17RA chain combines with the IL-17-RC chain for binding of IL-17A and IL-17F, with the IL-17RE chain for binding of IL-17C, and with the IL-17RB chain for binding of IL-17E (Figure 1).[6] Antibodies directed against IL-17A selectively neutralise IL-17A and the IL-17A/F heterodimer.[5,7,8] However, as the IL-17RA chain is part of several heterodimeric IL-17 chain receptors, blocking IL-17RA interferes with the signalling of most members of the IL-17 cytokine family, including IL-17C and IL-17E, and therefore IL-17RA blocking has a much broader effect. This broader inhibitory activity may explain the greater efficacy that has been observed with antibodies directed against the IL-17RA chain compared with those against IL-17A. This improvement in efficacy is exemplified by the comparative efficacy of brodalumab (an anti-IL-17RA antibody) and secukinumab (an anti-IL-17A antibody) in the treatment of chronic plaque psoriasis. Although no head-to-head clinical trials have been conducted, Phase III clinical data from the AMAGINE-2 and AMAGINE-3 (both brodalumab) and ERASURE (secukinumab) studies show that both treatments are highly effective in patients with plaque psoriasis, with approximately 80% of brodalumab-treated patients and 65% of secukinumab-treated patients becoming clear or almost clear of psoriasis.[9,10] However, a greater proportion of patients treated with brodalumab attained ≥75% improvement in Psoriasis Area Severity Index (PASI) 75, PASI 90, and PASI 100 responses as compared with secukinumab.[9,10] Importantly, the response can be maintained over time, which has been shown in

recently published data showing that psoriasis treatment with secukinumab is associated with sustained PASI responses through 3 years of treatment.[11]

An alternative approach to blocking the Th17/IL-17 effector response is to block the upstream cytokine IL-23. As mentioned previously, inhibition of IL-23 interferes with the stabilisation and expansion of Th17 cells without affecting the differentiation of Th17 populations and consequently IL-23 inhibition has regulatory effects on memory effector T cells (i.e., those involved in the pathogenic response), but not on naïve or central memory T cells.[4] Currently, clinical data are available for three IL-23 inhibitors in the treatment of psoriasis: tildrakizumab, guselkumab, and risankizumab. Although differences in the overall response to each of the IL-23 antibodies have been observed in clinical trials, blocking IL-23 appears to be highly efficacious. An improvement of >90% in PASI is realistic and clinical trials have reported that, at Week 12 or 16 (depending on the study), 12–14% of patients treated with tildrakizumab, 34–37% of patients treated with guselkumab, and 48% of patients treated with risankizumab achieved complete clearance of psoriasis (i.e., PASI 100 response).[12,13] Tildrakizumab seems to be associated with a slower initial clinical response, but the efficacy appears to 'catch-up' with the other IL-23 inhibitors over time, and 67–69% of patients achieve a Physicians' Global Assessment of 0 or 1 (indicating clear or almost clear of psoriasis) by 28 weeks.[12,13] However, it is important to note that these data are not from head-to-head comparisons of the IL-23 inhibitors and the outcomes reported for risankizumab are from a Phase II clinical trial. Clinically, the effect of blocking IL-23 has been shown to be superior to blocking tumour necrosis factor (TNF)-α.[14] The VOYAGE 1 trial, which compared guselkumab with the anti-TNF-α inhibitor adalimumab in patients with moderate-to-severe psoriasis, reported that specific interference with the maintenance of activation of Th17 cells via IL-23 inhibition achieved PASI 75, PASI 90, and PASI 100 responses in a significantly higher percentage of patients than did TNF-α blockade.[14]

Although blocking either IL-17 or IL-23 targets the same Th17 effector pathway, there is a difference in the effects of each of these approaches on the immune response.[15-18] Blocking IL-23 has been shown to be very effective in both psoriasis and CD, whereas anti-IL-17A or IL-17RA antibodies are highly effective for the treatment of psoriasis but may exacerbate CD in a subset of patients. This effect has been reproduced in a mouse model of colitis, in which IL-17 inhibition weakened intestinal epithelial barrier function and increased inflammation, while IL-23 inhibition enhanced regulatory T cell accumulation and attenuated inflammation. It is therefore important to be aware of this possibility because psoriasis and IBD are associated and can develop concurrently in some patients.

