Reviewer’s report

Title: Real-world effectiveness of abatacept for rheumatoid arthritis treatment in European and Canadian populations: a 6-month interim analysis of the 2-year, observational, prospective ACTION study

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Reviewer: László Hodinka

Reviewer’s report:

Review of the manuscript of Nuesslein HG and co-authors „Real world effectiveness of abatacept for rheumatoid arthritis treatment in European and Canadian populations: a 6-month interim analysis of the 2-year, observational, prospective ACTION study

The article fits into the article type considered by BMC Musculoskeletal Disorders as „research”, i.e. clinical research in this respect.

Confidential comments to the editors: none

Major Compulsory Revisions: none

Minor essential revisions: none

Discretionary revisions:

Assessment

The question posed by the authors is clear: the main question is to determine the retention rates to abatacept of rheumatoid arthritis patients among observational circumstances. The secondary endpoints, as clinical effectiveness and safety serve well to support the analysis of withdrawals, as well as the detailed analysis of the pre-treatment medication failures. A special value is the „real-world” approach, as in the second decade of the biological area more experience is necessary to complete the trial results obtained in highly selective protocols and therefore homogeneous patient populations. The multicentric assembly of investigators also contributes to the intended heterogeneity not only of patients but national treatment practices. The whole ACTION study is planned for two years but the interim analysis at 6 months is a correct decision as according to the experience the effectiveness of a biological can be judged on the basis of 3-months response (Aletaha, ARD) and the relevant adverse effects occur just in some months after starting a biological.

The methods correspond to the methods used in rheumatological especially in arthritis Randomised Clinical Trials and non-interventional clinical studies. Regarding the patient inclusion it would be noteworthy to explain there or to discuss the fact that majority of the patients had a disease longer than 6 years, 68,8 % in the second-line group and even 38,8 % in the first-line group and so 65,6 % in the overall population (Table 1). Similarly, as in the Fig 3 it is shown
that 1.4% (DAS28ESR) and 2.9% (DAS28CRP) of the second line patients (about 10 patients) were in remission at the baseline, it is disputable that what was the reason to start a new biological. Although remissions calculated by CDAI was 0.1%, which in absolute number is maximum one patient, in fact there were some patients inactive at the start of abatacept. A possible explanation may be that these patients experienced some kind of intolerance.

The data presented in the text and shown in the Figures and Tables are convincing and coherent. Checking the sums and the operations based on the published data reveal correct calculations and in this respect support the conclusions. The baseline data show, that the first-line and the second-line populations were comparable regarding activity, function, rheumatoid factor and anti-CCP positivity. In the first-line group the erosive arthritis was slightly less frequent (58% versus 71.4% in the second line group). This difference may be explained, that in the first-line group disease duration was shorter (6.9 versus 11.5 years in the second-line population). Data presented to illustrate the main endpoint, e.g. retention rates clearly support the statement that retention is better among first-line treated patients (text and Figure 2 A). Analyzing the causes of discontinuations (Primary and secondary ineffectivity and safety/intolerance, Figure 2 B) shows that discontinuations because of secondary ineffectivity start at about 40 days of treatment, about simultaneously with the withdrawals because of primary ineffectivity. The two Kaplan-Meyer graphs start to diverge at about 100 days. One would expect that secondary ineffectivity presents later in the treatment course being a result of induction of anti-drug antibodies. Abatacept being an anti-receptor fusion protein in itself is less antigenic for its specific domain as is a Ig Variable domain (it is proven for etanercept). Considering this the early presentation of the suspected secondary ineffectivity may be discussed. Although the statistical analyses used throughout the study are Kaplan-Meyer curves, means, standard deviations and confidence limits and no further statistics form group comparisons, the author use the term “significantly greater proportion of ... patients” when writing about the HAQ-DI response in the last paragraph of the “Effectiveness over 6 months” part of the Results. All the other data presented for abatacept response are completely shown and discussed.

The manuscript fully adhere to the relevant standards for reporting and data deposition. The sites participating in the investigation are acknowledged centres of rheumatology practice and clinical research and the authors have extensive experience in trials and presentation. That is a kind of guarantee for a well planned protocol, correct data collection and elaboration, proper evaluation and conclusion as well.

The presented data support the conclusion, i.e. that retention rates for abatacept treatment of rheumatoid arthritis patients are high, especially when started as a first biological. The discussion argues convincing that this is comparable to results presented in randomised clinical trials and collected in national registry databanks.

The limitations – using this term in positive sense - of the work are a
The authors clearly acknowledged the background results and discussed them. This is reflected in the References, containing the relevant publications, even „last minute” ones from this year.

The abstract summarises correctly the whole structure of the article mentioning the key elements. It is in itself informative and completely understandable concentrated description of the content of the detailed work.

As a conclusion of all of the above the manuscript is acceptable and recommended for publication.

Level of interest
Considering that the subject is a special research (retention rates) of a special population (rheumatoid arthritis patients treated with biologicals) within the spectrum of musculoskeletal disorders it can be classified as „an article of importance in its field”.

Quality of written English
A native English reviewer could properly evaluate the style and expressions. For a reader educated on the basic international business and especially on scientific English, the manuscript is clearly understandable.

Statistical review
Respecting the nature and source of the data collected the applied statistical measures are sufficient to support the conclusions. No further statistical analysis or review is recommended.

Declaration of competing interests
The reviewer is a local, national speaker and health economy counsellor for AbbVie, Amgen, Bristot-Myers Squibb, Egis, MSD, Novartis, Roche and UCB, conducts clinical trials as principal investigator for biologicals.

Recommended next step
Accept after discretionary revisions (which the authors can choose to ignore).

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.