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Concise report

Age at treatment predicts reason for discontinuation of TNF antagonists: data from the BIOBADASER 2.0 registry

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Abstract

Objectives. To assess the retention rate of TNF antagonists in elderly patients suffering from chronic arthropathies and to identify predictive variables of discontinuation by inefficacy or by adverse events (AEs).

Methods. All patients treated with TNF antagonists in BIOBADASER 2.0, with a diagnosis of either RA or spondyloarthritis (SpA: AS and PsA) were included and classified as <65 (younger) or $\geqslant 65$ years of age (older) at start of the treatment. Cumulative incidence function for discontinuation (inefficacy or AE) was estimated as being the alternative reason for a competing risk. Competing-risks regression models were used to measure the association between study groups, covariates and reason for discontinuation.

Results. A total of 4851 patients were studied; 2957 RA (2291 in the younger group and 666 in the older group) and 1894 SpA (1795 in the younger group and 99 in the older group). Retention curves were statistically differently stratified by age groups, with the SpA younger group having the largest retention rate. Competing-risks regression models showed that in the older group, AEs were the most common reason for discontinuation regardless of the diagnosis of the patient and TNF antagonist molecule, whereas in the younger group, the most common cause of discontinuation was inefficacy.

Conclusion. In conclusion, factors predicting discontinuation of TNF antagonists due to AEs are older age and diagnosis of RA. On the other hand, younger age predicts discontinuation due to lack of efficacy.

Key words: Safety, Effectiveness, Registry, Rheumatoid arthritis, Spondyloarthritis, Elderly, Competing risks.

Introduction

Although the peak of RA incidence occurs between the ages of 30 and 50 years, in around 20–30% of patients the disease begins after the age of 60 years. Spondyloarthritis (SpA) usually starts before the age of 40 years, but the incidence is unremitting throughout the entire lifetime. Elderly patients are thus an important group of patients with arthritis attending rheumatology clinics [1, 2], and many are offered biologic therapies. However, patients >65 years are often not included in clinical trials with biologics, and accordingly the average age in these trials ranges between 50 and 55 years. This leads to substantial lack of controlled information in this age group, and available data from observational studies are inconsistent.

In subset analysis in randomized clinical trials, no significant differences in adverse events (AEs) have been reported in patients $\geqslant 65$ years compared with younger patients (<65 years) treated with etanercept [3–5]. In an observational study on RA, the number of AEs was significantly higher in patients $\geqslant 65$ years compared with

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younger patients (between 18 and 65 years) [6]. Similarly, in an observational study on AS/RA, the safety profile of TNF antagonists in elderly patients was considered unfavourable compared with younger patients for severe infections [7]. On the contrary, in two studies on RA and SpA, the safety profile of TNF antagonists in patients $\geqslant$65 years and younger patients was comparable [8, 9]. In addition, the level of efficacy of TNF antagonists in the elderly is disputed. In a subset analysis of RA in a randomized controlled trial of patients treated with etanercept, efficacy in elderly patients $\geqslant$65 years did not differ from younger patients [10]. However, in an observational study of RA patients, TNF antagonists appear less effective in elderly compared with younger RA patients [11].

Therefore, the aim of this study was to investigate whether being older than 65 years predicts drug discontinuation and its cause in a cohort of patients treated with TNF antagonists.

Methods

BIOBADASER is a national drug registry of patients with rheumatic diseases starting treatment with any biologic and followed thereafter. It was established in February 2000. A sample from BIOBADASER 2.0 was studied (see Study groups and definitions). Patients entering the registry are followed prospectively and evaluated at the time an AE or a change in the biologic therapy occurs, thus providing specific cohorts for specific analyses. The following data are collected online and systematically by participating physicians: (i) patient data, including gender, date of birth, diagnosis and date of diagnosis, comorbidities and risk factors; (ii) treatment data, including types of biologics and dates of initiation and of discontinuation and concomitant treatment; and (iii) AE data, including date of occurrence, type and classification of AE according to the Medical Dictionary for Regulatory Activities (MedDRA), severity and outcome. Ethical approval for this study was obtained in 2006 from the Hospital Ramón y Cajal, Madrid, Spain.

For assessment of the consistency and quality, the database is constantly monitored online, and once a year participating units are advised to check the information on all patients and update it accordingly. Additionally, a random sample of patients is selected and audited *in situ* in all 14 centres annually. In 2008 and 2009, additional validation of data was also assured by direct contact with patients by the project managers to confirm whether patients were alive or had been admitted to a hospital for any reason in the preceding year.

