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FRI0108

SHORT-TERM EFFICACY OF BCD-089, NOVEL MONOCLONAL ANTI-IL-6 RECEPTOR ANTIBODY, IN COMBINATION WITH METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS: 12-WEEK RESULTS OF PHASE 2 AURORA STUDY

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Background: In the previous phase 1 study BCD-089 (INN: levilimab) was well-tolerated, had favorable safety profile and low immunogenicity¹. Here we report 12-week efficacy and safety results of ongoing phase 2 clinical study of BCD-089 in patients with active RA.

Objectives: This study is aimed to assess efficacy and safety of 2 dosing regimens of BCD-089 in patients with MTX-IR active RA.

Methods: During this multicenter double-blind placebo-controlled randomized clinical study (NCT03455842) 105 MTX-IR patients with active RA (ACR2010) were assigned (1:1:1) to receive 162 mg of BCD-089 s.c. (QW arm and Q2W arm) or PBO. MTX (10-25 mg/week) was used in all groups. After completion of 12-week blinded period patients from QW/Q2W arms continued the treatment, patients from PBO arm were switched to BCD-089 Q2W until Wk56. The primary efficacy endpoint was the rate of ACR20 at Wk12. Secondary endpoints included ACR50/70 and DAS28-CRP(4). The safety was routinely evaluated.

Results: The efficacy analysis showed that 95% confidence interval for BCD-089 treatment effect relative to PBO was [38.45 – 81.55] for QW arm and [16.53 – 63.4] for Q2W arm, which confirms the superiority to PBO of either dosing regimens. Summary of efficacy results is presented in table 1.

The majority of adverse events (AE) were laboratory abnormalities. The spectrum of AEs is similar to other IL6R inhibitors (Table 2). Three serious AE (SAEs) were reported: community-acquired pneumonia (QW arm, treatment-related), acute cholecystitis (PBO arm, not related, did not lead to treatment discontinuation), and acute heart failure leading to death (Q2W arm, not related). One case of moderate local reaction (erythema) was reported in QW arm.

Conclusion: BCD-089 in combination with MTX had superior efficacy compared with MTX plus PBO in MTX-IR patients with active RA. BCD-089 showed safety profile consistent with other IL6R inhibitors. Further clinical studies are needed.

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Table 1. Safety results (full analysis set), n (%)

Efficacy parameter	BCD-089 QW+MTX (n=35)	BCD-089 Q2W+MTX (n=35)	PBO +MTX (n=35)	p-value (Fisher's exact test)
ACR20	27 (77.1%)	20 (57.1%)	6 (17.1%)	<0.0001
ACR50	18 (51.4%)	11 (31.4%)	2 (5.7%)	0.0001
ACR70	10 (28.6%)	7 (20.0%)	1 (2.9%)	0.0106
DAS28-CRP(4) < 3.2	20 (57.1%)	10 (28.6%)	1 (2.9%)	<0.0001

Table 2. Safety results (full analysis set), n (%)

Safety parameter	BCD-089 QW+MTX (n=35)	BCD-089 Q2W+MTX (n=35)	PBO+MTX (n=35)
Any AE	26 (74.29%)	23 (65.71%)	14 (40.0%)
Any SAE	1 (2.86%)	1 (2.86%)	1 (2.86%)
Any grade 3-4 AE	10 (28.57%)	6 (17.14%)	2 (5.71%)

Grade 3-4 Neutropenia	3 (8.57%)	3 (8.57%)	0 (0.00%)
AE of special interest			
ALT/AST increased	4 (11.43%)	5 (14.29%)	1 (2.86%)
Leucopenia/Neutropenia	5 (14.29%)	6 (17.14%)	1 (2.86%)
Infections and infestations	2 (5.71%)	1 (2.86%)	2 (5.71%)
Total cholesterol increased	8 (22.86%)	8 (22.86%)	2 (5.71%)
AEs leading to treatment discontinuation	0 (0.00%)	1 (2.86%)	0 (0.00%)
Deaths	0(0.00%)	1(2.86%)	0(0.00%)

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FRI0109

EFFECTIVENESS AND SAFETY OF INFILIXIMAB, GOLIMUMAB AND GOLIMUMAB-IV IN RHEUMATOID ARTHRITIS PATIENTS FROM A PROSPECTIVE OBSERVATIONAL REGISTRY

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Background: Long-term registries are essential to evaluate new therapies in a patient population that differs from clinical trials and usually varies over time.

