Discover the Potential: Exploring New Frontiers of IL-23 Inhibitors

This symposium took place on 14th December 2018, as part of the 3rd Inflammatory Skin Disease Summit (ISDS) in Vienna, Austria

Chairperson: Antonio Costanzo

Speakers: Antonio Costanzo, Kilian Eyerich

1. Humanitas University, Milan, Italy
2. Technical University of Munich, Munich, Germany

Disclosure: Prof Costanzo has provided research support to Celgene, Janssen, LEO Pharma, and Novartis; he has received honoraria from, and has been a scientific advisory board member for, AbbVie, Celgene, Janssen, Novartis, Pfizer, and Sanofi. Prof Eyerich has declared no conflicts of interest.

Acknowledgements: Medical writing assistance was provided by Lorena Tonarelli.

Support: The symposium and the publication of this article were funded by Janssen via an educational grant. The views presented here are those of the speakers and not necessarily those of Janssen.

Citation: EMJ. 2019;4[1]:12-19.

Meeting Summary

Affecting up to 11.4% of the population worldwide, psoriasis is one of the most common chronic autoinflammatory diseases. It is associated with multiple comorbidities and can have profound negative effects on physical and emotional wellbeing and overall quality of life, making it a serious public health concern. A primary objective of this symposium was to explain the pathogenesis of psoriasis and its relation to the development of novel targeted immune therapies. Psoriasis is characterised by skin and systemic damage consequent to pathogenic cytokine production under the influence of both environmental and genetic factors. Differentiation of Th17 cells from naïve T cells is central to the development of psoriasis, and recently pathogenic models have identified IL-23 as the pathogenic cytokine responsible for promoting Th17 cell proliferation and IL-17 production. Therefore, selective blockade of IL-23 may be instrumental in controlling Th17-mediated inflammation in psoriasis. Another key objective of the symposium was to evaluate key learnings from the latest available clinical trial data on agents targeting the IL-23/Th17 signalling pathway and how these learnings can be harnessed to improve the management of patients with psoriasis. Both IL-17 inhibitors (e.g., ixekizumab and secukinumab) and IL-23 inhibitors (e.g., guselkumab and risankizumab) have demonstrated high efficacy and a good safety profile. Anti-IL-17 agents have faster onset of action and allow the achievement of good response rates very rapidly. Efficacy is better maintained over time with anti-IL-23 agents, including in patients who have stopped and those that then restarted anti-IL-23 therapy after a withdrawal period. Despite the availability of effective treatments, undertreatment in psoriasis is common. This can be attributed to factors such as the heterogeneous nature of psoriasis and relatively large prevalence of addictive behaviours in patients with the condition. When making treatment decisions, it is important to consider these factors as well as patient preferences and expectations, so that treatment can be
Advancing the Science of Psoriasis: The Underlying Pathology and the Role of IL-23

Professor Antonio Costanzo

Both genetic and environmental factors contribute to the development of psoriasis. From a genetic point of view, multiple loci are involved in harbouring psoriasis susceptibility genes, including human leukocyte antigen (HLA)-Cw6, IL-23R and IL-12B, and the two members of the late cornified envelope (LCE)-3 group, LCE3B and LCE3C. Sixteen new susceptibility loci have been identified within a large-scale meta-analysis of genome-wide association studies (GWAS), bringing the total number of known psoriasis-associated loci to 63. The majority of these loci are related to genes involved in lymphocyte differentiation and regulation, response to stimuli, and type 1 IFN/pattern recognition pathway. The highest degree of genetic predisposition has been reported for HLA-Cw6. This has been indicated as the psoriasis susceptibility 1 (PSORS1) risk allele conferring a predisposition specifically to psoriasis, particularly the early-onset (type 1) form of the disease. PSORS1 is considered the major genetic determinant of psoriasis, accounting for up to 50% of the heritability of the disease. Conversely, psoriasis susceptibility genes, such as IL-12B and IL-23R, are shared with other chronic autoimmune or inflammatory diseases, including psoriatic arthritis, Crohn’s disease, multiple sclerosis, asthma, and diabetes.

