

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

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Abstract

Background: To investigate whether the reason to discontinue the first TNF inhibitor (TNFi) affects the response to a second TNFi in axial spondyloarthritis (axSpA).

Methods: Patients with axSpA from the Rheumatic Diseases Portuguese Register (ReumaPt), who discontinued their first TNFi and started a second TNFi between June 2008 and May 2018 were included. Response was assessed by the Ankylosing Spondylitis Disease Activity Score (ASDAS) clinically important improvement (ASDAS-CII), major important improvement (ASDAS-MI), low disease activity (ASDAS-LDA) and inactive disease (ASDAS-ID). The reason for discontinuation of the first TNFi was defined, according to ASDAS-CII as: primary failure (no response ≤ 6 months); secondary failure (response ≤ 6 months but lost thereafter); adverse events; other. The association between the reason of discontinuation of the first TNFi and response to the second TNFi over time was assessed in multivariable generalized equation (GEE) models.

Results: In total, 193 patients were included. The reason of discontinuation of the first TNFi did not influence the response to a second TNFi, according to the ASDAS-CII. However, a difference was found with more stringent outcomes, e.g. there was a higher likelihood to achieve ASDAS-ID with the second TNFi for patients discontinuing the first TNFi due to secondary failure (OR: 7.3 [95%CI: 1.9; 27.7]), adverse events (OR: 9.1 [2.5; 33.3]), or other reasons (OR: 7.7 [1.6; 37.9]) compared to primary failure.

Conclusion: Patients with axSpA with secondary failure to their first TNFi, compared to those with primary failure, have better response to the second TNFi according to stringent outcomes.

Background

Tumor Necrosis Factor inhibitors (TNFi) have revolutionized the treatment of patients with axial spondyloarthritis (axSpA). Nevertheless, some patients discontinue TNFi [1] either because of inefficacy and/or safety reasons. The number of discontinuations varies across studies but can go up to 50–60% in 2 years [2]. In such circumstances the practicing clinician has to decide what to offer as second-line therapy, considering the available treatment options.

For many years, TNFi were the only biological disease modifying drugs (bDMARD) with proved efficacy in axSpA. More recently Secukinumab and Ixekizumab, both IL-17 inhibitors (IL-17i), have demonstrated efficacy in phase 3 randomized controlled trials (RCTs), [3–5] both in TNFi naïve and TNFi experienced patients with radiographic axial spondyloarthritis (r-axSpA). Part of these data already translated into a change in the 2016 update of the Assessment of SpondyloArthritis International Society – European League Against Rheumatism (ASAS-EULAR) management recommendations for axSpA [6] which prescribes switching to another TNFi or an IL-17i in case of failure of the first TNFi.

In 2019, the the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (ACR/SAA/SPARTAN) 2019 update on the treatment recommendations for axSpA, [7] prioritised an IL17i over a second TNFi in patients with primary non-response to the first TNFi and a second TNFi over an IL17i for those with secondary non-response (after 6 months). This recommendation reflects the long-lasting hypothesis that the reason for discontinuing the first TNFi affects the response to a second TNFi. However, evidence to support such hypothesis is still scarce. In absence of RCTs to address this clinically relevant issue, clinicians have relied on data stemming from observational studies yielding conflicting results, thus precluding definitive conclusions [2, 8–12].

The aims of this study were twofold: to compare the efficacy of TNFi as first-line and second-line therapy, and to assess whether the reason for discontinuation of the first TNFi affects the response to the second TNFi in patients with axSpA.

Methods

Patients and study design

In this prospective multicenter cohort study, adult patients with axSpA, according to their treating rheumatologists, registered in Reuma.pt (Rheumatic Diseases Portuguese Register) who discontinued their first TNFi (for any reason) and started a second TNFi between June 2008 up to May 2018, were included. Patients were required to have complete data on Ankylosing Spondylitis Disease Activity Score (ASDAS) at baseline, 3 and 6 months after starting the first TNFi. Patients were assessed at baseline, 3 months, 6 months and then every 6 months, up to 10 years of follow-up. Data was collected by the treating rheumatologist and stored centrally in the Reuma.pt online 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. A detailed report of the design of Reuma.pt and data management procedures has been published elsewhere [13].

