REVEALING A CLEAR PATH TOWARDS A NEW ERA IN THE MANAGEMENT OF PSORIASIS

Summary of Presentations from the Novartis-Supported Satellite Symposium, held at the 23rd EADV Congress, Amsterdam, the Netherlands, on 9th October 2014

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Disclosure: Prof Griffiths has been a paid adviser to and/or in receipt of research grants from Actelion, Abbvie, Pfizer, LEO Pharma, Galderma, Sandoz, Novartis, MSD, Amgen, Eli Lilly, Janssen, and Incyte. Prof Reich has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis including Abbvie, Amgen, Biogen-Idec, Celgene, Centocor, Covagen, Forward Pharma, GSK, Janssen-Cilag, LEO Pharma, Lilly, Medac, MSD, Novartis, Pfizer, Vertex, and Takeda. Prof Gordon has received research support from Abbvie, Amgen, Celgene, Eli Lilly, Janssen, and Merck, and has served as a consultant to Abbvie, Amgen, Celgene, Eli Lilly, Janssen, Medac, Novartis, and Pfizer.

Acknowledgements: Writing assistance was provided by Dr Nicola Ray, Apothecom Scopemedical Ltd.

Support: The publication of this article was funded by Novartis. The views and opinions expressed are those of the authors and not necessarily those of Novartis.

Citation: EMJ Dermatol. 2014;2:42-48.

MEETING SUMMARY

The meeting provided a bench-to-bedside overview of the targeting of interleukin-17 (IL-17) for the treatment of psoriasis. Prof Kristian Reich described state-of-the-art research into the IL-17 pathway in psoriasis, and how this pathway is being targeted by a new generation of biologics. An overview of the most up-to-date Phase II and Phase III data available for agents targeting the IL-17 pathway, along with a discussion of the link between clinical efficacy and quality of life (QoL) outcomes, was presented by Prof Kenneth Gordon. Finally, Prof Christopher Griffiths discussed how the superior efficacy of the new anti-IL-17 biologics enables physicians to aim higher in terms of achievable clinical benefits for patients, reaching beyond the current accepted clinical standard of PASI 75 - a 75% reduction in symptoms on the Psoriasis Area Severity Index (PASI) - and to have a greater impact on patient QoL.

Selective Targeting of IL-17 in Psoriasis: the State-of-the-Art Research

Professor Kristian Reich

Infiltration of T-helper Type 1 (Th1) cells into regions of affected skin has long been recognised as a major component of the immunopathogenesis of psoriasis. The importance of the Th1 immune pathway in this skin disease has been demonstrated recently by the development of a psoriasis-like skin response after intradermal injection of interferon-gamma - a Th1 cytokine - into clinically normal skin.[1] Furthermore, anti-Th1 cytokines, such as IL-10, can induce a clinical improvement in psoriasis symptoms after 6 weeks of use.[2]

More recently, however, the Th17 cell was identified;[3] so named because IL-17 is the key cytokine it produces. The identification of IL-17 inhibition as a

target in psoriasis has ushered in an exciting new era in the management of psoriasis. Current treatments, such as ustekinumab (a P40 inhibitor), acting upstream to the generation of IL-17, antagonises both IL-12, a driver of the Th1 response, and IL-23, a driver of the Th17 response. Clinically, ustekinumab has been shown to improve the PASI by 75% after 12 weeks in up to 76% of patients.[4] Similar clinical efficacy has been seen with tildrakizumab (a P19 inhibitor),[5] which specifically antagonises the IL-23/Th17 axis only, implying that it may not be necessary to target the IL-12/Th1 axis for effective treatment.

To target IL-17 effectively, it should be recognised that its expression in psoriatic skin does not depend entirely on the activation of Th17 cells, and that mast cells and neutrophils also release IL-17.[6] Furthermore, IL-17 comprises six isoforms (A to F) that can form homodimers or, in the case of A and F, heterodimers. Characterisation of the mRNA profile of these IL-17 isoforms in psoriatic skin revealed an overexpression of IL-17A, IL-17C, and IL-17F in lesional compared with non-lesional skin regions.[7] More recently however, using dermal open-flow microperfusion,[8] a higher level of IL-17A protein was observed in lesional versus non-lesional skin, while there was no significant difference in IL-17F protein levels,[9] implicating IL-17A as a key target for the treatment of psoriasis.

