Effectiveness of switching between TNF inhibitors in patients with axial spondyloarthritis: is the reason to switch relevant?

Abstract

Background Tumor Necrosis Factor inhibitors (TNFi) have revolutionized the treatment of patients with axial spondyloarthritis (axSpA). However, some patients may fail their first TNFi either because of inefficacy and/or safety reasons. The current recommendations for axSpA defend switching to another TNFi or an IL-17i in case of failure of the first TNFi. However, the recommendation is solely based on experience rather than evidence on efficacy.

Aims i) To assess and compare the efficacy of TNFi as first-line and second-line therapy in patients with axSpA; ii) To assess whether the reason of discontinuation of the first TNFi may affect the response to the second TNFi.

Patients and methods Patients with axSpA registered in the Reuma.pt who were treated with at least two TNFi and who started the second TNFi up to September 2016 will be included. Baseline characteristics will be described according to the reason of first TNFi discontinuation.

The proportion of patients meeting the primary (ie. Ankylosing spondylitis disease activity score clinically important improvement at 3 months) and secondary endpoints (eg. ASDAS inactive disease activity, Bath Ankylosing Spondylitis Activity Index 50 response, ASAS 20 and 40 responses, among others, both at 3 and 6 months) will be assessed both for the first and second TNFi. Response to the second TNFi in relation to the reason for discontinuation of the first TNFi will be tested in multivariable logistic/linear (depending on the outcome) regression models adjusting for a set of clinically defined potential confounders. Additionally, longitudinal analyses with generalized estimating equations (GEE) models taking all information from all visits into account will be conducted.

Expected results We hypothesize that in patients with axSpA response to a second TNFi is different as compared to the response to the first TNFi and that the reason to discontinue the first TNFi is associated with the response to the second TNFi.

1. Rationale of this application

1.1. Current knowledge

Since the beginning of the century Tumor Necrosis Factor inhibitors (TNFi) have been a revolutionary therapeutic option in the treatment of patients with axial spondyloarthritis (axSpA) (1). However, some patients may fail their first TNFi either because of inefficacy and/or safety reasons. In such a situation clinicians have to decide what to offer as second-line therapy, taking into account, among other factors like: i. The available treatment options; ii. The reason for failure of the first drug and; iii. The available evidence to support the decision.

In absence of the proper double-blind randomized placebo-controlled trials to address this clinically relevant issue, clinicians had, so far, to rely on observational studies (2, 3) and open-label trials (4). These have suggested that a second TNFi may be effective and safe in patients with axSpA who already experienced a previous therapeutic failure to a first TNFi. However, the intrinsic methodological limitations of this kind of study limit definitive conclusions. Only recently, a biologic disease-modifying drugs (bDMARDs) targeting a pathway other than the Tumor Necrosis Factor (TNF) has been approved and thus broadening the range of therapeutic options for axSpA patients. Secukinumab, an IL-17 inhibitor (IL-17i) monoclonal antibody, has shown efficacy in two phase 3 randomized controlled trials (RCTs) (5) both when used in TNFi naïve patients and patients who failed a TNFi. Of note, this was also the first data stemming from an RCT showing efficacy of a second bDMARD after failure of a first TNFi. These new data already

translated into a change in the international recommendations. The 2016 update of the ASAS-EULAR management recommendations for axSpA (6) defend switching to another TNFi or an IL-17i in case of failure of the first TNFi. However, the recommendation to preferentially use TNFi and not IL-17i as second-line therapy is solely based on the larger experience with the former, and not based on evidence supporting a different efficacy. Importantly, this update also embodies the generally accepted – but not proved – concept that in patients with a primary non-response to the first TNFi, may be more rational to switch to another class of drugs (eg.IL-17i). The expansion on therapeutic options and the possible lack of the proper head-to-head studies highlights the relevance of the proposed study.

1.2 Hypothesis

We hypothesize that in patients with axSpA, response to a second TNFi is different as compared to the response to the first TNFi and that the reason to discontinue the first TNFi is associated with the response to the second TNFi.

1.3 Innovation and significance

This study will provide evidence about the TNFi efficacy, as first and second line therapy, in the Portuguese axSpA population. We will also compare treatment-response between patients with primary failure and those with a secondary failure or withdrawal due to safety reasons.

Although RCTs are considered the gold-standard to address this issue, these are unlikely to be performed in the upcoming years. A methodological sound observational study including 'real-world' patients, instead of the "perfect" patients observed in RCTs who are 'hand-picked' after conforming to a long list of inclusion and exclusion criteria, provides valuable data to inform evidence-based treatment decisions.

2. Aims

2.1. Main aim

To assess and compare the efficacy of TNFi as first-line and second-line therapy in patients with axSpA.

2.2. Secondary aim

To assess whether the reason for discontinuation of the first TNFi affects the response to the second TNFi.