For the current study, a dedicated team of researchers from each participating center was assigned to compare information on a core set of variables between the central database and the medical records, in order to complete missing information whenever possible.

Reuma.pt has been approved by the ethics committees of the participating hospitals and complies with the Declaration of Helsinki. This specific study has been approved by the ethics committee of the NOVA Medical School, Lisbon, Portugal. Patients have signed a written informed consent before inclusion.

Outcomes

The main outcome was the ASDAS clinically important improvement (ASDAS-CII), defined as a decrease from baseline of ≥ 1.1 units of the ASDAS score. Secondary outcomes were: ASDAS major improvement (ASDAS-MI), defined as a decrease from baseline of ≥ 2.0 units; ASDAS low disease activity (ASDAS-LDA), i.e. an ASDAS < 2.1 ; [14] ASDAS inactive disease (ASDAS-ID), i.e. ASDAS < 1.3 ; and the Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI50), defined as 50% improvement compared to baseline.

Reason to discontinue TNFi

The reason for discontinuation of the first TNFi was defined as: i) Primary failure, if ASDAS-CII was not achieved at 3 or 6 months; ii) Secondary failure if ASDAS-CII was achieved at 3 or 6 months but lost in ≥ 1 subsequent visit; iii) Adverse event; iv) Other (e.g. pregnancy, surgery). Primary and secondary failure were defined *a posteriori* by computing the response according to the ASDAS-CII in patients with reported discontinuation due to lack of efficacy by the treating rheumatologist. For patients with ≥ 1 reason for discontinuation recorded by their treating rheumatologist, the 'main' reason was defined in a case by case decision-basis. For instance, if a patient experienced a severe adverse event by the time of discontinuation, this was selected as main reason even if ASDAS-CII had not been achieved.

An alternative definition of secondary failure to the first TNFi was used in a sensitivity analysis. A patient was considered to have a secondary failure if he/she experienced a flare (ASAS definition, 0.9 point increase in ASDAS

between two consecutive timepoints), [15] comparing to the immediately preceding visit (or to 2 previous visits, if the preceding was missing for ASDAS), at least once, after achieving ASDAS-CII at 3 or 6 months.

Statistical analysis

Baseline characteristics were described, at the start of the second TNFi, for the entire population and compared according to the reason of discontinuation of the first TNFi using analysis of variance (ANOVA) for continuous variables and the χ^2 test for categorical variables.

The proportion of patients meeting the efficacy outcomes, at 3 and 6 months, was assessed both for the first and second TNFi (in patients with complete data for each outcome and per timepoint), adjusting for potential confounders selected *a priori* on clinical grounds (age, gender and C-reactive protein (CRP) levels at baseline) in logistic regression models.

The association between the reason for discontinuation of the first TNFi and response to the second TNFi during up to 10 years of follow-up was tested in binomial generalized estimating equations (GEE) models, to take into account the within-patient correlation across repeated measures of the outcome over time. All models were adjusted for age, gender and CRP, the latter modelled as time-varying. Sensitivity analysis was conducted in the same way. *p* values lower than 0.05 were considered significant. Data analysis was performed using Stata version 14.0.

Results

Patient characteristics

In total, 346 patients with axSpA registered in Reuma.pt by the time of database lock (May 2018) had discontinued a first TNFi and started a second TNFi, out of these, 193 had available data for ASDAS at baseline, 3 and 6 months for the first TNFi and were therefore included. Patients had a mean age of 45 years, 53% were male, 61% were HLA-B27 positive and had a mean follow-up of 1.5 years (range: 3 months to 10 years). Patients eligible for the study were largely similar to those excluded (Online Supplementary Table S1).

Patients' characteristics according to the reason of discontinuation of first TNFi

Most baseline characteristics were similar across the reason of discontinuation of the first TNFi (Online Supplementary Table S2). The proportion of male patients was higher among patients who discontinued their first TNFi due to secondary failure (60%) and adverse events (59%), than in patients with primary failure (25%) and other reason for discontinuation (41%).

Only 31% of patients with primary failure had an elevated CRP (≥ 0.5 mg/dL) at baseline. This percentage was higher for secondary failure, adverse events and other reason, 70%, 55% and 53%, respectively.

