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Brief communication

When anti-TNF fails, anti-IL12-23 is an alternate option in psoriasis and psoriatic arthritis

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ABSTRACT

Patients with psoriasis and psoriatic arthritis respond to anti-TNF therapy, but not all patients maintain effective response, and some do not respond. In this article, we demonstrate the role of a new pathogenetic pathway to some extent TNF-independent in these patients. Anti-IL12-23 is a new and alternate mode of therapy for patients with recalcitrant response to anti-TNF.

Quando anti-TNF não obtém sucesso, anti-IL-12-23 é opção alternativa na psoríase e na artrite psoriásica

Palavras-chave:
Psoríase
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RESUMO

Pacientes com psoríase e artrite psoriásica respondem à terapia anti-TNF, mas nem todos os pacientes mantêm uma resposta efetiva e alguns não respondem. Nesse artigo, demonstramos o papel de uma nova via patogenética que, até certo ponto, independe de TNF nesses pacientes. Anti-IL-12-23 é um modo terapêutico novo e alternativo para pacientes com resposta recalcitrante à medicação com anti-TNF.

Introduction

Tumor necrosis factor alpha (TNF-α) is a proinflammatory cytokine involved in inflammation of the skin and synovium, making it a logical target for the treatment of psoriasis (Ps) and psoriatic arthritis (Psa). It has been demonstrated that this cytokine plays a fundamental role in the pathogenesis of both Ps and Psa through several pathogenetic mechanisms, including the expression of adhesion molecules to the surface of endothelial cells, keratinocytes, and dendritic cells promoting leukocyte migration.[1] In the joints, it triggers the production of a variety of cytokines, which in turn increase the inflammatory cascade. In the skin, TNF-alpha

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also leads to a decrease in the apoptosis of keratinocytes, thus contributing to a hyperproliferative epidermis. Anti-TNF-alpha has the potential to provide symptomatic relief and help prevent disease progression in Ps and Psa by decreasing joint and skin inflammation.[2]

Guidelines derived from evidence based clinical trials and from clinical practice has established the clinical usefulness of all the three anti-TNF agents for the treatment of axial and peripheral P and Psa. These agents selectively block the role of TNF-alpha and proved to be effective in clinical trials and also in clinical practice.[3] All the three agents – infliximab, etanercept, and adalimumab – have shown marked improvements in disease activity in the PASI-75 of the skin and in disease activity indexes ACR20, ACR50, ACR70 when compared to patients treated with placebo. However, in our and others' experience, not all patients respond to these agents, and in some of them, the initial response is lost after variable periods of time.[4,5] Although switching to another anti-TNF can boost a secondary response, this may also be variable, and, in some patients, no response at all can be observed. Currently, two new anti-TNFs are being evaluated for the treatment of Psa a humanized form of infliximab by subcutaneous route, golimumab and a pegylated form of anti-TNF, certolizumab pegol. Phase-2 preliminary studies indicate efficacy similar to the conventional anti-TNFs.[6,7] Surprise as it may be, a few patients develop Ps after the treatment with anti-TNFs, and several explanations are being developed for this enigmatic observation. One of the most attractive is the switch to another inflammatory pathway after prolonged blockade of TNF.[8-10]

Ustekinumab is an immunoglobulin, a human monoclonal antibody that binds with great affinity to the shared p40 subunit of human interleukin 12 and 23.[11,12] Increased production of IL-23 (but not of IL-12 mRNA) production can be observed in the skin of Ps patients. IL-23 is essential for the survival and proliferation of Th17 cells. Previous published data have shown CD4 and CD8 cells in Ps lesions, and Ps is considered a Th1 disease. However, it has been demonstrated that the CD4 cells secrete excessive amounts of IL17; they are Th17 cells, therefore, and one scenario consists in considering Ps as a Th1/Th17-mixed disease.[13]

Two clinical studies known as PHOENIX 1 and 2 evaluated patients with moderate to severe Ps. PHOENIX 1 studied 66 patients randomized to receive 45 mg or 90 mg at the weeks zero, four, and every 12 weeks. In PHOENIX 2, a similar study was performed, but in this time with adjustable doses in case of partial responses, totaling 70% of the patients in both studies against 3% in the group treated with placebo. After 52 weeks, besides a good index of response, no serious adverse events happened, except minor symptoms at upper respiratory tract (apparently common with the use of any immunobiological agents), neither anaphylaxis nor presence of tuberculosis, being these symptoms still associated with a very convenient way of administration subcutaneously every two to three months. When compared with etanercept, it was demonstrated that the response observed with ustekinumab was superior in efficacy and side effects (Figs. 1, 2, and 3).[14-17] Studies with ustekinumab in Psa are underway. The superiority of this agent has been demonstrated *versus* placebo in controlled trials, reducing signs

