# Efficacy and safety of biologics in the treatment of moderate to severe psoriasis: a comprehensive meta-analysis of randomized controlled trials

## Eficácia e segurança de agentes biológicos no tratamento da psoríase moderada a grave: uma meta-análise de ensaios clínicos randomizados e controlados

## Eficacia y seguridad de los agentes biológicos en el tratamiento de la psoriasis moderada a severa: un metaanálisis de ensayos aleatorios y controlados

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**Abstract**

*We conducted a systematic review and meta-analysis of randomized placebo-controlled trials in moderate-to-severe psoriasis treated with biological agents, with a follow-up of 10-14 weeks. Overall, 41 studies, with mean Jadad score of 4.4, and 15,586 patients were included. For the efficacy outcomes PASI 50, 75 and 90 our findings are not conclusive to point what biological agent has the greatest response in short term follow-up. There were no statistical differences between placebo and biologics for the occurrence of infections and serious adverse events. Ustekinumab 45mg showed lower withdrawal due to adverse events compared with the placebo. Based on data available up to now, it is not possible to determine which biological agent is the best for PASI 50, 75 or 90 after 10-14 weeks of treatment. At the same follow-up, overall safety seems to be the same for all biological agents and Ustekinumab 45mg the most well tolerated drug. To better understand efficacy and safety, indirect meta-analysis comparing drug-to-drug is required since randomized placebo-controlled trials may not be feasible.*

*Psoriasis; Biological Agents; Efficacy; Safety; Health Technology Evaluation*

**Resumo**

*Conduziu-se uma revisão sistemática e meta-análise de ensaios clínicos randomizados em pacientes com psoríase moderada a grave, tratados com biológicos ou placebo por 10 a 14 semanas. Foram incluídos 41 estudos, com escore de Jadad médio de 4,4, totalizando 15.586 pacientes. Para os desfechos de eficácia PASI 50, 75 e 90 os resultados não são conclusivos para definir qual é o melhor agente biológico no curto prazo. Não houve diferença estatística entre placebo e biológicos para ocorrência de infecções e eventos adversos sérios. Ustequinumabe 45mg foi o biológico com menor ocorrência de descontinuação por conta de eventos adversos. Baseado na evidência até então disponível, não é possível determinar qual agente biológico é o melhor para se atingir resposta PASI 50, 75 e 90 após 10-14 semanas de tratamento. Para o mesmo intervalo, a segurança global parece ser a mesma para todos os biológicos e ustequinumabe 45mg o tratamento melhor tolerado. Para melhor compreender a eficácia e segurança, meta-análise indireta comparando droga-a-droga são necessárias já que ensaios clínicos randomizados podem não ser viáveis.*

*Psoríase; Agentes Biológicos; Eficácia; Segurança; Avaliação de Tecnologias de Saúde*

## Introduction

The assessment of safety and efficacy of biological agents for treating moderate to severe psoriasis have been demonstrated to be important in multiple placebo-controlled trials [1,2,3]. Through a database search, we found meta-analyses that evaluated only one biological agent against placebo and others including more than one agent [4,5,6,7,8,9,10,11,12,13]. Of these, only Reich et al. [10] included the biologic ustekinumab in the meta-analysis. Moreover, few studies address safety outcomes [7,8,12]. Drugs included in this study were: adalimumab, alefacept, anakinra, briakinumab, certolizumab, efalizumab, etanercept, infliximab, golimumab, rituximab, siplizumab, onercept and ustekinumab. As the use of biologic medications for psoriasis is a recent development, the objective of this article is to provide comprehensive and up-to-date evidence regarding the efficacy and safety of the use of all biologic therapies available for moderate to severe psoriasis.

## Methods

### Trial search strategy

A systematic review was conducted according to the Cochrane Collaboration guideline [14]. We performed a comprehensive search for randomized controlled trials (RCTs) using as descriptors the keywords: "adalimumab", "alefacept", "anakinra", "briakinumab", "certolizumab", "efalizumab", "etanercept", "infliximab", "golimumab", "rituximab", "siplizumab", "onercept" or "ustekinumab" along with the terms "random", "controlled trial" and "controlled clinical trial" and "psoriasis". These drugs were considered eligible for the study as a result of an earlier literature review. The search was performed in the following databases: Cochrane, EMBASE, IPA (International Pharmaceutical Abstracts), LILACS, PubMed, SciELO, Science Direct, Scopus, and Web of Science. Manual search in relevant periodic, symposium and congress annals and reference lists of articles found in the search were performed. Only studies published up until May 2011 and written in English, Portuguese or Spanish were included.

### Study selection

Two reviewers independently selected the studies based initially on reviewing the title and abstract. Only RCTs that evaluated the treatment of moderate to severe psoriasis with biological agents versus placebo were included. Crossover trials were considered only if data from the first treatment period was reported separately. Additionally, we excluded abstracts published in congress proceedings because the available information was not sufficient to perform an analysis and RCTs evaluating concomitant biological agent treatment.

