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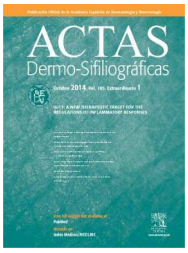


EDITORIAL

Therapeutic implications of IL-17A blockade in psoriasis

The discovery of T helper type 17 lymphocytes in 2005[1] represented an important advance in understanding the immunopathogenesis of immunologically mediated inflammatory diseases, by identifying an important source of cytokine IL-17A, whose role in autoimmune diseases has been identified in experimental models. Over 15 years ago, the role of IL-17A in the pathogenesis of psoriasis and its proinflammatory activity on the keratinocyte were postulated.[2] The eventual development of biological inhibitors of the IL-17A pathway and the demonstration of their effectiveness in treating psoriasis was a natural consequence of this discovery.

In psoriatic skin lesions, there is an increase in the number of T lymphocytes, neutrophils and mast cells that express IL-17A and are located in the epidermis (CD8+ T lymphocytes), the epidermal microabscesses and the dermis, respectively. High levels of mRNA for IL-17A, IL-17C and IL-17F (3 of the isoforms of this cytokine) have been detected, which, in the case of IL-17A, are correlated with disease activity.[3] The role of IL-17A in the pathogenesis of psoriasis is especially relevant. It affects the epidermis by increasing the expression of epidermal chemokines (such as CCL20, which recruits lymphocytes and dendritic cells, and those of the CXCL family, which determine the influx of neutrophils) and antimicrobial peptides, acting synergistically with tumor necrosis factor alpha (TNF-α).[4]

IL-17A plays a central role in the pathogenesis of psoriasis, not only due to its action on keratinocytes (as well as other cell types that intervene in the inflammation and vascularization of lesions) but also due to its involvement at the crossroads of the innate and acquired immune pathways. The first (in which cell types such as neutrophils, NK cells, gamma delta lymphocytes, mast cells and the keratinocytes themselves participate, among others) is gaining special importance. The second corresponds to the classical paradigm of activation of the naïve lymphocytes by dendritic cells (initially in the lymph node and eventually in the skin itself, becoming a secondary lymphoid organ). Dendritic cells, in the presence of IL-12 or IL-23, determine the polarization and proliferation of CLA+ activated T1 or T17 lymphocytes, respectively. These lymphocytes are then directed to the skin to release cytokines such as IL-2, gamma interferon and TNFα or IL-17 and IL-22, respectively, creating a vicious cycle of immunologic inflammation and activation that initiate and maintain the lesions.

A systematic review has recently been published on the therapeutic effects of biological agents that block the IL-23/IL-17 pathway;[5] however, in this editorial, we will limit ourselves to summarizing the available evidence for the three agents that are in phase III of clinical development and that act distally, blocking IL-17A (secukinumab and ixekizumab) or its receptor IL-17AR (brodalumab).

The proof of concept of the therapeutic role of IL-17A inhibition in psoriasis was a study of the effect of a single intravenous administration of secukinumab (a monoclonal human IgG1k antibody developed by Novartis) in 36 patients at a dose of 3 mg/kg. This caused an average reduction in the Psoriasis Area and Severity Index (PASI) of 58% at 4 weeks (compared with 4% in the placebo group),[6] which was maintained at 12 weeks. Two phase II studies have subsequently been published (dose ranging by subcutaneous and intravenous routes),[7] which are described in greater detail in other articles of this supplement, as well as a phase II study (proof of concept) of psoriatic arthritis (28 patients treated with 2 doses of 10 mg/kg administered intravenously with a 3-week interval and 14 treated with placebo) in which the percentages on the American College of Rheumatology 20 response index (ACR20) were 39% and 23%, respectively, at 6 weeks.[8]

The data from a recent review of phase II trials of secukinumab, ixekizumab and brodalumab for the treatment of psoriasis are summarized in Table 1.[9]

The clinical development program for secukinumab has been extraordinarily comprehensive;[10] two of the phase III studies on psoriasis have recently been published.[11]

These studies were 52-week, double-blind clinical trials that randomly assigned 738 patients (ERASURE) and 1306 patients (FIXTURE) to undergo treatment with subcutaneous secukinumab at a dose of 300 mg or 150 mg (administered once weekly for 5 weeks, then every 4 weeks), placebo, or (in the FIXTURE study only) etanercept at a dose of 50 mg (administered twice weekly for 12 weeks, then once weekly).

