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Effect of drug therapy on net cholesterol efflux capacity of HDL-enriched serum in rheumatoid arthritis

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Abstract

Background—Patients with rheumatoid arthritis (RA) have increased coronary heart disease (CHD) risk. Some RA therapies may modify this risk, but underlying mechanisms are unclear. HDL's cholesterol efflux capacity is associated with reduced CHD risk in non-RA populations; however, inflammation may impair HDL's function. We hypothesized that reduced inflammation from treatment with methotrexate (MTX), adalimumab (ADA) and tocilizumab (TOC) would increase net cholesterol efflux capacity (CEC) of HDL in patients with RA.

Methods—A longitudinal multi-center study (Treatment Efficacy and Toxicity in Rheumatoid Arthritis Database and Repository) provided clinical information and serum samples from 70 patients with RA before and 6 months after starting a new drug (MTX (n=23), ADA (n=22), and TOC (n=25)). Disease activity was measured by DAS28-ESR. Net CEC was measured in paired serum samples using THP-1 macrophages with fluorometric assay for cholesterol measurement.

Results—DAS28-ESR decreased with all treatments (P<0.001). Net CEC was not significantly changed after 6 months of new RA therapy (mean± SD, baseline, 36.9%±17.3% units vs. 6 months, 38.0%±16.9% units, P=0.58). However, change in net CEC was associated with change in DAS28-ESR (rho=−0.25, P=0.04). In post hoc analyses of patients with impaired baseline net CEC, TOC resulted in significant improvement in net CEC (baseline, 21.9%±14.7% units vs. 6 months, 31.1%±12.8% units, P=0.02), but this was not observed with MTX or ADA (all P>0.05).

Conclusion—HDL's net CEC did not change significantly after 6 months of new RA therapy, except in those with impaired baseline CEC receiving TOC. Change in disease activity was associated with change in net CEC.

Ischemic heart disease is increased almost 2-fold in patients with RA (1). In most populations increased low density lipoprotein (LDL) and decreased high density lipoprotein (HDL) cholesterol concentrations are among the strongest treatable cardiovascular (CV) risk

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factors identified. However, LDL cholesterol concentrations tend to be lower and HDL cholesterol concentrations are not substantially altered in RA, and thus do not account for the increased CV risk (2).

Recent evidence from non-RA populations indicates that HDL function, specifically its ability to remove cholesterol from macrophages (termed cholesterol efflux capacity) may be more important in protecting against CV risk than HDL cholesterol concentration (3). Moreover, another function of HDL, its ability to prevent oxidation of LDL, is frequently impaired in patients with RA (4,5). Thus, novel risk markers such as these or other measures of HDL function may be better indices of CV risk, particularly in populations such as RA in whom inflammation can cause changes to lipoproteins that are not detected by measuring cholesterol concentrations. In a small study, RA patients with high disease activity had impaired cholesterol efflux capacity compared to those with low disease activity or remission (6), suggesting that HDL dysfunction could potentially be reversed. Little is known about how RA treatment affects cholesterol efflux capacity.

Many of the drugs used to treat RA can increase LDL cholesterol concentrations (7,8), raising the possibility of increased CV risk. However, several drugs for RA such as methotrexate (MTX) and adalimumab (ADA) reduce rather than increase CV risk (9). We hypothesized that this improved CV risk is due to beneficial effects of the drugs on HDL cholesterol efflux capacity as a result of reduced inflammation or through treatment-specific mechanisms. Thus, we defined the effect of three different commonly used RA drugs, MTX, ADA, and tocilizumab (TOC), on HDL-mediated cholesterol efflux capacity in patients with RA.

