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Running title: Primary inefficacy of TNF inhibitors in axSpA

ABSTRACT

Objectives: Primary inefficacy of TNF inhibitors (TNFi) in axial spondyloarthritis (AxSpA) is infrequent. The objective was to assess the long-term evolution and final diagnosis of patients with primary inefficacy to TNFi in axSpA.

Methods: Systematic retrospective study of all patients receiving a TNFi for axSpA in one tertiary referral centre. Patients had axSpA according to the rheumatologist and were started on a first course of TNFi according to usual practice. If treatment was interrupted at 3 months for inefficacy by the rheumatologist, this was defined as primary inefficacy. Five to 10 years later, these patients were re-evaluated.

Results: Of 222 patients receiving a first TNFi for axSpA, 27 (12%) were considered as having primary inefficacy. These patients were more often females (48 vs 27%, p=0.04), had higher functional impairment (Bath Ankylosing Spondylitis Functional Index (0-100) 68 vs 42, p=0.001) and less increased CRP (50% vs 78%, p=0.008.) At the follow-up, 25 (92%) patients were re-evaluated: the diagnosis of axSpA was confirmed for 21/25 (84%) patients according to the ASAS criteria and 20/25 (80%) patients according to the rheumatologist; but 18/25 (72%) had at least one other cause of symptoms among osteoarthritis, widespread pain syndrome or depression. A second TNFi was prescribed for 16 patients and was efficacious for 9 (56%).

Conclusion: Most patients with primary inefficacy had a confirmed diagnosis of axSpA but often had other causes of pain. We suggest patients with primary inefficacy to TNFi should be screened for comorbidities that may interfere with axSpA activity assessment.

Key words: Spondyloarthritis, widespread pain syndrome, diagnosis, classification criteria, TNF inhibitors

Key messages

1. Primary inefficacy of TNF inhibitors in axial spondyloarthritis concerned 12% of 222 patients.
2. Eighty percent of 25 patients with primary inefficacy had a confirmed diagnosis of axSpA when followed-up 5 to 10 years later
3. Eighteen of the 25 patients with primary inefficacy had painful comorbidities such as widespread pain syndrome, depression or osteoarthritis.

INTRODUCTION

TNF inhibitors (TNFi) are extremely effective in axial spondyloarthritis (axSpA). Many studies have shown major improvement in SpA activity after TNFi therapy and currently, it is the only drug therapy approved for axSpA patients with insufficient response to non-steroidal anti-inflammatory drug (NSAIDs) [1] However, some patients are non-responders: primary inefficacy, i.e., an initial lack of treatment response appears infrequent in axSpA with rates around 5-15% [2-5].

The diagnosis of SpA is difficult and is based on a body of clinical arguments associated with laboratory tests and radiological signs [6-8]; several of the clinical criteria contributing to the diagnosis of axSpA, such as enthesitis pain, lack specificity [6]. Furthermore, some frequent diseases or conditions such as osteoarthritis, widespread pain syndrome and depression could interfere either with the activity of SpA (falsely heightened disease activity) or with the response to TNFi (falsely heightened inefficacy) [9-11]. Thus, considering the rarity of primary inefficacy and the difficulty to diagnose axSpA, it seemed useful to explore the cases of primary inefficacy to TNFi in axSpA: who are these patients who have primary inefficacy? What are their demographic and disease characteristics and their final diagnosis? Do they have comorbidities? Is a second course of TNFi of interest in these patients?

The objective of the present study was to describe axSpA patients with primary inefficacy after the first TNFi, 5 to 10 years after their prescription, in terms of diagnosis, comorbidities and current management.

PATIENTS AND METHODS

Study design

Systematic retrospective and prospective study conducted in one tertiary care centre in Paris, France.

Population

All patients with a diagnosis of axSpA according to an expert rheumatologist Amor criteria and receiving a first TNFi in the context of usual practice between 2004 and 2009 in the centre were analysed. The available information was retrospectively collected from the medical files [3]. For the present study, the focus was on those patients who had primary inefficacy to this first TNFi. Primary inefficacy was defined here as treatment interruption 3-4 months after treatment onset, with a

rheumatologist assessment in the medical file of lack of efficacy as reason for drug interruption. The rheumatologist reason to stop the treatment was based on a mixture of efficacy (assessed by BASDAI) as well as patient preference, in the context of usual practice.

