Research Review™
EDUCATIONAL SERIES

Evolution of the immunological treatment of psoriasis

Making Education Easy 2018

Independent commentary by Professor Wolfgang Weninger

Professor Weninger received his training in clinical dermatology at the Department of Dermatology, University of Vienna Medical School, Vienna, Austria (1992-1999). Thereafter, he spent four years as a postdoctoral fellow at Harvard Medical School, Boston, USA, where he investigated the mechanisms of immune cell migration in vivo. Between 2003-2007, Professor Weninger was a Faculty member at the Wistar Institute and the Department of Dermatology, University of Pennsylvania, Philadelphia, USA. In 2007, he was appointed Chair of the Department of Dermatology, University of Sydney. He heads the Department of Dermatology at Royal Prince Alfred Hospital, as well as an independent research group at the Centenary Institute of Cancer Medicine and Cell Biology. Prof. Weninger's clinical interests relate to inflammatory skin diseases, including the use of biologic therapies, and skin cancer. His research focuses on understanding the molecular basis of skin inflammation and anti-tumour immune responses. His highly cited work has been published in journals such as Nature, Science, Cell, Nature Immunology, Immunity and the Journal of Investigative Dermatology amongst others.

Abbreviations used in this issue:

IGA = Investigator's Global Assessment
DLQI = dermatology life quality index
HRQoL = Health-Related Quality of Life
IBD = inflammatory bowel disease
IGA = Investigator's Global Assessment
PASI = psoriasis area severity index
PASI 75 = 75% reduction in PASI
PASI 90 = 90% reduction in PASI
PASI 100 = 100% reduction in PASI
PBS = Pharmaceutical Benefits Scheme
PsA = psoriatic arthritis
Th17 = T-helper 17 cells
TNF = tumour necrosis factor
UV = ultraviolet

RESEARCH REVIEW
The Australian Perspective Since 2007

This literature review focuses on the evolution of treatments for psoriasis which has mirrored the increasing understanding of the important role the interleukin 23 (IL-23)/T-helper 17 cell (Th17) immune pathway plays in the immunopathogenesis of psoriasis. The intended audience for this review is dermatologists who manage psoriasis, as well as physicians who manage immune-mediated inflammatory diseases which may have psoriasis as a co-morbidity.

Introduction

Psoriasis is a complex, chronic, multifactorial, inflammatory disease, which can manifest in many different forms.[1-3] The most common type is chronic plaque psoriasis, which affects approximately 85%–90% of psoriatic patients.[4] Clinical signs are characterised by well-demarcated, thick reddish (erythematous) plaques covered by silvery white scaling.[5] Typically, the plaques are distributed symmetrically on knees and elbows, the trunk, the scalp and the sacral region.[6]

According to an Australian consensus statement,[3] two indices can be used to describe psoriasis severity. Patients with mild psoriasis have a psoriasis area severity index (PASI) of ≤10 and a dermatology life quality index (DLQI) ≤10. Patients with moderate-to-severe psoriasis have a PASI >10 and/or a DLQI >10.

The prevalence of psoriasis varies according to race, geography and environmental factors,[7] with rates in adults from various countries ranging between 0.51% to 11.43%.[8] In most developed countries, the prevalence is reported to be between 1.5% and 5%.[9, 10] In Australia, estimates of prevalence range from 2.30% to 6.6%.[10, 11]

Psoriasis is increasingly being seen not just as an inflammatory skin disorder, but rather as a systemic inflammatory disorder that is associated with an increased risk of comorbid conditions (**Figure 1**).[12] Psoriatic arthritis (PsA) develops in up to 30% of patients with psoriasis and can lead to joint damage and functional impairment if left untreated.[13] An Australian study of tertiary dermatological practices found that 9% of patients with chronic plaque psoriasis and no previous diagnosis of PsA had undiagnosed PsA.[14] In addition, psoriasis has been associated with an increased incidence of cardiovascular disease,[15-17] obesity,[18] type 2 diabetes,[19, 20] metabolic syndrome[21] and lymphoma.[22] These factors are more strongly associated with severe psoriasis. A large population-based study reported that the risk for any other type of serious illness was 11% higher for people with mild psoriasis, 15% higher for patients with moderate psoriasis and 35% higher for those with severe psoriasis.[23]

