Efficacy and Safety of Systemic Long-Term Treatments for Moderate-to-Severe Psoriasis: A Systematic Review and Meta-Analysis

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Psoriasis as a chronic inflammatory disease often requires effective long-term treatment; a comprehensive systematic evaluation of efficacy and safety of systemic long-term treatments in patients with moderate-to-severe psoriasis is lacking. Twenty-five randomized clinical trials were included. Results were pooled and quality of evidence was assessed using GRADE (Grading of Recommendations Assessment, Development and Evaluation). With respect to PASI 75 (psoriasis area and severity index), pooled risk ratios for infliximab (13.07, 95% confidence interval (CI): 8.60–19.87), secukinumab (11.97, 95% CI: 8.83–16.23), ustekinumab (11.39, 95% CI: 8.94–14.51), adalimumab (8.92, 95% CI: 6.33–12.57), etanercept (8.39, 95% CI: 6.74–10.45), and apremilast (5.83, 95% CI: 2.58–13.17) show superiority of biologics and apremilast in long-term therapy compared with placebo. With respect to the addressed safety parameters, no differences were seen between adalimumab, etanercept, or infliximab versus placebo. No placebo-controlled data on conventional treatments was identified. Head-to-head studies showed superior efficacy of secukinumab and infliximab versus etanercept and of infliximab versus methotrexate. A clear ranking is limited by the lack of long-term head-to-head trials. From the available evidence, infliximab, secukinumab, and ustekinumab are the most efficacious long-term treatments. Data on conventionals are insufficient. Further head-to-head comparisons and studies on safety and patient-related outcomes are needed to draw more reliable conclusions.

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INTRODUCTION

Psoriasis vulgaris is a chronic inflammatory disease with a substantial impact on the patients' quality of life (Lee *et al.*, 2010). Most studies focus on short-term induction periods. Placebo-controlled long-term studies are rare, and performing a meta-analysis of long-term data a challenge. However, to control and treat psoriasis, an effective and safe long-term therapy is required. In the current guidelines on systemic antipsoriatic treatment, four different conventional and four different biological therapies have been included (Pathirana *et al.*, 2009; Nast *et al.*, 2011). Recently, secukinumab, an IL-17 antagonist, and apremilast, an inhibitor of phosphodiesterase 4, were approved and/or recommended by the US Food and Drug Administration (Food and Drug Administration, 2014,2015) and/or the Committee for Medicinal Products for Human Use of the European Medical Agency as new treatment options for psoriasis (European Medicines Agency, 2014a, b).

Existing systematic reviews and meta-analyses on the treatment of psoriasis have focused on induction therapy or do not include the recently approved treatments (Spuls *et al.*, 1998; Woolacott *et al.*, 2006; Schmitt and Wozel, 2009; Lucka *et al.*, 2012; Liu *et al.*, 2014; Meng *et al.*, 2014; Schmitt and Wozel, 2014a). In addition, existing reviews have not used the already established GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to assess the quality of included studies.

PASI (psoriasis area and severity index) is the most widely used score in psoriasis trials, making meta-analysis of existing trials possible. The Dermatology Life Quality Index (DLQI) is a widely accepted patient-oriented score used in many trials. In psoriasis trials in general, the reporting of safety is very little standardized. For this reason, safety aspects have been neglected in existing reviews. The committee for the update of the European psoriasis guidelines has selected the outcomes: (a) 'number of patients with at least one adverse event (AE)', (b) 'number of patients with at least one serious AE (SAE)', and (c) 'withdrawal due to AE' as relevant and

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Abbreviations: AE, adverse event; b.i.d., twice daily; CI, confidence interval; CsA, cyclosporine A; DLQI, dermatology life quality index; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference; MTX, methotrexate; PASI, psoriasis area and severity index; PGA, physician global assessment; RCT, randomized controlled trial; RR, risk ratio; SAE, serious adverse event

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sufficiently standardized outcomes to be extracted and considered for the assessment of treatments in the European Guidelines (consultation draft, date: 26 January 2015).

The aim of this systematic review is to provide a comprehensive overview about evidence on the efficacy and/or safety of systemic treatments for moderate-to-severe psoriasis in long-term therapy in adult patients based on randomized controlled trials (RCTs).

RESULTS

Systematic search yielded 5,663 results. After deduplication, 4,102 records remained and were screened by title and abstract. Three additional references were retrieved by hand search through reference lists. Overall, 48 articles were assessed for eligibility in full text, whereas 31 publications reporting on 25 independent RCTs met the inclusion criteria (Figure 1). Reasons for exclusion of articles are listed in Supplementary Material Table 1 online.

