A systematic review of 457 randomised controlled trials using the Dermatology Life Quality Index: experience in 68 diseases and 42 countries

Running Head: Systematic review of treatment/intervention using the DLQI.

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Data availability: All data are incorporated into the article and its online supplementary material.

Ethics statement: Not applicable.
What is already known about this topic?
The DLQI has been used in clinical practice and research for 29 years and continues to be the most frequently used patient reported outcome (PRO) tool for dermatology. Previous systematic reviews of the DLQI have focused on psoriasis, biologics, or validation of the DLQI.

What does this study add?
This systematic review of 457 randomized controlled trials describing research on 198,587 patients provides information covering 68 diseases and a wide range of interventions to which the DLQI has been applied. Details of study settings and countries, numbers of patients recruited, ages, and DLQI assessment periods are summarised. Longitudinal studies where the minimal clinically important difference (MCID) was achieved have been identified and analysed, with a comprehensive analysis of bias. DLQI scores were primary endpoints in 24 (5.3%) studies.

What are the clinical implications of this work?
This systematic review allows structured access to inform future users of the DLQI, confirms the very extensive experience of the DLQI in RCTs in dermatology and demonstrates the utility of the DLQI as the patient reported outcome measure of choice over the last two decades. This systematic review provides valuable evidence to aid researchers and clinicians in its further use and help its continued implementation into routine clinical practice.
Abstract

Background: Over 29 years of clinical application, the Dermatology Life Quality Index (DLQI) has remained the most used PRO in dermatology due to its robustness, simplicity and ease of use.

Objectives: This systematic review aimed to generate further evidence of its utility in randomised controlled trials and is the first to cover all diseases and interventions.

Methods: The methodology followed PRISMA guidelines and included seven bibliographic databases, searching articles published from January 1 1994 until November 16, 2021. Articles were reviewed independently by two assessors, and an adjudicator resolved any opinion differences.

Results: Of 3220 screened publications, 457 articles meeting eligibility criteria for inclusion, describing research on 198,587 patients, were analysed. DLQI scores were primary endpoints in 24 (5.3%) of studies. Most studies were of psoriasis (53.2%), although 68 different diseases were studied. Most study drugs were systemic (84.3%), with biologics 55.9% of all pharmacological interventions. Topical treatments comprised 17.1% of total pharmacological interventions. Non-pharmacological interventions were 13.8% of the total interventions, mainly laser therapy and UV treatment. 63.6% of studies were multicentre, with trials conducted in at least 42 different countries, and 41.7% were conducted in multiple countries. Minimal importance difference (MID) was reported in analysis of 15.1% of studies, but only 1.3% considered full score meaning banding of DLQI. 61 (13.4%) of studies investigate the statistical correlation of DLQI with clinical severity assessment or other PRO/QoL tools. 62% to 86% of studies had within group scores differences greater than the MID in “active treatment arms”. The JADAD risk of bias scale showed that bias was generally low, as 91.4% of studies had JADAD scores of ≥3; only 0.44% of studies showed high risk from randomisation, 13.8% high risk from blinding and 10.4% high risk from unknown outcome of all participants in the studies. 18.3% of studies declared that they followed an intention-to treat (ITT) protocol, and imputation for missing DLQI data was used in 34.1% of studies.

Conclusions: This systematic review provides a wealth of evidence for use of the DLQI in clinical trials to inform researchers’ and clinicians’ decision for its further use. Recommendations are also made for improving the reporting of data from future RCT trials using DLQI.

Introduction

The Dermatology Life Quality Index (DLQI) is the most widely used dermatology patient reported outcome (PRO) measure in routine practice and clinical trials, because of the simplicity of reporting and application, a single meaningful summary score, its ease of completion in two minutes, comparability between studies and over time due to there being only a single version of the tool, and accessibility in over 139 different translations. It is embedded in national guidelines and disease registries in >45 countries and is available in 138 translations. However, users of the DLQI need structured access to evidence concerning its use. This should include the score changes seen (and to be expected) in intervention studies, and the range of diseases where it has been of value as an outcome measure.

