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Efficacy of treatment intensification with adalimumab, etanercept and infliximab in rheumatoid arthritis: A systematic review of cohort studies with focus on dose☆, ☆☆

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ABSTRACT

Objectives: To summarize the empirical evidence regarding the effect of treatment intensification on clinical outcomes in patients with rheumatoid arthritis treated with one of the TNF-α-inhibitors, adalimumab, etanercept or infliximab.
Methods: A systematic search of the bibliographic databases Embase, Medline, Web of Science and Cochrane Central identifying articles concerning treatment with adalimumab, etanercept or infliximab in adult patients with rheumatoid arthritis exposed to dose increase or shortening of dosing intervals was performed. Longitudinal cohorts, both clinical trials and observational studies, were included. ACR and EULAR response criteria and DAS28 were the preferred outcome measures.
Results: Out of 1135 records, eleven studies were included in the final evidence synthesis. One article concerned all the three TNF-α-inhibitors, eight used infliximab, one adalimumab and one etanercept. According to GRADE, evidence was weakened in particular by the lack of control groups, and for treatment intensification with adalimumab and etanercept, no conclusions could be drawn. With infliximab, two trials of high quality revealed contradictory results, but six studies described an improved clinical outcome following intensified treatment strategies. Some studies (2/2) also indicated that for infliximab, frequency increase was superior to dose increase.
Conclusions: Available studies indicate that intensifying treatment with infliximab in rheumatoid arthritis patients, preferably by increasing the frequency of drug administration, may lead to improved clinical outcome in some patients, but the evidence is weak. There is an urgent need for prospectively designed cohort studies to be able to draw a final conclusion.

Introduction

The current EULAR recommendations suggest TNF-α-inhibitors as the primary choice of biologic disease-modifying antirheumatic drug (bio-DMARD) [1]. At present five different TNF-α-inhibitors are available: adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®) and infliximab (Remicade®). The use of TNF-α-inhibitors has improved the treatment of rheumatoid arthritis (RA) to the point where the goal has become to control the disease and not only the symptoms. This goal is only reached in some patients, while others lack response or reach a diminished response to the TNF-α-inhibiting treatment. In these patients treatment may be intensified by increasing the dose or decreasing the dosing intervals, which is reflected in the Danish National Guidelines for treatment of RA with infliximab [2]. Adalimumab, etanercept and infliximab, marketed in 1998–2002, are still considered major players among these bio-DMARDs, and they have been in clinical use long enough to accumulate a substantial amount of clinical knowledge about them. The reported frequency of treatment intensification varies greatly and has presumably decreased in

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recent years, due to the increased number of alternative treatment options. Reports suggest that for adalimumab 12% of patients have experienced treatment intensification [3,4], for etanercept 1–17% [3–5], and with intensified treatment in 10–61% of patients, infliximab is the drug most often intensified [3–6].

According to the manufacturer's recommendations, adalimumab is given subcutaneously (s.c.) at a standard dose of 40 mg every other week (40 mg/2w), and treatment with adalimumab can be intensified by shortening the dosing interval to 1 week [7]. Etanercept is prescribed at a standard dose of 50 mg s.c. injected on a weekly basis, and at present it is not recommended to intensify treatment with etanercept [8]. Infliximab is given as 3 mg/kg every 8th week, following an induction period of 6 weeks. If the response is insufficient, the dose can be increased up to 10 mg/kg or the dosing interval shortened to 4 weeks [9].

Despite the rather frequent use of treatment intensification, there is a general lack of established guidelines regarding when, how, and to whom treatment intensification should be given. The literature on treatment intensification is scarce, and results regarding efficacy are diverging, which is why we felt a need for a systematic evaluation of the existing clinical data. To our knowledge, this is the first systematic review addressing the subject. The aim of this study was to summarize the empirical evidence regarding the effect of treatment intensification on clinical outcomes in RA patients treated with adalimumab, etanercept or infliximab.

Methods

Study selection, assessment of eligibility criteria, data extraction, and secondary statistical estimation and interpretation were performed based on a predefined protocol according to the Cochrane Collaboration guidelines [10]. The protocol was registered in the PROSPERO database of protocols of systematic reviews prior to start of study (http://www.crd.york.ac.uk/prospero registration number 42011001850).

Search strategy

We performed a structured literature search in the bibliographic databases, Medline (via Pubmed, from 1966), EMBASE (via OVID, from 1980), Web of Science (from 1900), and Cochrane Central Register of Controlled Trials, until January 16th 2012.

The extensive search strategy combined the terms regarding treatment (adalimumab OR Humira OR etanercept OR Enbrel OR infliximab OR Remicade), diagnosis (rheumatoid) and treatment intensification (dose × OR treatment interval × OR treatment intensification).

We scrutinized references of included studies and found reviews for additional eligible studies.

Box 1–Definitions of quality of evidence [28].

High quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality	Any estimate of effect is very uncertain

Inclusion criteria and selection process

The selection process was carried out in accordance with the PRISMA-criteria [11]. Studies were eligible for inclusion if they reported data from either a trial or an observational study with a minimum of 12 included participants. Participants of the study had to be diagnosed with rheumatoid arthritis according to the ACR 1987 criteria [12] and be $\geq$ 18 years of age. Participants had to be treated with adalimumab, etanercept or infliximab, and they had to be exposed to dose increase or shortening of dosing intervals during the study. Only a study period of at least 12 weeks was acceptable, and disease activity had to be measured prior to and following treatment intensification. No language restrictions were applied. The selection process was performed by the first author (GE). If there was doubt as to whether a particular study should be included, the first author consulted the last author (EB) and a consensus was reached.

Data extraction and data analysis

Data was extracted by the first author (GE). Extracted data included the following: design, material (demography regarding population subjected to dose increase), intervention (extent of treatment intensification), duration of study, outcome measures, and safety information.

A meta-analysis could not be performed due to the extent of heterogeneity in the design of the studies and the reported outcome measures. Evidence synthesis was therefore mainly descriptive, i.e., frequencies of responders according to each of the available outcome measures reported in the eligible studies.

Grade

For each included clinical or observational study, the quality of the study was evaluated according to the GRADE approach in a systematic manner by the first author. If uncertainty concerning this evaluation arose, the last author was consulted. According to this evaluation, the studies could be up- or down-graded and designated high, moderate, low, or very low quality (Box 1) [10]. We are aware that this grading system is not entirely comparable between clinical trials and observational studies, but it seemed the best tool available.

Results

Study inclusion

Out of the 1135 records retrieved, 11 studies were included in the final evidence synthesis. The selection process is shown in Figure 1. Of the 55 full-text studies assessed for eligibility, 44 were excluded. The characteristics of these 44 studies can be found in Appendix Table 1. One observational study included all three TNF-α-inhibitors. Eight additional studies met the inclusion criteria for infliximab, presenting data from a total of 627 patients. Adalimumab and etanercept were represented with one additional study each, presenting data from 53 and 189 patients, respectively. Three of the 11 included studies were observational (Table 1). The remaining eight were clinical trials, of which seven reported on the effect of dose increase as one of the main objectives.

Risk of bias and overall quality assessment

In the selected studies we found some heterogeneity regarding disease duration (mean ranging from 4.0 to 17.1 years),