Studies in Australia[24, 25] and worldwide[25-27] have shown that psoriasis imposes a significant psychosocial burden on patients, affecting their personal and professional relationships, social interactions and health-related quality of life (HRQoL). The decrease in the patient's HRQoL associated with psoriasis has been similar to that reported in cancer and diabetes.[28] Anxiety,[29, 30] depression,[30, 31] suicidal ideation,[30] smoking[32] and alcohol consumption[33] are more common in patients with psoriasis (**Figure 1**). The economic burden of psoriasis to both the individual and healthcare system is also substantial.[34-36]

The aetiology of psoriasis is multifactorial, and involves genetic, environmental and immunologic factors (**Figure 1**).[12, 37]

- *Genetic*: The genetic component of psoriasis is reflected by a higher incidence of cases in families (including those in Australia) of affected individuals.[5, 38] Numerous different gene loci, including the *HLA-Cw6* gene, and epigenetic alterations have been associated with the predisposition and progression of the disease.[5, 39, 40]
- *Environmental:* Exacerbations of psoriasis can be triggered by various environmental factors including cold, trauma, infections (e.g., streptococcal, human immunodeficiency virus), alcohol and certain drugs.[5]
- *Immunologic:* Psoriasis involves a complex interrelationship between activated and proliferating epidermal keratinocytes and several immune cells including T cells, neutrophils, dendritic cells and macrophages.[37, 41] Cytokines such as tumour necrosis factor-α (TNF-α), interleukin-23 (IL-23) and interleukin-17 (IL-17) have all be implicated.

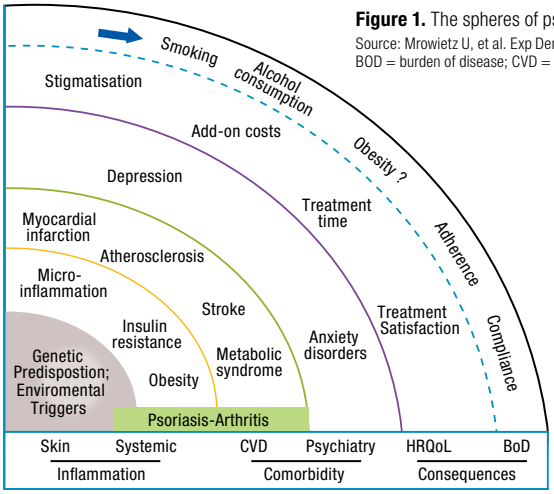
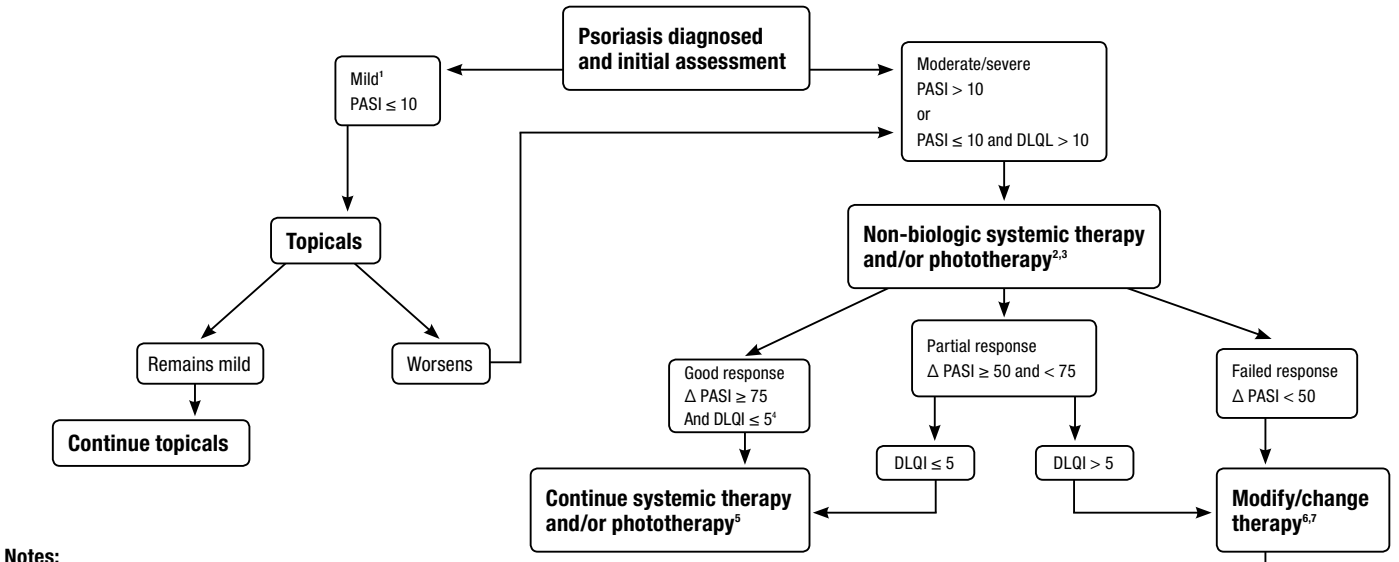


