Psoriasis is a chronic, immune-mediated inflammatory disorder affecting 2–3% of general population, being both physically and emotionally debilitating.\(^1\)\(^,\)\(^2\)

Due to the rapid advances in the understanding of psoriasis pathogenesis, several targeted medications, aiming specific components of the immune system, have been and are currently being developed.\(^3\) These biologic therapies are a major technological advancement over traditional immunosuppressive medications and have revolutionized the treatment of psoriasis. Currently available biologic agents for psoriasis treatment have shown to be very effective, even long-term, with a favorable safety profile.

The most widely used instrument for objective measurement of psoriasis severity and extension is the Psoriasis Area and Severity Index (PASI), which was developed in 1978.\(^4\) Even though it has a number of limitations (non-linearity because of the surface score, notorious floor effect and poor sensitivity to change for relatively small areas of involvement, lack of ponderation of the different qualities of the lesions and functional impairment associated with lesions involving visible areas, such as, the hands, feet, nails or genital areas and reduced reproducibility due to the variability associated to the determination of BSA\(^5\)), PASI has been considered the gold standard of psoriasis severity scale for decades.

A 75% reduction in the PASI score with respect to baseline (PASI 75) is the current standard of response assessment used for primary endpoints in most clinical trials of psoriasis and it has been considered the treatment goal for moderate to severe psoriasis in a recent European consensus.\(^6\)

However, not so long ago, some authors considered PASI 75 to be too stringent, placing potentially useful therapies at risk of failing to demonstrate efficacy, and PASI 50 to represent a clinically significant change for psoriasis patients and a better primary endpoint.\(^7\) This may have been true in an era of less effective drugs but, in the current status of biologic treatment, more ambitious outcome measures must be chose.

Although PASI 75 response is commonly used as the primary efficacy endpoint in clinical trials of biologics, PASI 90 and even PASI 100 response rates are commonly reported and are becoming important secondary endpoints. As is often the case, technological/therapeutic advances precede and eventually determine changes in therapeutic paradigms.

The efficacy showed by the IL-17 inhibitors (both IL-17A and IL-17 receptor subunit A inhibitors) in phase II and phase III clinical trials, which bears the promise of achieving PASI 90 response or better in the majority of patients, may make us rethink this issue again.

Methotrexate showed, in the randomized controlled comparative trials of infliximab and adalimumab, a 16 and 26-week PASI 90 response between 14–19.1% and 14.9%, respectively.\(^8,\)\(^9\)

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http://dx.doi.org/10.1016/j.ad.2014.10.001

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Considering biologic therapy, the week-12 PASI 90 rate in publish randomized trials of efalizumab, one of the first biologic agents approved for psoriasis and later withdrawn, was between 4-12%, while the results of a 3-year continuous dosing study, showed a PASI 90 response of 24.5%.11 The anti-TNFα therapies show better results, with the monoclonal antibodies infliximab and adalimumab showing a higher response rate than the soluble TNFα receptor etanercept in clinical trials. In a recently published meta-analysis the efficacy of biologics in the treatment of moderate-to-severe plaque psoriasis based on the available randomized controlled trials has been estimated.12 The probability of achieving a PASI 90 response at the primary endpoint time is 19.3% (95% CI: 16.6–22.0) for etanercept at week 12, 36.5% (95% CI: 25.7–47.4) for adalimumab at week 16 and 49.5% (95% CI: 45.6–53.4) for infliximab at week 10. At week 24 the probability of achieving a PASI 90 response is 27.8% (95% CI: 23.6–31.9), 45.7% (95% CI: 42.1–49.3) and 50.6% (95% CI: 45.3–55.9) respectively for etanercept, adalimumab and infliximab. In the long term, the reported PASI 90 response in the open-label extension studies RESTORE and REVEAL was 45% for infliximab at week 50 and 50% for adalimumab at 3 years.13,14 Regarding ustekinumab, the latest biologic agent approved for treatment of moderate to severe psoriasis, the results observed in the phase III clinical trials were similar to the response rates observed with the anti-TNFα monoclonal antibodies. In the same meta-analysis, the probability of achieving a PASI 90 response at week 12 and 24 is 47.2% (95% CI: 42.6–51.8) and 58.2% (95% CI: 53.7–62.8) respectively for the 45 mg dose.15 In the long-term efficacy analyses of ustekinumab in patients treated for up to 5 years in the PHOENIX 1 study, the 5-year PASI 90 response rate reported was 39.7%. The looking to the recently published results of phase II and phase III randomized trials of secukinumab, ixekizumab (both anti-IL-17A monoclonal antibodies) and brodalumab (anti-IL-17 receptor subunit A monoclonal antibody) PASI 90 and PASI 100 response rates are impressive. In the phase II, randomized, double-blind, placebo-controlled, dose-ranging study of brodalumab, a PASI 90 and PASI 100 response was observed in 75% and 62%, respectively of the patients in the 210 mg group at week 12.16 In the 48-week open-label extension of the phase II trial, 86% and 64% of the patients achieved, respectively, PASI 90 and PASI 100 at week 48. Concerning the phase II, double-blind, placebo-controlled trial with ixekizumab at 12 weeks, the percentage of patients with PASI 90 and PASI 100 response was 71% and 39% respectively, in the group of patients treated with 150 mg and 59% and 38% respectively in the 75 mg group. In the open-label extension, with a dose of 120 mg every 4 week, 79% and 57% achieved a PASI 90 and PASI 100 response after 52 weeks.17 In the phase II, randomized, double-blind, placebo-controlled dose-ranging study of secukinumab the 12-week PASI 90 response in the 150 mg group was 52%.20 In the phase III FIXTURE study, comparing two doses of secukinumab (300 mg and 150 mg) with etanercept and placebo, the 12-week PASI 90 and PASI 100 response in the 300 mg secukinumab group was 54% and 24% respectively.21 At week 52, 65% of the patients treated with secukinumab 300 mg monthly had a PASI 90 response.21 In other phase III study, the ERASURE study, the 12-week PASI 90 and PASI 100 response was 59.2% and 28.6% respectively. At week 52, nearly 60% of the patients treated with secukinumab 300 mg monthly had a PASI 90 response.21