The methodological quality of each RCT included was evaluated according to the method proposed by Jadad et al. [15] in duplicate, in which scores from 3 to 5 means high grade of quality and from 0 to 2 low grade. For assessing risk of bias in the included studies, we used the Cochrane Collaboration's tool, and considered the following biases: selection, performance, detection, attrition, reporting, and other biases.

### Outcome definition

Efficacy outcomes extracted were the improvement of 50%, 75%, and 90% in the *Psoriasis Area and Severity Index* (PASI 50, 75, and 90, respectively) at 10-14 weeks of treatment. Safety results were also extracted considering serious adverse events, adverse events leading to discontinuation of treatment (withdrawals), and infection occurrence along the same ranges of time.

### Data extraction

Data from published reports were extracted onto a standardized form by two reviewers working independently. The following items were extracted from each trial: number and characteristics (gender and mean age) of patients included; the duration of treatment; and results of efficacy and safety. Any discrepancies in data collection were resolved through consensus or by a third reviewer.

### Statistical methods

We used the random effects model and Mantel-Haenszel method to pool the relative risks (RRs) from individual studies. RR was chosen for providing more reliable results than odds ratio when frequent outcomes are analysed. When the outcome has positive aspects, values over 1.00 favour the drug being compared to placebo and when the outcome has negative aspects, values over 1.00 favour the placebo group. Confidence intervals that cross the line of invalidity (1.00) represent no statistical difference between the two compared groups at 5% significance level.

The heterogeneity of the results was evaluated by the index of inconsistency ($I^2$). Values $I^2 <$ 25% were considered as low heterogeneity, while

values $I^2$ of 25-50% were considered moderate to high. If meta-analyses showed $I^2 > 50\%$ (high heterogeneity), sensitivity analyses were performed to determine the characteristics of the study and whether statistical methods may have influenced the results. The sensitivity analysis was conducted by the hypothetical removal of each study in the meta-analysis and assessment of its impact on the overall result. All analyses were performed using Review Manager v. 5.1 statistical software (The Cochrane Collaboration, Copenhagen, Denmark).

The results were described according to the methodology proposed by the *PRISMA Statement* [16].

## Results

### Study selection

20,674 articles were found, of which 20,592 were excluded, resulting in 82 articles in which 41 clinical trials comparing biologics with placebo (six adalimumab [17,18,19,20,21,22,23,24,25,26,27], three alefacept [28,29,30,31,32,33,34,35,36,37], one briakinumab [38,39], one certolizumab [40], seven efalizumab [41,42,43,44,45,46,47,48,49,50,51], eight etanercept [52,53,54,55,56,57,58,59,60,61,62,63,64], one golimumab [65,66], eight infliximab [67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89], and three ustekinumab [90,91,92,93,94,95,96,97,98,99]) were published (Figure 1). The clinical trials included 15,586 patients of which 64.6% were male and the weighted average age was 44.1 (± 7.5) years. The average Jadad score was 4.4. For details about the characteristics of the studies, see Table 1. The risk of bias assessed by Cochrane's tool showed that 57%, 52%, 61%, 36%, 86% and 98% of the included trials have low risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting respectively. 41%, 48%, 36%, 64%, 14% and 2% of the included trials have moderate risk of bias considering the same aspects, respectively. Any other source of bias was detected.

We did not find any double-blind RCTs with the biologics abatacept, anakinra, onercept,

Figure 1

Plaque psoriasis. Selection of studies for meta-analysis.

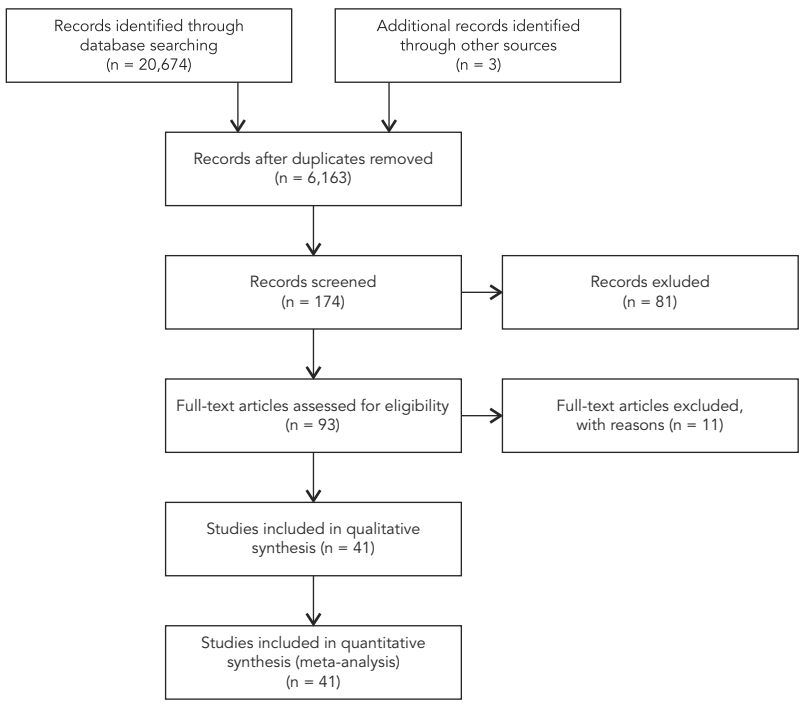


Table 1

Details of trials.