Figure 1. The spheres of psoriatic disease.[12]
Source: Mrowietz U, et al. Exp Dermatol. 2014;23(10):705-709.
BOD = burden of disease; CVD = cardiovascular disease

Expert Comment

While considerable progress into the understanding of chronic plaque psoriasis pathogenesis has been made, it is still not entirely clear whether this condition is a true autoimmune condition (comparable for example to type I diabetes or multiple sclerosis). The fact that psoriasis patients respond to immunosuppressive therapy, the link to certain HLA genes, and the identification of autoantigens argue for an autoimmune basis. However, the chronic inflammation observed in the skin typically does not result in scarring; indeed, thick, long- standing psoriasis plaques may leave behind normal skin following successful therapy. In addition, it is now clear that cytokines, in particular IL-17 and IL-23, play a central role in disease pathogenesis. Thus, some experts consider plaque psoriasis an autoimmune condition rather than an autoinflammatory disease. Another point to consider is that psoriasis is a heterogeneous group of diseases of the skin and skin adnexae, which may explain the different response of patients to certain drugs. Together, we still need to learn a lot about psoriasis so that we can optimise treatments for our patients.



Notes:

1. In absence of modifying features such as visible site, genital, palmoplantar, nails involvement, pruritus with excoriation.
2. Appropriate time to review varies with each treatment and the range is 6–24 weeks.
3. Non-biologic therapies include methotrexate, cyclosporin and acitretin.
4. Psoriasis area severity index (Δ PASI) ≥75 but dermatological quality of life index (DLQI) ≥5 may occur if modifying features such as the visible site, genital, palmoplantar, nail involvement or pruritus are present or the response is discordant with patient's expectations. Physician assessment whether to continue, modify or change therapy.
5. Continuation/discontinuation is modulated by toxicity and contraindication.
6. Treatment change to take into account patient wishes.
7. In addition to change of treatment, modify may include adding topicals, adding other systemic treatment, increasing dose or frequency or hospital admission.
8. The Australian consensus group propose that two of four therapies as reasonable and best practice. The current requirement of the Australian reimbursement body, the Pharmaceutical Benefits Scheme, is three of four therapies

Figure 2. Treatment algorithm for patients with psoriasis in Australia.[3]
Source: Baker C, et al. Australas J Dermatol. 2013;54(2):148-154.

