Formulário de acesso a dados do Registo Nacional de Doentes Reumáticos (Reuma.pt) da SPR, 2012-2014

1. Title

Drug survival and predictive factors for retention of TNF-α blockers in patients with ankylosing spondylitis: results from Reuma.pt

2. Background

2.1 Literature review

Ankylosing spondylitis (AS) is the paradigm disease of the spondyloarthritis group. It has an estimated prevalence of 0.1-1% and affects men three times more frequently than women[1]. The age of onset varies from the late teens to the mid-forties and, consequently, AS patients bear a significant personal, social and working burden[2]. Treatment aims to control symptoms, disease progression and disability. Although they have failed to demonstrate disease-modifying capability in AS, as opposed to rheumatoid arthritis (RA), TNF-alpha blockers remain the only therapeutic option when conventional treatment is insufficient to control disease activity.

It is of the utmost importance to determine which AS patients will respond and for how long they will retain TNF-alpha blocking therapies with an adequate disease control, as these are not innocuous or inexpensive therapies. There has been a growing interest in this matter in the last years. In 2007, *Luc et al*. have found increased baseline C reactive protein (CRP) as the only predictor of TNF-alpha inhibitor retention in AS[3]. In a Spanish study using the Spanish Society of Rheumatology biologics database, BIOBADASER, a younger age at treatment start was predictor of discontinuation due to lack of efficacy in AS patients[4]. Apparently, in AS, TNF-alpha blocker survival is superior when compared to RA[5] and after switching from one TNF-alpha inhibitor to another, retention of the second agent was similar to the first one[6]. In a very recent retrospective study using data from the Danish registry DANBIO, one-third of AS patients in clinical practice switched biological treatment with half of switchers achieving treatment response. Male gender and low BASFI predicted drug survival of the second TNF blocker[7].

2.2 Previous work

Our group has been doing several analyses in the spondyloarthritis context and in AS in particular. Epidemiological, clinical and genetic characterization of Portuguese AS patients were performed and published. This multicentric study was developed in the CORPOREA scenario, involving several Rheumatologic Departments from Portugal mainland. We intend to pursue this goal by continuing research in this field.

2.3 Hypothesis

- Knowing that biotechnological-naïve patients have different responses to TNF-alpha blocker therapy, we hypothesize that patients have different drug retention rates and that there are determinants that influence drug retention that should be considered when starting such therapies.
- When TNF-alpha blocker therapy fails or adverse events (AEs) occur, biotechnological medicine switch is usually the following step. We hypothesize that there are determinants that influence clinical response that should be considered when reintroducing such therapies.

2.4 Innovation and significance

The previously referred studies found different clinical and laboratorial parameters that predict drug survival. This heterogeneity may partially be explained by the unequal study methodology but also by the distinct origin of the studied populations. We know that patients from different countries present inherent particularities that influence response to therapy, hence we consider highly relevant to perform this type of assessment in a Portuguese population. The ascertainment of TNF-alpha blocker retention rate and retention predicting factors, as well as the ascertainment of clinical response at 12 weeks after biotechnological drug switch was never performed to date in Portuguese AS patients.

3. Specific aims

PRIMARY AIM

3.1. To **assess drug survival and** identify predictive factors of the first TNF blockers retention rate at 24 months in AS patients in Reuma.pt.

SECONDARY AIMS

3.2. To assess the reasons for discontinuing the first TNF blocker in AS patients during 24 months of follow-up.

3.3. To assess predicting factors of clinical response at 12 weeks after switching from the first to the second TNF blocker in AS.

3.4. To assess drug survival of the second and third TNF blocker in AS patients during 24 months of follow-up.

4. Methods

4.1. Study design

We will perform a retrospective cohort study including all AS patients (who fulfil the 1984 modified New York criteria) treated with TNF-α blockers registered at the Reuma.pt from June 2008 until October 2011. The study follow-up time will be 24 months.

Inclusion criteria: Biologically naïve patients that fulfil the Modified 1984 New York classification criteria for AS.

Exclusion criteria: Patients with spondyloarthritis other than AS.

4.2. Analysis plan

PRIMARY AIM

4.2.1. To assess drug survival and identify predictive factors of the first TNF blockers retention rate at 24 months in AS patients in Reuma.pt.