The registry protocol and materials of BIOBADASER 2.0 are available at http://biobadaser.ser.es/biobadaser/eng/index.html and were approved by the Ethics Review Committee of the Hospital Ramón y Cajal (Madrid) acting as reference committee. Starting in January 2008, all patients sign an informed consent that includes an agreement to be contacted by a member of the registry team to gather medical information, performed according to the principles of the latest Helsinki recommendations and complying with Spanish regulations for data protection and research.

Study groups and definitions

Although the registry contains information on all the rheumatic diseases for which the European Medicines Agency approves biological therapies, for the purpose of our study only patients receiving TNF antagonists for RA and SpA (AS and PsA) were analysed. For the analysis, patients were classified according to the age at treatment with the first TNF antagonists in two groups: $\geqslant$65 years of age (older group) and $<$65 years (younger group).

Exposure

Time of exposure is from the beginning of therapy with a TNF antagonist to the date of the last administration plus twice the half life of the TNF antagonist (3 days for etanercept, 20 days for infliximab and 14 days for adalimumab). Observation spans from entry into the cohort (beginning date of TNF antagonist) to censor date (last visit in a lost-to-follow-up patient or treatment discontinuation date), death or 29 October 2010, whichever occurred first. Only the first treatment with TNF antagonists was considered in the analysis.

Statistical analyses

Continuous variables are expressed as means with S.D.s, and categorical variables as total with percentages. The population is described using descriptive statistics indicated by the distribution of variables. Baseline characteristics in groups were compared using chi-square test or Student's two-tailed *t*-test.

Drug survival is described as the probability of discontinuation from any cause using Kaplan–Meier survival curves, and a log-rank test was done stratifying patients by study group for comparison. A cumulative incidence function of cause k of discontinuation (inefficacy or AE) defined by the probability, Prob ($T=t$, $F=k$), of failing from cause k before time t was also estimated as being the alternative reason for a competing risk.

Competing-risks regression models according to the method of Fine and Gray [12] were used to measure the association between study groups, covariates and reason for discontinuation. Association is expressed as sub-hazard ratios (SHRs), where the term sub-hazard has the same interpretation as the hazard in the non-competing risks setting, the instantaneous event rate.

Multivariate analyses were performed by backward stepwise selection of all variables with $P<0.2$ in the bivariate analysis. The following variables were included in the models: gender, age, disease duration, diagnosis, baseline concomitant treatment, baseline comorbidity and TNF antagonists. All analyses were performed with Stata 11.1 (StataCorp LP, College Station, TX, USA).

Results

A total of 4851 patients were included in the study: 2957 RA (2291 in the younger group and 666 in the older group) and 1894 SpA (1795 in the younger group and 99 in the older group). Baseline characteristics of patients by group are given in the supplementary table, available as supplementary data at *Rheumatology* Online. Gender distribution was uneven, with more women in the RA groups. Mean follow-up time was similar in the same age groups. Comorbidity and concomitant treatment were more common in the RA than in the SpA groups. Infliximab was the leading TNF antagonist used in all groups.

Retention curves (Fig. 1a) were statistically different ($P < 0.0001$, log-rank test) and show that 50% of patients are off therapy by 4 years, except young SpA patients who stay on therapy longer. Cumulative incidence curves (Fig. 1b and c) show that the younger groups were more likely to discontinue the TNF antagonists due to inefficacy, independently of diagnosis, whereas the older groups were more likely to discontinue treatment due to an AE, especially those with RA.

Competing-risks regression for inefficacy (Table 1) showed a larger SHR for the younger group compared with the older group. Also, females treated with glucocorticoids and infliximab have a significant SHR for inefficacy. Disease duration was inversely associated with inefficacy. Competing-risks regression for AEs (Table 1) showed a larger SHR for the older groups. Comorbidity such as hypertension, infliximab treatment and treatment with glucocorticoids were all variables associated with discontinuation for AE. MTX and adalimumab use seem to be a protective factor.

Discussion

In the present work we investigated the influence of age on drug retention and on the causes of discontinuation in patients treated with TNF antagonists. Our results show that age, along with the diagnosis of the patient, predicts the reason for discontinuation of TNF antagonists in patients suffering from RA and SpA.

Comparing older and younger patients, older patients have slightly, though significantly, lower drug retention, although the main reason for discontinuation is different. Older patients discontinue treatment more frequently as a result of an AE, and younger patients due to inefficacy. However, not only age but the patient's diagnosis predicts drug retention. Patients with RA discontinue biologic treatment for both inefficacy and AEs more frequently than patients with SpA. This is probably due to the features of the disease, influence of TNF on the physiopathology of the disease, fewer therapeutic alternatives in SpA and different population characteristics.

