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Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis.
Cochrane Database of Systematic Reviews 2017, Issue 12. Art. No.: CD011535.
DOI: 10.1002/14651858.CD011535.pub2.

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[Intervention Review]

Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

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Editorial group: Cochrane Skin Group.
Publication status and date: New, published in Issue 12, 2017.

Citation: Sbidian E, Chaimani A, Garcia-Doval I, Do G, Hua C, Mazaud C, Droitcourt C, Hughes C, Ingram JR, Naldi L, Chosidow O, Le Cleach L. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2017, Issue 12. Art. No.: CD011535. DOI: 10.1002/14651858.CD011535.pub2.

ABSTRACT

Background

Psoriasis is an immune-mediated disease for which some people have a genetic predisposition. The condition manifests in inflammatory effects on either the skin or joints, or both, and it has a major impact on quality of life. Although there is currently no cure for psoriasis, various treatment strategies allow sustained control of disease signs and symptoms. Several randomised controlled trials (RCTs) have compared the efficacy of the different systemic treatments in psoriasis against placebo. However, the relative benefit of these treatments remains unclear due to the limited number of trials comparing them directly head to head, which is why we chose to conduct a network meta-analysis.

Objectives

To compare the efficacy and safety of conventional systemic agents (acitretin, ciclosporin, fumaric acid esters, methotrexate), small molecules (apremilast, tofacitinib, ponesimod), anti-TNF alpha (etanercept, infliximab, adalimumab, certolizumab), anti-IL12/23 (ustekinumab), anti-IL17 (secukinumab, ixekizumab, brodalumab), anti-IL23 (guselkumab, tildrakizumab), and other biologics (alefacept, itolizumab) for patients with moderate to severe psoriasis and to provide a ranking of these treatments according to their efficacy and safety.

Search methods

We searched the following databases to December 2016: the Cochrane Skin Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and LILACS. We also searched five trials registers and the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) reports. We checked the reference lists of included and excluded studies for further references to relevant RCTs. We searched the trial results databases of a number of pharmaceutical companies and handsearched the conference proceedings of a number of dermatology meetings.

Selection criteria

Randomised controlled trials (RCTs) of systemic and biological treatments in adults (over 18 years of age) with moderate to severe plaque psoriasis or psoriatic arthritis whose skin had been clinically diagnosed with moderate to severe psoriasis, at any stage of treatment, in comparison to placebo or another active agent.

Data collection and analysis

Three groups of two review authors independently undertook study selection, data extraction, 'Risk of bias' assessment, and analyses. We synthesised the data using pair-wise and network meta-analysis (NMA) to compare the treatments of interest and rank them according to their effectiveness (as measured by the Psoriasis Area and Severity Index score (PASI) 90) and acceptability (the inverse of serious adverse effects). We assessed the certainty of the body of evidence from the NMA for the two primary outcomes, according to GRADE; we evaluated evidence as either very low, low, moderate, or high. We contacted study authors when data were unclear or missing.

Main results

We included 109 studies in our review (39,882 randomised participants, 68% men, all recruited from a hospital). The overall average age was 44 years; the overall mean PASI score at baseline was 20 (range: 9.5 to 39). Most of these studies were placebo controlled (67%), 23% were head-to-head studies, and 10% were multi-armed studies with both an active comparator and placebo. We have assessed all treatments listed in the objectives (19 in total). In all, 86 trials were multicentric trials (two to 231 centres). All of the trials included in this review were limited to the induction phase (assessment at less than 24 weeks after randomisation); in fact, all trials included in the network meta-analysis were measured between 12 and 16 weeks after randomisation. We assessed the majority of studies (48/109) as being at high risk of bias; 38 were assessed as at an unclear risk, and 23, low risk.

Network meta-analysis at class level showed that all of the interventions (conventional systemic agents, small molecules, and biological treatments) were significantly more effective than placebo in terms of reaching PASI 90.