Treatment with an anti-IL-17A agent – secukinumab: a fully human monoclonal antibody (mAb) – has been shown in a recent Phase II trial to clear neutrophils from lesional skin in patients within 2 weeks of a single intravenous dose.[2] At the same time, there was a marked reduction of the cytokine IL-8 and the chemokine CXC motif ligand 1, which are produced in keratinocytes under the influence of IL-17 and drive the chemoattraction of neutrophils into the skin. Based on these findings, a new potential paradigm (depicted in Figure 1) can be proposed, comprising two functional axes that drive psoriasis pathophysiology and the clinical symptoms seen in patients. The first is the widely recognised axis between dendritic cells and T cells. The second is an innate immune response axis where keratinocytes attract neutrophils, and the neutrophils activate keratinocytes through release of IL-17. There should be cross-talk between these two axes since it is known that Th-17 cells also release IL-17. Furthermore, in this model, IL-23 released from dendritic cells can induce neutrophils to further release IL-17.

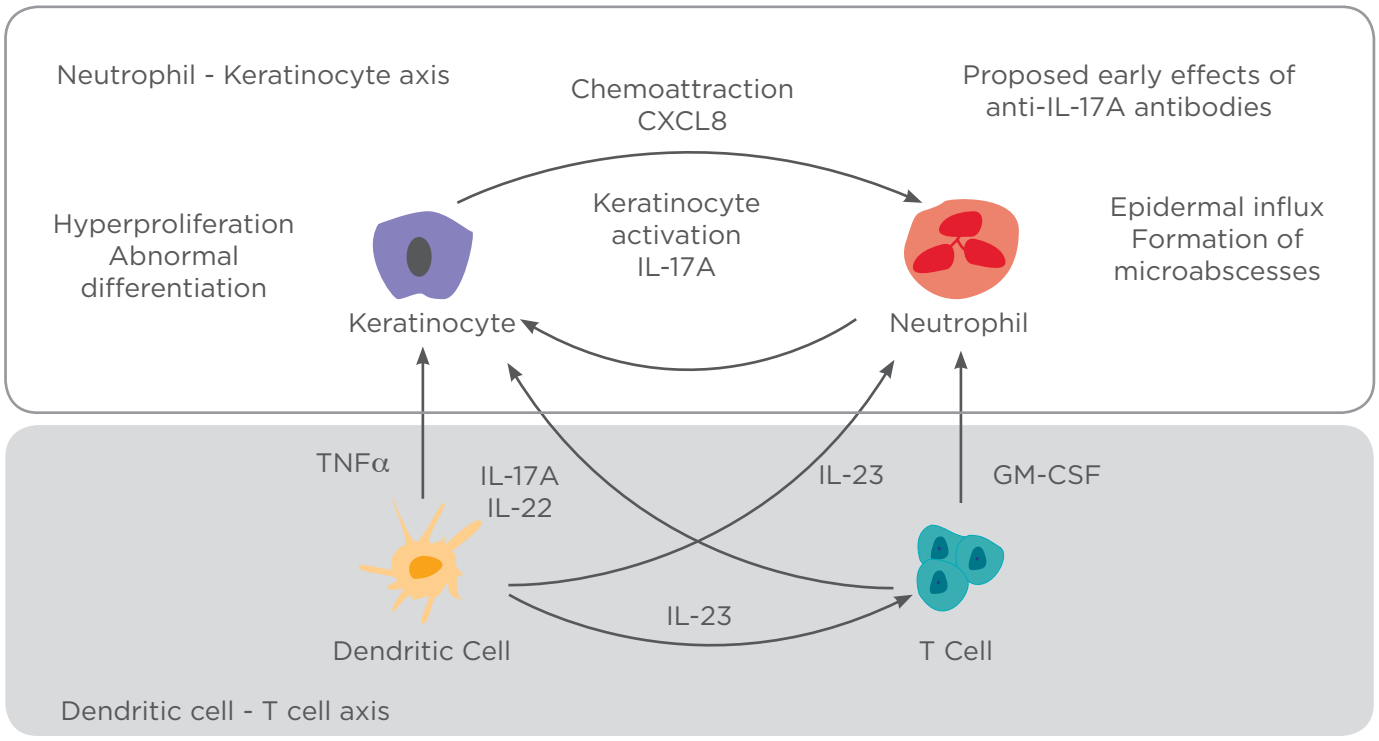


Figure 1: Proposed model of psoriasis immunopathogenesis 2.0.
CXCL8: CXC motif ligand 8; IL: interleukin; TNF: tumour necrosis factor; GM-CSF: granulocyte macrophage colony-stimulating factor.

Secukinumab has a novel mechanism of action in that it antagonises IL-17A. In doing so, it very likely has a dual mode of action by downregulating both the excessive innate and adaptive immune responses that drive the pathophysiology of psoriasis. It can be speculated that the early clinical response observed (i.e. after just 2–4 weeks of treatment) might owe more to neutrophils and the interruption of the neutrophil/keratinocyte axis than to the inhibitory effect of secukinumab on T-cells.

Challenging the Standard of Care with IL-17 Inhibition: the Evidence

Professor Kenneth Gordon

Currently, the primary endpoint in clinical trials, required for regulatory approval, in psoriasis is typically a 75% reduction in symptoms as measured by the PASI (PASI 75). It is now time to question whether this is sufficient for patients and whether, with the advent of new biologics (in particular anti-IL-17 antibodies) dermatologists should now be aiming for greater, faster, and stronger treatment responses and, ultimately, further improvements in patient QoL.

