FRI0120

HIGH LEVELS OF INTERLEUKIN-6 (IL-6) IN RA PATIENTS ARE ASSOCIATED WITH GREATER IMPROVEMENTS IN PATIENT-REPORTED OUTCOMES (PROs) FOR SARILUMAB COMPARED WITH ADALIMUMAB

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Background: Increased levels of cytokines, including interleukin-6 (IL-6), reflect inflammation and are predictive of therapeutic responses in patients with RA. IL-6 has been implicated in fatigue, pain and depression in RA but a formal association with PROs has not been performed. Sarilumab, a fully human monoclonal antibody directed against IL-6Ra, is approved for treatment of moderate-to-severely active RA. The phase 3 MONARCH randomized controlled trial (NCT01061736) compared the efficacy and safety of sarilumab monotherapy vs adalimumab in RA patients who should not continue methotrexate treatment due to intolerance or inadequate responses. Greater reductions in disease activity and improvements in the clinical signs of RA and physical function were demonstrated with sarilumab vs adalimumab. A better understanding of the association between IL-6 levels and PROs is warranted to evaluate as a biomarker for guiding RA clinical decision-making.

Objectives: To evaluate, by post-hoc analysis, the potential of baseline IL-6 levels to differentially predict the improvement in PRO with sarilumab vs adalimumab in MONARCH.

Methods: Serum IL-6 levels were measured at baseline in 300/369 patients in the ITT population. Patients were categorized into high, medium, or low IL-6 tertiles levels. Between-group comparisons of differences at Week 24 in Short Form-36 (SF-36) physical and mental component summaries (PCS, MCS) and domain scores, Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue, and morning stiffness visual analog scale (VAS) measures were performed within each tertile using a linear fixed effect model. In order to evaluate the differential effect of sarilumab vs adalimumab in the baseline high vs low IL-6 groups, an interaction test of treatment-by-baseline IL-6 group analysis was performed using low IL-6 group as the reference.

Results: At baseline, patients in the high IL-6 tertile presented a significantly worse MCS and morning stiffness scores ($P < 0.05$). The model interaction comparing high vs low IL-6 tertiles was significant for SF-36 PCS and physical functioning domains, and for morning stiffness. In patients with high IL-6, sarilumab treatment resulted in significant ($P < 0.05$) improvements vs adalimumab in SF-36 PCS (LS mean [LSM] of the difference: 5.57, 95%CI (2.85, 8.28)) and physical functioning (PF, 16.59 (8.15, 25.03)), role physical (9.44 (0.78, 18.10)), bodily pain (BP, 10.87 (3.92, 17.81)), vitality (8.93 (1.11, 16.74)), and social functioning (12.82 (3.07, 22.58)) domains (all raw values in **Figure**). Sarilumab also showed significant ($P < 0.05$) effects vs adalimumab in FACIT-Fatigue (4.86 (1.06, 8.65)) and morning stiffness VAS (-19.93 (-30.30, -9.56)), with LSM changes exceeding minimum clinically important differences (MCID).

Conclusion: Evaluation of IL-6 biomarker associations with PROs indicate that patients with high IL-6 levels report better improvements with sarilumab vs adalimumab with safety profile consistent with IL-6R blockade. The effects of adalimumab treatment are stable based on IL-6 tertiles but higher with sarilumab, particularly in the high IL-6 tertile group. Effects on PCS scores are mainly driven by the PF domain, consistent with previous reports of marked improvements in pain with high IL-6 levels.

Figure

* Significant between-group difference in change from baseline ($P < 0.05$)

SF-36 domains: BP, bodily pain; GH, general health; RP, role-physical; MH, mental health; PF, physical functioning; RE, role emotional; SF, social functioning; VT, vitality.

