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FRI0105 EXPRESSION OF UNCOUPLING PROTEIN-1 IN SUBCUTANEOUS FAT IS INCREASED BY TOCILIZUMAB

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Background: Adipose tissue is an important player in cardiovascular (CV) morbidity. Thermogenic brown adipocytes, rich with uncoupling protein 1 (UCP1), increase metabolic and CV health. (1)

Objectives: Study the impact of anti-rheumatic treatment on production of UCP1 in subcutaneous fat of RA patients.

Methods: Samples of subcutaneous fat were collected from 125 female RA patients by aspiration from periumbilical region. Expression of UCP1 and a reverse cholesterol transport protein ABCA1 were measured by qPCR and analysed with respect to anti-rheumatic treatment and clinical disease activity. At treatment, the patient comprised 4 major groups including tocilizumab (Toci, n=14), anti-TNF (n=29), methotrexate monotherapy (n=47) and methotrexate-sulfasalazine-hydroxychloroquine (triple therapy, n=15). CV risk was estimated with the Framingham risk algorithm.

Results: Measurable expression of UCP1 was found in 54.6% of the studied fat tissue samples. Patients on Toci had measurable expression of UCP1 in 79%, which was significantly more often than among TNFi-treated (45%, p=0.04) and MTX-treated patients (42%, p=0.02). Patients on triple therapy had also often measurable UCP1 levels compared to other groups (69% vs 43%, p=0.035). Toci patients have more lean body mass than patients treated with TNFi. This was based on lower BMI in Toci and TNFi treated patients compared to triple therapy (24.1 vs 27.1, p=0.041; 23.6 vs 27.1, p=0.017; respectively). Additionally, the estimated muscle mass by creatinin/height ratio was significantly lower in TNFi than in triple therapy (p=0.034) and Toci (p=0.008). Clinically, the treatment groups were similar in age, disease activity DAS28 and disease duration with the except for Toci. Toci patients were older (65 vs 57, p=0.04) and had numerically longer disease duration (17y vs 7y) and lower DAS28 (1.98 vs 3.11).

Notably, Toci patients had significantly higher TC compared to TNFi (p=0.027), and triple therapy (p=0.041). Triple therapy had the lowest TC levels (p=0.017). The differences were due to LDL, here patients on Toci had higher LDL than TNFi (p=0.09) and triple therapy (p=0.015). Serum HDL was similar. These differences in serum lipids were not related to expression of ABCA1 or UCP1. Despite the difference in the serum lipid profile, the estimated CV risk was significantly lower in Toci compared to MTX patients (4.1[0.87-5.75] vs 6.6[3.9-9], p=0.041).

Conclusion: In this study is Toci treatment is associated with persistent UCP1 production by adipose tissue. This was followed by lower estimated CV risk and favourable body composition in female RA patients.

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FRI0106

SARILUMAB AND TOCILIZUMAB RECEPTOR OCCUPANCY (RO), AND EFFECTS ON C-REACTIVE PROTEIN (CRP) LEVELS, IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA)

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Background:

Objectives: The in vitro binding affinity of sarilumab (K_D 61.9 pM) for the human interleukin-6 receptor (IL-6R) is 15- to 22-fold higher than tocilizumab.¹ We explored the relationship between IL-6R RO, relevant pharmacodynamic (PD) variables (eg CRP), and potential clinical relevance of the differences between sarilumab and tocilizumab.

Methods: Binding to total soluble IL-6R (sIL-6R) in vivo translates into the quasi-steady-state target-mediated drug disposition pharmacokinetics (PK) and indirect-response PD model with inhibition of elimination of sIL-6R and unbound sIL-6R concentration for both sarilumab and tocilizumab.²⁻⁵ PK/PD models were used to simulate sIL-6R RO dynamic profiles (% RO over time) for: sarilumab after subcutaneous (SC) doses of 200 and 150 mg once every 2 wks (q2w); tocilizumab after SC doses of 162 mg q2w and once every wk (qw); and tocilizumab after intravenous (IV) doses of 4 and 8 mg/kg once every 4 wks (q4w). In addition, RO profiles were compared with changes in observed CRP levels in patients with RA following administration of sarilumab SC and tocilizumab IV (ASCERTAIN study; NCT01768572). In this study, 60.8% of patients required an increase in tocilizumab dose from 4 to 8 mg/kg IV during the study period, based on clinical response.

Results: Sarilumab SC 200 mg q2w achieved >90% RO after the first dose, which was maintained over the dosing interval throughout the 24-wk treatment course; at the lower dose of 150 mg q2w, RO was >90% from the second dose onwards. RO for tocilizumab SC, at 162 mg q2w, was >90% immediately after the first dose but dropped below 50% prior to the second dose. Similarly, for tocilizumab IV at 4 mg/kg q4w, the RO was high immediately after the first dose (>99% at Wk 1) but decreased over the dosing interval. At trough steady-state (Wk 24), RO was greater with sarilumab SC 200 mg q2w (98%) and 150 mg q2w (94%) compared with tocilizumab SC 162 mg q2w (84%) and IV 4 mg/kg q4w (60%). The higher doses of tocilizumab SC 162 mg qw and tocilizumab IV 8 mg/kg q4w were able to maintain RO ≥99% at steady state, similar to sarilumab SC 200 mg at steady state. CRP levels in patients with RA were inversely associated with RO at trough; the greatest suppression in CRP was seen in patients who received sarilumab SC (at either dose) or the higher IV tocilizumab dose (Fig). However, proportionally smaller reductions in CRP levels were observed with the lower IV tocilizumab dose (4 mg/kg q4w), consistent with the lower RO of tocilizumab.

