Intern Emerg Med (2014) 9:223–224
DOI 10.1007/s11739-013-1024-9

THE CUTTING EDGE: RESEARCH UPDATE

Is it safe to withdraw etanercept in established rheumatoid arthritis after low disease activity achievement?

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Received: 10 November 2013 / Accepted: 15 November 2013 / Published online: 5 December 2013
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Background

Rheumatoid arthritis (RA) is an immunologically driven chronic condition characterized not only by persistent joint inflammation (synovitis) but also by systemic inflammation [1].

Uncontrolled active RA produces disability and a reduction of the health-related quality of life that result in loss of work and high medical and social costs [2]. The impact of RA on patients and society justifies treatment with biologics [2], expensive drugs that are not free from complications and adverse events, even severe [3].

The target of treatment in RA is achievement of low disease activity or remission [4]. It is yet to be clarified whether low disease activity or remission can be also sustained, not only by maintaining the recommended therapy but also by reducing or discontinuing the biologic treatment. In fact, a reduction or withdrawal of such treatment could imply a great amount of financial saving for the National Health Systems.

Although there are many observational studies regarding withdrawal of anti-TNF-alpha after a period of induction, evidence coming from randomized clinical trials is still lacking.

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Summary

In a randomized controlled trial, Smolen et al. [5] assessed whether the response to conventional doses of biologics and background methotrexate in patients with moderately active disease would be sustained after etanercept reduction or withdrawal. Patients aged between 18 and 70 with moderate disease activity, defined as a disease activity score on 28 joints (DAS28) value between 3.2 and 5.1 despite treatment with methotrexate were enrolled and given 50 mg etanercept plus methotrexate every week during an open label period of 36 weeks. Patients who completed the open label stage and achieved a sustained low disease activity (DAS28 < 3.2) were considered eligible for a subsequent double-blind period of 52 weeks. They were randomized in a 1:1:1 ratio to a weekly subcutaneous injection of 50 mg of etanercept plus methotrexate, 25 mg of etanercept plus methotrexate or etanercept placebo plus methotrexate.

The primary endpoint was the proportion of patients at week 88 with a low disease activity (DAS28 ≤ 3.2) in the groups given 50 mg of etanercept and etanercept placebo in the double-blind period. If low disease activity was maintained significantly more frequently when 50 mg etanercept was continued than with placebo, a conditional primary endpoint was the proportion of patients receiving 25 mg etanercept who achieved low disease activity. A conditional endpoint was the proportion of patients receiving 25 mg of etanercept who maintained a low disease activity. Secondary endpoints were remission based on DAS28 (<2.6) and remission based on simplified disease activity index criteria (≤ 3.3).

Out of the 834 enrolled patients, 604 were eligible for the double-blind period: 202 were assigned to 50 mg etanercept plus methotrexate, 202 to 25 mg of etanercept plus

methotrexate and 200 to placebo plus methotrexate. At the end of the double-blind period, 166 (82.6 %) of 201 patients receiving 50 mg of etanercept maintained a low disease activity as compared to 84 (42.6 %) of 200 receiving placebo (mean difference 40.8 %, 95 % CI 32.5–49.1 %; $p < 0.0001$). In addition, 159 (79.1 %) of 201 patients given 25 mg etanercept had low disease activity at the end of the double-blind period (mean difference from placebo 35.9 %, 95 % CI 27.0–44.8 %; $p < 0.0001$). Furthermore, significantly fewer patients in the withdrawal group attained remission based on DAS28 and simplified disease activity index.

Sponsorship of the PRESERVE study

The trial was sponsored by Pfizer, which was responsible for data collection and analysis. The academic authors and sponsor representatives were involved in the study design, data analyses, data interpretation, writing of the report, and the final decision to submit for publication.

Strengths of the study

- It addresses a relevant issue for pharmacoeconomic implications. Withdrawal or dosage reduction of biologic drugs would mean a significant positive impact on National Health System costs.
- It is the first double-blind randomized control study assessing maintenance of low disease activity and remission in RA after etanercept withdrawal.

Question marks

- It is not specified how often the follow-up visits were performed. Furthermore, it is not clear how the patients were evaluated during the follow-up visits.
- It is not a common clinical practice to abruptly discontinue etanercept in established RA. Would it have been better to discontinue etanercept after a period of gradual dose reduction instead of abruptly stopping it?
- Is there a subgroup of patients who may not experience a flare-up of the disease despite etanercept withdrawal? A subgroup analysis may have been useful to clarify this point.

Clinical bottom line

In patients with established RA who have their disease adequately controlled by methotrexate plus etanercept, the withdrawal of biologic treatment seems to be related to an increase of disease activity. Further studies will need to assess if a gradual tapering of biologic treatment would be safe.

Conflict of interest None.

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