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# Avaliação da eficácia das medicações imunobiológicas e inibidores de pequenas moléculas para psoríase: uma revisão sistemática da literatura e metanálise

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# Avaliação da eficácia das medicações imunobiológicas e inibidores de pequenas moléculas para psoríase: uma revisão sistemática da literatura e metanálise

Tese submetida ao Programa de Pós-Graduação em Patologia da Fundação Universidade Federal de Ciências da Saúde de Porto Alegre como requisito para a obtenção do grau de Doutor

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**Sumário**

**Lista de abreviaturas utilizadas**

17RA: Receptor da interleucina $17^{A}$

Anti-TNF alfa: molécula bloqueadora do fator de necrose tumoral alfa

AP: exame anatomopatológico

CI: intervalo de confiança (do inglês *confidence interval*)

DNA: ácido desoxirribonucleico (do inglês *deoxyribonucleic acid*)

EMDC: exame micológico direto e cultural

IL: interleucina

IMID: doença inflamatória imunomediada (do inglês *immune mediated inflamatory disease*)

JAK: Janus quinase (do inglês *Janus kinase*)

kg: kilograma

LL-37: peptídeo humano derivado de catelicidina

mg: miligrama

PASI: índice de área e gravidade da doença (do inglês *psoriasis area and severity index*)

PASI75: melhora de 75% sobre PASI inicial

PASI90: melhora de 90% sobre PASI inicial

PASI100: melhora de 100% sobre PASI inicial

PICO: acrônimo para paciente, intervenção, comparador e desfecho ( do inglês *patient, intervention, comparator and outcome*)

PDE4: fosfodiesterase-4 (do inglês *phosphodiesterase-4*)

PRISMA: acrônimo para Itens de reporte preferencial para revisões sistemáticas e metanálises (do inglês *Preferred reporting items for systematic reviews and meta-analyses*)

PUVA: combinação de tratamento com psoraleno e luz ultravioleta A

RD: diferença de risco (do inglês *risk diference*)

SBD: Sociedade Brasileira de Dermatologia

S.C.: subcutânea

TNF-alfa: fator de necrose tumoral alfa (do inglês *tumor necrosis fator-alpha*)

UVA: luz ultravioleta A

UVB: luz ultravioleta B

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**Resumo da Tese**

**Importância:** Psoríase é uma doença inflamatória imuno-mediada. O tratamento tem evoluído nos últimos anos devido à introdução de medicações imunobiológicas e inibidores de pequenas moléculas.
**Objetivo:** Conduzir uma revisão sistemática e metanálise para determinar a eficácia de medicações imunobiológicas e inibidores de pequenas moléculas pra tratamento de pacientes com psoríase moderada-a-grave.
**Fonte de dados**: Trabalhos publicados até 20 de julho de 2015 foram pesquisados nos bancos de dados EMBASE, MEDLINE, LILACS, WEB OF SCIENCE and CLINICALTRIALS.ORG.
**Seleção de estudos:** Somente ensaios clínicos randomizados, duplo-cego, controlados por placebo que avaliaram a eficácia de medicações imunobiológicas e inibidores de pequenas moléculas para tratamento de pacientes com psoríase moderada-a-grave. Foram selecionados por dois autores independentes. Nenhum restritor foi usado.
**Extração e síntese dos dados:** Dois autores extraíram independentemente os dados e uma metanálise com modelo de efeito randômico foi realizada.
**Desfecho principal e medidas:** O Psoriasis Area and Severity Index (PASI) 75 foi considerado o desfecho principal.
**Resultados:** 38 estudos foram incluídos. O efeito geral agrupado (*overall pooled effect*) favoreceu os biológicos e inibidores de pequenas moléculas em relação ao placebo (RD: 0.61; 95%IC:0.60-0.62). Ixekizumabe na dose de 160mg na semana 0 e então a cada 2 semanas (RD: 0,84; 95%IC: 0.76-0.91), brodalumabe 210mg (RD:0.79; 95%CI:0.76-0.82), infliximabe 5mg/kg (RD: 0.76; 95%IC:0.73-0.79) e secuquinumabe 300mg (RD: 0.76; 95%IC:0.71-0.81) mostraram maior chance de resposta (PASI75), quando comparados ao placebo.
**Conclusões e relevância:** Medicações anti-IL17, brodalumabe, ixekizumabe and secuquinumabe demonstraram chance igual ou maior de fazer os pacientes alcançarem 75% de melhora no PASI quando comparado com outras drogas revisadas.
**Palavras-chave:** psoríase, tratamento, meta-análise, revisão sistemática, biológicos

# 1. Introdução

## 1.1 Psoríase: etiologia e diagnóstico

Psoríase é uma doença inflamatória imuno mediada, caracterizada pelo acrônimo IMID, do inglês *Immune Mediated Inflamatory Disease*. Clinicamente, se caracteriza por manchas eritematosas e descamativas, localizadas mais comumente nos joelhos, cotovelos, cicatriz umbilical, região lombo-sacra e couro cabeludo (Figuras 2 e 3).Quando presentes, os sintomas variam, compreendendo prurido, dor e ardência ou queimação (Romiti e cols. 2010).

A psoríase cutânea pode estar acompanhada de doença articular (artrite psoriásica), que se manifesta por artrite inflamatória, com dor de ocorrência pela manhã, piora com repouso prolongado e melhora com atividade da articulação (rigidez matinal) (Wollina e cols. 2010). Outras associações encontradas nos pacientes psoriásicos compreendem a hipertensão arterial, hiperlipidemia, diabete melito e obesidade (juntas são caracterizadas como síndrome metabólica), doença inflamatória intestinal (doença de Crohn e retocolite ulcerativa), depressão e doenças autoimunes, como vitiligo e lúpus eritematoso (Malbris e cols. 2006, Gelfand e cols. 2007, Davidovici e cols. 2010, Cheng e cols. 2012). Os eventos cardiovasculares graves, como infarto agudo do miocárdio, também são associados à psoríase, principalmente em indivíduos jovens com doença grave (Gelfand e cols. 2006).

Do ponto de vista etiopatogênico, é caracterizada por uma hiperreatividade da imunidade celular, baseada em herança poligênica complexa e influenciada por fatores ambientais, aonde as células apresentadoras de antígenos e os linfócitos T, influenciados por uma cascata de citocinas e quimiocinas particulares, lideradas pelos sistemas TNF-alfa, IL 12/23 e IL17, reagem a antígenos ainda desconhecidos causando reação inflamatória descontrolada que, por fim, leva aos sinais e sintomas da doença (Kupper e cols. 2003, van De Kerkhoff e cols. 2007, Alsufani e cols. 2010). Ainda que no passado a doença tenha sido considerada uma desordem da queratinização, aonde o processo etiopatogênico inicial seria a proliferação acelerada e desorganizada da epiderme, hoje tem-se a noção de que o processo que leva a estes eventos epidérmicos é iniciado pela estimulação de células dentríticas plasmocitóides na

pele por um complexo de peptídeo antimicrobiano (LL-37) e partes do DNA do paciente (Fig 1). A cascata de citocinas e quimiocinas desencadeadas por este processo inicial, como fator de crescimento queratinocítico, fator de crescimento epidérmico e fator de crescimento endotelial, é a responsável pelas características clinicas das lesões (eritema/vasodilatação, descamação/hiperatividade queratinocítica, indução/ espessamento da epiderme) (Boehncke e cols. 2015).

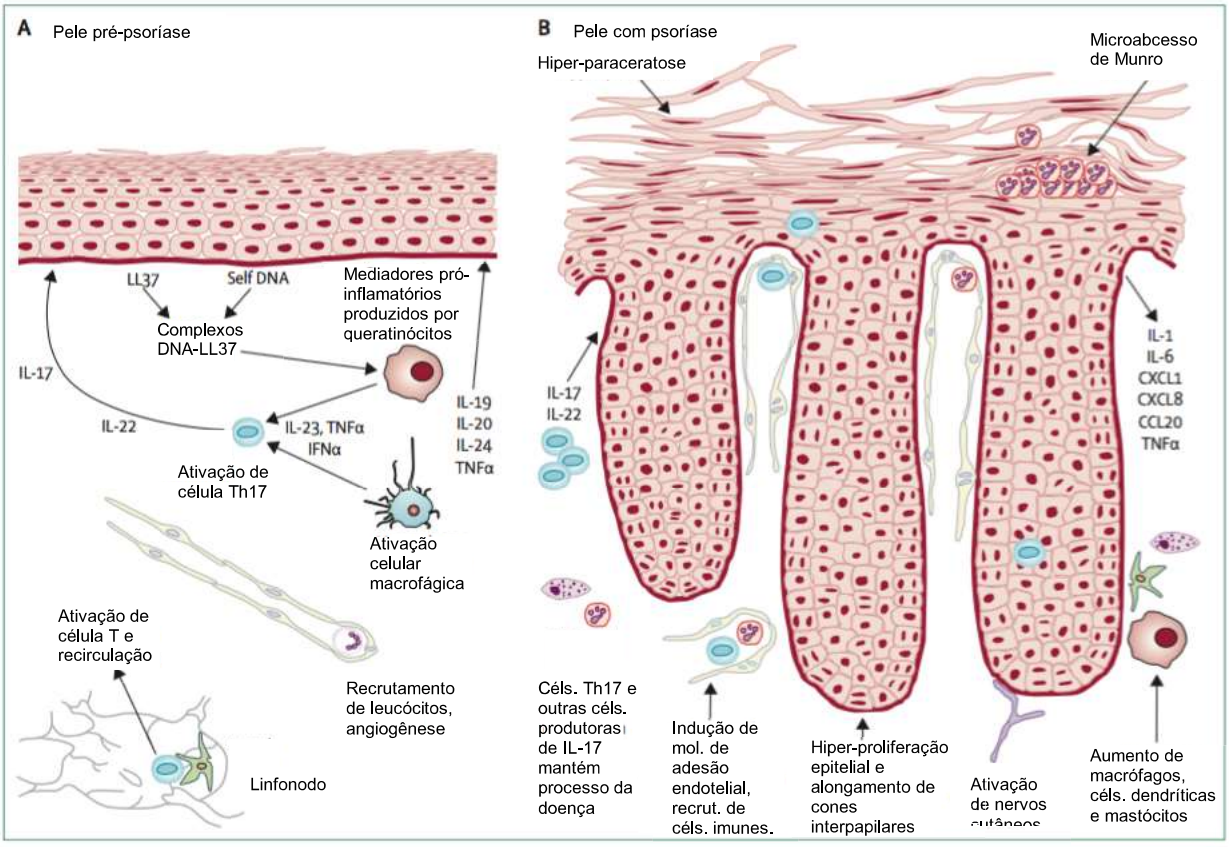



**Figura 1. Diagrama com a complexa interrelação de células do sistema imune e ação de quimiocinas e citocinas que acabam por determinar as formas clínicas da psoríase (Adaptado de Boehnck e cols. 2015).**

O diagnóstico da psoríase é eminentemente clínico e, nos poucos casos onde houver dúvida, os exames mais úteis para o esclarecimento diagnóstico são o exame micológico direto e cultural (EMDC) e o exame anatomopatológico (AP) (Romiti et cols. 2010).

Existem diferentes formas clínicas da doença, sendo que a **psoríase em placas** é a forma mais comum (Figura 2.). Pode acometer até 9% da superfície corporal do doente (localizada) ou acima de 9% da superfície corporal, sendo assim considerada generalizada.

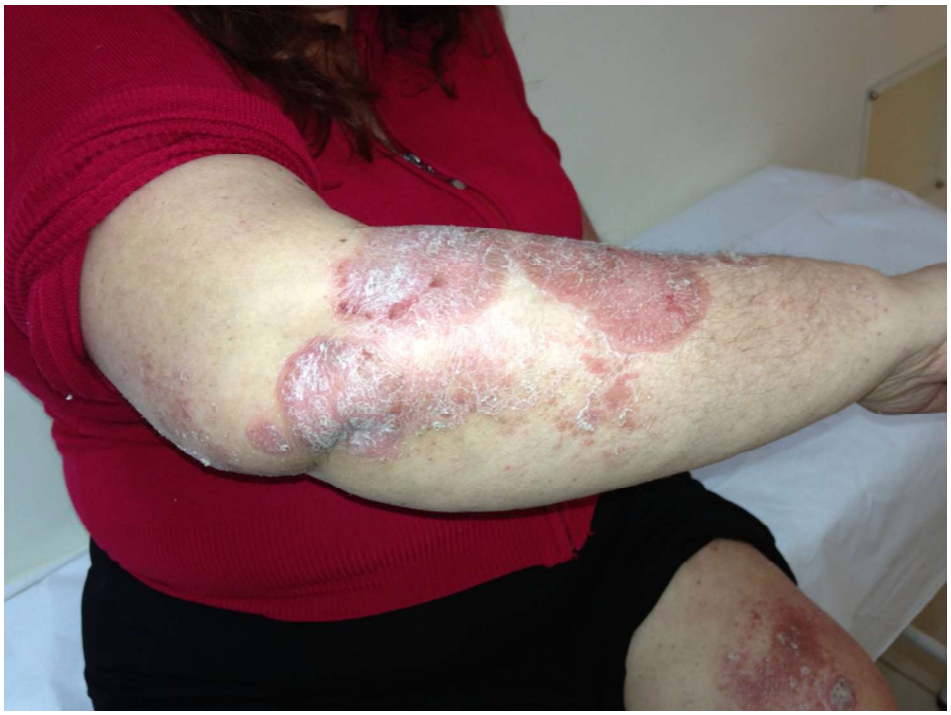


**Figura 2. Psoríase em placas**

A **psoríase eritrodérmica** é forma menos comum, mas não rara da doença, que acomete mais de 90% da superfície corporal. Pode ocorrer como evolução natural da psoríase em placas ou como resultado do tratamento intempestivo com glicocorticoides sistêmicos (Figura 3)( Boehncke e cols. 2015).

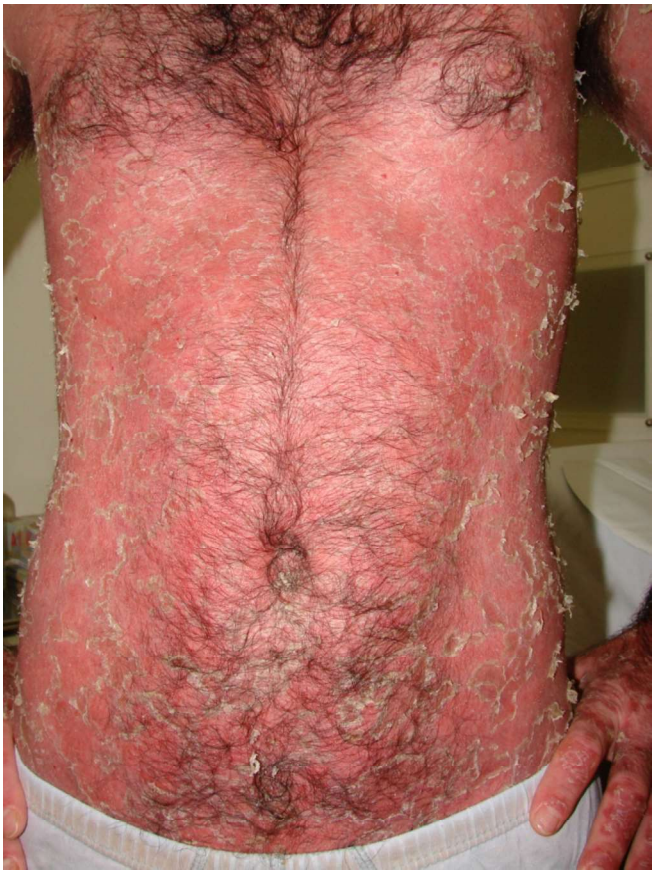


**Figura 3. Psoríase eritrodérmica**

Outras formas clínicas são a **psoríase pustulosa** (generalizada ou localizada), **psoríase gotada**, **psoríase palmo-plantar**, **psoríase invertida/ flexural** e **psoríase ungueal** (Romiti e cols. 2010).

A gravidade do quadro cutâneo é determinada pela extensão da doença, medida pela área corporal afetada e pelo índice de área e gravidade da doença, do inglês *Psoriasis Área and Severity Index* (PASI).

A medida da área corporal afetada é estimada levando em conta que a superfície da palma da mão do paciente com os dedos juntos e esticados perfaz 1% da superfície corporal total.

O PASI é medido através de uma tabela aonde o médico (ou prestador) calcula o grau de descamação, eritema e infiltração de acordo com a área corporal afetada (Tabela 1). O valor obtido varia de 0 a 72, onde pacientes com índice de 0 a 10 são considerados leves e pacientes acima de 10 são considerados moderados / graves. A diferenciação entre pacientes moderados e graves é controversa e não influi no tratamento (Romiti e cols. 2010).

**Tabela 1. PASI (*Psoriasis Area and Severity Index*)**

| | CABEÇA | TRONCO | MEMBROS SUPERIORES | MEMBROS INFERIORES |
|---|---|---|---|---|
| ERITEMA | | | | |
| INFILTRAÇÃO | | | | |
| DESCAMAÇÃO | | | | |
| **soma** | | | | |
| **AREA** | | | | |
| *X área* | | | | |
| X *índice* | 0 | 1,5 | 1,2 | 3,2 |
| **TOTAL** | | | | |

| | |
|---|---|
| **Escala de avaliação do eritema, infiltração e descamação:**<br>0 = Ausente<br>1 = Leve<br>2 = Moderado<br>3 = Grave<br>4 = Muito grave | **Escala de avaliação de área:**<br>1 < 10%<br>2 >10 e <30%<br>3 >30 e <50%<br>4 >50 e <70%<br>5 >70 e <90%<br>6 >90% |

Romiti e cols., Compêndio de psoríase 2011.

### 1.2 Psoríase: tratamento

O tratamento da psoríase cutânea, quando a doença for localizada, pode ser realizado com medicações de uso tópico baseados principalmente nos corticosteroides potentes ou superpotentes associados ou não ao calcipotriol tópico. A hidratação da pele é importante para melhor condução do quadro, mas é coadjuvante nos casos mais graves, não sendo indicada como monoterapia. Na falha da terapia tópica ou na doença generalizada, a fototerapia e os chamados tratamentos clássicos (metotrexato, acitretina e ciclosporina) são alternativas (Fig. 4)(Nast e cols. 2009, Menter e cols. 2009, SBD e cols. 2012).

Entretanto, um expressivo número de pacientes com doença cutânea, não responde ao tratamento clássico isolado ou em combinação. Nestes casos

refratários, o uso de medicações imunobiológicas e inibidores de pequenas moléculas tem sido usado com sucesso variável, de acordo com a forma clínica e comorbidades apresentadas (Fig. 5) (Menter e cols. 2009, SBD e cols. 2012, Nast e cols. 2015)

**Figura 4. ALGORITMO DE TRATAMENTO DA PSORÍASE LEVE SEGUNDO O CONSENSO BRASILEIRO DE PSORÍASE DA SOCIEDADE BRASILEIRA DE DERMATOLOGIA (SBD) 2012 (pontuação do instrumento de avaliação de diretrizes clínicas Agree II D1:25%;D2:50%; D3: 57%; D4:50%; D5:0%; D6:50%)**

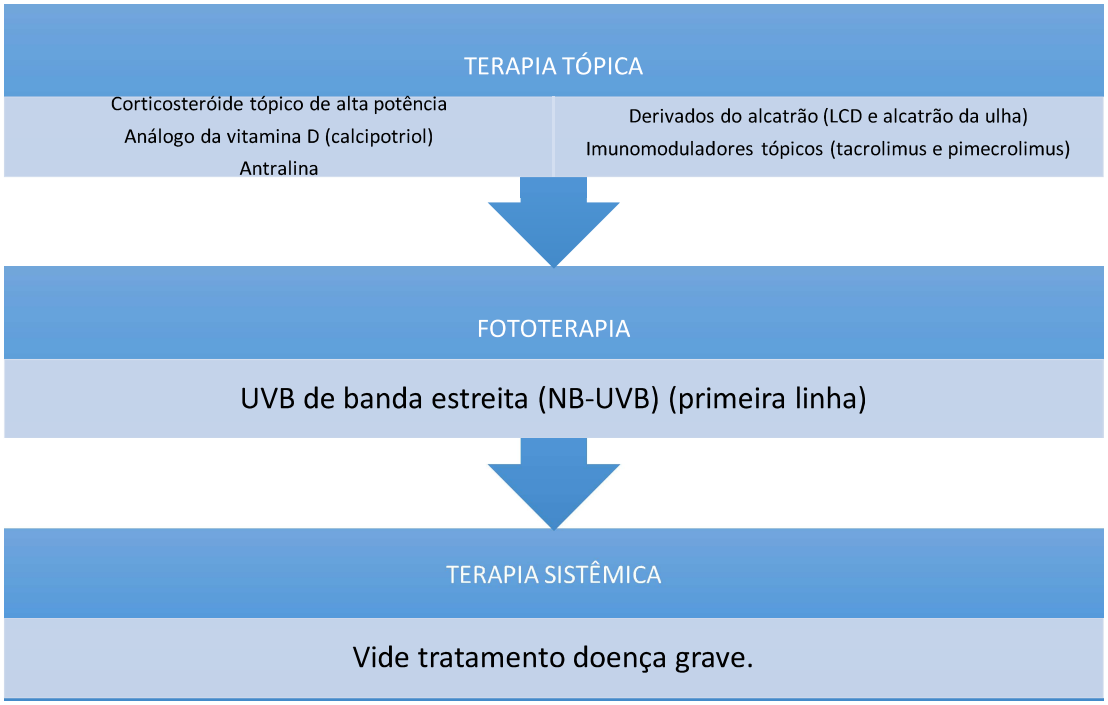
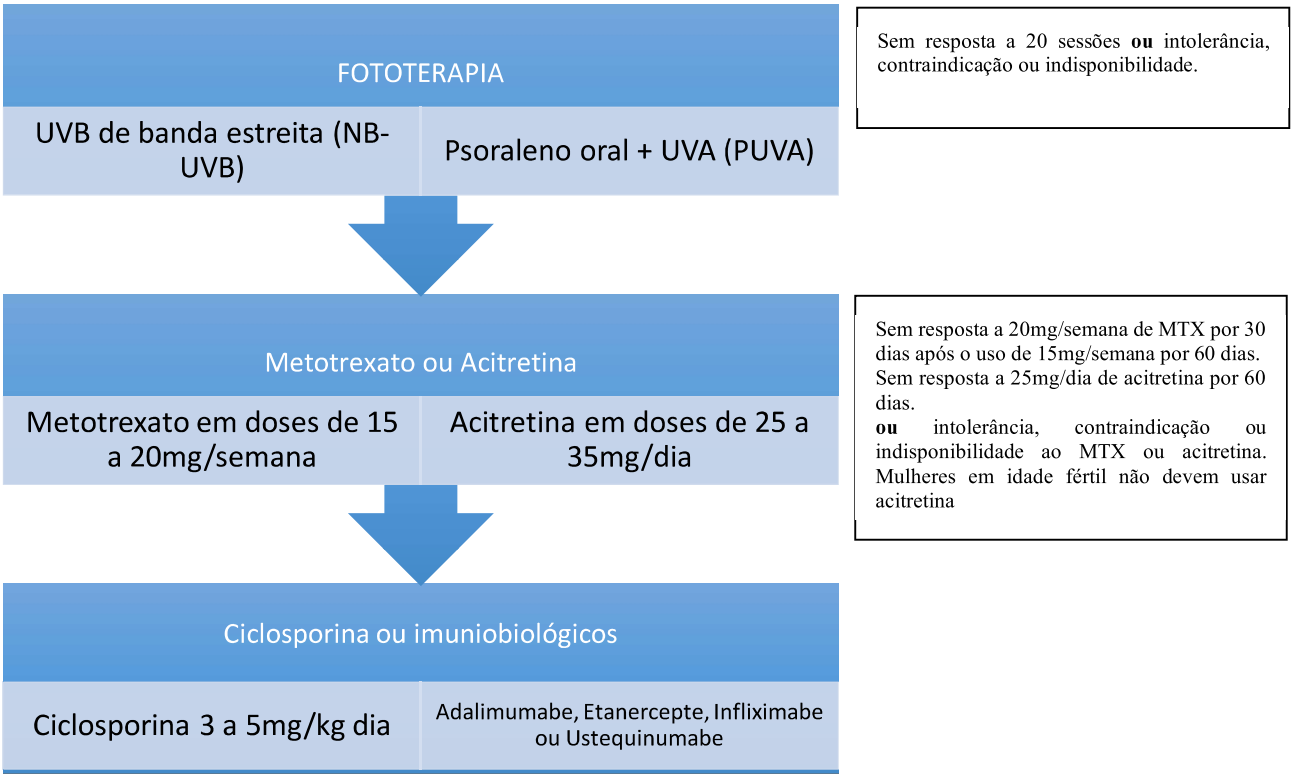


**Figura 5. TRATAMENTO DA PSORÍASE GRAVE SEGUNDO O CONSENSO BRASILEIRO DE PSORÍASE DA SOCIEDADE BRASILEIRA DE DERMATOLOGIA (SBD) 2012. (pontuação do instrumento de avaliação de diretrizes clínicas Agree II D1:25%;D2:50%; D3: 57%; D4:50%; D5:0%; D6:50%)**




Os medicamentos imunobiológicos e inibidores de pequenas moléculas para psoríase são drogas de alto custo e os estudos clínicos de eficácia realizados usualmente avaliam a droga em relação ao placebo, existindo poucos ensaios clínicos randomizados que comparem as medicações entre si (*head-to-head*), sendo que é pouco provável um estudo que realize a comparação entre todos os medicamentos disponíveis. De forma geral os estudos avaliam a reposta das medicações biológicas em doze semanas até 16, avaliando a gravidade da psoríase através do PASI *(Psoriasis Area and Severity Index)*, o escore mais usado para medir resposta às medicações nos ensaios clínicos publicados. O objetivo do tratamento é a diminuição de 75% no PASI (também chamado PASI 75) entre a consulta de base pré-tratamento e a avaliação após,

no mínimo, 12 semanas de tratamento (Magliocco e cols. 2004, Reich e cols. 2005, Gottlieb e cols. 2009, Papp e cols. 2011, Leonardi e cols. 2014). Este período para avaliação de eficácia (endpoint primário) corresponde ao período de indução destas medicações, aonde a posologia é, via de regra, maior ou mais frequente. O uso do PASI 90 ou 100 (90 ou 100% de melhora sobre o PASI antes do tratamento) é usado nos estudos como desfecho secundário e estudos mais antigos (realizados há mais de 5 anos) raramente incluem estas duas medidas em seus resultados.

