Clear or almost clear skin improves the quality of life in patients with moderate-to-severe psoriasis: a systematic review and meta-analysis

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Abstract
Psoriasis Area and Severity Index (PASI) 75 response is currently considered the gold standard for assessing treatment efficacy in moderate-to-severe psoriatic patients. PASI 90 response denotes better clinical improvement compared to PASI 75. Very few studies have assessed if a greater PASI clinical response is associated with greater improvements in Dermatology Life Quality Index (DLQI). A systematic review and meta-analysis was performed to assess the association between PASI response and DLQI. The study was conducted to assess whether greater improvement in PASI scores from PASI 75–89 to PASI 90 is associated with greater quality of life (QoL) improvements, specifically DLQI scores. Systematic searches were conducted in MEDLINE, EMBASE and Cochrane Library to identify studies evaluating biologic interventions in adult moderate-to-severe psoriasis patients reporting PASI response and their corresponding DLQI change from baseline score. The quality of evidence was assessed through Jadad score for randomized controlled trials and Downs and Black’s checklist for observational studies. Meta-analysis estimated change from baseline in DLQI for PASI 75–89 responders to be 78% (95% credible intervals [CrI]: 75–82%) and for PASI 90 responders to be 90% (95% CrI: 88–93%). This implies 12% greater improvement in DLQI score for PASI 90 responders compared with PASI 75–89 responders. In addition, the meta-analysis also showed a statistically significant difference in DLQI score of 0/1 between PASI 75–89 and PASI 90 responders (45% [95% CrI: 41.0–50.0%] and 73% [95% CrI: 70.0–76.0%], respectively, Bayesian P < 0.0001). In conclusion, substantial improvement in clinical efficacy is associated with improved QoL in patients with moderate-to-severe psoriasis suggesting that PASI 90 responders (clear or almost clear skin) could achieve a superior QoL compared to PASI 75–89 responders.

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Conflicts of interest
This study was sponsored by Novartis Pharma AG, Basel, Switzerland. Luis Puig- consultancy honoraria and participation in clinical trials sponsored by Novartis. Howard Thom- consultant for Novartis Pharma AG and Eli-Lilly; Patrick Mollon and Haijun Tian are employees of Novartis Pharma AG, and Ramakrishna GS is employee of Novartis Healthcare Private Limited

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Introduction
Psoriasis, a chronic, relapsing, immune-mediated, inflammatory skin disease affecting approximately 2–3% of the population is associated with a significant disease burden.1 A report by the International Federation of Psoriasis Associations indicates that in the US there is an approximate loss of 56 million hours of work and USD 2–3 billions spent on treatment every year (http://www.ifpa-psio.org/, accessed 18 Jan 2016). The World Health Organization (WHO) also recognizes psoriasis as a serious non-communicable disease. Patients with psoriasis
also have an increased risk of developing comorbid conditions such as psoriatic arthritis, cardiovascular diseases, infections, malignancies and autoimmune diseases. Therefore, patients with psoriasis have a significantly compromised health-related quality of life (QoL), leaving them stressed, socially withdrawn, and importantly, with suicidal tendency. Approximately 25–44% of patients have moderate-to-severe disease, and need an aggressive treatment due to increased severity of symptoms.

The goal of treatment is to reduce the signs and symptoms of the disease, possibly slowing the natural progression of the disease. Available systemic biologic treatments target the pathophysiological pathways modulated by several cytokines. Currently available options available in this class of drugs include anti-TNF agents (infliximab, adalimumab and etanercept), anti-interleukin (IL)-12/23 (ustekinumab) and anti-IL-17A agents (secukinumab). The Psoriasis Area and Severity Index (PASI) remains the most common efficacy endpoint in clinical trials and is considered as a gold standard since it accounts for both severity (erythema, induration and desquamation) and extent of disease (head, trunk, arms and legs). However, the benefit remains incomplete if this does not translate into improved quality of life. Therefore, evaluating the impact on patients’ QoL following treatment, and therefore, any reduction in the disease burden seems one of the most important aspects of treatment considering the tormenting impact of psoriasis. This is especially pertinent since treatment with biologic agents is costly, and would be appreciated when reflects in an improvement in QoL.