Table 1 PASI response results at week 12 in the phase II studies (dose-finding) of anti-IL-17 biological agents

Proportion of patients achieving reduction in PASI score (no.)			
	By ≥ 75%	By ≥ 90%	By 100%
Secukinumab			
Placebo (n = 22)	9% (2)	4% (1)	NR
25 mg (n = 26)	19% (5)	8% (2)	NR
75 mg (n = 21)	57% (12)[a]	19% (4)	NR
150 mg (n = 27)	82% (22)[b]	52% (14)[b]	NR
Ixekizumab			
Placebo (n = 26)	8% (2)	0	0
10 mg (n = 28)	29% (8)	18% (5)	0
25 mg (n = 30)	77% (23)[b]	50% (15)[b]	17% (5)
75 mg (n = 29)	83% (24)[b]	59% (17)[b]	38% (11)[b]
150 mg (n = 28)	82% (23)[b]	71% (20)[b]	39% (11)[b]
Brodalumab			
Placebo (n = 38)	0	0	0
70 mg (n = 39)	33% (13)[b]	18% (7)[c]	10% (4)[d]
140 mg (n = 39)	77% (30)[b]	72% (28)[b]	38% (15)[b]
210 mg (n = 40)	82% (33)[b]	75% (30)[b]	62% (25)[b]
280 mg (n = 42)	67% (28)[b]	57% (24)[b]	29% (12)[b]

[a]p = 0.002 for the comparison with placebo.
[b]p ≤ 0.001 for the comparison with placebo.
[c]p < 0.01 for the comparison with placebo.
[d]p < 0.05 for the comparison with placebo.
These were not "head-to-head" studies. NR: not reported.