Twenty-five studies with two to four study groups and a total of 11,279 randomized patients were included in the analysis. Ten trials were initially placebo-controlled, 11 trials had placebo and active treatment as control, and four trials had at least one active treatment as control. Three studies remained placebo-controlled until week 24 (Gottlieb *et al.*, 2003; Reich *et al.*, 2005; Asahina *et al.*, 2010) and were pooled to calculate a mean 'placebo response', which was used as a model for trials without long-term placebo control.

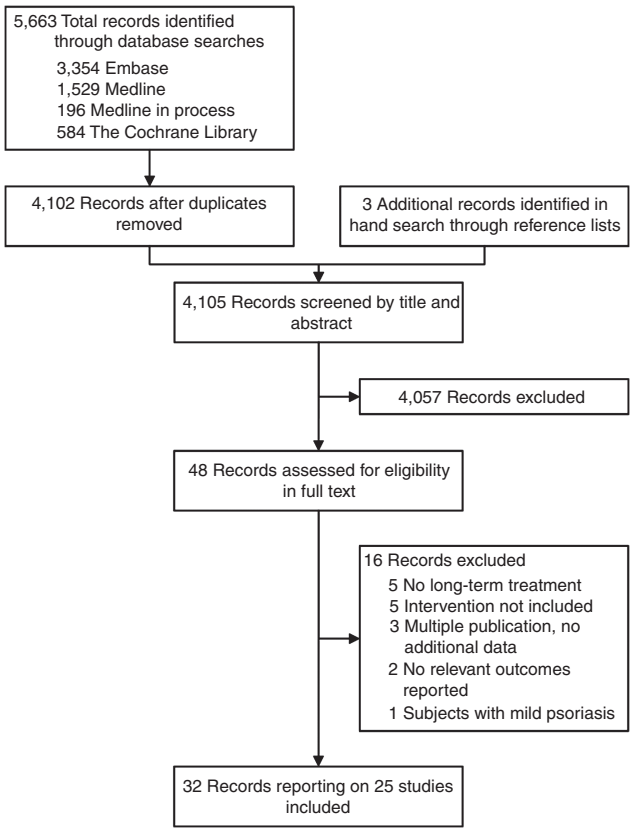

Figure 1. Identification of literature.

The study sample size varied from 48 to 1,306. Thirty-one percent of all study subjects were female. All included trials performed intention-to-treat analysis.

No studies investigating fumaric acid esters and cyclosporine A (CsA) in long-term treatment were available. Long-term data of direct comparisons of systemic therapies of up to 24 weeks were available for etanercept, infliximab, secukinumab, methotrexate (MTX), and acitretin. Detailed data on all included studies are presented in Supplementary Table 2.

There is only one included head-to-head trial reporting efficacy data beyond 28 weeks of treatment for the comparison with etanercept and secukinumab (Langley *et al.*, 2014) (see Supplementary Material, Table 3). All summary of finding tables are presented as part of the Supplemental Material (Table 4).

Risk of bias

The risk of bias among the included studies was partly heterogeneous, rated with low risk or unclear risk of bias. Of the 25 included RCTs, 13 (52%) reported an adequate randomization method and 14 (56%) supplied sufficient information to assess whether allocation concealment was properly ensured. In three studies (12%), the blinding of participants and personnel was insufficient (open (Barker *et al.*, 2011) or single blind (Gisondi *et al.*, 2008; de Vries *et al.*, 2013) study design). In 21 studies (84%), the risk of attrition bias was low, as incomplete outcome data were sufficiently addressed. The risk of reporting bias was low in most of the studies (80%). The risk of bias for each study is presented in Supplementary Material Figure 1.

Comparison of monotherapy versus placebo (at weeks 24–28)

Placebo-controlled studies were identified for all biologics and for apremilast but not for conventional treatments. These drugs have been shown to be effective in long-term therapy compared with placebo up to week 28. With respect to the addressed safety parameters, no differences were seen between the biologics and placebo. Data on PASI 75 response are presented in Figure 2 (Forest plots of other outcomes are available in Supplementary Material Figure 2).

Efficacy: assessor-oriented scores

PASI 75. All biologics and apremilast showed superior efficacy compared with placebo with respect to their PASI 75 response (Figure 2).

