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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Is secukinumab effective for psoriatic arthritis with insufficient response to initial treatment?

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Abstract

INTRODUCTION
Psoriatic arthritis is an inflammatory arthritis without a clear etiology. Biological therapy has become key for its treatment, especially in more severe cases. There are several alternatives for biological treatment, including secukinumab. However, it is not clear how effective and safe it is, which is particularly relevant considering its high cost.

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 eight systematic reviews including three randomized trials overall. We concluded secukinumab in psoriatic arthritis leads to an improvement of disease activity and symptoms, and it is probably not associated to severe adverse events.

Problem

Psoriatic arthritis is an inflammatory arthritis without a clear etiology. It is associated with psoriasis, and the majority of patients are seronegative for rheumatoid factor. Currently, there are some alternatives for its treatment, mainly based on drugs proven for rheumatoid arthritis. In recent years, the efficacy of new alternatives for psoriatic arthritis has been studied in greater depth, especially for those who are resistant to initial treatment, either with non-steroidal anti-inflammatories, disease modifying drugs (e.g. methotrexate) or biological drugs (e.g. TNF-inhibitors). Due to its high cost, it is important to evaluate their real effectiveness to achieve a good outcome. Among these new alternatives is secukinumab, an IL-17a 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

- Secukinumab leads to an improvement in disease activity and symptom related scales in psoriatic arthritis.
- Secukinumab probably leads to little or no difference in serious adverse events in psoriatic arthritis.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found eight systematic reviews [1],[2],[3],[4],[5],[6],[7],[8], that include three primary studies, reported in five references [9],[10], [11],[12],[13]. All of them correspond to randomized controlled trials.
What types of patients were included*	All of the trials included adult patients with clinical psoriatic arthritis diagnosed according to CASPAR criteria, with active disease and inadequate response with non-steroidal anti-inflammatories, disease modifying drugs or anti-TNF biological medication. The proportion of patients with plaque psoriasis lesions was not reported in the systematic reviews.
What types of interventions were included*	One trial [10] included subcutaneous secukinumab 75 mg, 150 mg or 300 mg once a week for four weeks. Then, the same dosage was repeated every four weeks. One trial [9] included subcutaneous secukinumab 10 mg/kg at the start, at week two and at week four. Then, followed by subcutaneous secukinumab 75 or 150 mg every four weeks. Another trial [11] included intravenous secukinumab 10 mg/kg at day one and then at day 22. All of the trials compared against placebo.
What types of outcomes were measured	The outcomes were pooled by the different systematic reviews as follows: • ACR 20 at 24 weeks • ACR 20 in patients with previous anti-TNF use • HAQ-DI (Health assessment questionnaire disability index) • PASI 75 (Psoriasis area severity index) • Das-28 (Disease activity score) • Serious adverse events • 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 secukinumab is based on three randomized trials that included 1045 patients overall [9],[10],[11]. All of these trials reported ACR 20, HAQ-DI and serious adverse events. Two trials reported PASI 75 and DAS-28. The summary of findings is the following:

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

Secukinumab for psoriatic arthritis

Patients Psoriatic arthritis with inadequate treatment response
Intervention Secukinumab
Comparison Placebo

Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT Secukinumab	**WITH Secukinumab**		
	Difference: patients per 1000			
ACR 20	173 per 1000	478 per 1000	RR 2.77 (2.15 to 3.58)	⊕⊕⊕⊕ High
	Difference: 305 more per 1000 (Margin of error: 198 less to 445 more)			
PASI 75	110 per 1000	506 per 1000	RR 4.6 (1.72 to 12.02)	⊕⊕⊕⊕[1] High
	Difference: 396 more per 1000 (Margin of error: 84 to 212 more)			
Serious adverse events	41 per 1000	38 per 1000	RR 0.92 (0.47 to 1.79	⊕⊕⊕◯[2] Moderate
	Difference: 3 less per 1000 (Margin of error: 22 less to 33 more)			
DAS-28**	4.1 points	3.46 points	--	⊕⊕⊕⊕ High
	Difference: 0.64 points less (Margin of error: 0.42 to 0.85)			
HAQ-DI***	0.95	0.77	--	--
	Difference: 0.18 points less (Margin of error 0.11 to 0.25 to less)		--	⊕⊕⊕⊕ High

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 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).