From a medical viewpoint, psoriasis can be defined as an exaggerated immune response to bacteria, as evidenced by elevated skin levels of certain antimicrobial peptides, such as β-defensin, the encoding genes of which are highly expressed in the genome of individuals with the condition. Notably, overexpression of β-defensin has been found in keratinocytes from psoriatic skin but not in those from atopic dermatitis lesions, despite the latter being remarkably similar to psoriatic lesions.

Cathelicidin hCAP18/LL37, another antimicrobial peptide frequently found in humans, is also overexpressed in psoriasis. Both cathelicidin hCAP18/LL37 and β-defensin are thought to play a prominent role in psoriatic plaque development. Stress, bacteria, and trauma can trigger LL37 overproduction and, in turn, the formation of LL37-DNA complexes that bind to plasmacytoid dendritic cells, thus activating them. Activated dendritic cells are then internalised by lymph nodes where they induce naïve T cells to differentiate into effector cells, such as Th1 and Th17 cells. Effector cells migrate into skin tissue followed by putative presentation of autoantigens to T cells and the release of IL-23. These and other processes eventually lead to the activation and proliferation of keratinocytes with consequent overexpression of β-defensin.

Importantly, Lande et al. demonstrated that LL37 is the key mediator of plasmacytoid dendritic cell activation in psoriasis. Specifically, the binding of LL37 to DNA induces plasmacytoid dendritic cells to produce IFN-α via activation of toll-like receptor (TLR)9. This pathway could potentially be a driver of autoimmunity in psoriasis.

Also of note is that, following internalisation in DNA complexes, LL37 is processed within the cell and presented to lymphocytes in the context of HLA-Cw6. The fact that HLA-Cw6 can present an autoantigen, such as LL37, to T cells would explain the observed high frequency of this particular type of HLA among patients with psoriasis, and this is supported by the higher peptide-binding selectivity of HLA-C, compared with HLA-A and HLA-B.

Autoantigens other than LL37 have recently been identified, most notably the melanocyte-expressed molecule ADAMTS-like protein 5 (ADAMTSL5), which can be presented to lymphocytes in the context of HLA-Cw6. Initially identified in the melanocytes of patients with psoriasis, ADAMTSL5 was discovered by Fuentes-Duculan et al. to be widely distributed in keratinocytes. Subsequent immunohistochemistry analyses by the same authors demonstrated that LL37 and ADAMTSL5 are significantly upregulated in lesional, versus non-lesional, skin biopsies from patients with
moderate-to-severe psoriasis (p<0.05). In both lesional and non-lesional skin, LL37 and ADAMTS15 are coexpressed by keratocytes, dendritic cells, and other leukocytes. The key event leading to psoriatic plaque formation is the differentiation of Th17 cells from naïve T cells following presentation to the latter of autoantigens by plasmacytoid dendritic cells. Several cytokines are necessary for Th17 cell differentiation and IL-17 production in humans, including TGF-β, IL-β, IL-6, IL-23, and IL-21. A crucial role is played by IL-21. In a human psoriasis xenograft mouse model, Caruso et al. discovered that IL-21 blockade via an IL-21-specific antibody reduced keratinocyte proliferation and transcript levels of both IFN-α and IL-17A, effectively inducing psoriatic plaque regression. IL-21 is directly involved in the expression of IL-17 receptors (IL-23R). Thus, the findings by Caruso et al. suggest that IL-21 plays a prominent role in T cell differentiation and the epidermal hyperplasia of psoriasis, probably via the activation of IL-23 receptors.