The pooled risk ratio (RR) for infliximab (Reich *et al.*, 2005,2006; Menter *et al.*, 2007; Feldman *et al.*, 2008; Torii *et al.*, 2010; Yang *et al.*, 2012), secukinumab (Langley *et al.*, 2014), ustekinumab (Leonardi *et al.*, 2008; Papp *et al.*, 2008; Tsai *et al.*, 2011; Igarashi *et al.*, 2012; Zhu *et al.*, 2013; Janssen *et al.*, 2014a,b), adalimumab (Gordon *et al.*, 2006; Menter *et al.*, 2008; Asahina *et al.*, 2010), etanercept (Gottlieb *et al.*, 2003; Leonardi *et al.*, 2003; Krueger *et al.*, 2005; Papp *et al.*, 2005; Tyring *et al.*, 2006,2007; van de Kerkhof *et al.*, 2008; Bagel *et al.*, 2012; Langley *et al.*, 2014), and apremilast (Papp *et al.*, 2012) are 13.07 (95% confidence interval (95% CI): 8.60, 19.87, $I^2 = 0\%$), 11.97 (95% CI: 8.83, 16.23,

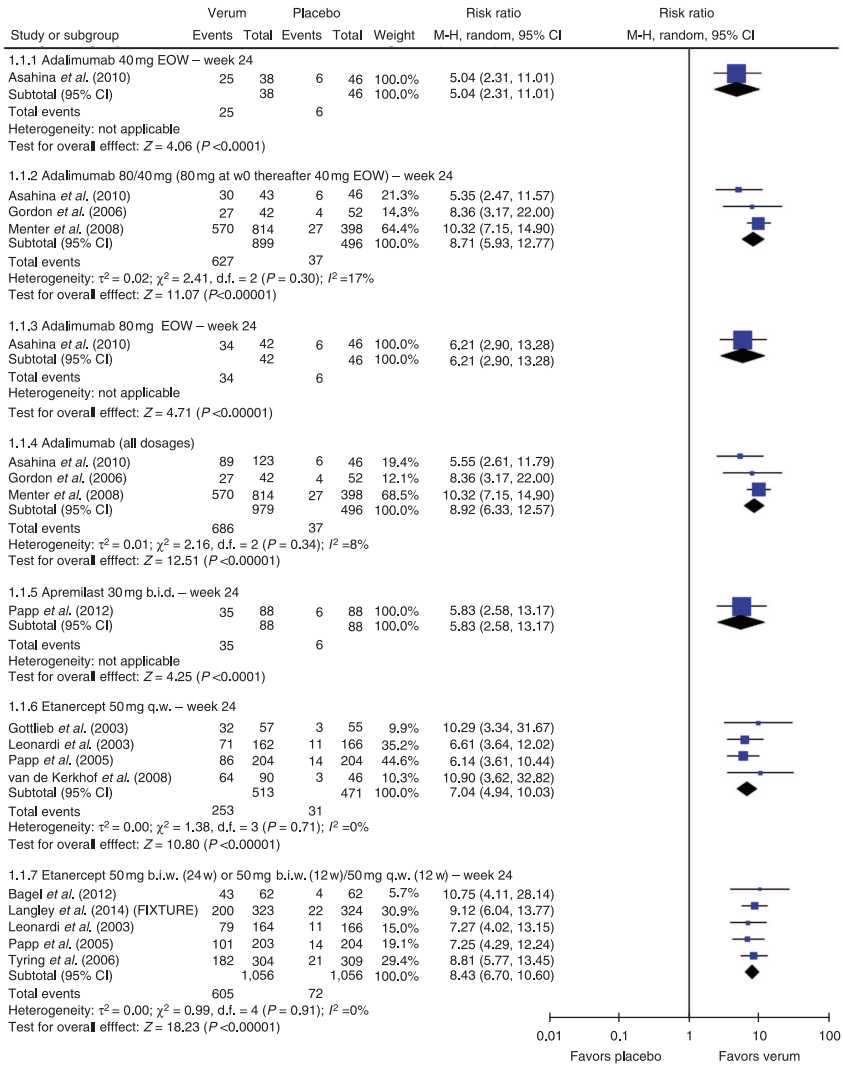

Figure 2. Forest plot: Verum versus placebo—PASI 75 at weeks 24–28. CI, confidence interval; b.i.d., twice daily; b.i.w., twice weekly; EOW, every other week; PASI, psoriasis area and severity index; q.w., once weekly; w, week.

$I^2 = 0\%$), 11.39 (95% CI: 8.94, 14.51, $I^2 = 0\%$), 8.92 (95% CI: 6.33, 12.57, $I^2 = 8\%$), 8.39 (95% CI: 6.74, 10.45, $I^2 = 0\%$), and 5.83 (95% CI: 2.58, 13.17), respectively, with low quality of evidence.