Materials and Methods

Study population

We performed a longitudinal study of 70 patients with RA, before starting MTX (N=23), ADA (N=22), or TOC (N=25) therapy and after 6 months of treatment with the respective drug. The patients were recruited as part of the Treatment Efficacy and Toxicity in Rheumatoid Arthritis Database and Repository (TETRAD) (NCT#01070121) from University of Alabama at Birmingham (coordinating center), Brigham and Women's Hospital, Duke University, Johns Hopkins University, North Shore Medical Center, Stanford University, University of Colorado Denver, University of Nebraska, and University of Pittsburgh. Patients met the following inclusion criteria: age 19 years or older; fulfilment of the American College of Rheumatology 1987 classification criteria for RA (10); willingness and ability to provide informed consent; starting MTX, or previous or current use of MTX and starting (or switching to) etanercept, infliximab, ADA, rituximab, abatacept, golimumab, certolizimab, or TOC as part of routine care. Patients who also had systemic lupus erythematosus, juvenile arthritis, psoriatic arthritis, hepatitis C infection, or were currently pregnant or lactating were excluded. For the present study only patients starting MTX, ADA, or TOC (index drugs) were included. Of the 70 patients included in the study, 5 patients changed index drug, and 6 patients stopped the index drug or had missing data for index drug at month 6. A sensitivity analysis was performed excluding patients who changed

or stopped the index drug or had missing data for index drug at month 6 (including 4 taking MTX, 5 taking ADA and 2 taking TOC).

Clinical and laboratory information

RA disease activity was determined by the DAS28-ESR score using erythrocyte sedimentation rate (ESR) (11). ESR was measured by the clinical laboratories at each center. Interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα) were measured by multiplex ELISA (Millipore Corporation, Billerica, MA, USA).

Measurement of net cholesterol efflux capacity of HDL-enriched serum

Net cholesterol efflux capacity was measured as previously described (12,13) with minor modifications. Human monocyte THP-1 cells were plated in 12 multi-well plates (1×10^6 cells/ 1 ml RPMI1640 with 10% fetal bovine serum and 0.1% phorbol myristate acetate). After 72 hours, the cells were incubated with 100μg/ml acetylated LDL (Intracel, #RP-045) for 72 hours, resulting in foam cell formation. Medium was changed to RPMI containing 4% fatty acid free bovine serum albumin (Sigma, #A6003) for one hour. Patient serum (250 μl) was added to 100 μl of polyethylene glycol (PEG) solution (20% PEG 8000 in 200mM glycine) and incubated at room temperature for 15 minutes and then centrifuged at 1900g. The supernatant was removed and used as apolipoprotein B (apoB) depleted serum or HDL-enriched serum (14). Cells were then washed and incubated with medium containing 2% apoB depleted serum. Acetylated LDL exposed cells exposed to medium only were used as a comparator. After 24 hours of incubation, cells were washed twice and air dried. Cellular lipids were extracted with isopropanol and total cellular cholesterol was measured by fluorometric assay (15). Cholesterol content was corrected for total cellular protein for each well. Cholesterol efflux capacity was defined as the % change in total cellular cholesterol content (in μg/mg protein) between wells exposed to medium and apoB depleted serum (16,17). Samples were run in duplicate. The mean intra-assay coefficient of variation was 20.1%. We defined impaired baseline net cholesterol efflux capacity as efflux capacity below the mean.

Statistical analysis

The primary outcome of interest was the overall effect of RA treatment on net cholesterol efflux capacity of HDL-enriched serum; prespecified subgroup analysis was the effect of individual drug (MTX, ADA, and TOC) on net cholesterol efflux capacity.

With 70 paired samples, we had 90% power to detect a 6.5% unit change in net cholesterol efflux, and based on a sample size of 22 paired samples (ADA group, which had the smallest sample size among the individual treatment groups), we had 80% power to detect a 12.0% unit change in net cholesterol efflux. This permitted more than sufficient power to detect change in cholesterol efflux of less than one standard deviation (17.3% units in our study) for all treatments combined and for individual therapies. A change in cholesterol efflux capacity of one standard deviation was deemed clinically important since a decrease of this magnitude was previously associated with a 20% reduction CV risk (18).

Descriptive statistics were calculated as mean ± standard deviation (SD) for normally distributed variables, median with interquartile range (median [IQR: 25th, 75th]) for skewed continuous variables, and frequency and proportions for categorical variables. Wilcoxon signed rank tests were used to compare variables at baseline and after drug therapy. Analysis of covariance (ANCOVA) was used to compare the effect of each drug on cholesterol efflux capacity. The dependent variable was efflux at 6 months and independent variables were efflux at baseline and index drug.

