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Original article

Switching from an anti-TNF monoclonal antibody to soluble TNF-receptor yields better results than vice versa: An observational retrospective study of 72 rheumatoid arthritis switchers

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ABSTRACT

Objectives: To evaluate the benefits for rheumatoid arthritis (RA) patients of switching from one tumor necrosis factor inhibitor (TNFi) to another based on reason for change (primary failure, escape or intolerance) and molecule-switching order.
Methods: Between 2000 and 2008, 356 RA patients prescribed a TNFi (infliximab [IFX], etanercept [ETA] or adalimumab [ADA]) and undergoing standardized evaluation were included in this retrospective study. Detailed demographic, clinical and biological data were collected before first biologic use and ≤ 6 months later to evaluate response based on EULAR-criteria. Primary failure, escape or intolerance of first TNFi triggered switch to another TNFi, the response of which was evaluated 6 months later. Propensity score then measured any interaction with baseline variables.
Results: Of the 356 RA patients, 38 switched from IFX/ADA to ETA, 26 from ETA to IFX/ADA, and eight from one monoclonal antibody (mAb; IFX/ADA) to another. Clinical parameters for switchers and non-switchers were comparable. Switchers changed therapies because of primary failure (36.1%), escape (33.3%), or intolerance (30.6%), with no difference found in these subgroups. More switchers responded to the second TNFi than the first ($P < 0.01$), respectively, regardless of switch (ETA to IFX/ADA: 50 vs. 23.1% [$P < 0.05$]; IFX/ADA to ETA: 57.9 vs. 15.8% [$P < 0.001$]) or reason for changing. In addition, DAS28 decreased more with the second antagonist ($P < 0.001$) and regardless of molecules switched ($P < 0.01$). Survival of the second TNFi was significantly longer with switch from mAb to the soluble receptor than vice versa ($P < 0.05$).
Discussion: Overall, any switching from one TNFi to another, especially mAb to soluble receptor, was often beneficial for RA patients.

1. Introduction

Therapeutic management of rheumatoid arthritis (RA) has evolved considerably over the past 10 years with the arrival of immunotherapies with proven efficacy at diminishing joint inflammation and slowing or even stopping osteocartilaginous destruction [1,2]. Tumor necrosis factor (TNF)-blocking agents have demonstrated most promise, with five molecules currently available: chimeric monoclonal antibody (mAb) (infliximab), soluble receptor (SR; etanercept), two fully human mAbs (adalimumab and golimumab), and a pegylated-Fab (certolizumab pegol). After the first 6 months of treatment with a first TNF inhibitor (TNFi), approximately 25% of patients were in remission and 41% had good responses based on European League Against Rheumatism (EULAR) criteria [3], with only 30–40% of non-responders. However, some patients who do not respond to one mAb might respond to an SR and vice versa [4,5], or infliximab non-responders might respond to another mAb, like adalimumab and vice versa [4,6]. In short, a patient's response to a TNFi is highly variable.

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The results of several studies or registries have demonstrated the usefulness of prescribing a second TNFi on stopping a first TNFi because of inefficacy or intolerance [6–14]. In the Danish DANBIO registry, which included 235 patients who changed anti-TNF molecules, 54% responded moderately to the first biologic agent, compared to 63% prescribed a second biologic agent ($P < 0.02$), due to therapeutic failure of the first. Percentage of good and moderate responders to first and second immunotherapies were comparable when the first was stopped because of intolerance (59% and 50%; $P = 0.38$) [11]. For patients who developed side effects to a TNFi, there was no increase in risk of developing an adverse effect to a second biologic agent [11,13]. According to data from the British Society of Rheumatology's registry on 856 patients, who switched TNFi due to inefficacy ($n = 503$) or intolerance ($n = 353$), 72% of patients received a second biologic agent for more than 6 months with satisfactory control of RA [13]. Based on a meta-analysis of 32 studies including 4,441 patients, Rémy et al. showed that switching to a second TNFi was beneficial for patients, especially when the first had been stopped because of intolerance [15]. Prescription of a second TNFi seems appropriate after failure or intolerance of the first.

In clinical practice, we are sometimes confronted with primary or secondary (escape) failure of TNFi [5,7,15,16]. Even though such failure has not yet been clearly defined, there is some consensus: primary failure is the absence of response during the first 6 months of treatment; secondary failure or escape is progressive loss of response after an initial response of varying duration. Few studies have analyzed the potential contribution of switching from one molecule to another according to type of failure (primary, escape or side effects) [5,7,16–18].