Previous reviews of the DLQI focussed on its use in psoriasis or validation and clinical results. This systematic review (SR) is the first to investigate the use of the DLQI from its inception in 1994 to 2021 in randomised controlled trials (RCTs) covering all diseases and both pharmacological/non-pharmacological interventions and whether DLQI outcomes show beneficial effects of the interventions by statistically significant or clinically significant improved scores.
Materials and Methods

Data sources

This study follows 2020 PRISMA guidelines for reporting systematic reviews and checklist. The study protocol and detailed search strategy was published on PROSPERO International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=290587) and is provided in the Supplementary Table 5. Medline (Ovid), Cochrane Library, EMBASE, Web of Science, SCOPUS, CINAHL (EBSCO) and PsycINFO online databases from 1st January 1994 (DLQI creation) to 17th November 2021 were searched independently by two authors (JJ, JV), and results corroborated. Search terms included ‘DLQI’ and ‘dermatology life quality index’. Database specific “article type/study type” keywords, language keywords (English) and age selection keywords were also used to search the required types of study to be included e.g. MESH terms for RCT. Duplicates were excluded.

Search strategy/Selection

Table 1 gives the eligibility criteria for included studies.

Search results were imported into EndNote20®, to keep track of references. Two authors (JJ, JV) independently compared study titles and abstracts retrieved by searches against the inclusion and exclusion criteria and examined full study texts that potentially met the criteria but whose abstracts lacked sufficient information. Rejected studies were recorded with reasoning. A third author (FA) resolved and recorded any study selection disagreements. A PRISMA flowchart gives search counts for inclusions and exclusions and reasons for study exclusions (Figure 1).

Studies not including new DLQI data, and previously published analyses were excluded, as were publications with no DLQI data (but use mentioned), and studies that combined previously randomised treatment arms, so that only single arm (no longer randomised) DLQI data was presented.

Outcome measures extracted

Information recorded included the study aim, disease studied, disease severity, systemic/topical drugs or other interventions, DLQI data collection duration, the research setting, e.g. trial, hospital, clinic, community, single or multi-centred (number of sites), patient demographics (mean or median age, gender, ethnicity stated, country), the number of subjects randomised to each intervention group, and whether DLQI was a primary or secondary endpoint.

Data was extracted from up to three arms for each study: generally, a control or placebo/comparator arm; and up to two intervention arms. Where studies reported multiple dosage strengths for the same drug, only data from the highest dosage arms were extracted. Therapeutic, non-drug interventions were also recorded.

If studies did not report primary data but extracted data from previously published RCT trials and performed post-hoc style analysis, data was obtained from the original published RCTs, particularly about methodology and study design. Sometimes these elements and DLQI score data were supplied in supplementary data files that were also consulted. Drug registrations e.g. NIH, U.S. National Library of Medicine: clinicaltrials.gov, were consulted for data on study protocols, particularly location of studies and number of sites used, if not provided in the articles.
Outcomes recorded relating to the DLQI were total or median scores at baseline and study endpoint, or score differences (if given) for each arm. Evidence of statistically significant and/or clinically significant change (based on minimal clinically important difference) were noted, and whether the DLQI was correlated with other PRO/QoL instruments. Using several PRO measures in combination and/or with disease severity scales in a study may achieve a better understanding of patient outcomes, e.g. capture difference aspects of QoL, or identify disease specific as well as general outcome aspects. Thus, additionally, other PRO tools/QoL measures used in combination with the DLQI were recorded to inform those seeking to use the DLQI (or one of the other outcome measures we captured).

Data extraction and synthesis

For data extraction, guidance of the Cochrane Handbook for Systematic Reviews of Interventions was followed\(^\text{19}\). A RedCAP database\(^\text{20-22}\) (a secure web application for building/managing online surveys and databases) was created based on the Cochrane Handbook Version 6.2\(^\text{23}\) and the updated guidance\(^\text{19}\) recommendations. The authors JJ and JV independently extracted data from the included publications to parallel RedCap database tables, and an adjudicator (FA) resolved any disagreements in data extraction. Missing data were noted in the data templates, but none was sufficiently important to contact original authors. Data was extracted from RedCap to MS-Excel for analysis of totals, means and percentages.