As medicações imunobiológicas para psoríase em placas moderada a grave disponíveis ou em estudo no início desta metanálise são descritas abaixo, seguidas dos seus mecanismos de ação e posologias:

**-Adalimumabe:** Anticorpo monoclonal humano bloqueador do fator de necrose tumoral alfa (anti-TNF alfa). Disponível na dose de 40mg em canetas automatizadas para auto-aplicação, é administrado na posologia de 80mg na semana 0, 40mg na semana 1 e, a partir daí 40mg a cada 2 semanas, por via subcutânea.

**-Apremilast:** Pequena molécula, inibidor da fosfodiesterase 4 (PDE4) é disponível em tabletes de 10, 20 e 30 mg e é auto-administrado por via oral na sequencia de um comprimido de 10mg no primeiro dia, um comprimido de 10mg 2x/dia no segundo dia, um comprimido de 10mg pela manhã e um comprimido de 20mg à noite no terceiro dia, um comprimido de 20mg 2x/dia no quarto dia, um comprimido de 20mg pela manhã e um comprimido de 30mg à noite no quinto dia e um comprimido de 30mg 2x/dia contínuo a partir do sexto dia.

**-Brodalumabe:** Anticorpo monoclonal humanizado, bloqueador da interleucina 17(IL-17RA). Ainda não disponível para uso comercial. Doses de 140mg ou 210mg aplicados por via subcutânea nas semanas 0,1,2,4,6,8, e 10 e a cada duas semanas a partir da semana 10.

**-Etanercepte:** Proteína de fusão, bloqueador do fator de necrose tumoral alfa solúvel (anti -TNF alfa). Disponível em seringas de 50mg prontas para aplicação subcutânea, sendo duas seringas por semana até a semana 12 e depois uma

seringa a cada semana contínuo.

**-Fezakizumabe:** Anticorpo monoclonal inibidor da interleucina-22. Ainda sem dosagem definida.

**-Guselkumabe:** Anticorpo monoclonal bloqueador da subunidade p19 da interleucina 23. Ainda não disponível comercialmente. Dose provável (ainda em fase II) de 100mg S.C. nas semanas 0,4, 12, 20 e depois a cada 8 semanas.

**-Infliximabe:** Anticorpo monoclonal quimérico bloqueador do fator de necrose tumoral alfa (anti -TNF alfa). Disponível em ampolas de 100mg. É infiltrado por via endovenosa em ambiente hospitalar na dose de 5mg/kg de peso. Medicamento diluído em soro fisiológico é infundido lentamente no período de no mínimo uma hora nas semanas 0, 2, 6 e então a cada 8 semanas

**-Ixekizumabe:** Anticorpo monoclonal humanizado, bloquador da interleucina 17A (IL-17A). Disponível na dose de 80mg em canetas automatizadas para auto-aplicação, é administrado na dose de 180mg na semana 0 e 80mg a partir daí a cada 4 semanas, por via sub-cutânea.

**-Secukinumabe:** Anticorpo monoclonal humano, bloquador da interleucina 17A (IL-17A). Disponível na dose de 150mg em canetas automatizadas para auto-aplicação, é administrado na dose de 300mg nas semanas 0,1,2,3,4,8 e a partir daí a cada 4 semanas, por via sub-cutânea.

**-Tofacitinibe / tasocitinibe:** Medicação inibidora de pequena molécula Janus Kinase 3 (JAK-3). Comprimidos de 5 com doses que variam de 5 a 10mg 2x/dia, por via oral.

**-Ustekinumabe:** Anticorpo monoclonal bloqueador da subunidade p40 das interleucinas 12 e 23. Disponível em ampolas de 45mg e é administrado por via subcutânea nas semanas 0, 4 e depois a cada 12 semanas. No caso de pacientes acima dos 100kg, a dose deve ser dobrada para 90mg.

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## 2. Objetivos

### 2.1 Objetivo geral

O objetivo deste trabalho é determinar a eficácia dos imunobiológicos e inibidores de pequenas moléculas para tratamento da psoríase moderada-a-grave quando comparados ao placebo quando analisada a melhora de 75% no PASI (*Psoriasis Area and Severity Index*) como desfecho primário.

### 2.2 Objetivos específicos

Avaliação da eficácia das mesmas medicações usando 90% de melhora do PASI (*Psoriasis Area and Severity Index*) como desfecho e a comparação dos resultados com metanálises previamente publicadas.

Avaliação da eficácia das mesmas medicações usando 100% de melhora do PASI (*Psoriasis Area and Severity Index*) como desfecho e a comparação dos resultados com metanálises previamente publicadas.

**3. Artigo científico redigido em inglês**

# “Efficacy of immunobiologic and small molecule inhibitors drugs for psoriasis: a systematic review and meta-analysis of randomized clinical trials.”

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Running head: Immunobiologic and small molecule inhibitors drugs for psoriasis: a systematic review and meta-analysis

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**ABSTRACT**

**Importance:** Psoriasis is an immune mediated inflammatory disease. Treatment has evolved over the past few years, due to the introduction of immunobiologic and small molecule inhibitor medications. A better understanding of comparative efficacies of drugs may help doctors to choose the most appropriate treatment for the patients.

**Objective:** To conduct a systematic review and meta-analysis to assess the efficacy of immunobiologic and small molecule inhibitor drugs for moderate-to-severe psoriatic patients.

**Data Sources:** EMBASE, MEDLINE, LILACS, WEB OF SCIENCE and CLINICALTRIALS.ORG databases were searched for trials published until July 20, 2015.

**Study selection:** Only randomized, double-blind, placebo controlled clinical trials that evaluated the efficacy of immunobiologics or small molecule inhibitors for moderate to severe plaque type-psoriasis were selected by two independent authors. No restrictions were used.

**Data extraction and synthesis:** Two authors independently extracted the data and a random effects model meta-analysis was performed.

**Main outcomes and Measures:** The Psoriasis Area and Severity Index (PASI) 75 was considered as the primary outcome, measured at each study's primary endpoint.

**Results:** 38 studies were included. The overall pooled effect favored biologics and small molecule inhibitors over placebo (RD: 0.59; 95%CI:0.58-0.60). Ixekizumab at a dose of 160mg on week 0 and then every 2weeks (RD: 0,84; 95%CI: 0.81-0.88), brodalumab 210mg (RD:0.79; 95%CI:0.76-0.82), infliximab 5mg/kg (RD: 0.76; 95%CI:0.73-0.79) and secukinumab 300mg (RD: 0.76; 95%CI:0.71-0.81) showed greater chance of response (PASI75), when compared to placebo.

**Conclusions and relevance:** Anti-IL17 drugs, brodalumab, ixekizumab and secukinumab showed equal or greater chance of making patients achieve 75% improvement on PASI compared to other reviewed drugs.

**Limitations:** The methodology of a traditional meta-analysis does not allow a ranking of drugs. Included studies used short term endpoints (10 to 16 weeks) to evaluate the primary outcome therefore, long term efficacy could not be determined.

**Keywords**: psoriasis, biologics, small molecule inhibitors, treatment, meta analysis.

Key points:

- Anti-TNF and anti-IL12/23 have already been shown to be effective to treat moderate-to-severe psoriasis patients.

- Anti-IL17 drugs showed equal or greater chance of leading patients to a 75% improvement in psoriasis when compared to other biologics/small molecule inhibitors.

- Ixekizumab showed higher efficacy among FDA approved drugs when 90 or 100% improvement over baseline PASI were analyzed.

## 1. INTRODUCTION

Psoriasis is an immune mediated inflammatory chronic disease, where an intricate immune process, mainly driven by the Th1/Th17 branch of the immune system, leads to persistent inflammation. (1-3)

Psoriasis treatment has been revolutionized by the introduction of biologic and small molecules inhibitors targeted therapy. Several of these have been released and are already available for general use, such as infliximab(4), adalimumab (5), ustekinumab (6), apremilast(7), etanercept(8), ixekizumab(9), and secukinumab(10), , while others are in phase II or later trials, e.g., brodalumab(11), guselkumab(12), certolizumab pegol(13) and tofacitinib (14). On the other hand, studies on the efficacy of briakinumab were halted because of safety concerns during phase III trials(15). Schmitt et al(16) recently carried out a meta-analysis that included studies that evaluated systemic treatments for psoriasis (biologics or not) published before October 2012. This review did not include anti-IL17 drugs, and infliximab 5mg/kg was superior to ustekinumab, adalimumab and etanercept. Xiong et al. published a systematic review that only included secukinumab, one of the anti-IL17 biologic drugs and concluded that anti-IL17 drugs would be more efficacious than currently available biologics(17). Chen et al., also in 2015, performed a meta-analysis comparing only anti-IL17 drugs and reported a greater chance of response of brodalumab 140mg, followed by ixekizumab 25mg and secukinumab 150mg(18).

As new drugs emerged in the last years(9) (14) (11,13) it is important to update previous reviews to provide the best evidence on the efficacy of recent treatments for psoriasis. This study aimed at systematically review the evidence on the efficacy of biologic and small molecule inhibitor drugs for the treatment of moderate-to-severe psoriasis

## 2. METHODS

This systematic review and meta-analysis was conducted using the recommendations of the Cochrane Initiative and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA)(19).

**2.1 Search strategy / Databases searched / Eligibility criteria**

The research question *("What is the efficacy, measured by the improvement of 75% over baseline Psoriasis Area and Severity Index (PASI), of biologic and small molecule inhibitor drugs for moderate-to–severe psoriasis patients when compared to placebo?"*) was formulated using the PICO method (Population, Intervention, Comparator, Outcome). EMBASE, MEDLINE, LILACS, WEB OF SCIENCE and CLINICALTRIALS.ORG databases were searched for double blind, randomized, placebo-controlled clinical trials (RCT) published until July 21st 2016. Search strategies involved the use of the terms "*psoriasis AND (abatacept OR apremilast OR CC-10004 OR adalimumab OR D2E7 OR briakinumab OR ABT-480 OR brodalumab OR certolizumab OR etanercept OR TNF Fc OR fezakizumab OR golimumab OR guselkumab OR CNTO1959 OR infliximab OR ixekizumab OR secukinumab OR Ly-2439821 OR sifalimumab OR siplizumab OR tasocitinib OR tofacitinib OR ustekinumab OR CNTO-1275 OR AbGn-168 OR RG-4934 OR APG-2305 OR MK-3222)".* Studies published online, in print or in press were reviewed. Although we considered all languages eligible for the review, only studies published in English were found to be relevant.

Initially, duplicates were excluded and two researchers (A.V.E.C and R.P.D.) independently reviewed the titles and abstracts to exclude those studies that were clearly irrelevant. The reviewers then evaluated the full text of the remaining manuscripts and relevant articles were identified. Disagreements were solved by consensus. Randomized clinical trials were eligible for inclusion in the present review if they fulfilled the following criteria: human based, double blind, randomized, placebo-controlled clinical trials which evaluated adult patients and used the Psoriasis Area and Severity Index (PASI) as

measurement for psoriasis severity. Phase II studies were included only if studied drugs or doses were identified in further phase III studies; or if drugs or doses were already approved by the FDA. In the case of studies with multiple study arms including approved and non-approved drugs or doses, only arms containing approved drugs/doses were included in the meta-analysis. Head-to-head studies without placebo arm were excluded from analysis. Studies that evaluated improvement of psoriatic arthritis as a primary outcome were excluded from the study. The reference lists of the articles included in the review was searched for additional studies.

The primary efficacy outcome was the number of patients that experienced an improvement of 75% on the disease, measured by the PASI (PASI75), at the time of the primary efficacy assessment. Secondary outcomes were 90% improvement (PASI90) and 100% improvement (PASI100).

**2.2 Data extraction**

Using a standardized protocol(20), entirely based on the Cochrane handbook for systematic reviews and interventions, reviewers extracted the following items from each study: authors; year of publication; intervention and comparator; total number of patients randomized; trial duration; mean disease duration; patients mean age; mean baseline PASI; number of patients achieving PASI75, 90 and 100; prior use of biologic or concomitant medications**.** Effect estimates were extracted with 95% confidence intervals (CI). Any disagreement was also solved by consensus. It was decided not to use any quality assessment of the studies (i.e. JADAD) and to evaluate its impact on the estimated pooled effect using meta-regression/sensitivity analysis. Data regarding randomization, blinding and complete reporting of the study results were also extracted to evaluate the risk of bias(20).

**2.3 Statistical analysis**

Effect measures were reported as pooled risk difference (RD) and a RD > 0 denoted that those subjects who received the “new drug” showed a higher risk of presenting the

outcome. Overall pooled effect of any treatment versus placebo was estimated running a separate analysis, with all treatment patients gathered in one group and all placebo patients on another one, to avoid the unit-of-analysis error. Number needed to treat (NNT) were also calculated.

Heterogeneity among studies was assessed using the Q-test and I-square; a random-effects model was used. Sensitivity analysis was performed excluding phase II studies when heterogeneity was found to be over 50%. Funnel plot and Egger test were used to investigate publication bias. We performed meta-regression to assess the influence of mean baseline PASI, previous use of biologics and duration of the disease on the heterogeneity among studies.

Meta-analysis using data extracted from the studies was performed using STATA v.14 software for Mac (StataCorp LP). Forest plots, funnel plots and risk of bias assessment graphs were made using Review Manager Version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

## 3. RESULTS

9544 records were identified through database search, with 5 aditional records identified through search of bibliographical references of published metaanalysis. After removing duplicates, 6513 records were screened and 6181 were excluded (3822 were not RCT; 2039 not about psoriasis; 100 were about drugs not encompassed in this review; 198 were additional duplicates).

Among the 332 manuscripts selected for full text review, 292 were excluded for the following reasons: 201 articles were not RCT, 16 were RCT that did not use placebo as a comparator, 45 due to lack of PASI as primary outcome, 5 were studies in the pediatric population, 4 were phase II studies without further confirmatory phase III studies, 8 were studies with doses not approved by the FDA, 9 were about psoriatic arthritis and 4 were additional duplicates. (**Fig1**).

A total of 40 studies (4,5,7-11,14,21-53) were included in the meta-analysis, providing 56 comparisons of 11 different interventions. In total, 22884 patients were evaluated. Medications studied were adalimumab, apremilast, brodalumab, etanercept, infliximab, ixekizumab, secukinumab, tofacitinib and ustekinumab. Of the 40 studies included in the meta-analysis, 6 used a 10 week endpoint, 6 used a 16 week endpoint and 28 used a 12 week endpoint. Primary endpoints for outcomes assessment were correlated with the induction period of the drugs and can be considered short-term therapy. All studies shared similar inclusion criteria and baseline characteristics (**Table 1**). Risk of bias assessment showed that high risk of bias was low among the studies. (**online resource 1 and 2**)

At FDA approved dose regimens, 1054 patients were randomized to adalimumab, 650 to apremilast, 2957 to etanercept (535 to 50mg/wk and 2422 to 100mg/wk), 844 to infliximab, 1169 to ixekizumab, 691 to secukinumab and 1678 to ustekinumab (949 to 45mg and 729 to 90mg). Concerning drugs still not approved by the FDA, 2554 patients were randomized to brodalumab (1278 to 140mg and 1276 to 210mg) and 2197 to tofacitinib (1124 to 5mg and 1073 to 10mg).

Considering PASI75 as a primary endpoint, ixekizumab (160mg wk 0 and 80mg every 2 wks) was the drug that achieved the higher risk difference (RD:0.84; 95%CI:0.81-0.88), followed by brodalumab at a dose of 210mg (on weeks 0,1,2,4,6,8 and 10) (RD: 0.79; 95%CI: 0.76-0.82). Figure 2 **(Fig2)** shows the remaining comparisons. Infliximab 5mg/kg (RD:0.76; 95%CI:0.73-0.79) and secukinumab 300mg (RD: 0.76; 95%CI:0.71-0.81) performed comparably. The overall pooled effect favored treatment when compared to placebo (RD: 0.59; 95%CI:0.58-0.60) (**Fig3**). The estimated number-needed-to-treat (NNT), when analyzing PASI75 as an outcome, for ixekizumab, brodalumab 210mg, infliximab and secukinumab were 1.19, 1.26, 1.31 and 1.31, respectively. A summary of comparisons is found on **Table 2**.

When PASI90 was used as an outcome, both doses of brodalumab, 210mg (RD: 0.75; 95%CI:0.61-0.89) and 140mg (RD: 0.72; 95%CI:0.57-0.86, achieved higher chances of improvement, followed by ixekizumab (RD: 0.69; 95%CI:0.65-0.72). Secukinumab and infliximab showed the same RD, with exactly the same CI (RD: 0.53; 95%CI: 0.46-0.60). Remaining comparisons can be seen in figure 4 (**Fig4**). The overall pooled effect favored treatment in relation to placebo (RD: 0.39; 95%CI:0.38-0.40) (**Fig5**)

Brodalumab 210mg was also the drug that achieved higher RD if PASI100 was used as the outcome (RD: 0.44; 95%CI:0.35-0.53). Approved drugs performed as follows: ixekizumab (RD: 0.37; 95%CI: 0.35-0.40), secukinumab (RD: 0.28; 95%CI: 0.22-0.34), adalimumab (RD: 0.18; 95%CI: 0.12-0.24) and ustekinumab 45mg (RD: 0.16; 95%CI: 0.10-0.21). Other comparisons are seen on figure 9 (**Fig6**). Overall pooled effect of treatment versus placebo was also favorable to treatment (RD: 0.24; 95%CI: 0.23-0.25) (**Fig7**)

Hetrogeneity ($I^2$) on the PASI75 outcome analysis was below 40% in the following drugs: adalimumab ($I^{2=}$13%), apremilast ($I^{2=}$34%), brodalumab 210mg ($I^{2=}$0%), etanercept 50mg ($I^{2=}$0%), infliximab ($I^2$=0%), tofacitinib 5mg ($I^{2=}$0%) and ustekinumab 45mg ($I^{2=}$33%). A moderate heterogeneity was found in the etanercept 100mg ($I^{2=}$59%), secukinumab ($I^{2=}$46%) and tofacitinib 10mg ($I^{2=}$58%) groups. Substantial heterogeneity was seen on the following groups: brodalumab 140mg ($I^{2=}$71%), ixekizumab ($I^{2=}$64%) and ustekinumab 90mg ($I^{2=}$67%) (Fig 2). Heterogeneity for remaining outcomes (PASI 90 and 100) can bee found on figures 4 and 6.

The funnel plot of PASI75 outcome did not disclose discrepancies regarding magnitude of the effect measured and study size. PASI 90 and PASI 100 funnel plots are not typical and the lack of symmetry observed may be an indication of publication bias. (**online resources 3, 4 and 5**).

Meta-regression was performed to evaluate the contribution of mean baseline PASI, previous use of biologics and duration of the disease to the heterogeneity among studies (**online resources 6**). None of these variables explained the heterogeneity.

## 4. DISCUSSION

In the present review, anti-IL17 drugs performed very well. Ixekizumab presented the higher RD in the primary outcome (PASI75). Brodalumab (210mg) performed well, following ixekizumab on primary outcome and achieving a higher RD on both secondary outcomes (PASI90 and PASI 100). Nevertheless, as CI overlapped, ixekizumab, brodalumab 210mg, and secukinumab, should be considered as having similar performances, even with different RD. On the other hand, ixekizumab and brodalumab 210mg were superior to all remaining drugs, with exception of infliximab and secukinumab, when PASI 75 was the outcome (no overlapping of CI).

Brodalumab (both doses) was the drug with higher RD, when analyzing PASI 90 as an outcome, but ixekizumab had similar performance as CI overlapped. Nevertheless, it is important to emphasize that only one brodalumab study(11) (both dosages) could be found that used PASI 90 as an outcome and it was a study with a low number of patients enrolled. Therefore, results concerning brodalumab at this particular outcome should be taken with caution. Ixekizumab was also the best performing drug, being superior than all remaining approved medications (no overlap of CI). Ixekizumab also showed the highest RD among approved drugs at PASI 100 and was superior to all remaining medications (no overlapping of CI), when drugs where compared to placebo. At the same outcome, brodalumab 210mg achieved a higher RD than ixekizumab, but effectiveness is comparable as CI overlapped. The number of studies included in the analysis of PASI 100 outcome for brodalumab was higher, enrolling more than 1200 patients, what makes these findings more robust than the ones found for brodalumab when PASI 90 was analyzed.

Among newer small molecule inhibitor drugs, tofacitinib, an anti-Janus kinase 1, also

performed well at the dose of 10mg, being superior, when compared to placebo, to lower dose etanercept and comparable to higher dose etanercept, adalimumab and low dose brodalumab (overlapping CI), considering PASI75 as the primary outcome.

