AB0379 EFFICACY OUTCOMES FOR ORIGINATOR TNF INHIBITORS AND BIOSIMILARS IN RHEUMATOID ARTHRITIS AND PSORIASIS TRIALS: A SYSTEMATIC LITERATURE REVIEW

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Background: Regulatory approval of biosimilar versions of innovator biopharmaceuticals requires that new biological products be highly similar to innovator products, with no clinically meaningful differences in safety, purity, and potency.^{1,2} Pre-specified margins for equivalence in efficacy have been met in comparative trials of biosimilars of tumour necrosis factor inhibitors (TNFis) in rheumatoid arthritis (RA)³ and plaque psoriasis (PsO),⁴ supporting biosimilarity, but differences in treatment responses between originator pivotal trials and biosimilar trials have posed some interesting questions.

Objectives: To compare American College of Rheumatology 20% response (ACR20) and Psoriasis Area Severity Index 75% (PASI75) responses to originator TNFis in pivotal trials with those to originator TNFis and TNFi biosimilars in biosimilar trials in RA and PsO.

Methods: Historical data from originator pivotal trials (averaged across trials) were obtained from published systematic literature reviews. Searches were conducted to identify comparative randomized clinical trials of approved or proposed biosimilars of adalimumab (ADA), etanercept (ETN), and infliximab (INF) using Embase®, MEDLINE®, the Cochrane Central Trials Register and Database of Systematic Reviews, and other Cochrane Library databases, and 2015/16 congress abstracts. To reduce variability, only studies conducted in disease-modifying antirheumatic drug-experienced patients treated with the same biologic dosages and assessed at the same time points were selected for analysis.

Results: Of 83 publications initially identified, 16 publications were included for analysis (RA: originators, n=4; biosimilars, n=6; PsO: originators, n=3; biosimilars, n=3). Higher proportions of ACR20 responders were found among RA patients receiving the originator biologics and biosimilars in biosimilar trials, than among patients receiving the originator biologics in pivotal trials (Table). Insufficient data were available from ADA and INF biosimilar studies in PsO; in ETN studies in PsO, a difference was also observed in the proportions of PASI75 responders between biosimilar and pivotal trials.

Table: ACR20 and PASI75 responders in pivotal vs biosimilar trials and differences in response rates

Product	RA trial type	Time point (wk)	ACR20 responders, %	Difference, pivotal vs biosim, %
ADA	Pivotal ^{5,6}	24	65	—
ADA	Biosim ⁷	24	72	10
ADA	Biosim ⁸	24	72	9
ABP 501	Biosim ⁷	24	75	13
SB5	Biosim ⁸	24	73	10
ETN	Pivotal ⁹	24	71	—
ETN	Biosim ³	24	80	12
ETN	Biosim ¹⁰	24	91	22
SB4	Biosim ³	24	78	9
CHS-0214	Biosim ¹⁰	24	91	22
INF	Pivotal ¹¹	30	50	—
INF	Biosim ¹²	30	59	15
INF	Biosim ¹³	30	59	15
CT-P13	Biosim ¹²	30	61	18
SB2	Biosim ¹³	30	56	10
Product	PsO trial type	Time point (wk)	PASI75 responders, %	Difference, pivotal vs biosim, %
ETN	Pivotal ^{14,15}	12	43	—
ETN	Biosim ⁴	12	72	40
GP2015	Biosim ⁴	12	70	39

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Conclusions: Differences were observed in treatment response rates between originator pivotal trials and more recent trials of originator biologics and their respective biosimilars. Such differences in outcomes may be attributable to fundamental differences in study design and/or baseline patient characteristics, which require further analysis. Additional research is also needed to explore the clinical relevance of these differences.

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AB0380 RESULTS FROM A RANDOMIZED, SINGLE-BLIND, SINGLE-DOSE, PARALLEL-GROUP STUDY IN HEALTHY SUBJECTS DEMONSTRATING PHARMACOKINETIC SIMILARITY BETWEEN ABP 710 AND INFILIXIMAB

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Background: ABP 710 is being developed as a biosimilar with the same amino acid sequence as infliximab, an anti-tumor necrosis factor therapy. Analytical and functional comparisons between ABP 710 and infliximab have been conducted and completed.

