SKIN

ORIGINAL RESEARCH

Reporting of Quality of Life in Clinical Trials of Biologics for Plaque Psoriasis: A Systematic Review

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ABSTRACT

Background: Psoriasis is a chronic remitting and relapsing skin disease. For many patients, improved quality of life (QoL) is as important as clinical improvement of lesions.
Objective: To review reporting of Dermatology Life Quality Index (DLQI) in randomized controlled trials (RCTs) of biologics for adult patients with plaque psoriasis.
Methods: A systematic review was conducted in 4 databases for RCTs that measured DLQI at baseline and endpoint. A data collection form was created for collecting study variables. Risk of bias was assessed using the Cochrane risk of bias tool.
Results: Thirty-four RCTs enrolling 16,784 patients were included. Complete baseline and final mean DLQI data was retrieved for 24 studies (70.6%). The mean DLQI at baseline was reported in 79.4% of RCTs. The median at baseline was reported in 14.7% of RCTs. The mean DLQI at endpoint was reported in 23.5% of RCTs and the median DLQI at endpoint was reported in 5.9% of RCTs. The mean change in DLQI was reported in 64.7% of RCTs.
Conclusions: DLQI was measured in most clinical trials assessing the efficacy of biologics for psoriasis. Studies did not adhere to uniform standards in publishing results, making analysis of the impact on DLQI challenging.

INTRODUCTION

Psoriasis vulgaris is a chronic relapsing and remitting inflammatory skin disease that affects 0.5-11.43% of the population worldwide.[1] Psoriasis negatively impacts patients' quality of life.[2,3] For many patients, improved quality of life is as important as objective clinical improvement of psoriasis lesions.[4]

Many different tools have been created to evaluate the effect of chronic skin conditions on quality of life (e.g. Dermatology Life Quality Index, Skindex, SF-36, among others). The Dermatology Life Quality Index (DLQI) was first reported in 1994 and is a validated tool used to assess the effect of dermatologic conditions on quality of life.[5,6] It is the most commonly used quality of life

measure in clinical trials in dermatology.[7] The DLQI is widely used due to its simplicity in scoring, quick completion in 2 minutes, among other reasons.[8-10] The DLQI uses 10 questions to assess the effect of a skin condition on a patient's symptoms and feelings, daily activities, leisure activities, work and school, personal relationships, and treatment.[5] Respondents have the ability to rate the effect on quality of life as "not at all", "a little", "a lot", and "very much." This in turn is scored from 0-3 for each of the 10 questions for a total possible score of 30 points. These summary scores can be banded into different levels of severity. A summary score of 0-1 signifies no effect on quality of life, 2-5 a small effect, 6-10 a moderate effect, 11-20 a very large effect, and 21-30 an extremely large effect.[11] Biologic therapy can lead to improvements in quality of life that are both statistically significant and clinically significant as seen when the banding concept of DLQI scores is applied.[11]

Thus, improving quality of life in patients with psoriasis should be of the utmost importance to clinicians. There are a variety of treatment options for moderate to severe plaque psoriasis and biologics have revolutionized the management of this disease. For patients with psoriasis treated with biologic therapy, there is a clear correlation between DLQI and PASI scores.[12]

At the time of writing this manuscript, six biologic medications were approved by the United States Food and Drug administration (FDA) for use in plaque psoriasis: adalimumab, etanercept, infliximab, ixekizumab, secukinumab, and ustekinumab. The use of these biologics for psoriasis is supported by data from randomized clinical trials (RCTs). Other reviews have examined the effect of biologic therapy on quality of life.[13,14] However, new drugs have been approved since the prior studies were published and many of the originally approved drugs have been withdrawn from the market. This review presents an updated assessment of quality of life studies in psoriasis.

METHODS

Data Sources:
We searched four computerized bibliographical databases for articles published since inception to August 2016: Pubmed, Cochrane Library CENTRAL, Ovid MEDLINE, and Embase. Search terms included: "Quality of Life," "DLQI," "Dermatology Life Quality Index," "Dermatology quality of life index," "psoriasis," "randomized controlled trials," "biologic therapy," "biologic," and the generic names for each of the drugs. The search was restricted to publications in English. This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Prospero registration no. CRD42016046523). The search strategy used is given in Appendix 1. We reviewed trial registers (clinicaltrials.gov) and searched grey literature. Reference lists of all included studies and of recent reviews were also assessed. Electronic publications in advance of print were also included.

Inclusion Criteria:
We included double-blind, RCTs of patients with plaque psoriasis treated with FDA approved biologic treatments that measured DLQI at baseline and endpoint in adults (aged >18 years).

Exclusion Criteria:
The exclusion criteria were as follows: trials that included only a subtype of psoriasis, trials that only randomized patients with

concomitant psoriatic arthritis, studies that included any patient less than 18 years of age, articles where the change in DLQI values from baseline to endpoint could either not be reliably calculated or could not be obtained after requesting additional information from the author or study sponsor, and abstracts and posters where further data were not available upon contacting the author.