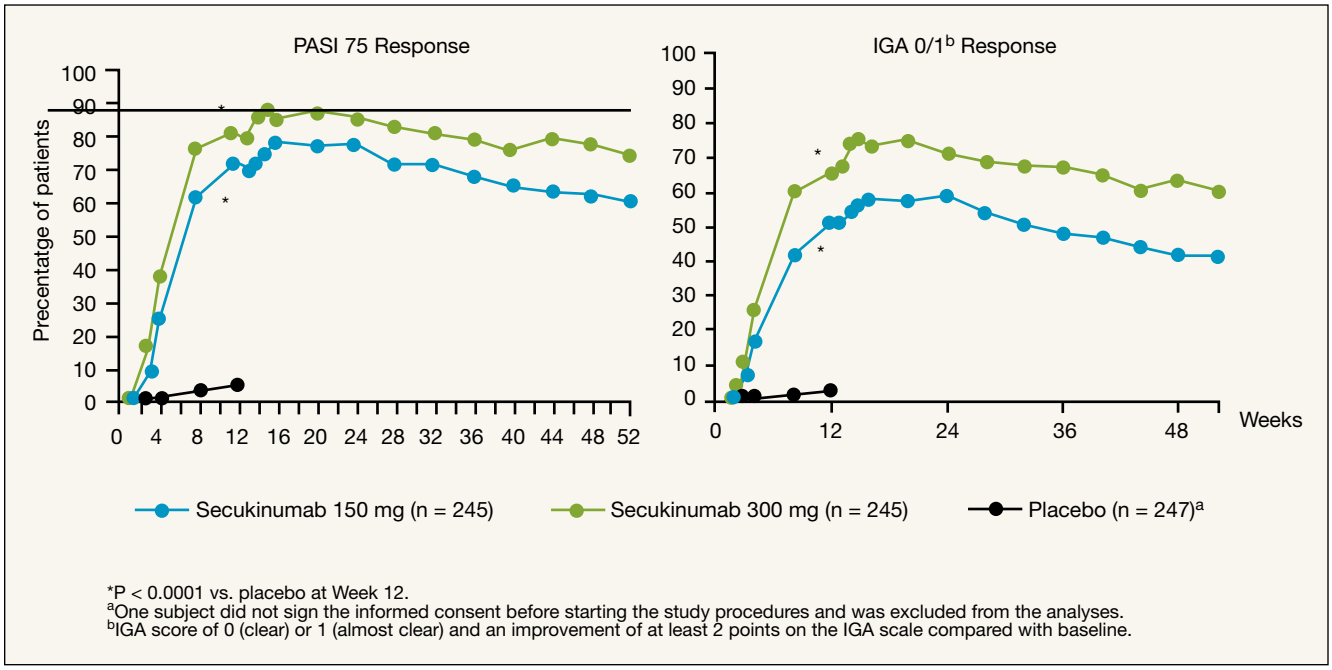
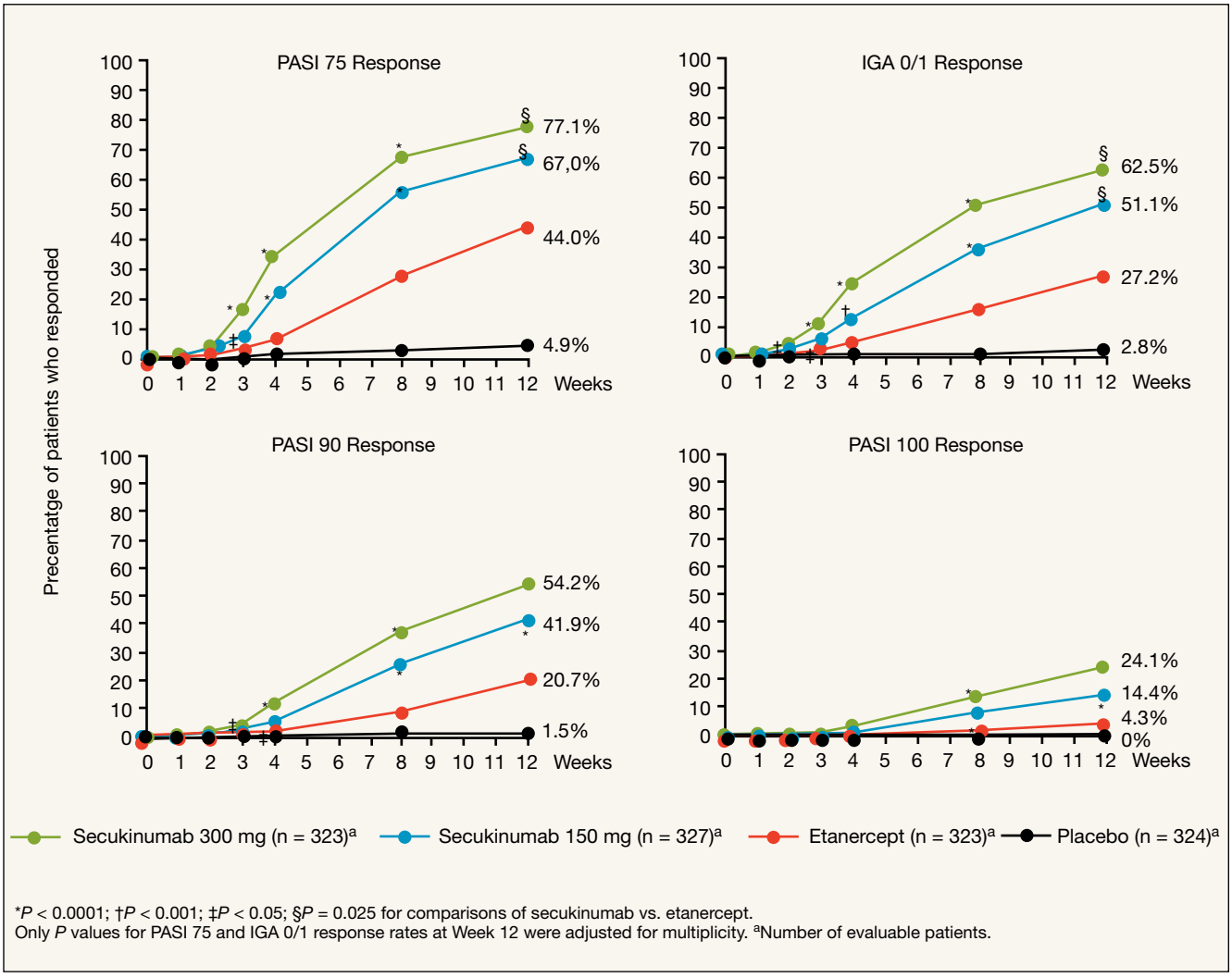


