Table 1. TNF inhibitor use during pregnancy and TNF inhibitor concentrations in mother's blood and cord blood.

	Certolizumab pegol (n = 68)	Etanercept (n = 28)	Adalimumab (n = 24)	Infliximab (n = 13)
Stop time point as recommended by EULAR	N/A	GA 30-32	GA 20	GA 20
Gestational age at time of stopping TNFi, median±IQR	37.29 (32.79 – 38.29)	25.43 (18.71 – 28.36)	18.79 (8.93 – 19.86)	18.86 (14.57 – 20.00)
Measurable TNFi in cord blood, n (%)	4 (5.9%)	0 (0%)	12 (50.0%)	8 (61.5%)
Maternal concentration of TNFi in the 1st trimester, median±IQR (µg/ml)	24.55 (19 – 31)	2.1 (0.8 – 2.5)	8.2 (1.5 – 10)	14 (7.98 – 21)
Maternal concentration of TNFi in the 2nd trimester, median±IQR (µg/ml)	22.52 (13 – 30.72)	1.4 (0.89 – 2.7)	6 (4.5 – 7.5)	6.37 (4.2 – 20)
Maternal concentration of TNFi in the 3rd trimester, median±IQR (µg/ml)	20.5 (13 – 29.58)	0.2 (0.2 – 0.67)	0.85 (0.1 – 1.4)	1.4 (0.09 – 1.9)
Concentration of TNFi in the cord blood if measurable, median±IQR (µg/ml)	0.25 (0.15 – 1.3)	-	0.45 (0.15 – 0.65)	0.4 (0.12 – 1.15)

Background: Increasing evidence suggests that TNF inhibitors (TNFi) are safe to use during pregnancy¹. A drawback of TNFi use during pregnancy is active transport across the placenta, which is affected by the structure of the TNFi¹. The European League Against Rheumatism (EULAR) defined points to consider (PtC) on the use of TNFi during pregnancy²: 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 PtC 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 concentrations 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 PtC resulted in no measurable levels or low concentrations of TNF inhibitor in the cord blood in a majority of patients.

REFERENCES:

- [1] Smeele HTW, Dolhain RJEM. Current perspectives on fertility, pregnancy and childbirth in patients with Rheumatoid Arthritis. *Semin Arthritis Rheum*. 2019;49(3S):S32-S35. doi:10.1016/j.semarthrit.2019.09.010
- [2] Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis*. 2016;75(5):795-810. doi:10.1136/annrheumdis-2015-208840

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POS0204

AUTOANTIBODIES AND SYSTEMIC LUPUS ERYTHEMATOSUS INDUCED BY ANTI-TUMOUR NECROSIS FACTOR ALPHA THERAPY IN RHEUMATOID ARTHRITIS

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Background: Anti-tumour necrosis factor alpha (anti-TNF-α) therapy is commonly used to treat inflammatory conditions such as rheumatoid arthritis (RA). Autoantibodies namely antinuclear antibodies (ANA) induced by these

treatments are well established. However, anti-TNF-α-induced systemic lupus erythematosus (SLE) is rarely described and its incidence is yet unknown.

Objectives: This study aimed to determine the prevalence of ANA seroconversion and to characterize the development of SLE induced by anti-TNF-α therapy in patients with RA over time.

Methods: An observational retrospective cohort study was conducted with at least one year of follow-up. Patients with diagnosis of RA, according to American College of Rheumatology criteria (ACR), and registered on Rheumatic Diseases Portuguese Register (Reuma.pt) who started their first anti-TNFα between 2003 and 2019 were included. Patients with positive ANA (titer ≥100) and/or positive double-strand DNA (dsDNA) antibodies and/or with a diagnosis of SLE at their first visit were excluded. Demographic, clinical and laboratory data were obtained by consulting Reuma.pt. As there are no recognized criteria for drug-induced SLE, the diagnosis of SLE induced by anti-TNF-α was considered if there is a temporal relationship between clinical manifestations and anti-TNF-α-therapy, the presence of at least 1 serologic ACR criteria (ANA or anti-dsDNA) and at least 1 nonserologic ACR criteria (arthritis, serositis, hematologic disorder or malar rash) [1]. Continuous variables are presented with mean, standard deviation, median, quartile 1 and quartile 3. Categorical variables are presented with absolute and relative frequencies.