Objectives: This report describes the results of analyses comparing the pharmacokinetics (PK), safety, and immunogenicity of ABP 710 and infliximab sourced from the European Union (EU).

Methods: This was a single-blind, single-dose, parallel-group study among healthy adults, 18 to 45 years of age and with a body mass index of 18 to 30 kg/m². Subjects were randomized to receive a 5 mg/kg intravenous infusion of either ABP 710 or infliximab. The primary objective of this analysis was demonstration of PK similarity of ABP 710 to infliximab based on area under the serum concentration-time curve from time 0 extrapolated to infinity (AUC_{inf}; primary endpoint). PK equivalence was deemed achieved if the geometric mean (GM) ratio and its 90% confidence interval (CI) for AUC_{inf} was within the range of 0.80 and 1.25. Secondary endpoints included maximum observed serum concentration (C_{max}), area under the serum concentration-time curve from time 0 to last quantifiable concentration (AUC_{last}), safety, and immunogenicity.

Results: Pharmacokinetics: A total of 49 subjects received ABP 710 and 49 subjects received infliximab. Following a single dose, the adjusted least square (LS) GM of AUC_{inf}, AUC_{last}, and C_{max} for ABP 710 was 33559 µg·h/mL, 31789 µg·h/mL, and 123 µg/mL, respectively. The adjusted LS GM of AUC_{inf}, AUC_{last}, and C_{max} for infliximab was 33706 µg·h/mL, 31847 µg·h/mL, and 121 µg/mL, respectively. Ratios of adjusted LS GMs (90% CIs) between ABP 710 and infliximab for AUC_{inf}, AUC_{last}, and C_{max} were 0.996 (0.904, 1.096), 0.998 (0.918, 1.086), and 1.021 (0.962, 1.083), respectively.

Safety: There was one subject in the infliximab group who developed polyarthrititis that resolved with treatment and the subject completed the study. There were no deaths, other serious adverse events, or treatment-emergent adverse events (TEAEs) leading to discontinuation from the study. The incidence of TEAEs was similar in the two treatment groups (ABP 710: 83.7%; infliximab: 83.7%); the majority of TEAEs were mild or moderate. The most frequently reported TEAEs were somnolence, headache, nasopharyngitis, upper respiratory tract infection, nausea, and lethargy.

Immunogenicity: All subjects tested negative for antidrug antibodies (ADAs) prior to dosing. At the end of study (Day 57), 40% of subjects in the ABP 710 group and 27% in the infliximab group were positive for binding ADAs, and 13% of subjects in the ABP 710 group and 19% in the infliximab group were positive for neutralizing ADAs.

Conclusions: Results of this phase 1 study demonstrate PK similarity between ABP 710 and infliximab sourced from the EU among healthy subjects. The safety and immunogenicity profile were comparable between the treatment groups.

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AB0381 CHANGE IS GOOD, BUT WHAT IS BETTER? RETROSPECTIVE STUDY IN CLINICAL PRACTICE FIRST SWITCH WITH DIFFERENT BIOLOGICAL THERAPIES IN RHEUMATOID ARTHRITIS

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Background: The effectiveness of the switch when the first anti-TNF failure in patients with rheumatoid arthritis has been demonstrated in multiple studies. But what is more effective, if you make the switch to another anti-TNF or another molecule, is not clearly defined.

Objectives: A retrospective study was performed in clinical practice to determine if there is a response to DAS 28 at 6 months of change and whether there is a difference in response if the switch is performed on another anti-TNF or another biological.

Methods: From a total of 254 that met ACR 2010 criteria for RA, which have been biologically treated at Rheumatology of the Parc Salut Mar from 2000 to 2016, 61 (24%) were the first switch and the DAS 28 response at 3 and 6 months of follow-up. The following variables were analyzed: age, sex, years of evolution RA, erosions, FR, ACPA, type of biological treatment, DAS 28 at the start of the switch, 3 months and 6 months, % of patients presenting DAS 28 <2, 6 at 6 months. The statistical study was performed with SPSS 20 for paired and independent quantitative variables with Student's T and chi2 for qualitative variables