Keeping this in view, we performed a systematic review and meta-analysis to understand if the improvement in PASI scores results in an overall improved QoL in adult patients with moderate-to-severe psoriasis where patients were treated with one of the approved systemic biologic agents. PASI was specifically chosen as the clinical efficacy endpoint of interest as it is the most commonly used score in psoriasis trials, making meta-analysis of existing trials possible. A 75% or greater improvement from baseline (PASI 75) is widely accepted as a useful and realistic clinical outcome. Importantly, PASI 90, meaning a 90% or greater improvement from baseline, fulfills the European regulatory definition of therapeutic success and appears to be better correlated with improved health-related QoL compared with PASI 75. For evaluating the impact on QoL, we used Dermatology Life Quality Index (DLQI), a commonly used PRO in psoriasis trials. The treatment goal for DLQI can be defined as a score of 0 or 1, implying that patient’s QoL is not affected by psoriasis. Patients achieving PASI 90 will have better clinical improvement compared to PASI 75. Almost clear skin (PASI 90) will be beneficial for patients if it leads to better quality of life (DLQI score). Here, we present the results from this systematic review, and meta-analysis from five clinical trials.

**Materials and Methods**

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The selection of databases, eligibility criteria, outcomes of the review and analyses methods were defined a priori in an internal protocol. Study selection, data extraction and quality assessment were performed independently by two assessors. Any discrepancy was reconciled by a third independent reviewer.

**Searches and data extraction**

A comprehensive literature search of MEDLINE (including Medline-in-Process), PubMed, EMBASE, the Cochrane Centre Register of Controlled Trials and National Health Service Economic Evaluation Database was carried out in Ovid for relevant articles for last 10 years (2004–2014). The detailed search strategy is presented in Table 1.

Published articles were included if they investigated one of the following treatments: all disease-modifying anti-rheumatic drugs (DMARDs) including biologics used for psoriasis treatment. The comparisons had to be done either vs. a placebo or an active treatment. Study design included randomized clinical trials (RCTs) with any blinding status, non-RCTs and observational studies. There was no restriction on treatment duration. Patient population consisted of adults (≥18 years of age) of any gender/race with moderate-to-severe psoriasis. The inclusion criteria in the clinical trials and studies were in line with the definition of moderate-to-severe psoriasis. Studies had to report at least one outcome of interest, that is, PASI 75–89 (≥75–<90% improvement (reduction) in PASI score with respect to baseline), PASI 90 (≥90% improvement (reduction) in PASI score), PASI 100 (complete clearance of psoriasis corresponds to absolute score PASI = 0) and their corresponding DLQI 0/1 response rates. Data were segregated by the time-point according to different

| Search criteria | Search terms/strings |
|-----------------|---------------------|
| **Disease** | PASI ((psoriasis area and severity index) or (psoriasis area severity index or PASI or PASI score or psoriasis area severity index 75 or PASI 75 or psoriasis area severity index 90 or PASI 90 or psoriasis area severity index 100 or PASI 100)).mp. |
| **Comorbidities** | (comorbidity or co-morbidity).mp. |
| **Quality of life** | (quality of life or quality-of-life or QoL or disability or morbidity or mortality or patient reported outcome or patient-reported outcome or PRO or Quality adjusted life years or QALY or Disability adjusted life years or Quality-adjusted life years or Disability-adjusted life years or DALY or prefer* or questionnaire or scale or score or satisfaction* or utility* or dermatology life quality index or DLQI or EQ-5D).mp. |

**Table 1 List of search terms used for retrieving relevant studies from various databases**
outcomes reported, both for the randomized phase or the long-
term maintenance phase.

Only articles in English language were included. Exclusion cri-
teria were as follows: use of conventional interventions, no subgroup analysis for disease of interest and studies not reporting secondary outcomes data (QoL) for the primary outcome of interest (PASI response).

After exclusion of duplicates, titles and abstracts were screened for inclusion and exclusion. Potentially relevant articles were checked in full text for inclusion. Study characteristics (e.g. study design, phase, blinding status, sample size), study population (e.g. age, sex, duration of psoriasis), and study results of included trials were extracted using a standardized form. Primary outcomes were PASI response defined as PASI 75–89, PASI 90 and PASI 100. Secondary outcomes included DLQI response of 0/1, defined as final DLQI equal to 0 or 1, DLQI score mean change from baseline and DLQI score mean change from baseline.

Quality assessment
The Jadad scoring system was used to appraise adequacy of randomization, blinding and reporting of withdrawals/discontinuations for RCTs, while the Downs and Black’s checklist was used to appraise the non-RCTs. Four studies attained a maximum score of 5 on the Jadad scale, suggesting adequate reporting of randomization, blinding and reporting of withdrawals/discontinuations. While one study17 had a score of 3, no other study reported a Jadad score of less than 4, indicating that studies included in the review were of good quality. The use of adequate method of allocation concealment was reported in all the included studies, resulting in allocation concealment grade ‘A’. None of the studies reported an inadequate method of allocation concealment or that method of concealment was not used in the study. The open-label single arm trials were of good quality in terms of reporting and assessment of bias – one study21 scored 16 and other study17 scored 18 on the Downs and Black’s checklist.

