Response to Tumor Necrosis Factor Inhibitors in Rheumatoid Arthritis for Function and Pain is Affected by Rheumatoid Factor

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Abstract: *Objectives*: To investigate differences in response to tumor necrosis factor inhibitor treatment (TNFi) in seropositive (rheumatoid factor positive; RF+) *versus* seronegative (RF-) patients with established RA as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI) and pain.

Methods: RA patients from an established RA cohort were studied according to rheumatoid factor (RF) status for change in HAQ-DI and pain (0-3 VAS) one year after starting treatment with a TNFi.

Results: There were 238 patients treated with TNFi who had follow-up data (178 RF+ and 60 RF-). Disease duration was longer in RF+ *vs* RF- (12±8 *vs* 8±8 years) but the proportion of females (82% *vs* 72%, P=0.7), baseline HAQ-DI (1.44±0.63 *vs* 1.41±0.63, P=0.8) and pain (1.92±0.67 *vs* 1.93±0.67, P=0.9) were not different. The mean duration of treatment of first TNFi was 2.8 *vs* 2.3 years, P=0.1 and 68% of RF+ *vs* 62% of RF- were still receiving first TNFi at last visit (P=0.5). For patients with data at baseline and one year, the one-year HAQ-DI change was significantly greater in 90 RF+ patients (-0.356) *versus* 38 RF- patients (-0.126; P=0.04). The mean pain improvement was also greater in 77 RF+ *vs* 32 RF- patients (-0.725 *vs* -0.332 respectively; P=0.03). Numbers are small, data are missing and comorbidities, DAS28 and anti-CCP were not collected.

Conclusion: Despite limitations in the data, in established RA after failure of DMARDs, RF+ patients may be more responsive to TNFi therapy as measured by changes in HAQ-DI and pain.

Innovation: There may be a better response to TNFi in RA if RF positive for function and pain.

INTRODUCTION

Rheumatoid arthritis (RA) is often a disabling inflammatory arthritis [1]. Treatment includes use of disease modifying anti-rheumatic drugs (DMARDs) [2] and often biologics such as tumor necrosis factor inhibitors (TNFi) when DMARDs fail. TNFi improve joint counts and function, and reduce radiographic joint destruction [3]. The Health Assessment Questionnaire Disability Index (HAQ-DI) is a validated patient-completed questionnaire of functional impairment. Pain is measured in patients with various scales including a 15cm long visual analog scale (VAS) and converted to a score from 0 to 3 [4]. Higher HAQ-DI scores in RA are associated with worse morbidity [5, 6]. Conversely, improvements in HAQ-DI are associated with improved survival [7].

Three-quarters of patients with established RA are seropositive for rheumatoid factor (RF+) [8]. Patients who are RF+ overall have a worse prognosis than RA patients who are RF negative (RF-) [9-11]. However, patients who are RF+ respond more favorably to treatments such as rituximab [12, 13]. Response to TNFi by RF status may be blunted in RF- patients [14], not different *vs* RF+ [15] or more favorable in RF- patients [16]. Responses to tocilizumab and abatacept may be better in RF+ patients with RA [17].

The aim of this study was to determine whether the presence or absence of RF influences the response to TNFis with respect to function and pain in an observational cohort of real world patients with established RA over the first year of TNFi treatment.

PATIENTS AND METHODS

Patients with established RA beginning with TNFi treatment were recruited by rheumatologists at St. Joseph's Hospital Rheumatology clinic in London, Ontario, which is affiliated with Western University. Patients are primarily

