REVIEW ARTICLE

PASI90 response: the new standard in therapeutic efficacy for psoriasis

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Abstract

In a non-life-threatening disease such as psoriasis, treatment goals should be referred to the improvement in severity and extent of the disease and their impact on patients’ perceived health-related quality of life (HRQoL), usually measured by the Dermatology Life Quality Index (DLQI). The ultimate goal of therapy is blanching, and an improvement of 90% or better (PASI90 response) with respect to baseline Psoriasis Area and Severity Index (PASI) is considered as treatment success by the European Medicines Agency. PASI75 response has become accepted as a less stringent reasonable therapeutic goal, but absolute PASI values might provide a better benchmark, irrespective of baseline PASI. Anyway, objective measures of psoriasis involvement are clinically meaningful only if they correlate with significant improvements in DLQI, and especially with the achievement of a DLQI = 0–1 status, corresponding to lack of effect of the disease on patient’s HRQoL. Even though PASI75 response meets therapeutic expectations in most patients, PASI90 response or better has a significantly higher impact on DLQI improvement and is associated with significantly higher DLQI = 0–1 response rates. The introduction of anti-IL17 drugs in clinical practice bears the promise of achieving PASI90 response or better in the majority of patients, and initial data suggest that the PASI90 benchmark provides better discriminatory value as regards achievement of DLQI = 0–1 response. Further research is required to confirm the value of absolute PASI cut-offs as a measure of therapeutic success independent of baseline and duration of treatment, and to develop newer, more practical and more accurate measures of psoriasis severity.

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There is general agreement that decisions on any therapeutic intervention should be individualized, agreed with the patient and based on the efficacy of the intervention shown in clinical trials, its efficiency in real clinical practice, safety (risk of adverse effects, to be distinguished from perception of hazard), convenience of administration and cost. In a generally non-life-threatening disease such as psoriasis, treatment goals ought to be defined in terms of severity and extent of the disease (and joint involvement if present) and their impact on patients’ perceived health-related quality of life (HRQoL). Dermatologic Life Quality Index (DLQI) is validated and widely used as an instrument for HRQoL in dermatology patients, despite the fact that it does not take into account the psychological burden of disease and is subject to marked transcultural variability. A set of DLQI score bands has been proposed according to a global question (GQ) score: DLQI = 0–1 imply no effect on patient’s HRQoL (GQ = 1), and DLQI = 2–5 imply a small effect on patient’s HRQoL (GQ = 1). As a matter of fact, one is left to wonder why should we not use the GQ anchor as a substitute for DLQI in clinical practice.

Despite several shortcomings (floor effect, non-linearity of surface score, etc.), Psoriasis Area and Severity Index (PASI) is the accepted standard for severity assessment in psoriasis, even though it does not take into account significant symptoms such as pruritus, the different impact of the erythema, thickness or desquamation components or visibility of the lesions or functional impairment (e.g. palmoplantar, nail, genital, scalp or flexural involvement). Patients’ or physician’s global assessment has been proposed as a more user-friendly measure, but it is rather meaningless if the body surface area is not taken into account, and PASI provides a composite assessment of both the signs and extension of psoriasis.

Both in clinical trials and in real life (especially since the advent of biological treatments), relative improvement of PASI
with respect to baseline is usually considered the benchmark to assess and compare the efficacy of psoriasis treatment. Thus, not achieving a PASI50 response (50% improvement) is generally considered as indicative of primary therapeutic failure. According to regulatory agencies, treatment success (PASI90 response or better) ‘is a very stringent requirement’, and ‘in studies enrolling severe patients, patients who achieve the result of “mild” (PASI > 75%) may also be considered as responders if defined prospectively’. Thus, PASI75 response has become accepted as a reasonable therapeutic goal for biologic treatment of psoriasis, and direct and indirect comparisons between treatments are based on the different PASI50, PASI75, PASI90 and PASI100 response rates. Nevertheless, with the advent of new biologicals potentially able to achieve PASI90 (and even PASI100) in a majority of patients perhaps the time is ripe to reconsider this tenet.