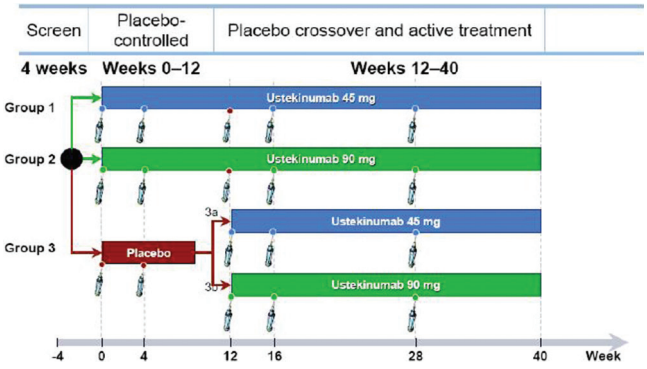

Fig. 1 – Phoenix 1 & 2: study design.

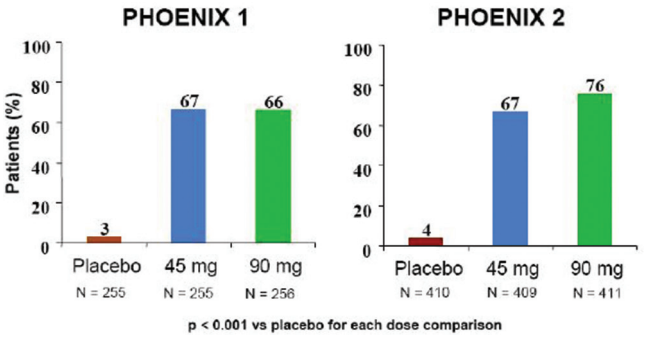

Fig. 2 – Ustekinumab pasi 75 responses at week 12 (after doses at weeks 0, 4).

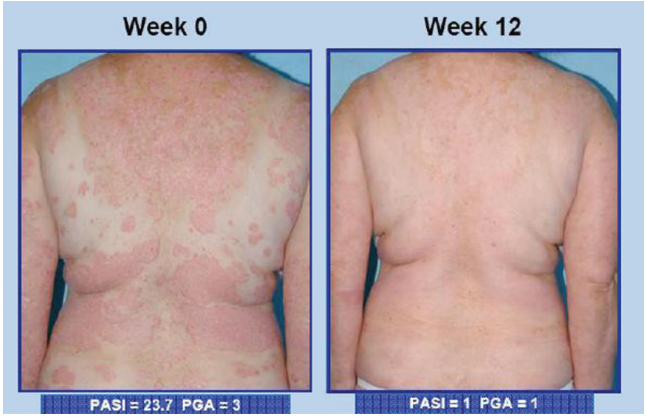

Fig. 3 – Significant efficacy after two injections.

and symptoms in the joints and also in the skin. Phase-3 results are still pending.[18,19] Briakinumab (ABT-974) is another fully human monoclonal antibody against the p40 subunit of IL12-23, that is currently under evaluation for Ps.[20] Preliminary results are similar to those observed with ustekinumab. Finally, as the activation of IL-23 depends on Th17,future biological agents for Ps and Psa might be directed at Th17 and their secreted product IL-17, a pathway still not taken in Psoriasis.[21] In summary, the current status on the therapy of Ps and Psa should now include new medications despite the fact that after TNF failure, we still lack proper guidelines.[22,23]

Conclusions

It is conceivable that we are not ready to replace anti-TNF as an alternative for the treatment of Ps, but it is a possibility, in case of Psa, until the ongoing phase-3 studies are available, it may also become a possibility in reducing articular signs and symptoms. So, what is the alternative if anti-TNF fails in patients suffering from Ps and Psa? Our understanding is that until comparative studies be performed, inhibition of new pathogenetic pathways should be considered and evaluated at the individual level; moreover, blocking IL12-23 is an alternative pathway initially indicated for the skin, although it also seems to be helpful in alleviating symptoms of arthritis.[24,25]

Conflicts of interest

The authors declare no conflicts of interest.

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