Binding of IL-23 to IL-23R on mature Th17 cells has been shown to maintain IL-17 production in vivo and to promote Th17 cell survival and pathogenic activity. It can, therefore, be assumed that IL-23, rather than IL-17, plays a central role in Th17-related autoimmunity and is a driver of inflammation mediated by innate lymphoid cells. Clinical data from other diseases support this view. For example, in animal models of inflammation, blocking IL-23 has been associated with a protective effect against immune colitis, whereas blocking IL-17 has been found to have no protective effect, or a worsening effect, on the condition.

Interestingly, Th17 cells are characterised by a high degree of plasticity, which is strongly dependent on the microenvironment. The phenotype of Th17 cells can change from one in which cells produce pathogenic cytokines to one in which cells produce anti-inflammatory cytokines, and is influenced by epigenetic mechanisms that affect whether relevant genes are expressed or silenced. This is illustrated in an in vitro study in which Aschenbrenner et al. were able to characterise two divergent activated subsets of Th17 cells. Of these subsets, one maintained proinflammatory activity; the other, however, acquired anti-inflammatory activity. A distinctive feature of the latter subset was the ability to produce IL-10, a potent anti-inflammatory cytokine. Expression of c-MAF was found to be upregulated in IL-10-positive Th17 cells, leading to the conclusion that it may be important in driving divergent fates of human Th17 cells.

Tissue-resident memory (TRM) T cells are thought to contribute to psoriasis development. This is substantiated by the finding that epidermal TRM cells are retained in resolved psoriatic lesions and can produce IL-17A and IL-22. Given the pivotal role played by these cytokines in the pathogenesis of psoriasis, TRM cells in resolved lesions have been indicated as potential drivers of recurrent disease. Defective Foxp3 regulatory T cells (Tregs) have been identified in psoriasis, which could also contribute to the development of the disease; Sanchez et al. found proliferating defective memory Tregs that produce IL-17 in human psoriatic skin. In other research, blood-derived Tregs from patients with severe psoriasis were more likely to differentiate into IL-17-producing cells, compared with Tregs from healthy subjects; on ex vivo stimulation, the increase in the percentage of intracellular IL-17A-producing cells (mean±standard error of the mean) was 9.3±2.4% (n=7) for patients with psoriasis and 3.2±0.7% (n=8) for healthy controls (p=0.0236). Crucially, supplementation of IL-23 increased the percentage of IL-17-producing Tregs, and the effect was more pronounced in patients with psoriasis than in controls (17.0±2.6%, n=6 versus 6.3±1.6%, n=8; p=0.0006). In another study, IL-23 was found to be central to the conversion of functional Foxp3 Tregs into IL-17-producing Foxp3 Tregs with pathogenic phenotype.

Importantly, Th17 cells are not the only lymphoid cells regulated by IL-23. Other targets include γδT cells and Type 3 innate lymphoid cells, both of which can produce pathogenic cytokines such as IL-17 and IL-22 in response to IL-23 stimulation. Neutrophils and mast cells are also influenced by IL-23, and have been indicated as the major producers of IL-17 in human psoriatic skin.

Updated pathogenic models of psoriasis attribute IL-23 with a central role in all stages of skin lesion formation; specifically, IL-23 is responsible for initiating Th17 cell activation and IL-17 production in pre-psoriatic skin, promoting
pathogenic Th17 cell expansion and survival in early psoriatic lesions, and maintaining IL-17 production in chronic psoriatic plaques.\textsuperscript{31}

It is evident that the IL-23/Th17 signalling pathway is of critical importance in the pathogenesis of psoriasis and that selective blockade of IL-23 may represent an effective, targeted approach to psoriasis treatment.\textsuperscript{31} In light of this, several anti-IL-23 agents have been approved in recent years (e.g., guselkumab, tildrakizumab, and ustekinumab) and others are being developed (e.g., mirikizumab and risankizumab). Anti-IL-23 agents typically target a specific subunit of IL-23, usually p19 or p40. Since these subunits are not exclusive to IL-23, but are shared with other cytokines, off-target activities must be considered.\textsuperscript{32}

It can be concluded that psoriasis is an autoimmune disease characterised by skin and systemic damage that occurs as a result of the secretion of cytokines, and that IL-23 is a key pathogenic cytokine in psoriasis development.

