

Biologics discontinuation in Rheumatoid Arthritis and Spondylarthritis

Retrospective analysis of reasons for discontinuation and outcome

Background

In the last decades, a revolution occurred in the treatment of Rheumatic inflammatory diseases and remission is now a realistic goal for most patients. A recent survey from the NOR-DMARD study shows doubling of remission rates in the last decade¹.

Treat-to-target (T2T) strategies have been used in the management of patients with rheumatoid arthritis (RA) and involve intensifying medication as long as low disease activity or remission is not achieved². In Spondyloarthritis (SpA) and Psoriatic Arthritis (PsA), similar approaches have been recently proposed by the European League Against Rheumatic Diseases (EULAR)³.

A state of sustained remission implies the dilemma of whether the disease is actually cured or just effectively suppressed by treatment. However, step down strategies have not been so well defined. EULAR 2010 RA treatment guidelines (and their 2013 update) propose that after tapering steroids, a discontinuation in biological therapy should be tried in patients in remission⁴. EULAR/ Assessment of SpondyloArthritis international Society (ASAS) guidelines for SpA management don't mention biologics tapering or discontinuation⁵.

The indefinite continuation of biologics is questionable. There is no clear benefit in maintaining biologics therapy in all RA or SpA patients. Furthermore long-term safety aspects remain unknown and the costs of a possible unnecessary continuation are not negligible. Feared risks in these reduction/discontinuation therapeutical schemes include the formation of antibodies against the drug, and therefore loss of efficacy, and damage accumulation⁶. Nevertheless, in BeSt, a study with infliximab discontinuation, when methotrexate was continued, about 50% of patients could stop infliximab without radiological damage progression, while others regain low disease activity after restarting infliximab⁷. In a prospective study, in patients with peripheral SpA (n=26) that discontinued adalimumab for 16 weeks, found no clear association between adalimumab serum levels or antiadalimumab ADAbs with clinical response to treatment or with relapse⁸.

In RA patients, a number of studies have concerned the discontinuation of biologics. Essentially, three types of studies have been conducted: randomized clinical trials (RCTs), single-arm prospective study and long-term extension of efficacy trial⁶. Other than the fact that there's a high heterogeneity in studies, remission and outcome definitions have also varied. Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR) with different cut-offs (2.7, 2.6, 3.2) is the commonest definition of remission. However, a common definition of disease flare, and therefore failure in the discontinuation, has not been encountered⁹.

In a study with early rheumatoid arthritis patients immediately started on full-dose etanercept-plus-methotrexate therapy, continuing combination therapy at a reduced dose resulted in better disease control than switching to methotrexate alone or placebo, but no significant difference was observed in radiographic progression at 52 weeks¹⁰. In the Retro study, 101 RA patients in stable remission at 6

months were randomized (1:1:1) to either continue, taper all disease-modifying antirheumatic drugs (DMARDs) conventional and/or biological or stop all treatments¹¹. This study suggests that tapering and even stopping allows more than half of the patients to maintain remission over 1 year. Anti-citrullinated protein antibodies (ACPA) positive patients presented a higher risk for relapse.

In SpA and PsA, there is a small number of controlled trials in the extension period of trial that lead to drug approval, and more recently in a SpA early disease cohort^{12,13,14}. The results in the latter study showed that, at 52 weeks, roughly half of the patients relapsed, in spite of treatment with naproxen¹⁴. Remission was defined by the T2T initiative as the combination of a low Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) <2.0, and normal C-reactive protein (CRP) or inactive Ankylosing Spondylitis Disease Activity Score (ASDAS) (cut-off <1.3)³.

An increasing number of studies in RA have been pursued in the last years; however, most data is originated from studies in trial settings and lack of resemblance to a clinical daily practice⁶. Small-sized samples have been studied in a setting closer to the clinical practice⁶. Furthermore, the identification of patients that are less likely to flare after discontinuation is yet to be achieved.

Registries represent an opportunity, as this type of data tends to provide more generalizable information. The combination of registries can be useful to increase power, but challenges in combining data from different countries and health-care system are expected¹⁵.

Objectives

1. We aim to perform a retrospective cohort study including all SpA and RA patients treated with biologic DMARDs that discontinued biologic therapy. Reasons for discontinuation (side effects, pregnancy, clinical remission or others factors) will be assessed and a stratified analysis of data will additionally be pursued. Discontinuation in the context of remission will be specially looked at.

1. Retrospective analysis of patients that underwent a discontinuation therapeutical scheme

Primary outcome: low disease activity (in RA DAS28<2.6; in SpA ASDAS<1.3 or BASDAI<2.0) at 12 months after discontinuation.

