Aus der Klinik für Dermatologie, Venerologie und Allergologie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Wirksamkeit von systemischen Antipsoriatika zur Behandlung der mittelschweren bis schweren Psoriasis vulgaris in der Langzeittherapie

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

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von

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aus Bremen

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Inhaltsverzeichnis:

1 Zusammenfassung

Hintergrund: Die Psoriasis vulgaris ist eine chronische Erkrankung vor allem der Haut. Die Prävalenz in der europäischen Bevölkerung liegt bei 2-3 %, mit einer Schwankung unter verschiedenen ethnischen Gruppen. Bisherige systematische Übersichtsarbeiten fokussieren sich meist auf die Kurzzeittherapie, wobei die Krankheit in der Regel chronisch verläuft.

Zielsetzung: Beurteilung der Effektivität zugelassenener systemischer Antipsoriatika in der Langzeittherapie bei mittelschwerer bis schwerer Psoriasis vulgaris.

Methoden: Es wurde eine systematische Suche in Medline, Embase und der Cochrane Library in Analogie zur deutschen Psoriasis S3 Leitlinie durchgeführt. Der Anteil an Studienpatienten mit einer Verringerung des Psoriasis Area Severity Index (PASI) von mindestens 75 % sowie die Reduktion im Dermatology Life Quality Index (DLQI) wurden zu verschiedenen Zeitpunkten erfasst. Die Studien wurden zusammengefasst hinsichtlich der Messzeitpunkte und des Studiendesigns. Davon wurden geeignete Studien in eine Metaanalyse eingeschlossen. Besondere Aufmerksamkeit wurde der statistischen Einberechnung von Studienabbrechern geschenkt.

Ergebnisse: 33 Publikationen, die Ergebnisse aus 27 verschiedenen Studien berichteten wurden in den Review eingeschlossen. 6575 Patienten erhielten eine „aktive“ Therapie. 7 randomisiert-kontrollierte Studien erfüllten die Einschlusskriterien für die Metaanalyse. Nach 24 Wochen Therapie waren Infliximab 5 mg/kg Körpergewicht [risk difference (RD) 78%, 95% confidence interval (CI) 72-83%] und Ustekinumab 90 mg (RD 77%, 95% CI 71-83%) die effektivsten Wirkstoffe. Adalimumab 40 mg (RD: 60%, 95% CI 45-74%) zeigte Ergebnisse vergleichbar mit Etanercept in verschiedenen Dosen (Etanercept 50 mg einmal pro Woche: RD 62%, 95% CI , 52-72%), (Etanercept 25 mg zweimal pro Woche: RD 45%, 95% CI 34-56%), (Etanercept 50 mg zweimal pro Woche: RD 56%, 95% CI 49-62%) und (Etanercept 50 mg zweimal pro Woche 12, dann 25 mg zweimal pro Woche : RD 50%, 95% CI 42-57%). Bei Therapien länger als 24 Wochen wurden nachlassende Therapieergebnisse für Infliximab, Adalimumab und Etanercept beobachtet.

Schlussfolgerung: Die aktuelle Datenlage erlaubt keine ausreichende Beurteilung der Wirksamkeit der systemischen Antipsoriatika, insbesondere bei Zeiträumen von über 24 Wochen. Mehr Langzeitstudien mit head-to-head Vergleichen zwischen verschiedenen Wirkstoffen wären wünschenswert.

Abstract

Background: Psoriasis vulgaris is a chronic disease that predominantly affects the skin. The prevalence is about 2-3 % in the European population with a variation among different ethnic groups. So far systemic reviews focused predominantly on short-term treatment, whereas symptoms usually persist throughout life.

Objective: Evaluation of effective systemic long-term treatments for moderate-to-severe psoriasis.

Methods: A systematic literature research in Medline, Embase and the Cochrane Library was conducted with a search strategy similar to the german Psoriasis S3 guideline. The proportion of patients with a decrease in the Psoriasis Area Severity Index (PASI) of at least 75 % and the reduction in the Dermatology Life Quality Index (DLQI) at different points in time during therapy were gathered. Studies have been summarized in terms of study designs and survey periods. Among these appropriate studies were included in the meta-analysis. Particular attention was given to the statistical approach with the handling of dropouts.

Results: 33 publications reporting on 27 trials with active treatment of 6575 patients were included in the systematic review. 7 randomized controlled trials were eligible for the meta-analysis. After 24 weeks of treatment infliximab 5 mg/kg bodyweight [risk difference (RD) 78%, 95% confidence interval (CI) 72–83%] and ustekinumab 90 mg (RD 77%, 95% CI 71–83%) were the most efficacious active agents. Adalimumab 40 mg (RD: 60%, 95% CI 45–74%) showed results within the range of different etanercept dosages (etanercept 50 mg once weekly: RD 62%, 95% CI, 52–72%), (etanercept 25 mg twice weekly: RD 45%, 95% CI 34–56%), (etanercept 50 mg twice weekly: RD 56%, 95% CI 49–62%) and (etanercept 50 mg twice weekly until week 12, then 25 mg twice weekly: RD 50%, 95% CI 42–57%). In studies lasting longer than 24 weeks a decrease in efficacy for inflximab, adalimumab and etanercept was observed.

Conclusion: More sufficient data is needed to draw reliable conclusions in efficacy of long-term treatments beyond 24 weeks and head-to-head comparisons of different active agents are necessary.

2 Eidesstattliche Versicherung

„Ich, Tilmann Christian Lucka, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Wirksamkeit von systemischen Antipsoriatika zur Behandlung der mittelschweren bis schweren Psoriasis vulgaris in der Langzeittherapie“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe. Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)“ des ICMJE -www.icmje.org) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o.) und werden von mir verantwortet.
Mein Anteil an der ausgewählten Publikation entspricht dem, der in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben ist.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum **19.11.2013** _____ **Unterschrift**

3 Ausführliche Anteilserklärung an der erfolgten Publikation

Publikation: Tilmann C Lucka, Delano Pathirana, Adel Sammain, Frank Bachmann, Stefanie Rosumeck, Ricardo Erdmann, Jochen Schmitt, Helmut Orawa , Berthold Rzany, Alexander Nast. Efficacy of systemic therapies for moderate-to-severe psoriasis: a systematic review and meta-analysis of long-term treatment. J Eur Acad Dermatol Venereol. 2012 Nov;26(11):1331-44.

Beitrag im Einzelnen:

- Identifizierung von geeigneten Publikationen aus der Psoriasis S3-Leitlinie von 2006. 568 Publikationen mit dem Veröffentlichungszeitraum von 1950 bis 2005 wurden von mir mit vordefinierter Ein- und Ausschlusskriterien (siehe Veröffentlichung) anhand tabellarischer Zusammenfassung der Studieneigenschaften aus der Leitlinie und ggf. mit dem Abstrakt der Publikation auf Relevanz für unsere Studie geprüft.

- 3018 Publikationen wurden durch eine neue Literaturrecherche in Medline, Embase und der Cochrane Library identifiziert. Diese Publikationen wurden von mir, sowie zusätzlich von Koautoren anhand des Abstrakts auf Ein- und Ausschlusskriterien überprüft.

- Alle relevanten Publikationen wurden anschließend von mir im Volltext durchgearbeitet und auf den endgültigen Einschluss in Absprache mit den Koautoren überprüft.

- Studienergebnisse (PASI 75 und DLQI) und Studieneigenschaften der 33 eingeschlossenen Publikationen wurden von mir nach dem Zeitpunkt der Ergebniserhebung in Wochen, dem Wirkstoff und der Art der statistischen Auswertung sortiert und in Form einer Excel-Tabelle zusammengefasst.