In terms of reaching PASI 90, the biologic treatments anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha were significantly more effective than the small molecules and the conventional systemic agents. Small molecules were associated with a higher chance of reaching PASI 90 compared to conventional systemic agents.

At drug level, in terms of reaching PASI 90, all of the anti-IL17 agents and guselkumab (an anti-IL23 drug) were significantly more effective than the anti-TNF alpha agents infliximab, adalimumab, and etanercept, but not certolizumab. Ustekinumab was superior to etanercept. No clear difference was shown between infliximab, adalimumab, and etanercept. Only one trial assessed the efficacy of infliximab in this network; thus, these results have to be interpreted with caution. Tofacitinib was significantly superior to methotrexate, and no clear difference was shown between any of the other small molecules versus conventional treatments.

Network meta-analysis also showed that ixekizumab, secukinumab, brodalumab, guselkumab, certolizumab, and ustekinumab outperformed other drugs when compared to placebo in terms of reaching PASI 90: the most effective drug was ixekizumab (risk ratio (RR) 32.45, 95% confidence interval (CI) 23.61 to 44.60; Surface Under the Cumulative Ranking (SUCRA) = 94.3; high-certainty evidence), followed by secukinumab (RR 26.55, 95% CI 20.32 to 34.69; SUCRA = 86.5; high-certainty evidence), brodalumab (RR 25.45, 95% CI 18.74 to 34.57; SUCRA = 84.3; moderate-certainty evidence), guselkumab (RR 21.03, 95% CI 14.56 to 30.38; SUCRA = 77; moderate-certainty evidence), certolizumab (RR 24.58, 95% CI 3.46 to 174.73; SUCRA = 75.7; moderate-certainty evidence), and ustekinumab (RR 19.91, 95% CI 15.11 to 26.23; SUCRA = 72.6; high-certainty evidence).

We found no significant difference between all of the interventions and the placebo regarding the risk of serious adverse effects (SAEs): the relative ranking strongly suggested that methotrexate was associated with the best safety profile regarding all of the SAEs (RR 0.23, 95% CI 0.05 to 0.99; SUCRA = 90.7; moderate-certainty evidence), followed by ciclosporin (RR 0.23, 95% CI 0.01 to 5.10; SUCRA = 78.2; very low-certainty evidence), certolizumab (RR 0.49, 95% CI 0.10 to 2.36; SUCRA = 70.9; moderate-certainty evidence), infliximab (RR 0.56, 95% CI 0.10 to 3.00; SUCRA = 64.4; very low-certainty evidence), alefacept (RR 0.72, 95% CI 0.34 to 1.55; SUCRA = 62.6; low-certainty evidence), and fumaric acid esters (RR 0.77, 95% CI 0.30 to 1.99; SUCRA = 57.7; very low-certainty evidence). Major adverse cardiac events, serious infections, or malignancies were reported in both the placebo and intervention groups. Nevertheless, the SAEs analyses were based on a very low number of events with low to very low certainty for just over half of the treatment estimates in total, moderate for the others. Thus, the results have to be considered with caution.

Considering both efficacy (PASI 90 outcome) and acceptability (SAEs outcome), highly effective treatments also had more SAEs compared to the other treatments, and ustekinumab, infliximab, and certolizumab appeared to have the better trade-off between efficacy and acceptability.

Regarding the other efficacy outcomes, PASI 75 and Physician Global Assessment (PGA) 0/1, the results were very similar to the results for PASI 90.

Information on quality of life was often poorly reported and was absent for a third of the interventions.

Authors' conclusions

Our review shows that compared to placebo, the biologics ixekizumab, secukinumab, brodalumab, guselkumab, certolizumab, and ustekinumab are the best choices for achieving PASI 90 in people with moderate to severe psoriasis on the basis of moderate- to high-certainty evidence. At class level, the biologic treatments anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha were significantly more effective than the small molecules and the conventional systemic agents, too. This NMA evidence is limited to induction therapy (outcomes were measured between 12 to 16 weeks after randomisation) and is not sufficiently relevant for a chronic disease. Moreover, low numbers of studies were found for some of the interventions, and the young age (mean age of 44 years) and high level of disease severity (PASI 20 at baseline) may not be typical of patients seen in daily clinical practice.