Explanatory variables and their measurements:

We will look at clinical and laboratorial predictor factors of anti-TNF treatment retention rate in AS patients. In this case our exposures will be the potential clinical and laboratorial predictors or covariates. We will evaluate as our clinical predictor factors: age at beginning of symptoms, time delay between starting symptoms and diagnosis, age at TNF blocker beginning, disease duration, presence of peripheral arthritis, presence of extra articular features (including acute anterior uveitis, enthesopathy, psoriasis, inflammatory bowel disease), gender, BMI, education level, tobacco and alcohol consumption, disease activity as assessed by baseline ASDAS and BASDAI, functional status as assessed by BASFI, metrological status as assessed by BASMI, previous conventional DMARD used (methotrexate, leflunomide, sulfasalazine), TNF blocker used (Etanercept, Infliximab, Adalimumab, Golimumab) and

corticosteroid therapy (oral and intra-articular). As our laboratorial predictors we will evaluate C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and HLA B27 positivity.

Outcomes and their measurements:

Our primary outcome will be the survival time during the first two years of therapy with TNF blockers measured in person-days. We will use a composite outcome including all causes for discontinuation of TNF blocker (no response, loss of response, or adverse events). Data will be censored at stopping TNF blocker, loss of follow-up for any reason or end of observation time up to 24 months.

Methods summary:

We will report drug survival as the median days of follow-up, its 95% confidence interval (CI) and the proportion of patients in treatment at prespecified time-points (6 months, 12 months, 18 months and at the end of follow-up time).

We will use Log rank test to identify which covariates measured at baseline (i.e. previous to anti-TNF therapy beginning) associates with TNF retention at 24 months on univariable analysis. Variables with p-values smaller than 0.25 will be included in the multivariable analysis. Using a Cox proportional hazards model with forward selection method for model building, we will create an algorithm to predict which patients from the baseline evaluation are more likely to retain therapy with the first TNF blocker at 24 months. We will include all variables that retain statistical significance on the multivariable model at the 5% level of significance. Finally, in this model we will include interaction terms and assess for confounding.

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, 14 days for adalimumab and 28 days for golimumab).

Overall drug survival will be assessed for all included patients. Additionally, we will perform a subgroup analyses stratified by specific TNF blocker (infliximab, etanercept, adalimumab and golimumab) drug.

The results will be presented graphically as Kaplan-Meier curves and as hazard ratios (HR) and 95% confidence intervals (95%CI). Receiver Operator Curves (ROC) will be applied to evaluate the discriminative power of our model to accurately predict the outcome. The STATA computer software package will be used to analyze the data collected from this study. Continuous variables will be reported as mean +/- standard deviation (or in case of non normal distribution as median and quartiles). Nominal variables will be displayed as frequency or proportions.

SECONDARY AIMS

4.2.2. To assess the reasons for discontinuing first TNF blocker in AS patients during 24 months of follow-up.

Methods summary:

In primary analysis we will use a composite outcome. As a secondary aim we want to analyze survival time stratified for reasons for discontinuation of the first TNF blocker. Patients will be divided into 3 groups based on reason for discontinuation of the first TNF blocker: nonresponsive, loss of response, or adverse events. Patients will be classified as responders if they achieve a change of at least 50% or 20 mm reduction in the BASDAI from baseline to week 12. Nonresponders will be defined as not achieving this outcome. Secondary failure (loss of response) will be defined as patients classified as responders at week 12 who loose this achievement in two or more evaluations thereafter.

We will perform Cox proportional hazards model to assess the HR and 95% CI for discontinuing TNF blocker as compared to those who remain in treatment during the 24 months of follow-up in each subgroup, adjusting for the covariates found significant on the overall multivariable model defined in primary aim.

4.2.3. To assess predicting factors of clinical response at 12 weeks after switching from the first to the second TNF blocker in AS.

In this analysis we will include those patients who switched from the first TNF blocker to the second during the 24 months of follow-up.

Explanatory variables and their measurements:

We will look at the same clinical and laboratorial predictor factors described in primary Aim. Additionally, we will include the following variables: time to switch, reason for switching and first TNF blocker used. For this analysis we will consider as baseline measurements, those performed immediately after the first TNF blocker discontinuation (time period for each drug described in primary Aim).

Outcomes and their measurements:

Our outcome will be **(1)** change of at least 50% or 20 mm reduction in the BASDAI from baseline to week 12. Moreover, we will perform a comparative analysis using as response criteria **(2)** Ankylosing Spondylitis Assessment Group (ASAS) 40 response criteria at week 12 and **(3)** ASDAS improvement ≥1.1 from baseline to week 12.

Methods summary:

We will use multivariate logistic regression with forward selection method for model building as described in primary Aim to assess which of the explanatory parameters assessed at baseline are associated with each of the three above described outcomes. We will create several models to identify the one with the highest adjusted R^2 (aR^2). In these models we will include interaction terms and assess for confounding. At the end we will be able to create an algorithm to predict which patients from the baseline are more likely to respond at week 12.

