Background: Increasing evidence suggests that TNF inhibitors (TNFi) are safe to use during pregnancy. 1 A drawback of TNFi use during pregnancy is active transport across the placenta, which is affected by the structure of the TNFi. The European League Against Rheumatism (EULAR) defined points to consider (PIC) on the use of TNFi during pregnancy: 2 to prevent placental transfer, etanercept should be discontinued at gestational age (GA) 30-32 weeks, and both adalimumab and infliximab should be discontinued at GA 20 weeks. Certolizumab pegol can be conditionally continued throughout pregnancy.

Objectives: The aim of this research is to validate the EULAR PIC by measuring the level of TNFi in cord blood.

Methods: Patients were derived from the PreCARA study, an ongoing prospective cohort study on inflammatory rheumatic diseases and pregnancy in the Netherlands. Patients were treated according to a treat-to-target approach, which included the use of TNFi. TNFi were, if possible, discontinued at recommended stop time points. Maternal blood samples were collected in each trimester. Cord blood was analyzed for the presence of certolizumab pegol, etanercept, adalimumab and infliximab. Levels of TNFi in the cord blood were compared between patients that stopped at the advised GA and patients who did not.

Results: Data from 111 patients with inflammatory rheumatic diseases were used for the current analysis. Most patients stopped treatment before the recommended GA (table 1). Certolizumab pegol (n = 68) was measured in a low number of cord blood samples (5.9%) and in low concentrations (median, IQR): 0.25 µg/ml (0.15 – 1.3). Etanercept was not detected in any cord blood samples (n = 28). Adalimumab (n = 24) and infliximab (n = 13) were measured more often in cord blood (in 50.0% and 61.5% of patients, respectively), this also was observed in patients that stopped before the recommended GA (in 47.7% for adalimumab and 60.0% for infliximab). However, the observed concentration levels were low: the maximum observed concentrations in cord blood were 2.1 µg/ml (stopped at GA 19.4 weeks) for adalimumab and 4.5 µg/ml (stopped at GA 21.1 weeks) for infliximab.

Conclusion: Stopping TNFi around the GA recommended by the EULAR PIC resulted in no measurable levels or low concentrations of TNFi inhibitor in the cord blood in a majority of patients.

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Background: Cardiovascular (CV) disease is the leading cause of premature mortality and sudden death in Rheumatoid Arthritis (RA). Conventional CV risk factors and disease specific risk factors are responsible for endothelial dysfunction (ED) in RA. ED is the barometer of CV health and key initial event in atherosclerosis. Tofacitinib, a JAK inhibitor, in clinical use since 2012 and has had the most extensive development program in RA, but its impact on ED has not yet been explored in humans.

Objectives: To investigate the impact of tofacitinib on endothelial dysfunction in RA

Methods: 40 RA patients fulfilling the 2010 Rheumatoid Arthritis classification criteria with active disease (DAS28>3.2) were randomized to receive 24 weeks of treatment with Tofacitinib (5mg bd, n=20) and placebo (n=20) as an adjunct to existing stable antirheumatic drugs. Primary endpoints included endothelial dysfunction assessed by FMD using AngioDefender and lipids were estimated at baseline and after 12 weeks of treatment. The secondary end points included: DAS28, ESR, CRP, HAQ-DI and cardiovascular risk using SCORE chart assessed at week 0 and 12.

Results: At baseline, endothelial function was impaired and levels of inflammatory measures were elevated in both groups. CV risk SCORE was high and HAQ-DI was impaired at baseline. After treatment, FMD improved significantly in the tofacitinib group from (8.16±1.38% to 10.98±2.33%), p≤0.05) as compared to placebo (7.12±0.25% to 8.04±0.30%, p=0.35) (Fig. 1A). DAS28 (Fig. 1B), ESR and CRP (Fig. 1C) levels improved significantly in tofacitinib group as compared to placebo (p≤0.05). Tofacitinib significantly decreased HAQ-DI and SCORE (Fig. 1D) values as compared to placebo. There was significant increase in HDL (p≤0.05) after treatment with tofacitinib as compared to placebo. There was significant decrease in DAS28, ESR and CRP decreased by 37.40%, 36.10% and 76.59% respectively as compared to tofacitinib. Significant negative correlation was observed between FMD and DAS28 (r=-0.50, p≤0.05) and CRP (r=-0.32, p≤0.05) after treatment with tofacitinib where as no such correlation was found in placebo group.

Conclusion: First study to show that tofacitinib, apart from its anti inflammatory activity, improves endothelial dysfunction and cardiovascular risk in RA. Thus, JAK inhibition with tofacitinib has vasculoprotective and cardio protective effect mediated through anti-inflammatory and probably other mechanisms. This study would stimulate further research in exploring the vasculoprotective and cardio protective potential of tofacitinib in RA.

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Figure 1. Impact of Tofacitinib on FMD, DAS 28, CRP & SCORE

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Background: Rheumatoid Arthritis (RA) is a systemic autoimmune disease with a prevalence of 0.5-1% worldwide1. Anti-cytokine antibodies, especially anti-Tumor Necrosis Factor (TNF) antibodies are considered the gold standard for RA therapy. However, there are some concerns regarding their lack of therapeutic efficacy in a significant proportion of patients2 and their potential systemic implications such as the risk of serious infections2. Developing novel agents with synovial targeting specificity might help to increase the therapeutic index while reducing systemic side effects of RA therapeutics.

Objectives: Our work aims to develop a novel bispecific tandem single-chain variable fragment (scFv)-Fc fusion protein combining synovium specificity with anti-TNFα activity. The potential advantage of this construct is a reduced systemic TNF-binding activity and increase delivery and activation of the TNF-neutralising capacity at the inflamed joints.

Methods: The therapeutic tandem scFvFc fusion protein comprises two external arms with synovium specific targeting ability linked through a metalloproteinase (MMP) cleavable linker to the anti-TNFα variable fragments of Adalimumab fused to the CH2 and CH3 domains of IgG1 (Figure 1). The external scFv regions with synovium specificity were previously identified by in vivo phage display using a SCID mouse model transplanted with human synovium3. The construct was tested for its ability to bind and neutralise in vitro and ex vivo targets.

Results: The fusion protein was tested by immunohistochemistry staining on RA synovium biopsies and an array of non-inflamed human tissues showing specific targeting of synovial microvasculature without any reactivity to the non-inflamed tissues. The TNFα binding and blocking capacity of the fusion protein was measured respectively by ELISA and cell assays measuring NF-κB activation, and it showed a two-fold decreased activity compared to the control antibody Adalimumab prior to detachment of the cleavable targeting fragment shielding the active anti-TNF fragment. Human synovial fluid and recombinant human MMP-1 efficiently cleaved the external arms of the antibody, releasing the anti-TNF scFv-Fc. The cleaved construct, detached from the synovium targeting arms, showed the same binding and anti-TNF inhibitory capacity/potency as Adalimumab.

Conclusion: The novel bispecific tandem scFvFc demonstrated specific synovium targeting ability and intended reduced anti-TNF activity in its intact form prior to reaching the joint. Following MMPs-induced cleavage present in RA synovial fluid the therapeutic activity was restored to the same level as Adalimumab. Overall, this construct has the potential of decreasing the anti-TNF off-site activity and consequently, reduce systemic toxicity while maintaining high on-site activity. Also, the presence of a synovium targeting domain has the advantage of increasing the delivery and retention within the inflamed synovium and possibly increase the therapeutic index of this anti-TNF therapeutics.

Figure 1. Schematic diagram of the bispecific tandem scFv-Fc fusion protein.