PASI 90. A higher probability to achieve a PASI 90 response compared with placebo at weeks 24–28 was seen with secukinumab (RR 40.15 (95% CI: 20.97, 76.89), $I^2 = 0\%$) (Langley *et al.*, 2014), ustekinumab (RR 31.63 (95% CI: 19.43, 51.51), $I^2 = 0\%$) (Leonardi *et al.*, 2008; Papp *et al.*, 2008; Tsai *et al.*, 2011; Igarashi *et al.*, 2012; Zhu *et al.*, 2013; Janssen *et al.*, 2014a, b), infliximab (RR 31.00 (95% CI: 13.45, 71.46), $I^2 = 0\%$) (Reich *et al.*, 2005, 2006; Menter *et al.*, 2007; Feldman *et al.*, 2008; Torii *et al.*, 2010; Langley *et al.*, 2014), adalimumab (RR 23.17 (95% CI: 12.51, 42.91), $I^2 = 0\%$) (Gordon *et al.*, 2006; Menter *et al.*, 2008; Asahina *et al.*, 2010), etanercept (RR 19.14 (95% CI: 11.59, 31.60), $I^2 = 0\%$) (Gottlieb *et al.*, 2003; Leonardi *et al.*, 2003; Tyring *et al.*, 2006,2007; van de Kerkhof *et al.*, 2008; Bagel *et al.*, 2012), and apremilast (RR 13.00 (95% CI: 1.74, 97.25)) (Papp *et al.*, 2012). The quality of the evidence for all results was low.

PGA 'clear/almost clear'. Based on PGA (Physician Global Assessment) 'clear/almost clear', the biologics and apremilast are superior to placebo. The RRs are 13.13 (95% CI: 8.45, 20.38, $I^2 = 0$), 9.91 (95% CI: 7.76, 12.66, $I^2 = 0$), 9.84 (95% CI: 7.25, 13.36, $I^2 = 0\%$), 8.06 (95% CI: 5.89, 11.04, $I^2 = 0$), 7.16 (95% CI: 5.35, 9.57, $I^2 = 0$), and 5.00 (95% CI: 2.19, 11.41) for infliximab (Reich *et al.*, 2005, 2006; Menter *et al.*, 2007; Feldman *et al.*, 2008; Yang *et al.*, 2012), ustekinumab (Leonardi *et al.*, 2008; Papp *et al.*, 2008; Tsai *et al.*, 2011; Zhu *et al.*, 2013; Janssen *et al.*, 2014a,b), secukinumab (Langley *et al.*, 2014), adalimumab (Gordon *et al.*, 2006; Menter *et al.*, 2008; Asahina *et al.*, 2010), etanercept (Gottlieb *et al.*, 2003; Leonardi *et al.*, 2003; van de Kerkhof *et al.*, 2008; Bagel *et al.*, 2012; Langley *et al.*, 2014), and apremilast (Papp *et al.*, 2012), respectively. All results have been assigned a low quality of evidence.