| Study | | | Patients | | Drug | |
|---|---|---|---|---|---|---|
| Trials | Year | Jadad | n | Inclusion criteria | Intervention | Dosage |
| Asahina [17] | 2010 | 4 | 169 | Diagnosis ≥ 6 months; stable 2 months; PASI ≥ 12 ou BSA ≥ 10 | Adalimumab | 80mg e posterior 40mg EOW – 16 week |
| CHAMPION [24,26,27] | | 5 | 271 | BSA ≥ 10%; PASI score ≥ 10 | Adalimumab | 80mg e posterior 40mg EOW – 16 week |
| Genovese [18] | 2007 | 4 | 100 | ≥ 18 years; ≥ 3 swollen joints and ≥ 3 tender or painful joints | Adalimumab | 40mg EOW – 16 week |
| Gordon [19] | 2006 | 4 | 148 | ≥ 18 years; diagnosis ≥ 12 months; BSA ≥ 5%; | Adalimumab | 40mg EOW – 16 week |
| REACH [21] | | 4 | 72 | Chronic plaque psoriasis on the hands and/or feets with PGA ≥ 3 | Adalimumab | 80mg e posterior 40mg EOW – 16 week |
| REVEAL [20,22,23,25] | | 5 | 1,212 | Psoriasis ≥ 6 months, Plaque psoriasis; BSA ≥ 10%; PASI score ≥ 12 | Adalimumab | 80mg e posterior 40mg EOW – 16 week |
| Ellis [28, 29] | 2001 | 3 | 229 | Diagnosis ≥ 12 months; BSA ≥ 10; candidates to systemic therapy | Alefacept | 0,075mg/kg/week (average weight 96,7kg) – 12 week |
| Krueger [30,1,32,33] | 2002 | 4 | 553 | Diagnosis ≥ 6 months; BSA ≥ 10; CD4+ normal; ≥ 16 years | Alefacept | 7,5mg/week – 12 week |
| Ortonne [34,36,37] | 2003 | 4 | 507 | PGA score mild to moderate (17%) and moderate to severe (83%); Plaque psoríasis; BSA ≥ 10%; PASI score ≥ 12 | Alefacept | 10mg/week – 24 week |
| Mease [35] | 2006 | 4 | 180 | ≥ 3 swollen joints and ≥ 3 tender joints | Alefacept + metotrexato | 15mg/week |
| Kimball [38,39] | 2008 | 3 | 180 | Diagnosis ≥ 6 months; 2 months stable; PASI ≥ 12; BSA ≥ 10; PGA moderate | Briakinumab | 200mg EOW 12 week |
| Ortonne [40] | 2007 | 3 | 176 | Plaque psoriasis; BSA ≥ 10%; PASI score ≥ 12 | Certolizumab | 200mg EOW 12 week |
| CLEAR [41,47,51] | | 4 | 793 | Psoriasis ≥ 6 months, Plaque psoriasis; BSA ≥ 10%; PASI score ≥ 12 | Efalizumab | 1mg/kg/week – 12 week |
| Gordon [42,45,46] | 2003 | 4 | 556 | 18-75 years; diagnosis ≥ 6 months; BSA ≥ 10; PASI ≥ 12; use systemic therapy | Efalizumab | 1mg/kg/week – 12 week |
| Lebwohl [43] | 2003 | 5 | 597 | 18-75 years; diagnosis ≥ 6 months; 3 months stable; BSA ≥ 10; PASI ≥ 12 | Efalizumab | 1mg/kg/week – 12 week |
| Leonardi [44] | 2005 | 4 | 498 | PASI ≥ 12; BSA ≥ 10%; diagnosis ≥ 6 months; stable for 3 months | Efalizumab | 1mg/kg/week – 12 week |
| Papp [48] | 2001 | 3 | 145 | Psoriasis ≥ 6 months, plaque psoriasis; BSA ≥ 10%; PASI score ≥ 12 | Efalizumab | 1mg/kg/week – 12 week |
| Papp [49] | 2006 | 4 | 686 | Psoriasis ≥ 6 months, plaque psoriasis; BSA ≥ 10%; PASI score ≥ 12 | Efalizumab | 1mg/kg/week – 12 week |
| Papp [50] | 2007 | 4 | 107 | Moderate to severe PSA – one of five subtypes and classified as ACR functional class 1, 2 or 3 | Efalizumab | 1mg/kg/week – 12 week |
| Gottlieb [52] | 2003 | 4 | 112 | ≥ 18 years; plaque psoriasis stable; BSA ≥ 10%; use systemic therapy | Etanercept | 25mg TW – 24 week |
| Leonardi [54] | 2003 | 3 | 672 | ≥ 18 years; PASI ≥ 10; BSA ≥ 10%; candidates to phototherapy or systemic therapy | Etanercept | 25mg W, 25mg TW, 50mg TW – 12 week |
| Mease [55] | 2000 | 5 | 60 | ≥ 3 swollen joints and ≥ 3 tender or painful joints | Etanercept | 25mg TW – 12 week |
| Mease [56,57] | 2004 | 4 | 205 | PSA with at least 3 swollen and 3 tender joints; plaque psoriasis with a qualifying target lesion (at least 2cm in diameter) | Etanercept | 25mg TW – 12 week |