The two reviewers independently assessed the risk of bias (quality) of included studies using the JADAD scale\(^\text{24-25}\). Assessment of bias was made at the individual study level. The domains included in bias analysis were bias arising from the randomisation process, bias due to blinding and bias due to not accounting for all patients. The appropriate reporting of baseline (i.e. imbalances in study arms) and whether any corrections were made in the analysis to account for baseline imbalance were also noted.

Results

A total of 3220 studies were provided by online database searching. There were 1842 duplicates and the remainder 1378 were assessed from the articles’ full text, of which 457 described research on 198,243 patients meeting the inclusion eligibility criteria (Figure 1). Publications of RCTs using DLQI are increasing exponentially, with 72 new studies reported in 2021 (Figure 2).

Study sites and settings

One-third (155, 33.9%) of the RCT trials were single site studies; the majority (291, 63.7%) were multicentre, with 11 (2.4%) study locations being indeterminate. Sixty-four (14.0%) trials were conducted at two sites, 16 (3.5%) at three to five sites, 12 (2.6%) at 6-10 sites, 19 (4.2%) at 11-20 sites, 72 (15.8%) at 21-50 sites, 54 (11.8%) at 51-200 sites, 36 (7.9%) at 101-200 sites and six (1.3%) at >200 sites.

Although the majority of studies (n=255, 55.8%) failed to report the study setting(s), 97 (21.2%) studies were conducted in hospitals, 31 (6.8%) in clinics, 22 (4.8%) in trial centres, 23 (5.0%) in outpatient/ambulatory care and 29 (6.3%) in other settings.

Trials were conducted in at least 42 different countries, although 178 (40.2%) reported multiple countries without listing details (Supplementary Table1). The majority of studies conducted in a single
country were mainly in Europe (excluding the UK) (n=74, 16.7%) while 16 studies (3.6%) were conducted in the UK alone and 30 studies (6.8%) in the USA alone (Figure 3). Ethnicity of subjects was explicitly mentioned in 208 (45.7%) studies.

A great majority of the studies (n=415; 90.8%) recruited both male and female subjects, 14 (3.1%) recruited only male, 21 (4.6%) only female, five (1.1%) studies recorded no gender and two (0.4%) studies recorded gender as ‘other’. Studies recruiting only females were concerning oligomenorrhoea and amenorrhoea in women with polycystic ovary syndrome (PCOS), hirsutism (PCOS), acne, striae distensae, systemic lupus erythematosus with permanent facial skin damage, axillary hyperhidrosis (n=3), plaque psoriasis, rosacea, breast cancer (n=3), xerosis in dialysis patients, hand-foot syndrome, vulvovaginal candidiasis, alopecia, cellulite, hyperpigmentation, peri-orbital pigmentation and melasma. Studies recruiting only males concerned hyperpigmented lips, plaque psoriasis (n=5), psoriatic arthritis, chronic skin lesions due to mustard gas (n=3), actinic keratosis, hidradenitis suppurativa, and lichen sclerosus (n=2). Participants’ average age (where given) of all study arms across all studies was 45 years (range 22-81 years).

**Disease profile**

Sixty-eight different diseases were studied (Table 2). Most studies were of psoriasis (n=243, 53.2%), followed by atopic dermatitis (n=26, 5.7%), urticaria (n=20, 4.4%), eczema (n=17, 3.7%), psoriatic arthritis (n=17, 3.7%), eczema/hand eczema (n=17, 3.7%) and hidradenitis suppurativa (n=11, 2.4%). Overall, studies recruited patients with mild (n=78, 10.2%), moderate (n=289, 38.0%) and severe (n=259, 34.0%) disease, with 136 (17.8%) unspecified. Psoriasis studies recruited mild (n=47, 10.3%), moderate (n=203, 44.4%), and severe (n=184, 40.3%) patients with 23 (5.0%) unspecified.

**Clinical severity and patient-reported outcomes assessment**

Clinical severity assessment tools used included a mixture of dermatology-specific and generic measures. The Psoriasis Area and Severity Index (PASI) was employed in 224 (39.6%) studies, along with Patient Global Assessment (PGA) 17.1%, Investigator Global Assessment (IGA) 9.0%, Nail Psoriasis Severity Index (NAPSI) 4.6%, Eczema Area and Severity Index (EASI) 3.5%, affected Body Surface Area (BSA) 3.4% and the Scoring Atopic Dermatitis (SCORAD) 2.8%. The PRO/QoL tools employed included the 36-Item Short Form Survey RAND Corporation (SF-36) 9.4%, the Hospital Anxiety and Depression Scale (HADS) 3.7% and the EuroQol EQ-5D 3.0%. Many other clinical severity assessment and PRO/QoL tools were also used (Supplementary Table 2).