Data analysis
Meta-analysis is a statistical technique to combine multiple estimates of a quantity into a single estimate.22 It is most commonly used to combine estimates of treatment effects from multiple trials but can be used to synthesize estimates of any quantity, as is often necessary in medical decision-making.23 For the current study, Bayesian meta-analysis was used to combine estimates of DLQI improvement in PASI responder subgroups when three or more studies are available. If sufficient data were available to fit both, a choice between fixed and random effects models was made on the basis of lowest Deviance Information Criterion (DIC) and residual deviance.24,25

The continuous data included DLQI score mean percentage change from baseline and DLQI score mean change from baseline. The dichotomous data were DLQI response of 0/1. Relative risks with 95% CrI for dichotomous data and mean differences with 95% CrI for continuous data were calculated. Classical statistically significant differences between DLQI effect in PASI 75–89 and PASI 90 responders, at 0.05 level, were assessed using one-sided Bayesian P-values; these are the Bayesian probability that DLQI effect was greater in one responder group than the other. Meta-analysis of studies was conducted using OpenBUGS (version 3.2.2 rev 1063).26

Meta-analysis of studies reporting DLQI percentage change from baseline and DLQI response of 0/1 was conducted for PASI 75–89 and PASI 90 separately. Sample size-weighted averages were used to impute mean and standard deviation of DLQI percentage change from baseline in studies that did not directly report for PASI 75–89 or PASI 90.

Results
Systematic search in databases (MEDLINE, EMBASE and Cochrane Library) yielded 1085 results. Due to the overlap of records across the databases searched, 292 abstracts were identified as duplicates. Following the first screening of these citations according to their titles and abstracts, 264 potentially relevant references were identified. A detailed evaluation of full-text reports of these citations was performed, and 251 studies were excluded due to non-reporting of the secondary outcome data (i.e. DLQI) for the patients achieving PASI 75–89 and PASI 90 responses. None of the studies reported secondary outcome data for PASI 100 (Fig. 1). Of the 13 studies extracted, four studies met the predefined eligibility criteria for inclusion in this meta-analysis, and all included patients with moderate-to-severe psoriasis. Apart from the four studies identified from systematic literature search, recently published results from CLEAR study were also included in the meta-analysis. CLEAR, a head-to-head trial, compared the efficacy and safety of secukinumab with ustekinumab in subjects with moderate-to-severe plaque psoriasis.

Primary objective of CLEAR study was to demonstrate superiority of secukinumab vs. ustekinumab with respect to PASI 90 response at week 16. DLQI response was also reported in the study.27 The details of the demographics and disease characteristics of study participants at baseline are listed in Table 2. Baseline demographics and clinical disease characteristics were comparable across the included studies. The mean age of the patients in the RCTs was about 40 years, and >65% patients were male. The mean duration of disease ranged from 15 to 18.8 years.

Qualitative analysis

Patients achieving primary efficacy endpoint (10–16 weeks)
Studies included in the analysis of the randomized phase of the
Table 2 The demographics and disease characteristics of study participants at baseline

| Trial Name       | Interventions                  | Number of participants | Gender Male n (%) | Gender Female n (%) | Age (years) Mean (SD) | Duration of psoriasis (years) Mean (SD) |
|------------------|--------------------------------|------------------------|-------------------|---------------------|-----------------------|-----------------------------------------|
| PSUNRISE trial  | Infliximab 5 mg/kg             | 215                    | 137 (63.7)        | 44.4 (13.3)         | 18.8 (11.4)            |
|                  | Adalimumab pooled              | 1469                   | 971 (66.1)        | 44.1 (13.1)         | 18.6 (11.6)            |
|                  | Adalimumab 40 mg EOW           | 108                    | 70 (64.8)         | 44.1 (13.2)         | 18.6 (12)              |
|                  | Placebo                        | 53                     | 35 (66)           | 45.4 (13.4)         | 18.8 (12)              |
| CHAMPION & REVEAL trials |                      |                        |                   |                     |                       |
| CHAMPION trial   | Secukinumab 300 mg             | 245                    | 169 (69.0)        | 44.9 (13.3)         | 17.4 (11.1)            |
|                  | Secukinumab 150 mg             | 245                    | 168 (68.6)        | 45.4 (12.6)         | 17.3 (12.4)            |
|                  | Placebo                        | 248                    | 172 (69.4)        | 46.5 (12.6)         | 17.3 (12.4)            |
| ERASURE trial    | Secukinumab 300 mg             | 327                    | 224 (68.5)        | 44.5 (13.2)         | 15.8 (12.3)            |
|                  | Secukinumab 150 mg             | 327                    | 236 (72.2)        | 45.4 (12.9)         | 17.3 (12.2)            |
|                  | Etanercept 50 mg               | 326                    | 232 (71.2)        | 43.8 (13.0)         | 16.4 (12.0)            |
|                  | Placebo                        | 326                    | 237 (72.7)        | 44.1 (12.6)         | 16.6 (11.6)            |
| FIXTURE trial    | Secukinumab 300 mg             | 337                    | 229 (68)          | 45.2 (13.96)        | 19.6 (12.9)            |
|                  | Secukinumab 150 mg             | 339                    | 252 (74.3)        | 44.6 (13.67)        | 16.1 (11.24)           |
| CLEAR trial      | Secukinumab 300 mg             |                        |                   |                     |                       |
|                  | Ustekinumab                    |                        |                   |                     |                       |

