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Rheumatoid arthritis - anti-TNF therapy

FRI0178 RITUXIMAB IS EFFECTIVE IN THE TREATMENT OF RHEUMATOID ARTHRITIS REGARDLESS OF BODY MASS INDEX

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Background: High body mass index (BMI) is known to be associated with inadequate clinical response to anti-TNF agents in rheumatoid arthritis (RA) patients.[1] However, there are limited data on the effect of high BMI on the response to rituximab in RA patients, who showed an inadequate response or intolerance to anti-TNF agents.
Objectives: To investigate the impact of BMI on clinical response in the post-hoc analysis of randomized controlled trial that demonstrated clinical equivalence between a biosimilar of rituximab, CT-P10 and innovator rituximab, RTX[2] (NCT02149121).
Methods: A total of 332 patients who received two courses of either CT-P10 or RTX were included in this analysis. Patients were classified into 3 groups; normal weight (<25kg/m^2), overweight (≥25 kg/m^2 ~<30 kg/m^2) and obesity (≥30 kg/m^2) as per WHO BMI category. Improvement in disease activity by the Disease Activity Score using C-reactive protein (DAS28-CRP), remission (≤2.6), low disease activity rate (LDA, ≤3.2) and ACR response at Week 24 (Week 24 of 1st course) and Week 48 (Week 24 of 2nd course) and duration of sustained LDA (from the first LDA observed to the last LDA observed up to Week 48) were analysed by BMI categories in the each and combined group of CT-P10 and RTX.
Results: In the pooled group of CT-P10 and RTX, the mean weights were 59 kg in normal weight, 73kg in overweight and 91kg in obesity. All other baseline characteristics were comparable among BMI groups including baseline disease activity based on DAS28; Moderate disease activity, 22.3% vs. 22.8% vs. 25.7%, respectively; High disease activity, 77.7% vs. 77.2% vs. 74.3%, respectively. There was no statistical difference among BMI groups in terms of DAS28 change from baseline and ACR 20/50/70 response (Table). No particular trend was observed in remission and LDA rate by DAS28 at Week 24 and Week 48 among BMI groups (Figure). Mean duration of sustained LDA (months) were also comparable among the groups (4.5 vs. 4.7 vs. 5.0, respectively). Additionally, similar trends in all analyses were observed in each treatment group; CT-P10 and RTX.
Conclusions: The BMI does not affect the clinical response in RA patients with rituximab treatment. Therefore, this result supports that rituximab could be a reasonable therapeutic option for obese RA patients with inadequate response to anti-TNF agents.

Table 1. DAS28, ACR responses by BMI subgroups

Parameter	Visit	Normal (N=148)	Over weight (N=114)	Obesity (N=70)
DAS28, mean (SD)	Baseline	5.88 (0.95)	5.81 (0.89)	5.69 (0.78)
	Week 24*	-2.43 (1.12)	-2.13 (1.19)	-2.39 (0.99)
	Week 48*	-2.76 (1.31)	-2.47 (1.32)	-2.74 (1.01)
ACR20, n (%)	Week 24	122 (82.4%)	86 (75.4%)	56 (80.0%)
	Week 48	119 (80.4%)	88 (77.2%)	60 (85.7%)
ACR50, n (%)	Week 24	80 (54.1%)	56 (49.1%)	39 (55.7%)
	Week 48	76 (51.4%)	62 (54.4%)	43 (61.4%)
ACR70, n (%)	Week 24	51 (34.5%)	33 (28.9%)	21 (30.0%)
	Week 48	47 (31.8%)	36 (31.6%)	26 (37.1%)

*Change from baseline.