Immunological treatment of psoriasis

The evolution of treatments for psoriasis has mirrored the ever increasing understanding of the immunopathogenesis of this disease.[37]

Early immunological treatments

The first breakthrough in systemically treating psoriasis as an immune disease was the use of the immuno-modulating drugs cyclosporin and methotrexate which provided broad non-specific immunosuppression.

- Cyclosporin. In 1979, cyclosporin A was first used to treat psoriatic skin eruptions. Cyclosporin-induced immuno-suppression was interpreted as indicating that the immune system was involved in the pathogenesis of psoriasis.[42] Cyclosporin A has been a key agent for the treatment of severe psoriasis and is still recommended as a first-line option for moderate-to-severe disease (**Figure 2**).[3]
- Methotrexate. Introduced in 1958, methotrexate is a folic acid antagonist that has immunosuppressive, cytostatic and anti-inflammatory activity.[43] It is inexpensive and is recommended as first-line treatment for those with moderate-to-severe psoriasis (**Figure 2**).[3,44] The psoriasis area severity index (PASI) 75 response rate for methotrexate is typically relatively low (<50%).[45]
- The retinoid acitretin is also used to systemically treat psoriasis (**Figure 2**). This non-immunosuppressive agent may offer an option for patients with contraindications to immunosuppression, such as patients with infections or cancer-prone patients.[46-48]

The earlier immunological systemic agents can be associated with serious adverse effects. For example, cyclosporin is associated with nephrotoxicity and arterial hypertension,[49] and methotrexate has been associated with hepatotoxicity and myelosuppression.[50] Given the need to find alternative therapies, researchers began to increasingly focus their attention on the pathogenic mechanism behind psoriasis.

Expert Comment

Additional therapies for chronic plaque psoriasis include ultraviolet (UV) light therapy alone or in combination with certain drugs. Despite the fact that UV therapy has been a mainstay of psoriasis treatment for decades, we still do not completely understand its mechanisms of action. Nevertheless, UV-induced immunosuppression may play a role in the excellent response of many psoriatic patients to this treatment regimen. Unfortunately, however, light therapy may have unwanted side effects including accelerated skin aging and the induction of skin cancer. Thus, with the advent of biologic therapies, UV treatment may be less important in the future. As a second point, the response of patients with psoriasis to immuno-suppressive drugs such as cyclosporin and methotrexate has been used as an indicator for the autoimmune pathogenesis of psoriasis. However, these drugs have pleiotropic effects beyond the immune system, including potential anti-proliferative effects on keratinocytes. Given the unfavourable safety profile of older "immuno-suppressive" drugs and retinoids, regulatory bodies and dermatologists will have to consider in the future whether it is ethically justifiable to put psoriasis patients on such drugs instead of biologics.

Newer biologic treatments

In the past decade, research has highlighted the importance of the IL-23/Th17 pathway (**Figure 3**).[37, 41] In psoriasis, IL-23 aids the differentiation of naïve T-cells into a distinct T-cell lineage (Th17), which is responsible for the secretion of the pro-inflammatory IL-17. In turn, IL-17 has broad inflammatory effects on keratinocytes and a variety of immune cells found in the skin.[37, 41] The greater understanding of the IL-23/Th17 pathway has led to the development of targeted biological therapies. In particular, newer biologics that target IL-23 and IL-17 have been developed.

