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Tocilizumab treatment leads to improvement in disease activity regardless of CCP status in rheumatoid arthritis

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Abstract

Objective—Autoantibodies can be useful in predicting response to certain treatments in rheumatoid arthritis (RA). We aimed to evaluate initial response to tocilizumab (TCZ) by change in physician and patient reported outcomes and laboratory parameters in a real world cohort of patients with RA. We analyzed data by autoantibody status to determine whether patients with seronegative RA had improved response to tocilizumab when compared to their seropositive counterparts.

Methods—Data from the CORRONA RA registry was analyzed. Patients were included if they were started on TCZ and had data from a follow up visit 4-8 months after initiation, as well as having information on serologic status. Serologic status was determined by presence of anti-cyclic citrullinated peptide (CCP) antibodies. Changes in disease activity measures from baseline to follow up visit were evaluated.

Results—Both CCP negative and positive groups had statistically significant improvement in physician reported measurements (physician rating of disease activity, joint counts), patient reported measures (disease activity, pain, fatigue), and acute phase reactants after 4-8 months of treatment with tocilizumab. The magnitude of improvement, however, did not differ significantly by CCP status.

Conclusion—Tocilizumab led to statistically significant improvement in all patient and physician reported measures of disease activity evaluated in this cohort of patient with RA. The response to tocilizumab did not differ by CCP status.

Keywords

Rheumatoid arthritis; CCP; tocilizumab

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Introduction

Biologic disease modifying anti-rheumatic drugs (DMARDs) have improved outcomes for patients with rheumatoid arthritis (RA). As more biologic DMARDs are approved for RA, it can be difficult to determine which medication to choose for a particular patient. Treatment guidelines have been published by the American College of Rheumatology to guide physicians in caring for early and established RA[1]. These guidelines, however, do not differentiate between starting TNF-inhibitors, non-TNF biologics, or tofacitinib when patients have moderate to high disease activity despite conventional synthetic DMARD monotherapy, due to lack of evidence that one biologic DMARD is more effective. Comorbidities like prior malignancy, viral hepatitis, or heart failure can determine which therapies to avoid[1], but there is little information in the published literature about how individual patient characteristics may predict enhanced response to particular biologic DMARDs.

One way to easily divide patients with RA into clinically relevant groups is by serologic status for rheumatoid factor (RF) or anti-cyclic citrullinated peptide antibodies (CCP). Clinical differences exist between seropositive and seronegative patients. Seronegative RA patients are less likely to develop erosive disease [23] but may present with higher initial disease activity[4]. Seronegative patients are also more likely to be male and older at presentation[4]. Autoantibody status may predict response to certain forms of therapy. For several biologic DMARDs, evidence exists that response differs by serologic status. Rituximab[56] and abatacept[78] have been shown to have better efficacy in those with anti-CCP antibodies in multiple studies. There is no evidence, however, for superior efficacy of any biologic DMARD in patients with seronegative RA.

Though the pathophysiology of seronegative RA is less well understood, there are differences in immune activation when comparing patients with and without RF and anti-CCP antibodies that may affect response to therapies. In particular, the IL-6/STAT3 signaling pathway seems to be relevant in seronegative RA pathogenesis. Recent studies have shown increased expression of genes and activation of transcription factors in IL-6/STAT3 pathways in anti-citrullinated peptide antibody (ACPA)-negative RA patients as compared to ACPA- positive patients[910]. Also, polymorphisms in the transcription factor STAT3 are associated with development of RA in seronegative patients to a greater degree than in seropositive patients[11]. Given the upregulation of IL-6/STAT3 signaling, there is a theoretical basis that targeting the IL-6 receptor with the monoclonal antibody, tocilizumab (TCZ), would be more effective in patients with seronegative RA. Indeed, IL-6 blockade has been shown to reverse STAT activation in leukocytes from patients with RA[12].

With this study, we aimed to evaluate responses to TCZ in a real world cohort of patients with RA by serologic status. We hypothesized that patients with seronegative RA would have increased improvement in measures of disease activity as compared to their seropositive counterparts. CCP status was chosen to define seropositivity since previous data on differences in immune pathophysiology has focused on ACPA antibodies.