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FRI0121

IMPROVEMENT OF MATRIX METALLOPROTEINASE-3 AT 12 WEEKS IS AN INDEPENDENT PREDICTIVE FACTOR FOR ACHIEVEMENT OF LOW DISEASE ACTIVITY AT 52 WEEKS IN BIO-SWITCH RHEUMATOID ARTHRITIS PATIENTS TREATED WITH ABATACEPT

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Background: Japanese post-marketing surveillance (PMS) data demonstrated that effectiveness of abatacept in rheumatoid arthritis (RA) patients with previous biologics treatment (bio-switch) was significantly lower than that in bio-naïve patients [1]. Useful predictive factors for good clinical response of abatacept is necessary especially in the bio-switch patients. Serum matrix metalloproteinase-3 (MMP-3) is an enzyme produced by synovocytes which can be used to predict clinical effectiveness and joint destruction in RA patients [2]. However, little is known about the relationship between MMP-3 and effectiveness of abatacept.

Objectives: This study aimed to study whether serum MMP-3 levels can predict good clinical effectiveness of abatacept in the bio-switch RA patients using data from a multicenter cohort.

Methods: Participants were consecutive 423 RA patients treated with abatacept, observed for longer than 52 weeks, and registered in the TBCR, a Japanese multicenter registry system for RA patients treated with biologics. Multivariate logistic regression analysis was used to study predictive factors for achievement of low disease activity at 52 weeks separately in bio-naïve and bio-switch group.

Results: A total of 189 bio-switch and 234 bio-naïve patients were included in this study. ROC analysis revealed that MMP-3 improvement rate at 12 weeks, compared to 4 and 24 weeks, had highest AUC and the best cut-off value was 20.0% at 12 weeks for predicting achievement of low disease activity (LDA) at 52 weeks in the bio-switch group (Figure 1, right panel). We performed multivariate logistic regression analysis to study independent predictive factors for LDA at 52 weeks using patients' background factors as well as 20% improvement of MMP-3 at 12 weeks. In the bio-naïve group, DAS28-CRP score at baseline was the only predictive factor, while the achievement of 20% improvement of MMP-3 at 12 weeks was an independent predictive factor (adjusted OR: 3.550, $p=0.005$) in addition to DAS28-CRP in the bio-switch group (Table). In the bio-switch group, patients that achieved 20% improvement of MMP-3 at 12 weeks demonstrated significantly higher achievement rate of LDA at 52 weeks compared to those that did not achieved 20% improvement (60.0 vs 33.3%, $p=0.001$) (Figure 2).

Multivariate analysis		
Bio-naïve	adjusted OR (95% CI)	p-value
Age	0.988 (0.955-1.022)	0.479
Male	0.693 (0.305-1.577)	0.382
RF positive	2.172 (0.945-4.990)	0.068
Concomitant MTX	1.769 (0.843-3.709)	0.131
Concomitant PSL	0.609 (0.294-1.262)	0.182
DAS28-CRP	0.544 (0.395-0.748)	<0.001
20% improvement of MMP-3 @12 weeks	1.918 (0.918-4.007)	0.083

Bio-switch	adjusted OR (95% CI)	p-value
Age	0.990 (0.952-1.029)	0.608
Male	1.010 (0.294-3.475)	0.987
RF positive	0.481 (0.151-1.532)	0.216
Concomitant MTX	1.120 (0.459-2.731)	0.803
Concomitant PSL	0.496 (0.202-1.221)	0.127
DAS28-CRP	0.603 (0.432-0.843)	0.003
20% improvement of MMP-3 @12weeks	3.550 (1.454-8.666)	0.005

Conclusion: In the bio-switch patients, we sometimes have difficulty to obtain good clinical response of abatacept and it would be even more important to judge whether to continue abatacept or whether to add other anti-rheumatic drugs as early as possible [3]. Our results suggested that the improvement of MMP-3 at 12 weeks would be a key to predict good clinical effectiveness of abatacept at 1 year. We would be better to note not only the major clinical indices such as DAS28 but also the change of MMP-3 to obtain the best clinical results in the bio-switch patients treated with abatacept.

REFERENCES:

- [1] Harigai M, et al. *Mod Rheumatol* 2016;26(4):491.
- [2] Hattori Y, et al. *Mod Rheumatol* 2018;28:119.
- [3] Takahashi N, et al. *Mod Rheumatol* 2013;23:904.

