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SPECIAL REPORT

Effectiveness of Biologic and Conventional Systemic Therapies in Adults with Chronic Plaque Psoriasis in Daily Practice: A Systematic Review

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The efficacy of biologic or conventional systemic therapies for psoriasis has been shown in randomized controlled trials. Effectiveness, however, has been studied in daily practice cohorts, and no aggregation of effectiveness data is available. This systematic review searched PubMed and EMBASE and summarized the real-world evidence on effectiveness of biologics (adalimumab, etanercept, infliximab and ustekinumab) and conventional systemic therapies (acitretin, cyclosporine, fumarates and methotrexate) for the treatment of plaque psoriasis in adults. Thirty-two studies were included. Few data were available on infliximab, ustekinumab and conventional systemics. Results show that biologics and conventional systemics were effective in real-life treatment of psoriasis, with large ranges in the percentage of patients reaching 75% improvement in psoriasis area and severity index score compared with baseline, especially for etanercept and adalimumab treatment. Combination therapies of biologics with conventional systemics, and dose adjustments of biologics were frequently applied strategies and may explain the large range in improvements between cohorts. *Key words: psoriasis; effectiveness; biologics; conventional systemic agents; registries; daily practice.*

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Psoriasis is a common chronic skin disease, with a prevalence of 2–4% (1). Different therapeutics have been developed to treat this burdensome disease (2–4). Randomized controlled clinical trials (RCTs) have analysed the efficacy of biologic agents (adalimumab, etanercept, infliximab and ustekinumab) and conventional systemic therapies (acitretin, cyclosporine, fumarates and methotrexate) (5–7). Effectiveness data from real-life, observational studies, however, are of added value, since patients and treatment strategies in daily practice differ substantially from those in RCTs (8). The aim of this study was to systematically search the literature to provide an overview of the current evidence on the effectiveness in daily practice of biologic and conventional systemic therapies for the treatment of adults with plaque psoriasis. Short-term (week 12–16), intermediate-term (>16–≤ 28 weeks) and long-term (≥ 1 year) Psoriasis Area and Severity Index (PASI) responses were investigated. The primary objective was to show the proportion of patients that reached PASI75 (a 75% reduction in PASI score) with biologic and/or conventional systemic agents at week 12–16.

MATERIALS AND METHODS

A systematic literature search was performed on the effectiveness of treatment with biologics or conventional systemics in patients with plaque psoriasis in daily practice. Inclusion and exclusion criteria are described in Table SI[1]. The decision was arbitrarily made to exclude studies in which the number of patients included at baseline was <30, since in these articles the influence of every additional patient reaching PASI75 has a large influence on the total percentage.

Outcomes

The following outcome measures were chosen (9): (*i*) PASI (10); (*ii*) Physician's Global Assessment (PhGA) on a scale of 0–5, 0–6 or 0–7 (11); and (*iii*) body surface area (BSA) (11).

Primary outcome. The primary outcome was the PASI75 score for biologic and conventional systemic agents in daily clinical practice at week 12–16.

Secondary outcomes. Secondary outcome measures were PASI75 with intermediate-term (17–28 weeks) and long-term (≥ 1 year data) treatment, as well as PASI50, PASI90, PASI100 and decrease in mean PASI, PhGA and BSA with short-, intermediate- and long-term treatment.

All measures were compared with baseline except if stated otherwise.

Search strategy

Two electronic databases (Pubmed and EMBASE) were systematically searched, and studies from 1990 until May 2014 were included. The term "psoriasis" was combined with terms

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for study design, treatments of interest and outcome measures for effectiveness (Table SII[1]).

