MEDwave

Living Friendly Summaries of the Body of Evidence using Epistemonikos (Frisbee)
Medwave 2018 Mar-Abr;18(2):e7173 doi: 10.5867/medwave.2018.02.7173

Is ustekinumab effective for psoriatic arthritis with insufficient response to initial treatment?

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Citation: Venegas-Iribarren S, Andino-Navarrete R. Is ustekinumab effective for psoriatic arthritis with insufficient response to initial treatment?. *Medwave* 2018 Mar-Abr;18(2):e7173 doi: 10.5867/medwave.2018.02.7173
Submission date: 23/11/2017
Acceptance date: 4/12/2017
Publication date: 2/3/2018
Origin: This article is a product of the Evidence Synthesis Project of Epistemonikos Fundation, in collaboration with Medwave for its publication.
Type of review: Non-blinded peer review by members of the methodological team of Epistemonikos Evidence Synthesis Project.

Abstract

INTRODUCTION
Psoriatic arthritis is an inflammatory arthritis without a clear etiology. Biological therapy is key for its treatment, especially in more complex patients. There are several alternatives for biological treatment, but due to its high cost, it is important to evaluate their real effectiveness.

METHODS
To answer this 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. 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 12 systematic reviews including three randomized trials overall. We concluded ustekinumab leads to clinical improvement in psoriatic arthritis, and probably is not associated to severe adverse effects.

Problem

Psoriatic arthritis is an inflammatory arthritis without a clear etiology. It is associated with psoriasis, and most are seronegative for rheumatoid factor. Currently, there are several treatment alternatives for this condition, many of them extrapolated from drugs proven in rheumatoid arthritis. The efficacy of new medications in psoriatic arthritis has been studied in greater depth recently, especially for patients resistant to initial treatment, either with non-steroidal anti-inflammatories, disease modifying drugs (e.g. methotrexate) or biological medication (e.g. TNF inhibitors). Among these new alternatives is ustekinumab, an IL-12 and IL-23 inhibitor.

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.

Key messages
- Ustekinumab leads to clinical improvement in psoriatic arthritis.
- Ustekinumab is probably not associated to serious adverse events.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found twelve systematic reviews [1],[2],[3],[4],[5],[6],[7],[8],[9],[10],[11],[12], that include three primary studies, reported in six references [13],[14],[15],[16],[17],[18]. All of them are randomized controlled trials. This table and the summary in general are based on the latter.
What types of patients were included*	All of these trials included adult patients with clinical psoriatic arthritis diagnosis and active disease (three or more tender joints, plus C-reactive protein of 3 mg/L [13],[14] or 15 mg/L [15]) and inadequate response or poor tolerance to the use of non-steroidal anti-inflammatories or disease modifying drugs in addition to plaque psoriasis with active lesion or previous history of disease. One trial [13] excluded patients with previous anti-TNF use. On the other hand, the other two trials [14],[15] did include patients with inadequate response or poor tolerance to the use of biological therapies.
What types of interventions were included*	Two trials [13],[14] included subcutaneous ustekinumab 45 mg or 90 mg at baseline, then at week four, then every twelve weeks. One trial [15] did not report the dose or administration scheme. All trials compared against placebo.
What types of outcomes were measured	The outcomes were pooled by the different systematic reviews as follows: • ACR 20 (American College of Rheumatology) • ACR 50 • ACR 70 • HAQ-DI (Health assessment questionnaire disability index) • PASI 75 (Psoriasis area severity index) • Das-28 (Disease activity score) • Dactylitis • Enthesitis

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

Summary of findings

The information on the effects of ustekinumab is based on three randomized trials that included 1073 patients overall [13],[14],[15]. Two trials reported ACR 20 , HAQ-DI, PASI-75 and DAS-28 [13],[14]. Three trials reported serious adverse events [13],[14],[15].

The summary of findings is the following:

- Ustekinumab improves ACR 20 in psoriatic arthritis. The certainty of the evidence is high.
- Ustekinumab improves PASI 75 in psoriatic arthritis. The certainty of the evidence is high.
- Ustekinumab probably leads to little or no difference in serious adverse events in psoriatic arthritis. The certainty of the evidence is moderate.
- Ustekinumab improves DAS-28 in psoriatic arthritis. The certainty of the evidence is high.
- Ustekinumab leads to an improvement of doubtful clinical relevance in HAQ-DI in psoriatic arthritis. The certainty of the evidence is high.

 doi: 10.5867/medwave.2018.02.7173

Ustekinumab for psoriatic arthritis

Patients Psoriatic arthritis with inadequate treatment response
Intervention Ustekinumab
Comparison Placebo

Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT ustekinumab	WITH ustekinumab		
	Difference: patients per 1000			
ACR 20**	219 per 1000	452 per 1000	RR 2.06 (1.64 to 2.58)	⊕⊕⊕⊕ High
	Difference: 233 patients more (Margin of error: 140 more to 347 more)			
PASI 75**	87 per 1000	616 per 1000	RR 7.07 (3.70 to 13.52)	⊕⊕⊕⊕ High
	Difference: 529 patients more (Margin of error: 235 more to 1090 more)			
Serious adverse effects	34 per 1000	19 per 1000	RR 0.56 (0.23 to 1.35)	⊕⊕⊕◯ Moderate[1]
	Difference: 15 patients less (Margin of error: 26 less to 12 more)			
DAS-28 (Remission <2,6)**	65 per 1000	172 per 1000	RR 2.67 (1.69 to 4.21)	⊕⊕⊕⊕ High
	Difference: 107 patients more (Margin of error: 45 more to 207 more)			
HAQ-DI**	1.3 points	1.09 points	--	⊕⊕⊕⊕ High
	MD: 0.21 points better (Margin of error: 0.15 to 0.28 points better)			