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FRI0122

REAL-WORLD SAFETY DATA FROM PATIENTS WITH RHEUMATIC DISEASES TREATED WITH CT-P13, AN INFILIXIMAB BIOSIMILAR: AN INTERIM ANALYSIS FROM AN OBSERVATIONAL STUDY

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Background: CT-P13, an infliximab biosimilar, has been available in Europe and Canada since 2015, and real-world experience with CT-P13 is important to support the safety of this medication. PERSIST is an ongoing, observational cohort study evaluating CT-P13 as treatment for rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) in a real-world setting.

Objectives: This interim analysis reports safety outcomes for patients who received CT-P13 as their first biologic (Biologic-naïve) or who switched from infliximab reference product (IFX-RP) to CT-P13 (Switched) based on data collected from September 2015 to December 2017.

Methods: Patients were recruited during usual care at 38 academic and community sites in 6 European countries and Canada. Adult RA, AS or PsA patients prescribed CT-P13 or locally-sourced IFX-RP at the investigator's discretion and according to the approved label were eligible. Data were analysed descriptively.

Results: This analysis included 329 patients (RA, n=134; AS, n=110; PsA, n=85). Of these, 6 (1.8%) were not treated, 3 (0.9%) completed study treatment, 244 (74.2%) were ongoing and 76 (23.1%) discontinued study treatment, most commonly due to lack of response (30 [9.1%]). Demographics and baseline characteristics were generally similar between groups (Table 1). Most treatment-emergent adverse events (TEAEs; Table 2) were of mild or moderate intensity; 7/129 events were severe. Most commonly reported adverse events were related to infection (n=33; 10.2%); most frequently reported infection-related TEAEs were nasopharyngitis (n=6; 1.9%), respiratory tract infection (n=5; 1.5%) and pneumonia (n=4; 1.2%). No case of tuberculosis was reported. Eight (2.5%) patients reported infusion related reactions.

Table 1. Disposition, population characteristics and drug utilisation patterns for patients receiving CT-P13

	Biologic-naïve (n=216)	Switched (n=107)	Total (N=323)
Age, median (range), years	54 (19-84)	53 (23-76)	54 (19-84)
Male, n (%)	97 (44.9)	59 (55.1)	156 (48.3)
Disease duration, median (range), months	45.34 (0.03-563.91)	159.51 (12.65-464.07)	86.77 (0.03-563.91)
Baseline dose			
Patients with data for baseline dose, n	202	102	304
Mean (SD), mg/kg	3.68 (1.05)	3.96 (0.94)	3.78 (1.02)
Baseline infusion frequency, n (%)			
Once every 6 or fewer weeks	72 (33.3)	43 (40.2)	115 (35.6)
Once every 8 weeks	76 (35.2)	44 (41.1)	120 (37.2)
Other	54 (25.0)	15 (14.0)	69 (21.4)
Missing	14 (6.5)	5 (4.7)	19 (5.9)

Table 2. All-causality TEAEs for patients receiving CT-P13

	Biologic-naïve (n=216)	Switched (n=107)	Total (N=323)
Number of TEAEs	87	42	129
Patients with ≥1 event, n (%)			
TEAEs	59 (27.3)	22 (20.6)	81 (25.1)
Serious TEAEs ^a	12 (5.6)	9 (8.4)	21 (6.5)
TEAEs of special interest ^b	18 (8.3)	7 (6.5)	25 (7.7)
Discontinued from study due to adverse events	3 (1.4) ^c	0	3 (0.9)
Deaths	0	0	0

^a Difference between groups due to higher incidence of infections in switched (3.7%) vs biologic-naïve (1.4%).

^b Difference between groups due to higher incidence of infusion related reaction in biologic-naïve (6.0%) vs switched (1.9%).

^c Included hepatobiliary disease, uterine cancer, and psoriasis.

TEAE=treatment-emergent adverse event.

Conclusion: Incidences of TEAEs were similar and there was no discernible pattern across the most common TEAEs between groups. These interim analysis results from the PERSIST study conducted in a real-world setting are consistent with the known safety profile of infliximab and do not demonstrate new safety information to change the benefit-risk profile of CT-P13.

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