**Interventions using DLQI in randomised clinical trials**

Summary data including disease, systemic, topical and non-medicinal interventions, total subjects randomised, mean or median age for each intervention arm, DLQI assessment period, clinical setting, most commonly used QoL tools, country of the study and JADAD score and domains from every included study are given in Supplementary Table 3.

Most study drugs were systemic (n=373, 85.1%), with biologicals (growth factors, immune modulators, monoclonal antibodies, and products derived from human blood and plasma) comprising 251 (55.8%) of
all pharmacological interventions. Topical treatments used in 77 studies comprised 17.1% of the total pharmacological interventions (Table 3).

32 different biologics were used in the studies, the most common being etanercept, ustekinumab, adalimumab, secukinumab and ixekizumab for psoriasis and psoriatic arthritis (Table 4).

The dominant non-pharmacological interventions were laser treatment (n=10, 15.9% of the total non-pharmacological interventions), followed by ultraviolet treatments (n=6, 9.5%), educational intervention (n=5, 7.9%), Chinese (traditional) herbal medicines (n=4, 6.3%), digital applications (n=3, 4.8%), motivational interviewing (n=2, 3.2%), low energy diets (n=2, 3.2%), microneedle (n=2, 3.2%) and platelet-rich plasma (n=2, 3.2%) with another 27 non-pharmacological interventions used in single studies (42.9%). Non-pharmacological interventions comprised only 12.3% of the total interventions.

**DLQI Scores**

The DLQI was reported as a primary endpoint in 24 (5.3%) of studies. Primary outcomes focused on clinical determinations of disease severity and progression, the most common being PASI. Generally, DLQI scores were reported as mean baseline and endpoint scores (from which we calculated differences), or as mean difference scores, or both. Mean DLQI baseline and endpoint scores were reported in arm1 (control) by 26.3% of studies, arm2 (intervention) by 27.8%, and arm3 (intervention) by 10.9% of studies. Some studies reported only median scores.

Reported difference scores often differed from differences calculated from reported baseline and endpoint mean scores, having been calculated per patient basis rather than the difference of the group means. There was a trend to report differences when these were deemed significant, otherwise baseline and endpoint scores were reported. Table 5 and Figure 4 give the DLQI score differences.

Sixty-nine studies (15.1%) used minimal importance difference (MID) in their analysis, but only six (1.3%) considered full score meaning banding of the DLQI scale. Many studies also used the proportion of patients achieving a final total DLQI score of 0 or 1 as an endpoint. In addition, 49 (10.7%) studies investigated statistical correlation of DLQI with other PRO/QoL tools.

**Study bias**

Randomisation was mentioned in 447 studies (97.8%), however the method was appropriate in only 318 studies (69.6%). Blinding was mentioned without further details in 77 studies (16.9%), 291 studies (63.8%) described appropriate blinding, 21 studies (4.6%) used an inappropriate blinding method, in 39 studies (8.6%) blinding was not mentioned under methodology, and in 26 studies (5.7%) study design made blinding irrelevant. Baseline data demographics were described across the study arms in 420 studies (92.3%), adjustments were made during analysis for baseline imbalances in three studies (0.7%) and were not mentioned in 28 studies (6.2%). Figure 5 gives the distribution of JADAD scores and summarises risk of bias.

Eight-four studies (18.4%) stated that they followed an intention-to-treat (ITT) protocol. Imputation for missing DLQI data was used in 157 (34.4%) studies. Several imputation methods were used, including fixed imputation (last observation carried forward) (n=76, 16.6%), non-responder imputation (n=47, 10.3%) and multiple imputation (n=20, 4.4%). Eighty-four studies (18.4%) used no imputation and the method was not stated in 151 (33.3%).
Discussion

This systematic review represents 27 years of global implementation of DLQI in RCTs compiling a wealth of information in this one-stop source. The global reach of the DLQI is demonstrated by its use in 42 different countries and by 40.2% of studies using it in multiple countries. Furthermore, 40.9% of studies were conducted at >10 sites and only 34% were conducted at a single site.