- Durch den Vergleich der Erhebungszeitpunkte und der Art der statistischen Auswertung wurden von mir 7 Publikationen für die Erstellung einer Metaanalyse identifiziert und in Absprache mit den Koautoren darin eingeschlossen.

- Die Ergebnisse der ausgewählten Publikationen mit dem Datenerhebungszeitpunkt nach 24 Wochen Therapie wurden von mir in den Cochrane Review Manager eingegeben.

- Durch den Mangel einer durchgehenden Placebo-Kontrollgruppe über 24 Wochen in 5 von 7 Studien wurde von mir mit Hilfe des Statistikers Helmut Orawa eine universelle Placebogruppe berechnet.

- Die Daten für die Metaanalyse wurden von mir mit dem Cochrane Review Manager als Risk Difference der Verum- gegenüber der Placebogruppe berechnet und als Boxplot Diagramm dargestellt.

- Alle Tabellen und Diagramme in der Publikation wurden von mir selbst erstellt.

- Über 80% des gesamten Textes in der vorliegenden Publikation wurden von mir selbst in englischer Sprache verfasst und geschrieben.

- Die Literaturstellen im Text wurden von mir selbst ausgewählt und im Literatur-verzeichnis dargestellt.

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers

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Unterschrift des Doktoranden

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4 Auszug aus der Journal Summary List (ISI Web of KnowledgeSM)

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Mark	Rank	Abbreviated Journal Title (linked to journal information)	ISSN	JCR Data						Eigenfactor® Metrics	
				Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor® Score	Article Influence® Score
	1	J INVEST DERMATOL	0022-202X	23976	6.193	6.065	1.898	264	8.5	0.04694	1.977
	2	PIGM CELL MELANOMA R	1755-1471	3385	5.839	5.434	1.397	68	6.2	0.01003	2.000
	3	J AM ACAD DERMATOL	0190-9622	19760	4.906	4.515	0.896	280	9.3	0.03474	1.482
	4	ARCH DERMATOL	0003-987X	12875	4.792	4.640	0.836	128	>10.0	0.01891	1.643
	5	BRIT J DERMATOL	0007-0963	19868	3.759	4.162	1.195	354	8.0	0.03997	1.313
	6	EXP DERMATOL	0906-6705	4027	3.578	3.613	0.483	172	4.3	0.01195	0.960
	7	J DERMATOL SCI	0923-1811	3017	3.520	3.807	0.457	92	5.7	0.00805	1.119
	8	ACTA DERM-VENEREOL	0001-5555	4131	3.487	3.792	0.782	78	>10.0	0.00767	1.198
	9	CONTACT DERMATITIS	0105-1873	4899	2.925	3.152	0.303	145	9.6	0.00553	0.640
	10	SKIN PHARMACOL PHYS	1660-5527	1355	2.885	3.099	0.476	42	6.2	0.00247	0.698
	11	WOUND REPAIR REGEN	1067-1927	3730	2.757	3.807	0.380	92	5.9	0.00889	1.039
	12	ARCH DERMATOL RES	0340-3696	2853	2.708	2.363	0.375	104	8.9	0.00504	0.652
	13	J EUR ACAD DERMATOL	0926-9959	4743	2.694	2.959	0.665	254	4.7	0.01467	0.869
	14	MELANOMA RES	0960-8931	1786	2.518	2.309	0.371	62	7.3	0.00399	0.740
	15	SEMIN CUTAN MED SURG	1085-5629	882	2.362	2.505	0.293	41	5.2	0.00286	0.849
	16	CLIN DERMATOL	0738-081X	2393	2.341	2.907	0.395	81	6.5	0.00568	0.864
	17	DERMATOLOGY	1018-8665	4688	2.024	2.393	0.170	106	9.8	0.00833	0.767
	18	DERMATOL THER	1396-0296	1218	1.963	2.255	0.129	85	4.8	0.00406	0.680
	19	DERMATOL SURG	1076-0512	6680	1.866	2.372	0.384	307	7.0	0.01229	0.593
	20	AM J CLIN DERMATOL	1175-0561	1362	1.844	1.930	0.306	36	7.7	0.00295	0.619

5 Druckexemplar der ausgewählten Publikation

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REVIEW ARTICLE

Efficacy of systemic therapies for moderate-to-severe psoriasis: a systematic review and meta-analysis of long-term treatment

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Abstract

Background Despite the chronicity of psoriasis, most systematic reviews focus on short-term treatment.

Methods The systematic search strategy and results from the German Psoriasis Guidelines were adapted. To update the data a literature search in Medline, Embase and the Cochrane Library was conducted. The proportion of participants achieving ≥75% decrease in Psoriasis Area and Severity Index (PASI) as well as Dermatology Life Quality Index (DLQI) reduction at different time points were assessed. Trials were summarized with respect to time periods and study designs. Suitable trials were included in a meta-analysis. Particular attention was paid to statistical approaches of handling dropouts.

Results A total of 33 articles including 27 trials totaling 6575 patients with active treatment were included in the systematic review. Seven randomized controlled trials were eligible for the meta-analysis. Over a 24 week treatment period infliximab [risk difference (RD) 78%, 95% confidence interval (CI) 72–83%] and ustekinumab 90 mg every 12 weeks (RD 77%, 95% CI 71–83%) were the most efficacious treatments. Adalimumab (RD: 60%, 95% CI 45–74%) showed results within the range of different etanercept dosages (etanercept 50 mg once weekly: RD 62%, 95% CI, 52–72%), (etanercept 25 mg twice weekly: RD 45%, 95% CI 34–56%), (etanercept 50 mg twice weekly: RD 56%, 95% CI 49–62%) and (etanercept 50 mg twice weekly until week 12, then 25 mg twice weekly: RD 50%, 95% CI 42–57%). After 24 weeks a decrease in efficacy for inflximab, adalimumab and etanercept was observed.

Conclusions More sufficient data is required to draw reliable conclusions in extended long-term treatment and head-to-head comparisons are necessary.

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Conflict of interest

AN has received honoraria for presenting at independent CME certified educational events, that received indirect or direct financial support from pharmaceutical industry, including Abbot, Pfizer/Wyeth, Janssen-Cilag. In addition AN received honoraria for participation in independent research projects, that were financed by unrestricted grants by Pfizer/Wyeth and Abbot. Independent CME-certified educational talks for Abbott, Biogen, Janssen-Cilag, MSD, and Pfizer. JS served as a paid consultant for Abbott and Novarits, and received research funding from Novartis and Wyeth.

Funding sources

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Introduction

Psoriasis is a systemic chronic-inflammatory disorder affecting predominantly the skin. The estimated prevalence in the European population is 2–3%, with variations among different ethnic groups.[1–3] Plaque-type psoriasis, the most common phenotype of psoriasis, may significantly affect the patients' quality of life. It constitutes a heavy economic burden and may be a risk factor for psychiatric morbidity and cardiovascular disease.[4–6] Among

patients with mild psoriatic symptoms, a topical therapy in combination with phototherapy has been shown to be a sufficient treatment.[7] For moderate-to-severe psoriasis, besides phototherapy the initiation of a systemic treatment is recommended.[8] Several systematic reviews have summarized the existing evidence on the efficacy of the available treatments during the induction period.[9,10] In addition, treatment guidelines have been developed in many countries on multinational levels to improve the standard of care provided to psoriasis patients. The entire existing guidelines so far refer to the induction period, only.[11–14] The focus on induction therapy in current reviews and guidelines stands in contrast to the chronicity of the disease. Nijsten *et al.* indicated in a 20 year lasting PUVA follow-up trial that the probability of showing the same global psoriasis severity during the subsequent year is 80%.[15] Therefore intervention strategies should be arranged for a lifelong disease with a constant long-term treatment.[16]

The spectrum of systemic treatments has been widely enlarged during the last decade. Traditional treatments comprise acitretin, ciclosporin, fumaric acid esters and methotrexate. New drugs include the groups of the so called biologics. They selectively interfere with the immune pathway that induces psoriasis. These biologics are monoclonal antibodies (adalimumab, infliximab, ustekinumab) or fusion proteins (etanercept and alefacept).The mechanism of action of these drugs has been described extensively elsewhere.[7,17–19]

The analysis of long-term data on psoriasis treatment is severly limited by methodological challenges due to different trial designs and the handling of dropouts. Most of the psoriasis trials are designed as parallel-group placebo-controlled trials for 12–16 weeks. Then the trials usually become open-label with a crossover for the patients in the placebo group to active treatment and the loss of the control groups.