EOW, every other week.
trials assessing the correlation between PASI response and QoL are listed in Table 3.

**DLQI mean change from baseline**

Two studies reported data for mean change from baseline in DLQI score for both PASI 75–89 and PASI 90 responders. Kalb et al.21 2013 only reported DLQI score for PASI ≥75 and PASI 90 but PASI 75–89 could be imputed as score in PASI ≥75 is the weighted average of PASI 75-89 and PASI 90; the imputed mean DLQI change from baseline was –8.33, with a standard deviation of 14.46 and sample size of 50.21 Score for PASI 90 in the study by Revicki et al.28 was imputed as the weighted average of PASI 90–99 and PASI ≥100; the mean change was –10.48 with a standard deviation of 5.11 and sample size of 447.

Meta-analysing these results, the mean reduction from baseline in DLQI score, that is, improvement, was greater for PASI 90 responders as compared with PASI 75–89 responders (Fig. 2). This difference was statistically significant in the pooled CHAMPION and REVEAL trials.28

**DLQI percent improvement from baseline**

Only one study reported data for mean percent improvement from baseline in DLQI score for both PASI 75–89 and PASI 90 responders. The mean percent improvement from baseline in DLQI score was greater for PASI 90 responders as compared with PASI 75–89 responders (91% vs. 75% respectively).29

**DLQI 0/1 response**

Two studies reported data for DLQI response of 0/1 for PASI 75–89 and PASI 90 responders.17,30 In both studies, greater proportion of PASI 90 responders achieved a DLQI response of 0/1 as compared with PASI 75–89 responders (74% vs. 56.7% and 85.7% vs. 50% respectively). This difference was statistically significant for studies with secukinumab (P < 0.001).30

**Patients on maintenance phase (26–52 weeks)** Studies included in the analysis of the maintenance phase of the trials assessing the correlation between PASI response and QoL are listed in Table 3.

**DLQI score mean change from baseline**

The mean reduction from baseline in DLQI score, that is, improvement, was greater for PASI 90 responders as compared with PASI 75–89 responders (–8.62 vs. –8.2 respectively) at Week 26.21

**Meta-analysis** Only two studies reported DLQI 0/1 response and one study reported DLQI mean change at maintenance

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### Table 3  List of studies included in the analysis of the primary efficacy endpoint at 10–16 weeks and meta-analysis

| Clinical trials included | Source | Interventions assessed |
|-------------------------|--------|------------------------|
| PSUNRISE (single arm)   | Kalb 2013 | Infliximab             |
| CHAMPION                | Navarini 2014 | Adalimumab |
| REVEAL                  | Revicki 2007 | Adalimumab |
| ERASURE                 | Internal | Secukinumab |
| FIXTURE                 | Internal | Secukinumab |
| CLEAR                   | Internal | Secukinumab |

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![Figure 2](image-url)  
**Figure 2**  Mean change in DLQI score from baseline by PASI responders. DLQI, dermatology life quality index.

![Figure 3](image-url)  
**Figure 3**  DLQI response by patients achieving PASI response. DLQI, dermatology life quality index; PASI, psoriasis area and severity index.

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phase; so, only the primary efficacy endpoint (10–16 weeks) was meta-analysed.

**Patients achieving primary efficacy endpoint (10–16 weeks)**

*Percentage change in mean DLQI from baseline* Four studies including the Novartis CLEAR study reported change in DLQI for PASI 75–89 and PASI 90 responders.\(^21,28,30\) Using a fixed effects model, the mean percentage reduction from baseline in DLQI scores, i.e. improvement, was greater (Bayesian probability >99.99%) in PASI 90 responders (90% [95% Credible Intervals, CrI: 88%, 93%]) as compared with PASI 75–89 responders (78% [95% CrI: 75%, 82%]). A forest plot for the studies included in this meta-analysis is presented in Figure 4.