Patients and Methods

Study population

Patients with physician-diagnosed RA were drawn from the Corrona registry. The Corrona RA registry is a prospective, multi-center, observational cohort of patients with rheumatoid arthritis. Patients were included if they were enrolled in the registry prior to starting TCZ, had baseline data on measures of disease activity before starting TCZ, and had a follow up visit 4-8 months after initiation of therapy.

Visit dates included in analyses ranged from 4/2/2009 through 6/15/2015.

Study measures

Demographic and clinical information from the baseline visit was recorded for included participants. RF and CCP status were reported by site investigators based on commercially available laboratory testing. As an observational registry, Corrona encourages but does not require laboratory test reporting. Serologic status was defined in three different ways: by CCP status, by RF status, and by RF/CCP status (those positive for RF OR CCP were defined as seropositive). Both patient and physician reported measures of disease activity were included, as well as CRP and ESR, when available. Physician reported measures were the number of tender and swollen joints in a 28-joint count and a global rating on a visual analog scale (VAS). Patient reported measures were pain VAS, fatigue VAS, global disease activity VAS, and modified Health Assessment Questionnaire (mHAQ). The clinical disease activity index (CDAI) and modified disease activity score (mDAS), both based on 28-joint counts in Corrona, were included.

Statistical analysis

Descriptive statistics were calculated for demographic and clinical features at baseline. Chi-square tests were used to compare CCP status and categorical baseline demographic and clinical variables. Student's t-tests were used to compare CCP status and baseline continuous variables that were normally distributed, and Wilcoxon two-sample tests were used to compare CCP status and variables that were not normally distributed. Wilcoxon signed-rank tests were used to test for differences in disease activity scores within CCP-positive or negative groups over time. Wilcoxon two sample tests were used to test for differences in change scores between the CCP serologic status groups over time. In addition, general linear models were used to predict follow up disease activity scores with the independent variable of CCP status, adjusting for disease duration and baseline disease activity score.

Results

Demographics

Of the 805 patients who were started on tocilizumab and had a follow up visit 4-8 months later, 316 of them had information on CCP status available and were included in the main analysis. There were no significant difference in age or sex of included participants, though the absolute percentage of women was higher in CCP-seropositive patients (table 1). The CCP-seronegative patients were more likely to be white as opposed to the seropositive

patients. The duration of RA was longer in CCP-seropositive patients (9 years vs. 8 years, table 1). There were no significant difference in prior DMARD treatment by CCP status nor was there a difference in the number of csDMARDs or biologic DMARDs (table 1).

Missing data

Since 489 (61%) of potentially eligible patients were missing data on CCP status, analyses were performed to evaluate whether or not those with missing CCP status differed systematically from those with who had CCP status recorded by measures of disease activity and severity. Baseline CDAI and presence of erosive disease at baseline did not differ significantly by whether the CCP status was missing. In considering other factors that may influence response to therapy, disease duration was also evaluated. Those with missing CCP status had a different distribution of disease duration with a higher mean and median duration than those with CCP status present.

Disease activity before and after tocilizumab therapy

The values for measures of disease activity at visit 1 (time of tocilizumab initiation) and visit 2 (4-8 months after initiation) are detailed in table 2. All measures of disease activity improved significantly from visit 1 to visit 2 with the exception of mHAQ in the CCP-seronegative group which did not change (table 2). The magnitude of change did not differ significantly according to CCP status for any of the measures.

Adjusted analysis

To account for differences in baseline disease activity and disease duration, general linear models were used to predict follow up disease activity scores with the independent variable of CCP status, adjusting for disease duration and baseline disease activity score. In most cases, CCP status was not statistically significant, with the exception of tender joint count, with borderline significance of 0.05, where seronegative patients had a higher predicted tender joint count at follow up. For almost all disease activity measures, the most predictive variable in the model was the baseline score. Disease duration was significantly associated with predicted follow up CDAI, tender joint count, and mDAS.

Sensitivity analyses

To evaluate the choice of CCP status to represent seropositive or seronegative RA, we performed the same analyses using different definitions of seropositivity. For one set of analyses, RF positivity was defined as seropositive, and for the other, patients with either RF or CCP positivity were defined as seropositive. In both sets of analyses there were statistically significant improvements in all measures of disease activity for both the seronegative and seropositive groups from baseline to follow up. Also in both analyses, there was no difference in magnitude change of disease activity by serologic status (supplemental tables 1, 2)

Discussion

In this study, patients from the Corrona RA registry who started on TCZ were evaluated for response to therapy with patient and physician reported disease activity measures, combined

disease activity indices and inflammatory markers. The data were analyzed by CCP status to determine if CCP negativity was associated with a greater response to TCZ. The study showed that both CCP-negative and positive groups had significant improvements in most disease activity measures studied, but the magnitude of improvement did not differ between the two groups. The same results were found when seropositivity was defined by RF or by a combined definition (RF or CCP positive).