Objectives: To describe the profile of rheumatoid arthritis (RA) patients treated with infliximab (IFX), golimumab subcutaneous (GLM) or intravenous (GLM-IV) in Canadian routine care, along with its effectiveness and safety.

Methods: 1577 RA patients treated with IFX, GLM or GLM-IV were enrolled into the Biologic Treatment Registry Across Canada (BioTRAC) between 2006-2015, 2010-2017 and 2014-2017, respectively. Study visits occurred at baseline and every 6 months thereafter. Effectiveness was assessed with changes in TJC28, SJC28, MDGA, PtGA, pain, HAQ, and acute phase reactants. Safety was evaluated with the incidence of adverse events (AEs) and drug survival.

Results: Of the 890 IFX-, 530 GLM- and 157 GLM-IV-treated patients, the proportion of females were 75.7%- 77.1%, the mean age were 55.8-57.7 and the mean disease duration were 6.5-8.6 years. Most patients were bio-naïve (> 80%).

A significant decrease in disease duration and disease activity scores (DAS, TJC, SJC, HAQ, AM stiffness, MDGA, PtGA, CRP, ESR) were observed in the IFX cohort over time (p<0.001). Interestingly, baseline disease duration and disease activity scores for the GLM cohort (DAS, TJC, SJC, PtGA, Pain, CRP, ESR) were higher than in the IFX cohort from 2010-2012 when GLM was first introduced while the mean MDGA remained the same between the two groups.

Treatment with IFX, GLM and GLM-IV significantly improved all disease parameters over time (P<0.001) from baseline to 6 months and up to 120, 78 and 42 months, respectively. The proportion of patients in SDAI remission at 12, 24 and 36 months reached 16.2%, 20.8% and 22.8% in IFX-patients; 34.7%, 47.5% and 52.7% in GLM-patients and 33.8%, 47.5% and 61.9% in GLM-IV-patients (p=0.1978 and p=0.0081 vs IFX).

AEs were reported for 61.5%, 67.4% and 59.2% (105, 113 and 82.6 events/100 PYs) and SAEs for 21.2%, 15.5% and 3.8% (11.7, 34.4 and 9.0 events/100 PYs) covering 2714, 1077 and 257 years of exposure for IFX, GLM and GLM-IV-treated patients, respectively. The most frequently occurring AEs were arthralgia and upper respiratory tract infection (>5%). Eighteen, 7 and 1 deaths occurred among IFX-, GLM- and GLM-IV-treated patients, respectively. The proportion of patients who discontinued treatment were 74.0% over a mean 3.0 years of exposure to IFX-,

52.8% over 2.0 years of exposure to GLM and 45.2% over 1.6 year of exposure to GLM-IV.

Conclusion: In this real-world study of Canadian patients with RA, differences in baseline characteristics between patients treated with an anti-TNF over time and between agents shows potential selection biases when selecting a given therapy and may impact the proportion of patients achieving a target-specific outcome. Treatment significantly reduced disease activity and improved functionality in a similar fashion and were also safe and well tolerated.

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FRI0110 RITUXIMAB BIOSIMILAR NON-MEDICAL SWITCH – DOES IT WORK?

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Background: Since the introduction of anti-TNF biosimilars in routine clinical practice, there has been a drive to implement the switch program for all biosimilars at the point of availability. Rituximab biosimilar was granted marketing authorisation by the EMA in February 2017. Our Trust was one of the first centres to embrace a CQUIN which required adoption of biosimilar within three months for new patients and one year for switchers. This could help deliver significant savings to the NHS whilst achieving similar clinical outcomes.

Objectives: We report our early experience of introducing rituximab biosimilar in people with RA.

Methods: A list of all patients prescribed rituximab was extracted through our database. A 'switch' letter was drafted and sent to all patients including Truxima information sheet. Patients were given the opportunity to contact nurse helpline for information or if disease control worsened/adverse effects developed. We reviewed all relevant records and collected data on any adverse events and disease outcome on either side of the switch. Patients were reviewed as originally planned by their respective clinicians.