Data collected at baseline

At baseline, demographic and disease (type of disease, presence of extra articular signs, HLAB27 status, the presence of imaging sign and of elevated acute phase reactants in particular C-Reactive protein (CRP) characteristics were collected .

Long-term follow up (prospective phase)

In 2013-2014, patients with primary inefficacy were contacted by letter and seen in outpatient clinic if possible for clinical examination and medical interview. If this was not possible, they were contacted by telephone and asked to fill in a questionnaire. If the patients did not answer the letter or the 2 reminders, their general practitioner was contacted to either ask the patient to participate to the study, or give us information on the patient status.

Patients gave their consent for the use of the collected data and the study was conducted in accordance with the Declaration of Helsinski so no separate ethical approval was required

Data collected at follow up

Disease characteristics were collected including the type of disease (axial only, or associated with enthesitic or peripheral arthritis), the presence of extraarticular signs, the HLAB27 status, the presence of imaging signs (sacroiliitis, syndesmophytes on the most recent available imaging), and of elevated acute phase reactants in particular C-Reactive Protein (CRP). AxSpA disease activity was evaluated through an investigator global visual analog scale (VAS), the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and the BASFI (Bath Ankylosing Spondylitis Functional Index) as well as a full clinical evaluation where possible [12, 13]. ASDAS was not used in 2014 because CRP was not always available. Current treatment was collected including NSAIDs intake, TNFi and type and treatment maintenance.

The association with widespread pain syndrome was assessed with the FIRST questionnaire; this validated questionnaire comprises 6 questions and a score≥5/6 is

strongly suggestive of widespread pain syndrome [14]. Concomitant spine or lower-limb osteoarthritis and concomitant or past depression were assessed by the physician (SK) during the visit, or by simple questions by phone and/or in the questionnaire. These data were confirmed where possible in the medical file.

The final diagnosis, i.e., confirmation of axSpA diagnosis or not, was evaluated both by applying the Assessment of SpondyloArthritis (ASAS) classification criteria for axSpA [12] and through the rheumatologist's opinion, based on the full evaluation including clinical assessment, imaging and biological results when available.

The fulfillment of the ASAS classification criteria for axSpA was also checked.

Statistical analysis

Descriptive data were summarised using means and standard deviations (SD) comparisons were performed by parametric tests. For patients who had received a second TNFi, the survival rate at one year was assessed using Kaplan Meier survival curves on SAS version 9.2.

RESULTS

SpA patients with primary inefficacy

Of 222 axSpA patients who received a first TNFi between 2004 and 2008, 27 (12%) interrupted the treatment for primary inefficacy (Table 1) [7]. When compared to the 195 patients not classified as primary inefficacy, these patients were more often female (48% vs 27 % in patients without primary inefficacy, p= 0.04), were older at initiation of the TNFi (45 vs 39 years, p=0.04), had higher BASFI (68 vs 42, p=0.03) and less frequently an increased CRP (abnormal value according to the laboratory limits: 33% vs 63%, p=0.02). Among the 27 patients with primary inefficacy, fifteen patients (56%) carried the HLA B27 and 18 (67%) had radiographic sacroillitis. There was no assessment of comorbidities in patients who did not have primary inefficacy

Long term follow up

Among these 27 patients with primary inefficacy, twenty five (92%) were re-evaluated after 5 to 10 years (mean follow-up, 6.0±3.1 years); 9 with a full clinic exam, 5 through a telephone interview, 5 through a self-reported questionnaire, and 6 were re-evaluated only through the medical file. One patient refused to participate in the

study and 1 patient was lost to follow up. Medical files were used to complement the findings for all patients and for 5 patients, the private practice physician also gave information. Among the 25 patients who were followed-up, thirteen (52%) were women, and mean age at the time of their follow-up was 52.6±14.6 years (Table 2). At the long term follow up, all the patients still presented symptoms and back pain although the level of symptoms was moderate: the mean BASDAI was 42±21.
Concerning their current treatment, nine (36%) were treated with TNFi and 9 (36%) were taking NSAIDs. The other patients were prescribed analgesic drugs and/or non-pharmacological measures.