Expert Comment

It is now clear that the IL-23/IL-17 cytokine axis is central to the pathogenesis of chronic plaque psoriasis. IL-17 is a group of effector cytokines with many downstream pro-inflammatory effects. In the skin, IL-17A induces the activation of keratinocytes in the epidermis, which in turn secrete a large number of cytokines and chemokines. The latter attract additional immune cells, most prominently neutrophils, into the skin. Several cell types can produce IL-17, including CD4+ helper T (Th) cells, gamma-delta T cells and innate lymphoid cells. The best understood of those are Th cells, which come in two flavours. One subset develops in the absence of IL-23; these cells are thought to have immune-protective function. These cells are found, for instance in the gut mucosa. A second subset, which requires IL-23 for their induction and maintenance, are pathogenic T cells found in psoriasis. Since IL-23 is upstream of these Th17 cells, it is considered a regulatory cytokine. Given that IL-17A can have both protective and damaging functions, it is worthwhile considering whether pan-inhibition of this cytokine is of advantage in all circumstances. In fact, some of the side effects observed under IL-17A blockade, such as fungal infections and worsening of inflammatory bowel disease, may be explained by interfering with the immune-protective activities of Th17 cells.

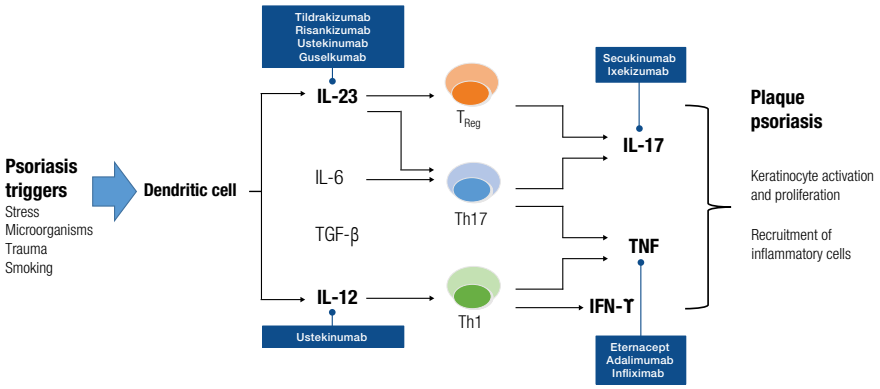


Figure 3. The IL-23/Th17 pathway and biologics targeting it.

TNF inhibitors

TNF-α inhibitors have a well-established role in the treatment of various inflammatory disorders and were amongst the first biologics to be used in psoriasis.[37, 51] TNF-α inhibitors approved for use in psoriasis include etanercept, a human TNF receptor fusion protein,[52] infliximab, a humanized chimeric anti-TNF monoclonal antibody,[53] and adalimumab, a fully human monoclonal antibody.[54] However, the broad mechanism of action of TNF inhibitors is associated with safety issues such as increased bacterial and viral infections and the potential for increased risk of cancer.[55]

Expert Comment

Literally millions of patients with autoimmune diseases, such as chronic plaque psoriasis, rheumatoid arthritis and IBD, have been treated with TNF inhibitors over the past 10 to 15 years. Thus, there is a high level of experience with these drugs and most dermatologists feel confident when prescribing them to psoriasis patients. In addition, they have been used in complex patients, for example psoriasis patients co-infected with HIV or hepatitis C virus. Further, the excellent efficacy in psoriatic arthritis still make TNF inhibitors a first-line choice for new psoriasis patients. Nevertheless, based on the success with IL-17 blockers, patients nowadays expect high efficacy rates, for example PASI 90 responses in the range of over 80%. Thus, in the future the anti-TNF family may see some decline in usage based on lower efficacy rates.

IL-12/23 inhibitors

Early after its identification in the year 2000, IL-23 was recognized as playing a crucial role in the pathogenesis of chronic psoriasis. This upstream regulatory cytokine acts early in the inflammatory cascade in psoriasis to maintain and expand the Th17 cell phenotype and so it plays a critical role in the production of downstream effector cytokines, such as IL-17A, IL-17F and TNF (**Figure 3**).[37, 56, 57]

Ustekinumab was the first approved biologic agent to target IL-23 (initial Australian Register of Therapeutic Goods registration in 2009).[58] This fully human monoclonal antibody inhibits the IL-12/23p40 subunit, thus inhibiting the action of both IL-12 and IL-23. In clinical trials, ustekinumab has demonstrated efficacy and is generally considered safe and well-tolerated.[59,60] Evidence from longitudinal, real-world studies[61] and long-term follow-up[62] support these outcomes.