Statistical analyses were performed using IBM SPSS Statistics version 22, and PS Power and Sample Size Calculations version 3.0. Two-sided P values less than or equal to 0.05 were considered statistically significant.

RESULTS

Clinical characteristics

Patients were mostly Caucasian (80%), female (84%), and rheumatoid factor positive (64%) with a mean age of 53 ± 12 years at study entry (Table 1). Disease activity by DAS28-ESR score was moderate to high at entry (mean ± SD: 4.7 units ± 1.3) (Table 1). Fifty one percent of all patients were taking prednisone; 82% of those starting ADA and 48% of those starting TOC were taking concomitant MTX (Table 1).

Change in disease activity with DMARD or Biologic therapy

DAS28-ESR scores improved significantly after 6 months of DMARD or biologic therapy (mean change: −1.4 ± 1.4 units, P<0.001); the change in disease activity was similar across initiators of individual drugs (MTX, ADA and TOC) with the mean change ranging from −1.3 to −1.5 units (Table 2). All drugs resulted in a significant reduction in ESR, and tender joint count (all P <0.05) (Table 2).

Net cholesterol efflux capacity of HDL-enriched serum before and after therapy

Baseline net cholesterol efflux capacity was 36.9 ± 17.3% in the entire group (Table 3) and there was no statistically significant change in net cholesterol efflux after 6 months of therapy (mean change: 1.1 ± 16.6%, P =0.58) (Table 3). Similarly, individual drugs did not have a statistically significant effect on net cholesterol efflux capacity: MTX (−3.3 ± 20.2%, P=0.38), ADA (2.3 ± 14.6%, P=0.44), or TOC (3.9 ± 14.2%, P=0.23) (Table 3). When those 5 patients who changed index drug and those 6 patients who stopped the study drug prior to or had missing data for index drug were excluded from analysis, there was no statistically significant change in net cholesterol efflux overall (P=0.90) or with individual drugs (MTX P=0.17; ADA P=0.69; TOC P=0.35). Additionally, we found that change in the use of prednisone (P=0.68) or non-steroidal anti-inflammatories (P=0.59) did not significantly change efflux capacity and that starting or stopping these drugs did not significantly change net cholesterol efflux capacity (Supplementary Table).

Net cholesterol efflux capacity of HDL-enriched serum among patients with impaired baseline efflux capacity

In an exploratory analysis we examined the impact of RA therapy on net cholesterol efflux capacity among those who had impaired baseline efflux capacity, assuming that those with impaired net cholesterol efflux capacity at baseline would be more likely to improve with treatment, but those with normal or high efflux capacity would likely not likely improve further. We defined impaired baseline net cholesterol efflux capacity as efflux capacity below the mean. Among those with impaired baseline net cholesterol efflux capacity, there was a significant increase in net cholesterol efflux capacity (mean change ± SD: 6.8% ± 15.7% units, P=0.02) (Table 3). Among individual drugs, TOC significantly improved net cholesterol efflux capacity (mean change ± SD: 9.4% ± 14.4% units, P=0.02), but neither MTX (P=0.80) nor ADA (P=0.27) changed net cholesterol efflux capacity significantly (Table 3). There was no significant change in the net cholesterol efflux capacity among those patients with high cholesterol efflux capacity at baseline (P=0.06) or among individual drugs (MTX P=0.17, ADA P=0.80, TOC P=0.20). Similarly, after excluding 5 patients who changed index drug and 6 patients who stopped the study drug prior to or had missing data for index drug, the results were similar: among those with impaired baseline net cholesterol efflux there was a significant increase in net cholesterol efflux overall (P=0.045), and with use of TOC (P=0.04), but not with MTX (P=0.69) or TOC (P=0.51).

Relationship between change in disease activity and change in net cholesterol efflux capacity

There was no significant association between baseline DAS28-ESR and baseline net cholesterol efflux capacity (rho=−0.14, P=0.24). The reduction in DAS28-ESR score after 6 months of a new DMARD or biologic therapy was correlated with an increase in cholesterol efflux capacity (rho=−0.25, P=0.04) (Figure 1).

