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Original article

Retention rates of adalimumab, etanercept and infliximab as first and second-line biotherapy in patients with rheumatoid arthritis in daily practice

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ABSTRACT

Objectives: To compare retention rates of adalimumab, etanercept and infliximab as first-line biotherapy in rheumatoid arthritis (RA), to determine causes of discontinuation, retention-associated factors, and retention rates of possible second-line TNF-α inhibitors (TNFi).
Methods: In this retrolective, multicentric study, medical charts of RA patients starting TNFi between March 2005 and April 2009 were reviewed, with follow-up between two and six years. The retention rate was estimated using the Kaplan-Meier method. Comparison between TNFi was done after adjustment using a Cox model. Factors associated with better retention were identified by multivariate analysis.
Results: Of the 706 patients included, the percentage continuing treatment after two years was 54.9, 61.9 and 48.7%, and the median retention was 31, 45 and 23 months for adalimumab, etanercept and infliximab, respectively. The hazard ratios (HRs) for discontinuation were greater with adalimumab and infliximab than etanercept (1.315, 95% CI [1.050–1.648] and 1.380, 95% CI [1.041–1.828], respectively). The HR for discontinuation due to inefficacy was significantly higher with adalimumab than etanercept. Adverse events were significantly higher with infliximab than etanercept. Past use of more DMARDs and higher baseline ESR were associated with better retention. The median retention of the second-line TNFi was 11, 43 and 19.1 months for adalimumab, etanercept, and infliximab, respectively. HRs for adalimumab discontinuation due to all causes were significantly greater than for etanercept.
Conclusions: Etanercept had a better retention rate than adalimumab and infliximab as first-line biotherapy in RA, and than adalimumab as second-line biotherapy.

1. Introduction

Use of tumor necrosis factor α (TNF-α) inhibitors (TNFi) has dramatically improved the management of rheumatoid arthritis (RA) [1]. The efficacy and safety of the three first licensed agents, *i.e.* adalimumab, infliximab and etanercept, have been demonstrated in large randomized controlled trials (RCTs) [2–4]. However, no RCT has done a head-to-head comparison of their efficacy. Meta-analyses have generally not demonstrated any significant differences between the three TNFi or are controversial [5–8]. Regarding safety, two recent Cochrane meta-analyses of patients withdrawn from RCTs due to AEs had different results [9,10]. Treatment retention rate in cohorts of treated patients is a good criterion for evaluating the efficacy/tolerance balance in real life. [11–17]

Retention rates of TNFi have been studied in several RA patients' registries with conflicting results. In addition, there is no TNF

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inhibitors registry in France, Therefore, we conducted an observational study to compare the retention rates of TNFi in daily practice in France. The primary objective was to compare retention rates of adalimumab, etanercept and infliximab administered as first-line biotherapy in RA. The secondary objectives were to compare retention rates of TNFi monoclonal antibodies (adalimumab and infliximab) and the soluble receptor (etanercept), to record the causes of discontinuing these treatments, to determine the factors associated with better retention of the first TNFi, and to compare retention rates of possible second-line TNFi.

2. Methods

2.1. Study design

This was a retrolective, multicentric study in eight French rheumatology centers. Data were collected from medical charts in a pre-established anonymous standardized case report form (CRF) by an independent investigator and entered into a computerized database. The protocol was validated by National Ethics Committees (*Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé*, no. 11.095, 10/02/2011; *Commission nationale de l'informatique et des libertés*, no. EGY/NDS/AR112220, 09/03/2011; and *Conseil national de l'ordre des médecins*, no. 201100493, 03/05/2011), and registered in the Clinicaltrials.gov database (NCT01692899).

2.2. Selection of patients

Medical charts of all patients with RA starting a first TNFi therapy between March 1, 2005 and April 30, 2009 were systematically reviewed by two investigators (AFM and A Remy-Moulard). Data were collected until April 30, 2011, which allowed a follow-up between two and six years. Patients were informed by mail that their data would be collected and had the possibility to refuse. Inclusion criteria were: RA defined by the 1987 ACR criteria [18]; first TNFi prescribed in the previously mentioned period, as first-line biotherapy; and patients had undergone at least one evaluation in the center after treatment initiation. Patients were excluded if:

- they had previously received another biotherapy;
- TNFi was prescribed in an RCT;
- they refused to participate.