Expert Comment

Ustekinumab was originally developed with the idea of blocking the p40 subunit of IL-12. Before the recognition of the importance of IL-17/23, psoriasis was considered a Th1 disease. Th1 cells mainly produce interferon-gamma, and are induced by IL-12. Co-incidentally, IL-23 shares the p40 subunit with IL-12; thus, it is likely that ustekinumab acts via inhibition of IL-23, rather than IL-12. Ustekinumab has been popular with patients and dermatologists due to its long half-life and consequent less frequent dosing, as well as its favourable safety profile.

IL-17A inhibitors

Skin biopsies from psoriatic lesions show increased levels of IL-17A and T cells, as well as higher IL-17A mRNA expression, compared with skin from healthy volunteers.[63] Given the discovery of the role IL-17 plays in inflammation and keratinocyte activation (**Figure 3**),[37, 64] it is unsurprising that IL-17 inhibitors have proven efficacy in psoriasis.

Secukinumab was the first IL-17A inhibitor to be approved in Australia in 2015 for the treatment of moderate-to-severe plaque psoriasis,[65] followed by ixekizumab a year later.[66] Secukinumab is a fully human immunoglobulin G1κ monoclonal antibody,[67] while ixekizumab is a humanized immunoglobulin G4 monoclonal antibody. Brodalumab, which also targets the IL-17 receptor, has recently been approved for the treatment of moderate-to-severe plaque psoriasis in the USA and Europe.[68, 69]

Common adverse side effects noted in clinical trials with IL-17 inhibitors include upper respiratory tract infections, headache, nasopharyngitis, mild neutropenia, *Candida albicans* mucocutaneous infections and diarrhea.[41, 65, 70] The increase in *Candida* infections with these IL-17 inhibitors is likely a reflection of the role of this cytokine in the innate immune response against infection from this organism.[71] IL-17A has a protective function in the intestinal tract, with studies in mice targeting IL-17 and the IL-17 receptor resulting in exacerbated IBD.[72] IBD flare or new onset IBD have been reported in a small proportion of psoriasis patients treated with ixekizumab (0.29 per 1000 patient-years)[73] or secukinumab (0.33 per 100 patient-years).[70] The Australian secukinumab[65] and ixekizumab[66] prescribing information notes that caution should be exercised when prescribing these agents to patients with IBD.

Expert Comment

IL-17 inhibitors have raised the bar in terms of treatment responses. PASI 90 or 100 responses, 90-100% clearance of skin lesions, is commonly achieved with these drugs. This is higher than success rates with TNF inhibitors and anti-p40. The safety profile of IL-17 inhibitors is also favourable. Nevertheless, our experience with this group of drugs is considerably less compared with anti-TNFs, as they have only been approved for a few years. In addition, the fact that IL-17 exerts some protective, physiologic functions, for example in the gut or in fungal infections, raises some questions regarding long-term safety of these drugs.

IL-23 inhibitors

As previously noted, IL-23 maintains the differentiation of naïve T-cells into a distinct T-cell lineage, Th17, which is responsible for the secretion of the pro-inflammatory IL-17 (**Figure 3**).[37] In light of this critical role played by IL-23, a new category of biologic agents that selectively inhibits the p19 subunit of IL-23 have been developed.[57]

Agents in this class include tildrakizumab,[74] risankizumab[75] and guselkumab.[76-79] These agents may offer several advantages over distal blockade of IL-17A or its receptor, or IL-12/23p40 inhibition. IL-12 has been implicated in tumour immune surveillance and defence against intracellular pathogens,[80] and so sparing IL-12 may preserve these roles. Moreover, contrary to IL-17 inhibition, clinical studies suggest that IL-23p19 blockade does not increase the risk of *Candida* infection, nor is it associated with IBD worsening.[74-79] However, long-term studies will be required to fully determine the tolerability profile of this class of agents.[41]