Outcome measures:
The primary outcome recorded was the mean DLQI score at baseline and endpoint. For studies with an open-label extension, the data were extracted only for the period of the study while it was randomized and controlled. For crossover trials, the data were extracted prior to the crossover.

Data extraction and synthesis:
One reviewer (G.P.) extracted data, another reviewer (A.N.) checked the extracted data for accuracy, and the reviewers met to discuss any disagreements.

We created and piloted a data collection form for recording study design, DLQI scores, drug administered, dosing schedule, and quality of the methodology. Risk of bias was assessed using the Cochrane risk of bias tool independently by 2 reviewers (G.P. and A.N.). Disagreements were resolved by discussion.

RESULTS

After screening 571 records, we identified 34 RCTs enrolling a total of 16,784 patients published between December 2003 and May 2016 that fit our inclusion and exclusion criteria. For these studies, 38 articles were retrieved, including those related to the original RCT publication as well as sub-analyses of the original RCT. Of the 34 original RCTs included, complete data, meaning baseline and final mean DLQI scores, was retrieved for 24 studies (70.6%). Of these 24 studies, 66.7% present unpublished data obtained from study authors and sponsors after contacting them for additional information.

The mean DLQI at baseline was reported in 79.4% of studies (Table 1). The median at baseline was reported in 14.7% of the studies. The mean DLQI at endpoint was only reported in 23.5% of studies and the median DLQI at endpoint was reported in 5.9% of studies. The mean change in DLQI was reported in 64.7% of studies.

Adalimumab. There were five RCTs comprising 1,918 patients that assessed DLQI data in patients treated with adalimumab. Of these studies, we obtained complete data for four RCTs (80%). The DLQI for the placebo group ranged from 8.4-14.6 at baseline and 7.6-12.3 at endpoint. For those treated with adalimumab, the mean DLQI ranged from 8.4-14.6 at baseline and 2.0-5.0 at endpoint.

Etanercept. There were eight RCTs comprising 2,968 patients that assessed DLQI data in patients treated with etanercept. Of these studies, we obtained complete data for four RCTs (50%). The DLQI for the placebo group ranged from 12.2-14 at baseline and 9.75-12.3 at endpoint. For those treated with etanercept, the mean DLQI ranged from 10-13.87 at baseline and 3.8-5.8 at endpoint.

Infliximab. There were five RCTs comprising 1,639 patients that assessed DLQI data in patients treated with infliximab. Of these studies, we obtained complete data for four RCTs (80%). The DLQI for the placebo group ranged 10.5-14.4 at baseline and 11.2-13.1 at endpoint. For those treated with infliximab, the mean DLQI ranged from

12.3-14.4 at baseline and 2.4-6.5 at endpoint.

Ixekizumab. There were four RCTs comprising 4,008 patients that assessed DLQI data in patients treated with ixekizumab. Of these studies, we obtained complete data for all 4 RCTs (100%). The DLQI for the placebo group ranged from 10.81-12.8 at baseline and 10.26-11.6 at endpoint. For those treated with ixekizumab, the mean DLQI ranged from 10.36-13.4 at baseline and 1.9-4.66 at endpoint.

Secukinumab. There were five RCTs comprising 3,294 patients that assessed DLQI data in patients treated with secukinumab. Of these studies, we obtained complete data for 2 RCTs (40%). The DLQI for the placebo group ranged from 12.0-13.4 at baseline and 10.9-11.5 at endpoint. For those treated with secukinumab, the mean DLQI ranged from 11.3-13.9 at baseline and 2.5-3.7 at endpoint.

Ustekinumab. There were seven RCTs comprising 2,957 patients that assessed DLQI data in patients treated with ustekinumab. Of these studies, we obtained complete data for 6 RCTs (85.7%). The DLQI for the placebo group ranged from 10.5-15.2 at baseline and 9.7-14.7 at endpoint. For those treated with ustekinumab, the mean DLQI ranged from 10.5-16.1 at baseline and 2.1-4.8 at endpoint.

Quality of Evidence for Included Studies. Appendix 2 provides an assessment of the risk of bias for the included studies. All studies were randomized controlled trials. Most studies limited the bias inherent to the trial by employing the use of random sequence generation, allocation concealment, and blinding of participants, personnel, and assessors.

Table 1: Summary of clinical trials investigating biologic therapy for patients with plaque psoriasis.