Trials can only be summarized in a meta-analysis if the available studies are clinically, methodologically and statistically homogeneous. Thus different trial protocols and assessment of efficacy are the main obstacles to overcome.

When interpreting and comparing long-term psoriasis trials special methodological issues such as the analyzed population on which the results are based upon intention-to-treat (ITT) vs. per protocol (PP) and the handling of missing data i.e. last observation carried forward (LOCF) and non-responder imputation (NRI) have to be taken into consideration.[20]

In order to provide a more sufficient basis for decision making in the selection of an efficious long-term antipsoriatic treatment, we undertook a systematic review of all published trials of biologic and non-biologic systemic treatments approved for moderate-to-severe plaque type psoriasis to assess their efficacy.

Methods

We systemically reviewed original articles reporting on controlled and uncontrolled clinical trials for biologic and non-biologic systemic therapies for patients suffering from moderate-to-severe psoriasis. The selection criteria of relevant interventions for the treatment of moderate-to-severe chronic plaque psoriasis were in accordance with the German and European guidelines for psoriasis.[7,11] All identified trials were summarized in a systematic review. In addition, for the trials providing data from a treatment period of 24 weeks, we attempted to summarize the data in form of a meta-analysis. For all other time intervals insufficient data were available and no such attempt was pursued. Trials that started as randomized controlled trials, but where comparisons were stopped over time, the remaining arm was included as a cohort and considered as an uncontrolled trial. Eligibility criteria of considered relevant trials for this systematic review are summarized in Table 1.

Identification of articles

In order to capture all relevant articles we performed different approaches. All relevant trials published until May 2005 were identified through the systematic literature review that our workgroup conducted for the German S3-psoriasis guidelines.[7] All relevant trials published between May 2005 and July 2011 (search date 13.07.2011) were identified through a systematic literature search in Medline, Embase and the Cochrane Library using the same search strategy and search terms as described in the methods report of the German psoriasis guidelines.[21]

We searched for trials investigating any systematic treatment approved for moderate-to-severe plaque psoriasis in at least one country, i.e. acitretin, ciclosporin, fumaric acid esters, methotrexate, retinoid, adalimumab, alefacept, etanercept, infliximab or ustekinumab. Alefacept was not part of the German guidelines, therefore a complete de novo search was performed for this agent with the search terms 'psoriasis' and 'alefacept' (search date 13.07.2011). Efalizumab was not included in the analysis, as its marketing authorization has been suspended.[14] The abstracts were independently screened by two investigators (DP, TL) for relevance, differences in the assessment were resolved by discussion.

Table 1 Eligibility criteria

Inclusion criteria
Prospective clinical trial
Language in English or German
Outcome measure provided by means of the PASI score or DLQI
Patients with moderate-to-severe psoriasis
Trials including data on adults, only
Exclusion criteria
Data for no more than 16 weeks
No continuous treatment for at least one arm
Long-term treatment arms with treatment groups that were preselected with respect to their performence in the first part of the trial
Not specified or inconstant combination treatments
Data not predominantely on plaque type psoriasis (e.g., nail psoriasis, pustular psoriasis and pustulosis palmoplantaris)

The full texts of the articles considered as relevant, were systematically assessed by means of a standardized data extraction form.

Data collection and data synthesis

Data were summarized in treatment periods of 24 weeks, 25–40 weeks, 41–60 weeks and more than 60 weeks. A further distinction was performed with respect to the statistical approaches as to how dropouts were handled, i.e. PP or ITT analysis using a NRI or a LOCF. Analysis of a PP population comprises only patients completing the treatment phase in full compliance with the study protocol. This tends to overestimate the overall treatment effect. For an ITT analysis, all patients have to be analyzed within the treatment group to which they where originally assigned. It usually provides a more realistic approach, reducing the risk of bias.

The LOCF approach uses the last data obtained before the patient dropped out of the study. In case of increasing efficacy over time and a dropping out before the maximum of the efficacy is reached, this approach leads to an underestimation of the efficacy. In case of a loss of efficacy over time after a good initial response, an LOCF is likely to show an overestimation of efficacy. A relative conservative approach is the NRI, where subjects not completing the trial are rated as non-responders. This leads to a general underestimation of the overall efficacy, especially in trials with a high rate of dropouts.

Primary outcome measures and quantitative methods

Primary outcome was the PASI 75 response rate, which is a proportion of participants with ≥75% decrease in the Psoriasis Area and Severity Index (PASI). The PASI 75 has been shown to correspond with good patient satisfaction with respect to their treatment response and has recently been adopted as a standard treatment goal by a European expert consensus group.[8] In addition to the PASI 75 response rates, the relative reduction in the Dermatology Life Quality Index (DLQI), a patient reported validated questionnaire, were assessed at different time points.[22] For trials providing no PASI 75 response rates but mean PASI changes only, a statistical estimate of the percentage of patients meeting the PASI 75 response criterium was generated by means of simulation. For the simulation a normal distribution of PASI scores was assumed within the trials. The simulation of the PASI 75 scores were performed using the available published parameters including baseline and subsequent mean PASI scores after 24 weeks of treatment as well as standard deviation and standard error.

All randomized placebo-controlled trials reporting PASI 75 response rates after 24 weeks of active treatment were included in the meta-analysis. In addition, randomized placebo-controlled trials that have a placebo control arm for at least 12 weeks were also eligible for meta-analysis. For these, data derived from other existing 24 week placebo arms were used as a substitute for those trials without a continuous 24 week placebo arm after ensuring homogeneity of the placebo arms during the first 12 weeks. Homogeneity was assessed by comparing the progression of PASI scores over time in individual trials. The risk differences (RD) of comparable studies were pooled for each intervention. The RD between any active intervention and placebo describes the excess chance of patients receiving treatment over the chance of those receiving placebo to meet the PASI 75 response criterion at week 24. Additional data on study design such as number of patients, blinding and randomization were collected and presented within the tables to allow an assessment of the quality of the trial and the reliability of the evidence. Although initially intended, meta-regression analysis was not performed due to the low number of trials included into meta-analysis.[23] SPSS 18 (IBM, Armonk, NY, USA) and RevMan 5.0.24 (Cochrane Collaboration, International network, www.cochrane.org) were used for data analyses.

Results

Literature search

A total of 33 articles met the inclusion criteria, with a total of 6575 patients receiving active treatment. Figure 1 details the results of the literature search.

