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Rheumatoid factor as predictor of response to abatacept, rituximab and tocilizumab in rheumatoid arthritis: Systematic review and meta-analysis ☆

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ABSTRACT

Objective: To identify if rheumatoid factor (RF) is predictor of response to rituximab (RTX), abatacept (ABT), and tocilizumab (TCZ) in rheumatoid arthritis (RA).
Methods: Systematic review and meta-analysis of clinical trials and observational studies based on a sensitive search. Meta-regression was used to explore causes of heterogeneity. Unpublished data of clinical trials provided by the authors were also included.
Results: The electronic search captured 3221 references and 422 meeting abstracts. By hand search, four additional articles were also identified. A total of 23 studies meet the purpose of the study and were included in the review. RF positivity at starting predicts better ACR20 [OR, 1.95 (1.24, 3.08)], ACR50 [OR, 5.38 (2.50, 11.60)] and EULAR response [OR, 3.52 (1.66, 7.45)] in 14 studies with RTX, and better ACR20 [OR, 1.51 (1.21, 1.90)] in 6 studies with TCZ. In 3 studies with ABT, no association was found between response and RF [OR 1.36 (0.97, 1.90)]. No asymmetries in the funnel plots or significant variables were found in the meta-regression.
Conclusion: In RA, RF positivity predicts better response to RTX and TCZ but not to ABT.

Introduction

Standard treatment for rheumatoid arthritis (RA) includes nowadays traditional DMARD commonly methotrexate, and biologics largely TNF antagonists for incomplete responders to DMARD [1–3]. Nevertheless, there is considerable heterogeneity in the response of RA patients, and a proportion of patients does not benefit from treatment with a certain biologic but may do well with a different one.

In RA, presence of rheumatoid factor (RF) is associated with worse prognosis [4,5]. This association suggests that B cells play an important role in the pathogenesis of RA as demonstrated by the depletion with rituximab (RTX). Strategies searching biomarkers that predict response to biologic therapies allowing for the selection of patients with the highest chance for response are pertinent. Whether RF is a biomarker of response to RTX is disputed [6–9].Similarly, results on the association between RF and response to treatment with TNF antagonists are also contradictory [10–12]. Also, the predictive value for response to biologics other than TNF antagonists is largely unknown. In the present work, we aim to summarize the evidence of the value of RF status and RF level to the response to abatacept (ABA), RTX and tocilizumab (TCZ) by systematic review and meta-analysis of available evidence.

Materials and methods

We performed a systematic literature review to identify all publications analysing the association between RF and response to non-TNFantagonist biological therapies. The protocol of the review is available online as supplementary material. Unpublished data of clinical trials provided by the authors were also included.

Systematic literature research

Medline, Embase, and the Cochrane Library were searched for articles published between 2000 and August 2011. The search strategy focused on synonyms of RF, response and synonyms of RTX, ABT and TCZ (see details in supplementary material), and was limited to articles published in English, Spanish, French, Italian, or Portuguese. Online abstracts of the European League Against Rheumatism (EULAR) and the American College of

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Rheumatology (ACR) congresses from 2001 to 2011 were also included.

Selection of articles

The selection criteria for articles and abstracts were as follows: (1) inclusion of patients with RA treated with RTX, ABT, and TCZ; (2) a baseline RF measure; (3) validate measured of clinical response; (4) inclusion of the association between FR and response to RTX, ABT, and TCZ, or sufficient data to calculate it; and (5) design of clinical trials, or retrospective or prospective observational study. Two reviewers (JRM and ES) screened articles and abstracts for selection criteria independently, using a third reviewer (LC) for consensus. Once unrelated articles were excluded, the full report of all the selected studies was reviewed. Subsequently, articles not fulfilling all selection criteria were excluded, and a table with the reasons for exclusion produced (published online as supplementary material). In addition, a hand search of articles found in the reference lists of the included articles was made.

Data extraction

Data collected included publication details, study design, characteristics of patients, RF assessment (status/titer and immunoglobulin subtype), biological treatment and definition of response.

Risk of bias

We created an *ad hoc* checklist to analyze the risk of bias of included studies, containing 30 items with punctuation from 0 to 100 (from higher to lower risk). This checklist was based on the guidelines for assessing quality in prognostic studies on the basis of framework of potential biases proposed by Hayden et al. (available upon request) [13].

