The final frontier or just another brick in the wall?

The title of the article by Ari Waisman published in March 2012 (“To be 17 again”) is illustrative of the mood and opinion towards pathogenic and therapeutic proposals for psoriasis resulting from the arrival of new anti-IL-17 drugs. Undoubtedly, the perspectives and aspirations of dermatologists have been rejuvenated and new challenges and hopes have been taken on under the umbrella of this new family of drugs.

This new concept originated a few years ago with the description of a “third pathway” in acquired immunity, represented, among other elements, by Th17 cells, which resolved a number of issues that could not be explained using the old-time model based on Th1 and Th2 lymphocytes. This first step helped to create the current pathogenic proposals for psoriasis, which is reflected in articles by Nestlé et al. and other contemporary authors during the first decade of this century. According to these authors, psoriasis should be considered a complex process in which both innate and acquired immunity work as a unit. The above-mentioned articles highlight new protagonists such as keratinocytes (with a renewed starring role through the release of antimicrobial peptides such as cathelicidin LL-37) and dendritic cells (in particular, the myeloid CD11c+ cells) and place special emphasis on the IL-12/IL-23 pathway, which initiates the clonal activation and proliferation of the lymphocyte subpopulations involved in the pathogenesis of psoriasis: Th12 and Th17, through their cytokine expression pattern. We currently have sufficient knowledge, at least from an experimental point of view, to confirm at a future point that psoriasis plaques can be generated in the absence of Th12 lymphocytes, a situation that shifts a large portion of the responsibility to the recently described Th17 lymphocyte subpopulation and, in particular, to its most distinctive molecular signature, the IL-17.

A review of recent articles on the latest findings in psoriasis can lead interested dermatologists to the conclusion that we are nearing the moment when we will have the key piece to the pathogenic puzzle of this disease. The presence of increased mRNA levels of various types of IL-17, the presence of IL-17A+ cells in the lesional skin and the inhibition of psoriasiform lesions in IL-17 receptor-deficient murine models point in this direction.

However, the chronologically short but intense experience in biological therapy requires us to be prudent, in the sense that, in the enormous immunologic complexity of any inflammatory process (including psoriasis), the latest or penultimate compound to be reported always appears to be the key one. The experimental evidence, even when powerful, is almost always indirect. In any case, there is no doubt that the results obtained by drugs that target the compounds involved in these new pathogenic steps (in particular, IL-17) will certify or not the soundness of the new strategy.

Throughout this supplement, authors of unquestionable international prestige in research and treatment explain and reflect on the innovative aspects of the nature and involvement of cell groups and cytokines in pathogenesis and their interaction in biological processes, all of which constitute the new framework of the development of psoriasis lesions, with special emphasis on IL-17. Naturally, they then review the known therapeutic, and safety profile results of a new group of compounds directed specifically at inhibiting IL-17 as a mechanism for controlling the disease.

The participation of IL-17 in the pathogenesis of psoriasis (and its therapeutic implications) represents, however, a significant qualitative leap beyond the consideration of this compound as the fundamental effector element of the Th17 lymphocyte. Interleukins are compounds produced by various cell types that regulate the communication between inflammatory cells for a wide range of actions, generally over a short distance, and have the ability to coordinate and regulate the inflammatory reaction. So far, the IL-17 family includes 6 distinct cytokines, labelled A to F, which can present as homodimers or heterodimers. To date, or at least at the time of writing this text, we only know the fundamental functions (both physiological and pathological) of IL-17A, IL-17F and IL-25 (IL-17 E), which have been extensively discussed in this monograph. However, the considerable conceptual leap is due to the fact that Th17 lymphocytes are only one of the elements involved in the production of these cytokines, which can
result from a large number of cells belonging to the innate immune system (neutrophils, macrophages, mast cells, dendritic cells, natural killer cells, eosinophils, lymphoid CD4+ cells) and the acquired immune system (cytotoxic CD8+ T cells, natural killer T cells, gamma-delta T cells). In other words, we find ourselves in a situation where there is a notable gap in the concept of the IL-12/IL-23 pathway as the only logical path towards the development of effector compounds in the final stage of development of psoriasis plaques and, therefore, a new cooperation between the innate and acquired immune systems in this process. This relationship is probably synergistic and continuous, despite our attempt, for the sake of simplifying and understanding the nature of the cutaneous inflammatory process, to present the two systems as disjointed blocks.

The effects of IL-17 on various cell types are varied, complex and occasionally apparently contradictory. The known actions on keratinocytes appear to be particularly relevant in the development of psoriatic lesions. Specific receptors on the keratinocytes determine the release of molecules involved in neutrophil recruitment (chemokines CXCL 1, 3, 5, 6 and 8), innate immune system stimulation (antimicrobial peptides), disruption of the epidermal barrier (reduced number of filaggrins and adhesion molecules) and cell recruitment as well as myeloid dendritic cells and Th17 cells (CCR6+). In other words, the keratinocyte, a fundamental player in the genesis of the psoriatic plaque through the release of antimicrobial peptides such as cathelicidin LL-37, once again becomes a cornerstone of the process, not only through a profound change and dysregulation in the epidermal proliferation that becomes evident in clinical lesions but also in the maintenance of the underlying inflammatory disorder as a self-perpetuating inflammatory cycle.

