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Comparative effectiveness and survival of infliximab, adalimumab, and etanercept for rheumatoid arthritis patients in the Hellenic Registry of Biologics: Low rates of remission and 5-year drug survival☆

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ABSTRACT

Objective: To compare effectiveness, drug survival, and safety between infliximab, adalimumab, and etanercept, in a nationwide cohort of rheumatoid arthritis (RA) patients.
Methods: This study is a prospective cohort study of 1208 active RA patients. Effectiveness, drug survival, and serious adverse events during entire follow-up (median 2.9 years) were monitored.
Results: EULAR and CDAI responses were comparable between the three agents (EULAR good/moderate responses at 12 months ranged 76–79%). At 12 months, 15–23% achieved remission. For adalimumab and etanercept, adjusted hazard rate (HR) for EULAR/ACR remission (reference: infliximab) was 2.7 and 2.1 (95% confidence interval was 1.7–4.1 and 1.3–3.4, respectively); males (HR 1.6; 1.1–2.4), use of glucocorticoids (HR 2.0; 1.3–3.0), and swollen joint count >7 (HR 0.36; 0.24–0.55) were independent predictors. Five-year drug survival was 31%, 43%, and 49% for infliximab, adalimumab, and etanercept, respectively ($p = 0.010$). Infliximab was associated with significantly more withdrawals due to adverse events. Disease activity, CRP, and use of glucocorticoids predicted efficacy-related drug survival; age, use of methotrexate, and prior DMARDs failures predicted safety-related survival. Risk for serious infections was lower with adalimumab (odds ratio [OR] 0.62; 0.38–1.00) or etanercept (OR 0.39; 0.21–0.72) than infliximab, independent of the effects of age (OR 1.65; 1.37–2.00 per 10 years), tender joint count >10 (OR 1.86; 1.21–2.86), and glucocorticoids >35 mg/week (OR 1.83; 1.12–2.99).
Conclusions: Response rates were comparable among anti-TNF agents. Overall, 5-year drug survival was below 50%, with infliximab demonstrating increased safety-related discontinuations. Remission rates are low in clinical practice. Strategies to increase effectiveness and long-term survival of anti-TNF agents in RA are needed.

Introduction

Anti-TNFα agents are the most commonly used class of biologic agents for the treatment of active rheumatoid arthritis (RA) [1]. Among different anti-TNFα drugs, adalimumab, etanercept, and infliximab are the three most widely used. Although these agents differ in their mode of action, pharmacokinetics, and immunogenicity, it is not clear whether clinical outcomes also differ. This is

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due to paucity of head-to-head randomized controlled trials (RCTs) and the conflicting results of observational studies.

Information about the comparative effectiveness and safety of TNFα inhibitors can guide treatment decisions in clinical practice. Data from meta-analyses of RCTs have been used for indirect comparison of TNFα-inhibitors. A systematic review of RCTs and prospective cohort studies demonstrated comparable effectiveness of the three TNFα inhibitors, adalimumab, etanercept, and infliximab [2]. A network meta-analysis based on RCTs of biologics in RA concluded that there were no significant differences in efficacy measures between anti-TNFα agents though etanercept was safer than adalimumab and infliximab [3]. A more recent similar analysis showed that although the odds for serious infections were comparable between the three TNFα inhibitors, withdrawals due to adverse events were more likely with infliximab [4].

Results from observational studies provide complementary information to those of RCTs regarding long-term drug efficacy and safety [5]. In most European registries of RA patients, differential drug response rates in favor of etanercept and adalimumab as compared to infliximab have been observed [6,7]. In contrast, the Portuguese and the US CORRONA registries reported comparable effectiveness of adalimumab, etanercept, and infliximab, although in the latter study, infliximab was associated with higher survival rates [8,9]. In terms of safety, two retrospective studies in the US have reported a higher risk for serious infections with infliximab compared to etanercept and adalimumab [10,11]. Moreover, treatment with etanercept was associated with lower risk for serious infections compared to adalimumab and infliximab in the DREAM registry [12], while drug discontinuations due to adverse events were significantly lower for etanercept than for infliximab in the RADIUS [13] and the BIOBADASER [14] registries.