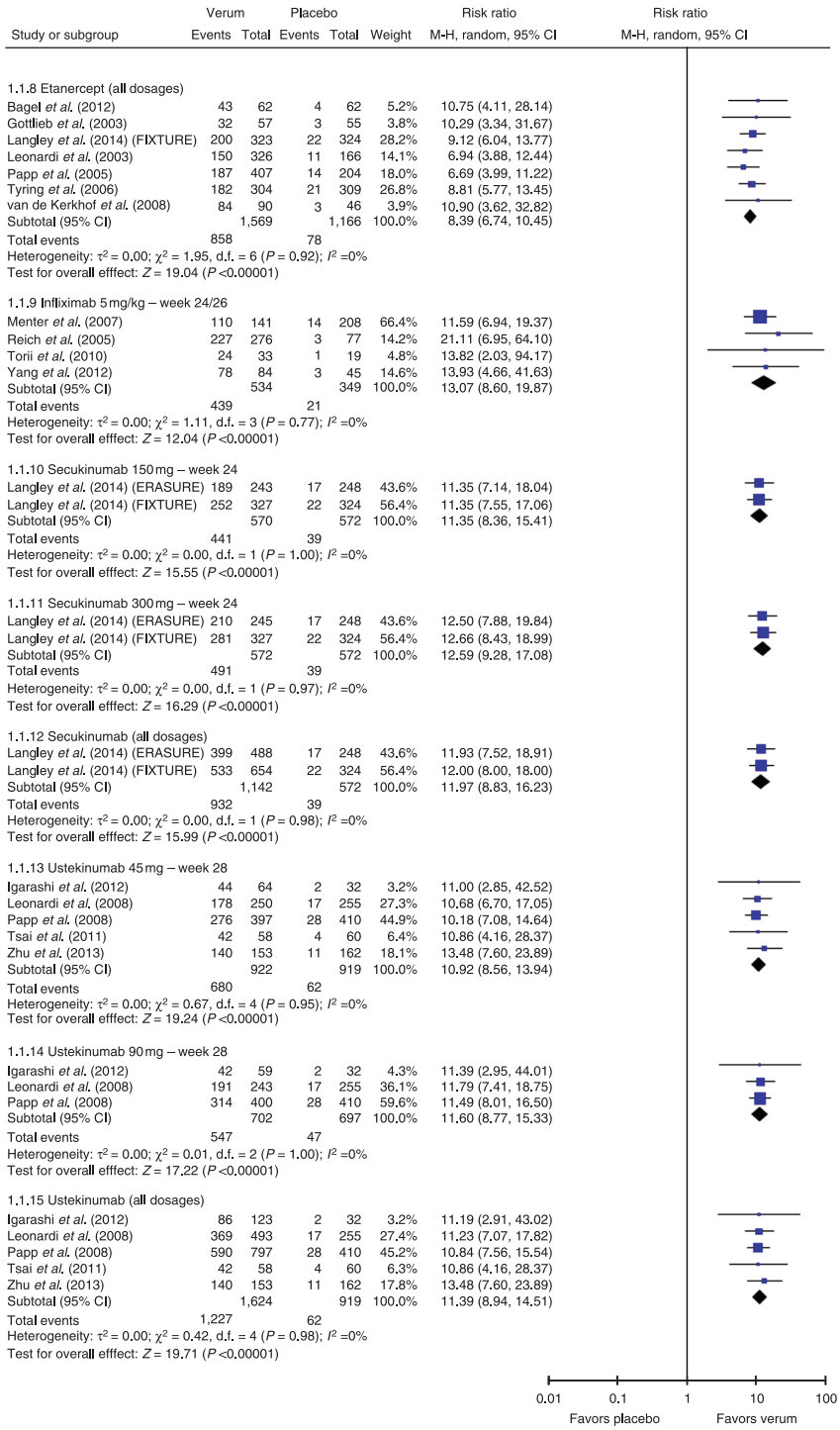

Figure 2. Continued

Efficacy: patient-oriented scores

DLQI

Absolute reduction in mean DLQI. With a mean difference (MD) in absolute reduction in mean DLQI of 9.80 (95% CI: 8.19, 11.41), infliximab is statistically significantly superior to placebo in long-term treatment (high quality) (Reich *et al.*, 2005,2006).Compared with placebo, a higher reduction in absolute DLQI in the long-term treatment was found for adalimumab 80 mg every other week (MD 5.70 (95% CI: 3.13, 8.27), moderate quality) (Asahina *et al.*, 2010), adalimumab with a loading dose of 80 mg and following 40 mg every other week (MD 4.20 (95% CI: 1.54, 6.86), low quality) (Asahina *et al.*, 2010), and for adalimumab 40 mg every other week (MD 3.30 (95% CI: 0.56, 6.04), low quality) (Asahina *et al.*, 2010). However, the effects were small for the last two dosing regimens.

Percentage reduction in mean DLQI. Etanercept 50 mg twice weekly (b.i.w.) has been shown to be superior to placebo in long-term treatment with an MD in percentage DLQI reduction in 57.00 (95% CI: 38.52, 75.48, high quality) (Gottlieb *et al.*, 2003).

Safety

Patients with at least one AE. After long-term treatment, no differences were found between adalimumab and placebo in the number of patients with at least one AE (RR 1.04 (95% CI: 0.93, 1.16), moderate quality) (Asahina *et al.*, 2010) and between infliximab and placebo (RR 1.15 (95% CI: 0.99, 1.34), moderate quality) (Reich *et al.*, 2005, 2006).

Patients with at least one SAE. Compared with placebo, no differences in the risks of SAE were shown for adalimumab (RR 0.75 (95% CI: 0.14, 3.95), low quality) (Asahina *et al.*, 2010), etanercept 50 mg once weekly (q.w.) (RR 0.64 (95% CI: 0.11, 3.70), moderate quality) (Gottlieb *et al.*, 2003), and infliximab (RR 2.16 (95% CI: 0.65, 7.17), $I^2 = 0\%$, moderate quality) (Reich *et al.*, 2005,2006; Yang *et al.*, 2012).