Source	Clinicaltrials.gov Number	Interventions	Trial Phase	Tx End-point Week	No. of PBO Pts at Base-line	No. of PBO Pts at End-point	No. of Tx Pts at Base-line	No. of Tx Pts at End-point	DLQI Measurement Reported in Publication	Doses Studied	Mean DLQI ± SD (SE)			
											PBO		Tx	
											Baseline	Endpoint	Baseline	Endpoint
Asahina 2010[26]	NCT00338754	Adalimumab vs. PBO	2/3	16 & 24	138	138	123	122	Mean at baseline Mean change score with SD	40mg EOW	8.4	N/A	8.4	N/A
										80mg at baseline then 40mg EOW	8.4	N/A	8.5	N/A
										80mg EOW	8.4	N/A	8.8	N/A
Gordon 2015[27]*	NCT01483599	Adalimumab vs. Guselkumab vs. PBO	2	16	42	42	43	39	Mean change score with SD	80mg at baseline then 40mg EOW	14.6 ± 5.91	12.3 ± 7.66	14.6 ± 7.17	5.0 ± 7.41
Shikiar 2007[28]/ Wallace 2005[29]	N/A	Adalimumab vs. PBO	2	12	104	104	95	94	Mean at baseline and endpoint with 95% CI Mean change score with 95% CI	80mg at baseline then 40mg EOW	12.2 (10.0-14.4)	10.7 (9.1-12.4)	13.3 (10.7-15.8)	2.8 (1.0-4.7)
										80mg at baseline then 40mg/wk	12.2 (10.0-14.4)	10.7 (9.1-12.4)	13.6 (11.3-15.9)	2.0 (0.3-3.8)
Revicki 2008[30]	NCT00235820	Adalimumab vs. MTX vs. PBO	3	12 & **16**	53	53	108	103	Mean at baseline and endpoint with SD	80mg at baseline then 40mg	11.7 ± 7.0	7.6 ± 6.4	11.8 ± 6.6	2.5 ± 4.0

									Mean change score with 95% CI	EOW				
Revicki 2007[31]	NCT00237887	Adalimumab vs. PBO	3	4 & **16**	398	397	814	808	Mean at baseline and endpoint with SD Mean change score with 95% CI	80mg at baseline then 40mg EOW	11.4 ± 7.0	9.2 ± 7.1	11.3 ± 6.6	3.0 ± 4.5
Bachelez 2015[32]/ Valenzuela 2016[33]*	NCT01241591	Etanercept vs. Tofacitinib vs. PBO	3	12	108	107	336	335	Mean at baseline and with SD and SE No. of pts with clinically meaningful decrease in DLQI	50mg twice/ wk	12.3 ± 7.1	10.3	12.7 ± 6.8	3.8
Strober 2011[34]*	NCT00710580	Etanercept vs. Briakinumab vs. PBO	3	12	72	66	139	127	No. of pts with DLQI=0 at baseline and endpoint	50mg twice/ wk	13.61 ± 6.918	10.73 ± 6.9464	13.87 ± 7.848	4.78 ± 5.497
Leonardi 2003[35]	N/A	Etanercept vs. PBO	2	12 & 24	166	166	486	486	Mean at baseline with SE % Change with SE at wk 12 and 24	25mg / wk	12.8 (0.6)	N/A	12.2 (0.5)	N/A
										25mg twice/ wk	12.8 (0.6)	N/A	12.7 (0.5)	N/A
										50mg twice/wk	12.8 (0.6)	N/A	11.3 (0.5)	N/A

Gottlieb 2003[36]/ Lowe 2002[37]	N/A	Etanercept vs. PBO	3	12 & 24	55	55	57	57	Mean at baseline % Change with SE at wk 24	25mg twice/ wk	14	N/A	10	N/A
Krueger 2005[38]	N/A	Etanercept vs. PBO	3	12	193	193	390	390	Mean at baseline with SD No. of pts with clinically meaningful decrease in DLQI Graphical representation of % change	50mg / wk	12.2 ± 6.8	N/A	11.5 ± 7.2	N/A
										50mg twice/wk	12.2 ± 6.8	N/A	11.4 ± 6.5	N/A
Tyring 2006[39]	NCT00111449	Etanercept vs. PBO	3	12	307	307	311	311	Mean at baseline with SD % Change at wk 12	50mg twice/wk	12.5 ± 6.7	N/A	12.1 ± 6.7	N/A
Reich 2009[40]	N/A	Etanercept vs. PBO	3	12	45	46	94	96	Mean at baseline and endpoint Mean change score % Change at wk 12 Graphical	50mg / wk	13.6	12.3	13.2	5.8