On the other hand, apremilast, an anti-phosphodiesterase 4 drug, performed poorly. Nevertheless, it is comparable to low dose etanercept (50mg/wk) and low dose tofacitinib (5mg) at primary outcome. PASI 90 and 100 analyses could not be performed for apremilast as no studies were found that could supply the appropriate data.

In accordance to previous meta-analysis(16,52), infliximab also performed well among approved biologics. Ustekinumab at both dosages (45 and 90mg) had basically the same performance, what may be explained by the fact that the included studies did not stratify the analysis by patient weight and dosage. The order of effectiveness measure by RD in which infliximab 5mg/kg, ustekinumab 90mg, ustekinumab 45mg, adalimumab, etanercept 100mg and etanercept 50mg were positioned in this meta-analysis was the same found by Schmitt et al. in a recent meta-analysis(16). Reich et al, using a different meta-analysis methodology (Bayesian, network meta-analysis)(54)found a similar ranking regarding chance of PASI75 response, with the exception of etanercept 100mg response rate, which was not contemplated in the study. It is important to notice that a rank of RD is somewhat deceiving, as CI may overlap. Nevertheless, the concordance of the rank seen in the work of Reich et al, witch used a Bayesian analysis, and the RD rank found in this work, indicates a consistent trend(54).

It is important to emphasize that the objective of this meta-analysis is to compare active treatments against placebo. A limitation to this work is that it is not inherently designed to make indirect comparisons of active treatments and, as stated before, overlapping CI determine that drugs are equally effective. A further Bayesian network meta-analysis should be performed to address this issue and, eventually, allow indirect comparisons to rank active treatments.

Considering approved doses and PASI75 as an outcome, heterogeneity inside each group has been found to be low ($I^2 \leq 40\%$) or moderate ($I^2 > 40$, $\leq 60\%$) (20) for all comparisons, except for ustekinumab 90mg ($I^2 = 67\%$), brodalumab ($I^2 = 71\%$) and ixekizumab ($I^2 = 64\%$). The heterogeneity of ustekinumab at a higher dose may be explained by the grouped analysis of populations of different weights (more than 100kg or less than 100kg). After performing sensitivity analysis, the heterogeneity found in the brodalumab subgroup was found to be due to a phase II study (11) with low number of participants. Heterogeneity for the brodalumab subgroup lowered to 48% after exclusion of this particular study. No reason was found to account for heterogeneity on the ixekizumab group, neither in meta-regression (online resources 6), nor in the sensitivity analysis. Heterogeneity of the pooled overall efficacy of active treatments compared to placebo was high, but this intergroup heterogeneity was expected due to the number of different treatments analyzed and the unit-of analysis error. Meta-regression was performed to analyze the impact of PASI score before treatment, duration of psoriasis or previous use of biologic or small molecule inhibitor drugs on heterogeneity. None of the predefined variables influenced the results. Random effects meta-analysis was performed as an attempt to incorporate heterogeneity.

Risk of bias assessment showed little percentage of high risk of bias categorization among studies included. On the other hand, 50% of the studies did not explicit well enough the random sequence generation or allocation concealment (selection bias), though being categorized as having unclear risk of bias.

The funnel plot of the primary outcome (PASI75) was interpreted as being symmetrical and, therefore, it is less likely that publication bias may have been present. Larger studies are gathered around the mean RD at the top of the plot. The lack of smaller studies is responsible for the empty space found at the bottom of the plot, but on can assume it is due to the inclusion and exclusion criteria of the systematic review (only placebo controlled RCTs). Two smaller studies are found on the plot, but they are symmetrically positioned on each side of the mean RD. PASI 90 and 100 funnel plot were asymmetric and

both showed smaller studies highly efficacious, resulting in a plot that had a lower left quadrant empty. One explanation for the asymmetry is that studies that evaluated less effective drugs may have chosen not to report PASI 90 and 100, while studies evaluating more effective drugs tend to report those outcomes. Therefore, publication bias can not be ruled out.

Time of assessment of outcomes may also be a limitation in the interpretation of the results. As the majority of RCT used a 12-week timeframe, extrapolation of the results for longer periods may not be appropriate.

In conclusion, this meta-analysis showed that biologics and small molecule inhibitors are highly effective for the treatment of moderate-to-severe psoriasis and that anti-IL17 drugs have the same, or even greater, efficacy than anti-TNF and anti-IL12/23 drugs when PASI 75 or PASI 90 are used as outcome. If PASI100 is used as outcome, newer drugs such as anti-IL17 tend to perform better than anti-TNF and anti-IL12/23. As the number of newer biologic and small molecule inhibitor drugs increases, the efficacy of these drugs compared to placebo, found in this meta-analysis, can help doctors to choose what is the most appropriate treatment for each particular patient.

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**Figure 1.** Flow diagram for database searches for meta-analysis of the efficacy of biologics and small molecule inhibitors for psoriasis.

**Table1.** Clinical trial identification and summary

**Figure 2.** Meta-analysis (random effects model) of the Psoriasis Area and Severity Index 75% response rate of biologic and small molecule inhibitors therapy for moderate-to-severe psoriasis in randomized, placebo controlled trials. CI, confidence interval; RD, risk difference.

**Figure 3.** Meta-analysis (random effects model) of the Psoriasis Area and Severity Index 75% response rate of all treatments combined for moderate-to-severe psoriasis in randomized, placebo controlled trials (overall pooled effect). CI, confidence interval; RD, risk difference.

**Figure 4.** Meta-analysis (random effects model) of the Psoriasis Area and Severity Index 90% response rate of biologic and small molecule inhibitor therapies therapy for moderate-to-severe psoriasis in randomized, placebo controlled trials. CI, confidence interval; RD, risk difference.

**Figure 5.** Meta-analysis (random effects model) of the Psoriasis Area and Severity Index 90% response rate of all treatments combined for moderate-to-severe psoriasis in randomized, placebo controlled trials (overall pooled effect). CI, confidence interval; RD, risk difference.

**Figure 6.** Meta-analysis (random effects model) of the Psoriasis Area and Severity Index 100% response rate of biologic and small molecule inhibitor therapies for moderate-to-severe psoriasis in randomized, placebo controlled trials. CI, confidence interval; RD, risk difference.

**Figure 7.** Meta-analysis (random effects model) of the Psoriasis Area and Severity Index 100% response rate of all treatments combined for moderate-to-severe psoriasis in randomized, placebo controlled trials (overall pooled effect). CI, confidence interval; RD, risk difference.

**Table 2.** Summary of results for drugs and doses sorted by drug class. RD: Risk difference; CI: Confidence interval; NNT: Number needed to treat.

**On line resource 1.** Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

**On line resource 2.** Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

**Online resource 3**: Funnel plot of biologic and small molecule inhibitor therapies for Psoriasis Area and Severity Index 75% response (PASI75) as primary outcome. Studies are plotted as colored symbols by effect size and standard error. SE: standard error. RD: risk difference.

**Online resource 4**: Funnel plot of biologic and small molecule inhibitor therapies for Psoriasis Area and Severity Index 90% response (PASI90) as primary outcome. Studies are plotted as colored symbols by effect size and standard error. SE: standard error. RD: risk difference.

**Online resource 5**: Funnel plot of biologic and small molecule inhibitor therapies for Psoriasis Area and Severity Index 100% response (PASI100) as primary outcome. Studies are plotted as colored symbols by effect size and standard error. SE: standard error. RD: risk difference.

**Online resource 6**: Meta-regression.

Figure 1

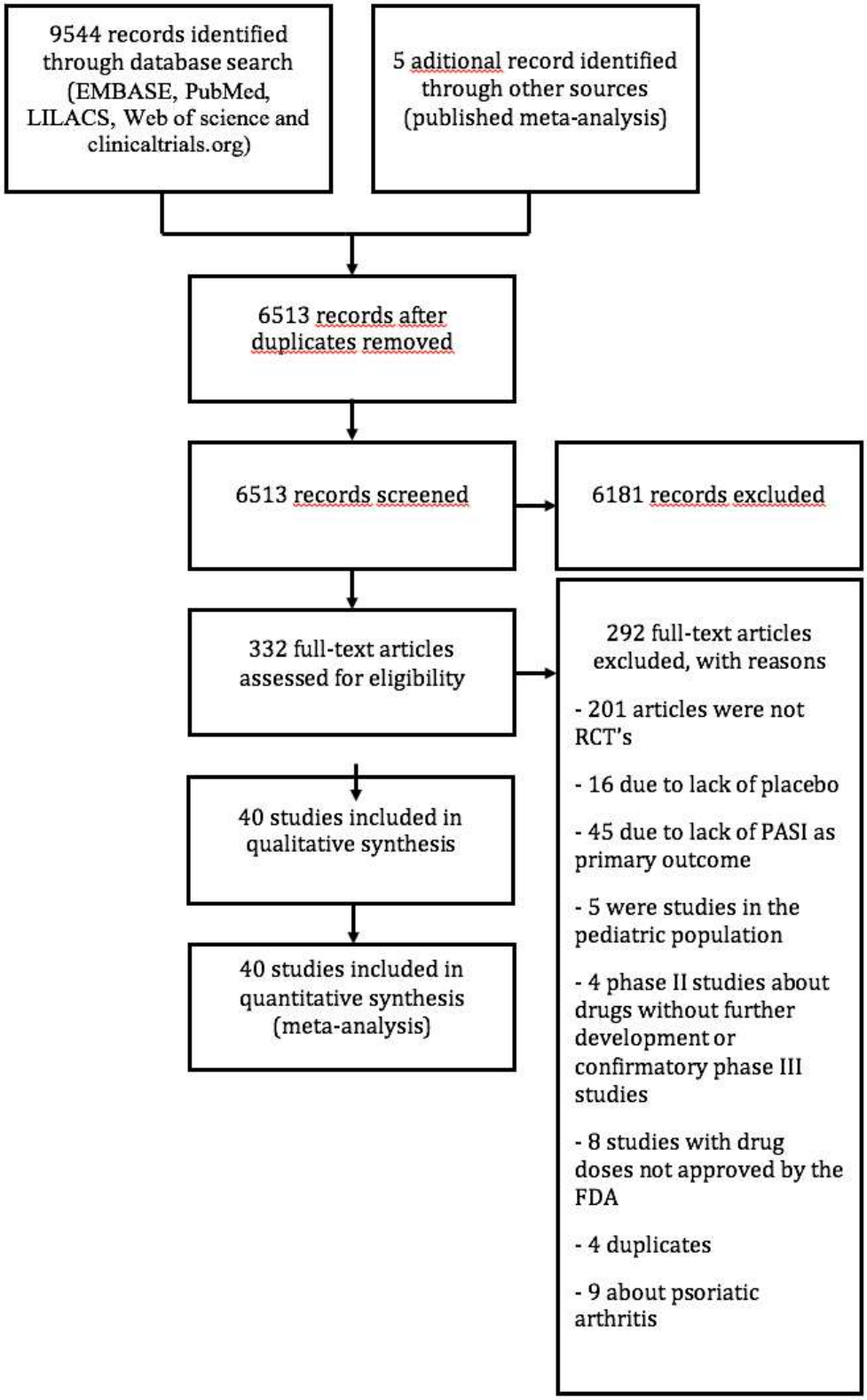

9544 records identified through database search (EMBASE, PubMed, LILACS, Web of science and clinicaltrials.org)
5 aditional record identified through other sources (published meta-analysis)
6513 records after duplicates removed
6513 records screened
6181 records excluded
332 full-text articles assessed for eligibility
292 full-text articles excluded, with reasons
- 201 articles were not RCT's
- 16 due to lack of placebo
- 45 due to lack of PASI as primary outcome
- 5 were studies in the pediatric population
- 4 phase II studies about drugs without further development or confirmatory phase III studies
- 8 studies with drug doses not approved by the FDA
- 4 duplicates
- 9 about psoriatic arthritis
40 studies included in qualitative synthesis
40 studies included in quantitative synthesis (meta-analysis)

**Figure 2.**

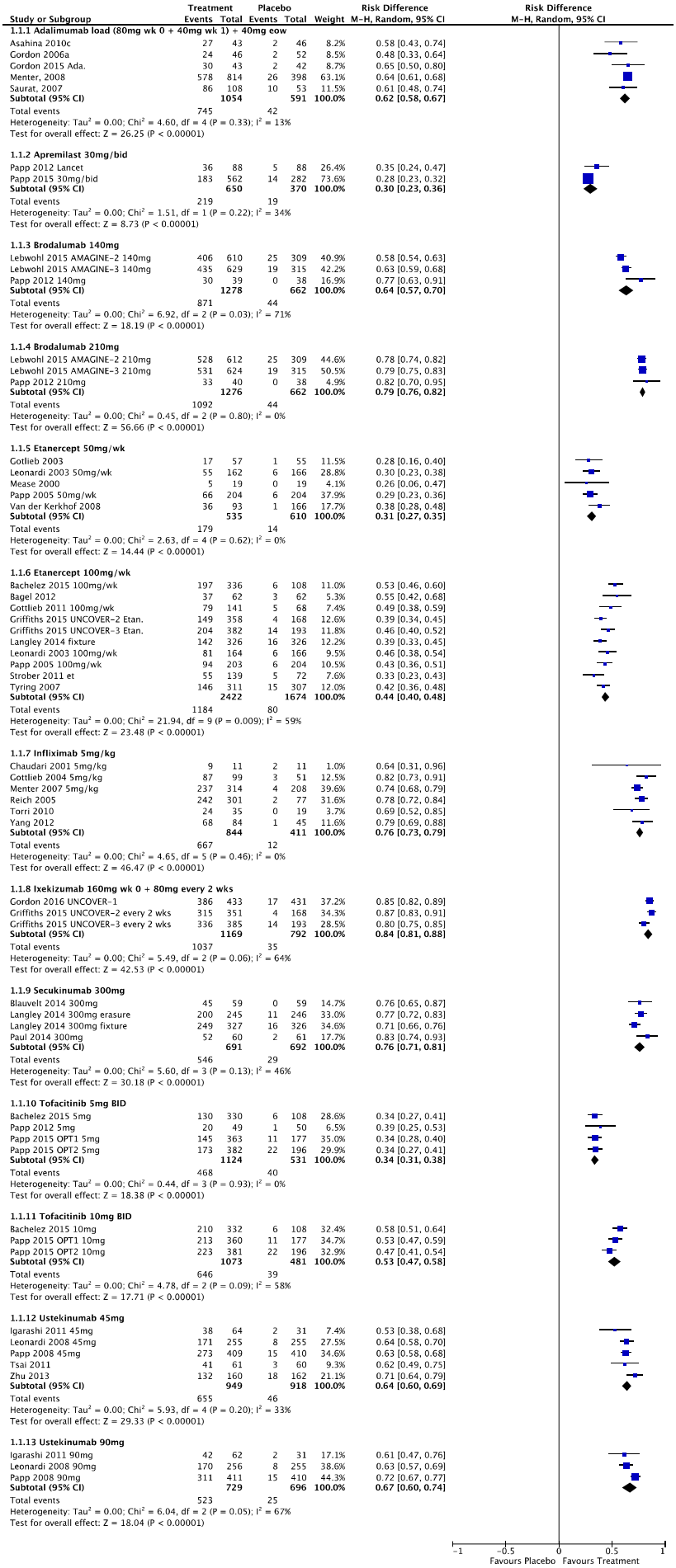

Treatment
Placebo
Risk Difference
Risk Difference
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.1.1 Adalimumab load (80mg wk 0 + 40mg wk 1) + 40mg eow
Asahina 2010c 27 43 2 46 8.2% 0.58 [0.43, 0.74]
Gordon 2006a 24 46 2 52 8.5% 0.48 [0.33, 0.64]
Gordon 2015 Ada. 30 43 2 42 8.7% 0.65 [0.50, 0.80]
Menter, 2008 578 814 26 398 63.1% 0.64 [0.61, 0.68]
Saurat, 2007 86 108 10 53 11.5% 0.61 [0.48, 0.74]
Subtotal (95% CI) 1054 591 100.0% 0.62 [0.58, 0.67]
Total events 745 42
Heterogeneity: Tau² = 0.00; Chi² = 4.60, df = 4 (P = 0.33); I² = 13%
Test for overall effect: Z = 26.25 (P < 0.00001)
1.1.2 Apremilast 30mg/bid
Papp 2012 Lancet 36 88 5 88 26.4% 0.35 [0.24, 0.47]
Papp 2015 30mg/bid 183 562 14 282 73.6% 0.28 [0.23, 0.32]
Subtotal (95% CI) 650 370 100.0% 0.30 [0.23, 0.36]
Total events 219 19
Heterogeneity: Tau² = 0.00; Chi² = 1.51, df = 1 (P = 0.22); I² = 34%
Test for overall effect: Z = 8.73 (P < 0.00001)
1.1.3 Brodalumab 140mg
Lebwohl 2015 AMAGINE-2 140mg 406 610 25 309 40.9% 0.58 [0.54, 0.63]
Lebwohl 2015 AMAGINE-3 140mg 435 629 19 315 42.2% 0.63 [0.59, 0.68]
Papp 2012 140mg 30 39 0 38 16.9% 0.77 [0.63, 0.91]
Subtotal (95% CI) 1278 662 100.0% 0.64 [0.57, 0.70]
Total events 871 44
Heterogeneity: Tau² = 0.00; Chi² = 6.92, df = 2 (P = 0.03); I² = 71%
Test for overall effect: Z = 18.19 (P < 0.00001)
1.1.4 Brodalumab 210mg
Lebwohl 2015 AMAGINE-2 210mg 528 612 25 309 44.6% 0.78 [0.74, 0.82]
Lebwohl 2015 AMAGINE-3 210mg 531 624 19 315 50.5% 0.79 [0.75, 0.83]
Papp 2012 210mg 33 40 0 38 4.9% 0.82 [0.70, 0.95]
Subtotal (95% CI) 1276 662 100.0% 0.79 [0.76, 0.82]
Total events 1092 44
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 2 (P = 0.80); I² = 0%
Test for overall effect: Z = 56.66 (P < 0.00001)
1.1.5 Etanercept 50mg/wk
Gotlieb 2003 17 57 1 55 11.5% 0.28 [0.16, 0.40]
Leonardi 2003 50mg/wk 55 162 6 166 28.8% 0.30 [0.23, 0.38]
Mease 2000 5 19 0 19 4.1% 0.26 [0.06, 0.47]
Papp 2005 50mg/wk 66 204 6 204 37.9% 0.29 [0.23, 0.36]
Van der Kerkhof 2008 36 93 1 166 17.7% 0.38 [0.28, 0.48]
Subtotal (95% CI) 535 610 100.0% 0.31 [0.27, 0.35]
Total events 179 14
Heterogeneity: Tau² = 0.00; Chi² = 2.63, df = 4 (P = 0.62); I² = 0%
Test for overall effect: Z = 14.44 (P < 0.00001)
1.1.6 Etanercept 100mg/wk
Bachelez 2015 100mg/wk 197 336 6 108 11.0% 0.53 [0.46, 0.60]
Bagel 2012 37 62 3 62 5.3% 0.55 [0.42, 0.68]
Gottlieb 2011 100mg/wk 79 141 5 68 7.4% 0.49 [0.38, 0.59]
Griffiths 2015 UNCOVER-2 Etan. 149 358 4 168 12.6% 0.39 [0.34, 0.45]
Griffiths 2015 UNCOVER-3 Etan. 204 382 14 193 11.8% 0.46 [0.40, 0.52]
Langley 2014 fixture 142 326 16 326 12.2% 0.39 [0.33, 0.45]
Leonardi 2003 100mg/wk 81 164 6 166 9.5% 0.46 [0.38, 0.54]
Papp 2005 100mg/wk 94 203 6 204 10.5% 0.43 [0.36, 0.51]
Strober 2011 et 55 139 5 72 7.6% 0.33 [0.23, 0.43]
Tyring 2007 146 311 15 307 12.0% 0.42 [0.36, 0.48]
Subtotal (95% CI) 2422 1674 100.0% 0.44 [0.40, 0.48]
Total events 1184 80
Heterogeneity: Tau² = 0.00; Chi² = 21.94, df = 9 (P = 0.009); I² = 59%
Test for overall effect: Z = 23.48 (P < 0.00001)
1.1.7 Infliximab 5mg/kg
Chaudari 2001 5mg/kg 9 11 2 11 1.0% 0.64 [0.31, 0.96]
Gottlieb 2004 5mg/kg 87 99 3 51 12.5% 0.82 [0.73, 0.91]
Menter 2007 5mg/kg 237 314 4 208 39.6% 0.74 [0.68, 0.79]
Reich 2005 242 301 2 77 31.6% 0.78 [0.72, 0.84]
Torri 2010 24 35 0 19 3.7% 0.69 [0.52, 0.85]
Yang 2012 68 84 1 45 11.6% 0.79 [0.69, 0.88]
Subtotal (95% CI) 844 411 100.0% 0.76 [0.73, 0.79]
Total events 667 12
Heterogeneity: Tau² = 0.00; Chi² = 4.65, df = 5 (P = 0.46); I² = 0%
Test for overall effect: Z = 46.47 (P < 0.00001)
1.1.8 Ixekizumab 160mg wk 0 + 80mg every 2 wks
Gordon 2016 UNCOVER-1 386 433 17 431 37.2% 0.85 [0.82, 0.89]
Griffiths 2015 UNCOVER-2 every 2 wks 315 351 4 168 34.3% 0.87 [0.83, 0.91]
Griffiths 2015 UNCOVER-3 every 2 wks 336 385 14 193 28.5% 0.80 [0.75, 0.85]
Subtotal (95% CI) 1169 792 100.0% 0.84 [0.81, 0.88]
Total events 1037 35
Heterogeneity: Tau² = 0.00; Chi² = 5.49, df = 2 (P = 0.06); I² = 64%
Test for overall effect: Z = 42.53 (P < 0.00001)
1.1.9 Secukinumab 300mg
Blauvelt 2014 300mg 45 59 0 59 14.7% 0.76 [0.65, 0.87]
Langley 2014 300mg erasure 200 245 11 246 33.0% 0.77 [0.72, 0.83]
Langley 2014 300mg fixture 249 327 16 326 34.6% 0.71 [0.66, 0.76]
Paul 2014 300mg 52 60 2 61 17.7% 0.83 [0.74, 0.93]
Subtotal (95% CI) 691 692 100.0% 0.76 [0.71, 0.81]
Total events 546 29
Heterogeneity: Tau² = 0.00; Chi² = 5.60, df = 3 (P = 0.13); I² = 46%
Test for overall effect: Z = 30.18 (P < 0.00001)
1.1.10 Tofacitinib 5mg BID
Bachelez 2015 5mg 130 330 6 108 28.6% 0.34 [0.27, 0.41]
Papp 2012 5mg 20 49 1 50 6.5% 0.39 [0.25, 0.53]
Papp 2015 OPT1 5mg 145 363 11 177 35.0% 0.34 [0.28, 0.40]
Papp 2015 OPT2 5mg 173 382 22 196 29.9% 0.34 [0.27, 0.41]
Subtotal (95% CI) 1124 531 100.0% 0.34 [0.31, 0.38]
Total events 468 40
Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 3 (P = 0.93); I² = 0%
Test for overall effect: Z = 18.38 (P < 0.00001)
1.1.11 Tofacitinib 10mg BID
Bachelez 2015 10mg 210 332 6 108 32.4% 0.58 [0.51, 0.64]
Papp 2015 OPT1 10mg 213 360 11 177 34.7% 0.53 [0.47, 0.59]
Papp 2015 OPT2 10mg 223 381 22 196 32.9% 0.47 [0.41, 0.54]
Subtotal (95% CI) 1073 481 100.0% 0.53 [0.47, 0.58]
Total events 646 39
Heterogeneity: Tau² = 0.00; Chi² = 4.78, df = 2 (P = 0.09); I² = 58%
Test for overall effect: Z = 17.71 (P < 0.00001)
1.1.12 Ustekinumab 45mg
Igarashi 2011 45mg 38 64 2 31 7.4% 0.53 [0.38, 0.68]
Leonardi 2008 45mg 171 255 8 255 27.5% 0.64 [0.58, 0.70]
Papp 2008 45mg 273 409 15 410 34.6% 0.63 [0.58, 0.68]
Tsai 2011 41 61 3 60 9.3% 0.62 [0.49, 0.75]
Zhu 2013 132 160 18 162 21.1% 0.71 [0.64, 0.79]
Subtotal (95% CI) 949 918 100.0% 0.64 [0.60, 0.69]
Total events 655 46
Heterogeneity: Tau² = 0.00; Chi² = 5.93, df = 4 (P = 0.20); I² = 33%
Test for overall effect: Z = 29.33 (P < 0.00001)
1.1.13 Ustekinumab 90mg
Igarashi 2011 90mg 42 62 2 31 17.1% 0.61 [0.47, 0.76]
Leonardi 2008 90mg 170 256 8 255 38.6% 0.63 [0.57, 0.69]
Papp 2008 90mg 311 411 15 410 44.3% 0.72 [0.67, 0.77]
Subtotal (95% CI) 729 696 100.0% 0.67 [0.60, 0.74]
Total events 523 25
Heterogeneity: Tau² = 0.00; Chi² = 6.04, df = 2 (P = 0.05); I² = 67%
Test for overall effect: Z = 18.04 (P < 0.00001)
-1
-0.5
0
0.5
1
Favours Placebo
Favours Treatment

