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 BSA⁵), 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.⁶,⁹
Considering biologic therapy, the week-12 PASI 90 rate in
publish randomized trials of efalizumab, one of the first bio-
logic agents approved for psoriasis and later withdrawn, was
between 4–12%,10 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 etaner-
cept 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.13 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 mono-
clonal 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) respec-
tively for the 45 mg dose.12 In the long-term efficacy analyze
of ustekinumab in patients treated for up to 5 years in the
PHOENIX I study, the 5-year PASI 90 response rate reported
was 39.7%.15

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 48.17 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.18
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.19 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 secukin-
umab (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
both 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 psori-
asis), 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 corre-
lation. 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.23,24 This data suggests that there is a true
quality-of-life benefit associated with higher levels of psori-
axis 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 mecha-
nism 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
advantages of biologics. The treatment advancements we have
seen with these agents make us believe that achieving clear-
cance or near-clearance of psoriasis will be possible. If in
the past, a PASI 50 and 75 response was possibly sufficient
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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