---

**New Horizons in Managing Psoriasis: Individualising Care One Patient at the Time**

**Professor Kilian Eyerich**

Psoriasis has been recognised by the World Health Organization (WHO) as a serious health problem of global importance that has a significant impact on quality of life.\textsuperscript{1} Over recent decades, our understanding of the pathogenic pathways of psoriasis has improved substantially and new, effective, targeted therapies have become available. However, this does not seem to have been paralleled by an improvement in the management of real-world patients in clinical practice. In a large population-based survey conducted in Europe and North America, 41% of patients with psoriasis with up to three palm lesions (n=2,112) reported they were not receiving any treatment.\textsuperscript{33} No treatment was also reported by 37% of patients with >10 palm lesions (n=166) and 32% of those with 4–10 palm lesions (n=393).\textsuperscript{33} In all three groups, only 1% of patients reported being on oral plus biologic treatment.\textsuperscript{33}

A key contributing factor may be the heterogeneity of psoriasis,\textsuperscript{34} which makes it important to provide treatment based on disease phenotype as well as patient expectations and characteristics. Regarding the last point, an important but often-overlooked issue is the high prevalence of addictive behaviour among patients with psoriasis.\textsuperscript{35} In a study by Zink et al.,\textsuperscript{35} 57 of 102 patients were assessed over a period of 4 months exhibited addictive behaviour. Of these, 41% were regular smokers, 23.8% were high-risk drinkers, 19% were compulsive gamblers, 11% were at risk of drug abuse, and 4.1% were at risk of food dependency. Providing effective therapies may not be enough for these patients, and this factor should be considered when making treatment decisions.

From an efficacy point of view, agents that can selectively block IL-17 (e.g., ixekizumab and secukinumab) or IL-23 (e.g., guselkumab and risankizumab) have demonstrated important benefits in patients with psoriasis.\textsuperscript{36-39}

In the UNCOVER-3 study, 80.5% of patients treated with the high-affinity monoclonal antibody ixekizumab achieved at least 75% improvement from baseline in Psoriasis Area Severity Index (PASI) at Week 156.\textsuperscript{36} Sixty-six percent of patients achieved PASI 90 and 45.1% achieved PASI 100.\textsuperscript{36} Ixekizumab achieved and sustained high responses of action and the observed skin improvements were maintained over the 3-year period, with no new safety signals identified.\textsuperscript{36} Notably, the number of nonresponders was limited despite the elevated heterogeneity of psoriasis. Similar results have been reported with secukinumab in a 5-year randomised (1:1), double-blind, noninferiority clinical trial (SCULPTURE) of adults with moderate-to-severe psoriasis.\textsuperscript{37} The study compared fixed-interval (FI) secukinumab with retreatment as needed (RAN) secukinumab. Both regimens demonstrated good efficacy, with superiority of FI 300 mg secukinumab. With this regimen, PASI 75, 90, and 100 response rates (as observed) were 88.9%, 68.5%, and 43.8%, respectively, at Year 1, and were maintained through Year 5 (88.5%, 66.4%, and 41.0% for PASI 75, 90, and 100, respectively).\textsuperscript{37}

Among IL-23 inhibitors, risankizumab has demonstrated superior sustained efficacy compared with ustekinumab in two Phase III
randomised, double-blind, placebo-controlled, and active comparator-controlled trials (UltIMMa-1 and UltIMMa-2). 38 Significantly more patients with moderate-to-severe psoriasis treated with risankizumab achieved PASI 90 at Week 16 compared with patients treated with ustekinumab or placebo (75.3% versus 42.0% and 4.9% in UltIMMa-1; and 74.8% versus 47.5% and 2.0% in UltIMMa-2; p<0.0001 versus placebo and ustekinumab for both studies). 38