**Figure 3.**

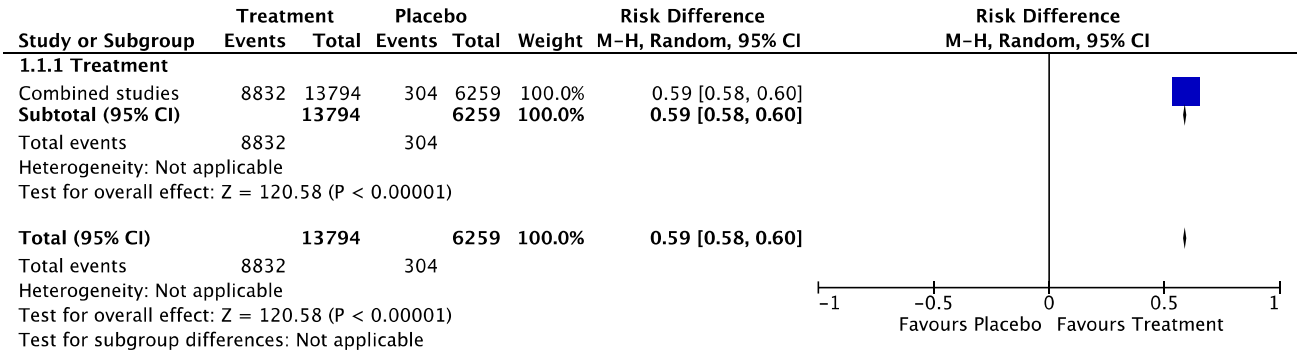

Treatment
Placebo
Risk Difference
Risk Difference
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
1.1.1 Treatment
Combined studies 8832 13794 304 6259 100.0% 0.59 [0.58, 0.60]
Subtotal (95% CI) 13794 6259 100.0% 0.59 [0.58, 0.60]
Total events 8832 304
Heterogeneity: Not applicable
Test for overall effect: Z = 120.58 (P < 0.00001)
Total (95% CI) 13794 6259 100.0% 0.59 [0.58, 0.60]
Total events 8832 304
Heterogeneity: Not applicable
Test for overall effect: Z = 120.58 (P < 0.00001)
Test for subgroup differences: Not applicable
-1
-0.5
0
0.5
1
Favours Placebo
Favours Treatment

Figure 4

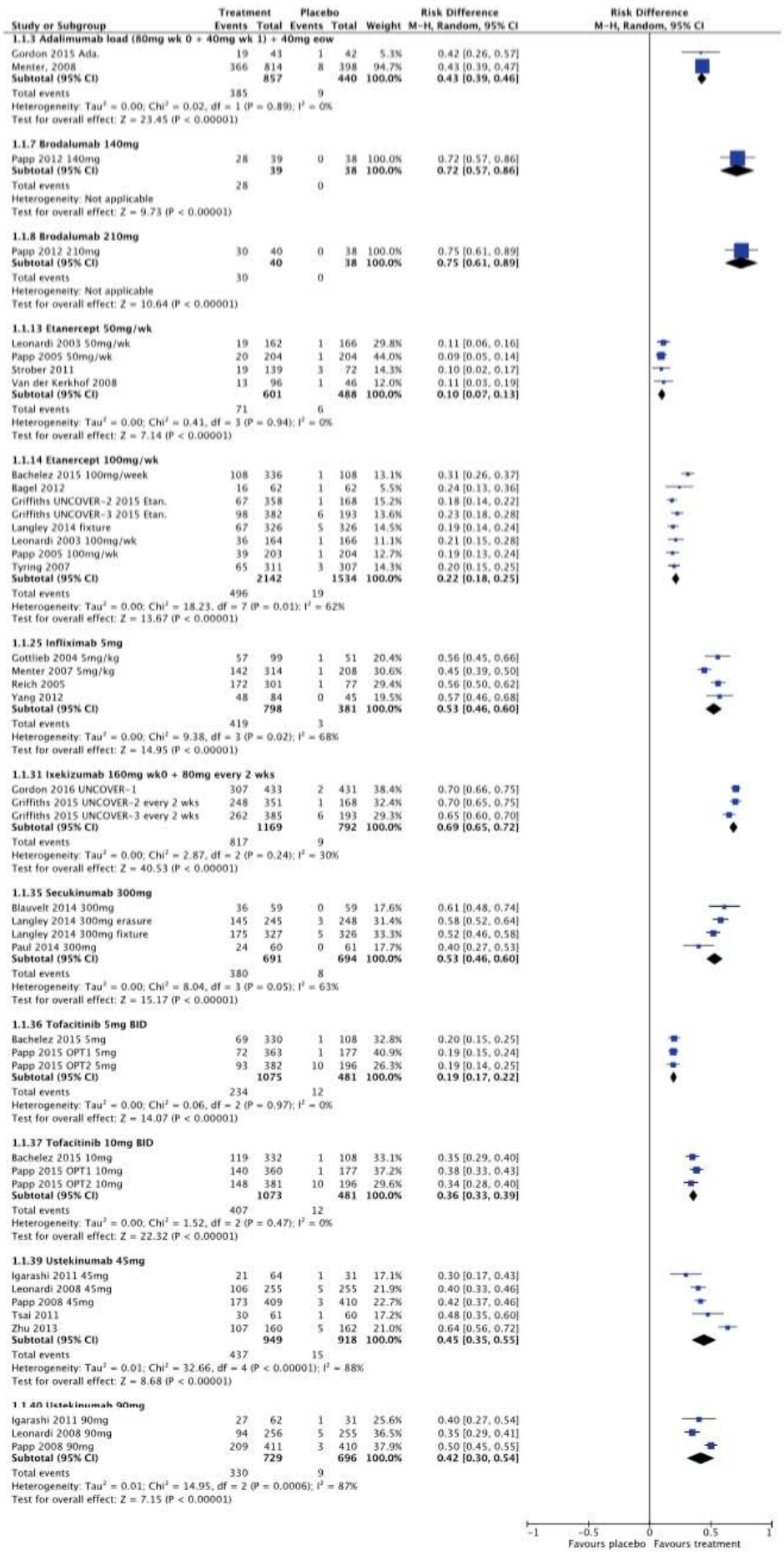

Treatment
Placebo
Risk Difference
Risk Difference
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.1.3 Adalimumab load (80mg wk 0 + 40mg wk 1) + 40mg eow
Gordon 2015 Ada. 19 43 1 42 5.3% 0.42 [0.26, 0.57]
Menter, 2008 366 814 8 398 94.7% 0.43 [0.39, 0.47]
Subtotal (95% CI) 857 440 100.0% 0.43 [0.39, 0.46]
Total events 385 9
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 23.45 (P < 0.00001)
1.1.7 Brodalumab 140mg
Papp 2012 140mg 28 39 0 38 100.0% 0.72 [0.57, 0.86]
Subtotal (95% CI) 39 38 100.0% 0.72 [0.57, 0.86]
Total events 28 0
Heterogeneity: Not applicable
Test for overall effect: Z = 9.73 (P < 0.00001)
1.1.8 Brodalumab 210mg
Papp 2012 210mg 30 40 0 38 100.0% 0.75 [0.61, 0.89]
Subtotal (95% CI) 40 38 100.0% 0.75 [0.61, 0.89]
Total events 30 0
Heterogeneity: Not applicable
Test for overall effect: Z = 10.64 (P < 0.00001)
1.1.13 Etanercept 50mg/wk
Leonardi 2003 50mg/wk 19 162 1 166 29.8% 0.11 [0.06, 0.16]
Papp 2005 50mg/wk 20 204 1 204 44.0% 0.09 [0.05, 0.14]
Strober 2011 19 139 3 72 14.3% 0.10 [0.02, 0.17]
Van der Kerkhof 2008 13 96 1 46 12.0% 0.11 [0.03, 0.19]
Subtotal (95% CI) 601 488 100.0% 0.10 [0.07, 0.13]
Total events 71 6
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 3 (P = 0.94); I² = 0%
Test for overall effect: Z = 7.14 (P < 0.00001)
1.1.14 Etanercept 100mg/wk
Bachelez 2015 100mg/week 108 336 1 108 13.1% 0.31 [0.26, 0.37]
Bagel 2012 16 62 1 62 5.5% 0.24 [0.13, 0.36]
Griffiths UNCOVER-2 2015 Etan. 67 358 1 168 15.2% 0.18 [0.14, 0.22]
Griffiths UNCOVER-3 2015 Etan. 98 382 6 193 13.6% 0.23 [0.18, 0.28]
Langley 2014 fixture 67 326 5 326 14.5% 0.19 [0.14, 0.24]
Leonardi 2003 100mg/wk 36 164 1 166 11.1% 0.21 [0.15, 0.28]
Papp 2005 100mg/wk 39 203 1 204 12.7% 0.19 [0.13, 0.24]
Tyring 2007 65 311 3 307 14.3% 0.20 [0.15, 0.25]
Subtotal (95% CI) 2142 1534 100.0% 0.22 [0.18, 0.25]
Total events 496 19
Heterogeneity: Tau² = 0.00; Chi² = 18.23, df = 7 (P = 0.01); I² = 62%
Test for overall effect: Z = 13.67 (P < 0.00001)
1.1.25 Infliximab 5mg
Gottlieb 2004 5mg/kg 57 99 1 51 20.4% 0.56 [0.45, 0.66]
Menter 2007 5mg/kg 142 314 1 208 30.6% 0.45 [0.39, 0.50]
Reich 2005 172 301 1 77 29.4% 0.56 [0.50, 0.62]
Yang 2012 48 84 0 45 19.5% 0.57 [0.46, 0.68]
Subtotal (95% CI) 798 381 100.0% 0.53 [0.46, 0.60]
Total events 419 3
Heterogeneity: Tau² = 0.00; Chi² = 9.38, df = 3 (P = 0.02); I² = 68%
Test for overall effect: Z = 14.95 (P < 0.00001)
1.1.31 Ixekizumab 160mg wk0 + 80mg every 2 wks
Gordon 2016 UNCOVER-1 307 433 2 431 38.4% 0.70 [0.66, 0.75]
Griffiths 2015 UNCOVER-2 every 2 wks 248 351 1 168 32.4% 0.70 [0.65, 0.75]
Griffiths 2015 UNCOVER-3 every 2 wks 262 385 6 193 29.3% 0.65 [0.60, 0.70]
Subtotal (95% CI) 1169 792 100.0% 0.69 [0.65, 0.72]
Total events 817 9
Heterogeneity: Tau² = 0.00; Chi² = 2.87, df = 2 (P = 0.24); I² = 30%
Test for overall effect: Z = 40.53 (P < 0.00001)
1.1.35 Secukinumab 300mg
Blauvelt 2014 300mg 36 59 0 59 17.6% 0.61 [0.48, 0.74]
Langley 2014 300mg erasure 145 245 3 248 31.4% 0.58 [0.52, 0.64]
Langley 2014 300mg fixture 175 327 5 326 33.3% 0.52 [0.46, 0.58]
Paul 2014 300mg 24 60 0 61 17.7% 0.40 [0.27, 0.53]
Subtotal (95% CI) 691 694 100.0% 0.53 [0.46, 0.60]
Total events 380 8
Heterogeneity: Tau² = 0.00; Chi² = 8.04, df = 3 (P = 0.05); I² = 63%
Test for overall effect: Z = 15.17 (P < 0.00001)
1.1.36 Tofacitinib 5mg BID
Bachelez 2015 5mg 69 330 1 108 32.8% 0.20 [0.15, 0.25]
Papp 2015 OPT1 5mg 72 363 1 177 40.9% 0.19 [0.15, 0.24]
Papp 2015 OPT2 5mg 93 382 10 196 26.3% 0.19 [0.14, 0.25]
Subtotal (95% CI) 1075 481 100.0% 0.19 [0.17, 0.22]
Total events 234 12
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 14.07 (P < 0.00001)
1.1.37 Tofacitinib 10mg BID
Bachelez 2015 10mg 119 332 1 108 33.1% 0.35 [0.29, 0.40]
Papp 2015 OPT1 10mg 140 360 1 177 37.2% 0.38 [0.33, 0.43]
Papp 2015 OPT2 10mg 148 381 10 196 29.6% 0.34 [0.28, 0.40]
Subtotal (95% CI) 1073 481 100.0% 0.36 [0.33, 0.39]
Total events 407 12
Heterogeneity: Tau² = 0.00; Chi² = 1.52, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 22.32 (P < 0.00001)
1.1.39 Ustekinumab 45mg
Igarashi 2011 45mg 21 64 1 31 17.1% 0.30 [0.17, 0.43]
Leonardi 2008 45mg 106 255 5 255 21.9% 0.40 [0.33, 0.46]
Papp 2008 45mg 173 409 3 410 22.7% 0.42 [0.37, 0.46]
Tsai 2011 30 61 1 60 17.2% 0.48 [0.35, 0.60]
Zhu 2013 107 160 5 162 21.0% 0.64 [0.56, 0.72]
Subtotal (95% CI) 949 918 100.0% 0.45 [0.35, 0.55]
Total events 437 15
Heterogeneity: Tau² = 0.01; Chi² = 32.66, df = 4 (P < 0.00001); I² = 88%
Test for overall effect: Z = 8.68 (P < 0.00001)
1.1.40 Ustekinumab 90mg
Igarashi 2011 90mg 27 62 1 31 25.6% 0.40 [0.27, 0.54]
Leonardi 2008 90mg 94 256 5 255 36.5% 0.35 [0.29, 0.41]
Papp 2008 90mg 209 411 3 410 37.9% 0.50 [0.45, 0.55]
Subtotal (95% CI) 729 696 100.0% 0.42 [0.30, 0.54]
Total events 330 9
Heterogeneity: Tau² = 0.01; Chi² = 14.95, df = 2 (P = 0.0006); I² = 87%
Test for overall effect: Z = 7.15 (P < 0.00001)
-1
-0.5
0
0.5
1
Favours placebo
Favours treatment

Figure 5.

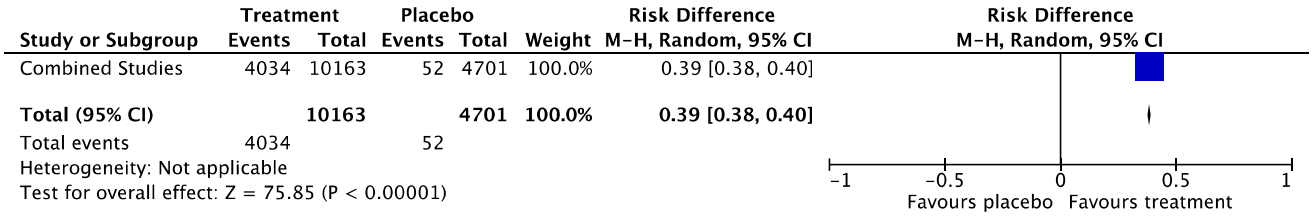

Treatment
Placebo
Risk Difference
Risk Difference
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
Combined Studies
4034
10163
52
4701
100.0%
0.39 [0.38, 0.40]
Total (95% CI)
10163
4701
100.0%
0.39 [0.38, 0.40]
Total events
4034
52
Heterogeneity: Not applicable
Test for overall effect: Z = 75.85 (P < 0.00001)
-1
-0.5
0
0.5
1
Favours placebo
Favours treatment

Figure 6.

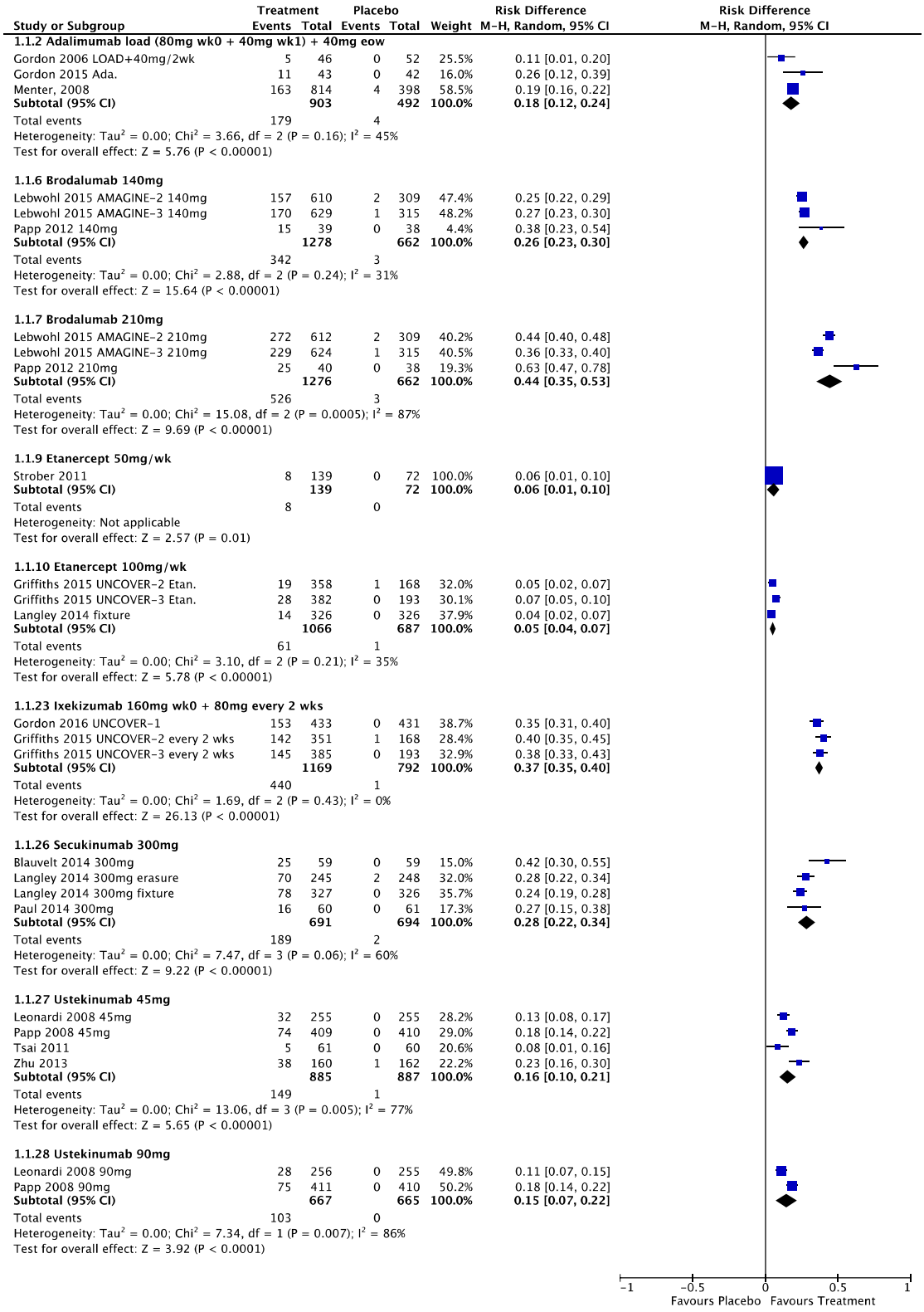
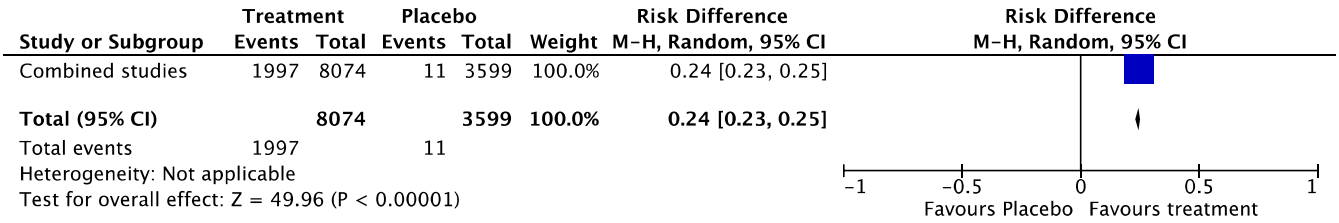
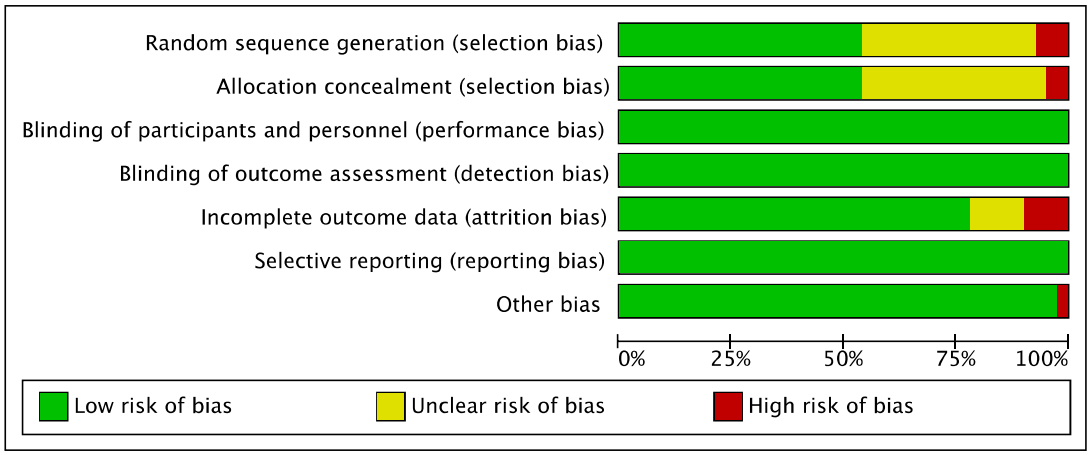

