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OP0017 THERAPEUTIC DRUG MONITORING COMPARED TO STANDARD TREATMENT OF PATIENTS STARTING INFLIXIMAB THERAPY: RESULTS FROM A MULTICENTRE RANDOMISED TRIAL OF 400 PATIENTS

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Background: A lack or loss of response to TNFα inhibitors (TNFi) has been associated with low serum drug levels and formation of anti-drug antibodies (ADAb). Therapeutic drug monitoring (TDM), an individualised treatment strategy based on regular assessments of serum drug levels, has been suggested to optimise efficacy of TNFi. It is still unclear if TDM improves clinical outcomes, and the value of TDM has recently been included in the research agenda across different specialities. This first randomised controlled trial on the effectiveness of TDM in a range of immune mediated inflammatory diseases including rheumatic diseases, the NORwegian DRUg Monitoring trial part A (NOR-DRUM (A)) focus on the induction period of infliximab (INX) treatment.
Objectives: To assess if TDM is superior to standard treatment in order to achieve remission in patients starting INX.
Methods: In the investigator-initiated, randomised, open-label, multicentre NOR-DRUM (A) study, adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), spondyloarthritis (SpA), ulcerative colitis (UC), Crohn's disease (CD) and psoriasis (Ps) starting INX therapy were randomly assigned to administration of INX according to a treatment strategy based on TDM (TDM arm) or to standard administration of INX without TDM (control arm). Study visits were conducted at each infusion. The primary endpoint was remission at week 30. In the TDM arm, the dose and interval were adjusted according to INX trough levels to reach the therapeutic range (Figure 1). If the patient developed significant levels of ADAb, INX was terminated. To guide the investigators, the TDM strategy was integrated in an interactive eCRF. The primary endpoint was analysed by mixed effect logistic regression in the full analyses set (FAS), adjusting for diagnoses. Infections and infusion reactions were specified as adverse events (AEs) of special interest. Clinical trial.gov: NCT03074656
Results: We enrolled 411 patients at 21 study centres between January 2017 and December 2018. 398 patients (RA 80, PsA 42, SpA 117, UC 80, CD 57, Ps 22) received the allocated strategy and were included in the FAS population. Demographic and baseline characteristics were comparable in both arms. TDM was not found to be superior to standard treatment with regard to the primary outcome. Remission at week 30 was reached in 100 (53%) and 106 (54%) of the patients in the TDM and control arm, respectively (adjusted difference, 1.5%; 95% confidence interval (CI), -8.2 to 11.1, p=0.78) (Figure 2). Consistent results were shown for all the secondary endpoints (Figure 3) and in the sensitivity analyses. Twenty patients (10%) in the TDM arm and 30 patients (15%) in the control arm developed significant levels of ADAb. The number of adverse events (AE) was similar in both groups, however infusion reactions were less frequent (5 patients (2.5%) vs 16 patients (8.0%)) in the TDM arm (difference 5.5% (95% CI 1.1, 9.8%))
Conclusion: NOR-DRUM (A) is the first randomised trial to address effectiveness of TDM in the induction period of TNFi treatment, and the first trial to address TDM in rheumatic diseases. In this study, TDM was not superior to standard treatment in order to achieve remission. Although improved safety is indicated by a reduction in infusion reactions, implementation of TDM as a general strategy in the induction period of INX is not supported by the NOR-DRUM (A) study.

Figure 1 Treatment strategy in the TDM arm

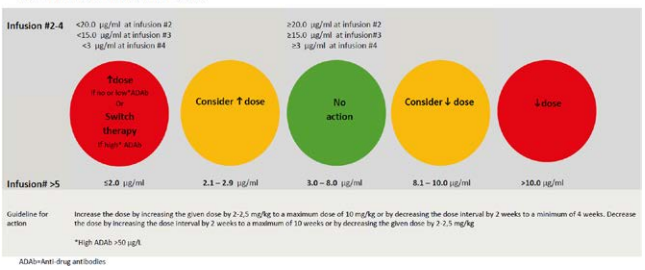
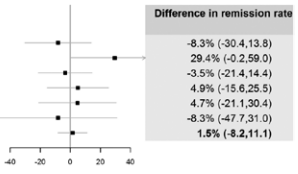