Expert Comment

As mentioned above, IL-23 is a regulatory cytokine upstream of IL-17. IL-23 is necessary for the induction of IL-17A in pro-inflammatory helper T cells and other IL-17 producing cells. However, protective Th17 cells do not rely on IL-23. This provides compelling rationale for interfering with IL-23 in psoriasis (and other autoimmune conditions). While IL-23 inhibitors have limited availability for psoriasis patients in Australia, data from clinical trials (see below) show efficacies similar to IL-17 inhibitors and a very favourable safety profile. Given the long experience with ustekinumab, it is plausible that IL-23 inhibitors will be a major player in the field of biologic therapy in the future.

Focus on guselkumab

Guselkumab, a fully human monoclonal antibody against the IL-23p19 subunit of IL-23, is indicated in Australia for the treatment of adult patients (18 years or older) with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[81]

The efficacy and tolerability of guselkumab has been investigated in three multicentre, randomised, double-blind trials (VOYAGE 1,[77] VOYAGE 2,[78] and NAVIGATE[79]) that enrolled patients aged ≥18 years with moderate-to-severe plaque psoriasis who were eligible for systemic therapy or phototherapy.

In the VOYAGE trials, 1829 patients were randomised to guselkumab, adalimumab or placebo. The studies comprised: a placebo-controlled period (weeks 0–16), after which patients taking placebo crossed over to receive guselkumab through week 48; and an active-controlled period versus adalimumab (week 0-48).

Both VOYAGE 1 and VOYAGE II trials demonstrated the efficacy of guselkumab. At week 16, the proportion of patients attaining a PASI 90, or an Investigator's Global Assessment (IGA) score of 0 ("cleared") or 1 ("minimal"), was significantly greater with guselkumab (p<0.001) than with adalimumab or placebo **(Table 1)**.

Table 1. Efficacy outcomes from the VOYAGE I and VOYAGE II trials in patients with moderate-to-severe plaque psoriasis[77, 78]

		VOYAGE I			VOYAGE II		
Patients[a] (%)		Guselkumab (n=329)	Adalimumab (n=334)	Placebo (n=174)	Guselkumab (n=496)	Adalimumab (n=248)	Placebo (n=248)
IGA 0/1[b]	Week 16	85.1*†	65.9	6.9	84.1*†	67.7	8.5
	Week 24	84.2*†	61.7		83.5*†	64.9	
	Week 48	80.5†	55.4		NA	NA	
PASI 90[b]	Week 16	73.3*†	49.7	2.9	70.0*†	46.8	2.4
	Week 24	80.2*†	53.0		75.2*†	54.8	
	Week 48	76.3	47.9		NA	NA	

Both VOYAGE trials compared guselkumab (100 mg at weeks 0 and 4 and every 8 weeks thereafter) with placebo or adalimumab (80 mg at week 0 and 40 mg at week 1, followed by 40 mg every other week thereafter).

[a]Patients had an Investigator's Global Assessment (IGA) score of ≥3 ("moderate") on a 5-point scale of overall disease severity, a PASI score ≥12, and a minimum affected body surface area (BSA) of 10%.

[b]Primary endpoint (vs placebo). *p<0.001 vs placebo, †p<0.001 vs adalimumab.

The phase III NAVIGATE trial showed that patients with moderate-to-severe psoriasis (n=268) who did not respond with ustekinumab could receive significant benefit by switching to guselkumab.[79] Nonresponders (IGA ≥2) at 16 weeks after initial treatment with open-label ustekinumab (45 mg or 90 mg at weeks 0 and 4) were randomised to guselkumab (100 mg at weeks 16, 20 and every 8 weeks thereafter) or to continue ustekinumab (every 12 weeks).