Results: Of the total of 61 first treatment changes, 27 (44.3%) were to another anti-TNF alpha, 23 (37.7) to tocilizumab (TCZ), 7 to abatacept (11.5%) and 4

to RTX (6.6). The demographic and response data DAS 28 are shown in Table 1. There are no differences in the years of evolution, % of women, FR or ACPA positive, erosions and disease activity, as measured by DAS 28, before the switch, between The two groups (anti-TNF vs non-anti-TNF). Patients in the anti-TNF group were slightly younger than non-anti-TNF. When the DAS 28 response is evaluated at 3 and 6 months, modifying the treatment is effective (DAS 28 beginning 4.40 vs DAS 28 6 months 2.8 $p < 0.001$). When assessing the response to change, there is no difference in the DAS 28 response at 3 months or 6 months, if you switched to anti-TNF or non-anti-TNF (3.18 vs 2.52 $p = 0.122$). When comparing the patients with anti TNF alpha vs TCZ, 62.5% of the patients with TCZ are in remission compared to 38, 5% ($p = 0.047$).

Table 1

	Total n=61	Switch anti-TNF alpha n=26	Switch No anti-TNF alpha n=35	p
Age (years)	60.08±11.5	56.19±8.4	62.97±12.8	0.023
Sex (% M)	80.3	84.6	77.1	0.532
Years evolution (years)	17.44±9.4	18.92±11.6	16.34±7.4	0.298
Erosion (%)	90.2	92.3	88.6	1.000
FR+ (%)	77.0	76.9	77.1	1.000
ACPA+ (%)	91.8	88.5	94.3	0.642

Table 2

	Total n=61	Switch anti-TNF alpha n=26	Switch No anti-TNF alpha n=35	p
DAS 28 Switch	4.40±1.38	4.61±1.5	4.21±1.3	0.216
DAS 28 3 months	3.18±1.52	3.52±1.09	2.96±1.7	0.167
DAS 28 6 months	2.8±1.54	3.18±1.74	2.52±1.3	0.122
DAS 28 <2.6 m (%)	52.5	38.5	62.5	0.047

Conclusions: In this retrospective study in daily clinical practice, it is evident that the change in treatment after failure of the first biological one, without differences if the change is to an anti TNF or another treatment. The percentage of patients who are remission at 6 months is higher if the change is at TCZ. Given the small number of patients, larger studies would be needed to confirm the results.

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AB0382 OUTCOMES OF ETANERCEPT THERAPY IN ELDERLY RHEUMATOID ARTHRITIS PATIENTS: AN INVESTIGATION OF THE AKITA ORTHOPEDIC GROUP ON RHEUMATOID ARTHRITIS REGISTRY

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Background: The Akita Orthopedic Group on Rheumatoid Arthritis (AORA) encompasses 32 physicians and 28 clinics providing medical care to rheumatoid arthritis (RA) patients in Akita Prefecture, Japan. The patient registry for this group (the AORA registry) reflects actual clinical data on RA therapy in Akita, where the proportion of elderly (age ≥65 years) residents in the population is the highest in Japan. Etanercept (ETN) is a tumor necrosis factor inhibitor reportedly associated with fewer adverse event-related treatment discontinuations than other drugs of this class. However, few evaluations of the efficacy and safety of ETN have been reported for elderly populations.

Objectives: Based on data from the AORA registry, we aimed to investigate the continuation rate for ETN therapy, reasons for discontinuation, and therapeutic effects among elderly RA patients living in Akita.

Methods: Among 204 AORA-registered patients starting ETN therapy between January 2009 and August 2014, data for the 73 patients (35.8%) who were ≥65 years old at the initiation of therapy were evaluated. Mean age was 72.4±4.7 years (range 65–83 years), and 79.5% were women. Mean disease duration was 15.1±12.6 years (range 9 months–55 years), 13.7% of patients were switching from another biologic agent, 49.3% could perform activities of daily living (ADL) independently, and 65.8% had at least one of the following comorbidities: hypertension, diabetes, respiratory disorder, cardiovascular disease, and cerebrovascular disease. We evaluated the 1-year cumulative continuation rate for ETN therapy using the Kaplan–Meier method, and investigated the characteristics of patients who discontinued treatment because of adverse events (AE cohort) or lack of efficacy (LOE cohort). We evaluated efficacy in 55 patients for whom Disease Activity Score – C-reactive protein assessments were possible, based on European League Against Rheumatism (EULAR) criteria.