The number of studies assessing systemic drugs (n=373, 85.1%) results from the large number of new biologics (n=251, 55.8% total drugs assessed) being developed, mainly for treatment of psoriasis, psoriatic arthritis, atopic dermatitis, urticaria and hidradenitis suppurativa. Topical treatments only comprised 17.1% (n=77 studies) of the pharmacological interventions studied. A recent systematic review has confirmed that biologics can significantly improve DLQI scores in patients with psoriasis. However, 68 different diseases were studied, emphasising the generic strengths of the DLQI as a dermatology-specific instrument and a broader interest within the research community.

Non-pharmacological interventions (n=63, 13.8% of total interventions) were mainly laser therapy (n=10, 15.9%) and UV treatment (n=6, 9.5%) as well as various non-pharmacological interventions used in single studies (42.9% of non-pharmacological interventions). The low number of traditional medicine interventions may be due to the required complexity of clinical trials, and novel laser or UV treatments have commercialisation potential whereas widely used traditional medicines cannot receive patent protection.

Results showed that 25.6%, 28.7% and 12.0% of studies reported DLQI scores difference for arm1, arm2 and arm3, respectively. In addition, in 59.3%, 65.2% and 25.4% of studies for arm1, arm2 and arm3 respectively, a score difference could be calculated from provided baseline and end of the study DLQI scores. Furthermore, 61% to 86% of studies in the “active arms” had within group scores differences greater than the MID representing differences for the control/placebo arm of 35%. Such a result might be expected as studies usually included only more severely affected patients (most often, in psoriasis, screened using PASI).

Risk of bias was generally low, as 91.6% of studies have JADAD scores of 3 or above, 0.44% of studies showed high risk from randomisation, only 13.6% having high risk of bias from blinding and 10.1% high risk from unknown fate of all participants in the studies. Although it might be expected that older studies had more potential for bias, this review showed no correlation between publication date and JADAD score (Spearman rank r² = 0.022). Allocation concealment, although now considered an important element in study bias, was barely mentioned. Most studies (92.6%) did check for baseline equivalence between study arms, although older studies often neglected to do so and very few indicated any baseline correction being performed during analysis.

Assessment of bias was made at the level of an individual result, rather than at a study or outcome level. The domains included in bias analysis were bias arising from the randomisation process, bias due to blinding and bias due to not accounting for all patients in the trial. The appropriate reporting of baseline (i.e. imbalances in study arms) and whether any corrections were made in the analysis to account for baseline imbalance were also noted.

This systematic review has some limitations. Although only English language articles were reviewed, these articles often reported on RCTs carried out using many different DLQI translations. The reports
generally amalgamated DLQI data and did not report score distribution for each language. It would be of interest if it were possible to analyse the original raw data to identify possible interpretation differences.

We examined and only studies with extractable DLQI data and did not capture all pharmacological interventions for complex studies involving multiple arms (>3), pre-treatments, multiple phases, crossover studies etc. and those which separately analysed multiple RCTs within the one study. However, all other data in our capture template for these studies were obtained. We did not capture all dosage regimens or administration routes, this being beyond the study’s scope. Limited data was available to describe study settings in most studies. Some studies published invalid data, for example scores greater than the maximum possible for the DLQI and these data were therefore not included.

Patients may respond “not relevant” to DLQI questions for a variety of reasons. The exceptional circumstances of the Covid-19 pandemic may have resulted in greater use of this response, as the pandemic restricted many aspects of people’s lives. However, considering the time from data collection to publication of a RCT, it is unlikely that any publications included in our study were conducted during the pandemic.

The DLQI has been widely used in dermatology clinical trials due to its robustness, simplicity and ease of use. The DLQI developers constantly engage in enhancing the utility of the DLQI, and this review of its use in clinical trials is the most comprehensive. The review allows structured access to inform future users of the DLQI, confirms the very extensive experience of the DLQI in RCTs in dermatology and demonstrates the utility of the DLQI as the PRO measure of choice over the last two decades. The use of the DLQI as a primary outcome measure in 24 RCTs represents a paradigm shift in the status accorded to PROs in dermatology. Traditionally researchers used only sign/symptom severity measures as primary endpoints in RCT protocols. PROs were secondary endpoints despite often more extensive validation. The use of the DLQI as a primary endpoint, with PROs’ precision similar to those of clinical/biomedical parameters, indicates growing confidence in giving PROs such status to be used for labelling in marketing authorisation of new health technologies as well as an aid to treatment decision making.