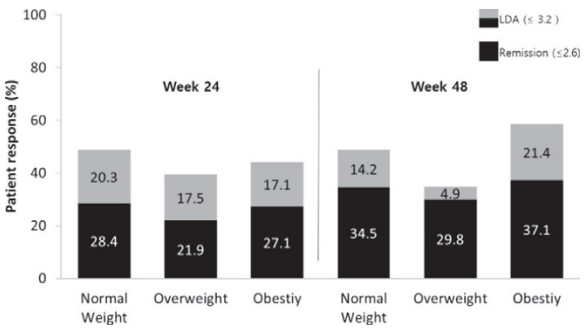

Figure 1. Remission and LDA by DAS28 by BMI group.

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FRI0179 MINIMAL TO NO TRANSFER OF CERTOLIZUMAB PEGOL INTO BREAST MILK: RESULTS FROM CRADLE, A PROSPECTIVE, POSTMARKETING, MULTICENTER, PHARMACOKINETIC STUDY

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Background: Women with active chronic rheumatic inflammatory conditions (RA, PsA, AxSpA) often face uncertainty regarding the safety of the use of biologics during breastfeeding.[1] Limited and non-validated data exist on the potential transfer of anti-TNFs into breast milk.[2] CRADLE (NCT02154425) was the first sponsored study to evaluate certolizumab pegol (CZP) concentrations in breast milk, and to estimate the Average Daily Infant Dose (ADID) of maternal CZP.
Objectives: To determine the concentration of CZP in breast milk and calculate the ADID of maternal CZP.
Methods: CRADLE was a pharmacokinetic study of lactating mothers (≥6 weeks postpartum) receiving commercial CZP. Decision to treat with CZP and breastfeed was independent of study participation. At steady state (≥3 CZP doses), breast milk samples were collected on Days 0, 2, 4, 6, 8, 10, 12, 14 (±28) from each mother across 1 dosing period. CZP was detected using a highly sensitive, CZP-specific electrochemiluminescence immunoassay validated in milk (lower limit of quantification [LLOQ]=0.032 μg/mL; 10-fold lower than previous assays). CZP stability in milk was confirmed.
Results: 18 CZP-treated mothers were screened: 17 entered the sampling period; 16 on CZP 200 mg Q2W; 1 on CZP 400 mg Q4W (7 RA; 5 SpA; 5 CD; Table A). Samples from 4/17 mothers had no measurable CZP in breast milk; 13/17 had quantifiable levels for at least 1 time point (highest concentration: 0.076 μg/mL; Table B). Estimated ADID ranged 0–0.0104 mg/kg/day; median Relative Infant Dose (RID; calculated post hoc[3]): 0.15%. Infants of CZP-exposed mothers had a

Table A: Baseline characteristics of mothers and infants

Mean (SD), unless otherwise stated	All mothers (N=18) [a]
Age, years	33.7 (4.2)
Weight, kg	68.9 (9.6)
BMI, kg/m²	23.6 (3.0)
Indication for CZP treatment, n [b]	
Rheumatoid arthritis	7
Psoriatic arthritis	3
Axial spondyloarthritis/ankylosing spondylitis	2
Crohn's disease	5
Infant age at mother's first sample, n (%)	**All infants (N=17)**
≤6 months	13 (76.5)
>6 months–≤12 months	2 (11.8)
>12 months–≤18 months	2 (11.8)

[a] Includes 1 screen failure; [b] n=17.

Table B: Concentrations of CZP (μg/mL) in breast milk

Mother no.	Relative time (days) 0	2	4	6	8	10	12	14	28
5	0.056	0.069	0.074	0.076	0.076	0.069	0.069	0.06	–
1	0.057	0.051	0.066	0.065	0.062	0.056	0.052	0.041	–
9	0.039	0.04	0.047	0.045	0.042	0.043	0.038	0.035	–
3	BLQ	0.032	0.049	0.053	0.037	0.037	0.033	0.033	–
16	0.04	0.033	0.036	0.037	0.043	BLQ	BLQ	BLQ	–
11	BLQ	BLQ	0.051	0.038	0.042	BLQ	0.033	BLQ	–
2	BLQ	BLQ	0.035	0.037	0.041	BLQ	0.043	BLQ	–
15	BLQ	BLQ	0.041	0.034	0.033	BLQ	0.037	BLQ	–
10	BLQ	BLQ	BLQ	0.033	0.042	0.042	BLQ	BLQ	–
8	BLQ	BLQ	0.035	0.034	0.043	BLQ	BLQ	BLQ	–
12	BLQ	BLQ	0.034	0.037	0.033	BLQ	BLQ	BLQ	–
6	BLQ	BLQ	0.044	0.048	BLQ	BLQ	BLQ	BLQ	–
7	BLQ	BLQ	BLQ	BLQ	BLQ	0.035	BLQ	BLQ	–
4	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	–
13	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	–
14	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	–
17	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ

Less than 3×LLOQ (<0.096 μg/mL)
Less than 2×LLOQ (<0.064 μg/mL)
BLQ (<0.032 μg/mL)
CZP plasma C_{trough} from the RAPID2 study: 15.7 μg/mL

BLQ: below the lower limit of quantification; LLOQ: lower limit of quantification.

safety profile consisting of events occurring in unexposed infants of similar age.
Conclusions: CZP was below the lower limit of quantification in 56% of the milk samples. When detectable, CZP concentrations were less than 3x LLOQ (<1% of expected plasma concentration of a therapeutic dose[4]), indicating no to minimal transfer of CZP from plasma to breast milk. RID was below 0.5% of maternal dose; <10% is unlikely to be of clinical concern.[3] CZP absorption via breast milk is unlikely, due to low bioavailability and its Fc-free molecular structure. These findings support continuation of CZP treatment during breastfeeding.
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FRI0180 MULTIPLE SCLEROSIS RISK-ALLELES STUDY IN PATIENTS WITH DEMYELINATING SIDE EFFECTS ON ANTI TNF ALPHA THERAPY

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Background: Tumor Necrosis Factor alpha (TNFα) is a key cytokine in inflammatory rheumatic diseases. TNF inhibitors (TNFi) has revolutionized treatment of rheumatic diseases, but may cause flares of multiple sclerosis (MS). Two Single Nucleotide Polymorphisms, (SNPs) *rs1800693* and *rs4149584*, located within *TNF receptor superfamilly 1* (*TNFRSF1A*) locus have been shown to increase the risk of developing MS [1]. The rs1800693*G allele leads to a dysfunctional TNFα soluble receptor that inhibits TNFα signaling while *rs4149584* is involved in TNF receptor associated periodic syndrome.
Objectives: The aim of this study was to look for a possible the association between *TNFRSF1A* polymorphisms and demyelinating complications occurring during TNFi therapy.
Methods: Patients who presented with a demyelinating disorder (central or peripheral involvement) while treated with TNFi (cases), were recruited between March 2013 and December 2015, through the physicians involved in the CRI ("Club Rhumatismes et Inflammation") a nationwide network of the French Society of Rheumatology. Rheumatoid arthritis patients treated with TNFi, from the French ReAct cohort, and who did not develop demyelinating complication constituted the control population (n=294). The frequency of *rs1800693* and *rs4149584* TNFRSF1A SNPs were compared between cases and controls.
Results: Twenty-four cases with demyelinating disorders, recruited from 11 centers with a median age of 39.7 years (range 30.4–75.8); of which 16 (67%) were females were included in the study. Neurological symptoms occurred after a median of 18.3 (1–66) months of anti TNFi; 15 (62.5%) had central neurologic involvement and 9 (37.5%) had peripheral involvement. The median follow-up was 26 (4–54) Months. No significant difference in the frequency of the *rs1800693* MS risk-alleles (39,5% for cases vs 38,6% for controls) was observed. Similarly no difference was observed between cases (2%) and controls (4%) for *rs4149584.*
Conclusions: This study was unable to show an association between MS-associated SNPs within *TNFRSF1A* locus and the occurrence of demyelination while taking TNFi, suggesting that demyelination might be linked to other genetic factors or other pathways.
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FRI0181 TAPERING OR CESSATION OF ANTIVIRAL AGENT IN HEPATITIS B VIRUS-INFECTED PATIENTS CONCOMITANTLY TREATED WITH BIOLOGIC AGENTS