Another major concern is that short-term trials provide scanty and sometimes poorly reported safety data and thus do not provide useful evidence to create a reliable risk profile of treatments. Indeed, we found no significant difference in the assessed interventions and placebo in terms of SAEs. Methotrexate appeared to have the best safety profile, but as the evidence was of very low to moderate quality, we cannot be sure of the ranking. In order to provide long-term information on the safety of the treatments included in this review, it will be necessary to evaluate non-randomised studies and postmarketing reports released from regulatory agencies as well.

In terms of future research, randomised trials comparing directly active agents are necessary once high-quality evidence of benefit against placebo is established, including head-to-head trials amongst and between conventional systemic and small molecules, and between biological agents (anti-IL17 versus anti-IL23, anti-IL23 versus anti-IL12/23, anti-TNF alpha versus anti-IL12/23). Future trials should also undertake systematic subgroup analyses (e.g. assessing biological-naïve patients, baseline psoriasis severity, presence of psoriatic arthritis, etc.). Finally, outcome measure harmonisation is needed in psoriasis trials, and researchers should look at the medium- and long-term benefit and safety of the interventions and the comparative safety of different agents.

PLAIN LANGUAGE SUMMARY

Systemic (oral or injected) medicines for psoriasis

What is the aim of this review?

The aim of this review was to compare different systemic medicines (oral or injected medicines that work throughout the entire body) used to treat chronic plaque psoriasis in adults (over 18 years of age), to find out which are the safest and most effective at clearing psoriasis. We wanted to rank the medicines in order of their safety and how well they work, to help the development of a treatment pathway for people with chronic plaque psoriasis. We collected and analysed all relevant studies to answer this question and found 109 studies.

Key messages

The results showed that a selection of treatments from the class of biological medicines appear to be the most effective systemic medicines for achieving a chronic plaque psoriasis score of PASI (Psoriasis Area and Severity Index) 90, which translates into a 90% improvement in psoriasis from the beginning of the study. We found no significant difference in serious adverse effects (SAEs) (i.e. serious side effects) when comparing any of the assessed treatments with placebo. However, as the evidence was of very low to moderate quality, we cannot be sure of these results.

For some of the interventions, we found low numbers of studies, so more research needs to be conducted to directly compare the systemic medicines with each other, rather than comparing them with placebo (an inactive substance) (once effect against placebo has been established by high-quality evidence). In addition, longer-term studies are needed to provide more evidence about the benefit and safety of systemic medicines and to compare their safety profiles. Indeed, the results of this review are limited to the induction treatment (i.e. outcomes were measured up to 24 weeks after participants were allocated to their treatment group), which is not an appropriate treatment option for a chronic disease.

We rated the certainty of the evidence as ranging from very low (mainly conventional medicines) to high (mainly biological medicines). We downgraded the certainty of the evidence due to risk of bias (concerns with the study methods) and then for either inconsistent results or imprecision (inaccuracy).

What was studied in the review?

Psoriasis is characterised by patches of red, flaky skin covered with scales (known as plaques) or other inflammatory effects that are seen on the skin or joints, or both. Psoriasis is caused by an abnormal response within the immune system in people who may have a genetic predisposition towards the condition.

Approximately 2% of the population have psoriasis, and 90% of those people have plaque psoriasis. Around 10% to 20% of people with chronic plaque psoriasis will need to have systemic treatments. Psoriasis impacts on quality of life, including a person's psychosocial life.