Data on the comparative efficacy and safety of different anti-TNFα agents in southern European RA patients are limited [8,15,16]. This is important in view of the variations in disease severity across different ethnic backgrounds and clinical settings [17]. In this paper, we report on effectiveness, survival, and safety profile of three anti-TNF agents, namely infliximab, adalimumab, and etanercept, in a Greek RA population from the Hellenic Registry of Biological Therapies. We also evaluate predictors of clinically important outcomes, such as major treatment responses, drug withdrawal, and serious infections.

Methods

Study design

The *Hellenic Registry of Biologic Therapies* is a nationwide, prospective, observational cohort of patients with inflammatory arthritides. Patients are enrolled by participating rheumatologists from seven academic and national health system rheumatology centers located at five different regions across the country. The registry was founded in 2004 and is under the auspices of the Hellenic Society for Rheumatology (HSR). Patients have an unrestricted access to anti-TNFα agents based on the decision made by their treating physician and in accordance with the HSR recommendations (updated in 2008) [18]. The study and data collection protocol follows that of the *South Swedish Arthritis Treatment Group* (SSATG) [19], and the database software was kindly provided by Dr. P. Geborek. Patients were enrolled during their regular clinical evaluation and completed forms were mailed to the Department of Rheumatology, University of Crete, for data entry and analysis. A dedicated physician (I.F.) reviewed all the patients' forms and communicated with the treating physicians if necessary to verify accuracy of the data. Approvals were obtained by local institutional review boards and all participants signed the informed consent forms.

Participants

We analyzed patients with a diagnosis of RA, according to the treating physician, who were started on anti-TNFα treatment with infliximab, adalimumab, or etanercept. According to the HSR recommendations, RA patients are considered candidates for anti-TNFα treatment if they have active disease (defined as DAS28 >5.1 or >3.2 plus at least two out of five adverse prognostic factors [rheumatoid factor or anti-cyclic citrullinated peptide antibodies positivity, bone erosions in hands or feet radiography, modified health assessment questionnaire [HAQ] score >1, large joints involvement, and extra-articular manifestations]) and have failed previous treatment with at least one disease-modifying drug (DMARD, methotrexate [MTX], or leflunomide included). No specific exclusion criteria were applied. Patients who were registered between 01/01/2004 and 31/12/2009 were included in the present analysis, and data were collected prospectively until 30/04/2011 or until anti-TNFα treatment was discontinued, whichever came first.

Variables and data collection

Specific forms with demographic, clinical, laboratory, and patient-reported variables were completed during patient evaluation. Data were collected prospectively every 6 months, or at the time of an event, or drug discontinuation, and included 28 tender and swollen joint counts, physician and patient global assessments of disease activity, patient assessment of pain, the modified HAQ for physical function, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). The following composite indices for RA disease activity were calculated: DAS28, SDAI, and CDAI [20]. Dosage of all RA medications was recorded. Patients reported the dosage scheme of glucocorticoids they received since their last follow-up, so that the cumulative glucocorticoid dose between two consecutive visits was calculated (averaged to mg of prednisone per week). Any withdrawal from treatment was registered prospectively and was classified by the treating physician as related to adverse event(s) [AE(s)], treatment failure, or other cause. If both treatment failure and AE(s) were reported, the cause of withdrawal was assigned to AE(s). Treating physicians described and recorded all events, their outcome, and attribution to anti-TNFα therapy. On data entry, events were classified according to seriousness, organ involvement, and type (infection, cancer, drug reaction, and other) according to the Rheumatology Common Toxicity Criteria, MEDDRA Version 1.5 [21]. Any treatment modifications were also recorded.

Outcome measures

The primary study outcomes [22] were *disease remission* defined by DAS28 [23], CDAI [24], and the ACR/EULAR criteria [25], and *low disease activity* defined by DAS28 [23]. Other outcomes included the following: (a) good and moderate responses based on the EULAR criteria [26], (b) CDAI-defined improvement [27,28], (c) anti-TNF drug survival stratified according to the cause of withdrawal, and (d) serious AEs, and in particular serious infections according to the Rheumatology Common Toxicity Criteria (RCTC) v.1.0 [21]. Both crude and LUNDEX-corrected responses ([fraction of starters still in the study after y months] $\times$ [fraction responding at y months]) [29] were calculated at 6-month intervals after treatment initiation. The number of valid observations varied across different measures of effectiveness since some patients lacked one or more variables at follow-up.