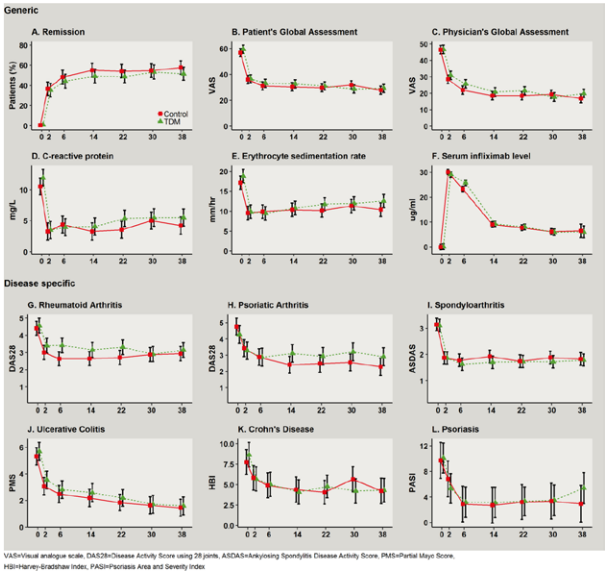
Figure 2. Difference in remission rate, overall and by disease

	TDM (n=198)	Control (n=200)	Difference in remission rate
Rheumatoid Arthritis	21/36 (58.3%)	21/42 (50.0%)	-8.3% (-30.4,13.8)
Psoriatic Arthritis	5/18 (27.8%)	12/21 (57.1%)	29.4% (-0.2,59.0)
Spondyloarthritis	23/57 (40.4%)	21/57 (36.8%)	-3.5% (-21.4,14.4)
Ulcerative Colitis	25/38 (65.8%)	29/41 (70.7%)	4.9% (-15.6,25.5)
Crohn's Disease	17/28 (60.7%)	17/26 (65.4%)	4.7% (-21.1,30.4)
Psoriasis	9/12 (75.0%)	6/9 (66.7%)	-8.3% (-47.7,31.0)
Overall	**100/189 (52.9%)**	**106/196 (54.1%)**	**1.5% (-8.2,11.1)**



TDM=Therapeutic drug monitoring arm, Control=Standard therapy arm

Figure 3. Generic (A-F) and disease specific (G-L) composite measures over study period.



VAS=Visual analogue scale, DAS28=Disease Activity Score using 28 joints, ASDAS=Ankylosing Spondylitis Disease Activity Score, PMS=Partial Mayo Score, HBI=Harvey-Bradshaw Index, PASI=Psoriasis Area and Severity Index

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LB0001 EFFICACY AND SAFETY OF UPADACITINIB VERSUS PLACEBO AND ADALIMUMAB IN PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS AND INADEQUATE RESPONSE TO NON-BIOLOGIC DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS (SELECT-PSA-1): A DOUBLE-BLIND, RANDOMIZED CONTROLLED PHASE 3 TRIAL

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Background: Upadacitinib (UPA) is an oral, reversible, JAK inhibitor approved for treatment of rheumatoid arthritis (RA) and currently under evaluation for treatment of psoriatic arthritis (PsA).
Objectives: To assess the efficacy and safety of UPA vs placebo (PBO) and adalimumab (ADA) in patients (pts) with PsA and prior IR or intolerance to ≥1 non-biologic DMARD (non-bDMARD).
Methods: Pts with active PsA (≥3 swollen and ≥3 tender joints), active or historical psoriasis, and on ≤2 non-bDMARDs were randomized 1:1:1:1 to once daily UPA 15mg (UPA15), UPA 30mg (UPA30), ADA 40mg every other week, or PBO. The primary endpoint was the proportion of pts achieving ACR20 for UPA vs PBO at Wk 12. Multiplicity controlled secondary endpoints for each dose of UPA vs PBO included change in HAQ-DI, FACIT-F, and SF-36 PCS (Wk 12); static Investigator Global Assessment of Psoriasis of 0 or 1, PASI75, and change in Self-Assessment of Psoriasis Symptoms (Wk 16); change in modified Sharp/van der Heijde Score (mTSS), proportion of pts achieving MDA, and resolution of enthesitis (LEI=0) and dactylitis (LDI=0) (Wk 24). For each dose of UPA, the multiplicity-controlled analysis also included non-inferiority and superiority vs ADA for ACR20 and superiority for HAQ-DI and pt's assessment of pain NRS (Wk 12). ACR50/70 at Wk 12 and ACR20 at Wk 2 were additional secondary endpoints. Treatment-emergent adverse events (TEAEs) through 24 wks are reported for pts who received ≥1 dose of study drug.
Results: 1705 pts were randomized; 1704 received study drug (53.2% female, mean age 50.8 yrs, mean duration of PsA diagnosis 6.1 yrs). 82% were on ≥1 concomitant non-bDMARD, of whom 84% received MTX +/- another non-bDMARD. At Wk 12, ACR20 rates were 70.6% with UPA15 and 78.5% with UPA30 vs 36.2% with PBO ($p < .001$ for UPA15/30 vs PBO) and 65.0% with ADA (non-inferiority, $p < .001$ for UPA15/30 vs ADA; superiority, $p < .001$ for UPA30 vs ADA). A greater proportion of pts achieved ACR50/70 with UPA15/30 vs PBO and UPA30 vs ADA. Improvements were observed with UPA15/30 vs PBO for all multiplicity controlled secondary endpoints and for UPA 15/30 vs ADA for HAQ-DI and UPA 30 vs ADA for improvement in pain (**Figure 1A-1B**). At Wk 24, change in mTSS was 0.25 for PBO, -0.04 for UPA15, 0.03 for UPA30, and 0.01 for ADA ($p < 0.001$ for UPA15/30 vs PBO). The rates of TEAEs and serious AEs, including serious infections, were similar in the PBO, UPA15, and ADA arms and higher with UPA30 (**Figure 2**). The rate of herpes zoster was similar for PBO and UPA15/30. No MACE was reported with UPA. One malignancy occurred in each of the PBO and UPA15 arms, and 3 malignancies were reported in each of the UPA30 and ADA arms. VTE were reported in 1 pt on PBO, 1 pt on UPA30, and 2 pts on ADA. One death occurred in the PBO arm.
Conclusion: In this non-bDMARD-IR PsA population, treatment with UPA15/30 demonstrated improvement in musculoskeletal symptoms, psoriasis, physical function, pain, and fatigue and inhibited radiographic progression; improvements were observed by Wk 2. At Wk 12, UPA15/30 were non-inferior to ADA for ACR20, with superiority demonstrated for UPA30. Greater percentages of UPA vs PBO pts achieved stringent measures of disease control (MDA, ACR50/70, sIGA 0/1). No new safety signals were identified compared with the safety profile observed in RA.

