Reducing Cardiovascular Risk with Immunomodulators: A Single Blind Randomized Active Comparator Trial Among Patients with Rheumatoid Arthritis

Supplemental Material

Supplementary Methods: Separate Files

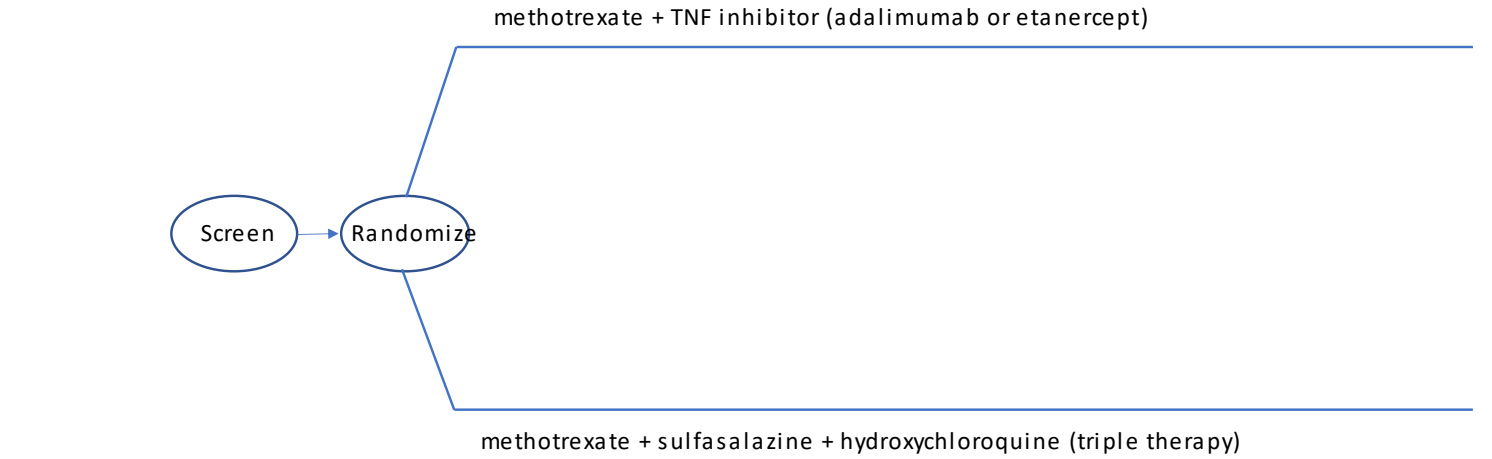
A. Statistical Analysis Plan
B. FDG PET/CT Vascular Image Assessment

Supplementary Table 1: Detailed Eligibility Criteria
(Subjects who met all of the following criteria at screening were eligible for enrollment into the study)