DISCUSSION

The major findings of this study are that after 6 months of treatment with a DMARD or biologic therapy the decrease in disease activity assessed by DAS28-ESR score was correlated with increased net cholesterol efflux capacity of HDL-enriched serum. While on average the net cholesterol efflux capacity did not improve significantly after treatment of RA with MTX, ADA or TOC, there was a significant improvement in net cholesterol efflux capacity among those patients with impaired baseline net cholesterol efflux capacity, particularly those receiving TOC.

A few cross-sectional studies have examined the relationship between inflammation or disease activity and cholesterol efflux capacity in RA. In a study comparing 18 RA patients with high disease activity (DAS28-ESR > 5.1) and 7 RA patients with low disease activity or remission (DAS28-ESR < 2.6), those with high disease activity had significantly lower cholesterol efflux capacity by HDL-enriched serum, and efflux capacity was inversely associated with ESR, but not other inflammatory markers (6). In another study including 30 patients with RA, cholesterol efflux capacity of HDL-enriched serum by only one transporter, ABCG1, was inversely associated with DAS28-ESR score, but not with ESR or

CRP. (19). We previously showed that among 134 patients with RA with relatively well controlled disease, there was no significant association between net cholesterol efflux capacity and disease activity or markers of inflammation (20, 21).

A few prospective studies have also examined the effect of reduction of inflammation or RA treatment on efflux capacity, a design that permits more robust examination of the relationship between inflammation and HDL function. A prospective observational cohort study of 90 patients with RA who had a reduction in CRP concentration of 10 mg/L or greater over one year found that after a substantial median reduction of CRP by 23.5mg/l and DAS28-ESR by 1.6 units, there was a small but statistically significant increase in cholesterol efflux capacity(22). There was a modest correlation between change in cholesterol efflux capacity and change in CRP (P=0.02) but not disease activity. Another study tested the effect of treatment with MTX (N=34) or ADA plus MTX (N=22) on whole serum-mediated cholesterol efflux capacity by different pathways (23). After 6 months of MTX use, SR-B1 and ABCG1-mediated cholesterol efflux capacity was increased; numerical values were not provided, but graphically the change appeared small, and contrary to what would be expected, when MTX was combined with ADA, there was no significant effect on cholesterol efflux capacity by any pathway (23).

We explored the possibility that the lack of an effect or small effect of RA therapy on HDL-mediated cholesterol efflux may be due to some patients having high baseline cholesterol efflux capacity and thus less likely to show improvement. In patients with low baseline efflux capacity we found that TOC, but not MTX or ADA, significantly increased cholesterol efflux capacity. This post hoc finding should be interpreted with caution. By splitting patients into these groups (below and above mean net cholesterol efflux capacity), we risk the possibility of our findings being due to regression to the mean even though the change in patients with high efflux capacity at baseline was not significant. Furthermore, TOC could increase HDL-mediated efflux by increasing HDL concentration rather than altering function. Though, because of the significantly decreased plasma reactive oxygen metabolites among users of TOC compared to DMARDs and anti-TNF agents (24), TOC could affect cholesterol efflux capacity though a reduction in oxidative stress, which likely affects HDL function (25,26). Future studies are needed that specifically evaluate the impact of TOC on oxidative stress and its resultant impact on HDL function and potentially CV risk reduction.

The impact of cholesterol efflux capacity on cardiovascular events in RA is currently unknown, but more is known in non-RA populations. In a prospective nested case control study from the EPIC-Norfolk study including 1745 patients with incident coronary heart disease and 1749 control subjects, for every standard deviation increase in cholesterol efflux capacity by HDL-enriched serum, the risk of incident coronary heart disease was reduced 20% independent of traditional CV risk factors (18). Similarly, in the Dallas Heart Study which included 2924 patients initially without CV disease who were followed for a median of 9.4 years, there was a 67% reduction in CV events in the lowest quartile of cholesterol efflux capacity compared to the highest quartile (27). However, not all studies have found this inverse relationship between cholesterol efflux capacity and CV disease. For example, among 1150 patients without acute coronary syndrome who underwent elective diagnostic

coronary angiography, increased cholesterol efflux capacity, despite being associated with decreased prevalent coronary artery disease, was associated paradoxically with increased risk of non-fatal MI or stroke and major adverse CV events over 3 years of follow-up (28). The relationship between net cholesterol efflux capacity and CV events and clinically relevant differences in efflux capacity in RA are therefore of interest.