Trial characteristics

We identified a total of 33 articles reporting 27 trials, whereas twenty trials were randomized. Six trials were initially placebo-controlled, ten trials had another active treatment as control, six trials had placebo and active treatment as control and five trials were completely uncontrolled. For the long-term period starting at week 24, three trials remained placebo-controlled, one of them continued as active treatment controlled trial and the other trials ended at this point of time. Thirteen trials started double-blind, three single-blind and eleven were open-label. During the long-term period eight trials remained double-blind, three single-blind and sixteen were open-label.

Pooled placebo arm

After 12 weeks of treatment all placebo arms included (seven trials) showed a mean PASI 75 response of 3.2% (SD: 1.13). Two placebo arms continued until week 24, with a mean PASI 75 response of 4.5% (SD: 0.71).

Results of efficacy for 24 weeks of treatment

Eight trials on non-biologic treatments and sixteen trials on biologic treatments provided data for PASI 75 ($n = 22$) or DLQI ($n = 6$) after 24 weeks. We included the following active agents: acitretin featuring one trial (ITT with LOCF), ciclosporin featuring three trials (1 PP/2 unclear ITT), fumaric acid ester featuring three trials (PP), methotrexate featuring one trial (PP), adalimumab featuring three trials (1 PP/2 ITT with LOCF), etanercept featuring 11 trials (3 PP/5 ITT with LOCF/3 modified ITT), infliximab featuring one trial (ITT with NRI) and ustekinumab featuring one trial (ITT with NRI). For study details and results see Table 2.

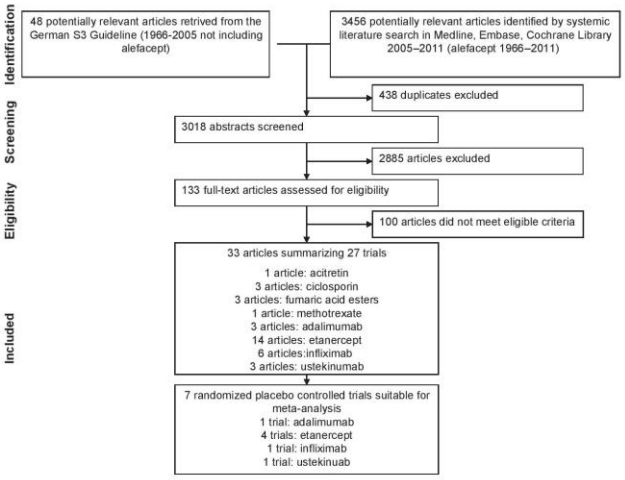

Figure 1 Flow chart of articles included in systematic review and meta-analysis.

Per protocol analysis for PASI 75/DLQI data A PASI 75 response rate of 84% was seen with ciclosporin 4 mg/kg/day. In this trial, the patients had the highest mean initial PASI among all trials of 30.1.[24] For fumaric acid esters, the PASI 75 response rates varied considerably between 60%, 75% up to a very high response rate of 92.8%.[25–27] A PASI 75 response of 63% was seen for methotrexate with a maximum dose of 30 mg weekly after 6 months of treatment.[28] With adalimumab, 83% of patients showed a PASI 75 response.[29] PASI 75 response for etanercept varied between 25–75.3% dependent on dosages.[30–32] 50 mg twice weekly showed a response rate of 59% compared to etancercept 25 mg twice weekly with a response rate of 44–57%.[31,32] Mazzotta *et al.*[30] treated with etanercept 50 mg twice weekly for 12 weeks, followed by 25 mg twice weekly until week 24 which lead to a PASI 75 response rate of 75.3%.

With etanercept 50 mg twice weekly DLQI changes of 73.8% were reported, whereas lower doses of etanercept 25 mg twice weekly and once weekly showed a less important reduction of 59.4% and 54.0%, respectively.[32,33]

Intention-to-treat analysis with last observation carried forward for PASI 75/DLQI data With acitretin at a dosage of 0.4 mg/kg daily a PASI 75 response rate of 30.0% was observed.[34] The results for adalimumab vary considerably between 64% (80 mg initially, then 40 mg every other week), 72% (80 mg initially, at week 0 and 1, then 40 mg every week) and 82% (40 mg every other week).[35,36] Twice weekly 25 mg etanercept treatment lead to PASI 75 response rates between 45–56%.[34,37,38]

A once weekly dosis of 50 mg yielded a 71.1% response rate whereas 50 mg twice weekly lead to a 60% response rate.[39,40] With the step down dosage of initially twice weekly 50 mg and then twice weekly 25 mg, a response rate of 54% was achieved.[37] The combination of acitretin 0.4 mg/kg daily and etanercept 25 mg twice weekly showed a PASI 75 response in 44% of the patients.[34]

As for etanercept 25 mg twice weekly, 50 mg once weekly and 50 mg twice weekly tapered to 25 mg twice weekly a mean DLQI decrease of 68%, 70.9% and 66% was seen, respectively.[39,41]

Modified or unclear Intention-to-treat analysis for PASI 75/DLQI data Two different products with the active agent ciclosporin and a dosis range from 2.5 to 5 mg/kg/day were compared. The microemulsion (Neoral®, Novartis, Basel, Switzerland) showed slightly better results than the soft gelatin capsules (Sandimmun®, Novartis, Basel, Switzerland) with a PASI 75 (unclear ITT) response of 68.8% and 62.5%.[42] In another trial 29.0% (unclear ITT) of patients showed a PASI 75 response after a daily treatment with ciclosporin 2.5 mg/kg. Within the control group of this trial a PASI response of 66.7% was seen with ciclosporin 2.5 mg/kg plus an additional low calorie diet.[43] For etanercept 50 mg once weekly a response rate of 25.8% was observed, whereas etanercept 50 mg twice weekly until week 12 followed by 50 mg once weekly showed a higher PASI 75 response of 30.6% (modified ITT).[44] Etanercept 25 mg twice weekly showed a PASI 75 response in 60.5% of patients (modified ITT).[45]

A DLQI improvement of 67% was observed after treatment with etanercept 25 mg twice weekly and of 66.6% after treat-

Table 2 Results for 24 weeks of treatment

First author	Publication year	Maximal duration of treatment	Date of evaluation	Number of patients	Intervention	Initial PASI	Results PASI 75	Mean DLQI improvement	Number of dropouts	Mean body weight	Randomization	Blinding	Placebo control	PP or ITT population and handling of misings
Vena # 24	2005	24 W	24 W	101	Ciclosporin 4 mg/kg daily	30.1	84%	-	8	-	+	Open-label	–	PP
Altmeyer # 25	1996	52 W	24 M	83	Fumaric acid esters increased to 645 mg daily and maximum of 1290 mg daily	26.0	92.8%*	–	4	–	–	Open-label	–	PP
Carboni # 26	2004	6 M	6 M	40	Fumaric acid esters maximum 320 mg daily	26.5	75%*	–	33	–	–	Open-label	–	PP
Litjens # 27	2003	24 M	6 M	20	Fumaric acid esters up to 6 tablets daily	14†	60%*	–	–	–	–	Open-label	–	PP
Ho # 28	2010	6 M	6 M	20	methotrexate max. 30 mg weekly	22.8	63%	–	1	–	+	Assessor blinded	Until end of trial	PP
				20	placebo	21.4	18%	–	3	–				
Papoutsaki # 29	2007	24 W	24 W	30	Adalimumab 40 mg once weekly	19.2	83%	–	3	–	–	Open-label	–	PP
Mazzotta # 30	2009	24 W	24 W	98	Etanercept 50 mg twice weekly until week 12, then 25 mg twice weekly	16.1	75.3%‡	–	-	–	–	Open-label	–	PP
Berends # 31	2007	24 W	24 W	14	Etanercept 25 mg twice weekly	16.3	57%	–	3	–	+	Open-label	–	PP
				14	Etanercept 50 mg twice weekly until week 12, then 25 mg twice weekly	25.1	50%	–	14	–				
Leonardi # 32 & Feldman # 33	2003 & 2005	24 W	24 W	160	Etanercept 25 mg once weekly	18.2	25%	54.0%	overall: 43	–	+	Double-blind until end of trial	Until week 12	PP
				162	Etanercept 25 mg twice weekly	18.5	44%	59.4%		–				
				164	Etanercept 50 mg twice weekly	18.4	59%	73.8%		–				