Data extraction

Two authors (JZ and MEO) independently screened titles and abstracts, and checked full articles for inclusion and exclusion criteria as well as references for other eligible studies. Data were extracted from text, tables or as numbers in figures and are shown in Table SIII[1]. Any differences in decisions about inclusion or extraction were resolved by consensus or discussion with a third author (EdJ). The results for PASI75 were divided into cohorts using monotherapy and cohorts combining biologic with conventional systemic treatments in some or all of the patients during the study period, prospective vs. retrospective and short-, intermediate- and long-term results of treatment. PASI75 from per protocol analyses are shown. Comparative studies are described in a separate section.

RESULTS

A total of 32 articles were included (Fig. 1): 28 on biologics, 3 on conventional systemic therapies, and 1 describing both biologic and conventional systemic treatment (Table SIII[1]). Seven articles reported results of adalimumab therapy, 20 of etanercept, 4 of infliximab, 4 of ustekinumab, 1 of acitretin, 2 of fumarates, 1 of cyclosporine and 3 of methotrexate. There were 12 prospective and 20 retrospective studies. Results from comparative studies and dosing of biologics are described below in separate sections. For all effectiveness results the reader is referred to Table SIII[1].

Biologic therapies

Twenty-eight articles (12–39) reported data on biologic therapies and one article (40) compared biologic and conventional systemic treatment. For adalimumab the mean baseline PASI scores of patient cohorts ranged from 10.9 to 20.1, for etanercept these ranges were 11.3–25.6, for infliximab 14.7–17.7, and for ustekinumab 9.6–22.9.

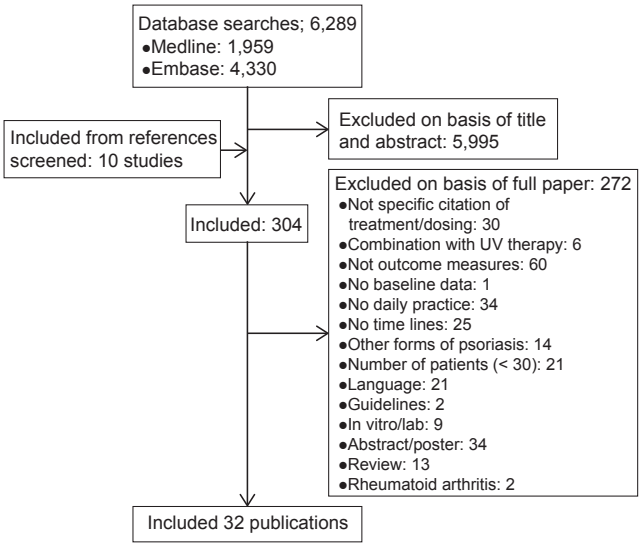

Fig. 1. Included and excluded studies.

Adalimumab

Study characteristics. Of the 7 articles studying the effectiveness of adalimumab, 3 were prospective (13, 17, 18) and 4 retrospective studies (12, 14–16), including a total of 461 patients. In the study of Van Lümig et al. (13), only those patients whose treatment with etanercept had failed and who had switched to adalimumab were included, and thus they represented a highly selected patient group. The results from this study were therefore not included for data aggregation. Dosing regimens varied amongst studies, as well as naïvety for biologics, and the number of patients using adalimumab in combination with a conventional systemic agent. One retrospective study (12) reported the results of adalimumab monotherapy. All 7 studies (12–18) reported on long-term therapy results. In all 7 studies (12–18) conventional systemic agents were allowed, but no specification was made of the duration and dosages used. Combination with a conventional systemic was used in 7–41% (12–18) of patients. Methotrexate was used most often. In all studies, the induction dose was per license (80 mg at the start and 40 mg at week 1). The maintenance dose was 40 mg every other week for most patients. However, in all studies dose adjustments were allowed. A dose increase to 40 mg weekly or 40 mg every 10 days was made in 2–36% (12, 14–16, 18) of patients. In 2 studies, the mean weekly dose of adalimumab was 23 mg (13) and 24 mg (17), respectively. In 2 studies (17, 18), a total of 46 patients were treated with 40 mg per 3–4 weeks. The mean duration of dose increases/decreases were not mentioned.