Figure 1. Efficacy Outcomes

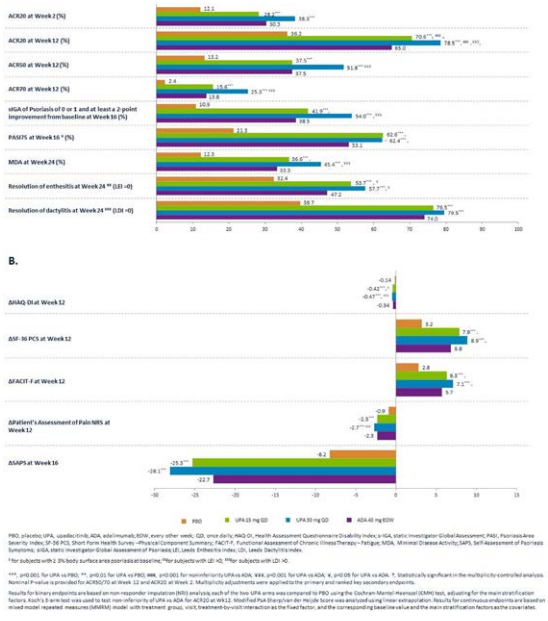
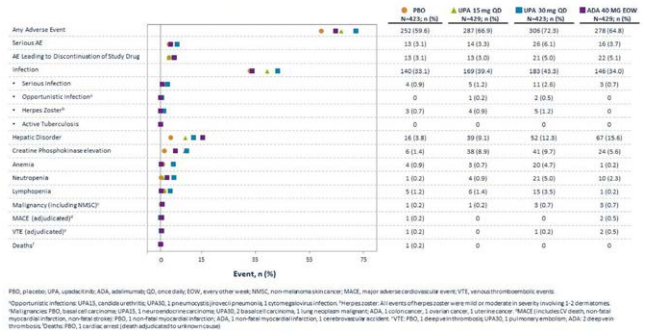


Figure 2. Safety Summary Through Week 24



PBO, placebo; UPA, upadacitinib; ADA, adalimumab; QD, once daily; EOW, every other week; NMSC, non-melanoma skin cancer; MACE, major adverse cardiovascular event; VTE, venous thromboembolic events

