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OPINION ARTICLE

Selective Il-23 Inhibitors: The New Kids on the Block in the Treatment of Psoriasis☆

Inhibidores selectivos de la IL-23: los recién llegados al tratamiento de la psoriasis

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The last two decades have been of great enthusiasm in the treatment of psoriasis. Our understanding of the pathogenesis of psoriasis has significantly expanded during these years, leading to the development of highly effective targeted therapies, the so-called biologic agents.[1] These therapies revolutionized the treatment of psoriasis and provided a new paradigm in the management of this highly impacting chronic skin disease.[1,2] Instead of rotational use of different drugs with cumulative end-organ toxicity and drug interactions, such as cyclosporine, acitretin and methotrexate, biological therapy can be potentially used continuously until loss of efficacy.[1]

The development of tumour necrosis factor (TNF)-α inhibitors was probably the first major step. Psoriasis was seen mainly as a T helper/cytotoxic type 1 cells (Th/Tc1) disease, and TNF-α was considered a major effector cytokine in psoriasis pathogenesis.[1] Later, with the identification of interleukin (IL)-12 as a primary mediator of Th1 response in psoriasis, a new biological agent targeting this cytokine started to be developed: ustekinumab.[1,3] IL-12 is a heterodimeric cytokine composed of 2 subunits (p40 and p35) and ustekinumab targets p40 subunit.[1,3] What would be known later was that by blocking the p40 subunit, IL-23, which is composed of the same p40 subunit and the IL-23-specific subunit p19, was also being inhibited, unveiling crucial role of IL-23 in the pathogenesis of psoriasis. Thus, ustekinumab was, in fact, the first agent to target IL-23, although it also inhibited IL-12, bringing a new mechanism of action for the treatment of psoriasis, with a better safety profile than TNF-α inhibitors, but mainly a very convenient dosing regimen (every 12 weeks). More recently, as the IL-23/Th17 axis, and essentially the inflammation driven by IL-17 was being recognized as the main pathogenic pathway in psoriasis, agents targeting this cytokine (secukinumab, ixekizumab and brodalumab) were developed and shown unprecedented efficacy results, leading to a paradigm shift in the medical management of psoriasis, where completely or almost completely clearance of skin has become the new therapeutic goal.[1–4] Even though, this therapy class is associated with some safety concerns, particularly, mucocutaneous candidiasis (reflecting the key role IL-17 plays in mucocutaneous defense against extracellular organisms such as Candida) and the risk of worsening inflammatory bowel disease, known to be increased in psoriasis patients.[1,3–5] Therefore, this led to the contraindication of these agents in psoriasis patients with Inflammatory bowel disease.

Along this last years, it has also become clearer that IL-12/Th1 axis do not exert an essential role in psoriasis contrary to IL-23/Th17 axis: p19 mRNA is increased

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in lesional versus non-lesional skin, while no significant difference in IL-12p35 mRNA has been observed and predisposition to psoriasis is linked with genes of the IL-23/Th17 axis, but not with those of the IL-12/Th1 pathway.[1,6]

For all these reasons, several agents specifically targeting IL-23p19 subunit started to be developed since these agents could offer advantages in efficacy and safety with respect to currently available biologic therapies. Currently, one selective IL-23 inhibitor (guselkumab) is already approved for the treatment of psoriasis, while tildrakizumab and risankizumab are in late stages of development for psoriasis.[6,7] Confirming the crucial role of the IL-23/IL-17 axis in the pathogenesis of other immune-mediated diseases, these agents and others (brazikumab, mirikizumab) are currently either in phase 2 trials or are awaiting testing in psoriatic arthritis and Crohn's disease.[3,8]

The clinical results of psoriasis trials have been impressive. The selective inhibition of IL-23 has been shown to result in rapid resolution of the clinical and histologic features associated with psoriasis, with a very convenient dose regimen (every 8-12 weeks), and the comparative head-to-head trials have demonstrated their superiority to etanercept (tildrakizumab), adalimumab (guselkumab), and ustekinumab (risankizumab), and the response rates in some cases seem to be numerically superior even to those of IL-17 blockers.[9–11]