Twelve weeks after randomisation, a significantly greater proportion of patients treated with guselkumab than ustekinumab achieved an IGA 0/1 with a ≥2 grade improvement (31% vs 14%; p=0.001). A greater proportion of patients treated with guselkumab than ustekinumab achieved a PASI 90 or PASI 100 (**Figure 4**) at week 52.

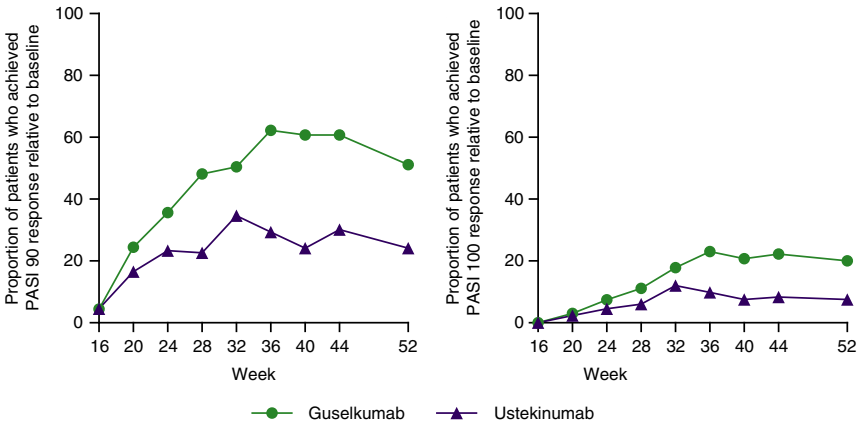


Figure 4. Proportion of patients who achieved PASI 90 or PASI 100 response relative to baseline from week 16 through week 52.

Source: Langley RG, et al. Br J Dermatol. 2018;178(1):114-123.

The most common (≥1%) adverse reactions associated with guselkumab include non-serious infections (upper respiratory infections, tinea infections, and herpes simplex infections), headache, injection site reactions, arthralgia, diarrhea, and gastroenteritis.[82] Additional studies will be able to provide better information regarding the long-term efficacy and safety profiles of guselkumab and other agents in this class of biologics.

Expert Comment

The results for guselkumab in clinical trials are very promising indeed. Guselkumab seems superior to ustekinumab and adalimumab in terms of efficacy, with a comparable safety profile. Although "real life" treatment and long-term safety data are obviously not available yet, IL-23 inhibitors appear very promising, in particular for patients who have failed one or more of the existing biologic therapies.

Expert's concluding comments

The advent of biologic therapies, with high efficacies and favourable safety profiles, have revolutionised the treatment of autoimmune conditions, including chronic plaque psoriasis.

Indeed, these are exciting times for patients and their families, as previously devastating diseases can now be managed with little side effects for long periods of times. In addition, the use of anti-cytokine therapies have taught us a lot about the pathogenesis of these conditions, and this information can be used to further develop new therapies and optimise treatment regimens and patient monitoring. IL-23 inhibitors promise to be highly efficient and safe therapies that will complement the existing armamentarium of drugs available to dermatologists.

Take home messages

- The aetiology of psoriasis is multifactorial, and involves genetic, environmental and immunologic factors.
- Research has highlighted the importance of the IL-23/Th17 pathway in the pathogenesis of psoriasis.
- In psoriasis IL-23 maintains the differentiation of naïve T-cells into a distinct T-cell lineage, Th17, which is responsible for the secretion of the pro-inflammatory IL-17. In turn, IL-17 has broad inflammatory effects on keratinocytes and a variety of immune cells found in the skin.
- The greater understanding of the IL-23/Th17 pathway has led to the development of targeted biological therapies.
- The efficacy and tolerability profile of novel biologics that target IL-17 and IL-23 confirm the central role that these cytokines play in psoriasis.

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