(continues)

Table 1 (continued)

| Study | | | Patients | | Drug | |
|---|---|---|---|---|---|---|
| Trials | Year | Jadad | n | Inclusion criteria | Intervention | Dosage |
| Paller [58,59] | 2008 | 4 | 211 | Plaque psoriasis; static PGA at lease 3; BSA ≥ 10% | Etanercept | 0,8mg/kg/week – 12 week |
| Papp [53,60] | 2005 | 5 | 583 | Plaque psoriasis; BSA ≥ 10%; PASI score ≥ 10 | Etanercept | 25mg TW, 50mg TW – 12 week |
| Siegfried [62] | 2010 | 3 | 138 | Plaque psoriasis; PGA ≥ 3; BSA ≥ 10%; PASI score ≥ 12 | Etanercept | 50mg OW – 12 week |
| Tyring [63] | 2006 | 5 | 618 | PASI score ≥ 10; BSA ≥ 10%; candidates to phototherapy or systemic therapy | Etanercept | 50mg TW – 12 week |
| van der Kerkhof [64] | 2008 | 4 | 142 | Plaque psoriasis; BSA 6-10%; PASI score ≥ 10 | Etanercept | 50mg OW – 12 week |
| Bissonnette [70] | 2011 | 5 | 24 | ≥ 18 years; palmoplanar psoriasis | Infliximab | 5mg/kg/week – 14 week |
| Chaudari [71,74] | 2001 | 4 | 33 | Plaque psoriasis; diagnosis ≥ 6months; BSA ≥ 5% | Infliximab | 5mg/kg/week – 6 week |
| EXPRESS I [82,83,84,85,86] | | 5 | 378 | Psoriasis ≥ 6 months, plaque psoriasis; BSA ≥ 10%; PASI score ≥ 12 | Infliximab | 5mg/kg/week – 10 week |
| EXPRESS II [72,80,81] | | 5 | 835 | Plaque psoriasis; BSA ≥ 10%; PASI score ≥ 12 | Infliximab | 3mg/kg/week, 5mg/kg/week – 10 week |
| Gottlieb [75] | 2004 | 5 | 249 | ≥ 18years; diagnosis ≥ 6 months; PASI ≥ 12; BSA ≥ 10%; candidates to phototherapy or systemic therapy | Infliximab | 3mg/kg/week, 5mg/kg/week – 10 week |
| IMPACT I [68,69,78] | | 4 | 104 | Diagnosis ≥ 6 months; peripheral polyarthritis active, morning stiffness ≥ 15 min, negative rheumatoid factor, tuberculosis negative | Infliximab | 5mg/kg/week – 16 week |
| IMPACT II [67,73,76,77,79,87,89] | | 4 | 200 | Diagnosis ≥ 6 months; swelling of the tendon or joints by at least 5; CRP ≥ 15mg/L | Infliximab | 3mg/kg/week, 5mg/kg/week – 10 week |
| Torii [92] | 2010 | 4 | 54 | Plaque psoriasis; BSA ≥ 10%; PASI score ≥ 12 | Infliximab | 5mg/kg/week – 10 week |
| Kavanaugh [75,76] | 2009 | 4 | 405 | Active psoriasis; 3 swollen and painful joints, rheumatoid factor negative, at least one type of psoriasis and plaque psoriasis than 2cm in diameter | Golimumab | 50mg EOW – 16 week |
| Gottlieb [90] | 2009 | 5 | 146 | ≥ 18 years; psoriatic arthrits; ≥ 3 swollen joints and ≥ 3 tender or painful joints; CRP ≥ 15mg/L; diagnosis ≥ 6 months; plaque psoriasis ≥ 2cm | Ustekinumab | 90mg week 0, 4 and every 12 week |
| PHOENIX I [92,93,94,95,98] | | 5 | 766 | Psoriasis ≥ 6 months, PASI score ≥ 12, BSA ≥ 10%, candidates to phototherapy or systemic therapy | Ustekinumab | 45mg, 90mg week 0, 4 and every 12 week |
| PHOENIX II [91,96,95] | | 4 | 1,230 | BSA ≥ 10%; PASI score ≥ 10 | Ustekinumab | 45mg, 90mg week 0, 4 and every 12 week |

ACR: American College of Rheumatology; BSA: body surface area; CRP: C-reactive protein; PASI: *Psoriasis Area and Severity Index*; PGA: *Physician's Global Assessment*; PSA: psoriatic arthritis.