We compared 19 systemic medicines by identifying studies that compared one or more of these medicines with either placebo or with another medicine to treat moderate to severe forms of plaque psoriasis in adults who were at any stage of treatment. The medicines we assessed were conventional systemic treatments (a varied group of treatments that are the oldest treatments given to clear psoriasis),

biologics (treatments that use substances made from living organisms, or synthetic versions, to target the immune system), and small molecules (which affect molecules inside immune cells). We included studies whose participants may also have had psoriatic arthritis. The main outcomes we were interested in were achievement of PASI 90 and any serious side effects that were thought to be associated with the medicines.

We combined all of the studies to allow indirect analysis of the treatments, so we could compare them with each other (network meta-analysis).

What are the main results of the review?

The 109 studies enrolled 39,882 people (all recruited from a hospital) with moderate to severe psoriasis: 26,902 men and 12,384 women; the overall average age was 44 years, the overall mean PASI score at the start of the study was 20 (range: 9.5 to 39), indicating a high level of disease severity. Most studies (n = 73) compared the systemic medicine with a placebo treatment, a total of 25 trials compared systemic treatments with other systemic treatments, and 11 trials compared systemic treatments with systemic treatments and placebo. Most studies were short-term, and in all, 86 trials were multicentric trials (two to 231 centres).

The outcomes presented here were measured 12 to 16 weeks after the study participants were randomised.

The results showed that compared with placebo, all treatments (assessed in the following groupings: anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha (i.e. the treatments known as the biologics); small molecule treatments; other biologics; and conventional systemic agents) were more effective in treating psoriasis when assessed using an index that required 90% improvement (PASI 90).

In relation to the same outcome (PASI 90), the biologic treatments anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha appeared to work better than the small molecules and the conventional systemic agents; and small molecules were associated with a better outcome compared to conventional systemic agents. (IL is an abbreviation of interleukin; TNF is an abbreviation of tumour necrosis factor - both are types of cytokine. A cytokine affects the behaviour of a cell.)

In terms of individual drugs, again when assessing the ability to reach PASI 90, all of the anti-IL17 drugs and guselkumab (an anti-IL23 drug) were more effective than the anti-TNF alpha drugs infliximab, adalimumab, and etanercept, but not certolizumab. Ustekinumab (an IL-12/-23 drug) was better than etanercept. No clear difference was shown between infliximab, adalimumab, and etanercept. Tofacitinib (a small molecule) was superior to methotrexate (a conventional systemic agent), and no difference was shown between the other small molecules and the conventional drugs.

Judged against placebo, six biological medicines worked best at clearing psoriasis lesions. These medicines were ranked as follows (most effective first): ixekizumab, secukinumab (both based on high-certainty evidence), brodalumab, guselkumab, certolizumab (all based on moderate-certainty evidence), and ustekinumab (high-certainty evidence). Regarding the outcomes PASI 75 and Physician Global Assessment (PGA) 0/1 (i.e. achieving 75% improvement and achieving a PGA score of 0 or 1), the results were very similar to the results for PASI 90.

For the risk of serious side effects, there were no clear differences between all of the systemic medicines compared with placebo treatment. Methotrexate had the best safety profile (based on moderate-certainty evidence), followed by ciclosporin (very low-certainty evidence), certolizumab (moderate-certainty evidence), infliximab (very low-certainty evidence), alefacept (low-certainty evidence), and fumaric acid esters (very low-certainty evidence) (all of these are conventional treatments except for certolizumab, infliximab (anti-TNF alpha drugs), and alefacept (classed under 'other biologics'). Major adverse cardiac events, serious infections, or malignancies were reported in both placebo and intervention groups. However, the number of serious side effects was very low, and our conclusions are based on low to very low- (for just over half of the results) or moderate-certainty evidence, so they should be interpreted with caution. The most effective treatments (in terms of reaching PASI 90) had the highest numbers of reported side effects; ustekinumab, infliximab, and certolizumab appeared to have the best compromise between effectiveness and side effects.

For all studies, little information was recorded about quality of life; one third of the medicines studied had no quality of life data.

How up-to-date is this review?

We searched for studies that had been published up to December 2016.