Withdrawal due to AE. In comparison with placebo, no statistically significant differences in withdrawal due to AE in long-term treatment were found for adalimumab (RR 0.87 (95% CI: 0.24, 3.23), low quality) (Asahina *et al.*, 2010), etanercept 50 mg q.w. (RR 0.32 (95% CI: 0.07, 1.53), moderate quality) (Gottlieb *et al.*, 2003), and infliximab (RR 1.38 (95% CI: 0.55, 3.46), moderate quality) (Reich *et al.*, 2005, 2006).

Head-to-head comparisons of systemic treatments (at weeks 24–26)

Five studies were identified providing long-term data of direct comparisons (see Supplementary Material Figure 3).

Acitretin 0.4 mg kg^{-1} once daily (q.d.) versus etanercept 25 mg b.i.w. After long-term treatment, no statistically significant differences were found between acitretin and etanercept with respect to PASI 75 (RR 0.66 (95% CI: 0.29, 1.49)) and with respect to the number of patients with at least one AE (RR 5.48 (95% CI: 0.28, 107.62), very low quality for both outcomes) (Gisondi *et al.*, 2008).

Acitretin 0.4 mg kg^{-1} q.d. versus combination of acitretin 0.4 mg kg^{-1} q.d. and etanercept 25 mg q.w. No differences were found between acitretin monotherapy and acitretin in combination with etanercept with respect to PASI 75 (RR 0.68 (95% CI: 0.29, 1.57)) and in the number of patients with at least one AE (RR 1.80 (95% CI: 0.18, 18.21), very low quality for both outcomes) (Gisondi *et al.*, 2008).

Etanercept 25 mg b.i.w. versus combination of acitretin 0.4 mg kg^{-1} q.d. and etanercept 25 mg q.w. There are no differences in PASI 75 response between etanercept combined with acitretin and etanercept monotherapy after long-term treatment period (RR 1.02 (95% CI: 0.51, 2.04)). With respect to the number of patients with at least one AE, it is uncertain whether there is any difference (RR 0.28 (95% CI: 0.01, 6.38). The quality of evidence is very low for both outcomes (Gisondi *et al.*, 2008).

Etanercept 50 mg b.i.w. for 12 weeks followed by 50 mg kg^{-1} q.w. versus combination of etanercept 50 mg b.i.w./q.w. and MTX 7.5–15 mg q.w. After long-term treatment, statistically significant differences with a small effect were observed in favor of the combination etanercept/MTX based on PASI 75 (RR 0.78 (95% CI: 0.69, 0.88), low quality), PASI 90 (RR 0.64 (95% CI: 0.51, 0.78), moderate quality), and PGA 'clear/almost clear' (RR 0.76 (95% CI: 0.66, 0.88), low quality). In contrast, a slightly increased risk for the occurrence of at least one AE was seen with the combination (RR 0.80 (95% CI: 0.70, 0.91), moderate quality), whereas no statistically significant difference was found for the number of patients with at least one SAE (RR 1.50 (95% CI: 0.25, 8.90), low quality) (Gottlieb *et al.*, 2012).

Etanercept 50 mg b.i.w. versus infliximab 5 mg kg^{-1}. After long-term treatment, etanercept was inferior to infliximab based on PASI 75 (RR 0.48 (95% CI: 0.26, 0.89), moderate quality) (de Vries *et al.*, 2013).

Etanercept 50 mg b.i.w./q.w. versus secukinumab 150–300 mg monthly. After long-term treatment, there are small statistically significant differences in favor of secukinumab 150 mg based on PASI 75 (RR 0.80 (95% CI: 0.72, 0.89), moderate quality), PASI 90 (RR 0.67 (95% CI: 0.57, 0.79), high quality), and PGA 'clear/almost clear' (RR 0.74 (95% CI: 0.64, 0.86), moderate quality) (Langley *et al.*, 2014). Secukinumab 300 mg is superior to etanercept based on PASI 75 (RR 0.72 (95% CI: 0.65, 0.79), moderate quality), PASI 90 (RR 0.54 (95% CI: 0.46, 0.63), high quality), and PGA 'clear/almost clear' (RR 0.61 (95% CI: 0.53, 0.69), high quality) (Langley *et al.*, 2014).

MTX 15–20 mg q.w. versus infliximab 5 mg kg^{-1}. MTX is inferior to infliximab in long-term treatment based on PASI 75 (RR 0.40 (95% CI: 0.33, 0.49)), PASI 90 (RR 0.29 (95% CI: 0.21, 0.41)), and PGA 'clear/almost clear' (RR 0.38 (95% CI: 0.31, 0.48), moderate quality for all outcomes) (Barker *et al.*, 2011). With respect to quality of life, MTX and infliximab showed a percentage reduction in DLQI of 62% and 84%, respectively. Because of missing measures of variance, no effect estimate was calculated (Barker *et al.*, 2011).