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

*The risk **WITHOUT ustekinumab** is based on the risk in the control group of the trials. The risk **WITH ustekinumab** (and its margin of error) is calculated from relative effect (and its margin of error).
**ACR 20 is a clinical scale that allows measuring the effectiveness of drugs in rheumatology, especially in rheumatoid arthritis. Patients with positive ACR 20 achieve at least 20% of improvement in their joint symptoms in a certain period of time; PASI 75 is a clinical scale that allows measuring severity of plaque psoriasis. This scale represents the number of patients that achieve at least 75% of improvement of their symptoms in a certain period of time; DAS-28 is a scale from 0 to 10, where values less than 2.6 indicate disease remission. Values between 2.6 and 3.2 indicate low disease activity. Values between 3.2 y 5.1 indicate moderate activity and values above 5.1 indicate high disease activity; HAQ-DI is a scale from 0 to 3. Values between zero and one represent mild to moderate disability, values between one and two represent moderate to severe disability, and values between two and three represent very severe disability.

[1] The certainty of the evidence was downgraded in one level for imprecision.

Following 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

- This evidence applies to adults with a clinical diagnosis of psoriatic arthritis, active disease and with inadequate response to non-steroidal anti-inflammatories, disease modifying drugs or anti-TNF biological medication.

About the outcomes included in this summary

- The outcomes included in this summary are those considered critical for decision-making by the authors of this summary. The selection coincides with most systematic reviews.
- ACR 20 and DAS 28 were selected because they are clinical scales that correlate with disease severity or improvement.
- PASI 75 was selected because it is a clinical scale that correlates with plaque psoriasis severity or improvement as a secondary outcome, since this would not be the primary purpose of the treatment.
- We considered serious adverse events, since non-severe effects should not affect decision-making, given they are more common in other therapeutic alternatives in these cases (e.g. anti-TNF).
- Finally, HAQ-DI was considered as it is a quality of life scale. This is an important outcome to be measured in the treatment of chronic diseases.

Balance between benefits and risks, and certainty of the evidence

- There is probably little to no difference in severe adverse events against placebo, and there are positive effects in most outcomes evaluated. So, the balance between benefits and risks is very favorable.

Resource considerations

- The cost of this drug varies according to the country, but in general is high in comparison with alternatives (e.g. anti-TNF).
- It is reasonable to conduct a formal economic analysis in the scenarios where this intervention is intended to be used, to obtain more adequate information.

What would patients and their doctors think about this intervention

- Faced with the evidence presented in this summary, most patients and clinicians should be inclined to use this intervention. However, substantial variability can be expected, driven by the cost and the lack of direct evidence comparing ustekinumab with other available alternatives for patients with insufficient response to first-line treatment.

Differences between this summary and other sources

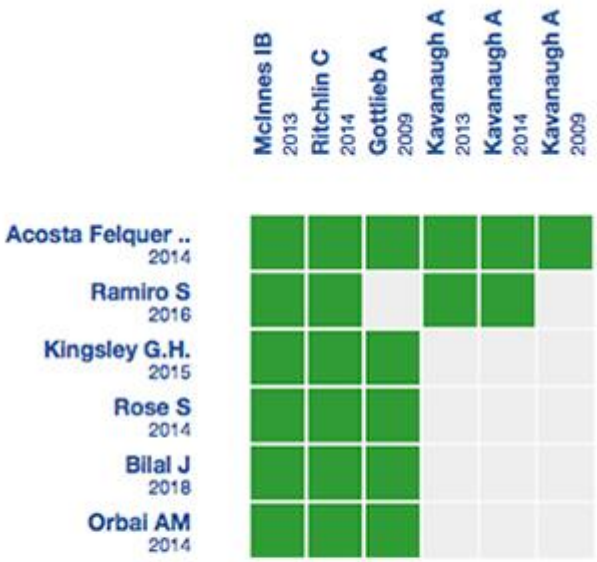
- The conclusions of this summary are consistent with those of the systematic reviews identified.
- The main clinical guidelines, such as those of the American academy of dermatology [19] and the British association of dermatologists [20] do not mention ustekinumab as part of the alternatives. However, it is important to mention this is a new therapy that was probably not available at the time of publication of **these** guidelines. The Spanish academy of dermatology and venereology [21] mentions ustekinumab as part of first line treatment along with anti-TNF in patients with moderate to severe psoriasis. Finally, the European league against rheumatism (EULAR) [22] recommends ustekinumab only as second line therapy in patients with psoriatic arthritis.

Could this evidence change in the future?

- The probability of future research changing the conclusions of this summary is low, given the certainty of the existing evidence.
- We did not identify ongoing trials according to 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: Ustekinumab for psoriatic arthritis

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).

Potential conflicts of interest
The authors do not have relevant interests to declare.

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