Table 2 *Continued*

First author	Publication year	Maximal duration of treatment	Date of evaluation	Number of patients	Intervention	Initial PASI	Results PASI 75	Mean DLQI improvement	Number of dropouts	Mean body weight	Randomization	Blinding	Placebo control	PP or ITT population and handling of misings
Gisondi # 34	2008	24 W	24 W	22	Etanercept 25 mg twice weekly	11.0	45.5%	–	0	79.5 ± 9.4 kg	+	Assessor blinded	–	ITT: LOCF
				20	Acitretin 0.4 mg/kg daily	10.4	30.0%	–	4	78.4 ± 10.3 kg				
				18	Etanercept 25 mg twice weekly acitretin 0.4 mg/kg daily	11.9	44.4%	–	0	77.5 ± 11.4 kg				
Vena # 35	2009	24 W	24 W	109	Adalimumab 40 mg every other week until week 24	18.8	82%	–	6	–	–	Open-label	–	ITT: LOCF
Gordon # 36	2006	60 W	24 W	45	Adalimumab 80 mg week 0 then 40 mg every other week	16.7	64%	–	4	93 (63–159) kg	+	Double-blind until 12 W	Until week 12	ITT: LOCF
				50	Adalimumab 80 mg week 0./1 then 40 mg once weekly	14.5	72%	–	6	99 (42–149) kg				
Van de Kerkhof # 39	2008	24 W	24 W	96	Etanercept 50 mg once weekly	21.4	71.1%	70.9%	20	83.4 ± 16.0 kg	+	Double-blind until 12	Until week 12	ITT: LOCF
Papp # 37 & Krueger # 41	2005 & 2005	24 W	24 W	196	Etanercept 25mg twice weekly	19.1	45%	68%	11	–	+	Double-blind until end of trial	Until week 12	ITT: LOCF
				194	Etanercept 50 mg twice weekly until week 12, then 25 mg twice weekly	19.5	54%	66%	9	–				
Tyring # 40	2007	96 W	24 W	311	Etanercept 50 mg twice weekly	18.3	60%	–	–	92.6 kg	+	Double-blind until	Until week 12	ITT: LOCF
Gottlieb # 38	2003	24 W	24 W	57	Etanercept 25 mg twice weekly	17.8	56%	–	9	91.8 kg	+	Double-blind until end of trial	Until end of trial	ITT: LOCF
				55	Placebo	19.5	5%	–	43	90.7 kg				
Koo # 42	1998	24 W	24 W	157	Ciclosporin Sandimmun 2.5–5 mg/kg daily	min. 15	62.5%*	–	32	–	+	Double-blind until end of trial	–	Unclear ITT
				152	Ciclosporin Neoral 2.5–5 mg/kg daily	min. 15	68.8%*	–	2	–				
Gisondi # 43	2008	24 W	24 W	31	Ciclosporin 2.5 mg/kg daily	14.1	29.0%	–	4	93.4 ± 12.8 kg	+	Investigator blinded	–	Unclear ITT
				30	Ciclosporin 2.5 mg/kg daily + low calorie diet	15.1	66.7%	–	4	94.8 ± 14.9 kg				
Prinz # 44	2011	24 W	24 W	373	Etanercept 50 mg once weekly	19.0	25.8%	–	28	28.4 (5 7)	+	Double-blind until week 12	–	Modified ITT
				379	Etanercept 50 mg twice weekly until week 12, then 50 mg once weekly	19.8	30.6%	–	29	BMI 27.5 (5 1)				
Ortonne # 45 & Dauden #46	2008 & 2009	54 W	24 W	352	Etanercept 25 mg twice weekly	21.9	60.5%*	67%	–	84.0 (SD: 18.4) kg	+	Open-label	–	Modified ITT

Table 2 *Continued*

First author	Publication year	Maximal duration of treatment	Date of evaluation	Number of patients	Intervention	Initial PASI	Results PASI 75	Mean DLQI improvement	Number of dropouts	Mean body weight	Randomization	Blinding	Placebo control	PP or ITT population and handling of misings
Gelfand # 47	2008	24 W	24 W	1272	Etanercept 50 mg twice weekly until week 12, then 50 mg once weekly	PGA only	PGA only	66.6%	–	Median 87.4 (41.4–218	+	Open-label	–	Modifie d ITT
Reich # 48 & Reich # 49	2005 & 2006	50 W	24 W	301	Infliximab 5 mg/kg week 0/2/6, then every 8 weeks	22.9	82%	78.7%	25	85.9 ± 20.1 kg	+	Double-blind until end of trial	Until week 24	ITT: NRI
				77	Placebo	22.8	4%	2%	0	89.3 ± 18.7 kg				
Leonardi # 50 & Lebwohl #51	2008 & 2010	76 W	24 W	255	Ustekinumab 45 mg week 0/4 then every 12 weeks	20.5	76.1%	–	–	93.7 (SD: 23.8) kg	+	Double-blind until end of trial	Until week 12	ITT: NRI
				256	Ustekinumab 90 mg week 0/4 then every 12 weeks	19.7	85.0%	–		93.8 (SD: 23.9) kg				

*PASI 75 simulated.
†Data out of graph.
‡Trial indicates arms with previous and no previous biologic treatment. Shown results are retrieved from arm with no previous treatment.
DLQI, Dermatology Life Quality Index; ITT, intent-to-treat; LOCF, last observation carried forward; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; PP, per protocol.

ment with 50 mg twice weekly reduced to 50 mg once weekly after twelve weeks (both modified ITT).[46,47]

Intention-to-treat analysis with non-responder imputation for PASI 75/DLQI data The trial on infliximab (standard dosage) showed a PASI 75 response rate of 82% and lead to a decrease in DLQI of 78.2%.[48,49] For ustekinumab 90 mg at week 0 and 4 followed by interventions every 12 weeks the PASI 75 response rate of 85.0% was superior to 76.1% with ustekinumab 45 mg at week 0 and 4 followed by interventions every 12 weeks.[50,51]

Results of meta-analysis

Seven trials fulfilled the criteria to be included into the meta-analysis. five of them used a LOCF analysis, two NRI. In the meta-analysis, 45 trial subjects received adalimumab, 854 etanercept, 276 infliximab, 511 ustekinumab. Figure 2 details the results of the meta-analysis.

Intention-to-treat analysis with last observation carried forward – meta-analysis Adalimumab (RD 60%, 95% CI 45–74%) and etanercept show comparable results after 24 weeks of treatment (RD 52%, 95% CI 44–59%). The response rates of etanercept differ considerably with different dosages (etanercept 50 mg once weekly: RD 62%, 95% CI 52–72%), (etanercept 25 mg twice weekly: RD 45%, 95% CI 34–56%), (etanercept 50 mg twice weekly: RD 56%, 95% CI 49–62%). A dose reduction from 50 mg twice weekly to 25 twice weekly after 12 weeks of treatment showed results within that range (etanercept 50 mg twice weekly until week 12, then 25 mg twice weekly: RD 50%, 95% CI 42–57%).