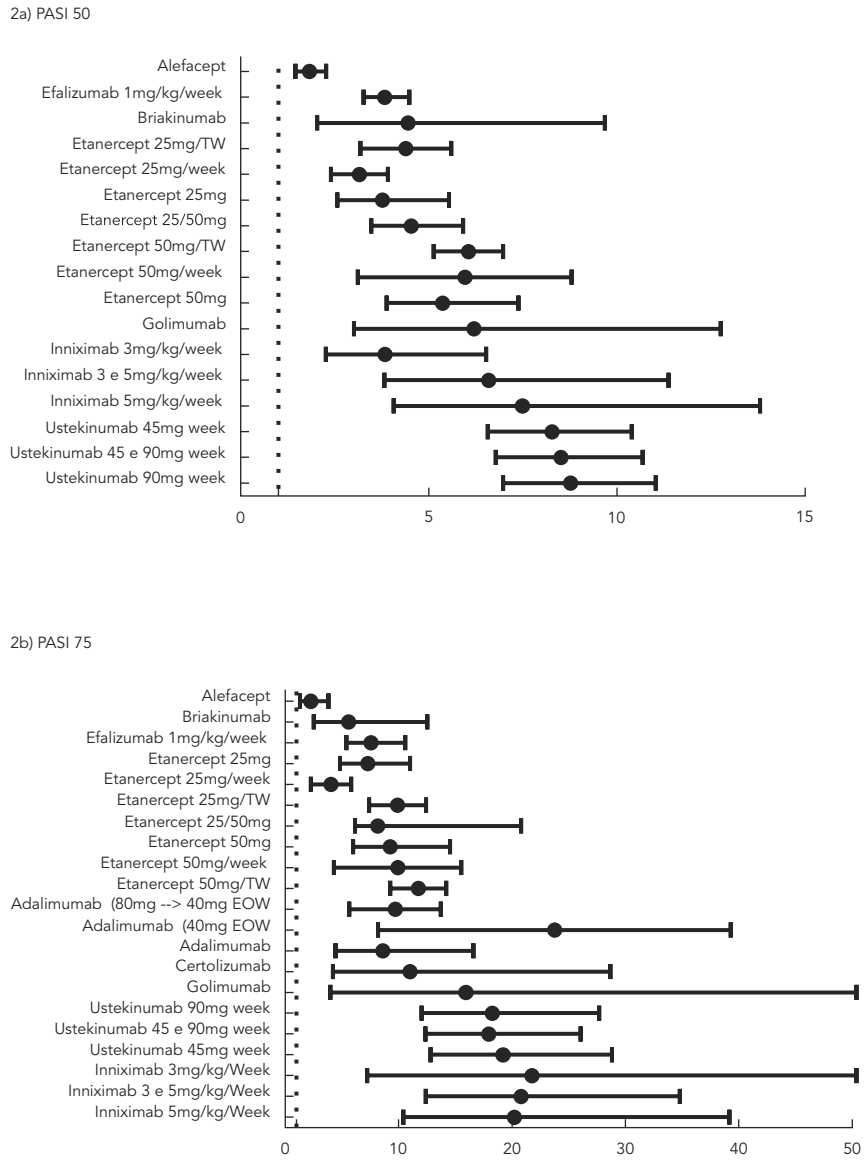
rituximab, or siplizumab used in the treatment of moderate-to-severe psoriasis.

## Clinical efficacy

Considering the endpoint PASI 50, the biologic with the highest RR was ustekinumab 90mg (RR: 8.77; 95%CI: 6.98-11.03), followed by ustekinumab 45mg (RR: 8.27; I95%CI: 6.57-10.40). There is a statistically significant difference, when compared with placebo, favoring ustekinumab 90mg and 45mg in relation to infliximab 3mg/kg/week (RR: 3.84; 95%CI: 2.26-6.53]), efalizumab (RR: 3.83; 95%CI: 3.27-4.49), and alefacept (RR: 1.83; 95%CI: 1.46-2.28), as shown in Figure 2a.

Figure 2

Plaque psoriasis. Relative risk of *Psoriasis Area and Severity Index* (PASI) 50, 75 and 90 with biologics treatment versus control.

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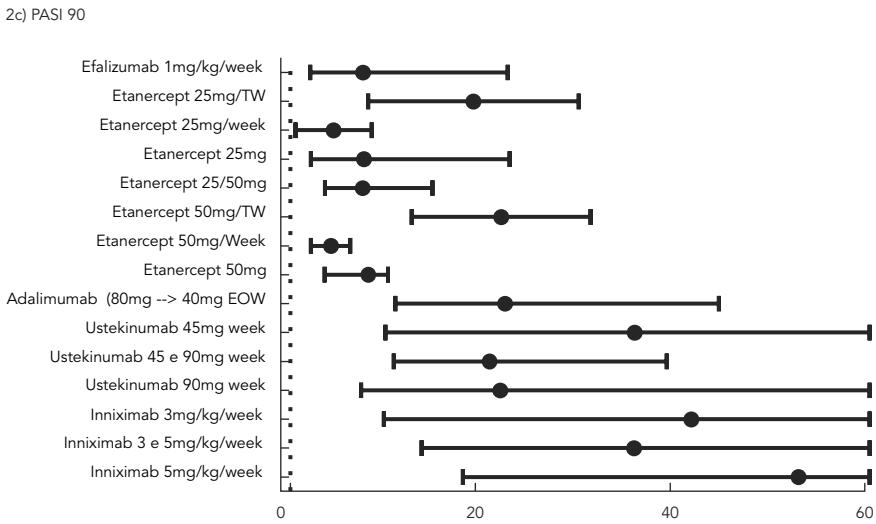
When the outcome evaluated was PASI 75, our findings were inconclusive. The greatest measure of effect observed were infliximab in both doses (3mg/kg/week – RR: 21.77; 95%CI: 7.24-65.45 and 5mg/kg/week – RR: 20.21; 95%CI: 10.42-39.19) and ustekinumab, also at both doses (45mg – RR: 19.22; 95%CI: 12.82-28.82 and 90mg – RR: 18.26; 95%CI: 12.04-34.82) (Figure 2b).