†Opportunistic infections: UPA15, candida urethritis; UPA30, 1 pneumocystis jirovecii pneumonia, 1 cytomegalovirus infection. ‡Herpes zoster: All events of herpes zoster were mild or moderate in severity involving 1-2 dermatomes. §Malignancies: PBO, basal cell carcinoma; UPA15, 1 neuroendocrine carcinoma; UPA30, 2 basal cell carcinoma, 1 lung neoplasm malignant; ADA, 1 colon cancer, 1 ovarian cancer, 1 uterine cancer. ¶MACE (includes CV death, non-fatal myocardial infarction, non-fatal stroke): PBO, 1 non-fatal myocardial infarction; ADA, 1 non-fatal myocardial infarction, 1 cerebrovascular accident. #VTE: PBO, 1 deep vein thrombosis; UPA30, 1 pulmonary embolism; ADA: 2 deep vein thrombosis. ‖Deaths: PBO, 1 cardiac arrest (death adjudicated to unknown cause)

Disclosure of Interests: Iain McInnes: None declared, Jaclyn Anderson Shareholder of: AbbVie Inc., Employee of: AbbVie Inc., Marina Magrey Grant/research support from: Amgen, AbbVie, and UCB Pharma, Consultant of: Novartis, Eli Lilly, Pfizer, and Janssen, Joseph F. Merola Consultant of: Merck, Abbvie, Dermavant, Eli Lilly, Novartis, Janssen, UCB, Celgene, Sanofi, Regeneron, Arena, Sun Pharma, Biogen, Pfizer, EMD Sorono, Avotres and Leo Pharma, Yi Liu: None declared, Mitsumasa Kishimoto Consultant of: bbVie, Eli Lilly, Celgene, Pfizer, Gilead, Janssen, and UCB Pharma, Speakers bureau: AbbVie, Eisai, Celgene, Pfizer, Novartis, Eli Lilly, Tanabe-Mitsubishi, Ayumi, Janssen, Astellas, and UCB Pharma, Sławomir Jeka Speakers bureau: AbbVie, Pfizer, Roche, Novartis, MSD, Sandoz, Eli Lilly, Egis, UCB, Celgene, Cesar Francisco Pacheco Tena: None declared, xin wang Shareholder of: AbbVie Inc., Employee of: AbbVie Inc., Liang Chen Shareholder of: AbbVie Inc., Employee of: AbbVie Inc., Patrick Zueger Shareholder of: AbbVie Inc., Employee of: AbbVie Inc., Aileen Pangan Shareholder of: AbbVie Inc., Employee of: AbbVie Inc., Frank Behrens Grant/research support from: Pfizer, Janssen, Chugai, Celgene and Roche, Consultant of: Pfizer, AbbVie, Sanofi, Lilly, Novartis, UCB, Genzyme, Boehringer, Janssen, MSD, Celgene, Roche and Chugai
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Biological DMARDs in RA I

OP0018

A MULTICENTER RANDOMIZED STUDY IN EARLY RHEUMATOID ARTHRITIS TO COMPARE ACTIVE CONVENTIONAL THERAPY VERSUS THREE BIOLOGICAL TREATMENTS: 24 WEEK EFFICACY RESULTS OF THE NORD-STAR TRIAL

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Background: The optimal first-line treatment of patients (pts) with early rheumatoid arthritis (RA) is yet to be established.
Objectives: The primary aim was to assess and compare the proportion of pts who achieved remission with active conventional therapy (ACT) and with three different biologic therapies after 24 wks. Secondary aims were to assess and compare other efficacy measures.
Methods: The investigator-initiated NORD-STAR trial (NCT01491815) was conducted in the Nordic countries and Netherlands. In this multicenter, randomized, open-label, blinded-assessor study pts with treatment-naïve, early RA with DAS28>3.2, and positive RF or ACPA, or CRP >10mg/L were randomized 1:1:1:1. Methotrexate (25 mg/week after one month) was combined with: 1) (ACT): oral prednisolone (tapered quickly); *or*: sulphasalazine, hydroxychloroquine and mandatory intra-articular (IA) glucocorticoid (GC) injections in swollen joints <wk 20; 2) certolizumab 200 mg EOW SC (CZP); 3) abatacept 125 mg/wk SC (ABA); tocilizumab 162 mg/wk SC (TCZ). IA GC was allowed in all arms <wk 20. Primary outcome was clinical disease activity index remission (CDAI≤2.8) at wk 24. Secondary outcomes included CDAI remission over time and other remission criteria. Dichotomous outcomes were analyzed by adjusted logistic regression with non-responder imputation (NRI). Non-inferiority analyses had a pre-specified margin of 15%.
Results: 812 pts were randomized. Age was 54.3±14.7 yrs (mean±SD), 31.2% were male, DAS28 5.0±1.1, 74.9% were RF and 81.9% ACPA positive. Fig 1 shows the adjusted CDAI remission rates over time with 95% CI. Table shows crude remission and response rates and absolute differences in adjusted