Intention-to-treat analysis with non-responder imputation – meta-analysis In the included trials, infliximab with standard dose (RD 78%, 95% CI 72–83%) and high dose ustekinumab 90 mg (RD 77%, 95% CI 71–83%) are the most efficacious treatments with respect to PASI 75 response. Low dose ustekinumab 45 mg (RD 70%, 95% CI 64–77%) also shows very good efficacy.

Results of efficacy for 25–40 weeks of treatment

No trial on non-biologic treatments and six trials on biologic treatments provided data for PASI 75 ($n = 6$) or DLQI ($n = 4$) for treatment periods between 25 and 40 weeks. We included the following active agents: adalimumab featuring one trial (ITT with LOCF), etanercept featuring one trial (ITT with LOCF), infliximab featuring two trials (1 PP/1 ITT with NRI) and ustekinumab featuring two trials (ITT with NRI). For study details and results see Table 3.

Per protocol analysis for PASI 75/DLQI data Infliximab showed a PASI 75 response in 69.4% of patients with standard dose after 26 weeks of treatment. A mean DLQI improvement of 69.4% was seen within the same trial after 26 weeks.[52]

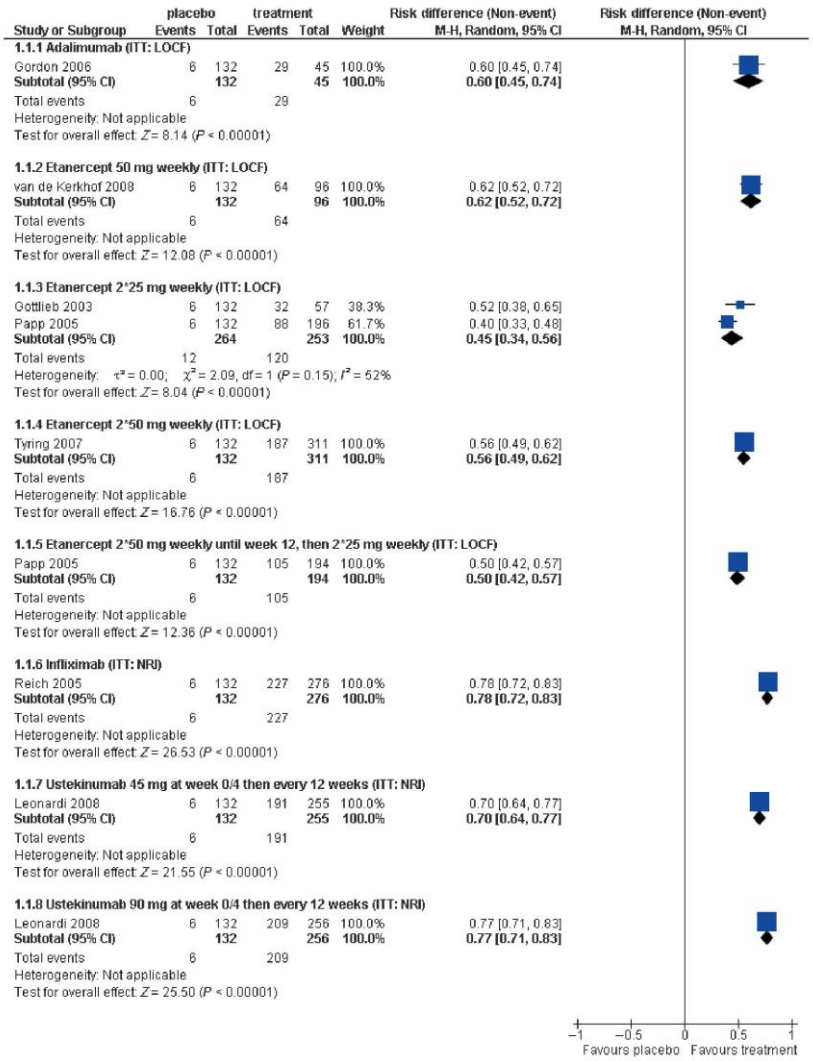

Figure 2 Results of meta-analysis after 24 weeks of treatment.

Intention-to-treat analysis with last observation carried forward for PASI 75/DLQI data A PASI 75 response was achieved with adalimumab after 36 weeks by 62% of the patients (initial 80 mg followed by 40 mg every other week). With a higher dosage (80 mg at week 0 and 1 and 40 mg adalimumab once weekly), a PASI 75 response was seen in 68% of the patients.[36] With high dose etanercept, a PASI 75 response was observed after 36 weeks in 60% of the patients (etanercept 50 mg twice weekly).[40]

Intention-to-treat analysis with non-responder imputation for PASI 75/DLQI data For infliximab standard dose after

Table 3 Results for 25–40 weeks of treatment

First author	Publication year	Maximal duration of treatment	Date of evaluation	Number of patients	Intervention	Initial PASI	Results PASI 75	Mean DLQI improv-ement	Number of dropouts	Mean body weight	Randomi-zation	Blinding	Placebo control	PP or ITT population and handling of missings
Torii # 52	2010	62 W	26 W	37	Infliximab 5 mg/kg week 0/2/6 then every 8 weeks	31.9	72.7%	69.4%	4	68.5 (SD: 13.4)	+	Double-blind until week 14	Until week 14	PP
Gordon # 36	2006	60 W	36 W	45	Adalimumab 80 mg week 0 then 40 mg every other week	16.7	62%	–	4	93 (63–159) kg	+	Double-blind until 12 W	Until week 12	ITT: LOCF
				50	Adalimumab 80 mg week 0/1 then 40 mg once weekly	14.5	68%	–	6	99 (42–149) kg				
Tyring # 40	2007	96 W	36 W	311	Etanercept 50 mg twice weekly	18.3	60%	–	–	92.6 kg	+	Double-blind until 12 W	Until week 12	ITT: LOCF
Menter # 53 & Feldmann # 55	2007 & 2008	50 W	26 W	150	Infliximab 5 mg/Kg week 0/2/6 then every 8 weeks	20.4	78.0%	–	–	92.2 ± 23.2 (median: 88.8)	+	Double-blind until end of trial	Until week 14	ITT: NRI
Papp # 54	2008	52 W	28 W	397	Ustekinumab 45 mg week 0/4 then every 12 weeks	19.4	69.5%	77.9%	43	90.3 (SD: 21.0) kg	+	Double-blind until end of trial	Until week 12	ITT: NRI
				400	Ustekinumab 90 mg week 0/4 then every 12 weeks	20.1	78.5%	81.7%	41	91.5 (SD: 21.3)				
Leonardi # 50 & Lebwohl # 51	2008 & 2010	76 W	28 W	255	Ustekinumab 45 mg week 0/4 then every 12 weeks	20.5	71.2%	72.9%	38	93.7 (SD: 23.8) kg	+	Double-blind until end of trial	Until week 12	ITT: NRI
				256	Ustekinumab 90 mg week 0/4 then every 12 weeks	19.7	78.6%	82.8%	19	93.8 (23.9) kg				

DLQI, Dermatology Life Quality Index; ITT, intent-to-treat; LOCF, last observation carried forward; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; PP, per protocol.