3. Methods

3.1. Study design

Prospective, multicentre, open cohort study using data from the Rheumatic Diseases Portuguese Register (Reuma.pt) (7).

3.2. Population

The study will include all patients with axSpA according to their treating rheumatologist (excluding patients with Psoriatic Arthritis) registered in the Reuma.pt who were treated with at least two TNFi and who started the second TNFi up to September 2016 (i.e. at least 6 months of follow-up for efficacy assessment).

A previous study with data from Reuma.pt in axSpA patients under TNFi therapy (treatment start up to 2014) included 954 patients and 289 discontinued their first TNFi (8). Our starting sample

will consist of the patients who failed to a 1st TNFi and switched to another TNFi. Interruptions of treatments, continuing thereafter with the same TNFi will be not counted as switches. Keeping in mind the constant increase of the number of patients included in Reuma.pt we anticipate that the sample size will be large enough to address our research question.

3.3. Reuma.Pt Database

Reuma.pt is a nationwide clinical register, established and managed by the Portuguese Society of Rheumatology, in which data from patients with various rheumatic diseases is recorded, using standardized protocols, by their treating rheumatologists in daily practice. A detailed report of the design of Reuma.pt and data management procedures has been published elsewhere.(7)

3.4. Endpoints

Primary endpoint

Ankylosing spondylitis disease activity score clinically important improvement (Δ ASDAS ≥ 1.1 as compared to baseline) at 3 months.

Secondary endpoints

ASDAS inactive disease activity (ASDAS < 1.3), ASDAS moderate disease activity (1.3 <ASDAS ≤ 2.1), Bath Ankylosing Spondylitis Activity Index (BASDAI) 50 response, Assessment of SpondyloArthritis International Society (ASAS) 20 response, ASAS 40 response, ASAS 5/6 response, ASAS partial remission, Δ ASDAS, Δ BASDAI and Δ Bath Ankylosing Spondylitis Functional Index (BASFI) (all Δ compared to the baseline value) both at 3 and 6 months. Δ ASDAS ≥ 1.1 at 6 months.

3.5. Grouping variable:

Reason of first TNFi discontinuation defined as follows: i) primary failure: response (ASDAS clinically important improvement) at 3 months is not achieved (8); ii) secondary failure: response (ASDAS clinically important improvement) at 3 months is achieved and then lost any time during follow-up before discontinuation. (8); iii) toxicity (adverse event); iv) other (eg. pregnancy, elective surgery, remission, personal preference by the physician or patient). For patients with more than one reason for discontinuation recorded, the 'main' reason will be used in a case by case decision-basis.

3.6. Potential confounders

The following variables may confound the association between the reason for the first TNFi discontinuation and the primary endpoint as well as other secondary endpoints defined by disease-activity measures: past bDMARD, any current or past conventional synthetic (cs) DMARD intake, nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids intake (either orally or injections), time between the start of the first TNFi and the second TNFi, year of start of the first TNFi, age at the start of the first TNFi, gender and factors possibly related to therapeutic compliance (eg. education). In addition to the above-mentioned possible confounders we will also take into account Bath Ankylosing Spondylitis Metrological Index (BASMI) and ASDAS when using Δ BASFI as an outcome.

3.7. Statistical analysis

Baseline characteristics (table 1) will be described for all included patients for both the start of the first TNFi and the start of the second TNFi. For the latter, they will also be stratified according to the reason of first TNFi discontinuation.

The proportion of patients meeting the primary and secondary endpoints will be assessed both for the first and second TNFi. Response to the second TNFi in relation to the reason for discontinuation of the first TNFi will be tested in multivariable logistic/linear (depending on the outcome) regression models. Additionally, longitudinal analyses with binomial/linear generalized estimating equations (GEE) models taking all information from all visits into account will be conducted. The same primary endpoint will be used and additionally also a continuous outcome (ASDAS-CRP) will be used. With these analyses we will test the association between the reason for discontinuation of the first TNFi and response to the second TNFi adjusting for a set of clinically defined potential confounders. p-values less than 0.05 will be considered significant.

Data analysis will be performed using Stata version 14.0.

3.8. Variables

Table 1 - Variables to be collected

Variables to be collected	
Clinical Characteristics (all visits)	Demographic - age, gender, education status, working status, smoking status Clinical - patient global visual analogue scale (VAS-PG; 0-100), pain VAS (0-100), BASDAI, BASFI, BASMI, ASDAS-CRP Lab results - erythrocyte sedimentation rate (ESR; mm/h), C- protein reactive (CRP; mg/dl), HLA B27
Disease Characteristics (all visits)	Disease duration, symptoms duration, number of tender joints (0-75), number of swollen joints (0-73), presence of dactylitis as well as enthesitis,
Therapy (all visits)	csDMARDs and bDMARDs, Oral AINEs and Steroids, Starting date of treatment, Stop date and reasons for discontinuation, Doses used, Frequency of administration Route of administration

4. Expected results and study limitations

4.1. Expected results

We expect to inform the rheumatology community on the effectiveness of a second TNFi in a 'real-world' setting. Moreover, we will assess how relevant the reason for discontinuation of a first TNFi will affect the effectiveness of second TNFi (same mechanism of action). Our study is of particular relevance given the recent approval of a drug targeting a pathway other than TNF for patients with axSpA.