Treatment
Placebo
Risk Difference
Risk Difference
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.1.2 Adalimumab load (80mg wk0 + 40mg wk1) + 40mg eow
Gordon 2006 LOAD+40mg/2wk 5 46 0 52 25.5% 0.11 [0.01, 0.20]
Gordon 2015 Ada. 11 43 0 42 16.0% 0.26 [0.12, 0.39]
Menter, 2008 163 814 4 398 58.5% 0.19 [0.16, 0.22]
Subtotal (95% CI) 903 492 100.0% 0.18 [0.12, 0.24]
Total events 179 4
Heterogeneity: Tau² = 0.00; Chi² = 3.66, df = 2 (P = 0.16); I² = 45%
Test for overall effect: Z = 5.76 (P < 0.00001)
1.1.6 Brodalumab 140mg
Lebwohl 2015 AMAGINE-2 140mg 157 610 2 309 47.4% 0.25 [0.22, 0.29]
Lebwohl 2015 AMAGINE-3 140mg 170 629 1 315 48.2% 0.27 [0.23, 0.30]
Papp 2012 140mg 15 39 0 38 4.4% 0.38 [0.23, 0.54]
Subtotal (95% CI) 1278 662 100.0% 0.26 [0.23, 0.30]
Total events 342 3
Heterogeneity: Tau² = 0.00; Chi² = 2.88, df = 2 (P = 0.24); I² = 31%
Test for overall effect: Z = 15.64 (P < 0.00001)
1.1.7 Brodalumab 210mg
Lebwohl 2015 AMAGINE-2 210mg 272 612 2 309 40.2% 0.44 [0.40, 0.48]
Lebwohl 2015 AMAGINE-3 210mg 229 624 1 315 40.5% 0.36 [0.33, 0.40]
Papp 2012 210mg 25 40 0 38 19.3% 0.63 [0.47, 0.78]
Subtotal (95% CI) 1276 662 100.0% 0.44 [0.35, 0.53]
Total events 526 3
Heterogeneity: Tau² = 0.00; Chi² = 15.08, df = 2 (P = 0.0005); I² = 87%
Test for overall effect: Z = 9.69 (P < 0.00001)
1.1.9 Etanercept 50mg/wk
Strober 2011 8 139 0 72 100.0% 0.06 [0.01, 0.10]
Subtotal (95% CI) 139 72 100.0% 0.06 [0.01, 0.10]
Total events 8 0
Heterogeneity: Not applicable
Test for overall effect: Z = 2.57 (P = 0.01)
1.1.10 Etanercept 100mg/wk
Griffiths 2015 UNCOVER-2 Etan. 19 358 1 168 32.0% 0.05 [0.02, 0.07]
Griffiths 2015 UNCOVER-3 Etan. 28 382 0 193 30.1% 0.07 [0.05, 0.10]
Langley 2014 fixture 14 326 0 326 37.9% 0.04 [0.02, 0.07]
Subtotal (95% CI) 1066 687 100.0% 0.05 [0.04, 0.07]
Total events 61 1
Heterogeneity: Tau² = 0.00; Chi² = 3.10, df = 2 (P = 0.21); I² = 35%
Test for overall effect: Z = 5.78 (P < 0.00001)
1.1.23 Ixekizumab 160mg wk0 + 80mg every 2 wks
Gordon 2016 UNCOVER-1 153 433 0 431 38.7% 0.35 [0.31, 0.40]
Griffiths 2015 UNCOVER-2 every 2 wks 142 351 1 168 28.4% 0.40 [0.35, 0.45]
Griffiths 2015 UNCOVER-3 every 2 wks 145 385 0 193 32.9% 0.38 [0.33, 0.43]
Subtotal (95% CI) 1169 792 100.0% 0.37 [0.35, 0.40]
Total events 440 1
Heterogeneity: Tau² = 0.00; Chi² = 1.69, df = 2 (P = 0.43); I² = 0%
Test for overall effect: Z = 26.13 (P < 0.00001)
1.1.26 Secukinumab 300mg
Blauvelt 2014 300mg 25 59 0 59 15.0% 0.42 [0.30, 0.55]
Langley 2014 300mg erasure 70 245 2 248 32.0% 0.28 [0.22, 0.34]
Langley 2014 300mg fixture 78 327 0 326 35.7% 0.24 [0.19, 0.28]
Paul 2014 300mg 16 60 0 61 17.3% 0.27 [0.15, 0.38]
Subtotal (95% CI) 691 694 100.0% 0.28 [0.22, 0.34]
Total events 189 2
Heterogeneity: Tau² = 0.00; Chi² = 7.47, df = 3 (P = 0.06); I² = 60%
Test for overall effect: Z = 9.22 (P < 0.00001)
1.1.27 Ustekinumab 45mg
Leonardi 2008 45mg 32 255 0 255 28.2% 0.13 [0.08, 0.17]
Papp 2008 45mg 74 409 0 410 29.0% 0.18 [0.14, 0.22]
Tsai 2011 5 61 0 60 20.6% 0.08 [0.01, 0.16]
Zhu 2013 38 160 1 162 22.2% 0.23 [0.16, 0.30]
Subtotal (95% CI) 885 887 100.0% 0.16 [0.10, 0.21]
Total events 149 1
Heterogeneity: Tau² = 0.00; Chi² = 13.06, df = 3 (P = 0.005); I² = 77%
Test for overall effect: Z = 5.65 (P < 0.00001)
1.1.28 Ustekinumab 90mg
Leonardi 2008 90mg 28 256 0 255 49.8% 0.11 [0.07, 0.15]
Papp 2008 90mg 75 411 0 410 50.2% 0.18 [0.14, 0.22]
Subtotal (95% CI) 667 665 100.0% 0.15 [0.07, 0.22]
Total events 103 0
Heterogeneity: Tau² = 0.00; Chi² = 7.34, df = 1 (P = 0.007); I² = 86%
Test for overall effect: Z = 3.92 (P < 0.0001)
-1
-0.5
0
0.5
1
Favours Placebo
Favours Treatment

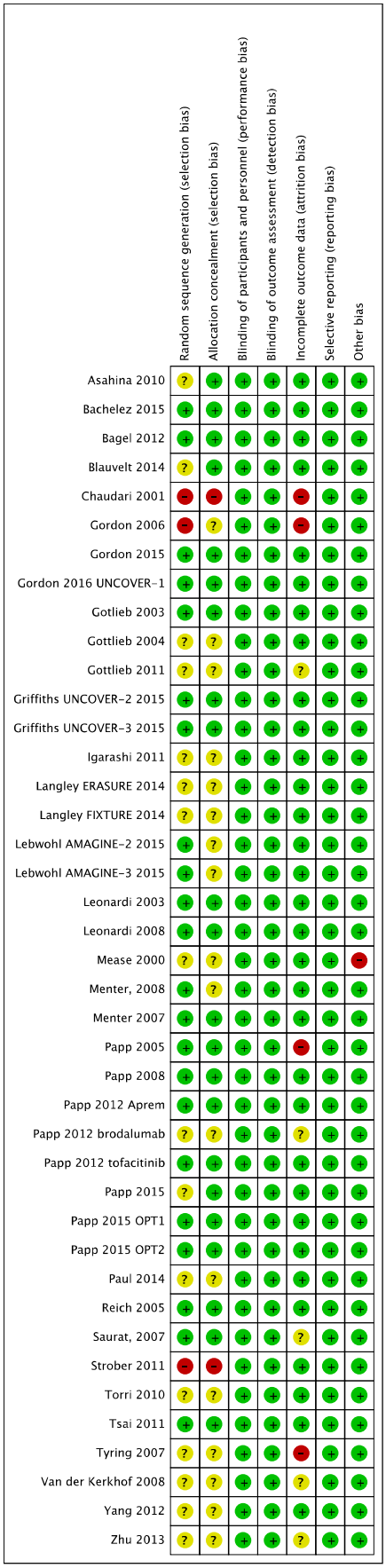
Figure 7.


Treatment
Placebo
Risk Difference
Risk Difference
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Combined studies 1997 8074 11 3599 100.0% 0.24 [0.23, 0.25]
Total (95% CI) 8074 3599 100.0% 0.24 [0.23, 0.25]
Total events 1997 11
Heterogeneity: Not applicable
Test for overall effect: Z = 49.96 (P < 0.00001)
-1
-0.5
0
0.5
1
Favours Placebo
Favours treatment

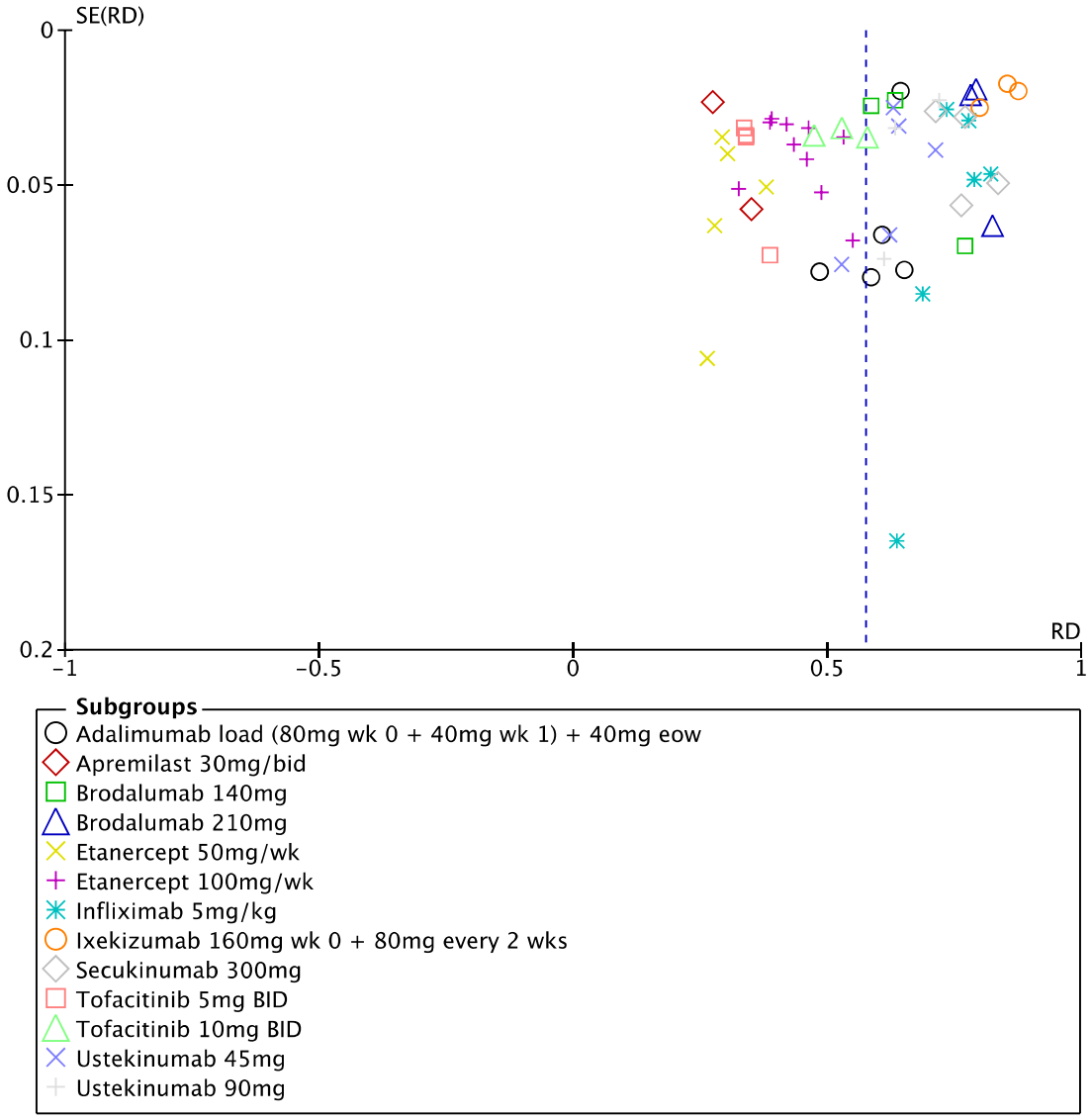
Online resource 1.



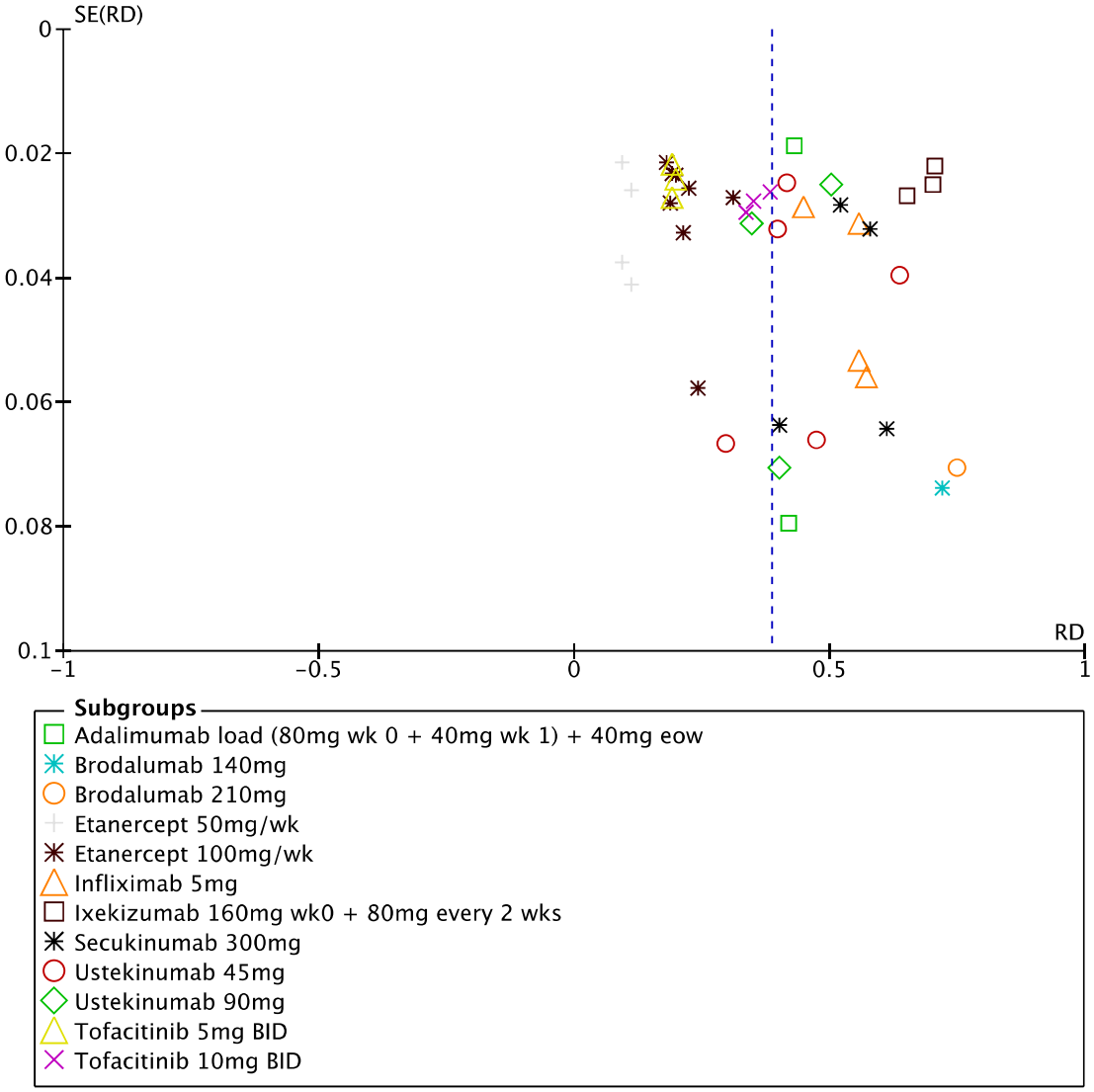
Online resource 2.



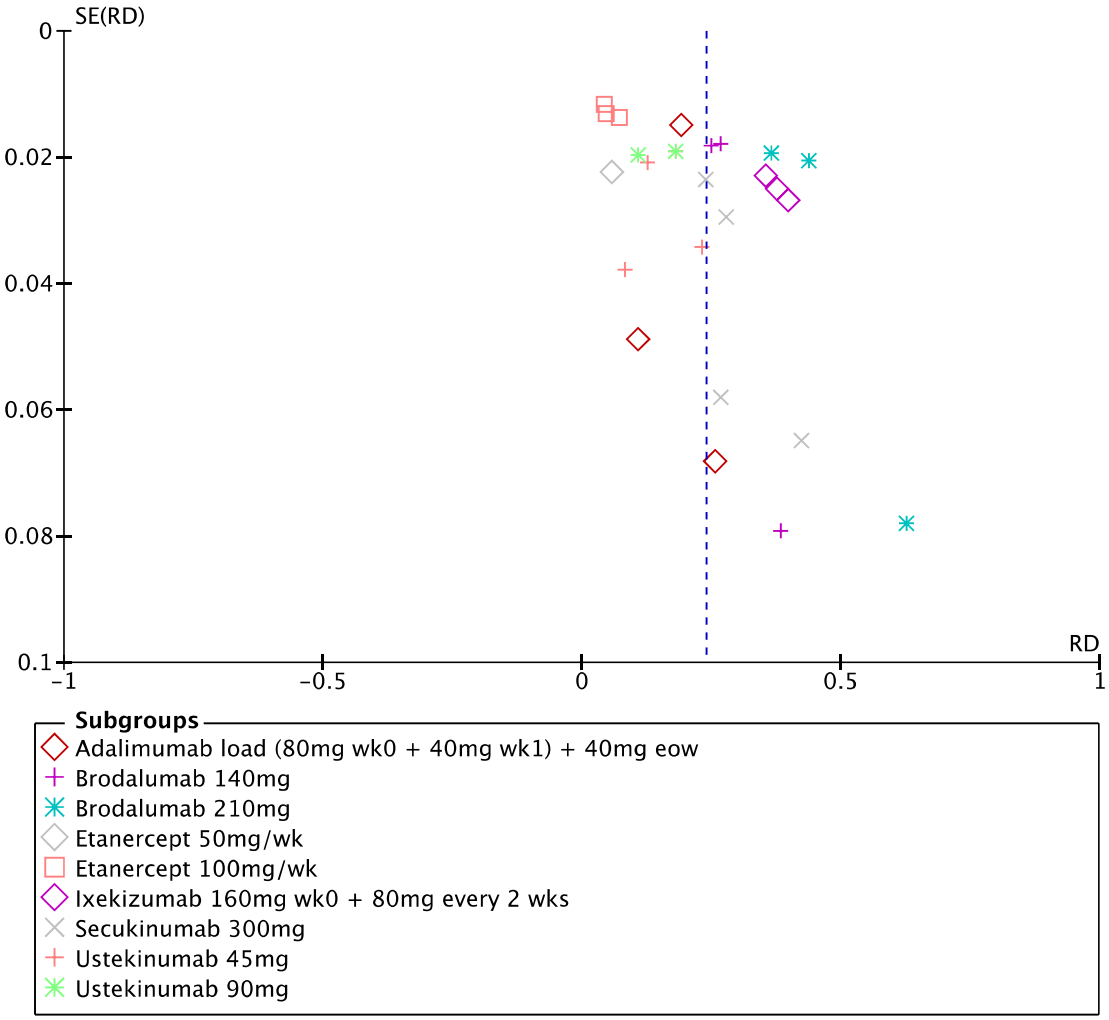
Online resource 3.



Online resource 4.



Online resource 5.



Online resource 6.

| | Pooled risk difference (95% confidence interval) | % heterogeneity explained | N |
|---|---|---|---|
| Mean PASI* >= 20 | | | |
| No | 0.56 (0.48; 0.63) | 6.03 | 24 |
| Yes | 12.52 (10.19; 15.38) | | 33 |
| Previous use of biologics/SMID# | | | |
| YES | 0.59 (0.53; 0.65) | | 39 |
| NO | 0.50 (0.37; 0.63) | 2.49 | 11 |
| Not Disclosed | 0.48 (0.34; 0.62) | | 7 |
| Duration of disease >= 17,8 years | | | |
| No | 0.56 (0.48; 0.63) | 0.00 | 24 |
| Yes | 0.56 (0.49; 0.63) | | 33 |

*PASI: Psoriasis Area and Severity Index;