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Background: Clinicians generally prescribe antiviral agents to patients with chronic hepatitis B (CHB) or to inactive carriers of the virus until 6–12 months after the cessation of biologic agents. However, the current antiviral prophylaxis regimen, in addition to biological therapy, is expensive and poses an economic burden to both patients and societies. We have had patients in our medical center quit or reduce antiviral prophylaxis due to economic reasons.
Objectives: To assess the outcome of tapering or discontinuation of antiviral agents in patients who were infected with hepatitis B virus (HBV) during biologic therapy.
Methods: We identified 45 patients who were infected with HBV and treated with biologic agents concomitantly from January 2005 to December 2016. They were diagnosed with rheumatoid arthritis (n=20), Crohn's disease (n=13), ankylosing spondylitis (n=8), ulcerative colitis (n=3), and psoriatic arthritis (n=1). The criteria of HBV reactivation was a 10-fold rise in HBV DNA compared with previous HBV DNA titers, resulting in HBV DNA of greater than 20,000 IU/ml (HBeAg-positive patients) or 2,000 IU/ml (HBeAg-negative patients), and an increase in AST or ALT to more than twice the upper normal limit (40 IU/l).
Results: Sixteen CHB patients and 29 inactive carriers were treated with biologic agent for 4.1±2.7 years. No reactivation case was observed in 23 patients (10 of CHB and 13 of inactive carrier) who maintained antiviral prophylaxis for 4.0±2.3 years. Among them, 4 patients (3 treated with infliximab and 1 with adalimumab) taking antiviral prophylaxis regimen on alternate days did not experience HBV reactivation for 28–42 months of follow-up period. In the discontinuation group (n=9), no reactivation case was observed in all inactive carrier patients (2 treated with etanercept, 1 with infliximab, and 1 with rituximab) after discontinuation of antiviral prophylaxis for 6–33 months of follow-up period. In contrast, 3 patients (2 treated with etanercept and 1 with adalimumab) among the 5 patients with CHB experienced reactivation after discontinuation of antiviral prophylaxis for 3–29 months of follow-up period.
Conclusions: During biologic therapy, HBV reactivations were frequently found in CHB patients who ceased to take antiviral prophylaxis. However, no reactivation after the cessation of prophylaxis was found in inactive carrier patients who were previously treated with prophylaxis. Based on our experience, tapering or discontinuation of antiviral agent in inactive carriers with economic problem undergoing concomitant biologic agent therapy could be considered viable, albeit with caution.
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FRI0182 DISEASE WORSENING AND SAFETY IN PATIENTS SWITCHING FROM ORIGINATOR INFLIXIMAB TO BIOSIMILAR INFLIXIMAB (CT-P13) IN THE NOR-SWITCH STUDY: EXPLORATIVE ANALYSIS OF RA PATIENTS

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Background: The NOR-SWITCH study was a 52-week randomized, double-blind, non-inferiority, phase IV switch trial in patients with Crohn's disease (CD), ulcerative colitis (UC), spondyloarthritis (SpA), rheumatoid arthritis (RA), psoriatic arthritis (PsA) and plaque psoriasis (Ps) on stable treatment with originator infliximab (Remicade®, INX) and was funded by the Norwegian government. Previously, the primary analyses of the pooled indications have been published[1].
Objectives: To investigate efficacy, safety and immunogenicity in RA patients treated with continous INX vs patients switched to CT-P13 (biosimilar infliximab, Remsima®) in the NOR-SWITCH study (explorative analyses).
Methods: Patients were randomized 1:1 to continued INX or switch to CT-P13. Serum drug levels were analysed in automated in-house assay. The primary