Secukinumab for plaque psoriasis

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Key words Plaque psoriasis, biological treatments, secukinumab, Epistemonikos, GRADE

Abstract

Introduction

Biological treatments have appeared as the main alternative for the management of patients with plaque psoriasis that do not respond to conventional treatment. So, evaluating its actual efficacy and safety is needed.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified 21 systematic reviews including ten studies overall, of which all were randomized trials. We concluded secukinumab achieves clinical improvement in patients with plaque psoriasis, although it is probably associated with serious adverse effects.

Problem

Approximately 20% of patients with plaque psoriasis have moderate to severe disease[1], requiring conventional systemic treatment, such as methotrexate, cyclosporine or acitretin, or phototherapy. However, for a large number of patients, these treatments are not sufficient, due to a limited therapeutic effect or to the presence of adverse effects.

In the search for more effective and safe treatments, biological therapies have emerged in the last years as an alternative. Secukinumab is a human monoclonal antibody that selectively neutralizes interleukin-17A, which has a major role in the pathogenesis of psoriasis. We aimed to evaluate the efficacy and safety of secukinumab in patients with plaque psoriasis.

Key messages

- Secukinumab leads to clinical improvement in moderate to severe plaque psoriasis.
- Secukinumab probably is associated to an increase in serious adverse events.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found 21 systematic reviews[2-22] that included ten primary studies, reported in 23 references [23-45], all corresponding to randomized controlled trials. However, four of these trials were excluded from our analysis: two because the intervention was not administered in usual doses[27,39] and two because no comparison was made against placebo[32-34,44,45]. This table and the summary in general are based on the six randomized trials that answer the question of interest[23,28,31,35,37,40].
What types of patients were included*	All trials included adult patients older than 18 years with plaque psoriasis on the trunk, upper and lower limbs, not including scalp, with moderate to severe disease determined by PASI ≥ 12, IGA 3-4, BSA ≥ 10%, without response to topical treatment, phototherapy or conventional systemic treatment. All trials excluded immunosuppressed patients, with a history of neoplasia or suffering an infection. Two trials[23,37] excluded patients who had received biological treatment with anti-interleukin-17.
What types of interventions were included*	Four trials[23,28,31,37] included subcutaneous secukinumab 150 mg or 300 mg weekly for four weeks and then in monthly doses. One trial[35] included an intervention group with subcutaneous secukinumab 150 mg at weeks 0,4 and 8. Another trial[40] included three intervention groups: subcutaneous secukinumab 150 mg in single dose; subcutaneous secukinumab 150 mg at weeks 0,4 and 8; and subcutaneous secukinumab 150 mg at weeks 0, 1, 2 and 4. All trials compared against placebo.
What types of outcomes were measured	The trials evaluated multiple outcomes, which were grouped in the systematic reviews as follows: • PASI (Psoriasis Area Severity Index): PASI 50, PASI 75, PASI 90, PASI 100 • IGA (Investigator's Global Assessment); PGA (Physician Global Assessment) • DLQI (Dermatology Quality of Life Index) • Adverse events (headache, pruritus, nausea) • Cardiovascular disease

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

	• Infections (upper respiratory tract infection, Candida infection, Herpes viral infection, reactivation of latent tuberculosis) • Neutropenia • Neoplasms • Crohn's disease • Discontinuation The average follow-up of the trials was 45 weeks, with a range between 28 and 52 weeks

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Summary of Findings

The information about the effects of secukinumab is based on six randomized trials including 2531 patients [23,28,31,35,37,40].

All trials reported PASI 75 and PGA/IGA (2531 patients) [23,28,31,35,37,40]. Five trials reported PASI 90 and serious adverse events (2482 patients) [23,28,31,37,40]. Two trials reported DLQI (1708 patients) [28,31].