Considering the findings of others and those of the current study, the evidence suggests that the overall effects of DMARD or biologic treatment on HDL-mediated cholesterol efflux are likely to be small and occur in patients with high disease activity; this is likely why we previously found no significant relationship between disease activity and net cholesterol efflux capacity in a cohort of relatively well controlled patients with RA and now show a modest correlation between change in DAS28 and CEC in a cohort of patients with higher disease activity starting new therapy for RA. Other functions of HDL, such as anti-oxidant (4,5) and anti-inflammatory effects may be more strongly influenced by medications and inflammation, and may have an important role in CV disease in RA. Further studies in this area would be helpful.

Limitations

Our study has some limitations. The relationship between cholesterol efflux capacity and increased risk of CV events in patients with RA is not known. Thus, although we found overall that the reduction in disease activity was correlated with increased cholesterol efflux capacity, and efflux capacity increased among patients with impaired baseline efflux capacity after TOC, the clinical relevance of the changes are not known. Additional studies to define the relationship between HDL-mediated efflux, and other function of HDL and CV events in patients with RA will be of interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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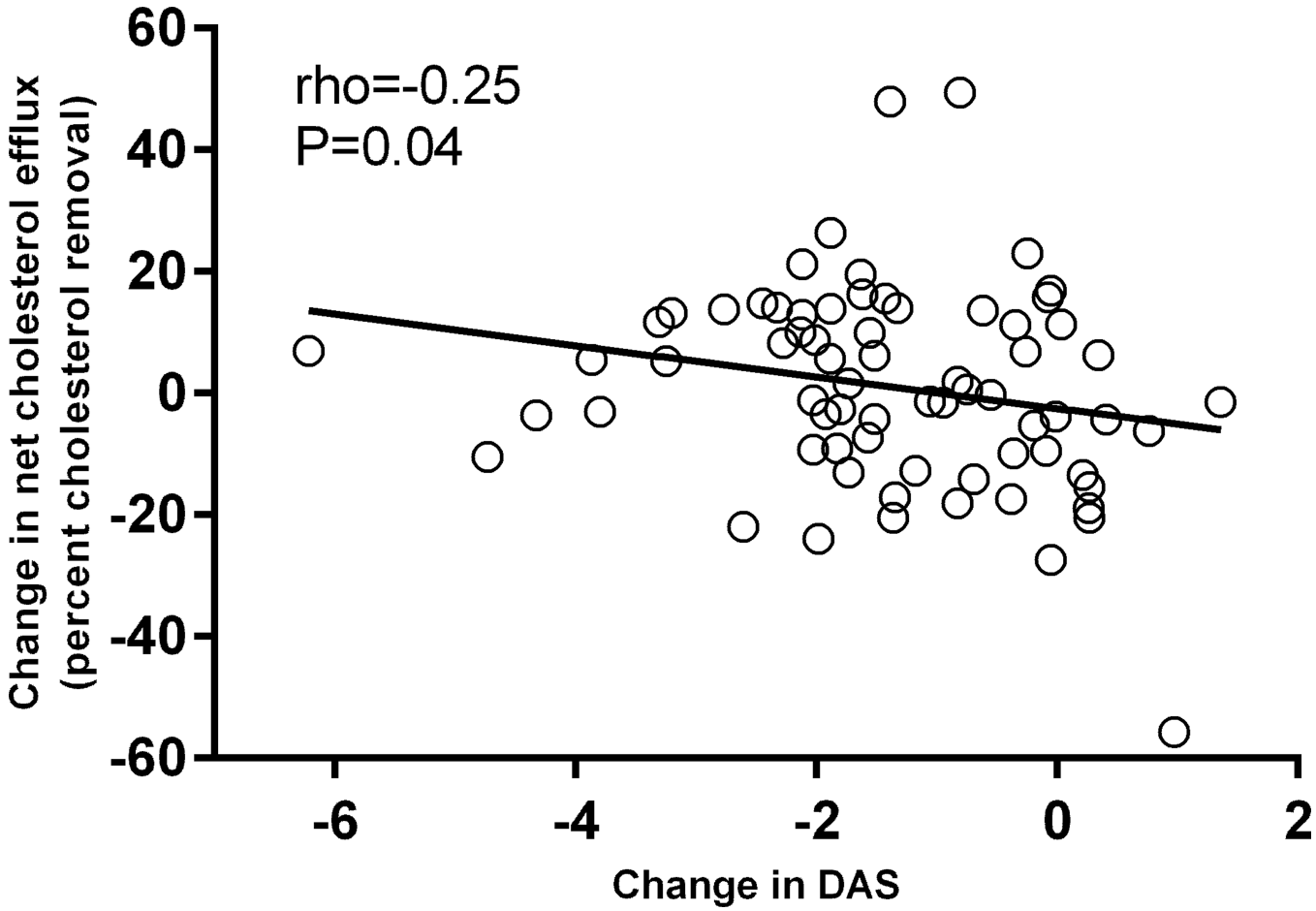