2.3. Study drugs

TNFi were prescribed by the treating rheumatologist according to the current national guidelines [19]. Only adalimumab, etanercept and infliximab were available at this time. Treatment was administered in routine care: TNFi were prescribed in almost every case at approved doses and concomitant disease-modifying anti-rheumatic drugs (DMARDs) or prednisone were administered if ordered by the treating rheumatologist.

2.4. Data collected

Baseline data were: age, sex, center, medical history (serious infections, cardiovascular events, cancer), comorbidities (smoking, hypertension, obesity, chronic obstructive pulmonary disease, interstitial lung disease, cardiac insufficiency, diabetes mellitus, osteoporosis, screening for tuberculosis), time since RA diagnosis, rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) status, number of previous DMARDs, DAS28[2]-ESR, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and associated treatments (DMARDS, steroids). Treatment data for the first and, if appropriate, second TNFi were the type of biologic treatment date of treatment initiation and dosage. Disease follow-up data (DAS28, ESR and CRP) were collected, at 3, 6, and 12 months and then every 12 months until April 30, 2011 or the last observation. Treatment follow-up data were the dates of temporary or definitive interruption of the TNFi, or the date of last observation on treatment. Reasons for treatment discontinuation were recorded.

2.5. Outcomes

The time to drug discontinuation was defined as the time period until the first definitive treatment interruption or last observation on treatment after initiation of the first and, if appropriate, second TNFi. Calculation was based on the exact time of discontinuation collected *via* the patient chart. Interruptions were considered definitive when indicated in the chart by the treating rheumatologist, or when no consecutive re-introduction of treatment was mentioned. The reasons for discontinuation were pre-determined and categorized as inefficacy (as judged by the rheumatologist); adverse events (AEs), which were described and classified into the MedDRA classification; and/or other reasons, including pregnancy, surgery, lost-to-follow-up, remission, or other reported reasons. Inefficacy was sub-grouped as primary or secondary, with primary inefficacy being pre-defined as a definitive discontinuation occurring before the end of the 6th month after initiation. AEs were attributed to the current TNFi independently of other past or current treatments. When there was more than one reason for treatment interruption, they were all taken into account.

2.6. Sample size calculation

The prescription rate of the three TNFi in RA was evaluated based on French market data at 29.4, 53.7 and 16.9% for adalimumab, etanercept and infliximab, respectively. With a hypothetical retention rate of 50% after two years for infliximab and adalimumab taken together [20], 780 included patients were needed to have a power of 80% for detecting a minimum difference in the retention rate of 10% between etanercept and monoclonal antibodies with a alpha risk of 5%, and considering a lost-to-follow-up rate of 10%.

2.7. Statistical analysis

Statistical analyses were performed by an independent Clinical Research Organization (Lincoln, Paris). Baseline demographic characteristics of patients were compared between the drugs using a Chi-square test or Fisher's exact test for categorical variables, and a univariate analysis of variance or Kruskall-Wallis test for continuous variables.

The retention rate was estimated using the Kaplan-Meier method at three, six, 12 and 24 months, and then every 12 months thereafter. The median time (months) of retention and the cumulative (patients-year) treatment exposure were calculated. These analyses were done on all TNFi together, drug by drug, and by mechanism of action (soluble receptor *versus* monoclonal antibodies) but only if no significant difference of retention rate have been observed between both monoclonal antibodies

Comparison of the risk of discontinuation of the first TNFi was done after adjustment for the inverse of a propensity score using a Cox regression analysis. Therefore, the presented HR are the ones resulting of adjusted Cox regression model. This score was derived from a multinomial logistic regression model using the first TNFi prescribed as the dependent variable, and baseline variables (including comorbidities) likely to influence this choice as explicative variables, determined by a step-by-step method applicated on every baseline variables, with 10% as entry significance level and 5% as removal level. To evaluate the propensity score for all patients,

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