Inclusion
• Written informed consent signed by the subject; • Fulfill ACR/EULAR 2010 criteria for RA; • Men ≥ 45 years and women ≥ 50 years of age; • Methotrexate for ≥ 8 weeks at ≥ 15mg weekly or on at least 7.5mg of methotrexate weekly for ≥8 weeks with a documented intolerance of higher methotrexate doses, and on a stable dose for the previous 4 weeks; • DAS28 score > 3.2; • Able to swallow pills; • Males and females with reproductive potential must agree to practice effective measures of birth control; • If taking prednisone (or equivalent corticosteroid), the dose must be ≤ 10 mg/day at the time of the baseline FDG PET/CT scan and must NOT change by more than ±3.0 mg for the four weeks prior to the baseline FDG PET/CT; • If taking a low- or moderate-intensity statin, the dose must be stable for six weeks prior to screening and must not change during the six months of the trial (please see Statins and PCSK9 Inhibitors below in Exclusions for further details); • Willing to comply with all study procedures and be available for the duration of the study; • Rheumatoid arthritis diagnosis without psoriasis or with psoriasis if rheumatoid factor ≥ 2x upper limit of normal or anti-CCP ≥ 2x upper limit of normal.
Exclusion
• Prior use of biologic DMARD or small molecule DMARD (i.e. tofacitinib) in the past 6 months, use of Rituximab ever; • If a subject is considered to be an etanercept (Enbrel) or adalimumab (Humira) failure by their primary rheumatologist; • Non-biologic DMARDs other than methotrexate or hydroxychloroquine for two months prior to screening; • Current use or use within the past 12 months of a high-intensity statin lipid lowering drug (atorvastatin/Lipitor 40-80mg, rosuvastatin/Crestor >10mg) or a PCSK9 inhibitor (alirocumab/Praluent, Evolocumab/Repatha, or Bococizumab); • Prior patient reported, physician diagnosed clinical CV event: myocardial infarction or heart attack, angina, stroke, uncompensated or severe heart failure (NYHA class III or IV), prior vascular procedure (coronary artery angioplasty or stenting, carotid endarterectomy, coronary artery bypass surgery); • Demyelinating disease; • Any of the following forms of arthritis that may otherwise explain the subject's RA symptoms: psoriatic arthritis, reactive arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, polymyalgia rheumatica • Any of the following other autoimmune and/or chronic inflammatory diseases: Inflammatory Bowel Disease, Crohn's disease, Cutaneous or Systemic Lupus, Systemic Vasculitis, Giant Cell Arteritis, Polymyositis, Dermatomyositis, Sarcoidosis, or Scleroderma; • Transient ischemic attack; • Revascularization for peripheral artery disease; • Cancer treated in last five years (except basal and squamous cell) or any lymphoma or melanoma;

- Type I diabetes mellitus or type II diabetes mellitus treated with insulin or uncontrolled with HbA1c ≥7%;
- Known pregnancy, HIV, hepatitis B, hepatitis C, active (or untreated latent) TB;
- Known sulfa allergy or other known hypersensitivity to any of the trial agents or G6PD deficiency;
- Known macular disease or known retinal disease;
- Baseline blood count, renal or liver abnormalities as follows: WBC < 3.5 x 1000 n/ul, Hematocrit < 30%, Platelet count < 90 x 1,000 n/ul, estimated glomerular filtration rate < 50 ml/min/1.7m2, AST >60 U/L, ALT>84 U/L;
- Intra-articular glucocorticoid injection within the 4 weeks prior to the potential baseline FDG PET/CT; and
- Two or more of the following high dose radiation scans in the past year: CT scan with contrast, angiogram, SPECT nuclear medicine scan, myocardial (cardiac) perfusion scan.