It is apparent from the evidence presented above that both IL-17 and IL-23 inhibitors are associated with considerable and sustained skin improvements, with the former class of drugs providing a more rapid response but slightly less sustainability than the latter class. Another factor to consider in treatment decision-making is the extent to which the benefits of a therapy can persist beyond withdrawal. This has been investigated in psoriasis by Reich et al. 39 in a Phase III, multicentre, randomised, double-blind, placebo and adalimumab comparator-controlled study (VOYAGE 2). Guselkumab-treated patients achieving ≥90% improvement from baseline in PASI score were randomised at Week 28 to either guselkumab (maintenance group) or placebo (withdrawal group). At Week 48, although PASI 75, 90, and 100 response rates were significantly higher (p<0.001) in the maintenance group (96.0%, 88.6%, and 59.0%, respectively), a large proportion of patients in the withdrawal group maintained PASI response (62.0%, 36.8%, and 20.0% for PASI 75, 90, and 100, respectively) despite the fact that they were no longer receiving treatment. 39 Upon retreatment with guselkumab, the majority of patients rapidly regained PASI 90 response; within 6 months of restarting guselkumab treatment, the PASI 90 response rate for this group of patients was 87.6%. 40

Recently, guselkumab has been compared with secukinumab in the ECLIPSE study. 42 Patients with moderate-to-severe plaque psoriasis were randomised to guselkumab 100 mg (administered by subcutaneous injection at Weeks 0, 4, 12, and then every 8 weeks thereafter through to Week 44; n=534) or secukinumab 300 mg (administered by subcutaneous injection at Weeks 0, 1, 2, 3, 4, and then every 4 weeks thereafter through to Week 44; n=514). 42 In total, patients treated with guselkumab received 7 active injections versus 30 active injections in patients treated with secukinumab. 42 The primary endpoint was PASI 90 response rate at Week 48. 42 Prof Eyerich proceeded to explain that baseline demographics, disease characteristics, and exposure to previous psoriasis treatment were similar across study arms. Guselkumab demonstrated superior long-term efficacy compared with secukinumab; at Week 48, PASI 90 response rate was 84.5% for guselkumab-treated patients and 70% for secukinumab-treated patients (treatment difference: 14.2%; 95% confidence interval [CI]: 9.6–18.8; p<0.001). 42 Secukinumab showed faster onset of action, consistent with what has been reported in other studies of anti-IL-17 agents. 42 Both drugs were highly effective, with PASI 90 reaching 80% at Week 15–20; however, the elevated response rate was better maintained by selectively targeting IL-23 with guselkumab. 42 In terms of safety, observations of both guselkumab and secukinumab demonstrated a profile that was consistent with previous reports, with three events of Crohn’s disease reported in the secukinumab group compared to none in the guselkumab group. 42

Clearly, multiple factors affect the treatment decision in psoriasis, which also needs to be individualised by addressing patient preferences, needs, and expectations. Options to consider might include topical therapy (PASI <10), conventional systemics (chronic stable disease with PASI >10), or first-line biologics (inflammatory unstable disease with PASI >10 or 20). The choice of conventional systemic depends on several factors. For example, methotrexate might be suitable for patients with psoriatic arthritis who have no liver damage, whereas dimethyl fumarate might be a more appropriate choice for patients with no psoriatic arthritis and lymphopenia who want flexibility and prefer
oral administration. Other options might include apremilast (as a second-line conventional in subjects with affected nails and enthesitis), retinoids (for cases of pustular palmoplantar psoriasis), and cyclosporine (for short-term use, if no renal dysfunction is present). For biologics, the choice can be influenced by the presence of certain comorbidities; for example, TNF/IL-12/IL-23 for patients with IBD or candida; IL-17/17R/12/23 if tuberculosis is present, and TNF/IL-12 for women with psoriasis who are pregnant. If convenience is a factor, IL-12/23 may be preferred due to the need for less frequent injections, whereas IL-17/17R may be more suitable if a fast response is required.