The summary of findings is as follows:

- Secukinumab leads to an improvement in PASI 75 and PASI 90 score in patients with moderate to severe plaque psoriasis. The certainty of the evidence is high.
- Secukinumab leads to an improvement in PGA/IGA score in patients with moderate to severe plaque psoriasis. The certainty of the evidence is high.
- Secukinumab probably leads to an improvement in DLQI score in patients with moderate to severe plaque psoriasis. The certainty of the evidence is moderate.
- Secukinumab probably leads to an increase in serious adverse events in patients with moderate to severe plaque psoriasis. The certainty of the evidence is moderate.

Secukinumab for plaque psoriasis

Patients Plaque psoriasis
Intervention Secukinumab
Comparison Placebo

Outcomes	Absolute effect*		Relative effect (IC 95%)	Certainty of evidence (GRADE)
	WITHOUT secukinumab	**WITH secukinumab**		
	Difference: patients per 1000			
Improvement in PASI 75**	41 per 1000	662 per 1000	RR 16.15 (11.53 to 22.62)	⨁⨁⨁⨁ High
	Difference: 621 more (Margin of error: 430 to 882 more)			
Improvement in PASI 90**	12 per 1000	401 per 1000	RR 33.43 (18.02 to 62.01)	⨁⨁⨁⨁ High
	Difference: 389 more (Margin of error: 201 to 721 more)			
Improvement in PGA/IGA**	23 per 1000	451 per 1000	RR 19.60 (11.81 to 32.52)	⨁⨁⨁⨁ High
	Difference: 428 more (Margin of error: 248 to 724 more)			
Improvement in DLQI**	81 per 1000	524 per 1000	RR 6.47 (4.09 to 10.26)	⨁⨁⨁◯ Moderate[1]
	Difference: 443 more (Margin of error: 249 to 747 more)			
Serious adverse events	8 per 1000	19 per 1000	RR 2.43 (1.02 to 5.79)	⨁⨁⨁◯ Moderate[2]
	Difference: 11 more (Margin of error: 0 to 38 more)			

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
GRADE: Evidence grades of the GRADE Working Group (see later).

*The risk **WITHOUT secukinumab** is based on the risk in the control group of the trials. The risk **WITH secukinumab** (and its margin of error) is calculated from relative effect (and its margin of error).

** PASI is a clinical score that allows to measure the severity of plaque psoriasis, improvement in PASI 75 and PASI 90 represent the number of patients achieving at least 75% and 90% improvement in their symptoms, respectively. PGA and IGA are clinical scores that evaluate the intensity of plaque psoriasis, patients with improvement in PGA/IGA are those who score 0 or 1, corresponding to the absence of psoriatic plaques and psoriatic plaques almost clear (minimum), respectively. DLQI is a score that assesses quality of life specifically in patients with dermatological diseases, with a score ranging from 0 (minimal impact on quality of life) to 30 (maximum impact on quality of life); DLQI improvement is considered for patients with a score of 0 or 1.

[1] The certainty of the evidence was downgraded in one level due to inconsistency (I2= 62%).
[2] The certainty of the evidence was downgraded in two levels due to imprecision, since in one extreme of the confidence interval adverse effects increase and in the other there is no difference.

Follow the link to access the interactive version of this table (Interactive Summary of Findings – iSoF)

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

The evidence presented in this summary apply to patients with a diagnosis of plaque psoriasis of the trunk, upper and lower limbs, with moderate to severe disease, non-responders to topical treatment, phototherapy, or conventional systemic treatment.

Although the trials did not evaluate children and adolescents, in the absence of direct evidence, it is reasonable to extrapolate these results to those who meet all other characteristics evaluated in the trials.

These results do not apply to the group of patients with psoriasis of the scalp or nails, who generally show a different response to treatment.

About the outcomes included in this summary

The outcomes analyzed in the summary of findings table are those considered critical for decision-making by the authors of this summary. They generally agree with those presented in the systematic reviews identified and in the main guidelines.

PASI 75, PASI 90 and PGA/IGA were selected, since they are clinical scores that correlate with severity or disease improvement.

Quality of life was measured using DLQI score (Dermatology Life Quality Index), a critical outcome that allows to know the direct impact of treatment with secukinumab in the life of patients with plaque psoriasis.