With the development of treatments such as adalimumab[10] (an antitumour necrosis factor alpha mAb) and ustekinumab[11] (anti-IL-12/23), dermatologists began to be able to achieve PASI 75 in up to 71% of patients and even PASI 90 (a 90% improvement on the PASI) in 45–50% of patients.[4,10] Psoriasis treatments are now at a stage where it is possible to extend treatment expectations further using the new generation of anti-IL-17 medications currently under development. Two of these agents, secukinumab and ixekizumab, specifically bind IL-17A, thereby preventing engagement of IL-17A (and A/F heterodimers) with the receptor.[12,13] A third IL-17 agent, brodalumab, by targeting the IL-17 receptor and inhibiting all IL-17 isoforms mediated by this receptor, has a potentially broader effect.[12,13] It is not yet known which of these IL-17 agents will be more clinically effective.

Phase II data for ixekizumab and brodalumab are now available. After 12 weeks of ixekizumab (150 mg), PASI 75 was achieved by 82% of patients. Furthermore, at the same dose PASI 90 and PASI 100 was achieved by 71% and 39% of patients, respectively.[14] In the brodalumab trial, at a dose of 140 mg/2 weeks, 77% of patients achieved PASI 75 after 12 weeks, while 72% and 38% of patients achieved PASI 90 and PASI 100, respectively.[15] Phase III studies are currently underway (NCT01695239, ixekizumab; NCT01708590, brodalumab).

Secukinumab is the first of the IL-17 agents that has been assessed in several 52-week Phase III studies, of which the two pivotal trials were recently reported in the *New England Journal of Medicine*.[16] Secukinumab at 150 mg and 300 mg (administered at Baseline, Weeks 1, 2, 3 and then every 4 weeks starting from Week 4) was compared with placebo in the ERASURE trial, or etanercept (at the indicated dose of 50 mg twice weekly, followed by 50 mg once weekly) in the FIXTURE trial. These studies found that secukinumab had superior efficacy at Week 12 (primary endpoint) to both placebo and etanercept with respect to the proportion of patients achieving PASI 75. Of patients receiving the 150 mg or 300 mg dose of secukinumab, 67% and 77%, respectively, achieved PASI 75. At 16 weeks the benefit was even greater, with 76% (150 mg) and 87% (300 mg) of patients achieving PASI 75. At the higher dose of secukinumab (300 mg), 72% of patients achieved PASI 90 (Figure 2), and 37% had a complete remission of their symptoms (PASI 100). Furthermore, with secukinumab, the response was rapid, with a 50% reduction in mean PASI score being achieved as early as 3 weeks. In the same period, etanercept achieved only a 25% reduction in symptoms, with a mean 50% reduction in PASI being achieved after 7 weeks.