# SMID: small molecule inhibitor drugs

## Table 1. Clinical trial identification and summary categorized by drug*

| DRUG | AUTHOR, YEAR | INTERVENTION/ COMPARATOR | N OF PTS RANDOMIZED (TOTAL PTS) | TOTAL TRIAL DURATION (wks) | MEAN DISEASE DURATION (years) | PTS MEAN AGE | MEAN BASE LINE PASI | PRIMARY OUTCOME MEASURE /PRIMARY ENDPOINT | N PTS ACHIEVING PASI 50 | N PTS ACHIEVING PASI 75 | N PTS ACHIEVING PASI 90 | N PTS ACHIEVING PASI 100 | PRIOR IMMUNOBIOLOGIC TREATMENT/ CONCOMITANT SYSTEMIC MEDICATION@ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Adalimumab** | Asahina, 2010 [22] | Adalimumab sc (40mg eow)¶ | 38 (169) | 24 | 14,2 | 47,8 | 25,4 | PASI75/wk16 | 28 | 22 | 14 | ND | No/No |
| | | Adalimumab sc (80mg wk 0 + 40mg eow starting wk 1) | 43 (169) | 24 | 14 | 44,2 | 30,2 | PASI75/wk16 | 35 | 27 | 17 | ND | No/No |
| | | Adalimumab sc (80mg eow)¶ | 42 (169) | 24 | 11,6 | 43,5 | 28,2 | PASI75/wk16 | 38 | 34 | 26 | ND | No/No |
| | | Placebo | 46 (169) | 24 | 15,5 | 43,9 | 29,1 | PASI75/wk16 | 9 | 2 | 0 | ND | No/No |
| | Gordon, 2006 [5] | Adalimumab 40mg sc (80mg wk 0 + 40mg eow starting week 1) | 46 (148) | 60 | 21 | 46 | 16,7 | PASI75/wk12 | ND | 24 | ND | 5 | ND/No |
| | | Adalimumab 40mg sc (80mg wk 0 and 1 + 40mg/wk starting wk 2)¶ | 50 (148) | 60 | 18 | 44 | 14,5 | PASI75/wk12 | ND | 40 | ND | 13 | ND/No |
| | | Adalimumab 40mg sc (80mg wk 0 and 1 + 40mg/wk starting wk 2)¶ | 50 (148) | 60 | 18 | 44 | 14,5 | PASI75/wk12 | ND | 40 | ND | 13 | ND/No |
| | | Placebo | 52 (148) | 60 | 19 | 43 | 16 | PASI75/wk12 | ND | 2 | ND | 0 | ND/No |
| | Gordon 2015 [48] | Guselkumab 200mg sc (wk 0, 4 and every 12 weeks)¶ | 42(293) | 52 | 19,4 | 46 | 19,4 | PASI75/wk16 | ND | 34 | 24 | 12 | 20(42)/ND |
| | | Guselkumab 100mg sc (every 8 weeks)¶ | 42(293) | 52 | 18,3 | 41,5 | 20,4 | PASI75/wk16 | ND | 33 | 26 | 14 | 17(42)/ ND |
| | | Guselkumab 50mg sc (wk 0, 4 and every 12 weeks)¶ | 42(293) | 52 | 18 | 44,5 | 22,3 | PASI75/wk16 | ND | 34 | 19 | 8 | 15(42)/ND |
| | | Guselkumab 15mg sc (every 8 weeks)¶ | 41(293) | 52 | 17,3 | 45 | 21,5 | PASI75/wk16 | ND | 31 | 14 | 5 | 14(41)/ND |
| | | Guselkumab 5mg sc (wk 0, 4 and every 12 weeks)¶ | 41(293) | 52 | 19.5 | 43 | 20.9 | PASI75/wk16 | ND | 18 | 14 | 4 | 19(41)/ND |
| | | Adalimumab sc (80mg wk0 and 1, then eow) | 43(293) | 52 | 19,3 | 50 | 20,2 | PASI75/wk16 | ND | 30 | 19 | 11 | 26(43)/ND |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Placebo | 42(293) | 52 | 18 | 46,5 | 21,8 | PASI75/wk16 | ND | 2 | 1 | 0 | 15(42)/ |
| | Menter, 2008 [32] | Adalimumab 40mg sc (80mg wk 0 and 40mg eow starting week 1) | 814 (1212) | 52 | 18,1 | 44.1 | 19 | PASI75/wk16 | ND | 578 | 366 | 163 | 97 (814)/No |
| | | Placebo | 398 (1212) | 52 | 18,4 | 45.4 | 18,8 | PASI75/wk16 | ND | 26 | 8 | 4 | 53 (398)/No |
| | Saurat, 2007 [39] | Adalimumab 40mg sc (80mg wk 0 + 40mg eow starting wk 1) | 108(271) | 16 | 17,9 | 42,9 | 20,2 | PASI75/wk16 | 95 | 86 | 55 | 18 | No/No |
| | | Methotrexate oral (7,5mg until 25mg/wk)¶ | 110(271) | 16 | 18,9 | 41,6 | 19,4 | PASI75/wk16 | 68 | 39 | 15 | 8 | No/No |
| | | Placebo | 53(271) | 16 | 18,8 | 40,7 | 19,2 | PASI75/wk16 | 16 | 10 | 6 | 1 | No/No |
| **Apremilast** | Papp, 2012 [7] | Apremilast 10mg oral bid¶ | 89 (352) | 24 | 18 | 44,4 | 18,1 | PASI75/wk16 | ND | 10 | ND | ND | ND/No |
| | | Apremilast 20mg oral bid¶ | 87 (352) | 24 | 19,2 | 44,6 | 18,5 | PASI75/wk16 | ND | 25 | ND | ND | ND/No |
| | | Apremilast 30mg oral bid | 88 (352) | 24 | 19,2 | 44,1 | 19,1 | PASI75/wk16 | ND | 36 | ND | ND | ND/No |
| | | Placebo | 88 (352) | 24 | 19,6 | 44,1 | 18,1 | PASI75/wk16 | ND | 5 | ND | ND | ND/No |
| | Papp, 2015 [35] | Apremilast 30mg BID | 562(844) | 52 | 19,8 | 45,8 | 18,7 | PASI75/wk16 | ND | 183 | 55 | ND | 162(562)/No |
| | | Placebo | 282(844) | 52 | 18,7 | 46,5 | 19,4 | PASI75/wk16 | ND | 14 | 1 | ND | 80(282)/No |
| **Brodalumab** | Lebwohl, 2015 Amagine2[21] | Brodalumab 210mg sc eow | 612(1831) | 52 | 19 | 45 | 18,6 | PASI75/wk12 | ND | 528 | ND | 272 | 177 (612)/ No |
| | | Brodalumab 140mg sc eow | 610(1831) | 52 | 19 | 45 | 18,9 | PASI75/wk12 | ND | 406 | ND | 157 | 179(610)/ No |
| | | Ustekinumab | 300(1831) | 52 | 19 | 45 | 18,9 | PASI75/wk12 | ND | 210 | ND | 65 | 84(300)/No |
| | | Placebo | 309(1831) | 52 | 18 | 44 | 18,6 | PASI75/wk12 | ND | 25 | ND | 2 | 90(309)/No |
| | Lebwohl, 2015 Amagine3[21] | Brodalumab 210mg sc (wks 0,1,2,4,6,8,and 10) | 624(1881) | 52 | 18 | 45 | 18,7 | PASI75/wk12 | ND | 531 | ND | 229 | 157(624)/Yes |
| | | Brodalumab 140mg sc (wks 0,1,2,4,6,8,and 10) | 629(1881) | 52 | 17 | 45 | 18,1 | PASI75/wk12 | ND | 435 | ND | 170 | 160(629)/Yes |
| | | Ustekinumab | 313(1881) | 52 | 18 | 45 | 18,7 | PASI75/wk12 | ND | 217 | ND | 58 | 75(313)/Yes |
| | | Placebo | 315(1881) | 52 | 18 | 44 | 19 | PASI75/wk12 | ND | 19 | ND | 1 | 76(315)/Yes |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Papp, 2012[11] | Brodalumab 70mg sc (wks 0,1,2,4,6,8,and 10)¶ | 39 (198) | 12 | 20,7 | 42,1 | 18,8 | PASI75/wk12 | 20 | 13 | 7 | 4 | 16(39)/No |
| | | Brodalumab 140mg sc (wks 0,1,2,4,6,8,and 10) | 39 (198) | 12 | 19,2 | 44 | 19,4 | PASI75/wk12 | 35 | 30 | 28 | 15 | 10(39)/No |
| | | Brodalumab 210mg sc (wks 0,1,2,4,6,8,and 10) | 40 (198) | 12 | 17,1 | 42,1 | 20,6 | PASI75/wk12 | 36 | 33 | 30 | 25 | 17(40)/No |
| | | Brodalumab 280mg sc monthly¶ | 42 (198) | 12 | 19,3 | 42,3 | 17,9 | PASI75/wk12 | 34 | 28 | 24 | 12 | 19(42)/No |
| | | Placebo | 38 (198) | 12 | 18,3 | 41,8 | 18,9 | PASI75/wk12 | 6 | 0 | 0 | 0 | 16(38)/No |
| **Etanercept** | Bachelez, 2015[45] | Tofacitinib 5mg bid | 330 (1106) | 12 | 16 | 44 | 21 | PASI75/wk12 | 216 | 130 | 69 | ND | 35(330)/No |
| | | Tofacitinib 10mg bid | 332 (1106) | 12 | 17 | 44 | 21 | PASI75/wk12 | 266 | 210 | 119 | ND | 29 (332)/ No |
| | | Etanercept 100mg/wk | 336 (1106) | 12 | 18 | 42 | 19,4 | PASI75/wk12 | 269 | 197 | 108 | ND | 37(336)/ No |
| | | Placebo | 108 (1106) | 12 | 17 | 46 | 19,5 | PASI75/wk12 | 22 | 6 | 1 | ND | 12(108)/ No |
| | Bagel, 2012[23] | Etanercept sc (100mg wk) | 62( 124) | 24 | 17,5 | 39 | 15,5 | PASI75/wk12 | 52 | 37 | 16 | ND | 6(62)/ No |
| | | Placebo | 62 (124) | 24 | 11,9 | 42 | 15,2 | PASI75/wk12 | 4 | 3 | 1 | ND | 7(62)/ No |
| | Gottlieb, 2003[26] | Etanercept sc (50mg/wk) | 57 (112) | 24 | 23 | 48,2 | 17,8 | PASI75/wk12 | ND | 17 | ND | ND | No/No |
| | | Placebo | 55 (112) | 24 | 20 | 46,5 | 19,5 | PASI75/wk12 | ND | 1 | ND | ND | No/No |
| | Gottlieb, 2011[49] | Etanercept sc (100mg/wk) | 141 (347) | 12 | 17 | 43,1 | 19,4 | PASI75/wk12 | ND | 79 | ND | ND | 20(141)/No |
| | | Briakinumab 200mg sc (wks 0 and 4 then 100mg wk 8) | 138(347) | 12 | 16,1 | 43.6 | 18.4 | PASI75/wk12 | ND | 113 | ND | ND | 39(138)/No |
| | | Placebo | 68(347) | 12 | 19,1 | 44 | 18,5 | PASI75/wk12 | ND | 5 | ND | ND | 10 (68)/No |
| | Griffiths, 2015 Uncover-2[46] | Ixekizumab sc (160mg wk0 and 80mg every 4 wks)¶ | 347 (1224) | 12 | 18 | 45 | 19 | PASI75/wk12 | ND | 315 | 248 | 142 | 84 (347)/Yes |
| | | Ixekizumab (160mg wk0 and 80mg every 2wks) | 351 (1224) | 12 | 19 | 45 | 20 | PASI75/wk12 | ND | 269 | 207 | 107 | 85 (351)/Yes |
| | | Etanercept (100mg/wk) | 358 (1224) | 12 | 19 | 45 | 19 | PASI75/wk12 | ND | 149 | 67 | 19 | 76 (358)/Yes |
| | | Placebo | 168 (1224) | 12 | 19 | 45 | 21 | PASI75/wk12 | ND | 4 | 1 | 1 | 43 (168)/Yes |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Griffiths, 2015 Uncover-3[46] | Ixekizumab sc (160mg wk0 and 80mg every 4 wks)[¶] | 385(1346) | 12 | 18 | 46 | 21 | PASI75/wk12 | ND | 336 | 262 | 145 | 58/ (385)Yes |
| | Ixekizumab (160mg wk0 and 80mg every 2wks) | 386(1346) | 12 | 18 | 46 | 21 | PASI75/wk12 | ND | 325 | 252 | 135 | 58 (386)/Yes |
| | Etanercept (100mg/wk) | 382(1346) | 12 | 18 | 46 | 21 | PASI75/wk12 | ND | 204 | 98 | 28 | 60 (382)/Yes |
| | Placebo | 193(1346) | 12 | 18 | 46 | 21 | PASI75/wk12 | ND | 14 | 6 | 0 | 33 (193)/Yes |
| Langley, 2014 Fixture[29] | Secukinumab 300mg sc (wks 0,1,2,3 and 4 then wks 8 and 12) | 327 (1306) | 52 | 15,8 | 44,5 | 23,9 | PASI75/wk12 | ND | 249 | 175 | 78 | 38 (327) / No |
| | Secukinumab 150mg sc (wks 0,1,2,3 and 4 then wks 8 and 12)[¶] | 327 (1306) | 52 | 17,3 | 45,4 | 23,7 | PASI75/wk12 | ND | 219 | 137 | 47 | 45 (327) No |
| | Etanercept sc (100mg/wk) | 326 (1306) | 52 | 16,4 | 43,8 | 23,2 | PASI75/wk12 | ND | 142 | 67 | 14 | 45 (326) / No |
| | Placebo | 326(1306) | 52 | 16,6 | 44,1 | 24,1 | PASI75/wk12 | ND | 16 | 5 | 0 | 35 (326) / No |
| Leonardi, 2003[31] | Etanercept sc (25mg/wk)[¶] | 160 (652) | 24 | 19,3 | 44,4 | 18,2 | PASI75/wk12 | 65 | 23 | 5 | ND | No/No |
| | Etanercept sc (50mg/wk) | 162 (652) | 24 | 18,5 | 45,4 | 18,5 | PASI75/wk12 | 94 | 55 | 19 | ND | No/No |
| | Etanercept sc (100mg/wk) | 164 (652) | 24 | 18,6 | 44,8 | 18,4 | PASI75/wk12 | 121 | 81 | 36 | ND | No/No |
| | Placebo | 166 (652) | 24 | 18,4 | 45,6 | 18,3 | PASI75/wk12 | 24 | 6 | 1 | ND | No/No |
| Mease, 2000[8] | Etanercept sc (50mg/wk) | 19 (38) | 12 | 19 | 46 | 10,1 | PASI75/wk12 | ND | 5 | ND | ND | ND/Yes |
| | Placebo | 19 (38) | 12 | 17,5 | 43,5 | 6,0 | PASI75/wk12 | ND | 0 | ND | ND | ND/Yes |
| Papp, 2005[50] | Etanercept sc (50mg/wk) | 204 (611) | 24 | 21,5 | 46 | 16,9 | PASI75/wk12 | 124 | 66 | 20 | ND | No/No |
| | Etanercept sc (100mg/wk) | 203 (611) | 24 | 18,1 | 44,5 | 16,1 | PASI75/wk12 | 147 | 94 | 39 | ND | No/No |
| | Placebo | 204 (611) | 24 | 17,5 | 44 | 16 | PASI75/wk12 | 18 | 6 | 1 | ND | No/No |
| Strober, 2011[51] | Etanercept sc (100mg/wk) | 139(350) | 12 | 15,2 | 45,2 | 18,5 | PASI75/wk12 | ND | 55 | 19 | 8 | 1(139)/No |
| | Briakinumab 200mg sc (wks 0 and 4 then 100mg wk 8) | 139(350) | 12 | 16.3 | 44.9 | 19,4 | PASI75/wk12 | ND | 112 | 77 | 40 | 15(139)/No |
| | Placebo | 72(350) | 12 | 15,5 | 45 | 18,3 | PASI75/wk12 | ND | 5 | 3 | 0 | 3(72)/No |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Tyring, 2007[42] | Etanercept sc (100mg/wk | 311(618) | 96 | 20,2 | 45,8 | 18,3 | PASI75/wk12 | 230 | 146 | 65 | ND | ND/No |
| | | Placebo | 307(618) | 96 | 19,7 | 45,5 | 18,1 | PASI75/wk12 | 43 | 15 | 3 | ND | ND/No |
| | Van der Kerkhof, 2008[28] | Etanercept sc (50mg/week) | 96 (142) | 24 | 19,3 | 45,9 | 21,4 | PASI75/wk12 | 66 | 36 | 13 | ND | ND/No |
| | | Placebo | 46 (142) | 24 | 17,3 | 43,6 | 21 | PASI75/wk12 | 4 | 1 | 1 | ND | ND/No |
| **Infliximab** | Chaudari, 2001[4] | Infliximab 5mg/kg iv (wks 0,2 and 6) | 11(33) | 10 | ND | 51 | 22,1 | PASI75/wk10 | ND | 9 | ND | ND | No/No |
| | | Infliximab 10mg/kg iv (wks 0,2 and 6) ¶ | 11(33) | 10 | ND | 35 | 26,6 | PASI75/week10 | ND | 8 | ND | ND | No/No |
| | | Placebo | 11(33) | 10 | ND | 45 | 20,3 | PASI75/wk10 | ND | 2 | ND | ND | No/No |
| | Gottlieb, 2004[47] | Infliximab 3mg/kg iv (wks 0,2 and 6) | 99 (249) | 30 | 18 | 45 | 20 | PASI75/wk10 | 83 | 71 | 45 | ND | 32 (99) /No |
| | | Infliximab 5mg/kg iv (wks 0,2 and 6) | 99 (249) | 30 | 16 | 44 | 20 | PASI75/wk10 | 96 | 87 | 57 | ND | 33 (99) /No |
| | | Placebo | 51 (249) | 30 | 16 | 45 | 18 | PASI75/wk10 | 11 | 3 | 1 | ND | 16 (51)/No |
| | Menter, 2007[33] | Infliximab 3mg iv (wks 0,2 and 6) | 313 (835) | 50 | 18,1 | 43,4 | 20,1 | PASI75/wk10 | ND | 220 | 116 | ND | 49 (313) No |
| | | Infliximab 5mg iv (wks 0,2 and 6) | 314 (835) | 50 | 19,1 | 44,5 | 20,4 | PASI75/wk10 | ND | 237 | 142 | ND | 45 (314)/No |
| | | Placebo | 208 (835) | 50 | 17,8 | 44,4 | 19,8 | PASI75/wk10 | ND | 4 | 1 | ND | 27 (208)/No |
| | Reich, 2005[38] | Infliximab 5mg iv (wks 0,2,6 and then each 8 wks) | 301(317) | 50 | 19,1 | 42,6 | 22,9 | PASI75/wk10 | 274 | 242 | 172 | ND | No/No |
| | | Placebo | 77(317) | 50 | 17,3 | 43,8 | 22,8 | PASI75/wk10 | 6 | 2 | 1 | ND | No/No |
| | Torri, 2010[40] | Infliximab 5mk/kg iv (wks 0,2, 6 and 8) | 35(54) | 78 | 14,2 | 46,9 | 31,9 | PASI75/wk10 | ND | 24 | ND | ND | ND/No |
| | | Placebo | 19(54) | 78 | 11,1 | 43,3 | 33,1 | PASI75/wk10 | ND | 0 | ND | ND | ND/No |
| | Yang, 2012[43] | Infliximab 5mk/kg iv (wks 0,2, 6, 14 and 22) | 84(129) | 26 | 16 | 40,1 | 23,9 | PASI75/wk10 | 79 | 68 | 48 | ND | ND/No |
| | | Placebo | 45(129) | 26 | 16 | 39,4 | 25,3 | PASI75/wk10 | 6 | 1 | 0 | ND | ND/No |
| **Ixekizumab** | Griffiths, 2015 Uncover-2[46] | Ixekizumab sc (160mg wk0 and 80mg every 4 wks)¶ | 347 (1224) | 12 | 18 | 45 | 19 | PASI75/wk12 | ND | 315 | 248 | 142 | 84 (347)/Yes |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Ixekizumab (160mg wk0 and 80mg every 2wks) | 351 (1224) | 12 | 19 | 45 | 20 | PASI75/wk12 | ND | 269 | 207 | 107 | 85 (351)/Yes |
| | | Etanercept (100mg/wk) | 358 (1224) | 12 | 19 | 45 | 19 | PASI75/wk12 | ND | 149 | 67 | 19 | 76 (358)/Yes |
| | | Placebo | 168 (1224) | 12 | 19 | 45 | 21 | PASI75/wk12 | ND | 4 | 1 | 1 | 43 (168)/Yes |
| | Griffiths, 2015 Uncover-3[46] | Ixekizumab sc (160mg wk0 and 80mg every 4 wks)[¶] | 385(1346) | 12 | 18 | 46 | 21 | PASI75/wk12 | ND | 336 | 262 | 145 | 58/ (385)Yes |
| | | Ixekizumab (160mg wk0 and 80mg every 2wks) | 386(1346) | 12 | 18 | 46 | 21 | PASI75/wk12 | ND | 325 | 252 | 135 | 58 (386)/Yes |
| | | Etanercept (100mg/wk) | 382(1346) | 12 | 18 | 46 | 21 | PASI75/wk12 | ND | 204 | 98 | 28 | 60 (382)/Yes |
| | | Placebo | 193(1346) | 12 | 18 | 46 | 21 | PASI75/wk12 | ND | 14 | 6 | 0 | 33 (193)/Yes |
| | Gordon, 2016 Uncover-1[53] | Ixekizumab sc (160mg wk0 and 80mg every 4 wks)[¶] | 433(1296) | 12 | 19 | 46 | 20 | PASI75/wk12 | ND | 357 | 279 | 145 | 168(432)/No |
| | | Ixekizumab (160mg wk0 and 80mg every 2wks) | 433(1296) | 12 | 20 | 45 | 20 | PASI75/wk12 | ND | 386 | 307 | 153 | 173(433)/No |
| | | Placebo | 431(1296) | 12 | 20 | 46 | 20 | PASI75/wk12 | ND | 17 | 2 | 0 | 181(431)/No |
| **Secukinumab** | Blauvelt, 2014[24] | Secukinumab 300mg s.c (wks 0,1,2,3,4,8) | 59 (177) | 12 | 18 | 45,1 | 20,7 | PASI75/wk12 | ND | 45 | 36 | 25 | 23(59)/No |
| | | Secukinumab 150mg s.c (wks 0,1,2,3,4,8)[¶] | 59 (177) | 12 | 20,4 | 46 | 20,5 | PASI75/wk12 | ND | 41 | 27 | 5 | 28(59)/No |
| | | Placebo | 59 (177) | 12 | 20,2 | 46,5 | 21,1 | PASI75/wk12 | ND | 0 | 0 | 0 | 26 (59)/No |
| | Langley, 2014 Erasure[29] | Secukinumab 300mg sc (wks 0,1,2,3 and 4 then wks 8 and 12)[¶] | 327 (1306) | 52 | 17,3 | 45,4 | 23,7 | PASI75/wk12 | ND | 219 | 137 | 47 | 45 (327) No |
| | | Secukinumab 150mg sc (wks 0,1,2,3 and 4 then wks 8 and 12)[¶] | 245 (738) | 52 | 17,5 | 44,9 | 22,3 | PASI75/wk12 | ND | 174 | 95 | 31 | 73 (245)/No |
| | | Placebo | 248 (738) | 52 | 17,3 | 45,4 | 21,4 | PASI75/wk12 | ND | 11 | 3 | 2 | 73 (248) / No |
| | Langley, 2014 Fixture[29] | Secukinumab 300mg sc (wks 0,1,2,3 and 4 then wks 8 and 12) | 327 (1306) | 52 | 15,8 | 44,5 | 23,9 | PASI75/wk12 | ND | 249 | 175 | 78 | 38 (327) / No |
| | | Secukinumab 150mg sc (wks 0,1,2,3 and 4 then wks 8 and 12)[¶] | 327 (1306) | 52 | 17,3 | 45,4 | 23,7 | PASI75/wk12 | ND | 219 | 137 | 47 | 45 (327) No |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Etanercept sc (100mg/wk) | 326 (1306) | 52 | 16,4 | 43,8 | 23,2 | PASI75/wk12 | ND | 142 | 67 | 14 | 45 (326) / No |
| | | Placebo | 326(1306) | 52 | 16,6 | 44,1 | 24,1 | PASI75/wk12 | ND | 16 | 5 | 0 | 35 (326) / No |
| | Paul, 2014[37] | Secukinumab 150mg sc (wks 0,1,2,3,4,8) | 61(182) | 52 | 20,6 | 43,9 | 22 | PASI75/wk12 | ND | 44 | 33 | 10 | 15(61)/No |
| | | Secukinumab 300mg sc (wks 0,1,2,3,4,8) | 60(182) | 52 | 21 | 46,6 | 18,9 | PASI75/wk12 | ND | 53 | 24 | 16 | 15(60)/No |
| | | Placebo | 61(182) | 52 | 19,8 | 43,7 | 19,4 | PASI75/wk12 | ND | 2 | 0 | 0 | 13(61)/No |
| **Tofacitinib** | Bachelez[45] | Tofacitinib 5mg bid | 330 (1106) | 12 | 16 | 44 | 21 | PASI75/wk12 | 216 | 130 | 69 | ND | 35(330)/No |
| | | Tofacitinib 10mg bid | 332 (1106) | 12 | 17 | 44 | 21 | PASI75/wk12 | 266 | 210 | 119 | ND | 29 (332)/ No |
| | | Etanercept 100mg/wk | 336 (1106) | 12 | 18 | 42 | 19,4 | PASI75/wk12 | 269 | 197 | 108 | ND | 37(336)/ No |
| | | Placebo | 108 (1106) | 12 | 17 | 46 | 19,5 | PASI75/wk12 | 22 | 6 | 1 | ND | 12(108)/ No |
| | Papp, 2012[14] | Tofacitinib 2mg oral bid | 49 (197) | 16 | 16,5 | 29 | 21,5 | PASI75/wk12 | ND | 12 | ND | ND | 10 (49)/ No |
| | | Tofacitinib 5mg oral bid | 49(197) | 16 | 16.4 | 29 | 21.2 | PASI75/wk12 | ND | 20 | ND | ND | 15 (49)/ No |
| | | Tofacitinib 15mg oral bid | 49(197) | 16 | 16.9 | 31 | 22,6 | PASI75/wk12 | ND | 33 | ND | ND | 10( 49)/ No |
| | | Placebo | 50(197) | 16 | 17.2 | 36 | 21.5 | PASI75/wk12 | ND | 1 | ND | ND | 16 (50)/ No |
| | Papp, 2015 OPT1[52] | Tofacitinib 5mg oral bid | 363(900) | 16 | 16 | 46 | 19.5 | PASI75/wk12 | ND | 145 | 72 | ND | 113(363)/ No |
| | | Tofacitinib 10mg bid | 360(900) | 16 | 16.9 | 46 | 20.4 | PASI75/wk12 | ND | 213 | 140 | ND | 113(360)/ No |
| | | Placebo | 177(900) | 16 | 15.7 | 45 | 19.8 | PASI75/wk12 | ND | 11 | 1 | ND | 53(177)/ No |
| | Papp, 2015 OPT2[52] | Tofacitinib 5mg oral bid | 382(959) | 16 | 15.2 | 47 | 20.7 | PASI75/wk12 | ND | 173 | 93 | ND | 92(382)/ No |
| | | Tofacitinib 10mg bid | 381(959) | 16 | 15.2 | 44 | 19.3 | PASI75/wk12 | ND | 223 | 148 | ND | 97(381)/ No |
| | | Placebo | 196(959) | 16 | 16.4 | 45 | 20.1 | PASI75/wk12 | ND | 22 | 10 | ND | 47(196)/ No |
| **Ustekinumab** | Igarashi, 2011[27] | Ustekinumab 45mg (wks 0, 4 and every 12wks | 64 (157) | 72 | 15,8 | 45 | 30,1 | PASI75/wk12 | 53 | 38 | 21 | ND | 1(64)/No |
| | | Ustekinumab 90mg (wks 0, 4 and every 12wks) | 62 (157) | 72 | 17,3 | 44 | 28,7 | PASI75/wk12 | 52 | 42 | 27 | ND | No/No |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo | 31 (157) | 72 | 16 | 49 | 30,3 | PASI75/wk12 | 4 | 2 | 1 | ND | No/No |
| Leonardi, 2008[30] | Ustekinumab 45mg sc (wks 0, 4 and every 12wks) | 255 (766) | 76 | 19,7 | 44,8 | 20,5 | PASI75/wk12 | 213 | 171 | 106 | 32 | 134 (255) / No |
| | Ustekinumab 90mg sc (wks 0, 4 and every 12wks) | 256 (766) | 76 | 19,6 | 46,2 | 19,7 | PASI75/wk12 | 220 | 170 | 94 | 28 | 130 (256) / No |
| | Placebo | 255 (766) | 76 | 20,4 | 44,8 | 20,4 | PASI75/wk12 | 26 | 8 | 5 | 0 | 128 (255) / No |
| Tsai, 2011[41] | Ustekinumab 45mg sc (wks 0, 4 and then every 12 wks) | 61(121) | 28 | 11,9 | 40,9 | 25,2 | PASI75/wk12 | 51 | 41 | 30 | 5 | 13(61)/No |
| | Placebo | 60(121) | 28 | 13,9 | 40,4 | 22,9 | PASI75/wk12 | 8 | 3 | 1 | 0 | 9(61)/No |
| Zhu, 2013[44] | Ustekinumab 45mg sc (wks 0, 4 and then every 12 wks) | 160(332) | 32 | 14,6 | 40,1 | 23,2 | PASI75/wk12 | 146 | 132 | 107 | 38 | 19(160)/No |
| | Placebo | 162(332) | 32 | 14,2 | 39,2 | 22,7 | PASI75/wk12 | 32 | 18 | 5 | 1 | 11(162)/No |