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English speaking, representing the full spectrum of disease severity, and were generally followed from one to four times a year depending on disease severity and flares. Ethics approval was obtained from University of Western Ontario, to perform a chart audit on all patients in the clinic with RA who were started on a TNFi. Information regarding HAQ-DI, using a 15 cm VAS converted to a score from 0 to 3 was collected and duration of treatment was assessed on patients in our single center database (described elsewhere) [5]. Inclusion criteria were as follows: diagnosis of RA according to the revised ACR/EULAR criteria [18], laboratory proof of RF status within the chart, treatment initiation with etanercept, infliximab, and/or adalimumab; known start date of first TNFi and at least one follow up after TNFi. This allowed for calculation of mean treatment duration by RF status and the proportion of patients still receiving their first TNFi at the last follow up visit. Then analyses were performed with respect to the outcome measures of interest where patients needed at least one HAQ-DI score just prior to and at 1 year ($\pm$ 12 weeks) of TNFi treatment. Pain scores where available (at initiation of TNFi and one year of TNFi treatment) were also analyzed. Only the data from the first TNFi treatment were used. Joint counts were not analyzed due to inter-observer variability, because different trainees having diverse expertise performed the joint counts that were recorded in the chart during routine visits. Charts of eligible patients were reviewed to determine if the rheumatoid factor lab result was available on the chart. Anti-CCP levels were not routinely collected as these patients had established RA often for years (before anti-CCP testing was available). The proportion of patients still taking the same TNFi at over time, and changes in HAQ-DI and pain (each on a 0-3 scale) (from one year of TNFi treatment minus baseline) were compared between RF positive and RF negative patients using Student t-tests (two-tailed, equal variance) and Chi square analyses.

Other parameters including patient age, disease duration, sex, baseline HAQ-DI and pain, and treatment duration were also compared between the RF positive and RF negative patients. All patients had been previously exposed to methotrexate, most had used combination DMARDs (methotrexate with sulfasalzine and hydroxychloroquine), and leflunomide and very few had also used injectable gold salts, azathioprine and D-penicallamine. Comorbidities were not collected. DAS28 was not calculated due to lack of standardization of joint counts. The treatment start date was not always known as when TNFis were initially introduced, there was a long lag time between writing the prescription and obtaining the biologic; usually due to delayed reimbursement, so these patients were excluded. The chart audit had to contain a start date that could be determined within one month.

RESULTS

We identified 340 patients with RA receiving TNFis. In 22%, RF status could not be confirmed by an actual laboratory report and 8% did not have a precise treatment start date for their first TNFi. Thus 238 RA patients with known RF status and a precise treatment start date and some follow up were included. Results are shown in Table **1**. For those analyzed, the disease duration was longer in seropositive patients. Only 128 (54%) had complete HAQ-DI scores just prior to TNFi

introduction and 1 year after TNFi initiation and 109 (46%) had paired pain scores. The majority of missing data at one year was due to treatment discontinuation prior to one year (approximately 23%), occurrence of a visit that was not within a 12-week window of one year and missing data (i.e. HAQ-DI was not available at the key visits). Baseline HAQ-DI and pain were not different between seropositive and seronegative patients. The change in HAQ-DI was significantly greater in RF positive patients at -0.356 compared to -0.126 with RF negative patients (P=0.04). This was also true for pain where seropositive patients improved more at one year (-0.725 *versus* -0.332; P=0.03). The mean treatment duration of the first TNFi was numerically longer but not significantly different in RF positive *vs* negative patients (2.8 years *versus* 2.3 respectively, P=0.1) and similar proportions still were taking their first TNFi at last follow up.

DISCUSSION

This study found that the response to TNFi in patients with established RA who had previously failed multiple DMARDs was better for pain and function at one year in seropositive compared to RF negative patients; even though their baseline functional impairment and pain levels were similar prior to treatment with TNFi. The RF positive patients had longer disease duration; which may have affected the results as could other unknown confounding. However with longer disease duration, one would expect that more of the HAQ-DI would be irreversible due to more potential damage as HAQ-DI can reflect impaired function from damage and disease activity. There would be an expected bias for those with longer disease duration to have less reversibility of the HAQ-DI due to more potential damage, but the results were in the opposite direction. Both pain and function can be affected from multiple factors including comorbidities but since the baseline results were nearly identical between the two groups one can infer that the differences were due to differential effects of the TNFi treatment that was initiated.