Responder rate was also evaluated on the modified Investigator's Global Assessment 2011 (IGA) 0/1,[17] which was a co-primary endpoint in these studies. The IGA is a 5-point static investigator evaluation and an IGA of 1 is recorded when patient symptoms can be described as almost clear, and 0 when they are completely clear. On this measure, 76% of patients achieved a score of 0 or 1 at 16 weeks.

Furthermore, the improvements seen at 16 weeks were maintained throughout the full 52 weeks of the study, suggesting that the efficacy of secukinumab is both rapid and sustained. These findings further suggest that secukinumab, and potentially also the other anti-IL-17A medications under development, have the power to 'raise the bar' for the treatment of psoriasis.

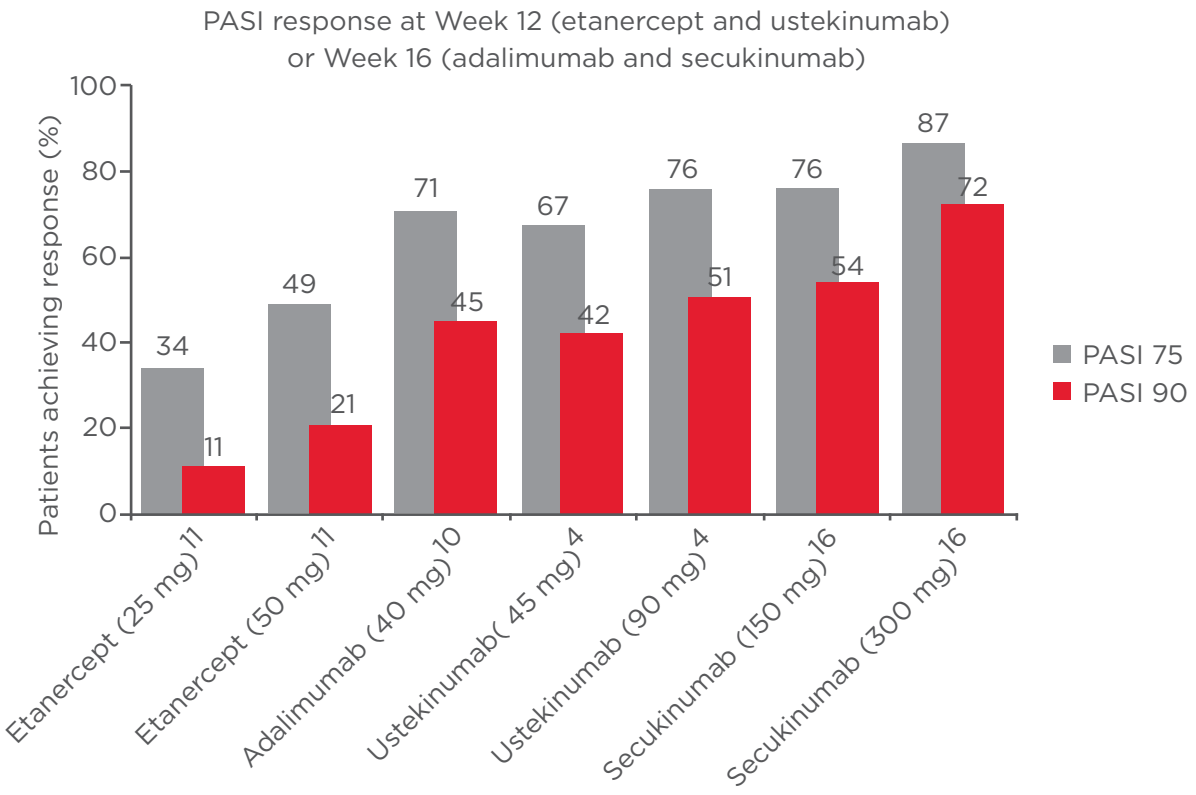
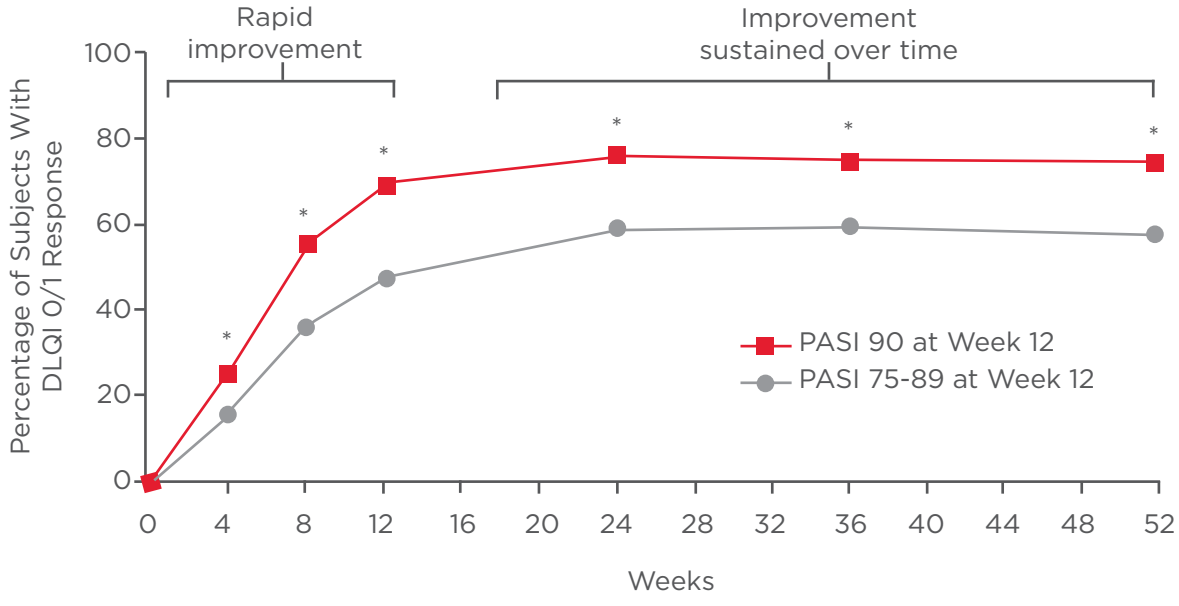