Since PASI75 (or any other) response rates apply to populations (e.g. in arms of clinical trials), they are not relevant for the assessment of minimal clinically significant difference (MCSD) in therapeutic outcome, which should be based on the correlation with patient-reported outcomes such as the DLQI and relative reduction of PASI with respect to baseline, or perhaps absolute PASI values below a defined threshold, which can be defined by clinicians’ consensus. The MCSD in DLQI for patients with moderate to severe psoriasis has been proposed to range between 2.3 and 5-point change. In a recently published systematic review of randomized clinical trials of biological agents for the treatment of moderate to severe psoriasis, when mean per cent reduction in PASI was plotted against mean reduction in DLQI across 22 treatment arms, a correlation coefficient value of 0.898 was observed. There appeared to be a difference in mean DLQI improvement between treatment arms: 5.37 in the <50% mean PASI improvement vs. 6.12 in the 50–75% mean PASI reduction group vs. 9.36 in the >75% mean PASI reduction group. The difference between the latter and the other two groups appears to be clinically meaningful, according to the proposed mean MCSD of 3.2, and suggests a true HRQoL benefit to higher levels of psoriasis clearance as demonstrated by PASI reduction >75% and that PASI75 response is an important end point.

A European consensus proposed PASI75 response as treatment goal, irrespective of DLQI score, both at the end of the induction period of 16–24 weeks and during the maintenance phase of treatment, whereas treatment regimen should be modified when PASI50 response is not achieved and in patients with less than PASI75 response and DLQI ≤ 5. Nevertheless, there is growing consensus (as reflected in the Spanish guidelines) that absolute PASI values lower than 2 or 3 might provide a better benchmark of therapeutic success, irrespective of the time of assessment; changes in treatment are often requested (and made) when PASI values exceed 5, regardless of baseline. This is especially relevant for patients with high baseline PASI values, namely >20, for whom a PASI value of 5 would still qualify as PASI75 response. Clearly enough, any patient, especially under biological treatment, is likely not to be satisfied with four plaques of psoriasis (erythema, thickness and desquamation 2/4) on the elbows (2) and the knees (2): PAT = 4.8; an additional 2-handprint plaque on the lumbar area would yield a PASI value of 6.6.

The use of absolute PASI values for benchmarking, and their correlation with DLQI at low values of both scores, is further supported by the results of infliximab clinical trials, where approximately 55% of patients with a PASI ≤ 2.5 at week 24 had DLQI = 0, compared to less than 5% of patients with PASI > 5.

Limited inter-rater agreement, especially at PASI values <20, should not prevent consistent assessment of 2–4 handprints per topographic area, even though a formal evaluation of inter-rater variability in the assessment of PASI values <5 has not been published. An ideal score should use its full range and be linear, non-skewed, sensitive to change, and correlated with patients’ reported outcome throughout all its range assessment of clinical improvement. In this respect, using the exact estimation of surface percentage involvement, and to a lesser extent its logarithmic transformation, instead of the non-uniform 0–6 area score for calculation, provides a better correlation with patients’ perception of improvement. Further refinement might be brought in by weighing the different characteristics (scale, redness, induration) of the plaques, the visibility (social handicap) and functional impairment of specific locations and the intensity of itch. A better clinically relevant outcome measure is clearly required, but full discussion of this subject is beyond the scope of this review.

In general, PASI does not correlate well with HRQoL measures, but improvement leading to PASI75 response or better tends to correlate with DLQI values implying a small to nil effect on patient’s HRQoL. On the other hand, relapse appears to increase the impact of PASI change on HRQoL, as shown following discontinuation of treatment (at week 33) of sustained PASI75 responders to adalimumab in the REVEAL clinical trial. An approximately twofold disproportionately greater degree of worsening of DLQI score compared with the degree of worsening of PASI was observed while patients underwent discontinuation of therapy (week 52) compared with early in treatment (week 4). There was a significant interaction (P < 0.0001) between the PASI-DLQI correlation and study period (week 4 or 52). The mean DLQI score in patients with responses lower than PASI50 was 9.5 at week 52 (loss of response following discontinuation) vs. 5.3 at week 4 (primary failure); conversely, in patients with PASI90 response, it was numerically higher in those who maintained their response despite discontinuation than at week 4.
scores compared to those with non-visible lesions, neck and/or décolletage area involvement being associated with the greatest HRQoL impairment. These findings provide further support for the convenience of weighing topographic aspects of area and severity assessment according to itch and/or visibility of lesions.