*: **Studies with multiple treatment arms were included more than once in the table.** @ Number of patients that received prior biologic or small molecule therapy. Total number of patients on study drug between parentheses. ;#Total number not disclosed. Wk: week. Wks: weeks. Eow: each other week. Bid: two times a day. sc: subcutaneous. iv: intravenous.ND: Not disclosed ¶ Drugs or doses not included in final analysis

**On line resource 6.** Summary of results for drugs and doses sorted by drug class.

| DRUG CLASS | DRUG/DOSE | PASI 75 | | PASI 90 | | PASI 100 | | PRIMARY ENDPOINT |
|---|---|---|---|---|---|---|---|---|
| | | RD (CI) | NNT | RD (CI) | NNT | RD (CI) | NNT | WEEKS |
| Anti-TNF | Adalimumab load (80mg wk0 + 40mg wk1)+40 mg eow | 0.62 (0.58-0.67) | 1.61 | 0.43 (0.39-0.46) | 2.32 | 0.18 (0.12 - 0.24) | 5.55 | 12 to 16 |
| | Etanercept 100 mg/wk | 0.44 (0.40-0.48) | 2.27 | 0.22 (0.18-0.25) | 4.54 | 0.05 (0.04 - 0.07) | 20 | 12 |
| | Etanercept 50 mg/wk | 0.31 (0.27-0.35) | 3.22 | 0.10 (0.07-0.13) | 10 | 0.06 (0.01 - 0.10) | 16.6 | 12 |
| | Infliximab 5 mg/kg | 0.76 (0.73-0.79) | 1.31 | 0.53 (0.46-0.60) | 1.88 | ND | ND | 10 |
| | **Overall pooled effect** | **0.54 (0.47-0.60)** | **1.85** | **0.28 (0.21 - 0.35)** | **3.57** | **0.10 (0.04 - 0.16)** | **10** | **-** |
| Anti-IL 12/23 | Ustekinumab 90 mg | 0.67 (0.60-0.74) | 1.49 | 0.42 (0.30-0.54) | 2.38 | 0.15 (0.07 - 0.22) | 6.66 | 12 |
| | Ustekinumab 45 mg | 0.64 (0.60-0.69) | 1.56 | 0.45 (0.35-0.55) | 2.22 | 0.16 (0.10 - 0.21) | 6.25 | 12 |
| | **Overall pooled effect** | **0.65 (0.62 - 0.69)** | **1.53** | **0.44 (0.37 - 0.51)** | **2.27** | **0.15 (0.11 - 0.19)** | **6.66** | **-** |
| Anti-IL17 | Brodalumab 210 mg | 0.79 (0.76-0.82) | 1.26 | 0.75 (0.61-0.89) | 1.33 | 0.44 (0.35 - 0.53) | 2.27 | 12 |
| | Brodalumab 140 mg | 0.64 (0.57-0.70) | 1.56 | 0.72 (0.57-0.86) | 1.38 | 0.26 (0.23 - 0.30) | 3.84 | 12 |
| | Ixekizumab 160mg wk0 and 80mg every 2 wks | 0.84 (0.81-0.88) | 1.19 | 0.69 (0.65 - 0.72) | 1.44 | 0.37 (0.35 - 0.40) | 2.70 | 12 |
| | Secukinumab 300 mg | 0.76 (0.71-0.81) | 1.31 | 0.53 (0.46 - 0.60) | 1.88 | 0.28 (0.22 - 0.34) | 3.57 | 12 |
| | **Overall pooled effect** | **0.76 (0.70 - 0.82)** | **1.31** | **0.61 (0.54 - 0.68)** | **1.63** | **0.35 (0.30 - 0.40)** | **2.85** | **-** |
| Small molecule inhibitors (anti-JAK/anti-PD4) | Tofacitinib 10 mg | 0.53 (0.47-0.58) | 1.88 | 0.36 (0.33 - 0.39) | 2.77 | ND | ND | 12 |
| | Tofacitinib 5 mg | 0.34 (0.31-0.38) | 2.94 | 0.19 (0.17 - 0.22) | 5.26 | ND | ND | 12 |
| | Apremilast 30 mg bid | 0.30 (0.23-0.36) | 3.33 | ND | ND | ND | ND | 16 |
| | **Overall pooled effect** | **0.43 (0.30 - 0.55)** | **2.32** | **0.27 (0.13 - 0.42)** | **3.7** | **ND** | **ND** | **-** |

RD: Risk difference; CI: Confidence interval; NNT: Number needed to treat. eow: each other week. wk:week. bid: two times a day. JAK: Janus Kinase. PD4: Phosphodiesterase 4. ND: Not Determined

## 4. Considerações finais

Este estudo originalmente foi concebido para avaliar a eficácia das diversas terapias imunobiológicas e inibidores de pequenas moléculas para tratamento da psoríase em placas moderada-a-grave através de uma revisão sistemática e metanálise. Inicialmente incluímos na metanálise estudos de fase II e drogas/doses que não foram aprovadas pelos órgãos regulatórios, internacionais ou nacional (Anexo I, II e III). Após a submissão do artigo resultante desta tese a uma revista internacional, os revisores arrazoaram que seria pouco relevante a inclusão de estudos de fase II que não dessem sequencia às doses estudadas em subsequentes estudos de fase III e que drogas já definitivamente retiradas do processo de submissão aos órgãos reguladores não são relevantes para a prática clínica, sendo melhor deixa-las de fora da metanálise.

Desta forma, refizemos toda a revisão sistemática com critérios de inclusão que estivessem de acordo com as sugestões dos revisores e incluímos na metanálise, por fim, um número menor de drogas e doses para submissão do artigo para revistas indexadas.

O resultado das análises, mesmo que não permita, por vezes, a comparação direta entre drogas, pois o estilo da metanálise tradicional não-bayesiana não é o ideal para tal, acaba mesmo assim podendo mesmo que indiretamente, através da comparação com o placebo, comparar drogas aonde os intervalos de confiança (CI) das diferenças de risco (RD) não se sobreponham.

Pois, desta forma, acabamos por concluir que novas drogas anti-interleucina 17 (secuquinumabe, ixequizumabe e brodalumabe) são altamente eficazes para tratamento da psoríase em placas moderada-a-grave em adultos e que a performance destas drogas é similar à performance da droga anti-TNF mais efetiva, infliximabe, quando o desfecho estudado é o PASI75. Pois, quando o desfecho é PASI 90 esta diferença entre drogas anti-IL17 (brodalumabe e ixequizumabe) é ainda mais evidente e a superioridade destas frente, inclusive, ao infliximabe é destacada (sem sobreposição nos CI). Vale ressaltar que o mesmo não pode ser afirmado do secuquinumabe, pois os intervalos de confiança das RD entre ele e infliximabe se sobrepõem. No desfecho mais otimista, PASI100 ou clareamento total da pele, não foram achados estudos duplo-cego randomizados controlados por placebo que avaliassem o infliximabe. Mas é pelo menos sensato supor que a diferença se manteria e todos os anti-IL17 obtiveram performance superior aos anti-TNFs incluídos na metanálise (adalimumabe e etanercepte), assim como ao anti-IL12/23 (ustequinumabe), sem sobreposição dos intervalos de confiança.

A sequencia deste trabalho é a realização de uma metanálise de comparações indiretas (*mixed treatment comparison –MTC)*, bayesiana com possibilidade de ranqueamento dos tratamentos e inclusão de estudos controlados por comparadores ativos e não somente por placebo.

# 5. Anexos

## 5.1 Normas para submissão à publicação

Normas para publicação da revista opdem ser acessados no link abaixo:
https://www.editorialmanager.com/drda/redirectToBanner.aspx?defaultTarget=AuthInstr.html

**5.2 Submissão à revista Drugs in Research and Development com extensas revisões requisitadas.**

Dear Dr. Carvalho,

I have received the comments from the reviewers of your manuscript, "Efficacy of immunobiologic and small molecule inhibitors drugs for psoriasis: a systematic review and metaanalysis of randomized clinical trials.", which you submitted to Drugs in R&D.

Based on our editorial assessment and the reviewer comments received I can advise that your manuscript could be reconsidered for publication should you be prepared to incorporate major revisions. When preparing your revised manuscript, you are asked to carefully consider the reviewer and editorial comments which can be found below, and submit a point-by-point summary of how you have dealt with each of the comments and highlight all changes in the revised manuscript. You are kindly requested to also check the website for possible reviewer attachment(s).These can be accessed by clicking on the "VIEW ATTACHMENTS' tab on the left hand side of the screen.

To submit a revision, go to http://drda.edmgr.com/ and log in as an Author. You will see a menu item called 'Submissions Needing Revision'. You will find your submission record there.

Your username is: avecarvalho
Your password is: available at this link
http://drda.edmgr.com/Default.aspx?pg=accountFinder.aspx&firstname=Andr%c3%a9&lastname=Carvalho&email_address=avecarvalho@me.com

I look forward to receiving your revised manuscript by 26 Oct 2016. Please do not hesitate to contact me should you need to discuss any of the points raised by the peer review process.

With kind regards,
Anton van Rensburg
Editor in Chief
Drugs in R&D
Adis Journals, Editorial Office

COMMENTS FOR THE AUTHOR:

From the Editor:
Please provide two to three short bullet points summarizing the key findings and implications of the paper. These should be pressented in non-technial language and not repeat vrbatim text found in teh abstract. They should be placed beneath the abstract under the title "Key Points".

Reviewer #1: The authors aim to give a recent overview on the efficacy on

approved and upcoming biologics for the treatment of psoriasis. However, the manuscript has some weaknesses.
After a rough overview from a methodological perspective, I have - among others - the following remarks:

- Page 3 line 52 to page 4 line 1: Spelling mistake: IC instead of CI. Please correct in wholde manuscript.
- Page 3 line 28: "controlled clinical that" - I assume the word 'trial' is missing.
- Page 3 line 44: In my opinion time point of measurement/evaluation should be added
- Page 5 line 22: 'Tofacitinib' / page 9 line 15 'Brodalumab' / page 11 line 33 'Tofacitinib' - low case - please check whole manuscript
- Page 5 line 55: "This study" - word missing
- Page 6 line 20: Unfortunately, the date of the systematic literature search is more than one year ago (20th July 2015). This should be updated (e.g. use AutoAlerts).
- Page 6 line 30/31: Why have you searched for "sifalimumab" and "siplizumab"? Development of these drugs was discontinued years ago.
- Page 7 line 41: spelling mistake 'polled'
- Page 8 'Results' section: I would recommend to include time point of measurements for each medication (if they differ) for each end point; state at least once the time point evaluation (short term/ long-term; the reader does not know it)
- Page 9 line 23: bad wording "[…]was the drug that achieved the best response rate" - RD is not the 'response rate'
- Page 9 line 26: different data for RD, see data reported in abstract
- Page 9 line 34 (see also PASI90, PASI100): it is questionable if an overall pooled effect is appropriate ☾ see e.g. $I^2$ = 96% / 97% / 98%; further explanations are missing
- Page 10 line 17 to 23 and Online Resource 2 to 4: Please check interpretation of funnel plots; maybe split the forest plots by drug classes. Otherwise I have some doubts that a systematic bias will be detected.
In my opinion these are not typical funnels - that means I would not preclude a publication bias.
- Page 10 line 47-55: The planed calculation of NNTs was not mentioned in methods section. These results should be stated in results section not in the discussion.
- Page 10 line 55: typo 'Nevetheless'
- Page 11 line 37: reference number 52 not listed in reference list; number 51 is twice
- Page 11 line 51: wrong reference number 17 (it is Xiong et al.)
- Page 11 line 54: reference 54 is not in reference list
- Page 12 line 8 (and Figure 2, 4 and 6): You mentioned "considerable heterogeneity among studies" - but you pooled all studies; this is not appropriate; in 13 out of 28 meta-analyses (all outcomes PASI75, PASI90, PSI100) $I^2$ is greater than 50% - please refer to Cochrane Handbook; explanations are needed
- Page 12 line 23: please add outcome PASI75
- Page 12 line 28: brodalumab 140mg with an $I^2$ of 71% is missing
- Table 1: column 'Prior immunobilogic treatment [spelling mistake]/

concomitant systemic medication': what does the number refer to, for example Gordon 2015 - 20(42)/ND? If applicable, please modify table header.
- Figure 2, 4 and 6 vs Figure 3, 5 and 7: please check numbers for overall effect estimates; numbers of placebo patients differ e.g. from Figure 1 (bottom) and Figure 2 ☾ however, in my opinion it is not acceptable to pool all medications (see $I^2$, stated above; different dosage regimes, etc.)
- Online resource Table 5: Please add an explanatory text. I assume that most readers are not able to interpret the stated statistical data. Please add at least one example as "How to read" the presented data for the variable 'Baseline PASI'.
- In general: the used method for, and the question of this systematic review is not appropriate to perform a ranking of different medications (see results section, online resource Table 2). If you would like to rank the different medications you should have choose the method of a network-meta-analysis.

Reviewer #2: Overall, the manuscript was written well fulfilling the PRISMA criteria for reporting on systematic reviews and meta-analysis. This study assessed the efficacy of immunobiologic and small molecule inhibitor drugs for the treatment of moderate to severe plaque psoriasis. Both published and unpublished databases were used for this study and various medicines were also included in these meta-analyses.However, some information should be clearly clarified or stated.

A) The title clearly identifies that the report is a systematic review and a meta-analysis. The word "metaanalysis" is an hyphenated word and not a single word.
B) Good structured abstract.
- However, the background ("importance") provided is very broad. Could be narrowed to focus more on why is it important to do this systematic review? For instance, there are various therapies to choose from to manage psoriasis, hence knowledge about the ranking of these therapies based on their efficacies would aid dermatologists' in choosing therapies for their patients.
- May add a line in the abstract to comment on the limitations of this review.
- Could emphasis more on the implications of the key findings of this review and its importance for clinical practice in the "conclusions and relevance" section of the abstract.
- The authors report in the result section of the abstract that "the overall pooled effect favoured biologics over placebo (RD 0.61)", however, the RD of 0.61 corrosponds to all treatment (biologics + small molecules) and not only biologics (Figure 3). This should be clarified more.
C) The rationale for the review in the context of what is already known is well high-lighted in the introduction. Although, I think it is important to emphasis more on the clinical importance of knowledge about the ranking of these therapies based on their efficacies. The question of research that is being addressed is explicitly stated, however there is no reference to the participants (psoriasis only patients or also PsA), interventions, comparisons (biologics vs.

placebo/ small molecule vs. placebo/ biologics vs. small molecules), outcomes and study design (PICOS). It will be helpful for the reader to have these clearly stated at the end of the Introduction/beginning of Methods.
D) When you performed meta-analyses, is it better to present the results of biologic therapies and small molecule inhibitors separately due to different types of drug? It may be more appropriate to present results separately for biologics vs. placebo/ small molecule vs. placebo/ biologics vs. small molecules.
E) What is the rationale for including in the search strategy biologic therapies that are not licensed for psoriasis, e.g. golimumab is licensed for PsA and not Pso - and the authors stated that their research question focuses on treatment for moderate-to-severe psoriasis?
F) What is the rationale for including in the search strategy fezakizumab, sifalimumab etc. as the development of these biologics was discontinued some years ago and may not be clinically relevant?
G) Search strategy section (page 6) does not include only search strategy but it mentioned database and eligibility criteria. Therefore, the title of the section should be changed in order to cover all contents in this section or you can separate the contents into separate subsections in order to make it clearer.
H) Could add more details to the flow chart (Figure 1):
- What were the additional resources through which 5 records were identified?
- Reasons for exclusion of 5692 records?

I) Could comment more on risk of bias of individual studies and across studies? On-line resource 1 could be supplemented with a detailed table reporting risk of bias for individual studies (clarify things to the reader).
J) Result section (page 9, last paragraph) and Figure 4, comparing between brodalumab 210, 140 mg, adalimumab, apremilast, tofalicitiniab 50 mg or 10 mg; and placebo involved only 1 study for each comparison when considering PASI 90 as an outcome. Was the number of included study for these comparisons too low? Moreover, both doses of brodamumab involved < 80 patients per comparison. When the authors presented that both doses of brodalumab achieved higher chances of improvement may lead to misinterpretation to readers (in result section (page 9) and discussion section page 11 paragraph 2).
K) In page 11 paragraph 3, the authors summarised that tofalizumab was superior to both doses of etanercept (RD = 0.31 for etanercept 50mg/week and RD 0.44 for etanercept 100 mg/week). Do you mean only tofalizumab 10 mg? If so, is this conclusion appropriate when you concluded this by being based on only 1 study for tofalizumab 10 mg?
L) Please check data extracted from the included RCT in table 1. For example, were patient mean age 44.1 (not 45.4) in adalimumab group and 45.4 (not 44.1) in placebo group in Menter, 2008 study (page 1 of table 1)? For Gordon et.al. 2015 study (page 1 of table 1), did this study measure efficacy outcome at week 16 (table 1 stated week 12)? There are duplicated rows for guselkumab 15 mg sc every 8 week and you did not present information of guselkumab 5 mg which was presented in the original paper.
M) The reporting of different RD in each of figure 3, and 7 and to the RD reported at the bottom of figure 2 and 6 may create confusion to the reader.

May want to consider adding a few lines explaining this difference to the reader or avoid reporting the pooled RD at the bottom of figure 2 and 6.

## 5.3 Cover letter

Title: Efficacy of immunobiologic and small molecule inhibitors drugs for psoriasis: a systematic review and metaanalysis of randomized clinical trials.

Running head: Immunobiologic and small molecule inhibitors drugs for psoriasis: a systematic review and metaanalysis

Authors:

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Dear Editor,

It was with great pleasure that we submit our paper to Drugs in R&D. Modifications were made according to the editor and reviewer's suggestions.

Systematic review and meta-analysis were updated and the suggestions were, in fact, crucial to make the text clearer and without misleading sentences that could lead to misunderstanding of the results.

On line resource 6 (Table 2) was reorganized to summarize all the results and, therefore, make it more palatable to the readers.

Heterogeneity was readdressed and a more complete discussion was performed.