For the PASI 90 outcome, it appears that there is no statistically significant difference between placebo and etanercept 25mg OW. Furthermore, it is observed that infliximab, ustekinumab and adalimumab present the highest results of RR (Figure 2c).

Some results of the meta-analysis show high heterogeneity ($I^2 > 50\%$). For the PASI 50 outcome, etanercept 25mg TW ($I^2 = 75\%$), etanercept 50mg W ($I^2 = 70\%$) and infliximab 5mg/kg/week ($I^2 = 64\%$) presented high heterogeneity. Also, for PASI 75, adalimumab (80mg > 40mg

Figure 2 (continued)




EOW) ($I^2$ = 76%), infliximab 3mg/kg/week ($I^2$ = 55%) and alefacept ($I^2$ = 70%) and for PASI 90 ustekinumab 45mg ($I^2$ = 58%) presented $I^2$ higher than 50%. The results of sensitivity analysis were described in Table 2.

## Safety outcome

Monitoring of adverse events in the included RCTs was done by patient and physician reports and direct observation by the researchers, especially for those double-blind studies.

The results of safety outcomes including infections and serious adverse events did not present statistically significant differences between biologic and placebo as observed in Figures 3a and 3b.

When considering withdrawal due to adverse events, the rate for ustekinumab 45mg was lower than that for the placebo group and the difference was statistically significant. For other biologics, at all dosages, there was no statistically significant difference between the drug´s result and placebo (Figure 3c).

## Discussion

Treatment for moderate to severe psoriasis is usually systemic and may involve biologic or non-biologic drugs [2,3,100]. Our search includes all biological agents studied for the treatment of psoriasis, taking into account different dosage regimens, providing information on efficacy and safety that is useful both for clinicians and for managers in decision-making processes.

It was observed in previously published meta-analyses that the best results with biological agents are achieved with infliximab and adalimumab. Our study has been updated to contain new clinical trials and newer drugs, such as ustekinumab, which in our review showed to be as good as those already mentioned when compared to placebo group. Reich et al. [10] included ustekinumab in the analysis and obtained similar results, but did not assess safety for Ustekinumab in either dosage.

Through our systematic review and meta-analysis, we found that when compared to placebo, all biologics demonstrated superior efficacy. Our results show a trend of ustekinumab 45mg and 90mg and infliximab 3mg/kg and 5mg/kg be the best biologics options, considering strictly PASI response as the outcome for moderate to severe psoriasis, after 10 to 14 weeks of treatment. However, it is not possible to affirm which biologic is better than other considering only these results. To that, mixed treatment comparisons, an indirect meta-analysis, are required since new RCTs head-to-head may not be feasible. Besides, since psoriasis is a chronic disease, results of long term follow-up are demanded to better understand the efficacy of these drugs. Unfortunately, RCTs do not have wide follow-up. To evaluate

Table 2

Sensitivity analysis for meta-analysis with $I^2 > 50\%$.

| Studies that influenced the $I^2$ | Biologic | RR (95%CI) pre-removal | $I^2$ (%) | RR (95%IC) post-removal | $I^2$ (%) | Characteristics of the studies |
|---|---|---|---|---|---|---|
| For outcome PASI 50 | | | | | | |
| | Etanercept 25mg TW | 4.12 (2.49- 6.82) | 75 | | | Hypothetical removal of any of the studies did not contribute to reduction of heterogeneity, which was the same as that for all possible analyses. More clinical trials are necessary to make the result consistent |
| Paller et al. [59] | Etanercept 0.8mg/kg to a maximum of 50mg W | 4.61 (1.86-11.41) | 70 | 5.42 (4.13-7.12) | 0 | Although many patients received 50mg weekly, some of them received lower doses since the patients were children and the dosage 0.8mg/kg/week |
| Gottlieb et al. [75] | Infliximab 5mg/kg W | 7.49 (4.07-13.80) | 64 | 10.07 (6.18-16.39) | 0 | This result may be related to a larger number of patients who achieved this outcome in the placebo group |
| For outcome PASI 75 | | | | | | |
| CHAMPION [27,28,29] | Adalimumab (80mg > 40mg EOW) | 8.01 (3.69-17.39) | 76 | 11.08 (7.73-15.90) | 0 | This result may be related to a greater number of patients who achieved this outcome in both the intervention and placebo groups |
| Mease et al. [35] | Alefacept | 2.25 (1.33-3.81) | 70 | 2.87 (2.06-4.00) | 0 | This may be related to the methodology of the study, including the use of methotrexate in both arms |
| | Infliximab 3mg/kg W | 21.77 (7.24-65.45) | 55 | | | There are only two studies considering this dosage, making the sensitivity analysis impossible<br>More clinical trials are necessary to make the result consistent |
| For outcome PASI 90 | | | | | | |
| CHAMPION [27,28,29] | Ustekinumab 45mg | 22.54 (8.25-61.61) | 58 | | | It was not possible to perform sensitivity analysis as only two studies were included |

