Originator Infliximab EU product information https://www.ema.europa.eu/documents/product-information/remicade-epar-product-information_en.pdf

Disclosure of Interests: Kyungmin Baek Shareholder of: Celltrion, Inc., Employee of: Celltrion, Inc., Yoon Jee Lee Employee of: Celltrion, Inc., Sujin LEE Employee of: CELLTRION, INC., HoUng Kim Shareholder of: Celltrion Healthcare.Co.,Ltd, Employee of: Celltrion Healthcare.Co.,Ltd, SeulGi Lee Employee of: Celltrion, Inc., Jeong Eun Park Employee of: Celltrion, Inc., SangJoon Lee Shareholder of: Celltrion, Inc., Employee of: Celltrion, Inc.

DOI: 10.1136/annrheumdis-2019-eular.6734

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

Lovisa Lyngfelt¹, Malin C. Erlandsson^{1,2}, Karin Me Andersson¹, Sofia Töyrä Silfverswärd¹, Maria I Bokarewa^{1,2}. ¹University of Gothenburg, Department of Rheumatology and Inflammation Research, Gothenburg, Sweden; ²Sahlgrenska University Hospital, Gothenburg, Sweden

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. Bt 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 exception 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.

REFERENCE:

- [1] Carpentier, A. C., Blondin, D. P., Virtanen, K. A., Richard, D., Haman, F., & Turcotte, É. E. (2018). Brown Adipose Tissue Energy Metabolism in Humans. *Frontiers in endocrinology*, 9, 447. doi:10.3389/fendo.2018.00447

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.7354

FRI0106

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

Christine Xu¹, Patrick Nolain², Qiang Lu¹, Anne Paccaly³, Melitza Iglesias-Rodriguez⁴, Gregory St John⁵, Chad Nivens³, Rafael Maldonado⁵, Tomonori Ishii⁶, Ernest Choy⁷, Vanaja Kanamaluru¹. ¹Sanofi, Bridgewater, NJ, United States of America; ²Sanofi Aventis, Montpellier, France; ³Regeneron Pharmaceuticals, Inc., Tarrytown, NY, United States of America; ⁴Sanofi Genzyme, Cambridge, MA, United States of America; ⁵Pompeu Fabra University, Barcelona, Spain; ⁶Tohoku University Hospital, Sendai, Japan; ⁷Cardiff University School of Medicine, Cardiff, United Kingdom

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.

REFERENCES:

- [1] Rafique A, et al. *Ann Rheum Dis* 2013;72: Abstr 797.
- [2] Xu C, et al. *PAGE Meeting* 2017; Abstr 7283.
- [3] Huizinga T, et al. *Ann Rheum Dis* 2014;73:1626–34.
- [4] Gibiansky L, et al. *J Pharmacokinet Pharmacodyn* 2012;39:5–16.
- [5] FDA Clinical Pharmacology Review for tocilizumab, 2013.

Acknowledgement: Study funding and editorial support (Helen Johns, Adelphi) provided by Sanofi and Regeneron Pharmaceuticals, Inc.