Figure.

Relationship between absolute change in DAS28-ESR score and absolute change in net cholesterol efflux after 6 months of new drug therapy. The change in disease activity after 6 months of DMARD or biologic therapy based on the DAS28-ESR score was significantly associated with the change in net cholesterol efflux capacity of HDL-enriched serum (rho= −0.25, P=0.04).

Table 1

Baseline patient characteristics

	All Patients (N=70)	Methotrexate (N=23)	Adalimumab (N=22)	Tocilizumab (N=25)
Age, year	53 ± 12	52 ± 12	56 ± 11	53 ± 13
Race, Caucasian	56 (80)	17 (74)	17 (77)	22 (88)
Sex,female	59 (84)	18 (78)	19 (86)	22 (88)
RF, positive	45 (64)	15 (65)	12 (55)	18 (72)
CCP, positive	44 (63)	17 (74)	11 (50)	16 (64)
DAS28-ESR, units	4.7 ± 1.3	4.6 ±1.2	4.8 ±1.4	4.8 ±1.4
Disease duration, year	9 ± 11	2.0 ± 5.7	7.7 ± 7.5	16.6 ± 13.7
Methotrexate use	44 (63)	-	18 (82)	12 (48)
Leflunomide use	6 (9)	2 (9)	3 (14)	1 (4)
Sulfasalazine use	1 (1)	1 (4)	-	-
Azathioprine use	2 (3)	-	1 (5)	1 (4)
Hydroxychloroquine use	12 (17)	6 (26)	5 (23)	1 (4)
Prednisone use	36 (81)	12 (86)	11 (58)	13 (54)
NSAID use	30 (63)	11 (73)	7 (54)	12 (60)

Data are presented at mean ± standard deviation for continuous data, and number (percent) for categorical data. RF= rheumatoid factor, anti-CCP= anti-cyclic citrullinated peptide antibody, DAS28-ESR= disease activity score based on erythrocyte sedimentation rate. Prednisone use available in N=57 total. NSAID use available in N=48 total.

