OP0022 TNFI AND TOFACITINIB MONOTHERAPY AND COMPARATIVE EFFECTIVENESS IN CLINICAL PRACTICE: RESULTS FROM CORRONA REGISTRY

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Background: TNF inhibitors (TNFi) can be used as monotherapy (mono) or in combination (combo) with conventional DMARDS (cDMARDS). Data from randomized clinical trials and European registries suggest there is evidence of better effectiveness of TNFi combo therapy than mono. Effectiveness of TNFi mono vs combo in US clinical practice, in particular among biologic naïve and experienced patients, has not been assessed. There have also been no assessments of tofacitinib (tofa) mono vs tofa combo nor tofa mono vs TNFi combo in US clinical practice. Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA.
Objectives: This study quantifies the prevalence and effectiveness of TNFi monotherapy use compared to TNFi combination therapy by line of therapy in US clinical practice. Secondary objectives were to compare tofa monotherapy use and effectiveness separately to tofa combo and to TNFi combo therapies.
Methods: RA patients initiating a TNFi (adalimumab, etanercept, infliximab, golimumab, certolizumab pegol) or tofa with a six month follow-up in Corrona US were identified. A subcohort of TNFi initiations after 11/6/2012 (market approval of tofa) were used for comparisons with tofa initiators. We defined combo therapy as TNFi or tofa used with MTX only and mono as no use of any cDMARD. The primary outcome was achieving LDA (low disease activity) or remission based on CDAI ($\leq$10) at 6 months. Patients switching to another biologic prior to 6 months were defined as non-responders. Secondary outcomes included modified ACR20/50/70 and mean change in CDAI. Combo and mono initiators were matched within line of therapy using a propensity score. Covariates for the model were selected if the standardized mean difference between the groups $>$0.1.
Results: From 10/2001 to 8/2016 there were 7976 eligible TNFi initiations in Corrona, with 2511 (31%) mono initiations. Mono by line of therapy was 21%, 36% and 42% for 2nd, 3rd and 4th line therapy, respectively. There were 555 tofa initiations with 338 (61%) mono and mono rates of 47%, 58% and 63% for 2nd, 3rd and 4th line therapy, respectively. In the matched populations, across outcome measures (Table 1), TNFi combo was more effective than TNFi mono in 2nd line therapy (55.6% LDA vs 47.1% LDA) and differences diminished with 3rd line (43.2% vs 36.6%) and 4th line (32.0% vs 34.0%). Tofa combo therapy was similar to mono in the matched 3rd and 4th + line populations combined (35.2% LDA vs 31.1% LDA). Tofa mono was similar to TNFi combo therapy in the matched 3rd and 4th + line populations combined (33.6% LDA vs 37.5% LDA).

Table 1 Matched Patients		TNF Combo vs TNF Mono			Tofa Combo vs Tofa Mono	TNFi Combo vs Tofa Mono
		2nd line* (n=1206)	3rd line* (n=1180)	4th line* (n=800)	3rd and 4th line (n=244)	3rd and 4th line (n=304)
LDA	OR [95% CI]	1.3 [1.0-1.6]	1.3 [1.0-1.7]	0.9 [0.7-1.2]	1.2 [0.7-2.1]	1.2 [0.7 – 1.9]
mACR20	OR [95% CI]	1.2 [1.0-1.6]	1.2 [0.9-1.6]	1.2 [0.9-1.7]	0.8 [0.4-1.6]	0.8 [0.5 – 1.4]
ΔCDAI	meanΔ [95% CI]	-0.7 [-2.2–0.8]	-1.1 [-2.6 - 0.3]	-1.5 [-3.5- 0.4]	-0.3 [-3.9 –3.3]	0.6 [-2.6 – 3.7]

*Line of Therapy defined as follows: 2nd line = prior use of at least one cDMARD and no prior use of any biologic; 3rd line = prior use of at least one cDMARD and prior use of 1 biologic; 4th line+ = prior use of at least one cDMARD and prior use of 2+ biologics

Conclusions: TNFi monotherapy is common in U.S. clinical practice. TNFi monotherapy is less effective than combination therapy especially in biologic naïve patients or with one prior biologic. There is no evidence that tofacitinib monotherapy is less effective than tofa combination therapy or TNFi combination therapy in the outcome measures reported.
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Progress in managment of SpA

OP0023 FOUR-YEAR IMAGING OUTCOMES IN AXIAL SPONDYLOARTHRITIS PATIENTS TREATED WITH CERTOLIZUMAB PEGOL, INCLUDING PATIENTS WITH ANKYLOSING SPONDYLITIS AND NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS

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Background: RAPID-axSpA (NCT01087762) was a long-term study in patients (pts) with axial spondyloarthritis (axSpA) treated with certolizumab pegol (CZP). This is the first report of 4-year imaging results in CZP-treated axSpA pts, including ankylosing spondylitis (AS) and non-radiographic (nr-)axSpA.
Objectives: To report 4-year X-ray and MRI data in CZP-treated axSpA pts.
Methods: RAPID-axSpA[1] was double-blind and placebo (PBO)-controlled to Wk24, dose-blind to Wk48, and open-label to Wk204. Pts fulfilling ASAS axSpA criteria were stratified using a local read according to presence/absence of radiographic sacroiliitis (AS/nr-axSpA) at randomization and had active disease. Wk0 CZP-randomized pts (200mg Q2W/400mg Q4W) continued assigned dose; PBO pts received CZP after Wk16/24. Centrally-read lateral X-rays of cervical/lumbar spine at baseline (BL), Wk96, and Wk204 were assessed using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). Sacroiliac (SI) joint X-rays were scored for sacroiliitis at BL and Wk204. MRI scans performed at BL, Wks12, 48, 96, and 204 were assessed using Spondyloarthritis Research Consortium of Canada (SPARCC) score for SI joints and Berlin score for spine. Data are shown for CZP-treated pts including those starting on PBO. SI joint X-rays (recorded at BL and Wk204) and magnetic resonance imaging (MRI) observed data are presented for pts with valid assessments. mSASSS data were estimated for all pts using observed data and by mixed model for repeated measures (MMRM) analysis.
Results: Of 315 CZP-treated pts, 196 had available spinal X-rays and were included in MMRM analyses (BL mean mSASSS: 9.47). 158 pts had MRI assessments (BL mean SPARCC: 8.17 [n=151]; Berlin score: 6.10 [n=153]) and 137 pts had SI joint X-rays at BL and Wk204 (BL: 67.9% radiographic sacroiliitis). In AS pts, mean mSASSS change between BL and Wk204 was 0.98; 0.67 from BL to Wk96, and 0.31 from Wk96 to Wk204 (0.06, -0.01, and 0.07 respectively for nr-axSpA) (Table A). MMRM estimates were similar to observed values (0.62 and 0.70, respectively [axSpA Wk204 mean change]). Limited changes in SI joint X-ray grading were observed to Wk204: only 4.5% of pts progressed to AS, whilst 4.3% moved from an AS classification to nr-axSpA. MRI assessments showed sustained improvement (Table B).

Table A: Mixed model for repeated measures (MMRM) estimates of mSASSS to Week 204 of the RAPID-axSpA study for all patients treated with CZP

	Baseline	Week 96		Week 204	
	LS mean score (95% CI)	LS mean score (95% CI)	LS mean change from BL (95% CI)	LS mean score (95% CI)	LS mean change from BL (95% CI)
axSpA (n=196)	9.47 (7.20–11.73)	9.86 (7.52–12.21)	0.40 (0.11–0.69)	10.08 (7.71–12.46)	0.62 (0.22–1.01)
AS (n=113)	13.17 (9.79–16.56)	13.84 (10.35–17.34)	0.67 (0.21–1.13)	14.16 (10.61–17.71)	0.98 (0.34–1.63)
nr-axSpA (n=83)	4.42 (2.02–6.82)	4.41 (1.97–6.84)	-0.01 (-0.19–0.17)	4.47 (2.06–6.88)	0.06 (-0.17–0.28)

Table B: MRI outcomes to Week 204 of the RAPID-axSpA study for all patients treated with CZP (observed values)

	Baseline		Week 204		
	n	Mean score (SD)	n	Mean score (SD)	Mean change from BL (SD)
SI Joint Inflammation (SPARCC)					
axSpA	151	8.17 (13.08)	72	1.90 (5.00)	-4.70 (9.40)
AS	91	8.50 (13.83)	41	1.84 (5.60)	-4.35 (8.49)
nr-axSpA	60	7.66 (11.93)	31	1.97 (4.18)	-5.16 (10.60)
Spinal Inflammation (Berlin)					
axSpA	153	6.10 (8.68)	82	2.13 (4.46)	-4.84 (8.33)
AS	92	7.38 (8.80)	50	2.62 (5.23)	-5.51 (7.61)
nr-axSpA	61	4.17 (8.21)	32	1.36 (2.75)	-3.78 (9.38)

Data shown for all CZP-treated patients with valid assessments (including patients re-randomized from PBO at Week 16 or 24). mSASSS: modified Stokes Ankylosing Spondylitis Spine Score; SPARCC: Spondyloarthritis Research Consortium of Canada; LS: least squares. SI: sacroiliac.

Conclusions: This is the first trial to report imaging data in both AS and nr-axSpA pts over 4 years. Limited spinal radiographic progression was observed in CZP-treated pts with lower progression between Wks96 and 204 compared with the first 96 wks. Limited change in radiographic sacroiliitis was observed. Early reductions in MRI inflammation were maintained to Wk204.

References:

[1] Landewé R. Ann Rheum Dis 2014;73:39–47.

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OP0024 DRUG TROUGH LEVELS AND ANTIDRUG ANTIBODIES IN NONSELECTED ANKYLOSING SPONDYLITIS PATIENTS USING SELF-INJECTED ANTITNF DRUGS

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Background: Immunization to biological drugs can reduce the treatment efficacy and increase the risk of adverse events.

Objectives: To determine the drug trough concentrations and anti-drug antibody (ADAb) levels of self-injected TNF-inhibitors, in non-selected patients with ankylosing spondylitis (AS) attending the rheumatological outpatient clinic, and to study the patient related factors affecting the immunization to antiTNF drugs.