As in many other areas, technological/therapeutic developments precede changes in paradigms of psoriasis treatment. According to a recent meta-analysis, the overall differential risk with respect to placebo of the available biologic treatments is 0.62 (95% confidence intervals, 0.61–0.64) for PASI75 and 0.44 (95% confidence intervals 0.42–0.45) for PASI90 at the end of the induction phase (week 24). Thus, PASI90 response being unlikely, achieving PASI75 response meets therapeutic expectations in most patients, even though 15.4% of them were not satisfied with the condition of their skin in one study. Nevertheles, combining data from two adalimumab trials, the PASI100 and PASI90 to <100 groups demonstrated a >10-point decrease in DLQI total scores at week 16, and these changes were significantly greater than those observed for the PASI75 to <90 group (8.5) and the other PASI response groups (P < 0.001). Furthermore, in Japanese phase III trials of infliximab, where PASI75 and PASI90 response rates at weeks 50/66 were 66.7% and 46.7% respectively, the DLQI = 0–1 response rates were significantly different (50% and 85.7%, P = 0.007).

Patients who achieved a PASI90 response had a significantly higher percentage of achieving a DLQI of 0 or 1 than the patients who achieved a PASI75 but not a PASI90 response. Interestingly, PASI90 response achievers were younger, and the median serum trough level of infliximab was maintained at 2 µg/mL or more in the PASI90 responders, whereas it was less than 1 µg/mL at week 30 and thereafter in the others.

The introduction of anti-IL17 drugs in clinical practice bears the promise of achieving PASI90 response or better in the majority of patients, even though their effect, especially regarding long-term efficacy, needs to be evaluated more extensively before definite conclusions can be drawn. In phase II clinical trials, PASI90 responses were achieved at week 12 in up to 52%, 71% and 75% of patients treated with secukinumab, ixekizumab and brodalumab, respectively. In phase III trials of secukinumab, PASI90 response is achieved by 69.8–72.4% of patients treated with the 300 mg dose at week 16, and their PASI100 response rates remain close to 40% since week 16 up to week 52.

A post-hoc analysis of ixekizumab phase II data provides further confirmation of the role of PASI90 as new therapeutic goal standard: DLQI = 0–1 response rates according to PASI response categories were 12.7% for PASI < 75, 33.3% for PASI75 < 90, 79.3% for PASI90 < 100 and 84.4% for PASI100 at week 16. Differences between the former two or the latter two categories were not significant, whereas significant differences were observed when any of the categories with PASI < 90 response was compared with any of the categories with PASI90 or higher response. The same applies to DLQI = 0 response, the corresponding percentages being 1.6%, 6.7%, 58.6% and 53.1%, respectively.

In conclusion, there is accumulating evidence in support of PASI90 response becoming the new therapeutic goal standard based on its better correlation with HRQoL improvement and DLQI = 0–1 status (absence of effect on HRQoL). Further research is required to confirm the value of absolute PASI cut-offs as a measure of therapeutic success independent of baseline PASI and duration of treatment, and to develop newer, more practical and more accurate disease-specific measures of psoriasis severity and therapeutic outcome taking into account the multiple factors that impact the patient’s HRQoL.

Biologic treatments have revolutionized the treatment of psoriasis, but their cost of acquisition has imposed a burden on health care systems and (at least in some of them) on clinicians charged with budget micromanagement. Generic preference-based measures are appropriate when comparing costs and benefits of treatment to make resource allocation decisions, as they reflect the social preferences of a population. The generic measure EuroQol 5D (EQ-5D) index has been chosen as an indirect utility measurement by several Health Technology Assessment agencies in cost-effectiveness analyses where costs are compared with the benefits of HRQoL, and the EQ-5D Visual Analogue Scale (VAS) is a convenient approach for direct validation.

An attempt should be made to correlate EQ-5D and EQ-5D VAS (‘mapping’) with disease-specific measures, including: (i) absolute or relative change of PASI with respect to baseline (pre-treatment) or maintenance status, (ii) absolute PASI values (with cut-off levels to be established as clinically meaningful anchors), (iii) patient-reported outcomes, (iv) banding of DLQI (or better performing disease-specific instruments) and (v) other elements such as visibility, functional/social impairment, psychological impact or musculoskeletal symptoms. Whenever possible, attempts should be made in randomized clinical trials, cross-sectional studies and registries to identify algorithms that allow conversion of disease-specific measures into utilities.

References


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