PASI75 outcome for adalimumab. Overall, PASI75 was attained by 27–68% with short-term, 31–82% with intermediate-term and 44–89% with long-term (1 and 2 year) adalimumab treatment (Table SIII[1]).

Adalimumab monotherapy. In the one retrospective study (12), adalimumab reached PASI75 percentages of 38% at week 16, 62% at week 24 and 69% at one year.

Cohorts using adalimumab with conventional systemic treatments. PASI75 results from prospective studies were 27–54% (17, 18) at week 12, 31% (17) at week 24, and 44% (17) at 2 years of adalimumab treatment. In retrospective studies, 56–68% (12, 14–16) of patients reached PASI75 at week 16 (of which only one study (14) used licensed dosing), 50–82% (12, 14–16) at week 24, 48–89% (12, 14–16) at 1 year and 83% (16) at 2 years.

Etanercept

Study characteristics. Twenty articles studied etanercept therapy in daily clinical practice (Table SIII[1]). Nine studies (13, 18, 20, 22, 24, 26, 32, 33, 35) were prospective and 11 retrospective (19, 21, 23, 25, 27–31, 34, 40), including a total of 2,079 patients. Five of 20 articles (21, 25, 29, 31, 40) reported results on etanercept monotherapy. In 7 studies (13, 21, 25, 27, 30, 33, 40) all patients were naïve for biologics, in 12 articles a proportion of patients was non-naïve for biologic therapy. In one article (28) a highly selected group of patients was treated with etanercept, since all patients switched from efalizumab therapy. Results from this study were not included for data aggregation, but can be found in Table SIII[1]. Dosing regimens varied amongst studies. It was explored whether PASI75 results differed between cohorts using either 50 mg biweekly or 25 mg biweekly as induction dose, but no direct comparisons were found. PASI75 percentage ranges were similar, and thus an aggregation of all PASI75 percentages is presented here.

Ten studies (13, 18, 23, 25, 29–33, 35) reported long-term results. No prospective studies reported solely on etanercept monotherapy. In 15 studies it was reported whether a combination therapy with a conventional systemic agent was prescribed and the percentages ranged from 0% to 69% (13, 18–20, 22, 24, 27, 28, 30–35, 40). When combination therapy was allowed, methotrexate was used most often. Eight articles studied the licensed dosing of etanercept in (part of) the study and 12 studies (13, 18, 19, 22–25, 27, 29, 32, 33, 35) mentioned the ability for physicians to adjust the dose, but did not always provide a detailed description. Nine to 26% (18, 23, 27, 29, 33) of patients had their dose adjusted to 50 mg biweekly during maintenance treatment and 3 studies reported a mean weekly dose of etanercept: 64.1 mg (35), 68.3 mg (32) and 73.4 mg (13).

PASI75 outcome for etanercept. Overall, PASI75 was attained by 12–66% with short-term, 19–85% with intermediate-term, and 49–92.3% with long-term (1- and 2-year) etanercept treatment.

Etanercept monotherapy. Retrospective studies reported a PASI75 of 36.1–54.1 (21, 31) at week 12, 66% (25) at week 16 and 60.5–85% (21, 25, 29, 31) at week 24. At 1 year PASI75 was 71.4–92.3% (25, 29, 31) and at 2 years 86.9% (31).

Cohorts using etanercept with conventional systemic treatments. In prospective studies, etanercept achieved a PASI75 in 12–63% (13, 18, 22, 26, 32, 33) at week 12 and 19–73.2% (13, 24, 26, 32, 33, 35) at week 24 in prospective studies and 25–69.2% (13, 32, 33, 35) at 1 year. In retrospective studies 21.4–26% (19, 27, 30, 34) of patients achieved PASI75 at week 12, 37–53% (23, 27, 30, 34) at week 24, and 49–54% (23, 30) at one year.