Methods: A total of 313 patients with AS were recruited. A blood sample, taken 1–2 days prior to next drug injection, was obtained from 273 patients. Trough concentration of the anti-TNF drugs were measured with capture-ELISA (Promonitor EIA, Progenica), the levels of ADAb with radioimmunoassay (Sanquin Laboratories, The Netherlands), and the serum TNF-blocking capacity by using an in-house reporter gene assay. The clinical activity of AS was assessed using the Bath AS Disease Activity Index (BASDAI), the Bath AS Functional Index (BASFI), and the Maastricht AS Entheses Score (MASES).

Results: ADAbs were observed in 21% of patients on adalimumab (n=99), in 0% of those on etanercept (n=83), in 3% of those on golimumab (n=79) and in 50% of those on certolizumab pegol (n=12). The BASDAI in ADAb positive patients was 1.4 (sd 1.4) and in the ADAb negative patients 2.0 (sd 1.8 p=0.060). Factors affecting the immunization to biological drug could be further analyzed in patients using adalimumab. Trough drug concentrations of adalimumab correlated with the presence of ADAb (r=-0.54, rp<0.0001). In adalimumab users higher BMI was associated with the presence ADAb (p=0.019, adjusted for gender, age, and the time of biological use). Of patients who used methotrexate (MTX) 12% were ADAb positive and of those who did not use MTX 28% were ADAb positive (p=0.048 adjusted for gender, age, weight, and the time of biological use). The use of sulphasalazine was not associated with lower number of ADAb positive patients. Of adalimumab users with ADAb+ the mean BASDAI was 1.2 (sd 1.4) and of those without ADAb 1.9 (sd 1.9) (p=0.091). Of adalimumab users the drug concentration was in the target range (5–10 mg/l) in only 33% of patients.

Conclusions: The disease activity of AS patients using self injected antiTNF drugs was low. The immunization to adalimumab was relatively common in nonselected AS patient population. However, no clear association was observed between the presense of ADAb and the disease activity.

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OP0025 ANTIDRUG ANTIBODIES DETECTION IS STRONGLY INFLUENCED BY THE TYPE OF ASSAY USED

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Background: Direct comparison of immunogenicity data is hampered due to different assays used with different sensitivity for drug interference. This is the first study to compare detection of antidrug antibodies (ADA) with different assays in ankylosing spondylitis (AS) patients. Studying immunogenicity in AS patients with a drug tolerant assay may contribute to a better understanding of development of ADA.

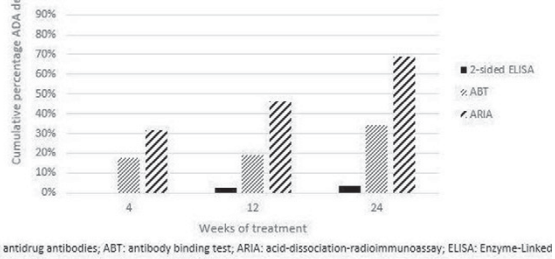
Objectives: To compare the detection of ADA in different assay techniques with differences in drug interference, acid-dissociation-radioimmunoassay (ARIA) antidrug binding test (ABT) and the more frequently used 2-sided Enzyme-linked Immuno Sorbent Assay (ELISA) in AS patients. Second, to study the relation of adalimumab drug levels with the detection of ADA.

Methods: In this study, the detection of the ADA in ARIA and ABT was compared with the detection of ADA in the 2-sided ELISA in 84 consecutive AS patient over a period of 24 weeks; at 4, 12 and 24 weeks of treatment. Adalimumab drug levels were measured using an ELISA. The assays were designed by Sanquin, Amsterdam. For the difference in drug levels we divided the patients in four different groups; all assays negative (group 0), only ARIA positive (group 1), ARIA and ABT positive, 2-sided ELISA negative (group 2) and all assays positive (group 3). We used last observation carried forward to imputate missing data.

Results: As shown in Figure 1, 26% of the patients tested positive for ADA in the ARIA compared to 14% in the ABT and no detection in the 2-sided ELISA at week 4. At weeks 12 and 24 respectively, cumulative 46% and 69% of patients, tested positive in the ARIA for ADA, compared to 19% and 35% in the ABT and 2% and 4% with the 2-sided ELISA.

Median adalimumab levels at week 24 in group 0, 1, 2 and 3 were 9.5 (5.3–13.3), 8.4 (5.3–11.0), 2.8 (0.9–4.3) and 0.002 (0.0–1.3) respectively. No significant differences were found in median adalimumab levels between patients with no ADA detection and patients tested positive in only the ARIA, respectively, 8.4 (5.3–11.0) and 9.5 (5.3–13.3) p=0.385. However, when both ARIA and ABT tested positive, drug levels significantly differed from patients with no ADA detection, 2.8

Figure 1. Cumulative percentages of ADA detection per assay type at different time points



ADA: antidrug antibodies; ABT: antibody binding test; ARIA: acid-dissociation-radioimmunoassay; ELISA: Enzyme-Linked Immuno Sorbent Assay