									representations of response ranges at baseline and endpoint, % of pts with DLQI= 0 or 1, and % of pts with clinically meaningful decrease in DLQI					
Gottlieb 2011[41]*	NCT00691964	Etanercept vs. Briakinumab vs. PBO	3	12	68	68	141	141	No. of pts with DLQI=0 at baseline and endpoint	50mg twice/wk	13.05	9.75	12.40	4.39
Feldman 2005[42]/ Gottlieb 2004[43]	N/A	Infliximab vs. PBO	2	10	51	51	198	198	Mean at baseline and endpoint with SD Median at baseline and endpoint with IQR Mean change score with SD % Change at wk 10 with SD	3mg/kg at wk 0, 2 , and 6	13.8 ± 6.6	11.2 ± 7.4	12.3 ± 7.3	3.4 ± 5.2
										5mg/kg at wk 0, 2 , and 6	13.8 ± 6.6	11.2 ± 7.4	13.2 ± 7.0	2.8 ± 5.0
Feldman 2008[44]/ Menter 2007[45]*	N/A	Infliximab vs. PBO	2	10	208	200	625	619	Mean at baseline with SD Mean change	3mg/kg at wk 0, 2 , and 6	13.4 ± 7.34	12.8 ± 7.46	12.8 ±6.89	3.3 ± 4.87
										5mg/kg at	13.4 ±	12.8 ±	13.1	2.5 ±

									score with SD Median at baseline Graphical representations of median change score, % of pts with DLQI=0 at endpoint	wk 0, 2 , and 6	7.34	7.46	±7.01	3.83
Yang 2012[46]	NCT01177800	Infliximab vs. PBO	3	10	45	44	84	82	Mean at baseline and endpoint with SD Mean change score with SD Graphical representation of mean scores	5mg/kg at wk 0, 2 , and 6	14.4 ± 6.3	13.1 ± 5.7	14.4 ± 6.2	6.5 ± 6.5
Torii 2010[47]	N/A	Infliximab vs. PBO	3	10 & 14	19	16	35	34	Mean at baseline with SD Median at baseline Mean change score with SD No. of pts with DLQI=0 at	5mg/kg at wk 0, 2 , and 6	10.5 ± 6.8	N/A	12.7 ± 6.8	N/A

									endpoint No. of pts with clinically meaningful decrease in DLQI Graphical representation of Mean change scores with SD					
Reich 2006[48]*	NCT01177800	Infliximab vs. PBO	3	**10** & 24	77	75	297	291	Mean at baseline with SD Mean change score with SD Graphical representation of % of pts with DLQI=0 at endpoint, response ranges at baseline and endpoint	5mg/kg at wk 0, 2, 6, then every 8 wk	11.8 ± 7.46	11.3 ± 8.10	12.7 ± 6.97	2.4 ± 4.16
Griffiths 2015[49]*	NCT01597245	Ixekizumab vs. Etanercept vs. PBO	3	12	168	168	I: 698 E: 358	I: 698 E: 358	Mean at baseline with SD Mean change score with SE No. of pts with	Ixekizumab 160mg at baseline then 80mg EOW	12.8 ± 7.24	10.6 ± 7.34	12.4 ± 6.86	1.9 ± 3.12
										Ixekizumab 160mg at	12.8 ± 7.24	10.6 ± 7.34	11.6 ± 6.65	2.6 ± 4.48

									DLQI=0 at endpoint	baseline then 80mg E4W				
										Etanercept 50mg twice/wk	12.8 ± 7.24	10.6 ± 7.34	12.7 ± 7.03	4.7 ±5.35
Griffiths 2015[49]*	NCT01646177	Ixekizumab vs. Etanercept vs. PBO	3	12	193	193	I: 771 E: 382	I: 771 E: 382	Mean at baseline with SD Mean change score with SE No. of pts with DLQI=0 at endpoint	Ixekizumab 160mg at baseline then 80mg EOW	12.7 ± 7.0	10.5 ± 7.23	12.4 ± 6.93	2.0 ± 3.30
										Ixekizumab 160mg at baseline then 80mg E4W	12.7 ± 7.0	10.5 ± 7.23	11.9 ± 6.97	2.4 ± 4.25
										Etanercept 50mg twice/wk	12.7 ± 7.0	10.5 ± 7.23	11.5 ± 6.84	3.8 ± 4.75
Leonardi 2012[50]*	NCT01107457	Ixekizumab vs. PBO	2	16	27	27	115	115	Mean at baseline with SD Mean change score with SD % of pts with DLQI=0 at endpoint	10 mg at wk 0, 2, 4, 8, 12, 16	10.81 ± 5.21	10.26 ± 6.92	10.61 ± 7.16	4.54 ± 6.04
										25 mg at wk 0, 2, 4, 8, 12, 16	10.81 ± 5.21	10.26 ± 6.92	11.63 ± 7.19	4.66 ± 6.47
										75 mg at wk 0, 2, 4, 8, 12, 16	10.81 ± 5.21	10.26 ± 6.92	11.10 ± 5.59	1.96 ± 3.27
										150 mg at wk 0, 2, 4, 8, 12, 16	10.81 ± 5.21	10.26 ± 6.92	10.36 ± 5.81	2.15 ± 3.30
Gordon 2015[51]*	NCT01474512	Ixekizumab vs. PBO	3	12	431	431	865	865	None in abstract	160mg at baseline	12.8 ± 7.11	11.6 ± 7.53	13.4 ± 7.02	2.0 ± 3.33