PASI: *Psoriasis Area and Severity Index*; RR: relative risk; 95%CI: 95% confidence interval.

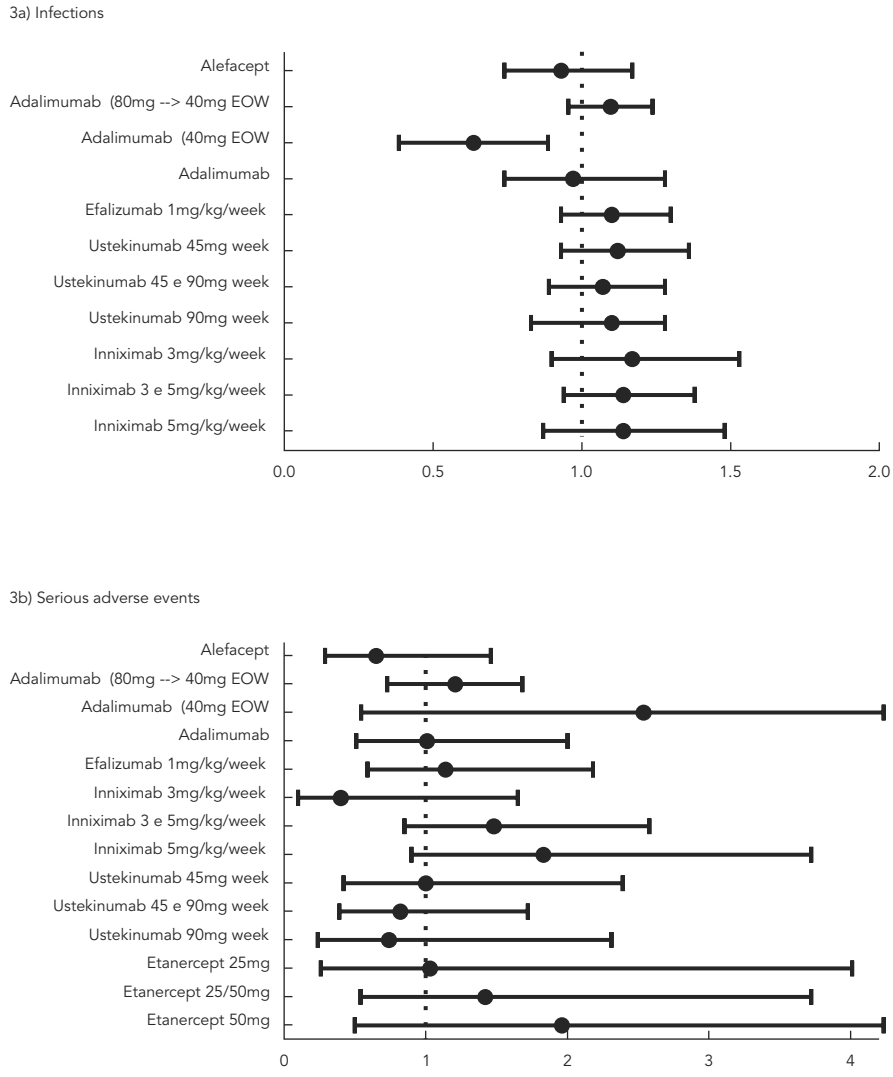
Note: the chart shows that even with exclusion of data collected from studies considered responsible for the high level of heterogeneity reported, the estimated global effect remained near to that found prior to the exclusion.

that, we suggest the conduction of a systematic review of cohort studies evaluating the maintenance of PASI 75 or 90 through a wide follow-up.

Ustekinumab 45mg achieved a statistically significant difference when compared to placebo for the outcome "withdrawn due to adverse events", meaning that those patients treated with ustekinumab 45mg had discontinued their treatment due to adverse events less than those treated with placebo. It could be explained considering an expected worsening of disease in placebo arm and a low number of adverse events caused by the biological agent during the first weeks of treatment. The same finding was not seen in patients treated with ustekinumab 90mg probably because at this dosage adverse events are more common. For other safety outcomes, there was no statistically significant difference between biological agents and placebo, as confirmed by other studies [7,8,12]. Nevertheless, these results must be considered cautiously by clinicians and managers. Serious adverse events and infections are complications dependent upon the drug exposure time, which means that the trials included in this study could not be able to detect some adverse events due to their short follow-up, ranging from 10 to 14 weeks. After this period of time, usually there were design changes in the trials, meaning that the meta-analysis of longer follow-up outcomes becomes unviable. Moreover, rare adverse events may not be detected in RCTs but only in phase IV studies.