Interactive Question and Answer Session

The symposium concluded with an interactive question and answer session chaired by Prof Costanzo.

The use of HLA-CW6 status as a biomarker of response to biologics was discussed. It was noted that a study by Gulliver et al. has demonstrated that positivity for the susceptibility gene is associated with improved efficacy of biologic therapies, such as ustekinumab, in patients with moderate-to-severe psoriasis. Therefore, early screening for HLA-CW6 might be a useful approach to individualising therapy.

The idea of psoriasis being a primary autoimmune condition was challenged and it was suggested that this might be characteristic of a subgroup of patients, rather than all subjects with the condition. Autoimmunity was said to be important in psoriasis, but it was acknowledged that the fact that certain patients have permanent clearance of psoriasis may indicate that the autoimmune phenotype is stronger in some individuals.

Regarding the impact of disease duration on TRM cells, it was highlighted that the number of T cells increases during the course of the disease. This may be important to consider in treatment decision-making. Early treatment initiation, as opposed to a ‘wait and see’ approach, was said to be preferred in psoriasis in that it may help prevent complications.

It was asked whether patients on ustekinumab should be switched to guselkumab, given the overlap of the mechanisms of action of the two drugs. There is evidence that this approach may be appropriate in some cases. In the NAVIGATE clinical trial, patients with psoriasis who did not fully respond to ustekinumab achieved a better response after switching to guselkumab. However, switching may not be appropriate for patients who are stable on ustekinumab. It was noted that there may also be risks in switching rapidly from one therapy to another, and that the reason for patients not responding to treatment should be investigated. Most patients respond to most biologics; lack of response is often due to noncompliance and other factors unrelated to the efficacy of the therapy.

The occurrence of Crohn’s disease in patients treated with the IL-17 inhibitor secukinumab in the study by Langley et al. presented earlier in the symposium was discussed, with some members of the audience arguing that the condition might have been pre-existent and therefore unrelated to the use of secukinumab. Abdominal complaints have been reported by patients on secukinumab, and some clinicians are increasingly referring these patients for endoscopy.

The importance of determining which patients will be long-term responders without being on drug was reiterated. It was noted that although predictors have been identified, as described by Prof Eyerich in his presentation, accurate predictions at the level of individual patients are not yet possible.

It was explained that young people with type 1 psoriasis tend to respond better to treatment. This may be due to the presence in this patient population of HLA-CW6 but also to the fact that treatment is initiated early in the life course.

The skin of patients with psoriasis was said to be an important indicator of the general activity of psoriasis; skin and extracutaneous manifestations of psoriasis may occur in parallel.

Conclusion

Differentiation of Th17 cells and production of IL-17 following stimulation of naïve T cells play a central role in psoriasis development and are
thought to be activated and maintained by the pathogenic cytokine IL-23. Clinical trial data indicate that selective inhibitors of IL-23 are associated with significant and sustained skin improvements, even when patients have stopped receiving treatment or are retreated after a period of withdrawal. Anti-IL-17 agents have also demonstrated good efficacy in psoriasis and have faster onset of action but less sustainability of response compared with anti-IL-23 agents. Despite the availability of these and other treatments, a large proportion of patients with psoriasis remain untreated. The heterogeneity of the condition and the presence of addictive behaviours may play a role in this, indicating that an individualised approach to psoriasis management is crucial to ensuring more patients receive the treatment they need.

References


27. Valeri M, Raffatelli M. Cytokines IL-17 and IL-22 in the host response to infection. Pathog Dis. 2016;74(9).


37. Mrowietz U et al. Secukinumab retreatment-as-needed versus fixed-interval maintenance regimen for


FOR REPRINT QUERIES PLEASE CONTACT: +44 (0) 1245 334450