The majority of the published studies include patients undergoing treatment with etanercept, and a few with infliximab or adalimumab [4, 5, 10, 13]. In our study with three TNF antagonists, we found that the pattern of efficacy or toxicity of the TNF antagonists differ between age

FIG. 1 Retention rate and discontinuation rate curves (inefficacy or AE). (**a**) Retention rate by age and diagnosis represented by means of a Kaplan–Meier curve; (**b**) discontinuation rate of inefficacy represented by means of cumulative incidence curves in age and diagnosis. Curves represent the probabilities of occurrence of inefficacy in each group. (**c**) Discontinuation rate of AE represented by means of cumulative incidence curves. Curves represent the probabilities of occurrence of AE. SpA: AS and PsA.

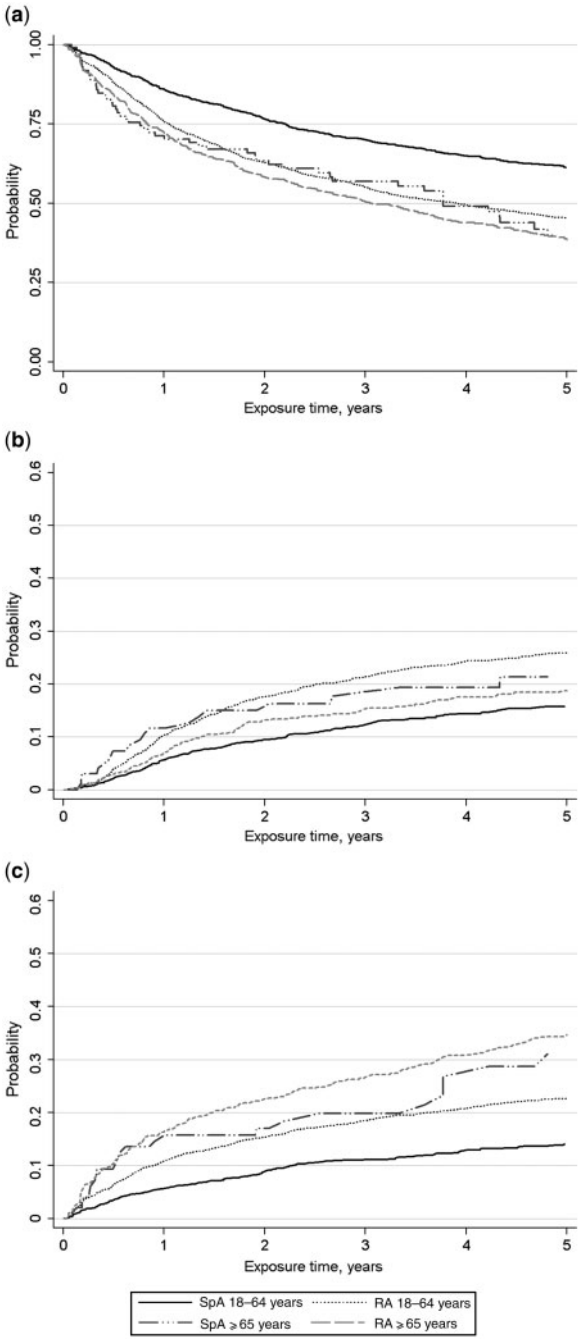

Table 1 Competing-risks regression models for reason of discontinuation (inefficacy or AE)

