

ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory disease causing joint damage and disability. While, remarkable progress in the treatment of RA over the past two decades has improved many outcomes, mortality rates in RA remain 1.5-3-fold above non-RA controls. Cardiovascular disease (CVD) is the leading cause of excess deaths in RA, and most experts believe that enhanced vascular inflammation underpins accelerated atherosclerosis and CV events. Yet, there has been no direct proof for this hypothesis. If true, then RA therapies that reduce joint inflammation might also reduce CV risk. The lack of an RA-specific CV risk tool hampers evidence-based guidelines, as general population tools perform poorly in RA. These gaps in knowledge create uncertainty for patients and providers in managing RA and its comorbidities.

While an RCT with CV events as the outcome would be an ideal study approach to investigate the effect of RA treatments on CVD, there are notable barriers, including very large sample size requirement (~10,000), long trial duration (~3years) requiring patients to maintain randomization, and the associated costs (~\$60M). Moreover, many DMARDs raise LDL presenting ethical challenges in a CVD prevention trial, where enrolling high-risk patients would be desired. Therefore, an alternative outcome utilizing a surrogate CV measure that directly reflects vascular inflammation and has been demonstrated to be responsive to treatment (e.g., with statins) would serve as a scientifically important and feasible proof-of-concept trial. We propose here to use ¹⁸F-fluoro-deoxyglucose by positron emission tomography/computed tomography (FDG PET/CT) as a novel imaging modality to detect baseline, and DMARD-associated changes in, vascular inflammation in RA.

We will compare the effects on FDG PET/CT of 2 treatment regimens in an RCT among methotrexate (MTX) inadequate responders, representing a critical and common decision point for rheumatologists and patients: addition of a TNFi vs sulfasalazine + hydroxychloroquine to background MTX (**Aim 1**). Recent RCTs show near equivalent reduction in articular disease activity, but the relative effects of these regimens on CV risk is unknown. Substantial basic science data as well as epidemiologic evidence support the superiority of TNFi on CV inflammation over non-biologic DMARDs, but this has never been studied in an RCT.

Using data from the RCT, we will also compare the effects on vascular inflammation of achieving low disease activity or remission vs remaining in moderate-high disease activity. These pre-specified secondary analyses will pool the treatment arms to examine whether achievement of a disease activity target associates with greater reduction in vascular inflammation. **Aim 2a** will use DAS-28 scores to categorize treatment response and correlate it with vascular inflammation. **Aim 2b** will use a multi-biomarker of RA disease activity to categorize treatment response and correlate it with vascular inflammation. **Aim 2c** will use joint inflammation as measured by FDG PET/CT to categorize treatment response and correlate with vascular inflammation.