These results are in fact very promising, but confirmation from further clinical trials and particularly daily clinical practice is necessary. PASI 90 may represent the best meaningful clinical response, instead of PASI 75, particularly in patients with very severe psoriasis. Considering patients with PASI above 20 (as seen in most studies in moderate to severe psoriasis), a PASI 75 response would associate to an absolute PASI around 5, compatible with a PGA score of 2, usually considered mild psoriasis (mild plaque elevation, light red coloration, predomination of fine scale). However PASI 90 response would equate to a PASI around 2, compatible with a PGA of 0/1 (almost clear). In this sense, PASI 90 response probably better reflects a “clear”/“almost clear” status than PASI 75.22 Moreover, it is well known that reduction in PASI predicts a reduction in DLQI with a good correlation. A recent systematic review showed that a PASI 75 response was associated with a considerably higher mean DLQI change (9.36) than a PASI 50–75 response (6.12).23 The difference between both groups was 3.24, higher than 3.2, the value considered clinically meaningful according to the proposed minimal clinically important difference for the DLQI in psoriasis.24 This data suggests that there is a true quality-of-life benefit associated with higher levels of psoriasis clearance, and that higher PASI reductions (for instance PASI 90) may probably determine even better quality-of-life benefits. As a matter of fact, combining data from two adalimumab trials, the PASI 100 and PASI 90 to <100 groups demonstrated a >10-point decrease in DLQI total scores at week 16, and these changes were statistically significantly greater than those observed for the PASI 75 to <90 group and the other PASI response groups (P < 0.001).25

The ultimate goal of psoriasis treatment is the complete clearance of all skin lesions and symptoms, however, when pushing the response rate so high, safety concerns must be considered. The immunomodulatory/immunosuppressive effects of these agents should not be forgotten and holding the balance is the key. Nevertheless the safety data on these new agents is reassuring, appointing to a favorable safety profile. The expected favorable safety/efficacy ratio of the IL-17 inhibitors is probably related to the selective mechanism of action of these new drugs, as a lower blockade in the inflammatory cascade may result in less immunosuppression and consequently in less risks of infection and malignancy, while maintaining a high efficacy through selectively acting at the level of this key effector cytokine.26

The psoriasis treatment paradigm has changed with the advent of biologics. The treatment advancements we have seen with these agents make us believe that achieving clearance or near-clearance of psoriasis will be possible. If in the past, a PASI 50 and 75 response was possibly sufficient enough and the PASI 90 achievement just a mirage, maybe sooner than many expected, clinicians will be disappointed if a PASI 90 response is not achieved.

Conflict of interest

Dr. T. Torres has participated in clinical trial sponsored by Abbvie, Amgen and Novartis and has received honoraria for

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acting as a consultant and/or as a speaker at events sponsored by Abbvie, Janssen, MSD and Pfizer.

Prof. L. Puig has participated in clinical trials sponsored by Abbvie, Amgen, Lilly, Merck, Novartis, Pfizer España, and VBL and has received honoraria for acting as a consultant and as a speaker at events sponsored by Abbvie, Merck, Janssen, Merck, Novartis, and Pfizer.

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