Table 2

Disease activity and markers of inflammation before and after DMARD or biologic

	Baseline	6 Months	Absolute Change	P value*
DAS28-ESR, units				
All drugs (N=70)	4.7 ± 1.3	3.4 ± 1.4	−1.4 ± 1.4	<0.001
Methotrexate (N=23)	4.6 ± 1.2	3.3 ± 1.1	−1.3 ± 1.2	<0.001
Adalimumab (N=22)	4.8 ± 1.4	3.6 ± 1.3	−1.3 ±1.3	0.001
Tocilizumab (N=25)	4.8 ± 1.4	3.3 ± 1.8	−1.5 ± 1.6	<0.001
ESR, mm/hr				
All drugs (N=70)	20 [10, 38]	8.5 [3, 23]	−8 [−17, 0]	<0.001
Methotrexate (N=23)	28 [10, 42]	19 [11, 40]	−4 [−16, 0]	0.01
Adalimumab (N=22)	18 [11, 30]	7 [4, 24]	−4 [−14, 1]	0.03
Tocilizumab (N=25)	19 [11, 40]	7 [2, 15]	−11 [−31, −2]	<0.001
Tender joint count, #				
All drugs (N=70)	7 [3, 14]	3 [1, 9]	−3 [−6, 0]	<0.001
Methotrexate (N=23)	5 [3, 11]	1 [0, 3]	−2 [−6, 0]	0.03
Adalimumab (N=22)	12 [3, 16]	6 [1, 10]	−3 [−8, 0]	0.003
Tocilizumab (N=25)	7 [5, 15]	6 [1, 11]	−3 [−7, 1]	0.006
Swollen joint count, #				
All drugs (N=70)	7 [3, 10]	2 [1, 5]	−3 [−7, 0]	<0.001
Methotrexate (N=23)	6 [3, 8]	1 [0, 3]	−3 [−7, −2]	0.001
Adalimumab (N=22)	9 [4, 13]	3 [1, 5]	−5 [−7, 0]	0.006
Tocilizumab (N=25)	6 [2, 10]	3 [1, 9]	−1 [−5, 1]	0.11
IL-6, pg/ml				
All drugs (N=70)	3.9 [0.0, 17.3]	3.1 [0.0, 26.0]	0.0 [−6.3, 10.8]	0.47
Methotrexate (N=23)	4.8 [0.0, 22.4]	1.6 [0.0, 6.7]	−0.3 [−7.0, 0.9]	0.20
Adalimumab (N=22)	4.0 [0.0, 23.1]	0.0 [0.0, 4.8]	0.0 [−13.5, 0.0]	0.03
Tocilizumab (N=25)	3.7 [0.0, 15.2]	27.5 [1.9, 61.7]	17.8 [0.0, 43.2]	0.004
TNF-α, pg/ml				
All drugs (N=70)	11.5 [7.4, 17.1]	10.2 [7.5, 14.7]	−0.7 [−3.7–1.6]	0.10
Methotrexate (N=23)	10.4 [7.3–15.3]	11.5 [7.8, 14.7]	−0.1 [−3.7, 1.7]	0.66
Adalimumab (N=22)	11.1 [8.5–17.3]	9.2 [7.6, 12.4]	−1.6 [−8.7, 0.3]	0.02
Tocilizumab (N=25)	12.5 [6.9–18.6]	13.8 [6.8, 17.7]	0.3 [−2.1, 2.3]	0.85

Data are presented as mean ± standard deviation for normally distributed data, and median [interquartile range] for skewed data.

*Using Wilcoxon signed ranks test. DAS28-ESR = disease activity score based on erythrocyte sedimentation rate, ESR = erythrocyte sedimentation rate, IL-6 = interleukin 6, TNF-α = tumor necrosis factor alpha.

Table 3

Net cholesterol efflux capacity before and after DMARD or biologic therapy

	Baseline	6 Months	Absolute Change	P value*
All patients				
All drugs (N=70)	36.9% ± 17.3	38.0% ± 16.9	1.1% ± 16.6	0.58
Methotrexate (N=23)	41.2% ±13.9	38.0% ±17.5	−3.3% ± 20.2	0.38
Adalimumab (N=22)	36.1% ±16.8	38.5% ± 18.2	2.3% ± 14.6	0.44
Tocilizumab (N=25)	33.7% ± 20.1	37.6% ± 15.8	3.9% ± 14.2	0.23
Patients with impaired baseline net cholesterol efflux				
All drugs (N=37)	24.1% ±11.3	31.0% ±12.4	6.8% ±15.7	0.02
Methotrexate (N=10)	28.8% ± 9.5	34.0% ± 12.6	5.1% ± 19.7	0.80
Adalimumab (N=12)	22.9% ± 6.6	28.0% ± 14.5	5.1% ± 14.4	0.27
Tocilizumab (N=15)	21.9% ± 14.7	31.3% ± 12.8	9.4% ± 14.4	0.02

*Using Wilcoxon signed ranks test.Data are presented at mean ± standard deviation.