Similar results were observed with infliximab treatment in a previous study where RA patients who were seropositive for either RF and/or anti-CCP experienced more improvement compared to seronegative patients. However, no specific cut off value for RF or anti-CCP could be determined to predict treatment response [14]. The reason for a potential differential response by RF status to some biologics is uncertain. It has been proposed that RF could impair drug clearance when large amounts of RF-monoclonal antibody complexes are formed [15]. RF-producing cells have been found in the inflamed rheumatoid synovium where it is believed that a TNFi can decrease local production of RF and this may correlate with a better treatment response [19,20].

This was a single site study where many rheumatologists treated RA patients and the criteria for use of TNFi treatment is only after failure of high doses of methotrexate and often several other DMARDs. Disease duration was long, so misclassification of patients with RA was unlikely. The baseline HAQ-DI and pain values were similar in RF+ compared to RF- groups despite longer disease duration in the RF+ group so comorbities if different between the two groups did not affect function and pain just before TNFi use. There are several limitations. Some data were missing with regards to patient RF status, and thus, these patients were excluded from analyses.

Table 1.   Summary of demographic information for established RA patient cohort receiving TNF inhibitors and response with respect to health assessment questionnaire disability index (HAQ-DI) and pain.

Established RA TNFi Treatment	Rheumatoid Factor Positive (RF+)	Rheumatoid Factor Negative (RF-)	P Value
Total N with RF results available (238) (% of included patients)	178 (75%)	60 (25%)	
% Female	82%	72%	0.7
Age (SD)	57 (14)	56 (12)	0.6
Disease duration {years} (SD)	12 (8)	9 (8)	0.017
N with available paired HAQ-DI results at 1 year# (% of included patients) N included 128	90 (70%)	38 (30%)	
Baseline HAQ-DI (SD) (0=3) prior to TNFi	1.44 (0.63)	1.41 (0.63)	0.8
HAQ-DI change Baseline to Year 1	-0.356 (0.60)	-0.126 (0.54)	0.04
N with available paired Pain results at 1 year[#] (% of included patients) N included 109	77 (71%)	32 (29%)	
Baseline PAIN (SD) (0-3)	1.92 (0.67)	1.93 (0.67)	0.9
PAIN change Baseline to Year 1	-0.725 (0.86)	-0.332 (0.82)	0.03
Mean treatment duration for first TNFi {Years} (SD) N=238	2.8 (2.0)	2.3 (1.6)	0.1
Proportion of patients still on same TNFi after at last follow up from the included 238 patients	68%	62%	0.5

Note of 340 identified patients, only 238 had some data available for analysis. SD = Standard Deviation; Age and Disease Duration is shown in Years; p-Value with significance at <0.05, [#]Only the patients with available data compose the N for each result. The demographics (age, sex, disease duration, baseline HAQ-DI, baseline pain) of the patients with available data was not significantly different from those with incomplete data.

Anti-CCP was missing for the majority of patients and thus not analyzed. Selection bias for TNFi prescription likely was present (but should not have been different in RF+ and RF- patients as demonstrated by similar baseline HAQ-DI and pain scores). RF status was confirmed in only 258 out of 340 patients and many patients had missing HAQ-DI or pain scores. However, demographics for patients included *vs* not included were not significantly different. Ideally anti-CCP should also be compared to determine if in prevalent RA there is a differential response to TNFi by anti-CCP status. Perhaps longer treatment could yield different results such as potentially in durability of response for seropositive *vs* seronegative patients. Our study is too underpowered to answer whether RF status affects the sustainability of treatment. The major changes in HAQ-DI and pain are early with TNFi treatment so our study is long enough for early treatment changes to be detected on these measures but whether the differences continue beyond a year is not known.

Perhaps, patients that are RF negative with established RA have a blunted response to several biologics including TNFi, and also rituximab and tocilizumab after failure of DMARDs [17]. The data do not agree with all studies. ACR20 and DAS28 responses from a meta-analysis of TNFi, did not find different responses in patients based on their rheumatoid factor status [15].

CONCLUSION

TNFi treatment varies between RF positive and negative patients with respect to changes in function and pain in this cohort and this has not been fully appreciated previously. Future studies should continue to explore differential responses by readily available biomarkers.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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