This study was one of the first to evaluate whether response to TCZ differed by serologic status outside of a clinical trial, in a large multicenter cohort. Other studies of different designs have tried to address the same question. In a smaller, single center observational study, the subgroup of patients who were RF-positive actually had a better response to tocilizumab[13]. In an open label study of 85 patients treated with tocilizumab from Spain, there was no difference in response by CCP or RF status[14]. In one phase IIIB clinical trial, there was no difference by RF status[15].

Strengths of this study include drawing from a population from diverse clinical sites and including patients not in clinical trials. Both of these features make the results more generalizable to practicing rheumatologists. Serologic status was also evaluated in three different ways, all yielding consistent results. This consistency of results strengthens the conclusion that serologic status did not influence response to TCZ for this cohort of patients.

The lack of difference in response by CCP status may reflect the complexity of RA immune pathogenesis. For example, even if IL-6/STAT3 is upregulated in seronegative RA, if this is not the dominant immune pathway responsible for disease pathogenesis, then blocking IL-6 signaling would not lead to differential benefit by serologic status. Additionally, the relationship between particular immune pathways and clinical disease activity is not well understood in RA. IL-6/STAT3 pathway activity may not be reflected in traditional measures of disease activity, as evaluated in this analysis. Alternatively this may reflect limitations of study design.

One limitation of this study was that CCP data was obtained from physician reports, and also came from heterogeneous assays. Also, using only commercially available CCP results prevents the detection of ACPA antibodies not recognized by commercially available assays, so patients may have been classified as CCP negative who indeed had other ACPA antibodies. Additionally, many patients had data on CCP status missing. Although those with missing data did not differ in disease activity or erosive disease from those without missing data, the disease duration was longer in patients with missing CCP status. Patients with longer disease duration may respond differently to biologic therapies like TCZ than those who are earlier in their disease process, which may have skewed our results. Future studies could test for CCP positivity at the initiation of tocilizumab for more accurate classification.

In conclusion, CCP seronegativity was not associated with increased response to TCZ in this multicenter cohort of patients with RA. TCZ treatment was associated with improvements in patient reported, physician reported, and combined disease activity measures regardless of serologic status. Understanding whether patients respond differently to biologics according

to easily evaluated biomarkers, like CCP status, can provide clinicians with a tool in helping to decide which treatment to choose in a particular patient. Future research in understanding the pathogenesis of seronegative RA may lead to new targets for biologic therapy in this subgroup of patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline clinical and demographic characteristics: Patients with non-missing CCP status, N=316

	CCP-Seronegative patients	CCP-Seropositive patients	Difference between CCP-pos&neg
	N=136	**N=180**	**p-value**
Female N (%)	102 (75%)	148 (82%)	0.12
Age at Initiation Mean (SD)	57.6 (13.2)	56.1 (11.7)	0.30 *
Race N(%)			
White	126 (93%)	153 (85%)	**0.04**
Mixed Race	4 (3%)	1 (1%)	White vs All Other
Black	3 (2%)	12 (7%)	Races
Asian	2 (1.5%)	5 (3%)	
Other/Unknown	1 (1%)	9 (5%)	
Duration RA (yrs)	8	9	**0.05** **
Median, IQR	4-13	5-17	
Erosive disease ever N (%)	42/113(37%)	80/151 (52%)	**0.01**
Prior DMARDs N (%)			
Methotrexate	122 (90%)	163 (91%)	0.80
Leflunomide	50 (37%)	77 (43%)	0.28
Sulfasalazine	30 (22%)	38 (21%)	0.84
Prior TNFi +	122 (90%)	171 (95%)	0.07
Abatacept	67 (49%)	74 (41%)	0.15
Tofacitinib	6/102 (6%)	4/112 (4%)	0.42
Rituximab	27 (20%)	29 (16%)	0.39
Number of prior DMARDs N (IQR)			
Biologic	2, 1-3	2, 1-3	0.67 **
Non-biologic	1, 0-2	1, 0-2	0.49 **

Results for above tests were made using chi square tests unless otherwise noted. Bold values indicate statistical significance.