**Recommendations**

Although the majority of RCTs included in this study reported data in appropriate detail, some publications had deficiencies, particularly reporting DLQI data. The following recommendations are made:

1. Publications reporting clinicals trials should include details of study settings, genders, ethnicity, and mean and range of participants’ age.
2. The sample size calculation, randomisation and blinding methods, including allocation concealment should be clearly stated, and correct baseline characteristics and comparisons of subjects presented.
3. Patient numbers should be reported, whether intention to treat or per protocol analysis was implemented, and the method(s) for data imputation of missing data.
4. DLQI baseline and final data collection point mean and median scores with interquartile range, as well as score differences should be published even when the DLQI outcome may be the percentage of 0 or 1 scores at the final data collection point. Presentation of percentage score changes should be discouraged.
5. Authors should analyse their DLQI data using MID and use score severity bands in interpreting results.
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Figure legends

1. Figure 1 PRISMA 2020 Flow diagram of article selection.
2. Figure 2 Number of randomised control trial studies using the DLQI over time.
3. Figure 3. Location of randomised controlled trial studies.
4. Figure 4. Published and calculated DLQI score differences for all interventions (N=469). Arm1,2,3 differences are published DLQI differences as reported. Arm1,2,3 calculated differences were determined from differences between reported baseline and endpoint DLQI scores, where reported. Arm1 is generally a control, with arms 2 and 3 being increasing dosages of the same drug or greater potency of alternative treatments (i.e. expectedly increasingly more effective treatments). Whiskers show maximum and minimum values. Bars show means. Dotted horizontal line shows the DLQI MID.
5. Figure 5. Distribution of JADAD scores and risk of bias.
Table 1. Eligibility criteria for study selection.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
</table>
| Patients | - Adults ≥ 18 years, any gender, ethnicity, settings, countries  
- Any inflammatory and non-inflammatory dermatological conditions | |
| Methods  | - Interventional RCTs published as full papers in peer-reviewed journals (including cross-over trials and trials with open-label extensions if initial treatment was continued after study completion)  
- Published between 1 January 1994 and 17 November 2021  
- Interventions included any drug, therapeutic intervention and alternative medicines e.g. acupuncture, fire needle, Chinese traditional (herbal) medicine, Ayurvedic, and educational or lifestyle interventions | - Not in English language  
- ‘Grey’ literature including dissertations, conference abstracts, reports, editorials, letters to editors, commentaries, protocols, reviews, conference abstracts, conference proceedings, and dissertations |
| Outcomes | - DLQI is primary or secondary outcome | - No DLQI data given |
Table 2. Diseases studied

<table>
<thead>
<tr>
<th>Disease type</th>
<th>Disease</th>
<th>Number of studies</th>
<th>%</th>
<th>Ref</th>
</tr>
</thead>
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<td>Atopic dermatitis</td>
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<td>Urticaria</td>
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<td>Eczema/Hand eczema</td>
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<td>317-321</td>
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<tr>
<td></td>
<td>Psoriatic arthritis</td>
<td>17</td>
<td>3.7</td>
<td>317-321</td>
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<td>Hidradenitis suppurativa</td>
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<td>2.4</td>
<td>322-327</td>
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<td>Lichen planus</td>
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<td>Chronic actinic dermatitis and polymorphous light eruption (PLE)</td>
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<td>Chronic sulphur mustard-induced cutaneous complications</td>
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<td>Disseminated superficial actinic porokeratosis</td>
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<td>Uremic pruritus</td>
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<td>Pyoderma gangrenosum</td>
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<td>Stasis dermatitis</td>
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<td>Striae distensae</td>
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<td>“Any skin disease”</td>
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</table>
### Table 3. Pharmacological interventions by drug type