Figure 2: Psoriasis Area Severity Index (PASI) responses achieved in Phase III trials with current biologic therapies and secukinumab*.

*Figure 2 does not represent data from head-to-head trials and should not be used to make direct comparisons.



*p<0.001

Figure 3: Dermatology Life Quality Index (DLQI) responses by Psoriasis Area Severity Index (PASI) responders (pooled active treatment).

Analysis stratified by subject's PASI response at Week 12; pooled data from two Phase III studies.

Adapted from McLeod JD et al.[19]

Secukinumab has demonstrated a positive safety profile,[16] based on extensive data gathered from one of the largest psoriasis development programmes to date across Phase II and III trials, showing no unexpected safety signals up to 52 weeks. The safety profile is comparable to the current standard treatment, etanercept.

It is relevant to look beyond the clinical improvements to examine the impact of treatment on patients' overall health and QoL. Previous studies have revealed a very strong relationship (R^2=0.81) between the change in PASI and the mean change in the Dermatology Life Quality Index (DLQI).[18] Phase II data from the brodalumab programme have shown improved QoL judgements in patients achieving PASI 75.[15] Moreover, based on pooled analysis from two Phase III studies of secukinumab, psoriasis subjects who achieved PASI 90 were estimated to have a 50% higher likelihood of achieving a DLQI 0/1 response than those who achieved PASI 75-89. (Figure 3).[19]

Fresh Perspectives on Maximising Psoriasis Patient Care

Professor Christopher Griffiths

There is little doubt that IL-17 is now seen as a key driver of psoriasis, and that targeting IL-17 produces significant benefit for patients. The translation of the basic science behind IL-17 into targeted therapies will continue to improve patient care as we move forward in the era of biologics. Treating psoriasis is much more than just managing what we can see on the skin. Psoriasis has very significant psychosocial consequences: about one-third of patients experience depression or anxiety,[20,21] 1 in 10 have contemplated suicide because of their psoriasis,[20] and about 20% are on antidepressant medication.[22] These findings suggest that in some cases psoriasis can be devastating.