Supplementary Figure 1: Study Schema



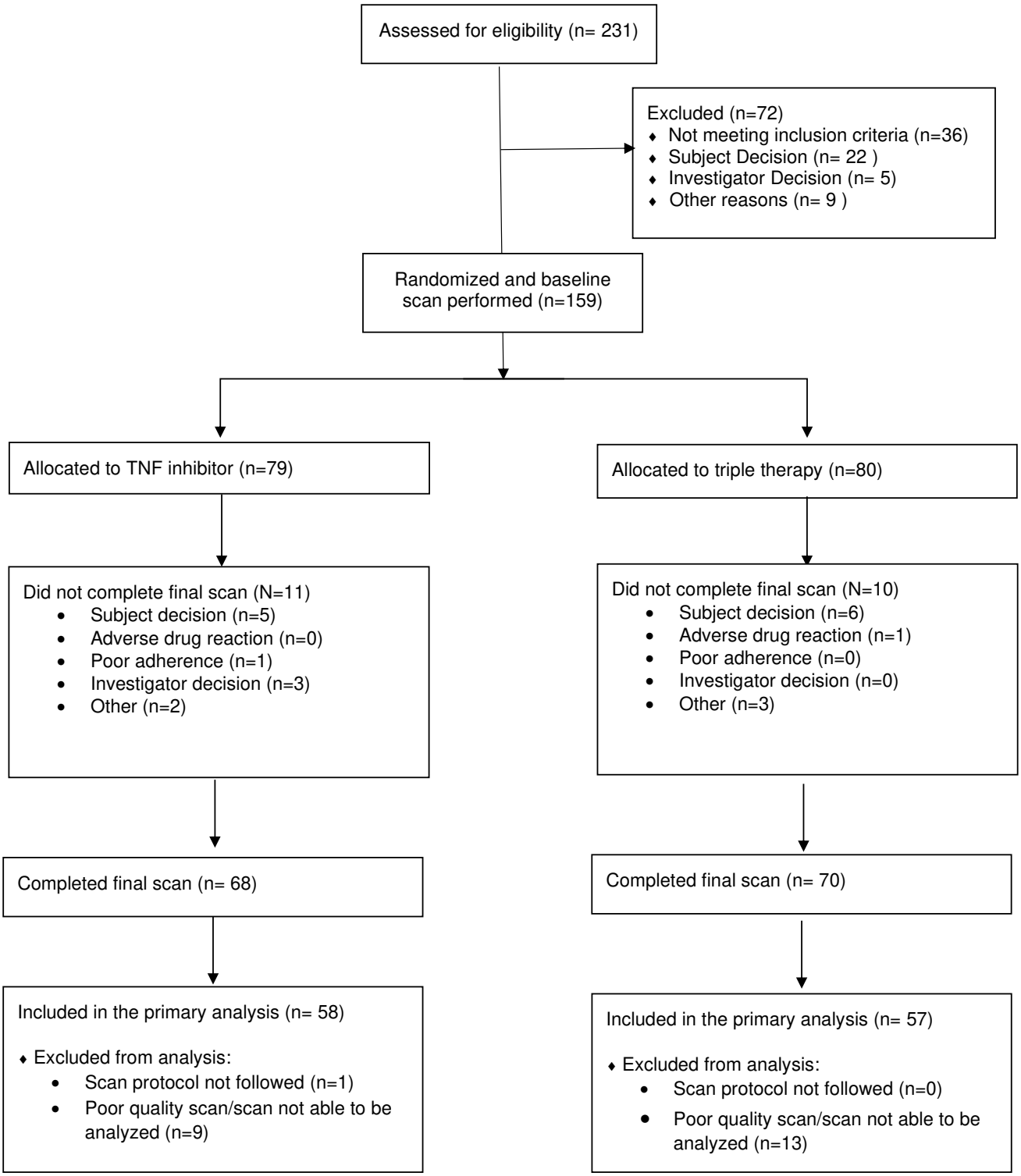
Supplementary Table 2: Baseline Patient Characteristics of Patients Included in Final Analyses Versus Those Excluded

	Included (n = 115)	Excluded (n = 44)	p-value
	N (%) or median (interquartile range)		
Age, years	58.0 (53.0, 65.0)	59.5 (56.0, 65.0)	0.29
Sex, female	82 (71.3)	37 (84.1)	0.096
Race			
White	90 (80.4)	29 (72.5)	0.38
Black	12 (10.7)	8 (20.0)	
Other	10 (8.9)	3 (7.5)	
Ethnicity			0.54
Hispanic	31 (27.0)	14 (31.8)	
Non-Hispanic	84 (73.0)	30 (68.2)	
RA disease duration, years	1.4 (0.5, 6.6)	3.8 (0.8, 7.9)	0.16
Serologic status, positive for RF or CCP	63 (56.8)	28 (68.3)	0.20
DAS28-CRP	4.8 (4.0, 5.6)	5.1 (4.7, 5.5)	0.11
hsCRP (mg/L)	3.9 (1.6, 9.8)	5.7 (1.7, 11.4)	0.50
Glucocorticoid use, daily	38 (33.0)	10 (22.7)	0.20
NSAID use	46 (40.0)	16 (36.4)	0.67
Aspirin use	28 (24.4)	11 (26.2)	0.75
Methotrexate weekly dosage (mg)	20.0 (15.0, 25.0)	20.0 (15.0, 25.0)	0.53
Heath assessment questionnaire	1.1 (0.5, 1.8)	1.4 (1.1, 2.1)	0.01
Body mass index (kg/m2)	29.3 (25.7, 33.2)	32.2 (27.9, 36.4)	0.01
Hypertension	52 (45.2)	16 (38.1)	0.43
Hyperlipidemia	23 (20.0)	6 (14.3)	0.40
Diabetes mellitus	2 (1.7)	1 (2.3)	1.00
Tobacco use			0.52
Current	14 (12.2)	3 (7.1)	
Past	30 (26.1)	9 (21.4)	
Never	71 (61.7)	30 (71.4)	
Statin use			0.37
None	93 (80.9)	38 (90.5)	
Low-moderate intensity	20 (17.4)	4 (9.5)	
High intensity	2 (1.7)	0 (0.0)	
At least one cardiovascular risk factor*	63 (54.8)	20 (47.6)	0.43