Comparison of the dosing regimens of the targeted biologic agents used in psoriasis highlights another interesting issue. Blocking the effector cytokines TNF-α and IL-17 requires more frequent and potentially higher doses of inhibitory antibodies than upstream interference with the regulation of Th17 activation through the inhibition of IL-23. Antibodies against TNF-α (adalimumab), IL-17 (secukinumab), and IL-17RA (brodalumab) have dose intervals of 2 or 4 weeks, while for anti-IL-23 antibodies (guselkumab, risankizumab) dosing intervals of up to 12 weeks are sufficient to maintain clinical response.[13,19-23] Adalimumab and guselkumab have similar serum half-lives (approximately 10–20 days);[19,23] however, achieving a sufficient response with adalimumab requires much more frequent dosing than with guselkumab. A 5 mg dose of guselkumab given four times over 40 weeks was sufficient to achieve a Physicians' Global Assessment of 0 or 1 in up to 40% of patients.[24,25] The differences are even more intriguing when the pharmacokinetics of guselkumab are examined. Although the mean serum concentration of guselkumab is almost zero 50 days after a 5 mg dose, a treatment response is maintained;[25,26] in other words, clinical efficacy outlasts the presence of the biologic inhibitor. From an immunological perspective, these data indicate that blocking effector cytokines, such as TNF-α, is associated with a different mechanism of action than the inhibition of IL-23; IL-23 antibodies appear to downregulate ongoing Th17 responses and provide disease control beyond the actual presence of active substance. This may be the major difference between blocking effector cytokines and blocking IL-23.

In summary, the extremely high clinical efficacy of IL-23 and IL-17 pathway inhibition has set a new standard for the treatment of plaque psoriasis and, for the first time, achieving complete clearance of disease has become a realistic treatment goal for many patients. Importantly, blocking IL-23 interferes

with the maintained activation of Th17 cells and Th17 differentiation, and preferentially regulates the memory effector cells involved in the pathogenic immune response. This is a different therapeutic pathway to inhibition of IL-17 or IL-17RA and long-term follow-up of the clinical effects of sustained IL-23 inhibition is required to assess potential safety benefits of IL-23 inhibition compared with direct inhibition of the IL-17 effector response.

Interleukin-23 Inhibition as a Strategy to Treat Immune-Mediated Inflammatory Diseases: Evidence from the Treatment of Inflammatory Bowel Disease

Professor Silvio Danese

Although the exact cause of IBD is not entirely understood, it is believed to involve a complex interaction between genes, the immune system, and environmental factors. Genetic susceptibility, the composition of the gut microbiome and an inappropriate immune response can all play a role in the development of IBD.[27] Indeed, genome-wide association studies have revealed major genetic variations in the IL-23 receptor and the IL-12 p40 subunit, both of which are involved in the immune inflammatory response in patients with CD and ulcerative colitis (UC). However, although there is a strong genetic susceptibility for IBD and >163 genetic associations for IBD have been identified, these account for <30% of all cases of IBD.[27] An inappropriate immune response is responsible for the development of IBD in the majority of patients and a targeted inhibition of key immune-mediated inflammatory pathways has emerged as a leading new therapeutic strategy. Among the plethora of potential lymphocyte and effector cytokine targets, T cells are the key drivers of the pathophysiology of IBD from early to late disease.[28] Although the immune pathways associated with IBD have many similarities with other autoimmune inflammatory diseases, such as psoriasis, there are patterns of cytokine-mediated pathology that are specific to IBD. Firstly, it must be noted that inhibition of effector cytokines in the Th17 pathway (e.g., with anti-IL-17A antibodies) can exacerbate inflammation in some patients with CD, as Prof Prinz explained previously, and this is important to remember when using such biologics in the clinic. With regard to the immunopathology of IBD, there is clinical evidence that shows upregulation of IL-12 occurs in patients with early CD compared with those who have UC or healthy controls.[29,30] Upregulation of IL-23 then occurs once CD is established.[30,31] A study in mice has shown that IL-12 continues to contribute to chronic intestinal inflammation during established colitis and consequently IL-12 has been identified as a key therapeutic target.[32] Additionally, experimental colitis models have shown that treatment with anti-IL-23 antibodies attenuated extensive inflammation in both the caecum and colon, and reduced inflammatory infiltrates and epithelial hyperplasia.[33] IL-23 inhibition has therefore also been identified as a key target for targeted biologic treatment in CD.