Results: The 1-year cumulative continuation rate for ETN therapy was 87.2%, and 24 patients discontinued treatment. The AE and LOE cohorts contained 12

and 7 patients, respectively. The AE cohort had a mean age of 75.5 years at the start of treatment, with a mean disease duration of 20.7 years, 8.3% of patients switching from another biologic agent, 16.7% performing ADL independently, and a comorbidity rate of 100%. Corresponding values for the LOE cohort were: mean age, 71.4 years; disease duration, 12.7 years; switching from another biologic agent, 42.9%; performing ADL independently, 57.1%; and comorbidity rate, 28.6%. Efficacy was noted for 81.8% of all patients with 52 weeks of ETN therapy, achieving good efficacy in 21 cases and moderate efficacy in 24 cases.

Conclusions: Retention rate and efficacy were considered satisfactory in elderly RA patients receiving ETN therapy. The risk of adverse events was suggested to increase with increasing age, declining ADL, and presence of comorbidities. These factors require attention when prescribing ETN therapy.

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AB0383 SUBCLINICAL BRAIN DAMAGE IN PATIENTS WITH RHEUMATOID ARTHRITIS AND ITS RELATIONSHIP TO TNF BLOCKER THERAPY

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Background: RA is a chronic disease with a yet unclarified etiology, which causes the activation of pro-inflammatory pathways that bring about joint and systemic inflammations (1). In recent years, the pathophysiology of brain damage that can occur in RA has drawn attention. Emphasis is being put on the possibility that brain damage occurs due to blood-brain barrier (BBB) damage that is linked to chronic inflammation

Objectives: In this study, we aimed to investigate the peripheral blood levels of brain-specific proteins such as S100 beta and GFAP (glial fibrillary acidic protein), the differences in these proteins in patients who did and did not undergo TNF blocker therapy and their relationship with cranial MR lesions, disease activity and cognitive functions with the purpose of determining CNS (central nervous system) damage in patients with rheumatoid arthritis (RA).

Methods: 58 RA patients (47 (81.0%) females, 11 (19.0%) males) and 34 healthy controls (24 (70.6%) females, 10 (29.4%) males) were included in the study. All RA patients were on synthetic DMARD therapy at the beginning. While 30 patients continued sDMARD therapy, 28 patients with high disease activity were started on TNF blocker therapy. All demographic characteristics of the patients were recorded. Disease activity was evaluated using DAS28. The Mini-Mental State Examination (MMSE) was used to evaluate cognitive functions, and the Fazekas Scale was used to assess the cranial MRI lesions. The peripheral blood S100 beta, GFAP, claudin, IL-17, IL-1 beta levels of the patients were measured at the beginning and on the 6th month.

Results: Demographic characteristics were similar between the two groups and no statistical difference was detected between the patient group and the control group in terms of sex, age, and BMI. ($p > 0.05$) S100 beta and GFAP levels were higher to a significant degree compared to the control group. ($p < 0.05$) In the group that was started on TNF blocker therapy, S100 beta and GFAP levels were detected to have decreased significantly 6 months after treatment compared to the start of treatment. ($p < 0.05$) No difference was found between the RA and control groups in terms of hyperintense lesions seen in the cranial MRI. ($p > 0.05$) As the lesions in the deep white matter seen in the cranial MRI of RA patients increased, their S100 beta levels were also seen to increase. ($p < 0.05$)

Conclusions: In conclusion, next to decreasing disease activity and joint erosions by suppressing inflammation, anti-TNF therapy in RA can also suppress potential brain damage linked to subclinical BBB (blood-brain-barrier) dysfunction. Further studies with broader participation and longer patient follow-up are needed to reinforce this hypothesis.

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AB0384 CLINICAL AND RADIOLOGICAL EVOLUTION IN RHEUMATOID ARTHRITIS (RA) PATIENTS AFTER DEINTENSIFICATION BIOLOGICS

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Background: RA is the most common chronic inflammatory arthritis. About 30% of patients are treated with biological therapy (BT). Deintensification of BT for patients in clinical remission, is a strategy used in clinical practice to reduce side effects and burden.

Objectives: The primary endpoint was evaluate clinical and radiological behavior of the RA in patients receiving BT at reduced doses.