** 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]Although there is significant inconsistency, the certainty of evidence was not downgraded in this item, since this is a result of trials with greater and less benefits.
[2] The certainty of the evidence was downgraded in one level for imprecision

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 applies to adult patients with clinical diagnosis of psoriatic arthritis according to CASPAR criteria. Also, with active disease and 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 results coincide with the outcomes mentioned by 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.
- Serious adverse events were also considered, since they are more common in first line treatments with anti-TNF. This would be an important issue to address because it could indicate some advantage, or no difference from first line treatment.
- Finally, HAQ-DI was considered as it is a quality of life scale. This is an important outcome to be measured in patients with chronic diseases.

Balance between benefits and risks, and certainty of the evidence

- Even though the certainty of the evidence is moderate, it is important to consider there is probably little or no difference in adverse events against placebo. This is important because adverse events are one of the main disadvantages of first line biological treatment, leading to dropouts and treatment failure.

Resource considerations

- The cost varies in each country, but in general it has a high cost. However, the total treatment cost could be less than first line anti-TNF treatment.
- It is reasonable to conduct a formal economic evaluation in the scenarios in which this intervention is intended to be incorporated.

What would patients and their doctors think about this intervention

- According to the evidence presented in this summary, secukinumab would be a good alternative to first line biological treatment. Especially, taking into account the lower rate of adverse events.
- Cost considerations could incorporate a variation in decision making.

Differences between this summary and other sources

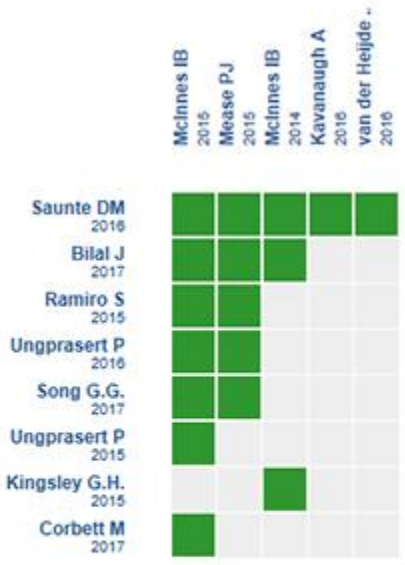
- The conclusions of this summary are consistent with those of the analyzed systematic reviews.
- The main clinical guidelines such as the American academy of dermatology [14], British association of dermatologists [15], and Spanish academy of dermatology and venereology [16], do not mention secukinumab as part of the therapy. However, it should be noted that this is a new treatment.

Could this evidence change in the future?

- The probability that future research changes the conclusions of this summary is low, due to the current high certainty of evidence.
- There are multiple ongoing trials evaluating this intervention in psoriatic arthritis. Trials comparing it against TNF inhibitors are particularly important, of which there is at least one in progress [17].
- We identified one review in progress adressing this question [18] in the International prospective register of systematic reviews (PROSPERO). It could offer relevant information, especially if it incorporates direct comparison data against other treatment alternatives.

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:** Secukinumab 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.