										then 80mg EOW				
										160mg at baseline then 80mg E4W	12.8 ± 7.11	11.6 ± 7.53	13.2 ± 7.02	2.3 ± 3.87
Augustin 2016[52]	NCT00941031	Secukinumab vs. PBO	2	12	67	58	337	322	Mean at baseline with SD Median at baseline and endpoint with IQR Graphical representation of % of pts with DLQI= 0 or 1	150mg at baseline	12.5 ± 6.2	N/A	11.3 ± 6.9	N/A
										150mg at baseline then E4W	12.5 ± 6.2	N/A	11.8 ± 7.1	N/A
										150mg at baseline then wk 1, 2, and 4	12.5 ± 6.2	N/A	11.8 ± 6.7	N/A
Thaci 2015[53]/ Blauvelt 2016[54]	NCT02074982	Secukinumab vs. Ustekinumab	3	16	-	-	S: 331 U: 333	S: 331 U: 333	No. of pts with DLQI=0 or 1 at endpoint	Secukinumab 300mg weekly for wk 0-4 then E4W	-	-	13.4 ± 7.63	N/A
										Ustekinumab 45 or 90mg at baseline, wk 4, then every 12 wk	-	-	13.2 ± 7.57	N/A
Langley 2014[55]	NCT01365455	Secukinumab vs. PBO	3	12	248	246	490	488	Mean at baseline and endpoint Mean change	300mg weekly for wk 0-4 then E4W	12.0	10.9	13.9	2.5

									score	150mg weekly for wk 0-4 then E4W	12.0	10.9	13.4	3.3
Langley 2014[55]	NCT01358578	Secukinumab vs. Etanercept vs. PBO	3	12	326	324	980	973	Mean at baseline and endpoint Mean change score	Secukinumab 300mg weekly for wk 0-4 then E4W	13.4	11.5	13.3	2.9
										Secukinumab 150mg weekly for wk 0-4 then E4W	13.4	11.5	13.4	3.7
										Etanercept 50mg twice/wk	13.4	11.5	13.4	5.5
Paul 2015[56]	NCT01636687	Secukinumab vs. PBO	3	12	61	61	121	121	Paper did not report any DLQI data but DLQI was measured according to protocol on clinicaltrials.gov	300mg weekly for wk 0-4 then E4W	N/A	N/A	N/A	N/A
										150mg weekly for wk 0-4 then E4W	N/A	N/A	N/A	N/A
Leonardi 2008[57]*	NCT00267969	Ustekinumab vs. PBO	3	12	255	252	511	503	Mean at baseline with SD Mean change score with SD Median change score with IQR	45mg at baseline and wk 4	11.8 ± 7.41	11.2 ± 7.45	11.1 ± 7.09	3.1 ± 4.26
										90mg at baseline and wk 4	11.8 ± 7.41	11.2 ± 7.45	11.6 ± 6.92	2.8 ± 3.64

									No. of pts with DLQI=0 or 1 at endpoint					
Papp 2008[58]*	NCT00307437	Ustekinumab vs. PBO	3	12	410	400	820	803	Mean at baseline with SD	45mg at baseline and wk 4	12.3 ± 6.86	11.8 ± 7.77	12.2 ± 7.07	2.9 ± 4.35
									Mean change score with SD Median change score with IQR No. of pts with DLQI=0 or 1 at endpoint	90mg at baseline and wk 4	12.3 ± 6.86	11.8 ± 7.77	12.6 ± 7.29	2.7 ± 4.01
Igarashi 2012[59]	NCT00723528	Ustekinumab vs. PBO	2/3	12	32	31	126	123	Mean at baseline with SD	45mg at baseline and wk 4	10.5 ± 6.2	N/A	11.4 ± 6.5	N/A
									Mean change score with SD Median change score No. of pts with DLQI=0 or 1 at endpoint	90mg at baseline and wk 4	10.5 ± 6.2	N/A	10.7 ± 6.4	N/A
Krueger 2007[60]*	NCT00320216	Ustekinumab vs. PBO	2	12	64	64	256	255	Mean at baseline with SD	45mg at baseline	12.0 ± 7.25	9.7 ± 7.10	11.9 ± 6.99	4.5 ± 6.24
									Mean change score with SD	90mg at baseline	12.0 ± 7.25	9.7 ± 7.10	13.4 ± 7.25	3.6 ± 5.10
										45mg	12.0 ±	9.7 ±	12.6 ±	2.5 ±