26 weeks of standard regime a PASI 75 response of 78% and after 30 weeks of 65.2% was seen.[53]

Ustekinumab shows a PASI 75 response of 69,5% (low dose: 45 mg loading dose at week 0 and 4 followed by ustekinumab 45 mg every 12 weeks) and 78,5% (high dose: 90 mg loading dose at week 0 and 4 followed by ustekinumab 90 mg every 12 weeks) after 28 weeks.[54] Additional data for ustekinumab after 28 weeks of treatment show a PASI 75 response of 71.2% (low dose: 45 mg loading dose at week 0 and 4 followed by ustekinumab 45 mg every 12 weeks) and 78.6% (high dose: 90 mg loading dose at week 0 and 4 followed by ustekinumab 90 mg every 12 weeks).[50]

DLQI improvement after 30 weeks of treatment with infliximab standard dose indicated 67.7%.[55] Ustekinumab 90 mg was superior to a 45 mg dose with 81.7% vs. 77.9%, respectively.[54] After 28 weeks of treatment with ustekinumab, a DLQI improvement of 72.9%% (45 mg) and 82.8% (90 mg) was observed.[51]

Results of efficacy for 41–60 weeks of treatment

No trials on non-biologic treatments and 7 trials on biologic treatments provided data for PASI 75 ($n = 7$) or DLQI ($n = 4$). We included the following active agents: adalimumab featuring one trial (ITT with LOCF), etanercept featuring two trials (1 ITT with LOCF/1 modified ITT) and infliximab featuring four trials (2 PP/2 ITT with NRI). For study details and results see Table 4.

Per protocol analysis for PASI 75/DLQI data A PASI 75 response rate of 62.5% at week 46 for infliximab standard dose was observed with a high dropout rate of 52.9%.[56] Another trial with infliximab standard dose showed a PASI 75 response of 71.9% and a mean DLQI improvement of 68% after 42 weeks of treatment.[52]

Intention-to-treat analysis with last observation carried forward for PASI 75/DLQI data After 60 weeks of treatment with adalimumab (80 mg loading dose followed by 40 mg every other week) a PASI 75 response of 56% was observed. In the same trial the control arm with adalimumab (80 mg loading dose at week 0 and 1 followed by 40 mg every week) showed a response of 64%.[36] For etanercept 50 mg twice weekly response rates of 63% at week 46 and 60% at week 60 were observed.[40]

Modified Intention-to-treat analysis for PASI 75/DLQI data 68% of improvement in DLQI after 54 weeks of treatment was observed after treatment with etanercept 25 mg twice weekly (modified ITT).[46]

Intention-to-treat analysis with non-responder imputation for PASI 75/DLQI data A continuous standard dose of infliximab shows after 46 weeks of treatment PASI 75 responses of 54.4%.[53]A PASI 75 response rate of 61% and DLQI improvement of 57.5% for infliximab with standard dose was seen after 50 weeks of treatment.[48,49]

Another trial showed 63.8% of DLQI improvement with infliximab standard dose after 50 weeks.[55]

Results of efficacy for more than 60 weeks of treatment

No trials on non-biologic treatments and 2 trials on biologic treatment provided data for PASI 75 and DLQI after more than 60 weeks of treament. For study details and results see Table 5.

Per protocol analysis for PASI 75/DLQI data For infliximab standard dose a PASI 75 response of 76.7% and mean DLQI improvement of 65.3% was observed after 66 weeks of treatment.[52]

Intention-to-treat analysis with last observation carried forward for PASI 75/DLQI data Tyring *et al.*[40] showed a PASI 75 response of 55% with etanercept 50 mg twice weekly at week 72. After 96 weeks of treatment the response rate of this arm decreased to 51%.

Discussion

Despite the fact, that psoriasis is a chronic disease and long-term treatment is a common practice, so far the data available is insufficient to draw clear and reliable conclusions about the efficacy of long-term treatments of psoriasis. The quality of the trials and the different methodological approaches vary considerably and any conclusion on the efficacy is still very uncertain. Results derived from studies with PP analysis have been found to differ largely from those with ITT analysis and can therefore not be directly compared.[20]

In our study only very few trials were suitable to be summarized in a meta-analysis, all of them investigating drugs belonging to the group of biologics. Among the biologics, infliximab and ustekinumab can be considered the most efficacious treatments for psoriasis after 24 weeks of treatment with PASI 75 reponses of 82% (infliximab) and 76.1% as well as 85.0% (45 mg and 90 mg dose ustekinumab). The efficacy of etanercept varies largely between 45% up to 71.1% with respect to the dosage, surprisingly with a better result for once weekly 50 mg than for twice weekly 50 mg. This paradox might be due to the lower body weight of the patients in the low dose group and a consequently higher dosage per kg bodyweight. The RD of adalimumab in the meta-analysis was within the range of a treatment with etanercept, whereas the PASI 75 response ranged from 64% to 72%. More trials are needed to allow for more reliable conclusions.

For the non-biologic agents, the available data is very scarce and not sufficiently reliable. None of the non-biologic agents fulfilled the requirements to be included in the meta-analysis. Especially the assessment of the efficacy with focus on the PP population leads to a high risk of overestimating the treatment effects.

Looking at the data with ITT populations, ciclosporin shows response rates between 29% and 68.8%. For all other non-biologic

Table 4 Results for 41–60 weeks of treatment

First author	Publication year	Maximal duration of treatment	Date of evaluation	Number of patients	Interv-ention	Initial PASI	Results PASI 75	Mean DLQI improve-ment	Number of dropouts	Mean body weight	Randomi-zation	Blinding	placebo control	PP or ITT population and handling of missings
Torii # 52	2010	62 W	42 W	37	Infliximab 5 mg/kg week 0/2/6 then every 8 weeks	31.9	71.9%	68.0%	5	68.5 (SD: 13.4)	+	Double-blind until week 14	Until week 14	PP
Bianchi # 56	2006	102 W	46 W	34	Infliximab 5 mg weeks 0/2/6 then every 8 weeks	28.4	62.5%	–	18	–	–	Open-label	–	PP
Gordon # 36	2006	60 W	60 W	45	Adalimumab 80 mg week 0 then 40 mg every other week	16.7	56%	–	17	93 (63–159) kg	+	Double-blind until 12 W	Until week 12	ITT: LOCF
				50	Adalimumab 80 mg week 0/1 then 40 mg once weekly	14.5	64%	–	11	99 (42–149) kg				
Tyring # 40	2007	96 W	46 W	311	Etanercept 50 mg twice weekly	18.3	63%	–	–	92.6 kg	+	Double-blin until 12 W	Until week 12	ITT: LOCF
			60 W				60%	–	–					
Dauden # 46	2009	54 W	54 W	352	Etanercept 25 mg twice weekly	21.9	–	68%	99	84.0 (SD: 18.4) kg	+	Open-label	–	modified ITT
Menter # 53 & Feldmann # 55	2007 & 2008	50 W	46 W	150	Infliximab 5 mg/kg week 0/2/6 then every 8 weeks	20.4	54.4%	–	–	92.2 ± 23.2 (median: 88.8)	+	Double-blind until end of trial	Until week 14	ITT: NRI
			50 W				–	63.8%	33					
Reich # 48 & Reich # 49	2005 & 2006	50 W	50 W	301	Infliximab 5 mg/kg week 0/2/6, then every 8 weeks	22.9	61%	57.5%	25	85.9 ± 20.1 kg	+	Double-blind until end of trial	Until week 24	ITT: NRI

PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; PP, per protocol; ITT, intent-to-treat; LOCF, last observation carried forward; NRI, non-responder imputation.