References

1. Corbett M, Chehadah F, Biswas M, Moe-Byrne T, Palmer S, Soares M, Walton M, Harden M, Ho P, Woolacott N, Bojke L. Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease-modifying antirheumatic drugs: a systematic review and economic evaluation. Health technology assessment (Winchester, England). 2017;21(56):1-326.
2. Paccou J, Wendling D. Current treatment of psoriatic arthritis: update based on a systematic literature review to establish French Society for Rheumatology (SFR) recommendations for managing spondyloarthritis. Joint Bone Spine. 2015 Mar;82(2):80-5. | CrossRef | PubMed |
3. Ramiro S, Smolen JS, Landewé R, van der Heijde D, Dougados M, Emery P, de Wit M, Cutolo M, Oliver S, Gossec L. Pharmacological treatment of psoriatic arthritis: a systematic literature review for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis. 2016 Mar;75(3):490-8. | CrossRef | PubMed |
4. Saunte DM, Mrowietz U, Puig L, Zachariae C. Candida infections in patients with psoriasis and psoriatic arthritis treated with interleukin-17 inhibitors and their practical management. Br J Dermatol. 2017 Jul;177(1):47-62. | CrossRef | PubMed |
5. Ungprasert P, Thongprayoon C, Davis JM 3rd. Indirect comparisons of the efficacy of subsequent biological agents in patients with psoriatic arthritis with an inadequate response to tumor necrosis factor inhibitors: a meta-analysis. Clin Rheumatol. 2016 Jul;35(7):1795-803. | CrossRef | PubMed |
6. Ungprasert P, Thongprayoon C, Davis JM 3rd. Indirect comparisons of the efficacy of biological agents in patients with psoriatic arthritis with an inadequate response to traditional disease-modifying anti-rheumatic drugs or to non-steroidal anti-inflammatory drugs: A meta-analysis. Semin Arthritis Rheum. 2016 Feb;45(4):428-38. | CrossRef | PubMed |
7. Kingsley G.H., Scott D. L. Assessing the effectiveness of synthetic and biologic disease-modifying antirheumatic drugs in psoriatic arthritis- A systematic review. Psoriasis: Targets and Therapy. 2015;5:71-81.
8. Bilal J, Riaz IB, Kamal MU, Elyan M, Sudano D, Khan MA. A Systematic Review and Meta-analysis of Efficacy and Safety of Novel Interleukin Inhibitors in the Management of Psoriatic Arthritis. Journal of clinical rheumatology: practical reports on rheumatic & musculoskeletal diseases. 2017.
9. Mease PJ, McInnes IB, Kirkham B, Kavanaugh A, Rahman P, van der Heijde D, Landewé R, Nash P, Pricop L, Yuan J, Richards HB, Mpofu S; FUTURE 1 Study Group. Secukinumab Inhibition of Interleukin-17A in Patients with Psoriatic Arthritis. N Engl J Med. 2015 Oct;373(14):1329-39. | CrossRef | PubMed |
10. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, van der Heijde D, Landewé R, Conaghan PG, Gottlieb AB, Richards H, Pricop L, Ligozio G, Patekar M, Mpofu S; FUTURE 2 Study Group. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015 Sep 19;386(9999):1137-46. | CrossRef | PubMed |
11. McInnes IB, Sieper J, Braun J, Emery P, van der Heijde D, Isaacs JD, Dahmen G, Wollenhaupt J, Schulze-Koops H, Kogan J, Ma S, Schumacher MM, Bertolino AP, Hueber W, Tak PP. Efficacy and safety of secukinumab, a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomised, double-blind, placebo-controlled, phase II proof-of-concept trial. Ann Rheum Dis. 2014 Feb;73(2):349-56. | CrossRef | PubMed |
12. Kavanaugh A, McInnes IB, Mease PJ, Hall S, Chinoy H, Kivitz AJ, Wang Z, Mpofu S. Efficacy of Subcutaneous Secukinumab in Patients with Active Psoriatic Arthritis Stratified by Prior Tumor Necrosis Factor Inhibitor Use: Results from the Randomized Placebo-controlled FUTURE 2 Study. J Rheumatol. 2016 Sep;43(9):1713-7. | CrossRef | PubMed |
13. van der Heijde D, Landewé RB, Mease PJ, McInnes IB, Conaghan PG, Pricop L, Ligozio G, Richards HB, Mpofu S. Brief Report: Secukinumab Provides Significant and Sustained Inhibition of Joint Structural Damage in a Phase III Study of Active Psoriatic Arthritis. Arthritis Rheumatol. 2016 Aug;68(8):1914-21. | CrossRef | PubMed | PMC |
14. American Academy of Dermatology Work Group, Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, Gottlieb A, Koo JY, Lebwohl M, Leonardi CL, Lim HW, Van Voorhees AS, Beutner KR, Ryan C, Bhushan R. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. J Am Acad Dermatol. 2011 Jul;65(1):137-74. | CrossRef | PubMed |
15. Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler DA, Finlay AY, Griffiths CE, Jackson K, McHugh NJ, McKenna KE, Reynolds NJ, Ormerod AD; (Chair of Guideline Group). British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. Br J Dermatol. 2009 Nov;161(5):987-1019. | CrossRef | PubMed |
16. Daudén E, Puig L, Ferrándiz C, Sánchez-Carazo JL, Hernanz-Hermosa JM; Spanish Psoriasis Group of the Spanish Academy of Dermatology and Venereology. Consensus document on the evaluation and treatment of moderate-to-severe psoriasis: Psoriasis Group of the Spanish Academy of Dermatology and Venereology. J Eur Acad Dermatol Venereol. 2016 Mar;30 Suppl 2:1-18. | CrossRef | PubMed |
17. Novartis Pharmaceuticals. Efficacy of Secukinumab Compared to Adalimumab in Patients With Psoriatic Arthritis. clinicaltrials.gov. 2017.
18. Mark Corbett, Laura Bojke, Fadi Chehadah, Thirimon Moe Byrne, Matthew Walton, Stephen Palmer, Nerys Woolacott, Melissa Harden. Certolizumab pegol and Secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs. PROSPERO 2016: CRD42016033357. | Link |

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