Results: A total of 211 patients (mean age of 49.9±10.9 years old; 84.4% female) were included with a median follow-up time of 6 [3-14] years. We found a seroconversion rate for ANA of 75.4% (n=159) with median treatment duration of 31 [8.5-70.5] months. The most common titre was 1/100 with diffuse and speckled patterns. ANA seroconversion was higher for etanercept (47.8%, n=76) than with adalimumab (23.9%, n=38), infliximab (13.8%, n=22), golimumab (12.6%, n=20) or certolizumab (1.9%, n=3). SLE induced by anti-TNF-α occurred in two patients (0.9%) with erosive and seropositive (rheumatoid factor and anti-citrullinated protein antibodies) RA previously treated with two conventional synthetic disease-modifying antirheumatic drugs, including methotrexate. The first patient, a female with 66 years old and 17 years of disease duration, developed SLE after 16 months of infliximab, with constitutional symptoms, abrupt worsening of polyarthritis, ANA titer of 1/320 diffuse pattern and positive dsDNA (248 UI/mL) antibodies. The second patient, a woman with 43 years old and 11 years of disease duration, developed SLE after 41 months of adalimumab with malar rash and ANA titer of 1/320 diffuse pattern, positive dsDNA (285 UI/mL), positive anti-histone antibodies and hypocomplementemia. In these two cases, anti-TNF-α therapy was stopped and recovery was spontaneous without treatment. The first patient switched to adalimumab and the second switched to golimumab without recurrence of SLE for more than ten years.

Conclusion: We found a high rate of ANA seroconversion induced by anti-TNFα therapy in patients with RA. However, similar to previous literature, only 0.9% of patients developed SLE with mild manifestations without major organ involvement. Although the drug with the highest ANA seroconversion rate was etanercept, those responsible for induced SLE were infliximab and adalimumab. Patients improved after discontinuation of therapy and tolerated an alternative anti-TNF-α drug without recurrence of induced SLE over time. Therefore, ANA and SLE induced by anti-TNF-α should be considered and reported in the follow-up of RA patients. Further research is needed to explore the impact of this adverse event on the outcomes of treatment over time.

REFERENCES:

- [1] Hochberg MC. *Arthritis Rheum*. 1997;40(9):1725.

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POS0205

AMELIORATION OF ENDOTHELIAL DYSFUNCTION WITH JAK INHIBITION IN RHEUMATOID ARTHRITIS: JAK CV-RISK REDUCTION STUDY

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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, is 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 $8.16 \pm 1.38\%$ to $10.98 \pm 2.33\%$, $p=0.05$ as compared to placebo ($7.12 \pm 0.25\%$ to $8.04 \pm 0.30\%$, $p=0.35$) (Fig. 1A). DAS28 (Fig. 1B), ESR and CRP (Fig. 1C) levels improved significantly in tofacitinib group as compared to placebo ($p \leq 0.05$). Tofacitinib significantly decreased HAQ-DI and SCORE (Fig. 1D) values as compared to placebo. There was significant increase in HDL ($p \leq 0.05$) after treatment with tofacitinib as compared to placebo. After 12 weeks of treatment, FMD and HDL increased by 34.55% and 13.58% respectively where as DAS28, ESR and CRP decreased by 37.40%, 36.10% and 76.59% respectively in the tofacitinib group. Significant negative correlation was observed between FMD and DAS28 ($r = -0.50$, $p \leq 0.05$) and CRP ($r = -52$, $p \leq 0.05$) after treatment with tofacitinib where as no such correlation was found in placebo group.

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

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 cardioprotective effect mediated through anti-inflammatory and probably other mechanisms. This study would stimulate further research in exploring the vasculoprotective and cardioprotective potential of tofacitinib in RA.

REFERENCES:

- [1] Tofacitinib reversed endothelial dysfunction in rheumatoid arthritis: mechanistic insights from the rat adjuvant-induced arthritis model. <http://dx.doi.org/10.1136/annrheumdis-2020-eular.2747>

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POS0206

DESIGN AND CHARACTERISATION OF A THERAPEUTIC BISPECIFIC TANDEM SCFV-FC FUSION PROTEIN WITH ANTI-TNF AND SYNOVIUM-TARGETING SPECIFICITY FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

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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 infections³. 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-TNF α 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 scFv-Fc fusion protein comprises two external arms with synovium specific targeting ability linked through a metalloproteinase (MMP) cleavable linker to the anti-TNF α 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 synovium⁴. The construct was tested for its ability to bind and neutralize *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 no reactivity to the non-inflamed tissues. The TNF α binding and blocking capacity of the fusion protein was measured respectively by ELISA and cell assays measuring NF- κ B 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 scFv-Fc 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.