Comorbidities

Five (20%) patients had widespread pain syndrome according to the FIRST questionnaire; all were female. Ten (40%) patients had osteoarthritis of the lower-limb peripheral joints or of the spine; 8 (32%) patients had a self-declared diagnosis of depression of whom 3 (12%) were taking anti-depressant drugs. Overall, eighteen (72%) patients had at least one of these 3 comorbidities.
These patients had the following characteristics: 9 (36%) carried HLA B27, 12 (48%) had radiographic sacroiliitis, 10 (40%) had an increased CRP, 7 (28%) had a family history of spondyloarthritis and 13 (52%) were considered good responders to NSAIDs.

TNFi after primary inefficacy

In all, 16 (64% of 25) patients switched to another TNFi: 9 (36%) received 2 TNFi and 7 (28%) received 3 or more prescriptions of TNFi. Among the patients who had at least a second TNFi, the treatment was considered efficacious for 9 (56% of 16) patients whereas 7 presented with primary inefficacy to the second TNFi. The retention rate of the second TNFi at one year was 50%. At the time of follow up, 9 (36%) patients were still prescribed a TNFi. Note that overall (patients with primary inefficacy and without), 111 (57%) patients stopped the first TNF inhibitor over duration of follow up with a mean follow up of 29 months (SD: 20.1).

Final diagnosis

In all, 21 (84%) patients satisfied the ASAS classification criteria for axSpA [12]. Furthermore, the diagnosis of axSpA was confirmed according to the

rheumatologist's opinion for 20 (80%) patients. Seventeen (68%) patients fulfilled both conditions.

DISCUSSION

This study confirms the infrequent nature of primary inefficacy of TNFi in axSpA (12%) and shows that most of the patients with primary inefficacy to their first TNFi had confirmed axSpA, but also that most of them had comorbidities that could affect axSpA evaluation. This is important because practitioners might consider that primary inefficacy to TNFi leads to reconsidering the diagnosis of SpA (i.e., the notion of a TNFi prescription used as diagnostic test). We suggest here that primary inefficacy should not be considered as equivalent to a diagnostic error, and that a second prescription of TNFi may be of use in such patients, although painful comorbidities should certainly be screened for and taken into account.

This study has strength and weaknesses. We performed a systematic assessment of all patients receiving a TNFi in a single centre over a defined period of time, allowing a true assessment of the frequency of primary inefficacy. We also managed to reassess almost all the patients with initial primary inefficacy, with a long-term follow-up (mean, 6 years) which allows true reconsideration of the evolution and diagnosis of the patients. Wherever possible, patients were assessed fully through clinical examination, history-taking and imaging at follow up. No such data was available at baseline,in particular there was no assessment of comorbidities. However, the number of patients assessed was low, due to the relative rarity of primary inefficacy. Not all patients accepted to come into the clinic for a full physical assessment; in fact, for 6 patients we could only use the hospital medical file which is a limitation to the systematic character of the study. And finally, the definition used here for primary inefficacy, i.e., an interruption of the TNFi therapy in the 3-4 months following its introduction, with the physician putting as reason primary inefficacy can be discussed. Indeed, 3 months may be a little too short to properly assess the efficacy of TNFi; and a quantitative assessment such as the BASDAI would have been more optimal [15]. However, this is a clinical practice, real-life assessment and we believe that the patients who did interrupt their treatment at 3 months were indeed in a situation of primary inefficacy.

This study showed that patients with axSpA who had primary inefficacy had slightly different clinical characteristics and above all, much comorbidity such as widespread pain syndrome, depression or osteoarthritis. Widespread pain syndrome is not rare in SpA and in particular in the absence of radiological signs of SpA, it raises the question of non-radiographic forms of axSpA [16]. The present study does not give new data regarding non radiographic axSpA but does confirm widespread pain syndrome should be considered when physicians are faced with primary inefficacy in axSpA. The FIRST questionnaire used in the present study is a user-friendly questionnaire for clinical practice, which may be of use for the diagnosis of widespread pain syndrome if its performances are confirmed [14].