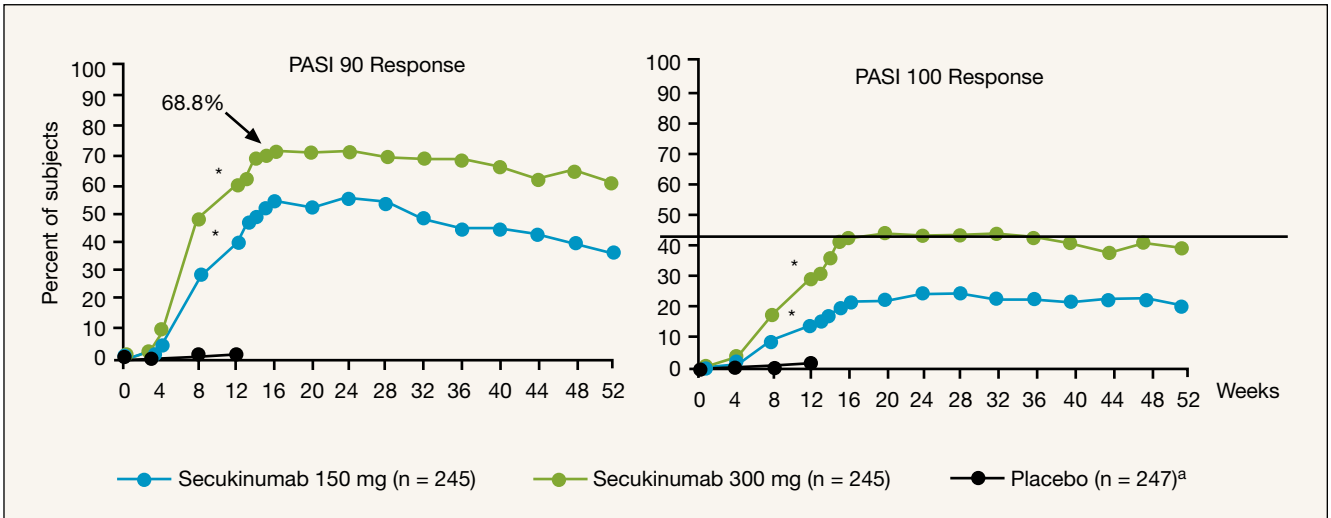
Figure 1 Response rates at week 12 in the ERASURE study.

The objective of each study was to show the superiority of secukinumab over placebo at week 12 with respect to the proportion of patients who had a reduction of 75% or more from baseline in the psoriasis area-and-severity index score (PASI 75) and a score of 0 (clear) or 1 (almost clear) on a 5-point modified investigator's global assessment (coprimary end points). The PASI 75 response rates at week 12 were higher for both secukinumab doses when compared with placebo and etanercept. In the ERASURE trial, the percentages were 81.6% (300 mg of secukinumab), 71.6% (150 mg) and 4.5% (placebo) (Figure 1). In the FIXTURE trial, the percentages were 77.1% (300 mg), 67.0% (150



*P < 0.0001; †P < 0.001; ‡P < 0.05; §P = 0.025 for comparisons of secukinumab vs. etanercept.
Only P values for PASI 75 and IGA 0/1 response rates at Week 12 were adjusted for multiplicity. [a]Number of evaluable patients.

Figure 2 Response rates up to week 12 in the FIXTURE study.



*P < 0.0001 vs. placebo at Week 12.
[a]One patient did not sign the informed consent before starting the study procedures and was excluded from the analyses.

Figure 3 Response rates up to week 52 in the ERASURE study.

