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Do patients with active RA have differences in disease activity and perceptions if anti-TNF naïve versus anti-TNF experienced? Baseline results of the optimization of adalimumab trial

PI

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: The chance of a good response in RA is attenuated in previous anti-TNF users who start new anti-TNF therapy compared to biologic naïve patients. In active RA, those with previous anti-TNF exposure compared to anti-TNF naïve may have different baseline disease activity and patient perceptions when starting a new anti-TNF treatment that could explain the observed response differences.

Material/Methods: The aim of this study was a post hoc analysis of baseline characteristics of patients enrolled in the Optimization of Adalimumab study that was a treat to target *vs.* routine care study in patients initiating adalimumab. As per the protocol, a maximum of 20% anti-TNF experienced patients were enrolled in the 300 patient trial. Twelve (4.0%) were excluded who previously used other biologics. Baseline characteristics including age, gender, tender and swollen joint counts, disease activity (DAS28), function (HAQ-DI), patient global assessment, patient satisfaction with current treatment, and inflammatory markers (CRP, ESR), were compared between previously anti-TNF experienced [etanercept or infliximab (EXP)], and anti-TNF naïve patients (NAÏVE).

Results: The mean (SD) age was 54.8 (13.3) years; 81.0% were female, and 237 (79.0%) were anti-TNF naïve while 51 (17.0%) patients were anti-TNF experienced (29 with etanercept, 16 with infliximab, and 6 for both). The mean (SD) baseline in EXP versus NAÏVE groups respectively was: CRP=21.7(32.9) *vs.* 17.5(20.7); ESR=28.7(22.5) *vs.* 29.8(20.4); SJC=10.5(6.0) *vs.* 10.7(5.6); TJC=12.8(7.1) *vs.* 12.3(7.3); and DAS28=6.0(1.2) *vs.* 5.8(1.1). None of the between-group differences were statistically significant, however, the HAQ-DI in EXP was 1.7(0.6) compared to 1.5(0.7) for the NAÏVE (P=0.021). Additionally, EXP patients had a higher patient global score [71.3(26.1) *vs.* 61.9(26.2), P=0.021].

Conclusions: Although anti-TNF naïve and experienced patients who initiated adalimumab were similar, with respect to several baseline characteristics, significant differences in subjective measures were observed, which may indicate more severe patient measures (function and global disease activity) in anti-TNF experienced patients.

key words: **anti-TNF naïve • anti-TNF experienced • active rheumatoid arthritis • disease activity • real-world treatment • anti-TNF treatment**

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Background

Patients with Rheumatoid Arthritis (RA) previously treated with anti-TNF inhibitors have a reduced chance of obtaining a low disease state with subsequent anti-TNF therapies or other biologic treatment (abatacept, rituximab, and tocilizumab) [1–11]. They are also more likely to discontinue their next biologic sooner than patients who have not been exposed to previous biologics [12,13]. The reasons for this could include drug resistance, neutralizing antibodies, or other patient factors. The purpose of this study was to determine if patients starting an anti-TNF treatment as part of a real world trial in RA have different characteristics and patient reported outcomes if they have been previously treated with anti-TNF treatment compared to those who have not been exposed (i.e. comparing those starting an initial anti-TNF treatment). Our aim was to determine if there are differences in characteristics such as disease activity and patient reported factors between previous anti-TNF exposed compared to anti-TNF naïve patients with active RA who are about to start a new anti-TNF treatment. Data were obtained from a randomized trial in active RA that included both populations.

Material and Methods

The Optmization of Adalimumab Trial is a multicenter, randomized, controlled, parallel-group, single-blind trial with a total of 32 sites across Canada. Patients with active RA, who were naïve to treatment with adalimumab, were enrolled and initiated adalimumab under routine care. Physicians were randomized, using a computer-generated, site-stratified, blocked schedule that assigned physicians from the same geographical region to 1 of 3 treatment goals: 1) achieving a 28-joint Disease Activity Score (DAS28) <2.4 [14]; 2) achieving swollen joint count (SJC) = 0; or 3) patients treated as per routine care. Patients were treated with 40 mg of adalimumab subcutaneously every other week and other anti-rheumatic drugs were allowed according to physician discretion. The study planned that 20% of patients could be anti-TNF experienced and still be enrolled in the study. The inclusion criteria were: ⩾18 years of age, diagnosis of RA, naïve to adalimumab therapy, access to reimbursement for standard care, and active RA as defined by the treating physician and thus a decision to add adalimumab was made when each patient consented into the study. Patient demographic, disease, and treatment characteristics were collected at baseline. Patients were considered previously TNF exposed if they had ever taken etanercept or infliximab for their RA. They could have stopped the anti-TNF drug at the baseline visit for this trial; or any time in the past. Other biologics were excluded as they are far less commonly used as the first biologic treatment in RA. This was a sample of convenience (a post hoc analysis) of baseline characteristics from a real world trial. A total of 300 patients were enrolled in the study. Twelve patients received other biologics and were excluded from analyses of anti-TNF naïve *vs.* experienced patients.