Figure 3

Plaque psoriasis. Relative risk of infections, serious adverse events and withdrawal due to all adverse events with biologics treatment versus control.

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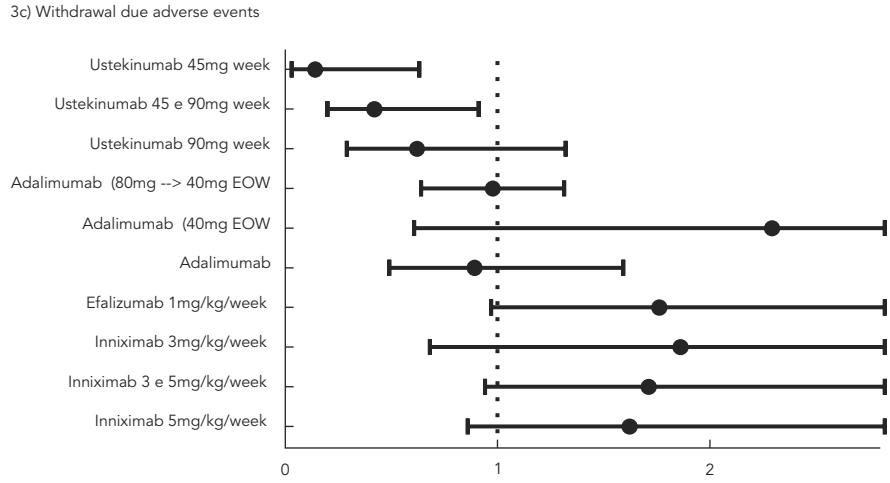
## Limitations

The low number of studies comparing some biologics to placebo means it is not possible to perform a meta-analysis for some drugs. In addition, differences in duration of clinical trials, ranging from 10 to 14 weeks, may influence the clinical results. However, it did not affect the robustness of our results, as can be observed through the sensitivity analysis in those cases of meta-analyses with high heterogeneity.

Although meta-analysis of RCTs brings results of high level evidence, this limits the results to short term treatment only.

The selection of only RCTs has an influence on the results regarding short follow-up.

Figure 3 (continued)




## Conclusion

Given the absence of primary studies that compare biological agents to each other, we conducted a systematic review followed by meta-analysis from trials comparing biological agents versus placebo. We understand that there is no need to develop new randomized clinical trials of biological agents controlled by placebo but instead, they should be compared to each other or with the best treatment options currently available.

Although we cannot conclude which bioagent is the best to treat moderate to severe psoriasis, we can point to a trend from ustekinumab 45mg and 90mg and infliximab 3mg/kg and 5mg/kg to be the best ones on achieving PASI response of 50%, 75% and 90% after 10 to 14 weeks of treatment. Moreover, considering the current evidence about safety in RCTs, our findings show a similar safety profile among biologics in the short-term treatment and a result signalizing ustekinumab 45mg as the most well tolerated biological agent in the first three months of treatment. However, a study assessing subgroups, such as cardiovascular, dermatologic and malignant diseases as well as indirect meta-analysis among those drugs regarding efficacy and safety are required to better understand the advantages and disadvantages for each biological agent in the short-term treatment of moderate to severe psoriasis.

## Resumen

*Se realizó una revisión sistemática y metaanálisis de ensayos controlados aleatorios en pacientes con psoriasis moderada a severa tratados con biológicos o placebo por 10-14 semanas. Se incluyeron 41 estudios con una puntuación de Jadad de 4,4, un total de 15.586 pacientes. Para variables de eficacia PASI 50, 75 y 90, los resultados no son concluyentes para definir cuál es el mejor agente biológico en el corto plazo. No hubo diferencia estadística entre el placebo y la ocurrencia biológica de las infecciones y los eventos adversos graves. Ustequinumabe 45mg fue el biológico con una menor incidencia de la interrupción debido a eventos adversos. Basado en la evidencia disponible hasta el momento, no es posible determinar qué agente biológico es lograr la mejor respuesta PASI 50, 75 y 90 después de 10-14 semanas de tratamiento. Para el mismo período, la seguridad global parece ser el mismo para todos los tratamientos y ustequinumabe 45mg el mejor tolerado. Para comprender mejor la eficacia y seguridad, es necesario un metaanálisis indirecto comparando medicamento a medicamento.*

*Psoriasis; Agentes Biológicos; Eficacia; Seguridad; Evaluácion de Tecnologías de Salud*

## Contributors

C. J. Correr and M. F. Otuki contributed to the elaboration of the study subject, delimitation of the study, interpretation of the results and manuscript review. I. Rotta, T. S. Teles, R. R. Godoy and P. R. Gonçalves contributed to the development of systematic review and meta-analysis, interpretation of results and manuscript review. B. S. Riveros and M. M. Garcia contributed to the development of systematic review and meta-analysis, interpretation of results, elaboration and manuscript review.

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## Conflict of interest

None declared.

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