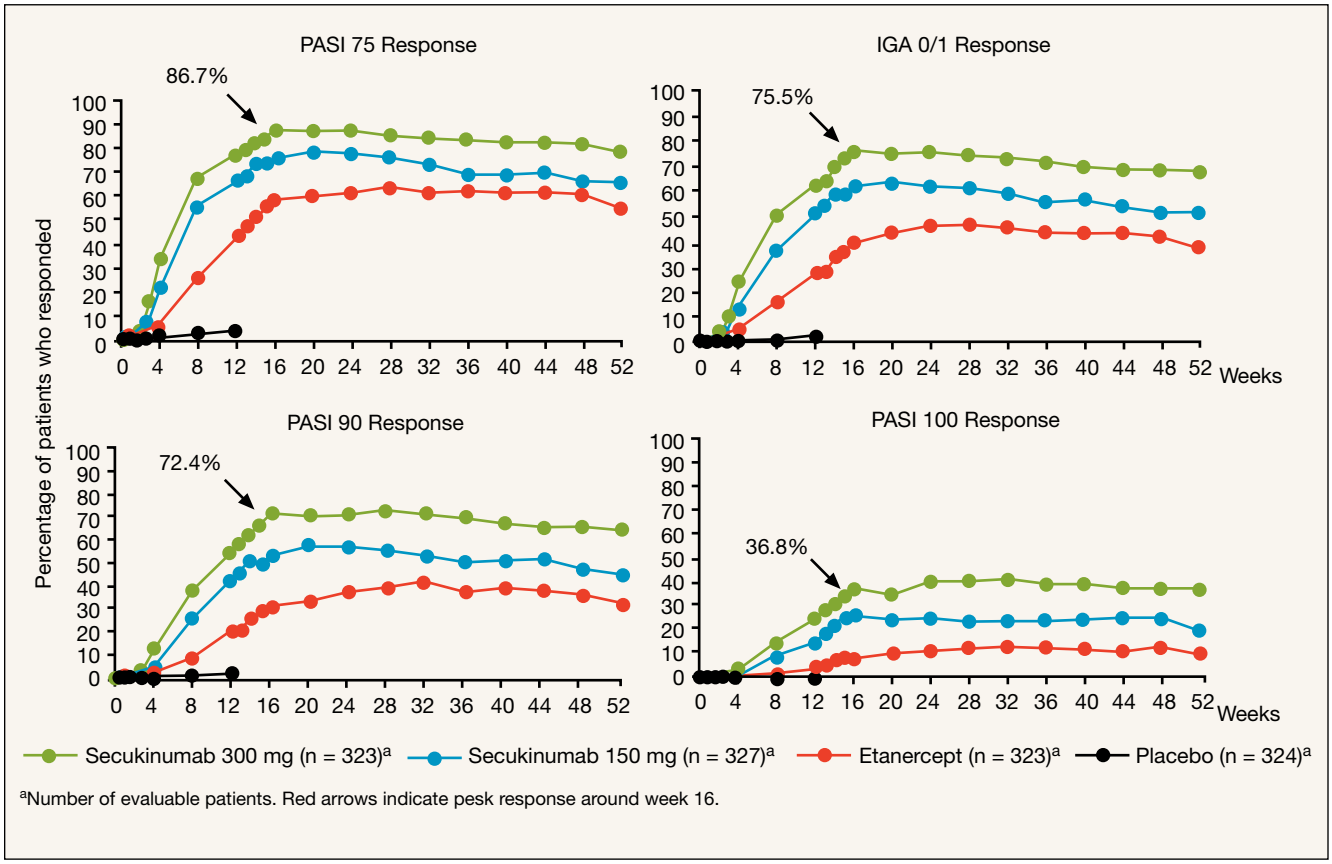


Figure 4 Response rates up to week 52 in the FIXTURE study.