The Health Assessment Questionnaire Disability Index (HAQ-DI) is a validated self reported brief questionnaire that asks patients about function for routine activities and is scored from 0 to 3 with higher values being worse [15]. DAS28 is a validated composite disease activity measure that includes a complicated mathematical formula using the patient global assessment, an inflammatory marker and the 28 tender and swollen joint counts [14]. Patient Global Assessment of disease activity is measured from 0 to 100 mm on a continuous 100 mm visual analog scale and the higher the number the worse the disease activity.

Patient dissatisfaction was determined by asking satisfaction with current treatment with 5 possible answers: very well satisfied, well satisfied, moderately satisfied, a little satisfied, not satisfied, and the latter 3 were combined for the variable ' dissatisfied'.

Statistical analysis

Patients were identified as either anti-TNF experienced (if previously treated with etanercept or infliximab) or anti-TNF naïve, after removing patients who had been treated previously with other biologic drugs that are not anti-TNFs. Baseline characteristics were compared for patients who were anti-TNF experienced and anti-TNF naïve by using chi-square tests for categorical variables and independent sample student t-tests for continuous variables. A p-value (two tailed) of $p<0.05$ was considered significant. The analyses were done using SPSS.

Results

Of the 300 patients within the trial, 237 (79.0%) were naïve and 51 (17.0%) patients were experienced with anti-TNF treatment. Twenty-nine had received entanercept, 16 had received infliximab, and 6 had previously received entanercept and infliximab. For previous users of a single anti-TNF (n=45), primary non-responders to anti-TNF occurred in 11% (never achieved a satisfactory response), whereas over 56% were secondary non-responders (achieved satisfactory response initially, but lost it over time, or had a lack of efficacy with or without side effects); 24% had stopped due to side effects or intolerance. In the six patients who previously used both etanercept and infliximab, none had stopped due to side effects alone.

Table 1 summarizes the baseline patient demographic characteristics for the 300 patients. Eighty-one percent of the patients were females with the mean age of 54.8 years. Anti-TNF experienced patients had a significantly greater patient global assessment score than anti-TNF naïve patients (Table 1). The mean score for anti-TNF experienced *vs.* naïve patients was 71.3±26.1 *vs.* 61.9±26.2 ($p=0.021$), respectively. Anti-TNF experienced patients also had significantly greater HAQ-DI [15] scores than anti-TNF naïve patients [1.7±0.6 *vs.* 1.5±0.7 ($p=0.021$), respectively]. The differences between anti-TNF experienced *vs.* naïve were not statistically significant for all other characteristics evaluated (Table 1). The mean CRP was higher in the anti-TNF experienced group but this did not at all approach statistical significance.

Patient satisfaction with current RA treatment (prior to first dose of adalimumab) demonstrated no between groups differences. Most patients were dissatisfied with their previous RA treatment (82% in TNF experienced and 73% in TNF naïve, $p<0.215$). Figures 1 and 2 show the box plots for CRP and ESR for the anti-TNF naïve and experienced groups.

Table 1. Baseline characteristics by anti-TNF category prior to starting adalimumab*.

Characteristics	All patients (n=300)**	Anti-TNF experienced (n=51)	Anti-TNF naïve (n=237)	P-Value***
Age (years)	54.8±13.3	52.1±13.1	55.5±13.4	0.100
Female (%)	81	82.4	80.6	0.847
Number of DMARDs	3.5±1.4	3.7±1.7	3.5±1.3	0.360
TJC (0–28)	12.5±7.3	12.8±7.1	12.3±7.3	0.656
SJC (0–28)	10.7±5.6	10.5±6.0	10.7±5.6	0.811
Patient global assessment of disease activity (0–100 mm VAS)#	63.4±26.4	71.3±26.1	61.9±26.2	**0.021**
DAS28	5.8±1.1	6.0±1.2	5.8±1.1	0.328
ESR (mm/hr)	29.6±20.6	28.7±22.5	29.8±20.4	0.726
CRP (mg/L)	18.1±23.4	21.7±32.9	17.5±20.7	1.423
HAQ-DI	1.5±0.7	1.7±0.6	1.5±0.7	**0.021**

CRP – C-reactive protein; DMARDs – disease-modifying antirheumatic drugs; ESR – erythrocyte sedimentation rate; HAQ-DI – Health Assessment Questionnaire Disability Index; PaGA – Patient global assessment of disease activity; VAS – visual analog scale. # Higher value is worse. Values are mean±SD except for the category Female (%).
* Anti-TNF Experienced is ever use (current or prior). ** 300 is the total # of patients enrolled in the trial and 12 were removed when comparing the two groups as they had other biologics in past (non anti-TNF biologics). *** P-Values are for group comparison (anti-TNF-experienced *vs.* anti-TNF-naïve) from chi-square tests for categorical variables and Student t tests for continuous variables. Bold values are statistically significant.