Dosing of etanercept. Of the 8 articles studying the licensed dosing of etanercept in (part of) the study, 20–43% and 50–73.2% of patients achieved PASI75 at short- and intermediate-term, respectively (Table SIII[1]).

Infliximab

Study characteristics. Four articles were included, 2 prospective (18, 36) and 2 retrospective studies (40, 41), including a total of 215 patients starting on infliximab. Two of 4 articles (36, 40) reported on infliximab monotherapy. Except for one study (18), all studies prescribed the licensed dose of infliximab. No study mentioned long-term results for PASI75. Combination therapy with a conventional systemic was prescribed in 5% (18) and 81% (41) of patients. Methotrexate was used most often. In 2 studies (18, 41) physicians decreased the dose interval (=dose increase) of infliximab in 10–23% of patients.

PASI75 outcome for infliximab. Overall, PASI75 was attained by 38–53% at short-term and 69% at intermediate-term treatment with infliximab.

Infliximab monotherapy. There were no PASI75 results from studies at week 12, 24 or on long-term treatment with infliximab monotherapy. At week 28, PASI75 was 69% (36) in one prospective study.

Cohorts using infliximab with conventional systemic treatments. In the prospective study with combination therapy and dose adjustment (18), 38% of the patients who previously used biologics and 53% of biologic naïve patients reached PASI75 at week 12.

Ustekinumab

Study characteristics. Four articles described results for ustekinumab; 2 prospective (36, 37) and 2 retrospective studies (38, 39), including a total of 315 patients starting on ustekinumab. Both prospective studies (36, 37) reported on ustekinumab monotherapy. In all but one article (39) a licensed dose of ustekinumab was prescribed. One retrospective study (38) showed long-term results. Combination therapy with a conventional systemic was prescribed in 9–14% (38, 39) of patients and methotrexate was used most often. In one study (39) the dose interval of ustekinumab was adjusted (dose increase) in 8% of treated patients due to a partial relapse several weeks prior to the next injection.

PASI75 outcome for ustekinumab. Overall, PASI75 was attained by 63–80% at short-term, 58–75.9% at intermediate-term, and 65.5% at long-term (1 year data) with ustekinumab treatment.

Ustekinumab monotherapy. Prospectively, PASI75 was attained by 80% (37) of patients at week 16 and 58% (36) at week 28 with ustekinumab monotherapy.

Cohorts using ustekinumab with conventional systemic therapy. Two retrospective studies, of which one (39) was with dose adjustments, were included and presented a PASI75 of 79.3% (39) at week 12 and 63% (38) at week 16, 66.7–75.9% (38, 39) at week 24, and 65.5% (39) at 1 year.

Naïve vs. non-naïve patients treated with biologics

Only a minority of included articles tried to assess the difference in biologic response between naïve and non-naïve patients, but in most of these articles baseline PASI score between both groups was not compared. In only 3 articles (2 adalimumab and 1 ustekinumab) (16, 17, 39) it was stated that baseline PASI score was comparable between groups. For adalimumab, biologic naïve patients seemed to respond better compared with non-naïve patients, as measured with PASI75 at certain time-points and for ustekinumab the same phenomenon was found for anti-tumour necrosis factor alpha (TNF-α) naïve and non-naïve patients.

Conventional systemic therapies

Four articles (40, 42–44) reported on conventional systemic treatment. One article was prospective (43) and 3 retrospective (40, 42, 44). No articles were included on combination of 2 conventional systemic agents as this was an exclusion criteria in order to explore the true effectiveness of conventional systemic agents in daily practice. Except for one study on methotrexate (40), all studies reported a mean PASI score above 10 at start of treatment (11.6–26.5), which represents patients with moderate to severe psoriasis.

Acitretin

Study characteristics. One retrospective study (42) including 62 patients starting on acitretin was included. No prospective studies were available.