A recent study using qualitative methodology, which has highlighted how patients with psoriasis feel about their disease and related treatment,[23] is illustrated by the following quotations:

- "The GP was reluctant to refer me to a dermatologist. He did eventually but it took a long time."
- "There is never any offer of a consultation. You go once, they look you up and down and say you have got psoriasis, have some cream."
- "When I go to my doctors, it is not really about psoriasis because they are not going to be able to help me."

These views reveal that there is a desire for dedicated professional engagement, yet it takes a long time for patients to get access to a dermatologist in the UK, and suggests that patients cope with what they see as ineffective care by disengaging from the medical profession. Many patients with severe psoriasis report inappropriate treatment;[24] it is difficult to manage psoriasis affecting >10% of the body surface area with topical therapies, yet 57% of these patients are on topical therapy and only 15% are on biologics. A further 22% of patients receive traditional systemic therapies.

Table 1: Improvements in quality of life are most evident when PASI 90 to PASI 100 is achieved.[25]

PASI Improvement Status	Percentage of Patients with DLQI Total Score = 0 at Week 16
PASI <25 (n=333)	2.1
PASI 25 to <50 (n=139)	5.8
PASI 50 to <75 (n=170)	10.6
PASO 75 to <90 (n=288)	24.3
PASI 90 to <100 (n=255)	44.3
PASI 100 (n=192)	65.1

PASI: Psoriasis Area Severity Index; DLQI: Dermatology Life Quality Index.

QoL and psychological outcomes need to be prioritised. Current treatment guidelines suggest that we should be aiming for at least a PASI 75 and an improvement or reduction in the DLQI. We know that the greater the reduction in the PASI, the greater the reduction in the DLQI. In fact, >50% of patients achieving PASI 90 or even PASI 100 have a DLQI of 0 (Table 1),[25] which means the disease no longer has an impact on their QoL. With IL-17-targeted therapy, PASI 90 and PASI 100 are now achievable for large proportions of patients, and dermatologists treating psoriasis should now be aiming for these more ambitious outcomes.

In terms of an 'ideal therapy' for psoriasis, treatments should be convenient for the patient to take; patients report a higher degree of satisfaction with injectables versus oral medication or photo/light therapy.[26] Treatments should also be effective in both the short and long term, and they should be safe. The Phase II and III data discussed above for IL-17-targeting therapies reveal that appreciable numbers of patients have improved symptoms for up to 52 weeks. They also reveal that they have an acceptable safety profile, but this needs to be corroborated worldwide using long-term pharmacovigilance registries.

Across medicine, there is a drive for selective, patient-targeted therapy. For moderate-to-severe psoriasis patients this means that dermatologists should be prescribing the right biologic the first time they see the patient. By aggregating data on clinical, genetic, and immune biomarkers to predict and reproducibly stratify the response of psoriasis patients to biologics, healthcare can be improved and costs reduced. In the UK there is an ongoing precompetitive collaboration - Psoriasis Stratification to Optimise Relevant Therapy[27] - which brings together industry partners, academics, and patient support groups. The aim of this group is to find the stratifiers that will allow us to target therapy better, thereby providing patients with bespoke individualised treatments.

Meeting Summary

Understanding the basic science behind the Th17/IL-17 pathway and the pathophysiology underlying psoriasis has led to a new era of treatment, where both physicians and patients can now expect greater, more rapid symptom control that has long-term sustainability. With these efficacy benefits come improvements to patient QoL - an outcome that is now achievable in a greater number of patients than before. A better understanding of the prognostic markers that predict patient response to treatment will improve patient care further by allowing us to provide effective patient-targeted therapy at the first presentation of psoriasis symptoms.

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