Serious adverse events were considered as they are key for decision-making. For serious adverse events, the definition of ICH (International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) was used, which includes deaths, life-threatening events, hospital admission or prolongation of hospitalization, and adverse events that require intervention to prevent harm or permanent deterioration.

Balance between benefits and risks, and certainty of the evidence

The use of secukinumab has benefits on most outcomes, with clinical improvement that translates into better quality of life for patients. However, it should be kept in mind that there are serious adverse events, mainly cardiac events, infections and neoplasms, which although infrequent, should be considered in clinical practice. It is important to note that all of the primary studies evaluating secukinumab in plaque psoriasis were funded by the pharmaceutical company that developed secukinumab (Novartis Pharmaceuticals).

Resource considerations

Biological treatments, and in particular secukinumab, have a cost considerably higher than conventional systemic treatments (e.g. methotrexate, cyclosporine, acitretin), however they have high effectiveness in the management of plaque psoriasis. A cost-effectiveness systematic review of biological treatments (infliximab, etanercept, adalimumab, apremilast, ustekinumab, secukinumab, and ixekizumab) in moderate to severe plaque psoriasis, places secukinumab in third place considering cost-effectiveness, followed closely by adalimumab in second place, both widely overtaken by infliximab[22].

A formal economic analysis directly evaluating this intervention might be needed in order to reach more accurate estimations. It is important to adjust for healthcare systems with different levels of resources, considering factors such as the costs associated with disease progression, quality-adjusted life years (QALY) and the possible impact on work disability.

What would patients and their doctors think about this intervention

Faced with the evidence presented in this article, most patients and clinicians should be inclined in favor of the use of this intervention, due to its high clinical effectiveness. However, significant variability might be expected, mainly due to the high cost, the increase on serious adverse effects, and the existence of multiple alternative biological treatments, such as infliximab, adalimumab, ixekizumab, among others.

Differences between this summary and other sources

The conclusions of this summary agree with those of the systematic reviews that were analyzed.

The main guidelines, such as the American Academy of Dermatology[1] and the European Academy of Dermatology and Venereology[46] do not mention secukinumab as an alternative for psoriasis, probably because it is a treatment that was not available at the time of their publication. However, the British Association of Dermatologists[47] in its last update (2017), suggests secukinumab as a first-line biological agent in adults with psoriasis, with or without psoriatic arthritis.

Could this evidence change in the future?

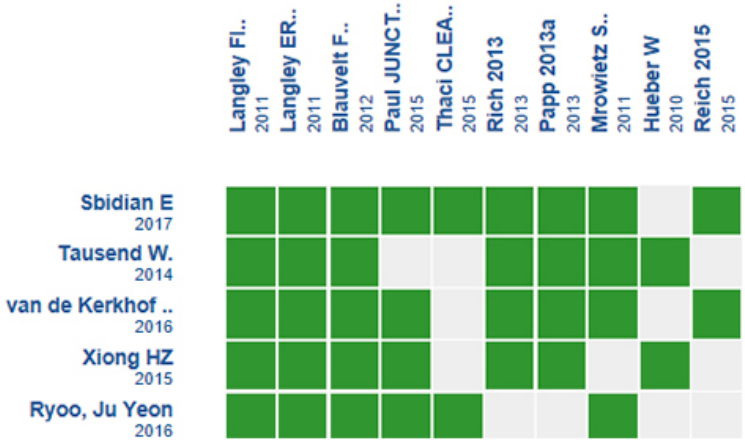
The likelihood that future research changes the conclusions of this summary is low, due to the high certainty of the existing evidence.

We identified ten ongoing systematic reviews in the International prospective register of systematic reviews (PROSPERO) of the National Institute for Health Research about secukinumab for plaque psoriasis compared against placebo[48-57].

We identified two ongoing randomized trials in adult population[58,59] and one in pediatric and adolescent population[60] in the International Clinical Trials Registry Platform of the World Health Organization.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Hypothermic machine perfusion versus static cold preservation in kidney transplantation

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

www.epistemonikos.org.

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