

Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)

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Is rituximab effective for induction of remission in ANCA-associated vasculitis?

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Abstract

Adding rituximab to the treatment with corticosteroids has been proposed as a therapeutic alternative for inducing remission in anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis, especially when fertility is a concern, or when there is contraindication or intolerance to cyclophosphamide.

Problem

Immunosuppression with cyclophosphamide and corticosteroids has constituted the standard treatment for induction of remission in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis for years. Given the multiple adverse effects of cyclophosphamide, alternatives have been searched, such as the anti-CD20 antibody rituximab.

Clinical guidelines recommend it as a therapeutic alternative, especially in patients concerned about fertility preservation that maintain disease activity after standard treatment, or those that have contraindication or do not tolerate it.

Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information we generated a structured summary 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, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- Rituximab may slightly increase induction of remission rate, but it may also increase the risk of infection.
- It is not clear whether rituximab increases the risk of cancer, or whether it increases or decreases mortality because the certainty of the evidence is very low.
- The conclusions of this summary are in agreement with the systematic review identified but they disagree with the main guidelines.

About the body of evidence for this question

<p>What is the evidence. See evidence matrix in Epistemonikos later</p>	<p>We found one systematic review [1] including 37 primary studies reported in 42 references [2],[3],[4],[5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29],[30],[31],[32],[33],[34],[35],[36],[37],[38],[39],[40],[41],[42],[43]. Three studies correspond to randomized controlled trials, reported in eight references [2],[3],[11],[13],[20],[21],[37],[43]. This table and the summary in general are based on the latter.</p>
<p>What types of patients were included</p>	<p>All studies included patients with ANCA-associated vasculitis. All studies included patients with Wegener's granulomatosis or microscopic polyangiitis, and two studies also included renal limited vasculitis [2],[11],[37],[43]. Average age was 52 years [3],[13],[20],[21], 68 years [37],[43] and it was not reported in one study [2],[11]. Two studies reported the percentage of patients with new disease: 66% [3],[13],[20],[21] and 100% [37],[43]. The degree of disease activity measured with BVAS was 8.4 [3],[13],[19],[20],[21],[37],[43], and it was not reported in one study [2],[11].</p>
<p>What types of interventions were included</p>	<p>All studies considered rituximab as the intervention. Two studies [3],[13],[20],[21],[37],[43] administered 375 mg/m²/week during four weeks. One study [2],[11] administered an infusion of 500 mg per day at days 1 and 15, then at 5.5 months and when completing 18 months. One study [37],[43] added cyclophosphamide 15 mg/kg during the first and third rituximab infusion. Two studies [3],[13],[20],[21],[37],[43] used cyclophosphamide as comparison. One of them [3],[13],[20],[21] employed a dose of 2 mg/kg/day and the other [37],[43] used 15 mg/kg every 2 weeks for the first three doses, then every 3 weeks until achieving remission. Both studies switched cyclophosphamide to azathioprine after achieving remission. The third study [2],[11] used azathioprine as comparison in an initial dose of 2 mg/kg/day during 22 months.</p>
<p>What types of outcomes were measured</p>	<p>Induction and maintenance of remission, serious adverse events, defined as hospitalizations, cancer or mortality; other adverse effects as infections or hematological events.</p>

Summary of findings

The information on the effects of rituximab is based on three randomized trials including 350 patients. All studies reported mortality and adverse effects. Only two studies reported remission [3],[13],[20],[21],[37],[43].

- Rituximab may slightly increase induction of remission rate. The certainty of the evidence is low.
- Rituximab may increase the risk of infection. The certainty of the evidence is low.
- It is not clear whether rituximab increases the risk of cancer because the certainty of the evidence is very low.
- It is not clear whether rituximab increases or decreases mortality because the certainty of the evidence is very low.

Rituximab for ANCA-associated vasculitis				
Patients	ANCA-associated vasculitis			
Intervention	Rituximab			
Comparison	Control			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT Rituximab	WITH Rituximab		
	Difference: patients per 1000			
Induction of remission	560 per 1000	638 per 1000	RR 1.14 (0.93 to 1.40)	⊕⊕○○ ^{1,2} Low
	Difference: 78 patients more per 1000 (Margin of error: 39 to 224 more)			
Mortality	49 per 1000	23 per 1000	RR 0.47 (0.16 to 1.35)	⊕○○○ ^{1,2} Very low
	Difference: 26 patients less per 1000 (Margin of error: 41 less to 17 more)			
Infections	113 per 1000	127 per 1000	RR 1.12 (0.54 to 2.34)	⊕⊕○○ ^{1,2} Low
	Difference: 14 patients more per 1000 (Margin of error: 52 less to 152 more)			
Neoplasms	24 per 1000	17 per 1000	RR 0.70 (0.17 to 2.87)	⊕○○○ ^{1,2} Very low
	Difference: 7 patients less per 1000 (Margin of error: 20 less to 45 more)			

RR: Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

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

1 The studies did not report data to assess risk of bias, so it is assumed they have risk of bias.
2 The confidence interval included both clinically important benefits and risks. We downgraded the certainty of the evidence in two levels for mortality and infection considering the confidence interval is wider, including large benefits and risks.

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

- All studies included patients with ANCA-associated vasculitis, including Wegener's granulomatosis, microscopic polyangiitis and renal limited vasculitis, so this evidence should only be applied to patients with these conditions.
-

About the outcomes included in this summary

- The outcomes presented in this summary are those considered critical for decision-making by the authors of this summary. Additionally, they are in agreement with those mentioned in the main guidelines [44],[45]. and studies.
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Balance between benefits and risks, and certainty of the evidence

- The intervention might lead to risks, and there is not enough certainty about superiority on relapse or less adverse effects. On the other hand it might lead to little or no difference in mortality. The risk/benefit ratio is probably not favorable.
-

Resource considerations

- It is a high cost intervention. Given the uncertainty about its benefits it is not possible to provide an adequate cost/benefit estimation.
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Differences between this summary and other sources

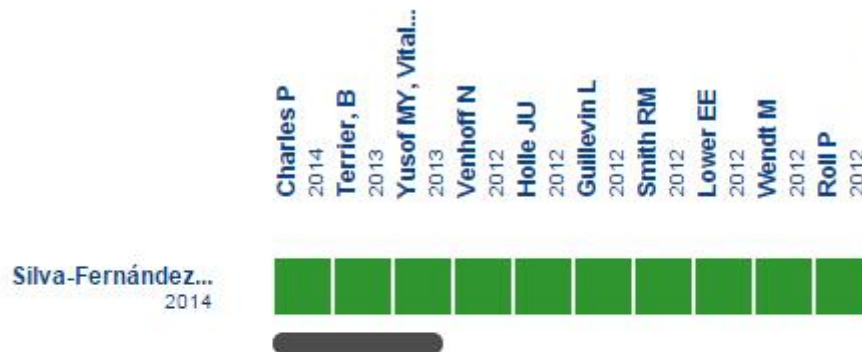
- The conclusions presented in this summary are in agreement with the only systematic review identified [1].
 - The conclusions of this summary differ from the main guidelines [44],[45], which recommend rituximab as an alternative to cyclophosphamide with the goal of reducing adverse effects.
-

Could this evidence change in the future?

- The likelihood of future research changing the information presented in this summary is high, because of the low certainty of the evidence. There is at least one ongoing randomized trial for this question [46].
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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.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.

The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.

The rows represent systematic reviews that share at least one primary study, and columns display the studies.

The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version**: [Rituximab in ANCA-associated renal vasculitis](#)

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.

The details about the methods used to produce these summaries 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).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest

The authors do not have relevant interests to declare.

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