Sincerely

The authors

**5.4 Resposta aos revisores e ressubmissão do artigo**

**Comentários dos revisores/editores em negrito e respostas abaixo sem negrito e em itálico**

COMMENTS FOR THE AUTHOR:

From the Editor:

**-Please provide two to three short bullet points summarizing the key findings and implications of the paper. These should be pressented in non-technial language and not repeat vrbatim text found in teh abstract. They should be placed beneath the abstract under the title "Key Points".**

*The key points were added to the text as suggested and are as follows*

*“Key points:*

- *Anti-TNF and anti-IL12/23 have already been shown to be effective to treat moderate-to-severe psoriasis patients.*
- *Anti-IL17 drugs showed equal or greater chance of leading patients to a 75% improvement in psoriasis when compared to other biologics/small molecule inhibitors.*
- *Ixekizumab showed higher efficacy among FDA approved drugs when 90 or 100% improvement over baseline PASI were analyzed.”*

**-Reviewer #1: The authors aim to give a recent overview on the efficacy on approved and upcoming biologics for the treatment of psoriasis. However, the manuscript has some weaknesses.**
**After a rough overview from a methodological perspective, I have - among others - the following remarks:**

**-Page 3 line 52 to page 4 line 1: Spelling mistake: IC instead of CI. Please correct in wholde manuscript.**

*It’s been corrected*

**-Page 3 line 28: "controlled clinical that" - I assume the word 'trial' is missing.**

*The reviewer is right. We added the missing word in the text.*

**-Page 3 line 44: In my opinion time point of measurement/evaluation should be added**

*The reviewer's suggestion has been added to the sentence.*

**-Page 5 line 22: 'Tofacitinib' / page 9 line 15 'Brodalumab' / page 11 line 33 'Tofacitinib' - low case - please check whole manuscript**

*It's been corrected*

**-Page 5 line 55: "This study" - word missing**

*It's been corrected*

**-Page 6 line 20: Unfortunately, the date of the systematic literature search is more than one year ago (20th July 2015). This should be updated (e.g. use AutoAlerts).**

*The systematic review and meta-analysis have been updated.*

**-Page 6 line 30/31: Why have you searched for "sifalimumab" and "siplizumab"? Development of these drugs was discontinued years ago.**

*The objective was to broad the search and avoid losses of drugs in study arms that could be" hidden" in studies conducted about those discontinued drugs. One example was the study about briakinumab, that included an etanercept study arm, that could be lost if briakinumab was not included in the search strategy.*

**-Page 7 line 41: spelling mistake 'polled'**

*It's been corrected*

**-Page 8 'Results' section: I would recommend to include time point of measurements for each medication (if they differ) for each end point; state at least once the time point evaluation (short term/ long-term; the reader does not know it)**

*The reviewer suggestion has been added to the text.*

**-Page 9 line 23: bad wording "[…]was the drug that achieved the best response rate" - RD is not the 'response rate'**

*We agree with the reviewer. It has been changed in the text, as follows: "…drug that achieved the higher risk difference".*

**-Page 9 line 26: different data for RD, see data reported in abstract**

*It has been reviewed and corrected.*

**-Page 9 line 34 (see also PASI90, PASI100): it is questionable if an overall pooled effect is appropriate ☾ see e.g. $I^2$ = 96% / 97% / 98%; further explanations are missing**

*There is always an issue with meta-analysis that includes studies with more than two study arms, which is: how to include the same placebo population in both comparisons? This always result in a falsely larger number of participants on the placebo group, as they are included twice in the analyses.*
*This is called 'Unit-of-analyses error" by the Cochrane handbook.*

*In our opinion, the best way to deal with this issue, as indicated also by the Cochrane handbook, is to gather all the events of all studied drugs in one group and all the events of the placebo of all studies in another one. The meta-analyzed result is the overall pooled effect. In this case, the I2 calculated does not reflect real heterogeneity, because after all studies and placebos are grouped as one single study, I2 is not possible to be measured.*

*Subgroup heterogeneity is better analyzed inside subgroups of drugs/doses, as we indicated in the text.*

*All these considerations have been incorporated in the text.*

**-Page 10 line 17 to 23 and Online Resource 2 to 4: Please check interpretation of funnel plots; maybe split the forest plots by drug classes. Otherwise I have some doubts that a systematic bias will be detected.**
**In my opinion these are not typical funnels - that means I would not preclude a publication bias.**

*The reviewer has a valid point considering that funnel plots are not too typical. The problem with funnel plots is that they rely only on visual interpretation and even the Cochrane Handbook (citing Terrin 2005) refers that researchers have a limited ability to identify publication bias in a series of meta-analyses. That said, our interpretation on the PASI 75 funnel plot is that this is a fairly symmetrical plot. Larger studies are grouped on the top of the plot and two studies with a lower number of participants scattered at a lower position, one at each side of the mean RD. The lack of studies with low number of patients, what is expected according to the meta-analysis inclusion criteria (placebo controlled RCT, phase III studies), is in our opinion the cause of the empty space in the lower quadrants of the plot.*

*We agree with the reviewer, after reanalyzing the plots, that PASI 90 and 100 funnel plots can not exclude a possible publication bias.*
*All these considerations have been incorporated in the text of the meta-analysis.*

**-Page 10 line 47-55: The planed calculation of NNTs was not mentioned in methods section. These results should be stated in results section not in the discussion.**

*We thank the reviewer for the correction and suggestion and it has been changed.*

**-Page 10 line 55: typo 'Nevetheless'**

*It's been corrected*

**-Page 11 line 37: reference number 52 not listed in reference list; number 51 is twice**

*It's been corrected*

**-Page 11 line 51: wrong reference number 17 (it is Xiong et al.)**

*It's been corrected*

**-Page 11 line 54: reference 54 is not in reference list**

*It's been corrected*

**-Page 12 line 8 (and Figure 2, 4 and 6): You mentioned "considerable heterogeneity among studies" - but you pooled all studies; this is not appropriate; in 13 out of 28 meta-analyses (all outcomes PASI75, PASI90, PSI100) $I^2$ is greater than 50% - please refer to Cochrane Handbook; explanations are needed**

*The reviewer is right. It was not effectively clear what we wanted to say. We have made explicit the heterogeneity for every subgroup in the results section and further discussed this matter in the discussion section of the paper.*

**-Page 12 line 23: please add outcome PASI75**

*It has been added*

**-Page 12 line 28: brodalumab 140mg with an $I^2$ of 71% is missing**

*The reviewer is absolutely right and we corrected it in the text, including the data from sensitivity analysis that was missing.*

**-Table 1: column 'Prior immunobilogic treatment [spelling mistake]/ concomitant systemic medication': what does the number refer to, for example Gordon 2015 - 20(42)/ND? If applicable, please modify table header.**

*The spelling mistake has been corrected. Using the symbol @ and the abbreviation ND, the explanation for the numbers are in the bottom of the table as:*

*"header: PRIOR IMMUNOBIOLOGIC TREATMENT/ CONCOMITANT SYSTEMIC MEDICATION@*

*bottom of the table: @ Number of patients that received prior biologic or small molecule therapy. Total number of patients on study drug between parentheses. ND: Not disclosed"*

*Modifying the header would make the table cell cluttered with text and hard to format. But if the reviewer still believes this was not enough to clarify the issue for the reader, we will be happy to change the header.*

**-Figure 2, 4 and 6 vs Figure 3, 5 and 7: please check numbers for overall effect estimates; numbers of placebo patients differ e.g. from Figure 1 (bottom) and Figure 2 ☹ however, in my opinion it is not acceptable to pool all medications (see $I^2$, stated above; different dosage regimes, etc.)**

*There is always an issue with meta-analysis that includes studies with more than two study arms, which is: how to include the same placebo population in both comparisons? This always result in a falsely larger number of participants on the placebo group, as they are included twice in the analyses.*
*This is called 'Unit-of-analyses error" by the Cochrane handbook.*

*In our opinion, the best way to deal with this issue, as indicated also by the Cochrane handbook, is to gather all the events of all studied drugs in one group and all the events of the placebo of all studies in another one. The meta-analyzed result is the overall pooled effect. In this case, the I2 calculated of the pooled studies does not reflect real heterogeneity because, after all studies and placebos are grouped as one single study, I2 is not possible to be measured.*

*Subgroup heterogeneity is better analyzed inside subgroups of drugs/doses, as we indicated in the text. We have added a more detailed text about heterogeneity in each group in the results and further considerations about the issue on the discussion.*

*Total for each outcome have been suppressed as it may cause confusion to the reader.*

**-Online resource Table 5: Please add an explanatory text. I assume that most readers are not able to interpret the stated statistical data. Please add at least one example as "How to read" the presented data for the variable 'Baseline PASI'.**

*We agree with the reviewer that the information, the way it was provided, did little to inform readers. We have simplified the information in a table that informs only the important information (pooled estimates after meta-regression, number*

*of patients in each group and percentage of the heterogeneity explained by each variable).*

**-In general: the used method for, and the question of this systematic review is not appropriate to perform a ranking of different medications (see results section, online resource Table 2). If you would like to rank the different medications you should have choose the method of a network-meta-analysis**.

*We agree with the reviewer. Only a network Bayesian meta-analysis can rank treatments (to make it clearer to the reader, we have added explanations about this issue on the discussion, also). We have reorganized the table by drug class and not by RD, in order not to give the reader a false impression that it is a ranking.*

**Reviewer #2: Overall, the manuscript was written well fulfilling the PRISMA criteria for reporting on systematic reviews and meta-analysis. This study assessed the efficacy of immunobiologic and small molecule inhibitor drugs for the treatment of moderate to severe plaque psoriasis. Both published and unpublished databases were used for this study and various medicines were also included in these meta-analyses.However, some information should be clearly clarified or stated.**

**A)The title clearly identifies that the report is a systematic review and a meta-analysis. The word "metaanalysis" is an hyphenated word and not a single word.**

*We have corrected the spelling of the word.*

**B) Good structured abstract.**
**- However, the background ("importance") provided is very broad. Could be narrowed to focus more on why is it important to do this systematic review? For instance, there are various therapies to choose from to manage psoriasis, hence knowledge about the ranking of these therapies based on their efficacies would aid dermatologists' in choosing therapies for their patients.**

*We agree with the reviewer and a sentence concerning the suggestion has been added to the text of the abstract.*

- May add a line in the abstract to comment on the limitations of this review.

*We included the following text to the abstract:*

***"Limitations:** The methodology of a traditional meta-analysis does not allow a ranking of drugs. Included studies used short term endpoints (10 to 16 weeks) to evaluate the primary outcome therefore, long term efficacy could not be*

*determined."*

**- Could emphasis more on the implications of the key findings of this review and its importance for clinical practice in the "conclusions and relevance" section of the abstract.**

*The last paragraph of the conclusion has been reviewed and improved with reviewer's suggestion.*

**-The authors report in the result section of the abstract that "the overall pooled effect favoured biologics over placebo (RD 0.61)", however, the RD of 0.61 corrosponds to all treatment (biologics + small molecules) and not only biologics (Figure 3). This should be clarified more.**

*We thank the reviewer for pointing it out. It has been corrected.*

**-A)The rationale for the review in the context of what is already known is well high-lighted in the introduction. Although, I think it is important to emphasis more on the clinical importance of knowledge about the ranking of these therapies based on their efficacies. The question of research that is being addressed is explicitly stated, however there is no reference to the participants (psoriasis only patients or also PsA), interventions, comparisons (biologics vs. placebo/ small molecule vs. placebo/ biologics vs. small molecules), outcomes and study design (PICOS). It will be helpful for the reader to have these clearly stated at the end of the Introduction/beginning of Methods.**

*We have added the reviewer's suggestions to the rationale and methods, always making it clear that a true ranking can not be made with the methodology of a traditional meta-analysis but, according to RDs and CIs, some assertions can indeed be made and, at least, a trend can be observed when comparing this meta-analysis to pre-existent meta-analysis.*

**-D) When you performed meta-analyses, is it better to present the results of biologic therapies and small molecule inhibitors separately due to different types of drug? It may be more appropriate to present results separately for biologics vs. placebo/ small molecule vs. placebo/ biologics vs. small molecules.**

*We tend to agree with the reviewer, however the objective of this meta-analysis was to compare biologics to placebo and that is what a traditional meta-analysis can do best (one-way, direct comparison). To make indirect comparisons and to specifically rank drugs a Bayesian network meta-analysis shall be performed.*

*There are no head-to-head studies that compare tofacitinib or apremilast to Secukinumab, for example, or any other drug than Etanercept. So, it would not be possible to effectively compare biologics vs. small molecule inhibitors.*

*We believed that dividing the forest plots in to three different forest plots categorized by drug class could make the reader miss the whole comparison picture and clutter the paper with additional figures. But the reviewer is correct in pointing that it is a useful information, so we categorized the results of on-line Figure 6 (Summary of the results) by drug class and incorporated it into the text as Table 2. This way we believe that the data is made even clearer to the reader than the forest plot.*

**-E) What is the rationale for including in the search strategy biologic therapies that are not licensed for psoriasis, e.g. golimumab is licensed for PsA and not Pso - and the authors stated that their research question focuses on treatment for moderate-to-severe psoriasis?**
**-F) What is the rationale for including in the search strategy fezakizumab, sifalimumab etc. as the development of these biologics was discontinued some years ago and may not be clinically relevant?**

*E, F) The reason for that is that we tried to make a broader search in order to be able to find drugs of interest hidden in studies of other drugs and do not loose a potential comparator. As an example, Strober et al 2011 study about briakinumab, where there is a study arm with Etanercept. There have been studies carried to evaluate Golimumab for plaque type psoriasis and the rationale for including it in the search strategy is the same as stated before*.

**-G) Search strategy section (page 6) does not include only search strategy but it mentioned database and eligibility criteria. Therefore, the title of the section should be changed in order to cover all contents in this section or you can separate the contents into separate subsections in order to make it clearer.**

*The title of the section has been changed in order to make it clear that all contents as covered.*

**-H) Could add more details to the flow chart (Figure 1):**
**- What were the additional resources through which 5 records were identified?**

*It has been added to the diagram (Figure 1) that the references of published meta-analises were the additional source of the 5 records.*

**- Reasons for exclusion of 5692 records?**

*After updating the systematic review, the PRISMA diagram for database searches has been modified. To avoid clutter in the diagram, reasons for exclusion are listed in the text and are as follows:*

*"9544 records were identified through database search, with 5 additional records identified through search of bibliographical references of published metaanalysis. After removing duplicates, 6513 records were screened and 6181*

*were excluded (3822 were not RCT; 2039 not about psoriasis; 100 were about drugs not encompassed in this review; 198 were additional duplicates).*

*Among the 332 manuscripts selected for full text review, 292 were excluded for the following reasons: 201 articles were not RCT, 16 were RCT that did not use placebo as a comparator, 45 due to lack of PASI as primary outcome, 5 were studies in the pediatric population, 4 were phase II studies without further confirmatory phase III studies, 8 were studies with doses not approved by the FDA, 9 were about psoriatic arthritis and 4 were additional duplicates. (**Fig1**).*

**-I) Could comment more on risk of bias of individual studies and across studies? On-line resource 1 could be supplemented with a detailed table reporting risk of bias for individual studies (clarify things to the reader).**

*As suggested by the reviewer, a study-by-study analysis of risk of bias graph has been added to the on-line resources*

**-J) Result section (page 9, last paragraph) and Figure 4, comparing between brodalumab 210, 140 mg, adalimumab, apremilast, tofalicitiniab 50 mg or 10 mg; and placebo involved only 1 study for each comparison when considering PASI 90 as an outcome. Was the number of included study for these comparisons too low? Moreover, both doses of brodamumab involved < 80 patients per comparison. When the authors presented that both doses of brodalumab achieved higher chances of improvement may lead to misinterpretation to readers (in result section (page 9) and discussion section page 11 paragraph 2).**

*We agree with the reviewer that one or two studies per subgroup is not the ideal. Nevertheless, it is what is available in the timeframe of the meta-analysis and is all that we have to work with. Even the Cochrane systematic reviews include some groups with one or two studies if it is important in the context, what we believe is the case with the present meta-analysis.*
*The reviewer is absolutely correct, a better clarification about the weakness of a conclusion about a comparison with a study with low number of patients enrolled was necessary and it has been added to the discussion, as follows:*

*“Brodalumab (both doses) was the drug with higher RD, when analyzing PASI 90 as an outcome, but ixekizumab had similar performance as CI overlapped. Nevertheless, it is important to emphasize that only one brodalumab study (11) (both dosages) could be found that used PASI 90 as an outcome and it was a study with a low number of patients enrolled. Therefore, results concerning*

*Brodalumab at this particular outcome should be taken with caution."*

**-K) In page 11 paragraph 3, the authors summarised that tofalizumab was superior to both doses of etanercept (RD = 0.31 for etanercept 50mg/week and RD 0.44 for etanercept 100 mg/week). Do you mean only tofalizumab 10 mg? If so, is this conclusion appropriate when you concluded this by being based on only 1 study for tofalizumab 10 mg?**

*It was indeed confusing the way it's been previously stated in the paper. We've re-written the paragraph to make it clear that it is 10mg Tofacitinib we are talking about. As reviewer 1 asked for an update in the systematic review, results of the meta-analyzed data has changed and Tofacitinib 10mg is no longer superior to Etanercept 100mg. The paragraph mentions only primary outcome (PASI75) and comparisons are made only about PASI75. As a result of the updated systematic review, 3 studies are part of the updated Tofacitinib 10mg subgroup now. Below, the resulting paragraph:*

*Among newer small molecule inhibitor drugs, Tofacitinib, an anti-Janus kinase 1, also performed well at the dose of 10mg, being to superior to lower dose etanercept and comparable to higher dose Etanercept, adalimumab and low dose brodalumab (overlapping CI),considering PASI75 as the primary outcome.*

**-L) Please check data extracted from the included RCT in table 1. For example, were patient mean age 44.1 (not 45.4) in adalimumab group and 45.4 (not 44.1) in placebo group in Menter, 2008 study (page 1 of table 1)? For Gordon et.al. 2015 study (page 1 of table 1), did this study measure efficacy outcome at week 16 (table 1 stated week 12)? There are duplicated rows for guselkumab 15 mg sc every 8 week and you did not present information of guselkumab 5 mg which was presented in the original paper.**

*The reviewer is correct and we deeply appreciate that he had pointed it out. Table I has been reviewed for typing and data extraction mistakes.*

**-M) The reporting of different RD in each of figure 3, and 7 and to the RD reported at the bottom of figure 2 and 6 may create confusion to the reader. May want to consider adding a few lines explaining this difference to the reader or avoid reporting the pooled RD at the bottom of figure 2 and 6.**

*Totals have been removed from figures 2 and 6 to avoid further confusion. It was indeed leading to misunderstanding.*

## 5.5 Confirmação da aceitação para publicação do artigo na revista Drugs Research and Development.

DI

**De: Drugs in R&D** em@editorialmanager.com **Assunto:** Your Submission DRDA-D-16-00036R1

**Data:** 31 de outubro de 2016 01:50**Para:** André Vicente Esteves de Carvalho avecarvalho@me.com

Dear Dr. Esteves de Carvalho,

I am pleased to inform you that your manuscript, "Efficacy of immunobiologic and small molecule inhibitors drugs for psoriasis: a systematic review and meta-analysis of randomized clinical trials.", has been accepted for publication inDrugs in R&D.

Please remember to quote the manuscript number, DRDA-D-16-00036R1, whenever inquiring about your manuscript. With best regards,

Anton van RensburgEditor in ChiefDrugs in R&DAdis Journals, Editorial Office

## 5.6 Declaração de conflito de interesses dos autores

Adis

### AUTHOR DECLARATION FORM

At submission, **EVERY AUTHOR** listed in the manuscript must **READ** and **COMPLETE** the following statements on: (A) Authorship Responsibility, (B) Authorship Criteria, (C) Authorship Contribution, (D) Funding Disclosures, (E) Contributor Disclosures/Acknowledgments, and (F) Conflicts of Interest Disclosures.

It is important that you return this form as early as possible in the publication process. **EVERY AUTHOR MUST COMPLETE AN INDIVIDUAL COPY OF THE FORM, AND EVERY SECTION OF THE FORM MUST BE COMPLETED.** We will **NOT** consider your manuscript for publication until every author has completed the form and returned it to us.

Your name (please print): Bernardo Lessa Horta E-mail: blhorta@gmail.com

Journal name:Drugs in research & Development Corresponding author: André Vicente E. de Carvalho

Manuscript title: Efficacy of immunobiologic and small molecule inhibitors drugs for psoriasis: a systematic review and metaanalysis of randomized clinical trials.

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## 5.7 PRISMA checklist (como encaminhado à publicação)

### PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 5 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 6 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | x |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 6 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 6-7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 7 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 7-8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 7 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 8 |

## PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 7 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 8 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 8 (fig1) |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 8 (table1) |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 9 (efig1) |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 9 (Fig 2) |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 9-10 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 8-9 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 9-10 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 10-13 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 12 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 12-13 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 2 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

# Tabela com sumário dos resultados da avaliação pelo Grading of Recommendations, Assessment, Development and Evaluations (GRADE)

**Sumário de Resultados:**

## Biológicos e inibidores de pequenas moléculas comparado a placebo para psoriase em placas grave

**paciente ou população**: psoriase em placas grave
**Contexto**:
**Intervenção**: Biológicos e inibidores de pequenas moléculas
**Comparação**: placebo

| Desfechos | **Efeitos absolutos potenciais*** (95% CI) | | Efeito relativo (95% CI) | № de participantes (estudos) | Qualidade da evidência (GRADE) | Comentários |
|---|---|---|---|---|---|---|
| | **Risco com placebo** | **Risco com Biológicos e inibidores de pequenas moléculas** | | | | |
| Biologic - Adalimumab load (80mg wk 0 + 40mg wk 1) + 40mg eow | 71 por 1.000 | **0 por 1.000** (0 para 0) | não estimável | 1645 (5 ECRs) | ⨁⨁⨁⨁ ALTA | |
| Biologic - Apremilast 30mg/bid | 51 por 1.000 | **0 por 1.000** (0 para 0) | não estimável | 1020 (2 ECRs) | ⨁⨁⨁⨁ ALTA | |
| Biologic - Brodalumab 140mg | 66 por 1.000 | **0 por 1.000** (0 para 0) | não estimável | 1940 (3 ECRs) | ⨁⨁⨁⨁ ALTA | |
| Biologic - Brodalumab 210mg | 66 por 1.000 | **0 por 1.000** (0 para 0) | não estimável | 1938 (3 ECRs) | ⨁⨁⨁⨁ ALTA | |
| Biologic - Etanercept 50mg/wk | 23 por 1.000 | **0 por 1.000** (0 para 0) | não estimável | 1145 (5 ECRs) | ⨁⨁⨁⨁ ALTA | |
| Biologic - Etanercept 100mg/wk | 48 por 1.000 | **0 por 1.000** (0 para 0) | não estimável | 4096 (10 ECRs) | ⨁⨁⨁⨁ ALTA | |
| Biologic - Infliximab 5mg/kg | 29 por 1.000 | **0 por 1.000** (0 para 0) | não estimável | 1255 (6 ECRs) | ⨁⨁⨁⨁ ALTA | |
| Biologic - Ixekizumab 160mg wk 0 + 80mg every 2 wks | 44 por 1.000 | **0 por 1.000** (0 para 0) | não estimável | 1961 (3 ECRs) | ⨁⨁⨁⨁ ALTA | |
| Biologic - Secukinumab 300mg | 42 por 1.000 | **0 por 1.000** (0 para 0) | não estimável | 1383 (4 ECRs) | ⨁⨁⨁⨁ ALTA | |
| Biologic - Tofacitinib 5mg BID | 75 por 1.000 | **0 por 1.000** (0 para 0) | não estimável | 1655 (4 ECRs) | ⨁⨁⨁⨁ ALTA [a] | |
| Biologic - Tofacitinib 10mg BID | 81 por 1.000 | **0 por 1.000** (0 para 0) | não estimável | 1554 (3 ECRs) | ⨁⨁⨁⨁ ALTA | |
| Biologic - Ustekinumab 45mg | 50 por 1.000 | **0 por 1.000** (0 para 0) | não estimável | 1867 (5 ECRs) | ⨁⨁⨁⨁ ALTA | |
| Biologic - Ustekinumab 90mg | 36 por 1.000 | **0 por 1.000** (0 para 0) | não estimável | 1425 (3 ECRs) | ⨁⨁⨁⨁ ALTA | |

* **O risco no grupo de intervenção** (e seu intervalo de confiança de 95%) é baseado no risco assumido do grupo comparador e o **efeito relativo** da intervenção (e seu IC 95%).

**CI:** Confidence interval

**Sumário de Resultados:**

## Biológicos e inibidores de pequenas moléculas comparado a placebo para psoriase em placas grave

**paciente ou população**: psoriase em placas grave
**Contexto**:
**Intervenção**: Biológicos e inibidores de pequenas moléculas
**Comparação**: placebo

| Desfechos | **Efeitos absolutos potenciais**[*] (95% CI) | | Efeito relativo (95% CI) | № de participantes (estudos) | Qualidade da evidência (GRADE) | Comentários |
|---|---|---|---|---|---|---|
| | **Risco com placebo** | **Risco com Biológicos e inibidores de pequenas moléculas** | | | | |

**O níveis de qualidade do grupo de trabalho do GRADE**
**Qualidade Alta:** Existe muita confiança que o efeito real encontra-se próximo ao efeito estimado
**Qualidade Moderada:** Existe moderada confiança no efeito estimado: O efeito real está provavelmente próximo ao efeito estimado, mas há possibilidade que seja substancialmente diferente
**Qualidade Baixa:** A confiança no efeito estimado é limitada: o efeito real pode ser substancialmente diferente da estimativa de efeito
**Qualidade Muito Baixa:** Existe muito pouca confiança no efeito estimado: O efeito real é provavelmente substancialmente diferente do efeito estimado

a. Nenhuma explicação fornecida

References