First, we will assess the overall treatment response for the second TNF blocker (all drugs as a group). An analysis of the variables predicting treatment response will also be performed for each drug separately.

The results will be presented as odds ratio (OR) and 95% confidence intervals (95%CI). P-values less than 0.05 will be considered significant.

4.2.4. To assess drug survival of the second and third TNF blocker in AS patients during 24 months of follow-up.

As for primary aim, we will report drug survival as the median days of follow-up, its 95% confidence interval (CI) and the proportion of patients in treatment at prespecified time-points (6 months, 12 months, 18 months and at the end of follow-up time).

4.2.4 Sample size

Our primary outcome will be the survival time during the first two years of therapy with TNF blockers. From previous knowledge[8] we expect that approximately 60% of the patients will remain in treatment at the end of follow-up. Based on that, the estimated required sample size to achieve 80% power to detect 33% reduction in the hazard of discontinuing treatment (HR = 0.67) by using a two-sided 0.05-level log-rank test with Freedman method is 202 patients.

From the December 2012 report we know that 570 AS patients under TNF blocker therapy are registered in Reuma.pt. Since we will include all AS patients treated with TNF-α blockers

registered at the Reuma.pt from June 2008 until October 2011 we don't expect difficulties in achieving the calculated sample size.

5. Limitations and expected results

Expected results:

- We hope to identify the retention rate and predictors of survival of TNF-alpha blocker therapy in Portuguese patients with AS. These predictors are expected to improve treatment success since they may contribute to adequate treatment choice according to patient and drug specificities.
- We hope to identify predictors of clinical response at 12 weeks after TNF-alpha blocker switch in Portuguese patients with AS. These predictors are expected to allow for a well informed decision concerning alternatives after treatment failure, as well as adequate timing for switching the biotechnological drug when there is an incomplete response to treatment.

Limitations include:

- Possible information bias due to incomplete filling of database fields by rheumatologists.
- Outcome assessment bias, since patient evaluation and database filling are performed by different rheumatologists from multiple Portuguese centres.

6. Timeline

	January 2014	(…)	May 2014	June 2014
Data extraction				
Data evaluation and analysis				
Data presentation and publication			XVII Congresso Português de Reumatologia	EULAR meeting

7. Institutions

The Project is open to all National Centers interested to cooperate.

8. Research Team

Alexandre Sepriano, MD; Filipe Araújo, MD; Teresa Pedrosa, MD; Sandra Falcão, MD, PhD Student; Fernando Pimentel-Santos, MD, PhD; Jaime C. Branco MD, PhD.

9. Co-authors

All clinicians who actively work on the project will be co-authors with a maximum of four co-authors for each participating Institution.

10. Funding and conflicts of interest

No conflicts of interest and no external funding to declare.

References

(1) Healy PJ, Helliwell PS. Classification of the spondyloarthropathies. Curr Opin Rheumatol 2005;17:395-399.

(2) Jacobs P, Bissonnette R, Guenther LC. Socioeconomic burden of immune-mediated inflammatory diseases--focusing on work productivity and disability. J Rheumatol Suppl 2011;88:55-61.

(3) Luc M, Gossec L, Ruyssen-Witrand A, et al. C-reactive protein predicts tumor necrosis factor-alpha blocker retention rate in axial ankylosing spondylitis. J Rheumatol 2007;24:2078-2081.

(4) Busquets N, Tomero E, Descalzo MÁ, et al. Age at treatment predicts reason for discontinuation of TNF antagonists: data from the BIOBADASER 2.0 registry. Rheumatology (Oxford) 2011;50:1999-2004.

(5) Scirè CA, Caporali R, Sarzi-Puttini P, et al. Drug survival of the first course of anti-TNF agents in patients with rheumatoid arthritis and seronegative spondyloarthritis: analysis from the MonitorNet Database. Clin Exp Rheumatol 2013 Aug 26. [Epub ahead of print].

(6) Dadoun S, Geri G, Paternotte S, et al. Switching between tumour necrosis factor blockers in spondyloarthritis: a retrospective monocentre study of 222 patients. Clin Exp Rheumatol 2011;29:1010-3.

(7) Glintborg B, Østergaard M, Krogh NS, et al. Clinical response, drug survival and predictors thereof in 432 ankylosing spondylitis patients after switching tumour necrosis factor α inhibitor therapy: results from the Danish nationwide DANBIO registry. Ann Rheum Dis 2013;72:1149-1155.

(8) Li, Seah Q., Michelle Y., et al. Long-Term Drug Survival of Anti-TNF Therapy in Ankylosing Spondylitis. Arthritis Rheum 2010;62 Suppl 10 :1942.