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.

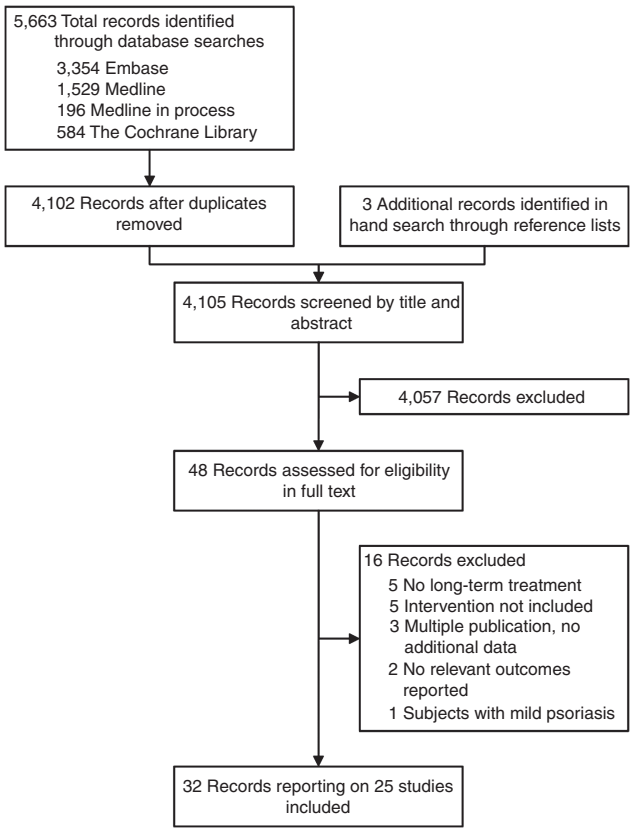

Figure 1. Identification of literature.

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,