DISCUSSION

This systematic review summarizes the evidence for efficacy and safety of systemic drugs in long-term treatment of moderate-to-severe psoriasis.

Placebo-controlled studies could be identified for adalimumab, etanercept, infliximab, secukinumab, ustekinumab, and apremilast. Based on low quality of evidence, all biologics and apremilast have been shown to be clinically effective in long-term therapy compared with placebo. Patient relevant outcomes support this finding with high to low quality of evidence. With respect to the addressed safety outcomes, none of the results showed a statistically significant difference for adalimumab, etanercept, or infliximab compared with placebo. However, a trend of a less favorable safety profile of infliximab over placebo can be assumed from these data.

For secukinumab, ustekinumab, and apremilast, no data for the selected safety outcomes were available.

Head-to-head trials allow a much better direct comparison of efficacy and safety. However, the number of direct long-term comparisons is limited. With respect to efficacy, based on PASI 75, superiority of secukinumab over etanercept, of

infliximab over MTX (dosages of 15–20 mg), and of infliximab over etanercept was shown in head-to-head trials of at least 24 weeks (moderate quality of evidence). As our addressed safety parameters were not provided in these studies, no conclusion with respect to safety was possible.

In head-to-head comparisons, the combination of etanercept plus methotrexate has been found to be superior to etanercept monotherapy with a low to moderate quality of evidence. This effect was accompanied by a slight increase in AEs. Acitretin as a combination partner to etanercept low dose was shown to have some dose sparing potential compared with monotherapy with high-dose etanercept.

For comparison of the other interventions, only indirect comparisons can be carried out. Summarizing the data from the indirect comparison for PASI 75 responses, the best results were seen for infliximab, secukinumab, and ustekinumab followed by adalimumab and etanercept. Apremilast showed the lowest PASI 75 response rate. Indirect comparisons of the DLQI data underline the superiority of infliximab over adalimumab. This ranking has been associated with limited strength as for indirect comparisons the assumption of clinical and methodological similarity of the included studies cannot be completely assured.

Summarizing safety data is a critical issue; however, it is highly limited by feasibility due to a lack of standardised reporting. Further harmonization of reporting should be pursued; an excellent approach to harmonizing outcome reporting has been carried out for eczema and could be initiated for psoriasis safety reporting as well (Schmitt *et al.*, 2014b). A Cochrane review investigated the safety of biologic treatments in any indication, including non-antipsoriatic treatments such as abatacept and rituximab. The review showed an increased risk of tuberculosis reactivation (odds ratio 4.68, 95% CI: 1.18–18.60) compared with control. The rates of SAE, serious infections, lymphoma, and congestive heart failure were not significantly different. Pooling all these different biologics and different populations into one group is questionable (Singh *et al.*, 2011).

Patient registries are another possible approach to generate long-term data on efficacy and especially safety. Gniadecki *et al*. (2015) have published drug survival data from Danish psoriasis registry (DERMBIO), which showed longer drug survival on ustekinumab compared with the anti-TNF agents. Similar results were found by van den Reek *et al*. (2015) in the Dutch Bio-CAPTURE network, with better overall drug survival of ustekinumab over etanercept and a trend over adalimumab.

Limitations

In most of the long-term studies, the placebo groups were discontinued after induction. We performed an imputation approach to make long-term efficacy data of the drugs derived from original placebo-controlled studies suitable for meta-analyses. In this imputation approach, we calculated a mean placebo response of efficacy outcomes based on available placebo-controlled trials. The original sample size of the placebo group was also considered. We are aware that this imputation approach has been associated with uncertainties; consequently, we downgraded the quality of evidence.

The assessment of safety remains a challenge. Reporting needs to be more standardised. Even when using the very broad categories number of patients with 'at least one AE', 'at least one SAE', and 'withdrawal due to AE', evidence is strongly limited. As we could not make assumptions on occurrence of AEs during long-term placebo treatment, imputations of placebo data for safety outcomes were not performed. In addition, among biologics, data reported in publications on ustekinumab and secukinumab were not suitable for analyzing our predefined safety outcomes, and conclusions on potential harms based on these parameters could not be drawn.