Comparison of response between first and second TNFi

In total, 96 patients had data for ASDAS for the first and second TNFi at baseline and 3 months and 79 at baseline and 6 months. The adjusted response rate to the second TNFi was lower compared to response to the first TNFi (Table 1). For some outcomes the difference was large; eg, ASDAS-CII at 3 months (41% vs 51%) and 6 months (35% vs 56%) and ASDAS-MII at 3 months (13% vs 33%) and 6 months (22% vs 32%).

Association between reason of discontinuation of the first TNFi and efficacy of the second TNFi

There was no association between the reason to discontinue the first TNFi and response to the second TNFi as defined by ASDAS-CII. Such association could be found with the most stringent outcomes, namely ASDAS-MI and ASDAS-ID (Table 2). For instance, compared to patients who discontinued their first TNFi due to primary failure, patients were more likely to achieve ASDAS ID with the second TNFi if they discontinued their first TNFi due to secondary failure (OR: 7.3 [95%CI: 1.9; 27.7]), adverse events (OR: 9.1 [2.5; 33.3]), or other reason (OR: 7.7 [1.6; 37.9]).

When considering the alternative definition of secondary failure (i.e. according to ASAS Flare), results were mostly similar. However, patients who discontinued their first TNFi due to secondary failure were also more likely to achieve ASDAS-CII with the second TNFi (OR: 3.0 [(95%CI: 1.1; 8.5)] compared to those who had primary failure to their first TNFi (Online Supplementary table S3).

Discussion

In this prospective observational cohort study, we have compared the response to a second TNFi according to the reason of discontinuation of the first TNFi in patients with axSpA using longitudinal data. Response was better for patients discontinuing the first TNFi due to secondary failure compared to those with primary failure. These results can help the practicing clinician to decide on which drug, or drug-class, to use as second-line therapy in daily practice in patients with axSpA.

We found a lower response to the second TNFi compared to the first TNFi. In a Finnish cohort study with 543 patients, BASDAI50 response after 6 months was achieved by 52% and 25% of the patients with their first and second TNFi treatments, respectively. [12] Retention of the second TNFi was shorter than of the first TNFi. In a French study with 244 patients (101 under the first TNFi and 143 on their second TNFi), the drug survival for the first and second TNFi was 22 and 15 months, respectively ($p < 0.01$), regardless of the individual drug [16]. Concerning ASDAS outcomes, as observed in our study, in a Swiss study ASDAS-ESR inactive disease state was reached by 4% of patients after previous primary failure against the 22% after secondary failure [2].

Compared to patients with primary failure, those with secondary failure to the first TNFi had a better response to a second TNFi, but only for the most stringent outcomes (ASDAS-MI and ASDAS-ID). This may explain previous negative results. Studies in which the subtle association between the reason of discontinuation of the first TNFi and efficacy of the second TNFi was not found using BASDAI, [9–11] or ASAS40 as efficacy outcomes, [9] which are far less strict than ASDAS-ID. Differences in the population and also in the methods used to define primary and secondary failure may also contribute to explain differences across studies. In our study patients with a primary failure to the first TNFi had, at baseline of the second TNFi, lower levels of CRP and were also most likely female, which are known to associate with worse response to TNFi treatment [17, 18]. However, a worse response was still seen despite adjustment for these characteristics.

Our study is not without limitations. First, residual confounding can still explain the differences found between patients discontinuing the first TNFi due to primary and secondary failure. The number of confounders that we could adjust for was also limited by the small sample size. However, residual confounding is an inherent problem in observational research and, arguably, we have adjusted for the most relevant confounders. Secondly, we could not

compare the efficacy of starting a second TNFi or a IL17i, after failing the first TNFi due to small numbers of patients treated with IL17i. Our data suggest that it could be better to choose a drug with a mechanism of action other than TNFi in case of primary failure to a TNFi and future studies should give resolution whether that is the case for IL17i.

Conclusions

In summary, on average, response to a second TNFi is worse than the response to a first TNFi, especially among patients that never responded in first place to this class of drugs.