Results: 44 patients with RA on 2 g dose six-monthly were identified established on rituximab. Four had stopped treatment prior to switching. All 40 agreed to switch to Truxima that was completed by February 2018. Mean age of switchers was 58.6 (range 26-80 years). Eight were men and remaining 32 (80%) were women. Fourteen (35%) were Asian, one Afro-Caribbean and the rest (62%) were White Caucasian. DAS28 scores were available for all participants. Prior to the switch median DAS28 was 3.0 (range 0.6-5.1). Following the switch it was 2.95 (range 1.5-5.7). Amongst these, eight (20%) reported adverse effects. Four had serum sickness reaction within the first week of the second dose with loss of efficacy. One required admission to ED (<24 hrs) for further management. All decided against further biosimilar and three were swapped back to the originator with no further concerns. In one case the clinician decided to change the class of drug to a TNF inhibitor. Three patients had mild intolerance and agreed to continue Truxima with no further issues. One patient developed military tuberculosis and was taken off biologic therapy.

Adverse events related to Rituximab biosimilar switch

Age	Gender	Previous Mabthera Cycles	Prior DAS28	Post switch DAS28	Adverse effects	Final drug choice
39	F	1	3.5	5.1	Gen unwell, achy, flu like symptoms	Humira
70	M	3	2.1	1.8	Itchy scalp, brain fog	Truxima
49	F	2	4.4	2.8	Vomiting, diarrhoea	Mabthera
48	F	2	3.1	5.5	Palpitations, dizziness	Mabthera
48	F	4	1.8	2.8	Headache, flushing	Truxima
58	F	4	4.5	5.1	Nausea, flushing, headache	Truxima
37	F	5	3.5	4.5	Body pains, headache, distaste, lethargy (hospitalised)	Mabthera
76	F	1	2.2	2.5	Miliary TB	Biologic withdrawn

Conclusion: Our experience of switching rituximab patients is certainly not as smooth as it was for infliximab and etanercept. All were happy to switch after receiving a letter and having the opportunity to contact if necessary. Substantial annual cost savings of nearly £140,000 were achieved once the switch process completed. At group level there were no major differences in disease outcomes. However, 10% had severe serum sickness reaction with loss of efficacy and loss of confidence in the drug. One patient developed military TB despite having one previous originator cycle with no issues. We support the routine switching from originator to biosimilar rituximab however close monitoring is required certainly in the first few weeks of dose administration.

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FRI0111 ASSOCIATION BETWEEN RHEUMATOID FACTOR STATUS AND DISCONTINUATION OF TUMOR NECROSIS FACTOR INHIBITORS DUE TO INEFFECTIVENESS IN RHEUMATOID ARTHRITIS

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Background: As for the treatment of rheumatoid arthritis (RA), the influence of rheumatoid factor (RF) positivity on the long-term efficacy of tumor necrosis factor inhibitors (TNFi) is controversial.

Objectives: We conducted an exploratory study in a large cohort of RA patients to evaluate the relationship between RF status and the discontinuation of TNFi treatment due to ineffectiveness in a clinical setting.

Methods: This study included bio-naïve RA patients enrolled in the Tsurumi Biologic Communication Registry in Japan. The crude comparison of TNFi discontinuation due to ineffectiveness between seropositive and seronegative patients was analyzed using the cumulative incidence function of competing events and Gray test. We assessed the associations between baseline patient characteristics and discontinuation of TNFi therapy due to insufficient response using Fine-Gray proportional hazard regression. Fine-Gray proportional hazard analysis considered competing events of interest, including insufficient response, adverse event, palliation, and personal reasons.

Results: Demographic and clinical characteristics of each group are described in Table 1. There was a higher discontinuation rate due to insufficient response in RF positive patients than in RF negative patients using Gray test (Figure). RF positivity was significantly predictive of the discontinuation of TNFi therapy due to ineffectiveness using Fine-Gray proportional hazard regression analysis after adjusting for baseline characteristics, including age, sex, stage, class, disease activity at baseline, methotrexate use, and prednisolone use (Table 2).