More long-term head-to-head trials are needed to allow for comparisons of efficacy and safety with a higher validity. The RCT setting is preferable, as it generates the more robust data. Additional data will be generated from the ongoing patient registers providing information on safety and drug survival rates in the general patient population.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Moher *et al.*, 2009). 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 differences were solved by discussion and mutual agreement.

Predefined eligibility criteria

Published RCTs were included if they investigated one of the following treatments in commonly used dosages: acitretin, adalimumab, apremilast, CSA, etanercept, fumaric acid ester, infliximab, MTX, secukinumab, or ustekinumab. Comparison had to be done versus placebo, versus another included active treatment, or versus a combination of two included treatments. Data had to be available for a treatment duration of at least 24 weeks. Patient population consisted of adults suffering from moderate-to-severe plaque-type psoriasis. Studies had to report at least one efficacy or safety outcome for long-term treatment. No language restrictions were applied.

Information sources and search

Systematic literature searches were conducted in Medline, Medline in Process, and Embase using OvidSP platform. In addition, the Cochrane Library was searched via its online search platform. Search dates were from inception to 5 January 2015. The search strategy for Medline is presented in Supplementary Material Table 5. In addition, reference lists of relevant reviews and included studies were screened.

Study selection and data extraction

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. medication and dosage for intervention and control, number of randomized patients, trial and treatment duration, inclusion criteria, and sponsor), study population (e.g. age, sex, weight, previous treatment, disease severity), and study results of included trials were extracted using a standardized data extraction form. Efficacy and safety data were sought for one time point of long-term treatment, defined as a treatment of at least 24 weeks. Outcomes were PASI 75 (primary), PASI 90, PGA 'clear/almost

Table 1. Available placebo outcome data for week 24

Study	Comparator to placebo	Placebo response		
		PASI 75	PASI 90	PGA 'clear/almost clear'
Asahina *et al*. (2010)	Adalimumab	6/46 (13.0%)	2/46 (4.3%)	5/46 (10.9%)
Gottlieb *et al*. (2003)	Etanercept	3/55 (5.5%)	0/55 (0.0%)	Not available
Reich *et al*. (2005)	Infliximab	3/77 (3.9%)	1/77 (1.3%)	2/55 (3.6%)
	Total placebo response	12/178 (6.7%)	3/178 (1.7%)	7/101 (6.9%)

Abbreviations: PGA, Physician Global Assessment; PASI, psoriasis area and severity index.

clear', reduction in mean DLQI, patients with at least one AE, patients with at least one SAE, and withdrawal due to AE.

Data analysis

RRs with 95% CI for dichotomous data and MDs with 95% CI for continuous data were calculated for each study comparison. The effect estimates of the individual studies were pooled in the meta-analysis using a random-effects model (Review Manager 5.3.4). Inconsistencies among the estimates were quantified using the I^2 test. Wherever heterogeneity among the included studies was substantial (Higgins and Green, 2011), study results were not pooled but presented individually.

Limited placebo-controlled data were available for long-term treatment. Most of the placebo control arms did not continue beyond the induction period of usually 12 to 16 weeks. However, to calculate effect estimates, a placebo arm is necessary. Three included studies provided placebo data for up to week 24. The long-term placebo data of efficacy outcomes from these three studies were pooled to calculate a mean 'placebo response', which was used as a model for trials without long-term placebo control. Placebo data at week 24 were available for PASI 75, PASI 90, and PGA 'clear/almost clear' Table 1.

Quality of the evidence

The quality of the individual included trials was assessed using the Cochrane Risk of Bias Tool (Higgins *et al.*, 2011). The available evidence and its quality were summarized using the GRADE approach (Atkins *et al.*, 2004) for each available outcome in each comparison. Using the GRADEprofiler software (Brozek *et al.*, 2008), GRADE evidence profiles were developed for each available treatment comparison. The quality of the evidence for each comparison was categorized into one of the four categories, from 'very low' (+ − − −) to 'high' (+ + + +) based on the criteria risk of bias, inconsistency, indirectness, imprecision, publication bias, and large effects (Balshem *et al.*, 2011). In addition to the general criteria for risk of bias, the quality was downgraded by two points if imputed placebo data were used for calculation of the effect estimate to reflect the limited validity of the results. Likelihood of publication bias was graded as 'undetected' for each outcome, although no analysis such as funnel plots or statistical tests for asymmetry could be carried out due to the small number of included studies for each comparison.

CONFLICT OF INTEREST

Dr Nast has received honoraria for CME certified educational talks that received direct or indirect sponsoring from Abbott (now AbbVie) and Pfizer. The Division of Evidence-Based Medicine has received research grants from Pfizer. No other disclosures were reported.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

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