Secondary outcomes: low disease activity (in RA DAS28<2.6; in SpA ASDAS<1.3 or BASDAI<2.0) at 6 months after discontinuation; the subsequent evolution in functional status (Health Assessment Questionnaire - HAQ, Bath Ankylosing Spondylitis Functional Index - BASFI) after discontinuation at 12 months; subsequent changes in other related therapy; characterization of steroid use and dosing, as well as conventional DMARD use; time to new biologic/ re-initiation of the same biologic after the follow up period (12 months); and safety data (incidence of adverse events and serious adverse events).

Methods summary

Inclusion criteria:

- Patients with RA or SpA that started discontinuation of biologic therapy for at least 6 months, until April 2014.
- RA patients should fulfill classification criteria EULAR/ACR 2010 and SpA according to ASAS 2009 classification criteria.
- Previous treatment includes all biological therapies (except anti-CD20 monoclonal antibody).

Exclusion criteria:

- Prednisolone >10mg (or equivalent).
- Switch or re-initiation of biological therapy within 12 months from the time of discontinuation.

Statistical analysis

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. Differences of parameters by stratum will be based on hypothesis test: Chi-square test or F-test for binary variables, t-test and analysis of variance for normally distributed continuous variable and Mann-Whitney and Kruskal-Wallis tests to non-normal distributed variable.

Primary outcome

We will compare clinical and laboratorial characteristics in groups of patients according to disease activity groups (low disease activity and non-low disease activity) with the cut-offs DAS28 < 2.6 (RA); ASDAS < 1.3/BASDAI < 2.0 (SpA) after 12 months. Predictor factors for low disease activity will be determined by uni and multivariate logistical regression analyses. Candidate covariates were entered in the multivariate model by backward selection if $p < 0.05$ in univariate analysis. A significant level of 5% was used in all analyses. The STATA computer software package will be used to analyze the data collected from this study.

Covariates

We will evaluate as our clinical predictor factors separately for both diseases.

- Some clinical and demographic variables will be analyzed in both groups: gender, body mass index (BMI), education level, tobacco and alcohol consumption, age at beginning of symptoms, time delay between starting symptoms and diagnosis, age at biologic beginning, disease duration, presence of extra articular features, previous and concomitant conventional DMARD used (methotrexate, leflunomide, sulfasalazine), previous TNF blockers, steroid therapy, CRP and ESR.

- In RA patients: erosive disease, baseline DAS28 and functional status as assessed by HAQ, IL6 blocker use.
- In SpA patients: ASDAS/BASDAI, functional status assessed by BASFI and metrological status as assessed by BASMI (last measurements before discontinuation).

Secondary Outcomes

To investigate the proportion of patients with clinical low disease activity (DAS28 < 3.2, ASDAS < 1.3/BASDAI < 2.0) at 6 months after discontinuation, we will compare clinical characteristics and laboratorial in groups of patients according to the presence of low disease activity. Predictor factors for low disease activity will be determined by multivariate logistical regression analyses, as described above.

To examine the subsequent evolution in functional status (HAQ, BASFI) after discontinuation, we will compare clinical characteristics and laboratorial in groups of patients according to the presence of significant change in functional status (Δ HAQ > 0.22, Δ BASFI > 50%) after 12 months (last recorded value between 6 and 12 months will be counted). Predictor factors for significant change in the functional status will be determined by multivariate logistical regression analyses, as described above.

Time to new biologic

We will report drug free survival as the median days of follow-up, its 95% confidence interval (CI) and the proportion of patients without new biological treatment. We will use Log rank test to identify which covariates measured at baseline (previous to biologic therapy discontinuation) associate with continued low disease activity after 12 months on univariate analysis. Variables with p-values smaller than 0.5 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 not to flare. 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. Overall drug-free survival will be assessed for all included patients.

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.

Limitations: It is a retrospective analysis and outcome after biologic discontinuation can vary broadly amongst causes of discontinuation.

We expect missing data following biologic discontinuation, though we hope to minimize this problem with the cooperation of other Rheumatology centers.

Calendar

The project will start in March 2015 and will be developed during 6 months after receiving the database. Submission to relevant rheumatology conferences is anticipated.

Budget

Financial support is not being requested to Reuma.pt/Sociedade Portuguesa de Reumatologia.

Conflicts of Interest

The research team declares no conflicts of interest.

Research team

Proponents: Maria João Gonçalves, Helena Canhão

Co-authoring we will be attributed to all the clinicians that collaborate directly in the project, namely improving the quality of data (maximum number of authors per center: 3).

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