If the association of SpA and depressive syndrome is known [17], this study reveals that depression could explain therapeutic failures in axSpA and may support the concept of systematically screening for depression. However, simple-to-use tools to diagnose depression in the setting of a rheumatology clinic, are currently lacking [18].

The present results suggest the importance of a global approach to manage these patients. Widespread pain syndrome, osteoarthritis and depression are very common comorbidities and should systematically be screened and treated, for a better therapeutic management. It would be interesting to do other studies to compare the link between comorbidities and response to TNFi.

The present study indicated a switch to a second TNFi may be worthwhile, for patients who show lack of response to a first TNFi. Indeed, in the present study, sixteen patients received a second TNFi and importantly, the treatment was considered effective in 9 (56%) patients. Although previous studies had indicated the efficacy of TNFi switches in axSpA, this is the first study to specifically look at patients with primary inefficacy to a first TNFi [2-5].

The fact that patients who underwent primary inefficacy to their first TNFi often have a confirmed diagnosis of axSpA confirms the TNF pathway is not the only one involved in these pathologies [19], explaining why some patients do not respond to TNFi therapy. Data regarding the efficacy of new therapeutics developed against the IL17/IL23 pathway in these patients, would be of interest [19].

In conclusion, SpA, like other chronic inflammatory diseases, justifies a holistic approach with appropriate assessment and management of potential comorbidities. Primary inefficacy of a first TNFi should not bar a second TNFi prescription but a

careful assessment of potentially painful comorbid conditions is useful in such a situation.

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Table 1: Comparison between axSpA patients with and without primary inefficacy to a first TNFi

Increased CRP: value above the laboratory upper limit of norm

	Patients with primary inefficacy n=27	Patients without primary inefficacy n=195	P value
Age at first TNFi introduction, years, mean (SD)	45 (14)	39 (12)	0.04
Female, n (%)	13 (48)	53 (27)	0.04
BASDAI (0-100) at introduction of first TNFi, mean (SD)	48 (19)	49 (20)	0.9
BASFI (0-100) at introduction of first TNFi, mean (SD)	68 (28)	42 (21)	0.03
Increased CRP, n (%)	9 (33)	123 (63)	0.02
HLAB27 presence, n (%)	15 (56)	141 (72)	0.1
Radiographic sacroillitis, n (%)	18 (67)	157 (81)	0.2
Axial involvement at time of TNFi introduction, n (%)	26 (96)	192 (98)	0.4
History of peripheral arthritis, n (%)	18 (67)	105 (54)	0.3
History of psoriasis, n (%)	4 (15)	35 (18)	1
History of inflammatory bowel disease, n (%)	5 (19)	20 (10)	0.2
History of enthesitic pain, n (%)	16 (59)	87 (45)	0.2
History of uveitis, n (%)	5 (19)	49 (25)	0.6

Table 2. Long term outcomes of 25 patients with primary inefficacy to the first TNFi

Characteristic at time of follow-up	All patients with follow up n=25
Peripheral arthritis since first assessment, n (%)[a]	0
Enthesitis since first assessment, n (%)	1 (4)
Uveitis since first assessment, n (%)	2 (8)
Inflammatory bowel disease since first assessment, n	0
Psoriasis since first assessment, n (%)	1(4)
Increased CRP at follow up, n (%)	3 (12)
CRP, mg/l, mean (SD) [n data available]	8 (11) [11]
Pain VAS, mean (SD) [n data available]	44 (26) [18]
Global assessment of disease activity by patient, VAS, mean (SD) [n data available]	57 (33) [15]
BASDAI (0-100), mean (SD) [n data available]	42 (21) [16]
BASFI (0-100), mean (SD) [n data available]	40 (27) [15]
Current TNFi treatment, n (%)	9 (36)

[a]Since first assessement: Occurrence of this manifestation over follow up period (between interruption of the first TNF I and long-term follow up assessment). VAS :visual analog scale.