Declarations

Ethics approval and consent to participate

Reuma.pt has been approved by the ethics committees of the participating hospitals and complies with the Declaration of Helsinki. This specific study has been approved by the ethics committee of the NOVA Medical School, Lisbon, Portugal. Patients have signed a written informed consent before inclusion.

Consent for publication

Not applicable

Availability of data and material

The data that support the findings of this study are available from Reuma.pt (Portuguese Society of Rheumatology) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Reuma.pt Scientific Committee.

Competing interests

SRM: Honoraria as speaker: Janssen, Novartis

AS: Honoraria as speaker: Novartis

SR: Consulting and/or speaking fees: AbbVie, Eli Lilly, MSD, Novartis, Pfizer, Sanofi, UCB

AB: Consulting and/or speaking fees: AbbVie, Eli Lilly, MSD, Novartis, Pfizer.

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Author Contributions

SRM wrote the first draft of the manuscript, which was then reviewed and edited by all authors. The study was conceptualized by SRM, AS, FPS, NG, AB, JCB and SR. The statistical analyses were carried out by SRM with the

advice, support and critical interpretation of the results from AS and SR. All authors read and approved the final manuscript.

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Tables

Table 1. Efficacy of the first and second TNFi (adjusted models)[§]

Outcome at 3M defined (n=96*)	1 st TNF	2 nd TNF
	% (95% CI)	% (95% CI)
ASDAS CII	51 (42;60)	41 (31;50)
BASDAI50	45 (36;54)	39 (29;48)
ASDAS MII	33 (25;42)	13 (6;19)
ASDAS LDA	42 (32;51)	26 (18;35)
ASDAS Inactive	19 (12;26)	16 (9;22)
Outcome at 6M defined (n=79*)	1 st TNF	2 nd TNF
	% (95% CI)	% (95% CI)
ASDAS CII	56 (46;66)	35 (26;45)
BASDAI50	46 (35;56)	33 (23;43)
ASDAS MII	32 (22;41)	22 (13;30)
ASDAS LDA	41 (30;51)	29 (19;39)
ASDAS Inactive	11 (5;18)	15 (8;22)

[§] Percentages and 95% CI are derived from logistic regression models adjusted for age, gender, CRP at baseline. * 96 patients had ASDAS and BASDAI outcomes available at baseline and 3 months for both TNFi; 79 patients had ASDAS and BASDAI outcomes available at baseline and 6 months for both TNFi. ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Activity Index; LDA: Low disease activity; ID: Inactive disease; CII: Clinically important improvement; MII: Major important improvement; BASDAI50: Bath Ankylosing Spondylitis Disease Activity Index 50; TNFi: Tumor necrosis factor inhibitor; M: months.

Table 2. Association between the reason for discontinuation of the first TNFi and response to the second TNFi over time

Reason to discontinue first TNFi*	Outcome for the second TNFi				
	OR (95% CI)				
	ASDAS-CII (n=135)	ASDAS-MII (n=135)	ASDAS-LDA (n=166)	ASDAS-ID (n=166)	BASDAI50 (n=147)
(ref Primary failure)					
-Secondary failure	1.9 (0.7;4.8)	4.8 (1.3;18.2)	1.2 (0.6;2.4)	7.3 (1.9;27.7)	1.4 (0.6;3.0)
-Adverse events	1.5 (0.6;3.5)	2.4 (0.6;9.6)	0.9 (0.5;1.7)	9.1 (2.5;33.3)	1.1 (0.5;2.3)
-Other	1.0 (0.3;3.8)	1.7 (0.1;19.4)	1.0 (0.4;2.4)	7.7 (1.6;37.9)	0.5 (0.1;1.7)

*Generalised estimated equation (GEE) models with the reason of discontinuation of the first tumor necrosis factor inhibitor (TNFi) as predictor (reference category: Primary failure); all models adjusted for age, gender and C-reactive protein. Models include all visits during follow-up of up to 10 years. Odds Ratios (OR) in bold are significant ($p < 0.05$). ASDAS: Ankylosing Spondylitis Disease Activity Score; LDA: Low disease activity; ID: Inactive disease; CII: Clinically important improvement; MII: Moderately important improvement; BASDAI50: Bath Ankylosing Spondylitis Disease Activity Index 50; N: number.

Supplementary Files

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