The high efficacy rate of IL-23 inhibitors (mainly guselkumab and risankizumab) is probably related to the upstream effect in the IL-23/IL-17 cytokine pathway. IL-23 has a key role in the development, expansion, and activity of pathogenic Th/Tc17 cells and stimulates the expression of multiple effector cytokines; thus, its neutralization reduces the expression of IL-17A but also other cytokines, such as, IL-17F, IL-21, and IL-22, that also contribute to psoriasis pathogenesis, though to a lesser extent.[1,6,7] Additionally, targeting IL-23p19 avoids effects on the IL-12/Th1 axis, observed with p40 inhibitors such as ustekinumab. IL-12 inhibition may even have a negative effect in the treatment of psoriasis, as shown in an imiquimod murine model, where IL-12 been shown to exert a regulatory function inhibiting the infiltration of an IL-17-committed $\delta\gamma$ T-cell subset and initiating a protective transcriptional program that limits skin inflammation through IL-12 receptor signaling in keratinocytes.[1,6,7]

In addition, in contrast to other biological agents, interfering with IL-23 may be associated with prolonged and sustained duration of clinical response. In 2 early clinical studies with risankizumab relatively long-term treatment responses were observed in some patients with just a single dose[10]; in the phase 3 clinical trial of guselkumab, VOYAGE 2, 56 of 182 patients who were re-randomized to placebo/withdrawal at week 28 maintained a high clinical response (PASI 90 response) at week 72. Interestingly, maintaining this response after withdrawal of the drug was associated with continuous suppression of IL-17A, IL-17F and IL-22, while loss of response was associated with increased levels of these circulating cytokines.[12]

This long-term clinical responses can be explained in part by promoting transdifferentiation of Th17 cells into regulatory T cell (Treg), restoring an altered Treg cell function (shown by the relatively high levels of FoxP3 (forkhead box protein 3) mRNA in post-treatment biopsy specimens of patients treated with risankizumab), as well as a profound effect of upstream blockade of the IL-23/IL-17 axis, impairing survival or phenotypic change of pathogenic Th/Tc-17 cells, reducing the expression of multiple pro-inflammatory cytokines that depend on IL-23 (IL-17A, IL-17F, IL-21, and IL-22).[1,6,7,10,12]

Naturally, when facing drugs with such a high efficacy, safety concerns may arise. Nevertheless, to date, safety data from the clinical trials did not reveal specific patterns among serious AEs.[9–11] No significant increase in the rate of malignancy, tuberculosis, or serious infections were observed with the use of these agents.[9–11] Avoiding the blockade of the IL-12/IFN-γ axis, which does not seem relevant in psoriasis pathogenesis, the immune response and surveillance mediated by this axis is preserved. IL-12 is required for appropriate Th1 response and may have potential role in tumor immune surveillance and in host defense against intracellular pathogens, due to the role of IL-12 in the production of interferon (INF)-γ from T-cells and natural killer cells.[1] In contrast to IL-17A blockers, no significant increase in candida infections has been reported in patients treated with any anti-IL-23p19 agent.[9–11] IL-23-specific blockade results in a lower production of IL-17A by Tc/Th17 cells, while preserving an overall adequate cytokine response, as other IL-17A-producing cells (mast cells, innate lymphoid cells and neutrophils) remain functional.[1] Also, no exacerbation or new-onset of inflammatory bowel disease has been reported with any IL-23 inhibitor[9–11]; in fact, risankizumab is actually being tested in phase II trials for the treatment of Crohn's disease, showing promising results.[13] These findings are clinically relevant, as candida infection are more frequent in obese and diabetes patients (comorbidities frequently associated with psoriasis) as well as inflammatory bowel disease that is more frequent in psoriasis patients than general population.[1]

Selective IL-23, mainly guselkumab and risankizumab have shown exceptional rates of complete or near complete clearance of skin disease combined with a convenient dosing regimen (every 8 or 12 weeks, respectively), and a very acceptable safety profile so far, without the broad effect on immune system of TNF-α inhibitors, the effects on the IL-12/Th1 axis of ustekinumab and the side effects of the IL-17 inhibitors. Also, in some patients, long-term remission of psoriasis activity may start to be a possibility. Finally, preliminary data on psoriatic arthritis and Crohn's disease are also promising.

If the real-world evidence and other head-to-head trials corroborate these initial trials findings, we can anticipate that these agents may take the front in the treatment of psoriasis, offering a more effective, safe and convenient alternative to the current biologic treatment repertoire for psoriasis, actually representing a step forward in the treatment of patients with psoriasis, but also with psoriatic arthritis and Crohn's disease.

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