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<tr>
<th>Drug Type</th>
<th># uses</th>
<th>%</th>
<th>Refs</th>
<th>Drug Type</th>
<th># uses</th>
<th>%</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
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<td><strong>Systemic</strong></td>
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<td></td>
<td><strong>Topical</strong></td>
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<td>Biologics</td>
<td>252</td>
<td>56.0</td>
<td>See Table 4</td>
<td>Antidepressant (doxepin)</td>
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<td>0.22</td>
<td>440</td>
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<tr>
<td>Analgesics</td>
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<td>0.89</td>
<td>430,437,465,466</td>
<td>Antifungal</td>
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<td>395,433-435</td>
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<tr>
<td>Anti-diabetics</td>
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<td>0.89</td>
<td>79,93,137,151</td>
<td>Anti-infectives</td>
<td>9</td>
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<td>184,202,203,368</td>
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<tr>
<td>Natural Products and Supplements</td>
<td>7</td>
<td>1.6</td>
<td>222,276,287,337,381,430,441</td>
<td>Natural Products and Supplements</td>
<td>4</td>
<td>0.89</td>
<td>152,404,410,458</td>
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<tr>
<td>---------------------------------</td>
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<td>NSAID</td>
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<td>NSAID</td>
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<td>Retinoids</td>
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<td>28,69,122,473</td>
<td>Statins (atorvastatin)</td>
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<td>Tyrosine kinase 2 inhibitors</td>
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<td>240,416</td>
<td>TRPM8 agonists (menthoxypropanediol)</td>
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<td>0.22</td>
<td>443</td>
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<tr>
<td>Vitamin D3/Vitamin D derivatives</td>
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<td>120,225,417,496</td>
<td>Vitamin D3/Vitamin D derivatives</td>
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<td>2.0</td>
<td>145,146,151,186,189,190,268,340</td>
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<tr>
<td>Others</td>
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<td>363,421,427,448,452</td>
<td>Others</td>
<td>5</td>
<td>1.1</td>
<td>246,373,464,472,476</td>
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</table>

Note: #uses refers to number of studies using a particular drug of that type. Some studies used multiple drugs of that type (e.g. both bilastine and levocetirizine as antihistamines in the same study), so the number of references may not match the number of uses.
<table>
<thead>
<tr>
<th>Biologicals</th>
<th>Number of uses</th>
<th>% of total pharmacological interventions</th>
<th>Diseases studied</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>secukinumab</td>
<td>32</td>
<td>7.10</td>
<td>psoriasis, psoriatic arthritis</td>
<td>30,58,59,97,109,112,123,142,148,149,185,196,197,200,208,210,22-216,272,279,282,331</td>
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<tr>
<td>guselkumab</td>
<td>15</td>
<td>3.33</td>
<td>palmoplantar pustulosis, psoriasis, psoriasis</td>
<td>32,56,108,141,150,171,198,199,201,204,205,244,390,392</td>
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<td>brodalumab</td>
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<td>2.44</td>
<td>psoriasis</td>
<td>59,138,139,157,167,175,178,191,226,258,264</td>
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<td>Infliximab</td>
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<td>1.77</td>
<td>psoriasis</td>
<td>48,77,81,82,207,247,248,267</td>
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<td>dupilumab</td>
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<td>1.33</td>
<td>atopic dermatitis</td>
<td>282,284,288,298,299,302</td>
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<td>efalizumab</td>
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<td>psoriasis</td>
<td>102,159,160,173</td>
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<td>risankizumab</td>
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<td>0.89</td>
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<td>psoriasis</td>
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<td>psoriatic arthritis</td>
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<td>brikinumab</td>
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<td>0.44</td>
<td>psoriasis</td>
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<td>2</td>
<td>0.44</td>
<td>Schnitzler syndrome, urticaria</td>
<td>319,420</td>
</tr>
<tr>
<td>certolizumab pegol (CPZ)</td>
<td>2</td>
<td>0.44</td>
<td>psoriasis</td>
<td>253,254</td>
</tr>
<tr>
<td>cetuximab</td>
<td>2</td>
<td>0.44</td>
<td>oesophageal cancer, radiodermatitis of head and neck cancer</td>
<td>407,424</td>
</tr>
<tr>
<td>lebrikizumab</td>
<td>2</td>
<td>0.44</td>
<td>atopic dermatitis</td>
<td>289,300</td>
</tr>
<tr>
<td>tilikizumab</td>
<td>2</td>
<td>0.44</td>
<td>psoriasis</td>
<td>60,209</td>
</tr>
<tr>
<td>bermekimab</td>
<td>1</td>
<td>0.22</td>
<td>hidradenitis suppurativa</td>
<td>364</td>
</tr>
<tr>
<td>clazakizumab</td>
<td>1</td>
<td>0.22</td>
<td>psoriatic arthritis</td>
<td>334</td>
</tr>
<tr>
<td>Cytokines (cytokines IL4, IL10 and IL11)</td>
<td>1</td>
<td>0.22</td>
<td>psoriasis</td>
<td>220</td>
</tr>
<tr>
<td>golimumab</td>
<td>1</td>
<td>0.22</td>
<td>psoriatic arthritis</td>
<td>333</td>
</tr>
<tr>
<td>Drug</td>
<td>Titer</td>
<td>% Positive</td>
<td>Condition</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-------</td>
<td>------------</td>
<td>-----------------------------------</td>
<td></td>
</tr>
<tr>
<td>IFN-γ</td>
<td>0.22</td>
<td></td>
<td>chronic sulfur mustard-induced cutaneous complications</td>
<td></td>
</tr>
<tr>
<td>itolizumab</td>
<td>0.22</td>
<td></td>
<td>psoriasis</td>
<td></td>
</tr>
<tr>
<td>mirikizumab</td>
<td>0.22</td>
<td></td>
<td>psoriasis</td>
<td></td>
</tr>
<tr>
<td>nemolizumab</td>
<td>0.22</td>
<td></td>
<td>atopic dermatitis</td>
<td></td>
</tr>
<tr>
<td>panitumumab</td>
<td>0.22</td>
<td></td>
<td>metastatic colorectal cancer</td>
<td></td>
</tr>
<tr>
<td>rituximab</td>
<td>0.22</td>
<td></td>
<td>Pemphigus vulgaris</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>252</td>
<td>55.86</td>
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<td></td>
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</tbody>
</table>
Table 5. DLQI score differences (n=458)