									Median change score with IQR No. of pts with DLQI=0 at endpoint	weekly for 4 wk	7.25	7.10	6.63	3.75
										90mg weekly for 4 wk	12.0 ± 7.25	9.7 ± 7.10	10.5 ± 6.73	2.1 ± 4.01
Zhu 2013[61]*	NCT01008995	Ustekinumab vs. PBO	3	12	162	159	160	158	Mean at baseline with SD Mean change score with SD	45mg at baseline and wk 4	13.1 ± 7.51	11.2 ± 7.88	13.7 ± 7.57	4.4 ± 5.39
Tsai 2011[62]*	NCT00747344	Ustekinumab vs. PBO	3	12	60	60	61	59	Mean at baseline with SD Mean change score with SD Median change score with IQR	45mg at baseline and wk 4	15.2 ± 6.95	14.7 ± 7.97	16.1 ± 6.09	4.8 ± 5.25
Papp 2016[63]*	NCT02054481	Ustekinumab vs. Risankizumab		12 & **24**	-	-	40	40	Median at baseline Median % Change at wk 12 % of pts with DLQI=0 or 1 at wk 24	45 or 90mg at baseline, wk 4, wk 16	-	-	15.8 ± 6.5	2.8 ± 4.3

Abbreviations:
Week of treatment endpoint used for endpoint columns denoted in bold.
*Denotes trials for which additional unpublished data was obtained after contacting authors and study sponsors.

&: and
EOW: every other week.
E4W: Every 4 weeks.
IQR: Interquartile range.
MTX: Methotrexate.
N/A: Not available.
- : Not applicable.
SD: Standard Deviation.
SE: Standard Error.
PBO: PBO
Pts: Patients.
Tx: Treatment.
Wk: Week.

DISCUSSION

Psoriasis can have a comparable negative effect on quality of life as cancer, myocardial infarction, and chronic lung disease.[3] Patients with psoriasis have decreased work productivity, increased incidence of depression, and difficulties in personal relationships.[15-17] Patients with more severe disease manifestations have even greater impairment in these areas of life.[18] This disease results in cumulative life course impairment that influences how patients make major life decisions, develop social relationships, and pursue their life goals.[19] Achieving significant improvements in quality of life measures should be the goal for any clinical trial assessing treatment efficacy in patients with psoriasis.

It has previously been shown that biologic therapy significantly improves DLQI compared to conventional systemic therapy.[20] Most clinical trials define efficacy and safety as primary endpoints and relegate quality of life measures as secondary endpoints. This systematic review demonstrates a clear improvement in quality of life, as evidenced by reductions in DLQI scores for patients with plaque psoriasis treated with biologics.

The first generation of biologic therapies for plaque psoriasis were the TNF-alpha inhibitors (adalimumab, etanercept, and infliximab). More recently, the targeted therapies against interleukin (IL)-17 and IL-12/23 have heralded a new era of biologic therapies. Although there were slight differences between the endpoint scores for the TNF-alpha inhibitors and the newer biologics, it is not clear whether these slight differences correspond to clinically significant differences in quality of life. Comparing the ranges of DLQI scores reported across the different drugs, most patients reported a "small effect" of their psoriasis symptoms on quality of life after treatment.

When discussing improvement in quality of life, it is important to keep in mind the concept of minimal clinically important difference (MCID). MCID is defined as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management."[21] Taken from the patient's perspective, this may mean a significant improvement in quality of life and symptomatology; while taken from the clinician's perspective, this may mean a significant improvement in the treatment or prognosis of the disease. Several studies using different methodologies have attempted to determine the minimum clinically important change in DLQI score and results have ranged from 3-5.[22] Four studies included in this review reported some measure of patients who achieved a meaningful decrease in DLQI (either number or percentage of patients).

It is possible that the DLQI may not be the best quality of life metric for patients with psoriasis. The DLQI is a scale used to objectively quantify the effect of dermatologic conditions on quality of life. It was surprising to note that there were no significant differences in DLQI scores among the different biologic drugs. Most biologic drugs achieved a final DLQI of 2-5 after starting at a baseline of 8-14. The most recent clinical trials tout major differences in PASI scores as evidence for the efficacy of certain drugs over others. This difference in efficacy was not evident when looking at DLQI in isolation. The DLQI instrument as a measure of quality of life may not be

sensitive enough to detect minor improvements attributable to increased skin clearance and then translate these improvements to effects on quality of life.

Considering the minor differences in final DLQI scores among the different medications, it is important to keep in mind economic costs when prescribing a biologic therapy. The annual costs of these drugs range from $30,001 for infliximab to $69,762 for ixekizumab.[23] Older TNF-alpha inhibitors such as adalimumab and etanercept are less expensive than the newer specific IL inhibitors. There are limited healthcare resources available and many patients struggle to afford their medications, therefore it is reasonable to utilize more affordable medications given the comparable effects on quality of life. A recent meta-analysis found no difference in risk of serious infections among different biologic therapies.[24] However, newer medications offer less frequent dosing schedules, which can also augment perceived quality of life for patients.