Notes: *Cardiovascular risk factors include the presence of hypertension, diabetes, hyperlipidemia, or current tobacco use (all self-reported).

Abbreviations: RA, rheumatoid arthritis; hsCRP, high sensitivity C-reactive protein; NSAID, non-steroidal anti-inflammatory drugs.

Supplementary Figure 2: CONSORT Diagram Demonstrating the Construction of the Trial Population



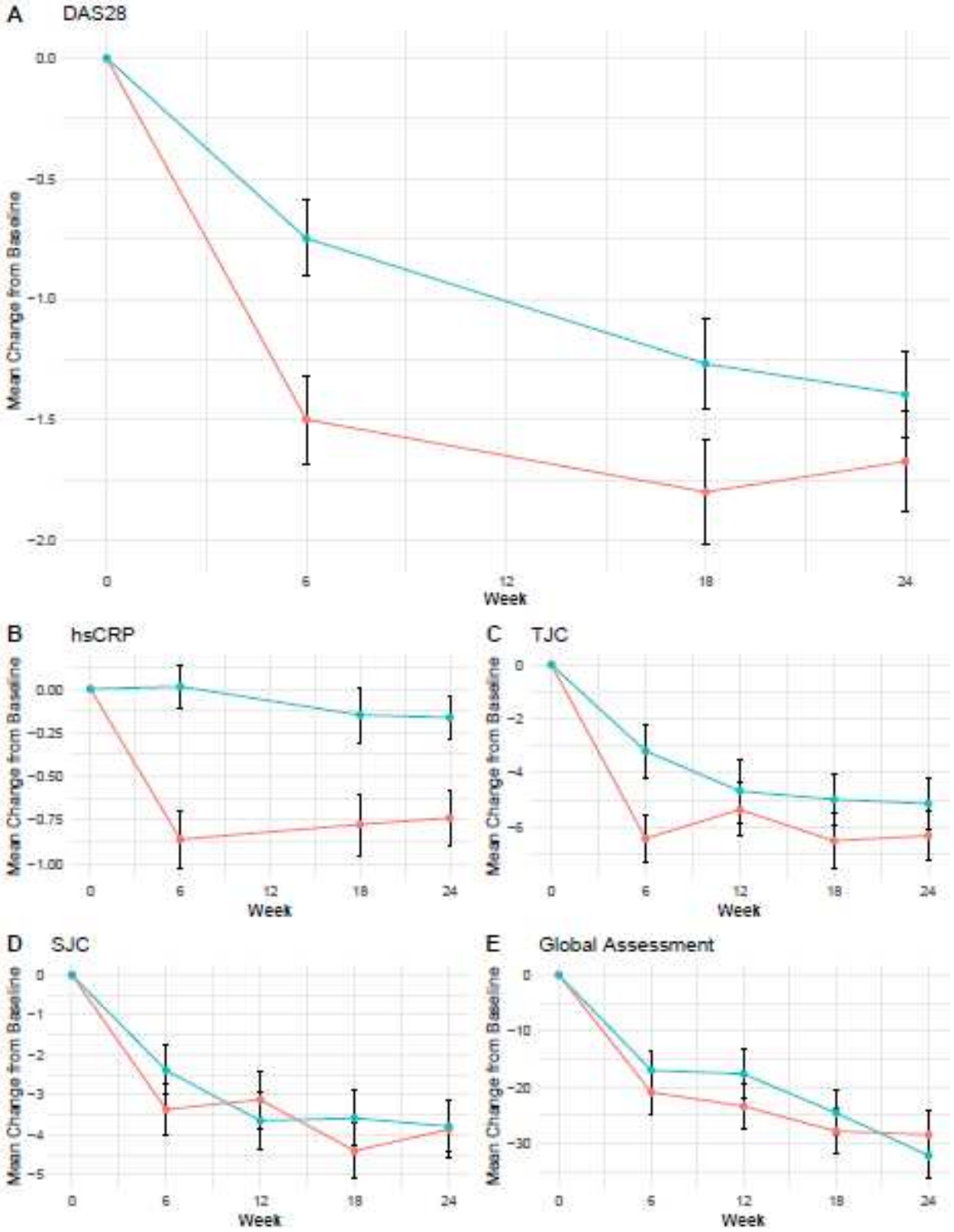
Supplementary Table 3: Main Outcome Results Based on Different Definitions of Adherence