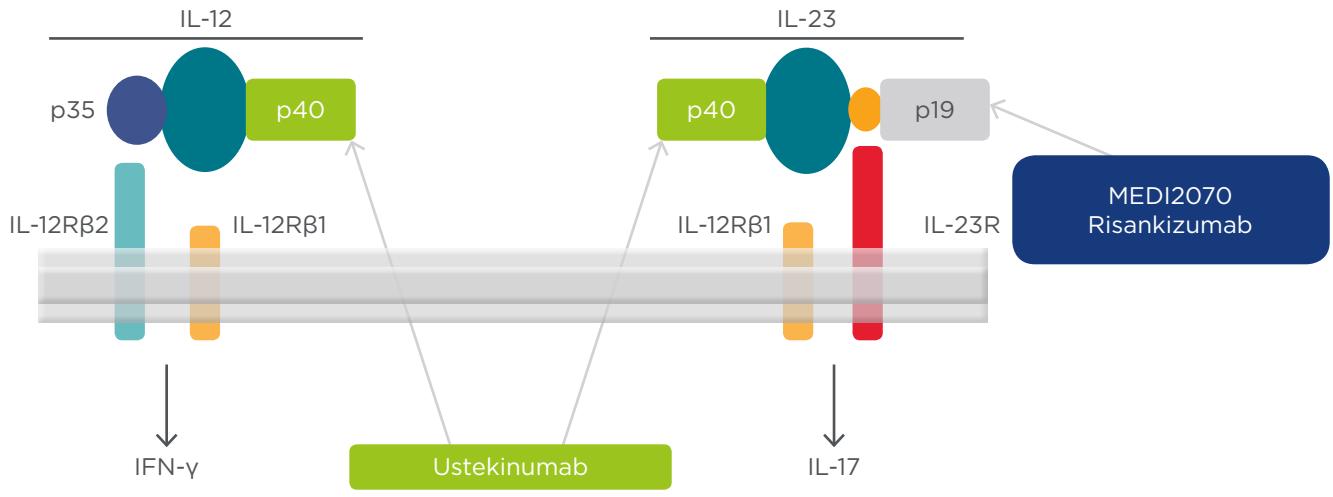


Figure 2: Targets for interleukin-12 and interleukin-23 inhibition in Crohn's disease.
IFN: interferon; IL: interleukin; R: receptor.

Table 1: Response to ustekinumab in patients with Crohn's disease who have previously failed anti-tumour necrosis factor-α or conventional treatment (Week 6).[34,35]

Treatment group	Proportion of patients (%)	p value versus placebo
UNITI-1 TNF antagonist failure		
Placebo (n=247)	21.5	NA
130 mg (n=245)	34.3	0.002
˜6 mg/kg (n=249)	33.7	0.003
Combined (n=494)	34.0	<0.001
UNITI-2 Failed conventional treatment		
Placebo (n=209)	28.7	NA
130 mg (n=209)	51.7	<0.001
˜6 mg/kg (n=209)	55.5	<0.001
Combined (n=418)	53.6	<0.001

NA: not applicable; TNF: tumour necrosis factor.

A number of biologic treatments are being developed for targeted inhibition of IL-12 and IL-23 in patients with CD (Figure 2). Ustekinumab, the first such biologic to be approved for the treatment of CD, targets the p40 subunit that is present on both IL-12 and IL-23. Risankizumab is another biologic that is in clinical development and targets the p19 subunit, which is present on IL-23 but not on IL-12 (Figure 2).

Phase III clinical data have shown that the approved dose of ustekinumab, 6 mg/kg, was associated with a clinical response in a significantly higher proportion of patients than placebo in both patients who had previously failed treatment with anti-TNF-α and those who had previously failed conventional treatment (Table 1).[34] Maintenance treatment with ustekinumab has also been shown to be effective in maintaining clinical remission in CD, administered as a subcutaneous dose of 90 mg either every 12 weeks or every 8 weeks.[35] Similar clinical data are emerging for risankizumab, which is currently in clinical development and awaiting approval for the treatment of CD.

To conclude, the development of IL-12 and IL-23 targeted inhibitors is a classic example of the gene-to-clinic approach, providing an effective, novel therapeutic strategy in CD. Clinical studies are ongoing to evaluate the efficacy of IL-12 and IL-23 inhibitors for the treatment of UC, and the publication of the clinical data is eagerly awaited.

Question and Answer Session

Q: In dermatology, when you clear a lesion with a systemic drug there is usually one lesion that stands out and recurs, and that recurrent lesion is frequently the very first lesion that the patient had. This could be a residual lesion that is somehow different to the rest of the skin lesions; do you see that in UC as well, or in IBD?

A: Prof Danese replied that this is a great point and is also seen in patients with CD. For example, when a patient with CD is given an anti-TNF-α drug, healing is observed in the ileum but not in the rectum, and treatment with two drugs is needed because the disease is driven by different mechanisms of action in the different sites. Currently, we have little understanding of zonal gene expression and the mechanisms that drive inflammation in the gut, and this should be the focus of research efforts to understand the differences between different disease sites and locations in order to determine effective drug treatment combinations. Prof Prinz also commented that in dermatologic indications there appears to be a residual scar or residual lesion that is characterised by a greater tendency to restart inflammation, potentially due to low levels of residual inflammation.

Q: As alluded to in the symposium, there are patients who have CD and develop paradoxical psoriasis, and patients with psoriasis who develop

CD. Do you have any insights into the genetics, the immunology, and the management of those patients?

A: Prof Danese replied that, at present, although the clinical characteristics of these patients have now been elucidated, as yet nothing is known about the underlying genetics in such cases. We only know that the disease is somehow driven, again, by IL-23 and that these patients respond very well to ustekinumab treatment.

Click here to view the full symposium.

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