Our systematic review was extensive with a precisely executed search strategy and selection process. It serves as an up to date resource for quality of life data in clinical trials of psoriasis. The last similar review was published in 2006 with several drugs that are not currently available in the U.S.[13] Additionally, the studies included in our review were all randomized controlled trials that are less susceptible to sources of bias.

Our systematic review has some limitations. First, there was significant heterogeneity among the included studies in terms of length of study, characteristics of enrolled patients, and biologic therapy protocol. These studies were conducted with different objectives and comparison treatments across different trials. Although we originally planned to conduct a meta-analysis that would allow us to combine the results across several trials for each drug and thus compare drugs to one another, this proved to be impossible due to significant heterogeneity. Since we were unable to conduct the meta-analysis, it is not clear which drug is the most effective at improving quality of life. Future studies should determine whether clinically significant differences in quality of life (keeping in mind efficacy and cost-effectiveness) exist between the studied drugs.

Second, most studies did not uniformly report DLQI data. In these cases, significant efforts were made to contact study authors and sponsoring companies for additional information. Many complied with our requests for further information. However, several study sponsors declined to provide unpublished data for use in this study. Poor reporting of quality of life data continues to be a significant problem in dermatology research[25] and others have had similar experiences in which a lack of reporting guidelines for quality of life data resulted in data analysis difficulties.[7]

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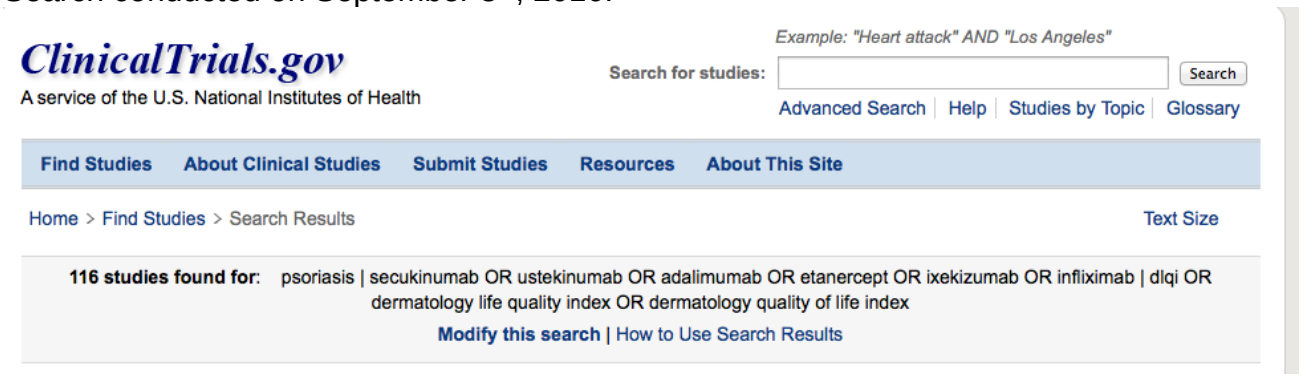
Appendix 1. Detailed search strategy.

Search conducted on September 8th, 2016:



Search conducted on August 30th, 2016:

PubMed search			
Category	**Search**	**Query**	**Items found**
Quality of Life terms	#1	Quality of life	278,988
	#2	DLQI	795
	#3	Dermatology life quality index	1,802
	#4	Dermatology quality of life index	1,802
	#5	**(#1 OR #2 OR #3 OR #4)**	279,007
Drug Terms	#6	Secukinumab	213
	#7	Adalimumab	5,323
	#8	Infliximab	11,143
	#9	Ixekizumab	102
	#10	Ustekinumab	828
	#11	Etanercept	6,676
	#12	Biologic Therapy	516,999
	#13	Biologic	1,386,214
	#14	**(#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)**	1,871,108
Disease Term	#15	Psoriasis	40,998
Design terms	#16	Randomized Controlled Trials as Topic [MeSH Major Topic]	15,816
	#17	"randomized controlled trials as topic" [MeSH Terms]	105,636
	#18	Random Allocation [MeSH Terms]	87,192
	#19	double blind method [MeSH Terms]	135,739
	#20	"controlled clinical trial" [Publication Type]	503,881
	#21	"randomized controlled trial" [Publication	418,036

		Type]	
	#22	"clinical trials as topic" [MeSH Terms]	292,996
	#23	"clinical trial" [Publication Type]	738,696
	#24	**(#16 or #17 or (#18 and (#19 or #22 or #23)) or #20 or #21)**	607,554
	#25	(((randomised and control and clinical and trial) or (randomized and control and clinical and trial)))	129,757
	#26	((((double or single or triple or treble) and (blind* or mask*) and (random*))))	164,021
	#27	(((random and allocat*) and control* and trial))	22
	#28	(#25 OR #26 OR #27)	258,498
	#29	(#24 AND #28)	231,144
Language term	#30	**English [Language]**	21,827, 863
Compilation of quality of life, drug terms, disease term, and design terms	#31	(#5 AND #14 AND #15 AND #29 AND #30)	76