*DLQI 0/1 response* Three studies including Novartis CLEAR study reported data for DLQI response of 0/1 for PASI 75–89 and PASI 90 responders.\(^27,29,30\) Using a fixed effects model, a greater proportion of PASI 90 responders (Bayesian probability >99.99%) achieved a DLQI score of 0/1 (76% [95% CrI: 70%, 76%]) as compared with PASI 75–89 responders (45% [95% CrI: 41%, 50%]). A forest plot for the studies included in this meta-analysis is presented in Figure 5.

**Discussion**

The present analysis demonstrated that improvement in QoL as evaluated by DLQI score was commensurate with a higher clinical response as evaluated by PASI response. Overall, the improvement in QoL was greater in PASI 90 responders as compared with PASI 75–89 responders in both short- and long-term. The improvement in QoL was sustained over 26–52 weeks in PASI 90 responders while being in maintenance phase.

The present systematic review and meta-analysis focused on an important outcome in psoriasis trials, that is, the clinical improvement, and the benefit based on PRO, both critical to establishing the therapeutic effectiveness and satisfaction with treatment, especially biologics. This is principally pertinent because of two reasons. First, psoriasis is associated with significant negative impact on emotional, physical, psychological and social functioning, and second is the cost consideration for treatment with biologics.

The data from studies included in this systematic review demonstrated a consistent association between the clinical response as assessed by PASI 75–89 and PASI 90, and disease-specific QoL as assessed by DLQI during a short-term treatment (10–16 weeks); the reduction in PASI scores was directly associated with the improvement in DLQI scores. PASI 90 responders had a greater improvement in DLQI scores as compared with PASI 75–89 responders, which reflected the clinical benefit with QoL. The mean percentage reduction from baseline in DLQI scores was greater in PASI 90 responders as compared with PASI 75–89 responders (91% vs. 75% respectively).\(^29\) This additional 16% improvement in DLQI scores for PASI 90 responders vs. PASI 75–89 responders seems meaningful. Similar and sustained benefit was noted during long-term maintenance phase (26–52 weeks). The 52-week maintenance phase data showed that a significantly greater proportion of PASI 90 responders achieved a DLQI score of 0/1 vs. PASI 75–89 responders,\(^30\) suggesting a sustained improvement in clinical response and QoL.

Meta-analysis estimated a 78% and 90% change from baseline in DLQI scores for PASI 75–89 and PASI 90 responders, respectively, at the primary endpoint of 10–16 weeks. Similarly, a greater proportion of patients achieved a DLQI score of 0/1.
representing no impact on QoL, as compared with PASI 75–89 responders (73% vs. 45%). These results are consistent with data reported for individual studies where a better clinical response was associated with an improved QoL. Similar results were reported by a recent review where PASI 75 responders had a significant reduction in mean DLQI scores as compared to those having a 50–75% or <50% PASI response. Overall, a consistent trend of association was observed between improvement in PASI and DLQI scores; a reduction in PASI score was directly related with the improvement in DLQI. This supports the importance from the patients’ QoL perspective of achieving the highest possible response, PASI 90. The treatment options provided should include therapies which can achieve higher proportion of patients with PASI 90 or above scores resulting in better QoL for patients with psoriasis.

These analyses provide evidence of superiority in DLQI outcomes in PASI 90 compared to PASI 75–89 responders. However, there are certain limitations that should be considered while interpreting the results of this review. There were limited publications with relevant data corresponding to the spectrum of PASI improvement. Also, the study conclusion was based on studies that reported DLQI data; results of other HRQoL tools were not adequately reported. There was also insufficient evidence available for meta-analysis at the maintenance phase; so, longer term effects are uncertain. There was also lack of real-world evidence to support the conclusions.

It was not possible to perform a meta-analyses looking at correlation between PASI 75–89 and PASI 90 response and mean change DLQI and DLQI score of 0/1 in subgroups stratified by age, sex or other covariates due to the limited number of studies included in the analyses (there were only four studies in the mean change DLQI analysis and three in the DLQI score of 0/1 analysis), and none of the published studies (PSUNRISE, CHAMPION, REVEAL) reported the requisite subgroups. While it would be possible to re-analyse the FIXTURE, ERASURE and CLEAR data to obtain the subgroup information, this would still lead to a very limited evidence base for meta-analysis. Findings showed PASI 90 translated into greater QoL compared with PASI 75–89 in both short- and long-term but the underlying causal explanations remain unknown. More research is needed to explore and interpret the association between PASI and DLQI.

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