Using standardized collection of clinical and biological data obtained from biologic-treated RA patients, this retrospective, monocenter study was undertaken to evaluate the impact of prescribing a second TNFi after failure of the first, based on type of failure and molecule-switching order (mAb to SR: mAb/SR; SR to mAb: SR/mAb; or mAb to mAb: mAb/mAb).

2. Methods

2.1. Patients

Between January 2000 and June 2008, 356 RA patients meeting American College of Rheumatology criteria were included in this study [19]. The patients had active RA, with disease activity score-28 (DAS28) ≥ 3.2. They had been taking a disease-modifying anti-rheumatic drug (DMARD; methotrexate or leflunomide) combined with a TNFi (adalimumab, etanercept or infliximab). Adalimumab (40 mg every 2 weeks) or etanercept (25 mg twice weekly or 50 mg once a week) was administered subcutaneously. Infliximab (3 mg/kg) was infused at weeks 0, 2 and 6, then every 8 weeks, but the treating physician was able to increase this dose or change the schedule as necessary.

2.2. Baseline assessment

At the start of each immunotherapy, data on demographics (age, gender, and RA duration), clinical status (number of painful joints, number of swollen joints, and DAS28), treatments (DMARD combined, dose, date of start and stop of first TNFi, biologic type, and corticosteroids) and biological status (anti-cyclic citrullinated peptide antibodies [ACPA], rheumatoid factors, erythrocyte sedimentation rate [ESR/1st hour] and C-reactive protein [CRP]) were collected in a standardized manner.

2.3. Follow-up

Treatment efficacy was evaluated every 6 months for patients who received etanercept or adalimumab and before each infusion for those prescribed infliximab. At each visit, the numbers of painful and swollen joints, ESR, CRP and DAS28 were recorded.

2.4. Primary outcomes

Patients were considered to be responders when their DAS28 had improved after 6 months of treatment compared to initial DAS28 > 1.2. Primary failure, according to EULAR criteria, was total absence of response during the first 6 months of treatment, i.e., delta DAS28 was ≤ 1.2 and DAS28 > 5.1 at endpoint, or delta DAS28 was ≤ 0.6, whatever the level of DAS28 at the endpoint. Therapeutic escape was defined as good (delta DAS28 was > 1.2, and DAS28 ≤ 3.2 at endpoint), or moderate (delta DAS28 was > 0.6, and DAS28 < 5.1 at endpoint) initial response during the first 6 months of treatment or beyond, followed by gradual loss of response. Intolerance meant side effect(s) occurred at some time leading to definitive withdrawal of the first TNFi.

For patients experiencing primary failure or intolerance to a first or second biologic agent, the agent's efficacy was evaluated, respectively as difference in DAS28 between initiation and discontinuation, or between initiation and 6 months of therapy. For patients escaping under a first or second TNFi, the efficacy of the first and second agents was evaluated as difference in DAS28 between initiation and after 6 months of exposure to each molecule.

2.5. Secondary outcomes

Three other endpoints were assessed: percentages of good, moderate and non-responders as defined by EULAR criteria [20,21]; the differences, for each agent, between initial and $\leq$6-month DAS28, and first and second TNFi treatment durations.

2.6. Statistical analyses

Clinical and biological parameter values were compared with non-parametric tests, e.g. Fisher's exact test for qualitative variables and Mann–Whitney or Wilcoxon test for quantitative variables. Mean differences in DAS28 between the first and second TNFi prescribed were assessed by analysis of variance (ANOVA). Times to discontinuation of TNFi were analyzed using Cox–Mantel hazard ratio model. Treatment durations of the two TNFi were evaluated, but only the duration of the second was analyzed based on molecule-switching order and reason for stopping the first. Kaplan–Meier curves were drawn to estimate the probability of continuing treatment with the second TNFi: < 0.05 defined significance.

Given concerns regarding treatment-selection bias, we used a propensity score (PS) to reduce selection bias in this observational study. We compared the mean survival of treatment groups switching from one TNFi to another based on molecule-switching order (mAb/SR; SR/mAb). PS was estimated using a multivariable logistic regression model using the following key variables: age, gender, disease duration, DAS28, swollen joint count, ESR, CRP, anti-CCP status and rheumatoid factor status, concomitant DMARD, and corticosteroid treatments. PS measured similarity in terms of a vector of observable characteristics between mAb/SR and SR/mAb. Multiple quantile regressions were used to compare the median between different groups or categories. Times to discontinuation of TNFi were analyzed using Cox–Mantel hazard ratio model adjusted with PS to compare the mean survival of treatment groups switching from one TNFi to another based on reason for change (primary failure, escape or intolerance) and