Compliance definitions	Number of compliant subjects by each definition		Difference in differences in TBR (95% CI)	p-value
	TNFi	Triple therapy		
>80% on all pills	29	25	0.11 (-0.10, 0.31)	0.30
>80% on all pills excluding methotrexate	36	29	0.03 (-0.20, 0.26)	0.80
>80% on all pills or compliant at all visits according to site reports*	43	35	0.04 (-0.15, 0.23)	0.68
>80% on all pills or compliant at all but one visit according to site reports	49	42	0.01 (-0.17, 0.18)	0.93

*In addition to providing pills counts at each visit, sites were asked to report if the subject's compliance was "good" at each visit.

Supplemental Figure 3: Disease Activity by Treatment Group at Baseline, 6 weeks, 8 weeks, and Final Follow-up

Figures demonstrate the mean change from baseline across the DAS28-CRP (Panel A), hsCRP (Panel B), swollen joint count (Panel C), tender joint count (Panel D), and patient global (Panel E). The blue line indicates the triple therapy group and the red line indicates the TNFi group. The p-values were estimated in ANCOVA models comparing change from final to baseline assessment. P-values (to be inserted on the figure): DAS28 – 0.19; hsCRP – <0.001; TJC – 0.24; SJC – 0.88; Global Assessment – 0.71.


A DAS28
Mean Change from Baseline
0.0
−0.5
−1.0
−1.5
−2.0
0
6
12
18
24
Week
B hsCRP
Mean Change from Baseline
0.00
−0.25
−0.50
−0.75
−1.00
Week
C TJC
Mean Change from Baseline
0
−2
−4
−6
Week
D SJC
Mean Change from Baseline
0
−1
−2
−3
−4
−5
Week
E Global Assessment
Mean Change from Baseline
0
−10
−20
−30
Week

Supplementary Table 4: Simple Mediation Analyses

	N	β (95% CI)
Triple therapy remaining in moderate to high disease activity	34	Ref
Triple therapy achieving low disease activity or remission	23	-0.11 (-0.36, 0.14)
TNFi + MTX remaining in moderate to high disease activity	21	0.03 (-0.23, 0.30)
TNFi + MTX achieving low disease activity or remission	36	-0.18 (-0.41, 0.05)

We divided participants into four groups according to randomized treatment assignment and whether they achieved low disease activity or remission (DAS28-CRP≤3.2) versus remaining at moderate-high disease activity (DAS28-CRP>3.2); this was defined by the DAS28-CRP at 18 weeks. We used an ANCOVA model estimating the change in index vessel TBR as a function of the baseline TBR, randomization strata, the four groups combining information on treatment assignment and treatment response, a term for length of time between baseline and follow-up FDG-PET/CT scan, and the following potential confounders as measured at baseline: age, gender, disease duration, smoking status, serologic status, and body mass index.

Supplementary Table 5: Glucocorticoid Use at Baseline and During Follow-Up, Percentages

	Screening	Week 6	Week 12	Week 18	Week 24
Triple therapy (N=57)	31.6%	38.6%	37.5%	36.4%	37.5%
TNFi (N=58)	34.5%	29.3%	31.0%	24.1%	24.1%