Conclusion: The higher binding affinity of sarilumab to IL-6R compared with tocilizumab translated into higher RO and greater reduction in CRP levels for sarilumab than tocilizumab, confirming the expected association between RO and PD effect. Sarilumab SC 200 mg q2w led to a rapid and sustained suppression of CRP over the 24-wk interval investigated; however, a higher dose (IV) or frequency of administration (SC) of tocilizumab was required to maintain the same degree of RO and CRP suppression. CRP may be a useful tool in clinical practice for patients treated with an IL-6R blocker.

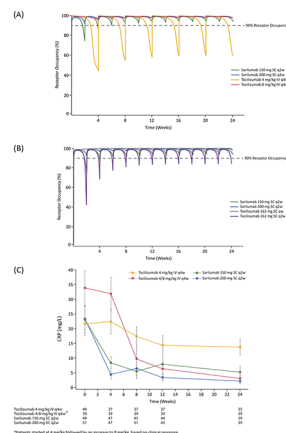
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Figure. sIL6-R RD for (A) sarilumab SC vs tocilizumab IV and (B) sarilumab SC vs tocilizumab SC, and (C) CRP levels after sarilumab SC and tocilizumab IV



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FRI0107

THE EFFECT OF CO-MEDICATION WITH METHOTREXATE OR OTHER CONVENTIONAL SYNTHETIC DISEASE MODIFYING ANTI-RHEUMATIC DRUGS ON FIRST TUMOR NECROSIS INHIBITOR DRUG SURVIVAL IN PATIENTS WITH RHEUMATOID ARTHRITIS: DATA FROM THE CZECH ATTRA REGISTRY

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Background: Tumor necrosis factor inhibitors (TNFi) should be used for the treatment of rheumatoid arthritis (RA) in combination with conventional synthetic

disease modifying anti-rheumatic drugs (csDMARD), preferably methotrexate (MTX). However a significant proportion of RA patients receive TNFi in combination with other csDMARD or in monotherapy.

Objectives: To assess the effect of co-medication with MTX or other csDMARDs on drug survival of TNFi treated RA patients.

Methods: All adult patients with RA followed in the Czech national registry ATTRA who started TNFi therapy after January 1st 2012 were considered. Six-year drug survival for patients on TNFi in combination with MTX, with other csDMARD or in monotherapy was analyzed using Kaplan-Meier method, log rank test was used to compare differences between groups. Reasons for TNFi discontinuation were analyzed. ATTRA is a centralized prospective computerized registry of patients receiving biologic disease modifying anti-rheumatic drugs (bDMARD) therapy for rheumatic diseases collecting data on efficacy, safety and quality of life of all patients treated with bDMARDs in the Czech Republic. TNFi therapy is indicated for patients with RA who have failed treatment with at least one csDMARD.

Results: A total of 1841 RA patients initiated first bDMARD treatment during the studied period, with 1724 patients receiving TNFi. 1307 patients (76%) started TNFi therapy in combination with MTX, 267 patients (15%) with other csDMARD and 150 patients (9%) as monotherapy. Overall unadjusted TNFi drug survival was better in patients receiving MTX co-medication (median survival 53 months) compared to those receiving other csDMARD (median survival 36 months) or those being on monotherapy (median survival 21 months; $p < 0.001$ for monotherapy vs MTX co-medication) (Figure). The most common reason for TNFi discontinuation was loss of efficacy (33%, 37% and 28% for MTX, csDMARD combination and monotherapy respectively) followed by primary inefficacy (20%, 19% and 27%) and adverse events (19%, 15%, 23%).

Conclusion: In this registry study of patients with RA, use of MTX co-medication was associated with significantly better first TNFi drug survival compared to other csDMARD co-medication and to monotherapy.

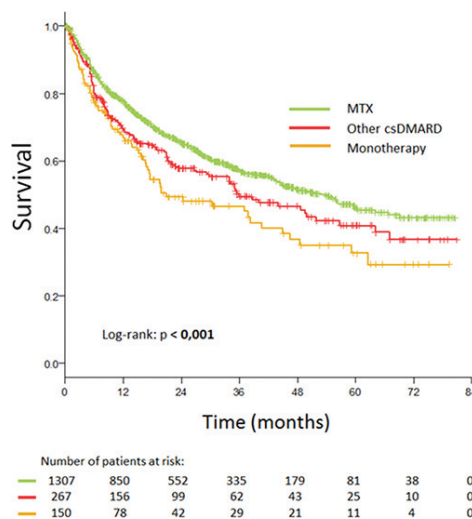


Figure. Kaplan-Meier curves of 6-year drug survival of the first TNFi based on co-medication

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