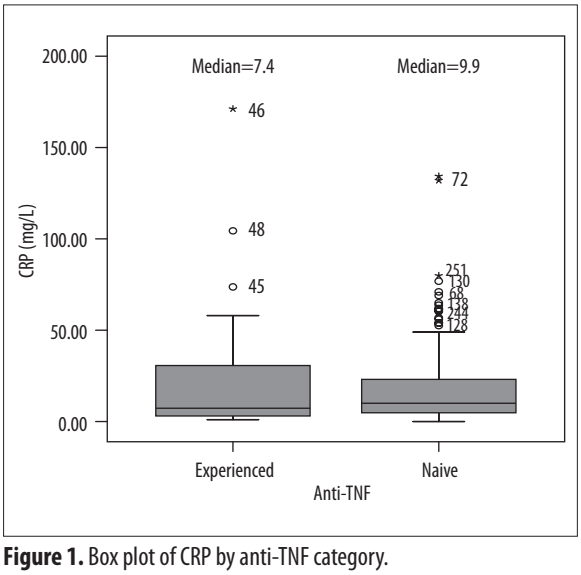

Figure 1. Box plot of CRP by anti-TNF category.

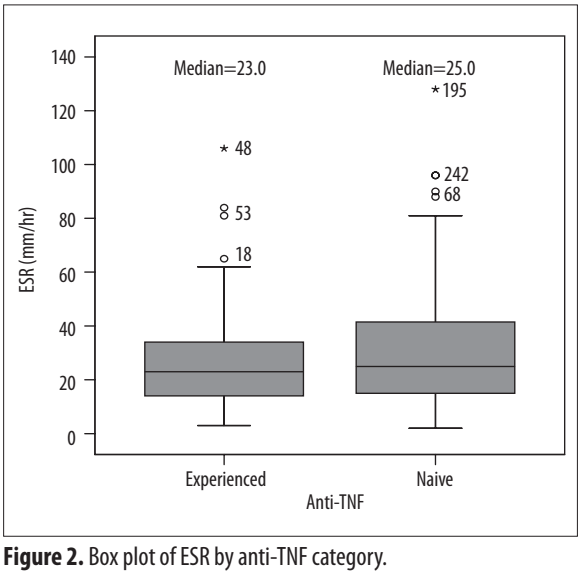

Figure 2. Box plot of ESR by anti-TNF category.

The anti-TNF experienced had a slightly lower median and inter-quartile range for the inflammatory markers.

Discussion

The patients with active RA who were previously exposed to TNF inhibitors did not look different with respect to joint counts compared to those who had not received biologics in past. However, the HAQ-DI and patient global assessment of disease activity were worse in those with previous anti-TNF exposure who had active RA. Patient satisfaction with current treatment (active RA, prior to starting adalimumab), not surprisingly, was not significantly different, as patients chosen for this study were deemed by the investigator to have active RA requiring a change in therapy.

This study has some limitations. Disease duration was not collected, which may have impacted on the results. We cannot comment on whether the physician global assessment was different (that is to say if the rheumatologists would rate the disease activity as higher in one group or the other), as the data for physician global were not collected. There were no other biomarkers done that could perhaps help to further differentiate the two groups. We included patients

who were ever exposed to anti-TNFs irrespective of when they discontinued therapy. It may be that after failing anti-TNF therapy, more patients have drug resistance but they are more likely to have an attenuated response to any biologic that is next used, not just anti-TNF therapies [1–11].

One could postulate that anti-TNF experienced RA patients would be worse as they had failed treatment or had worse disease previously. However, many patients in the real world who stop their first anti-TNF do so as secondary failures – more disease activity at some point even though they had initially responded. Partial responders to previous anti-TNF treatment could be partially treated and begin their next biologic at a lower disease state compared to those not exposed to biologics but this also did not occur. However, some patients who discontinue TNF inhibitor treatment even though they are not optimally responding can rebound, flaring with drug discontinuation. For those who stop anti-TNF treatment due to side effects, they are more likely to have a better response to the second anti-TNF treatment compared to those who stopped their first TNF inhibitor for other reasons [16]. From this study we cannot compare those who stopped the previous biologic just before enrolling in this trial to those who stopped far longer ago to determine if there were baseline differences. The baseline differences measured in this trial do not account for the blunted response to the next biologic treatment that is routinely seen after TNF inhibitor exposure.

Conclusions

It is perhaps surprising that the joint counts and inflammatory markers were not different in biologic naïve compared to previously exposed patients. The differences between anti-TNF experienced and the others with active RA were the patient reported outcomes (HAQ and patient global assessment), where those who had received anti-TNFs rated themselves as worse.

Statement

The trial (Optimization of Adalimumab in RA) was an investigator initiated trial that was funded by a grant from Abbott Laboratories. The data used for this study were on the baseline characteristics, and this study was not funded or influenced by Abbott. The trial was registered at *ClinicalTrials.gov* Registration (register@clinicaltrials.gov) # NCT01585064.

All subjects signed informed consent and ethics approval was obtained centrally and also locally where indicated.

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