4.2. Limitations include:

Residual confounding cannot be excluded and may affect interpretation of the treatment effect-size. This is an inherent limitation to all observation studies assessing efficacy of drugs without random treatment allocation. Nevertheless, there are no reasons to expect that this is different in a first line TNFi compared to a second line TNFi, and therefore such an analysis is valid and insightful.

Possible information bias can happen due to incomplete filling of database fields by rheumatologists, which leads to missing values in the analysis. We will anyway make the best efforts to complete the dataset with information from the medical charts, when available. This is an effort that has recently been done in the context of a project of our team, also dealing with patients with axSpA from Reuma.pt.

5. Timeline

Timeline for the several steps of this study are presented in Table 2. Globally this study will take 9 months to be concluded.

Table 2 - Timeline

Timeline						
	May-June 2017	July-January 2018	January 2018	February-April 2018	May-November 2018	December 2018
Data extraction						
Data evaluation and analysis						
Abstract submission						
Data presentation					EULAR 2018 CPR 2018	
Manuscript preparation						
Manuscript submission						

6. Ethical considerations

This study will be conducted according to the Declaration of Helsinki (revised in 2013, in Fortaleza (Brazil)), and the International Guidelines for Ethical Review of Epidemiological Studies. This study will be submitted for evaluation and approval to a competent Ethics Committee. Results will be presented in an objective way, and will not be hidden or manipulated.

Data protection will be assured by data encryption according to the Portuguese law (Law n.67/98 de 26th of October) and according to National Committee for Data Protection deliberation n.227/2007, which provided guidelines to the processing of personal data carried out under scientific clinical research.

7. Partnership

All Portuguese departments of rheumatology will be invited to participate.

The final protocol will be submitted to the Scientific Committee of Reuma.pt.

8. Roles of research-team' members

Santiago Rodrigues Manica[1,2]: study design, protocol development, database management, statistical analysis, interpretation and discussion of results, preparation and revision of communications and scientific articles.

Alexandre Sepriano[1,2,3]: study design, protocol development, database management, statistical analysis, interpretation and discussion of results, preparation and revision of communications and scientific articles.

Fernando Pimentel Santos[1,2]: study design, protocol development, interpretation and discussion of results, preparation and revision of communications and scientific articles.

Nélia Gouveia[1]: study design, protocol development, project funding, interpretation and discussion of results, preparation and revision of communications and scientific articles.

Anabela Barcelos[4]: study design, protocol development, interpretation and discussion of results, preparation and revision of communications and scientific articles.

Jaime C. Branco[1,2]: study design, protocol development, interpretation and discussion of results, preparation and revision of communications and scientific articles.

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8. References

1. Brandt J, Haibel H, Cornely D, Golder W, Gonzalez J, Reddig J, et al. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab. Arthritis Rheum. 2000;43(6):1346-52.

2. Coates LC, Cawkwell LS, Ng NW, Bennett AN, Bryer DJ, Fraser AD, et al. Real life experience confirms sustained response to long-term biologics and switching in ankylosing spondylitis. Rheumatology (Oxford). 2008;47(6):897-900.

3. Pradeep DJ, Keat AC, Gaffney K, Brooksby A, Leeder J, Harris C. Switching anti-TNF therapy in ankylosing spondylitis. Rheumatology (Oxford). 2008;47(11):1726-7.

4. Cantini F, Niccoli L, Benucci M, Chindamo D, Nannini C, Olivieri I, et al. Switching from infliximab to once-weekly administration of 50 mg etanercept in resistant or intolerant patients with ankylosing spondylitis: results of a fifty-four-week study. Arthritis Rheum. 2006;55(5):812-6.

5. Baeten D, Sieper J, Braun J, Baraliakos X, Dougados M, Emery P, et al. Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis. N Engl J Med. 2015;373(26):2534-48.

6. van der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017.
7. Canhão H, Faustino A, Martins F, Fonseca JE, Rheumatic Diseases Portuguese Register Board Coordination PrSoR. Reuma.pt - the rheumatic diseases portuguese register. Acta Reumatol Port. 2011;36(1):45-56.
8. Sepriano A, Ramiro S, van der Heijde D, Ávila-Ribeiro P, Fonseca R, Borges J, et al. Effect of Comedication With Conventional Synthetic Disease-Modifying Antirheumatic Drugs on Retention of Tumor Necrosis Factor Inhibitors in Patients With Spondyloarthritis: A Prospective Cohort Study. Arthritis Rheumatol. 2016;68(11):2671-9.