The strength of the data concerning the involvement of IL-17 in the development of psoriasis has helped support to the development of new compounds that, based on the already fully established philosophy of biological treatment, target this compound.

We currently have several drugs directed against IL-17. All of these drugs are backed by phase II and III clinical studies on psoriasis and/or psoriatic arthropathy; their results have been presented in international Dermatology meetings and several publications have already appeared. Despite the common underlying philosophy, their nature, structure and even the mechanism through which they inhibit IL-17 can vary. Thus, secukinumab (IgG1) and ixekizumab (IgG4) are directed against IL-17A, while brodalumab (IgG2) targets the IL-17A and IL-17RA receptors. Both secukinumab including brodalumab are completely human, while which ixekizumab is humanized.

While the mechanisms of action for secukinumab and ixekizumab are similar despite their different nature, the mechanism of action for brodalumab has a number of somewhat different implications. Brodalumab inhibits the receptor that serves for IL-17A, IL-17 A/F and IL-17F, on one hand, and IL-25 on the other. Thus, although the anti-inflammatory effects can be more extensive, the effects resulting from the suppression of the physiological effects of these interleukins can also be greater.

The data from this new group of drugs, a significant portion of which are the results of phase II clinical trials and their extensions and (in a preliminary way) of phase III trials, allow us to cautiously conclude that we could be dealing with a new paradigm in therapeutic perspectives. The chances of achieving complete or almost complete remission (corresponding to PASI 90 or PASI 100 response or to PGA 0 or 1) are significantly greater when compared with previous generations of biological therapies. This situation is relevant, given that it has been shown how these responses are the ones associated with more consistent improvements in patients’ quality of life indices, far from those corresponding to improvements in the PASI index that are considered sufficient (PASI 75) for approving the drug.

As with any new therapeutic strategic, one of the potential disadvantages is the problem of safety. The knowledge acquired from genetic processes characterized by IL-17 deficiencies (such as autoimmune polyendocrine syndrome, hyper IgE syndrome and dectin-1 deficiency), in which an increase in Candida spp. and staphylococci infections have been detected, serves as a theoretical reference. However, the results from clinical trials (still limited in the number of patients and length of follow-up) reflect a very safe profile for most treated patients. We should also remind ourselves of the physiological effects of IL-17, such as neutrophil recruitment, endothelial cell migration and angiogenesis, whose potential inhibition by anti-IL-17 drugs has also to date not been associated with relevant problems in the studies. It is likely that the considerable quantity of redundant and short-circuit pathways (many of them presumably unknown) are able to safeguard the fundamental functions of the immune system, as generally happens in patients who undergo biological therapy. However this situation does not rule out the need for a more than careful follow-up.

The articles developed in this supplement combine and broaden all the information developed in the previous sections. In their article, Chiricozzi et al. reviewed the new pathogenic proposals for psoriasis and the involvement of IL-17 in this disease, as well as the clinical results from studies on the available compounds directed against this new target. The authors highlight the broad clinical program for secukinumab, which assesses not only the clinical results in monotherapy but also the comparative study with etanercept, the study of intermittent treatment and the potential indications in palmoplantar psoriasis, onychopathy and psoriatic arthropathy. Lastly, the authors review the new drugs from a safety standpoint, referencing their potential involvement in cardiovascular morbidity, infections and neoplasms.

Mitra et al. emphasized the functional role of IL-17 in psoriasis and joint diseases and its determinant effects on synovial fibroblast proliferation and synoviolin release, which promote the perpetuation of the inflammatory process, its action on osteoclastogenesis and the irreversible damage that it can cause. The authors remind us of how the available research confirms the pathogenic importance of IL-17 in the genesis of psoriasis lesions and joint lesions, having detected the overexpression of CD4+ cells that produce IL-17 and IL-17 receptor in the fibroblasts (particularly of the PsA) when compared with other inflammatory joint processes.
Finally, Blake and Teng described the role of IL-17 and that of other cytokines such as IL-22 in autoimmune diseases, psoriasis and cancer, taking into account that both cytokine are often secreted jointly. The authors note the ambivalence of a number of these compounds, for example, how IL-22 can develop ambivalent functions depending on the neoplasm, the location and tumor microenvironment.

In short, we look at a single issue from various perspectives, which serve as a basis for better understanding the conceptual progress in inflammatory pathogenesis. This understanding is applicable not only to psoriasis but also to other diseases, with therapeutic implications that might indicate a new qualitative leap in the potential for improvement in our patients.

From a practical point of view, we offer new therapeutic perspectives and possibilities associated with a new family of drugs, which, by not sharing the same objective, cannot stop demonstrating profound differences in terms of long-term efficacy, safety and maintenance. Finally, there are new possibilities for dermatologists and their patients with moderate to severe psoriasis, and they should show their worth in our daily clinical practice.

Conflicts of interest

JMC has perceived consultancy and speakers’ honoraria from Novartis and Lilly and participated in clinical trials sponsored by Novartis, Lilly and Amgen.

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References


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