Monotherapy. In one retrospective study, PASI75 response was attained by 27% (42) of patients with a mean dose of 0.38 mg/kg/day at week 12. No prospective or retrospective data were available on long-term treatment with acitretin.

Fumarates

Study characteristics. Two articles (43, 44) reported the effectiveness of fumarates in daily practice, including a total of 312 patients starting on fumarates. One study (43) was prospective and one (44) was retrospective. In one study (43) a maximum daily dose of 360 mg was prescribed at week 6 and in the other study (44) this was 720 mg at week 9.

Monotherapy. One retrospective study showed a PASI75 of 47% (44) at week 12, 63% (44) at week 24, and 76% (44) at 1 year. No long-term results from prospective studies were available.

Cyclosporine

Study characteristics. One retrospective article (42) studied the effectiveness of cyclosporine in daily practice, including a total of 36 patients starting on cyclosporine. In this study, a mean dose of 3.5 mg/kg/day was given.

Monotherapy. In one retrospective study, 46% (42) of patients reached a PASI75 at week 12.

Methotrexate

Study characteristics. Three articles (40, 42, 44) studied the effectiveness of methotrexate in daily practice, including 189 patients starting on methotrexate. All studies were retrospective. In one study (40) the methotrexate dose was 15 mg weekly and was given intramuscularly. In another study (44) methotrexate initial dose of 10 mg once weekly was increased to a maximum of 20 mg once weekly. Piaserico et al. (42) gave methotrexate in a mean weekly dose of 11.7 mg.

Monotherapy. In the retrospective studies, between 40% and 49% (42, 44) of patients treated with methotrexate 10–20 mg weekly achieved PASI75 at week 12 and 62% (44) at week 24. Eighty-one percent (44) achieved PASI75 at 1 year. No prospective data were available.

Comparative studies

Three retrospective studies (40, 42, 44) and 2 prospective studies (18, 36) compared anti-psoriatic agents within the study. Piaserico et al. (42) showed that the proportion of patients achieving PASI75 with acitretin (27%) was significantly lower than that of patients treated with methotrexate (49%, $p = 0.01$), etanercept (64%, $p < 0.0001$), adalimumab (65%, $p < 0.01$) and infliximab (93%, $p < 0.001$) at week 12. Mean baseline PASI score appeared similar between these treatments (methotrexate: 12.7; acitretin 14.8; etanercept 14.9; adalimumab 14.3; infliximab 14.8). Inzinger et al. (44) showed that, when prescribed as a primary treatment, the effectiveness of methotrexate was similar to that of fumarates; however, the mean PASI at start of methotrexate (18.3) was higher than for fumarates (11.6). In this study, no significance tests were performed for baseline variables. Gisondi et al. (40) compared mean PASI decrease between methotrexate, etanercept and infliximab at week 24. Mean PASI decrease was significantly higher for infliximab compared with methotrexate, infliximab compared with etanercept, and etanercept compared with methotrexate. Patients treated with etanercept or infliximab, however, had higher baseline PASI scores compared with patients

receiving methotrexate ($p = 0.0001$). Between etanercept and infliximab treated patients, there was no significant difference in baseline PASI score ($p = 0.6$). The prospective study of Gisondi et al. (36) showed no significant differences between ustekinumab and infliximab for mean PASI decrease at weeks 4 and 28. Mean baseline PASI scores did not differ between these 2 groups ($p = 0.1$). The prospective study of Menting et al. (18) showed no significant difference in mean change in PASI scores between adalimumab, etanercept and infliximab at weeks 12 and 24. Baseline PASI did not differ between the 3 groups.

DISCUSSION

To our knowledge, this is the first systematic review on effectiveness in daily practice of biologics (etanercept, adalimumab, infliximab and ustekinumab) and conventional systemic agents (acitretin, cyclosporine, fumarates and methotrexate). Effectiveness data from real-life, observational studies are of added value, since patients and treatment strategies in daily practice substantially differ from those in RCTs (8). A substantial proportion of patients were achieving PASI75 with short- (week 12–16), intermediate- (17–28) and long-term (≥ 1 year) treatment with biologics and conventional systemic agents, except for acitretin monotherapy.