Search conducted on August 25th, 2016:

Embase search			
Category	**Search**	**Query**	**Hits**
Design terms	#1	"randomized controlled trial (topic)"/exp	102,487
	#2	"randomized controlled trial"/exp	410,524
	#3	"randomization"/exp	70,729
	#4	"double blind procedure"/exp	130,636
	#5	[controlled clinical trial]/lim	607,113
	#6	[randomized controlled trial]/lim	510,524
	#7	"clinical trial"/exp	1,105,349
	#8	"clinical trial (topic)"/exp	200,673
	#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6	783,138
	#10	singl*:ab,ti OR doubl*:ab,ti OR treb*:ab,ti OR tripl*:ab,ti AND (blind*:ab,ti OR mask*:ab,ti)	212,673
	#11	"placebo"/exp	292,811
	#12	random* AND (clinical OR control*) AND trial OR (placebo* AND ("randomly	676,434

		allocated" OR (allocated AND random*)))	
	#13	(#7 OR #8) AND (#10 OR #11 OR #12)	672,466
	#14	#9 OR #13	890,573
Disease terms	#15	'Psoriasis'	63,602
Drug Terms	#16	'Secukinumab'	931
	#17	'Adalimumab'	21,275
	#18	'Infliximab'	37,012
	#19	'Ixekizumab'	467
	#20	'Ustekinumab'	3,014
	#21	'Etanercept'	23,852
	#22	'Biologic Therapy'	3,346
	#23	'Biologic'	76,906
	#24	(#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23)	123,128
Quality of Life Terms	#25	DLQI	1,709
	#26	'Dermatology life quality index'	2,316
	#27	'Dermatology quality of life index'	63
	#28	'Quality of Life'	386,267
	#29	(#25 OR #26 OR #27 OR #28)	386,734
Language Terms	#30	[english]/lim	25,124,781
Final		(#14 AND #15 AND #24 AND #29 AND #30)	461

Search conducted on August 25th, 2016:

Ovid/MEDLINE search			
Category	**Search**	**Query**	**Hits**
Design terms	#1	Randomized Controlled Trials as Topic/	109,437
	#2	Randomized Controlled Trial/	428,678
	#3	Random Allocation/	88,489
	#4	Double Blind Method/	138,784
	#5	controlled clinical trial.pt.	91,573
	#6	randomized controlled trial.pt.	428,678
	#7	Clinical Trial/	504,873
	#8	clinical trial.pt.	504,873

	#9	Clinical Trials as Topic/	179,085
	#10	1 or 2 or 3 or 4 or 5 or 6	698,072
	#11	7 or 8 or 9	613,026
	#12	((singl* or doubl* or treb* or tripl*) and (blind* or mask*)).ab,ti.	150,294
	#13	Placebos/	33,637
	#14	((random* and (clinical or control*) and trial) or (placebo* and ("randomly allocated" or (allocated and random*)))).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	501,456
	#15	12 or 13 or 14	555,680
	#16	11 and 15	259,650
	#17	10 or 16	713,005
Disease terms	#18	Psoriasis/	29,520
Drug Terms	#19	secukinumab.mp.	134
	#20	Infliximab/	8,053
	#21	Adalimumab/	3,520
	#22	Ixekizumab.mp.	47
	#23	Ustekinumab/	439
	#24	Etanercept/	4,798
	#25	Biologic Therapy/	1,836
	#26	Biologic.mp.	48,461
	#27	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	61,907
Quality of Life Terms	#28	DLQI.mp.	638
	#29	Dermatology life quality index.mp.	879

	#30	Dermatology quality of life index.mp.	26
	#31	Quality of Life/	142,263
	#32	28 or 29 or 30 or 31	142,443
Final	#33	17 and 18 and 27 and 32	99

Cochrane Library search			
Category	**Search**	**Query**	**Hits**
	#1	Psoriasis	4125
Quality of Life Terms	#2	DLQI	320
	#3	Dermatology life quality index	723
	#4	Dermatology quality of life index	723
	#5	Quality of Life	58281
	#6	#2 or #3 or #4 or #5	58286
Drug Terms	#7	secukinumab	150
	#8	Infliximab	1371
	#9	Adalimumab	1106
	#10	Ixekizumab	27
	#11	Ustekinumab	196
	#12	Etanercept	1170
	#13	Biologic Therapy	1322
	#14	Biologic	2011
	#15	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	4728
Final	#16	#1 and #6 and #15	234

Appendix 2. Risk of bias table for the included studies.