<table>
<thead>
<tr>
<th></th>
<th>Arm1 diff</th>
<th>Arm2 diff</th>
<th>Arm3 diff</th>
<th>Arm1 calculated diff</th>
<th>Arm2 calculated diff</th>
<th>Arm3 calculated diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies with DLQI difference scores</td>
<td>123</td>
<td>131</td>
<td>53</td>
<td>270</td>
<td>296</td>
<td>114</td>
</tr>
<tr>
<td>% studies with DLQI difference scores</td>
<td>25.6</td>
<td>28.7</td>
<td>12.0</td>
<td>59.3</td>
<td>65.2</td>
<td>25.4</td>
</tr>
<tr>
<td>Number of studies with no data available</td>
<td>337</td>
<td>330</td>
<td>407</td>
<td>181</td>
<td>168</td>
<td>346</td>
</tr>
<tr>
<td>No. of studies score diff &gt;MID of 4.0</td>
<td>34</td>
<td>78</td>
<td>32</td>
<td>182</td>
<td>219</td>
<td>95</td>
</tr>
<tr>
<td>No. of studies score diff &lt;MID of 4.0</td>
<td>86</td>
<td>49</td>
<td>18</td>
<td>84</td>
<td>70</td>
<td>16</td>
</tr>
<tr>
<td>% of studies with score diff &gt;MID of 4.0</td>
<td>28.3</td>
<td>61.4</td>
<td>64.0</td>
<td>68.4</td>
<td>75.8</td>
<td>85.6</td>
</tr>
</tbody>
</table>

Notes: Arm1,2,3 differences are published DLQI differences as reported. Arm1,2,3 calculated differences were determined from differences between reported baseline and endpoint DLQI scores, where reported.
Figure 1
159x90 mm (x DPI)
Figure 3

Number of studies

Multiple countries excl. UK
Europe excl. UK
North America
Middle East
China
Asia
Not specified
UK
SE Asia
Japan
South America
Oceania
Africa
Others

41.7%
17.3%
8.4%
7.5%
4.9%
4.7%
4.7%
4.0%
3.7%
1.6%
0.9%
0.5%
0.2%

108x92 mm (x DPI)