Table 5 Results exceeding 60 weeks of treatment

First author	Publication year	Maximal duration of treatment	Date of evaluation	Number of patients	Interv-ention	Initial PASI	Results PASI 75	Mean DLQI improve-ment	Number of dropouts	Mean body weight	Randomi-zation	Blinding	placebo control	PP or ITT population and handling of missings
Torii # 52	2010	62 W	66 W	37	Infliximab 5 mg/kg week 0./2./6 then every 8 weeks	31.9	76.7%	65.3%	7	68.5 (SD: 13.4)	1	Double-blind until week 14	until week 14	PP
Tyring # 40	2007	96 W	72 W 96 W	311	Etanercept 50 mg twice weekly	18.3	55% 51%	– –	– 78	92.6 kg	+	Double-blind until 12 W	until week 12	ITT: LOCF

PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; PP, per protocol; ITT, intent-to-treat; LOCF, last observation carried forward; NRI, non-responder imputation.

agents, only PP analyses are available, which in some trials yield extremely high PASI 75 response rates with up to 92.8% for fumaric acid esters and 84% for ciclosporin, which are most likely due to the large numbers of dropouts. There is also no reliable data to compare the non-biologic agents vs. the biologic agents.

The available data on the maintenance treatment beyond 24 weeks are extremely scarce and heterogenous. Any estimate has to be considered as very uncertain. Only data on biologic agents are available. Adalimumab, etanercept and infliximab show a trend towards a loss of efficacy after 24 weeks of treatment. Insufficient data for ustekinumab restricts an estimate. The strongest decrease is seen for infliximab with a decrease from 82% to 61% after 50 weeks, which may be particularly strong due to the non-responder imputation used for the handling of the dropouts. For adalimumab a decrease from 64% to 56% at week 60 (LOCF) has been shown. For etanercept (twice weekly 50 mg) efficacy remains more stable, with a PASI 75 response of 60% from week 24 to week 60, and a decrease to 55% and 51% in week 72 and 96, respectively. The applied LOCF approach may even have caused a bias towards a less prominent loss of efficacy. For ustekinumab no trial is available providing sufficient data to draw a conclusion on long-term efficacy over 28 weeks.

Summarizing long-term data for psoriasis is a challenging task especially if an at-tempt for a meta-analysis is pursued. Unfortunately different methods of reporting and trials missing placebo control arms for more than 12 weeks do not allow a direct comparison for most of the trials. After careful analysis and comparison of homogeneity of the 12 weeks placebo arms, we were able to perform a meta-analysis using a combined 24 weeks placebo arm. Generally we have seen a relatively stable progression in efficacy within the placebo arms with a mean PASI 75 of 3.22% (SD: 1.13) after 12 weeks of treatment. Two placebo arms continued until week 24, with a mean PASI 75 response of 4.5% (SD: 0.71). Due to these findings we have developed our approach with our statistician for a pooled placebo arm as an estimate for each trial. Theoretically, this may have introduced an over- or underestimation of the risk difference (RDs) of each active agent in the meta-analysis. However, as the placebo-effect was relatively stable within treatments and between trials, we do not believe that this theoretical bias substantially influenced the conclusions to be drawn from our paper. The transformation of mean PASI reduction results to PASI 75 response rates was an even greater challenge. The results were used with particular care and not used for the part of the meta-analysis. A possible bias for over- or underestimation of the treatment effect has to be considered when looking at the results of the transformation. Due to the fact that most maintenance treatment trials at one point become uncontrolled open-label trials, we decided to include these trials due to the otherwise resulting in complete lack of any evidence. When looking at open-label trials, a possible overestimation of treatment effects has to be considered.

For long-term treatment, the generation of the data based on the PP or ITT populations as well as the methods used to deal with dropouts can have a very significant impact on the results and therefore special attention was given to these aspects in this review. We generally do not consider results from PP analysis comparable to an ITT analysis and even within the ITT groups different patient populations such as NRI or LOCF have to be distinguished. The impact of these different statistical approaches has been highlighted in a retrospective analysis of efficacy data of infliximab using PP, ITT – NRI, ITT – LOCF underlining the non-comparability of these approaches. The differences become even more prominent over time. Papoutsaki *et al.*[20] calculated for the same patients the PASI 75 response rates after 24 weeks of treatment with infliximab as per protocol analysis of 81.4%, LOCF analysis yielding 79.3% and a non-responder imputation of 75.6%. After a period of three years the differences were even more dramatic showing PASI 75 responses of PP: 75%, LOCF: 65.6% and NRI: 41.2%.

Besides efficacy, safety is an important concern during long-term therapy. For a valid assessment of safety, numerous trials with high numbers of patients are necessary to gain data on 'rare' and 'very rare' adverse events. The available data, however, is already insufficient to assess efficacy thoroughly, an attempt to make an estimate on safety in the basis of the included trials would be even more unreliable and was therefore not attempted. Patient registries are likely to allow a better assessment of safety in the future.[57,58]

For a better comparability of trial results, a harmonization of outcomes, assessment time points and statistical approaches has to be achieved. In addition, there is a strong need for head-to-head long-term trials to allow direct comparison of the agents. In general, it has to be questioned if trials on patients with psoriasis should still be performed with placebo control with respect to a large variety of possible comparators.

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ANNOUNCEMENT

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Call for Applications - EADV Fostering Courses

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Course chair: Dr. Mihaela Leventer
Course registration fees:
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Places: 20 (allocated on a "first come, first served" basis)
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ERRATUM

DOI: 10.1111/j.1468-3083.2012.04634.x

In the publication "Efficacy of systemic therapies for moderate-to-severe psoriasis: a systematic review and meta-analysis of long-term treatment" by Lucka *et al.* the results of two studies were reported incorrectly.[1] Changes are printed below in bold. They have no influence on the meta-analysis itself.

1) **Prinz *et al.***
Page 4: right column, line 21–25
For etanercept 50 mg once weekly a response rate of **62.3%** was observed, whereas etanercept 50 mg twice weekly until week 12 followed by 50 mg once weekly showed a higher PASI 75 response of **70.3%** (modified ITT).[44]
Page 6: table 2, Prinz # 44, column "Results PASI 75"
Etanercept 50 mg once weekly: **62.3%**
Etanercept 50 mg twice weekly until week 12, then 50 mg once weekly: **70.3%**

2) **Torii *et al.***
Page 7: right column, line 49–52
Infliximab showed a PASI 75 response in **72.7%** of patients with standard dose after 26 weeks of treatment. A mean DLQI improvement of **80.3%** was seen within the same trial after 26 weeks.[52]
Page 9: table 3, Torii # 52, column "Mean DLQI improvement" 80.3%
Page 10: left column, line 28–31
Another trial with infliximab standard dose showed a PASI 75 response of 71.9% and a mean DLQI improvement of **78.7%** after 42 weeks of treatment.[52]
Page 11: table 4, Torii # 52, column "Mean DLQI improvement" 78.7%
Page 10: right column, line 9–12
For infliximab standard dose a PASI 75 response of 76.7% and mean DLQI improvement of **75.6%** was observed after 66 weeks of treatment.[52]
Page 12: table 5, Torii # 52, column "Mean DLQI improvement" 75.6%

Reference

1 Lucka TC, Pathirana D, Sammain A *et al.* Efficacy of systemic therapies for moderate-to-severe psoriasis: a systematic review and meta-analysis of long-term treatment. *J Eur Acad Dermatol Venereol.* 2012; doi: 10.1111/j.1468-3083.2012.04492.x. [Epub ahead of print].

6 Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

7 komplette Publikationsliste

- Tilmann C Lucka, Delano Pathirana, Adel Sammain, Frank Bachmann, Stefanie Rosumeck, Ricardo Erdmann, Jochen Schmitt, Helmut Orawa, Berthold Rzany, Alexander Nast. Efficacy of systemic therapies for moderate-to-severe psoriasis: a systematic review and meta-analysis of long-term treatment. J Eur Acad Dermatol Venereol. 2012 Nov;26(11):1331-44.

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