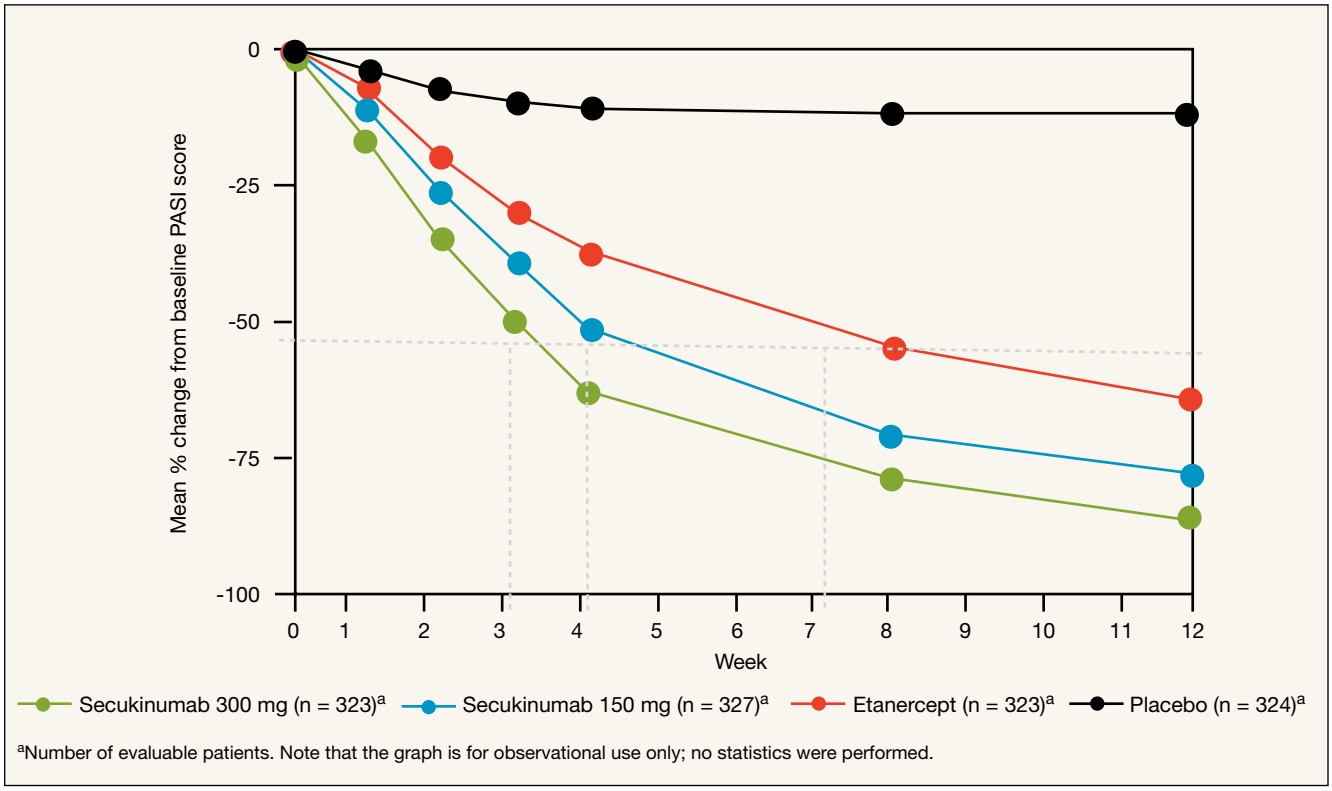


Figure 5 Percentage of improvement with respect to baseline PASI (average) over time in the FIXTURE study.

mg), 44.0% (etanercept) and 4.9% (placebo) ($p < .0001$ for each dose of secukinumab versus the comparators) (Figure 2). Furthermore, the IGA mod 2011 0/1 response rate at week 12 was higher ($p < .0001$) for both secukinumab doses. In the ERASURE trial, the percentages were 65.3% (300 mg), 51.2% (150 mg), and 2.4% (placebo) (Figure 1). In the FIXTURE trial, the percentages were 62.5% (300 mg), 51.1% (150 mg), 27.2% (etanercept) and 2.8% (placebo) (Figure 2). The responses were maintained up to week 52 in both studies (Figures 3 and 4), reaching a maximum at week 16 with the 300-mg dose of secukinumab, which was faster in terms of starting its effect. In the FIXTURE study, the average time it took for patients treated with this dose to achieve a 50% improvement with respect to baseline PASI scores was 3 weeks, compared with 4 and 7.5 weeks for the patients treated with 150 mg of secukinumab and etanercept, respectively (Figure 5). The rates and characteristics of the adverse events associated with the two doses of secukinumab and etanercept were comparable.

A third phase III study (FEATURE) has subsequently been published, designed to determine the efficacy, safety and ease of use of the preloaded syringe at 12 weeks of treatment. This trial included 177 patients who were randomly assigned to 300 mg or 150 mg of secukinumab or placebo (weekly subcutaneous administration until week 4 and in week 8). At week 12, a PASI 75 response was observed in 75.9%, 69.5% and 0% of the patients, and an IGA mod 2011 response of 0 or 1 was observed in 69.0%, 52.5% and 0% of the patients, respectively. Administration with the preloaded syringe was successful in 100% of the patients at 1 week of treatment. The results of this study indicate that the syringe preloaded with secukinumab is a reliable and comfortable form of administration for patients with moderate to serious psoriasis.

In summary, the efficacy observed in the phase II and phase III trials with the new monoclonal antibodies blocking IL-17A or its receptor confirm the central role of this cytokine in the pathophysiology of psoriasis. These results support the expected future approval of a new family of drugs that will likely establish a new standard in terms of speed and intensity of response (PASI 75 and PASI 90 response rates of approximately 80% and 70%, respectively), with a safety profile comparable to that of other biological agents.

Conflicts of interest

LP has perceived consultancy and speakers' honoraria from Novartis and participated in clinical trials sponsored by Novartis.

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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