Statistical analysis

Results are presented as summary effect measures assembled by RF status or isotype, and by response definition. When a measure of association was not available, this was calculated from the available data. Incomplete data were requested by email to five authors, and response was obtained from 3.

Meta-analyses were performed using random-effects approach with DerSimonian and Laird method computing summary OR[14].Meta-analysis was only done if at least 3 studies or subanalyses with similar design were available. For every single analysis, the effect was plotted by the inverse of its standard error to identify risk of publication bias assessing visually the symmetry of funnel plots, and its statistical significance was calculated using Egger test [15]. In the meta-analysis, heterogeneity refers to consistency or inconsistency of the findings. In this review, it was tested as proposed by Higgins and Thompson using I^2[16,17]. An I^2 value $>40\%$ was arbitrarily chosen as high levels of heterogeneity. High value of I^2 indicates low consistency of results. If high statistic heterogeneity was present, possible factors of heterogeneity were investigated using sensitivity analysis and meta-regression. Meta-regression was performed to analyze the contribution of time to assess response, number of patients, quality of the data, time of disease duration, prospective design of the study, and level of evidence to the OR. A $p<0.10$ was considered significant in the meta-regression[18]. Stata version 11.1 (Stata/IC 11.1 for Windows, StataCorp LP, Texas, USA) was used in all statistical analysis.

Results

The search captured 3221 references and 422 meeting abstracts. After title/abstract screening, 37 articles were retrieved for full text review. A total of 26 articles were excluded after detailed review (see supplementary material) [32–57]. Eleven articles fulfilled the inclusion criteria (Fig. 1) [6–9,19–25]. Six meeting abstract were also incorporated [26–31]. By hand search, four articles and two abstracts were additionally included [58–63].

A total of 5832 patients were included in 23 studies from the 23 articles. Characteristics of selected articles, age and sex, duration of RA, anti-citrullinated protein antibodies status, baseline DAS28, and baseline treatments are presented in Table 1. Time to assess response ranged from 12 to 48 weeks. Association between RF and response was analyzed in 14 studies with RTX, 3 with ABT, and 6 studies with TCZ (an article included data from three studies). Risk of bias of the included studies was moderate–high, with only 25% of studies reaching a score of 70. The results of individual studies by biologic treatment and by response definition are shown in Table 2.

Rituximab

A total of 2103 patients treated with RTX were included in 14 studies. Eleven articles analyzed the predictive value for response of RF status. Four studies analyzed also the association of response with RF titer. IgM RF was the most frequently studied isotype, but IgA RF and IgG RF isotypes were studies in two and one study, respectively.

Individual results

Five studies reported significant association of IgM RF positivity and clinical response but other four studies did not found this association [6–9]. In another report from ten European registries, IgM RF was a significant predictor of response in univariate analysis but not after adjustment for relevant variable in multivariate analysis [20]. Similarly in one study, no significant association of IgM RF $>$ 20 UI/L with clinical response was found. However, a positive association with IgM RF $>$ 30 UI/L was detected [30].

In two studies, there was a significant association between high titers of IgM RF and clinical response [26,30]. In contrast no significant association of IgM RF titer and EULAR response was reported in one study [25].

One study reported the significant association of IgA RF status and clinical response [30]. Two studies reported a significant association of IgG RF and IgA RF titer with clinical response [26,27].

Meta-analysis of OR for EULAR response

Six studies contributed to the meta-analysis of IgM RF and EULAR response. Combined OR for IgM was 3.52 (95% confidence interval (CI): 1.66, 7.45); $I^2=65.0\%$ (Fig. 2a). There was no evidence of funnel-plot asymmetry (Egger test, $p=0.118$). This analysis showed significant heterogeneity of results but the meta-regression did not identify contributing factors.

Meta-analysis of OR for ACR20 response

Only tree studies were included in this meta-analysis. The summary OR was 1.95 (95%CI: 1.24, 3.08), $I^2=0.0\%$ (Fig. 2b). No evidence of asymmetry in funnel-plot (Egger test, $p=0.801$) or heterogeneity were found.