* t test was used (two-sided)

** Wilcoxon two-sample test (two-sided) was used

+ Prior TNF inhibitors: etanercept, adalimumab, infliximab, golimumab, or certolizumab.

Table 2

Disease activity at time of Tocilizumab initiation and follow up (matched by patient at baseline and follow-up visit)

	CCP Seronegative, N=136			CCP Seropositive, N=180			
Measure of disease activity	**Visit 1 Median, IQR**	**Visit 2 Median, IQR**	**Visit Change p-value**	**Visit 1 Median, IQR**	**Visit 2 Median, IQR**	**Visit Change p-value**	**p-value Difference Between Groups**
CDAI	28.5 17-38.6	17.0 8.7-27.6	**<0.0001**	23.2 15-35	13.7 8.1-20.7	**<0.0001**	0.72
mHAQ (di) N=136, 175	0.625 0.27-1.0	0.625 0.25-1.0	0.27	0.625 0.25-1	0.5 0.13-0.88	**0.02**	0.42
Tender Joint Count	10 4-19	5 1-12	**<0.0001**	7 3-12.5	3 1-7	**<0.0001**	0.41
Swollen Joint Count	5.5 2-9.5	2 0-6	**<0.0001**	6 2-10	3 0-6	**<0.0001**	0.50
Patient VAS Disease Activity	55 40-70	50 25-70	**<0.0001**	55 30-70	45 25-61.5	**<0.0001**	0.92
Patient VAS Pain	61.5 43.5-80	50 30-75	**<0.0001**	55 33-75	40 25-70	**<0.0001**	0.94
Patient VAS FatigueN=128, 154	60 43-80	50 28-75	**0.008**	60 30-80	50 25-75	**0.005**	0.90
Physician VAS Disease Activity	45 30-60	30 15-40	**<0.0001**	40 26-60	21.5 10-40	**<0.0001**	0.57
ESR N=44, 59	13.5 4.5-38	2.5 1-19	**<0.0001**	28 7-53	10 4-26	**<0.0001**	0.40
CRP (mg/L) N=50, 70	7.1 2.1-15	2 0.3-7	**0.0005**	10.8 5-31	2.2 0.73-11	**0.0003**	0.34
mDAS N=136, 175	5.4 4.4-6.2	4.5 3.2-5.3	**<0.0001**	4.9 4.0-6.0	4.1 3.2-4.8	**<0.0001**	0.99

Bold values indicate statistical significance

Table 3

Summary of least-squares means at follow up and significance levels from general linear models predicting scores of disease activity by CCP serological status, adjusting for disease duration and baseline disease activity

	Adjusted follow up least-squares means; 95% confidence interval		Significance levels		
Measure of disease activity	**Sero-negative**	**Sero-positive**	**Sero-status**	**Disease Duration**	**Baseline**
CDAI	17.7 15.9-19.6	16.6 15.1-18.3	0.39	**0.016**	**<0.0001**
mHAQ (di)	0.63 0.54-0.71	0.60 0.52-0.67	0.63	0.49	**<0.0001**
Tender Joint Count	6.88 5.8-7.9	5.47 4.6-6.4	**0.05**	**0.0013**	**<0.0001**
Swollen Joint Count	3.44 2.7-4.1	4.18 3.6-4.8	0.13	0.21	**<0.0001**
Patient VAS Disease Activity	44.76 40.6-48.9	43.28 39.7-46.9	0.60	0.68	**0.0003**
Patient VAS Pain	48.83 44.4-53.2	44.63 40.8-48.4	0.16	0.21	**<0.0001**
Patient VAS fatigue	51.13 46.4-55.9	49.43 45.2-53.6	0.60	0.76	**0.0038**
Physician VAS Disease Activity	29.39 26.1-32.6	26.95 24.1-29.8	0.27	0.81	**<0.0001**
ESR	11.48 6.6-16.3	17.29 12.9-21.7	0.08	0.12	0.35
CRP	7.22 -2.6-17.0	14.50 5.7-23.3	0.28	0.52	0.51
mDAS	4.26 4.1-4.7	4.13 4.0-4.3	0.35	**0.019**	**<0.0001**