At short-term, PASI75 was 35–68% for adalimumab, 12–66% for etanercept, 38–53% for infliximab, 63–80% for ustekinumab, 27% for acitretin, 47% for fumarates, 46% for cyclosporine and 40–49% for methotrexate. At long-term (1- and 2-year data), PASI75 was 44–89% for adalimumab, 49–92.3% for etanercept, 65.5% for ustekinumab, 76% for fumarates and 81% for methotrexate. We encountered a high heterogeneity in study design (prospective/retrospective), treatment regimen (e.g. dose adjustments, combination with conventional systemic agents) and patient population (e.g. baseline PASI scores, naïve/non-naïve) especially in studies on biologic treatments. Possible explanatory factors for the large ranges in PASI75 percentages, especially in etanercept and adalimumab therapy, were the use of combination strategies with a conventional systemic agent and dose adjustments.

In most studies on biologic therapies, concomitant conventional systemic agents were allowed and prescribed by physicians (24/29 studies). Methotrexate was mostly prescribed as combination therapy. In these studies, data were not analysed separately for patients using combination therapy. Therefore, we reported studies on combination therapy separately, but found similar PASI75 ranges between monotherapy and combination therapy. There is some evidence from RCTs on combining biologics with conventional agents, with most data for etanercept combined with methotrexate (45). In daily clinical practice, however, combination strategies are often applied in case of ineffectiveness, and may explain the similar results found in patients with and without combination therapies. More studies are needed into combination therapy of conventional systemic agents with biologic therapies.

Another explanation for the heterogeneity in study results is that dosing regimens differed between studies, especially for etanercept and adalimumab treatment. In adalimumab studies, all articles described dose increases and in studies with etanercept in more than half of included studies a dose increase was allowed. Aforementioned PASI75 results were therefore achieved with higher doses than licensed dose. Dose adjustments were less common in studies on infliximab and ustekinumab, although the number of included articles was too small to draw definitive conclusions. If this is indeed the case, dose adjustments could lead to higher costs for biologic treatment with etanercept and adalimumab compared with infliximab and ustekinumab.

Heterogeneity is typical in treating real-life patients and is not studied in RCTs. The results from daily practice studies enrich the body of evidence and can be of added value to current data from RCTs and guidelines when the quality of data reporting is improved. In order to improve this quality, it is strongly advised that authors of future studies report the items included in the STROBE statement (46). The following issues are of particular importance: study design (prospective, retrospective, wash-out period and method of analysis); and patient characteristics (age, sex, body weight, baseline PASI score, duration of psoriasis, previous treatments, presence of psoriatic arthritis, number of patients with and treatment duration of combinations of systemic anti-psoriatic therapies and dosages used). In case of biologic treatment in particular, it is important to describe naivety to biologics, previous biologic therapies, and dosing regimens.

Comparative studies were scarce and were hampered by differences at treatment start. Some RCTs (47–51) compared agents head-to-head. Data from pragmatic randomized daily practice studies or comparative effectiveness studies adjusted for confounders could be informative and decrease this gap in the evidence in the literature.

In conclusion, biologic and conventional systemic agents are effective in daily practice. Combination therapies of biologics with conventional systemic treatments and dose adjustments of biologics were frequently applied strategies, especially for adalimumab and etanercept, and could explain the large ranges in PASI75 results. There was a high heterogeneity in study design, treatment regimen and patient population between included studies. We made recommendations in order to improve the quality of reporting in daily practice studies. Gaps identified were daily practice data on infliximab, ustekinumab, conventional systemic therapies, long-term treatment,

combination therapy and results of direct comparisons on effectiveness between anti-psoriatic agents.

The authors declare no conflicts of interest.

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