Demographic and clinical characteristics	Inefficacy		AEs	
	Bivariate SHR (95% CI)	Multivariate SHR (95% CI)	Bivariate SHR (95% CI)	Multivariate SHR (95% CI)
Gender: women	1.51 (1.31, 1.74)***	1.29 (1.09, 1.53)**	1.23 (1.07, 1.4)**	–
Age group, years				
<65	Ref.	Ref.	Ref.	Ref.
⩾65	0.89 (0.74, 1.07)	0.76 (0.63, 0.93)**	1.9 (1.63, 2.2)***	1.51 (1.28, 1.77)***
Diagnosis				
SpA	Ref.	Ref.	Ref.	Ref.
RA	1.66 (1.44, 1.92)***	1.45 (1.21, 1.74)***	1.83 (1.58, 2.12)***	1.66 (1.41, 1.94)***
Disease duration (5-year periods)	0.94 (0.9, 0.98)**	0.95 (0.91, 0.99)*	1.05 (1.02, 1.09)**	–
Comorbidity (baseline)				
Diabetes	0.88 (0.66, 1.19)	–	1.5 (1.18, 1.91)***	–
Hypercholesterolaemia	1.08 (0.88, 1.31)	–	1.07 (0.88, 1.3)	–
Hypertension	1.02 (0.86, 1.2)	–	1.47 (1.27, 1.71)***	1.29 (1.1, 1.5)***
Concomitant treatment (baseline)				
MTX	1.16 (1.02, 1.32)*	–	0.92 (0.81, 1.04)	0.77 (0.66, 0.88)***
Other DMARDs	1.25 (1.08, 1.46)**	–	1.17 (1.01, 1.36)*	–
Glucocorticoids	1.39 (1.22, 1.58)***	1.17 (1.02, 1.35)*	1.41 (1.24, 1.61)***	1.3 (1.12, 1.51)***
TNF antagonists				
Etanercept	Ref.	Ref.	Ref.	Ref.
Infliximab	1.41 (1.21, 1.65)***	1.46 (1.24, 1.72)***	1.33 (1.14, 1.54)***	1.38 (1.19, 1.61)***
Adalimumab	1.22 (1, 1.47)*	1.21 (0.98, 1.48)	0.81 (0.66, 0.99)*	0.78 (0.64, 0.95)*

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. SpA: AS and PsA; Ref.: reference.

and diagnosis groups. Previous studies on the efficacy of TNF antagonists in randomised controlled trials by age did not show a difference in elderly patients compared with younger patients [5, 7, 8, 10, 14]; however, in agreement with a previous observational study, comparison of the efficacy in our study demonstrated that discontinuation for lack of efficacy in elderly RA patients is lower than in the younger group, probably as a reflection of better efficacy, although other explanations, such as greater reluctance to switch in older patients or greater acceptance of a lesser response in the elderly, may also be possible. This is different from what happens in SpA.

Our data were gathered from a national registry of biologics. Measuring the survival of drugs in registries such as BIOBADASER has limitations. The quality of our database was ensured by repeated external audits of centres. In addition, the quality and consistency of data were ensured by a clear definition of its aim, an optimized number of variables and an easy method of data collection that allowed for consistency checks. Furthermore, BIOBADASER 2.0 data were validated by calling and checking with the patients and *in situ* audits. Information was found to be accurate in 92.6% of the cases, and all inconsistencies and missing data were amended. This consistency, valuable for data interpretation, strengthens the relevance of the present work.

Retention of a drug can be taken as an indicator of drug effectiveness in the clinical setting. However, these studies face limitations such as confounding by indication, patient selection and the absence of a washout period [15]. The decision to start or to stop treatment, although guided by recommendations, was based finally on the physician's clinical opinion, and thus a possible influence of the physician on the results cannot be excluded; other aspects characteristic of retrospective study designs may also have limited the ability of the study. Criteria for the assignment of cause for drug discontinuation vary, and are clearly different in clinical trials than in observational studies. It is conceivable that on some occasions the drug was stopped in patients who presented both mild associated toxicity and a lesser measurable therapeutic effect. In our study, designation of the reason for drug discontinuation may have been arbitrary and different from rheumatologist to rheumatologist. This should be borne in mind when the results are compared with previous reports. Nevertheless, our findings may provide useful information because of the long-term follow-up, the large number of patients involved, the consistency of data and the clinical practice setting.

The treatment of elderly patients with TNF antagonists poses a challenge to the prescribing physician, as AEs are more common in this age group [16]. Infections are a major issue. In the elderly, infections are more difficult to prevent than in young people, as vaccination is less effective, and infections are the most frequent AE in patients treated with TNF antagonists [17]. However, other AEs have to do with comorbidities, drug interactions and dose adjustments [18, 19]. In our study, hypertension and treatment with glucocorticoids were associated with

AEs leading to discontinuation. Also, TNF inhibition in the elderly may have additional benefits, as the level of circulating TNF is elevated and correlates with increased mortality and depression [20, 21], and there is increasing evidence that elderly patients may benefit as much as their younger counterparts from aggressive treatment, not only in rheumatology, but also in oncology [3, 6]. In conclusion, factors predicting discontinuation of TNF antagonists due to AEs are older age, diagnosis of RA, glucocorticoid use and hypertension. On the other hand, younger age predicts discontinuation due to lack of efficacy.

Rheumatology key messages

- Patients aged <65 years with chronic arthropathies tend to discontinue TNF antagonist due to inefficacy.
- Patients aged >65 years tend to discontinue TNF antagonist due to AEs.
- RA patients discontinued TNF antagonist more frequently for inefficacy and AEs than SpA patients.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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