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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.

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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.

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POS0207

REAL-WORLD RETENTION OF JAK INHIBITORS IS LONGER THAN bDMARDs IN RHEUMATOID ARTHRITIS

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Background: Biological disease modifying anti-rheumatic drugs (bDMARDs) and Janus Kinase inhibitors (JAKi) are both recommended post conventional synthetic disease modifying anti-rheumatic drug (csDMARD) therapy failure in active rheumatoid arthritis (RA), but the data on long-term durability are limited. **Objectives:** The objective of this study is to analyze a database of patients at the Western University, Rheumatology Center who initiated a bDMARD or JAKi and compare the proportion and characteristics of patients associated with retention of a drug class.

Methods: This was a single-center study of 215 adult RA patients (82.76 % females, age 59.8 ± 12.0 years, disease duration 15.5 ± 10.0 years; table 1) failing multiple csDMARDs prior to initiating either bDMARDs (TNF inhibitors, abatacept, rituximab, tocilizumab) or JAKi, between June 2014 (when tofacitinib was approved in Canada) and April 2020. All patients enrolled had failed traditional DMARDs, including methotrexate, hydroxychloroquine, sulfasalazine and/or leflunomide. Durability and predictors of discontinuation were analyzed by Kaplan-Meier and Cox regression analyses for all treatment trials, and for patients receiving bDMARDs/JAKi as a first line after csDMARDs failure.

Results: In 215 patients, there were 320 treatment events (148 bDMARDs, 172 JAKi) and 142 discontinuations (53.5% bDMARDs, 46.5% JAKi). Figure 1 represents the Kaplan-Meier survival curve for time to therapy discontinuation in 215 patients receiving bDMARDs vs JAKi. The Cox proportional hazards model was significant with better retention for JAKi, with a hazard ratio (HR) for treatment discontinuation of JAKi compared with bDMARDs of 0.676 (95% CI 0.47-0.97, p=0.034), adjusted for gender, age, disease duration, and line of therapy (Table 1). Moreover, the analysis revealed better retention for both groups as first line advanced therapy compared to later lines of therapy; 57.6% of JAKi and 31.1% of bDMARDs were used as first line advanced therapy. HR for treatment discontinuation for first line vs later lines of therapy was 0.593 (95% CI 0.40-0.88, p=0.01), adjusted for drug class, gender, age, and disease duration (Table 1). The most common reasons for discontinuations were inefficacy (60%), side effects (22%), or other reasons (18%). Inefficacy (58% vs 62%, p=0.8) and side-effects (16% vs 27%, p=0.4) were equally common for bDMARDs and JAKi. Sex, age at treatment onset, and RA duration did not predict discontinuation by Cox regression analyses, and after sub-grouping into bDMARDs and JAKi.

Conclusion: EULAR guidelines have placed bDMARDs equal to JAKi as post csDMARD failure therapy in active RA. However, this study demonstrates that JAKi has a greater durability than biologics regardless of gender, age, disease duration, and line of therapy. Therefore, JAKi may be considered as a preferable method of treatment post csDMARD failure in active RA.

Figure 1. Kaplan-Meier survival curves for (A) time to discontinuation of therapy in all RA patients receiving bDMARDs versus JAKi; P-value represents Cox regression adjusted for gender, age, disease duration, and line of therapy (B) time to discontinuation of therapy in patients using bDMARDs/JAKi as first line of advanced therapy; P-value represents Cox regression adjusted for drug class, gender, age, and disease duration

Table 1. Patient demographics and hazard ratios for discontinuation of bDMARDs versus JAKi by Cox regression model

Characteristic	JAKi (N=172)	bDMARD (N=148)	Mean
Age (years)	60.9	58.5	59.8
Sex (% F)	77.8	88.5	82.8
Disease duration (years)	15.3	15.8	15.5
Line of advanced therapy (% first line)	57.6	31.1	45.3
Drug used (%)	Tofacitinib: 93.5	Rituximab: 26.4 Etanercept: 19.6 Adalimumab: 17.6	
Predictors of Drug Discontinuation			
Crude Model	JAKi vs bDMARDs	0.60 (0.43, 0.84)	0.003
Adjusted model	JAKi vs bDMARDs	0.68 (0.47, 0.97)	0.034
	Male vs female	0.77 (0.46, 1.31)	0.342
	Age	1.01 (0.99, 1.03)	0.123
	RA duration	0.99 (0.97, 1.01)	0.500
	Treatment line 1 vs >1	0.59 (0.40, 0.88)	0.010

Disclosure of Interests: Karla Machlab: None declared, Samir M. Iskandar: None declared, Tatiana Nevskaya: None declared, Louise Vanderhoek: None declared, Jillian Bylsma: None declared, Sara Hewitt: None declared, Janet Pope Speakers bureau: AbbVie, Amgen, BMS, BI, Gilead, Galapagos, Janssen, Lilly, Medexus, Merck, Novartis, Pfizer, Sanofi, Sandoz, Consultant of: AbbVie, Amgen, BMS, BI, Celltrion, Gilead, Galapagos, Janssen, Lilly, Medexus, Merck, Novartis, Pfizer, Roche, Samsung, Sanofi, Sandoz, Teva, UCB, Grant/research support from: AbbVie, BMS, Merck, Pfizer, Roche, Seattle Genetics

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POS0208

GENDER DIFFERENCES IN RESPONSE TO BIOLOGICALS. WOMEN FARE WORSE ACROSS INFLAMMATORY ARTHRITIS DISEASES - DATA FROM THE BIOREG

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Background: Gender differences in prevalence and disease course are known in various rheumatic diseases; however, investigations of gender difference concerning therapeutic response have yielded variable results.

Objectives: The aim of this retrospective study was to investigate, whether a gender difference in response rate to biological disease-modifying antirheumatic drugs (bDMARDs) and apremilast in bDMARD-naïve patients could be observed across the three most prevalent inflammatory arthritis diseases: rheumatoid arthritis (RA), spondylarthritis (SpA) and psoriatic arthritis (PsA). Additionally, a response to individual TNF blockers was investigated in this respect.

Methods: Data from bDMARD-naïve RA-, SpA- and PsA-patients from Bioreg, the Austrian registry for biological DMARDs in rheumatic diseases, were used. Patients with a baseline (Visit 1=V1) and follow-up visits at 6 months (Visit 2=V2) and 12 months (Visit 3=V3) were included and response to therapy with TNF-inhibitors (TNFi), furthermore to therapy with rituximab, tocilizumab and apremilast was analyzed according to gender. The remaining bDMARDs were not analyzed due to small numbers. Key response-parameter for RA was disease activity score (DAS28), whereas for PsA the Stocker Activity Score for Psoriatic Arthritis (SASPA) and for SpA the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were employed; in addition, the Health assessment Questionnaire