Kasei Pharma Corp., Taisho Toyama Pharmaceutical Co., Ltd., SymBio Pharmaceuticals Ltd., Janssen Pharmaceutical K.K., Celltrion Inc., Nipponkayaku Co. Ltd., and UCB Japan, Consultant for: Astra Zeneca K.K., Eli Lilly Japan K.K., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Co., Abbivie GK, Nipponkayaku Co.Ltd, Janssen Pharmaceutical K.K., Astellas Pharma Inc., Taiho Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., Taisho Toyama Pharmaceutical Co. Ltd., GlaxoSmithKline K.K., UCB Japan Co. Ltd., Consultant for: AbbVie, Asahi Kasei, Astellas, AstraZeneca, AYUMI, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Eisai, Eli Lilly Japan, Janssen, Mitsubishi Tanabe, Nippon Kayaku, Novartis, Pfizer Japan Inc, Taiho, Taisho Toyama, Takeda, Teijin, Consultant for: Astra Zeneca K.K., Eli Lilly Japan K.K., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Co., Asahi Kasei Medical K.K., AbbVie GK, Daiichi Sankyo Co., Ltd., Bristol Myers Squibb, and Nipponkayaku Co. Ltd., Speakers bureau: Astellas Pharma Inc., Bristol Myers Squibb, Chugai Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Santen Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Teijin Pharma Ltd., AbbVie GK, Asahi Kasei Pharma Corp., Taisho Toyama Pharmaceutical Co., Ltd., SymBio Pharmaceuticals Ltd., Janssen Pharmaceutical K.K., Celltrion Inc., Nipponkayaku Co. Ltd., and UCB Japan, Speakers bureau: AbbVie, Asahi Kasei, Astellas, AstraZeneca, AYUMI, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Eisai, Eli Lilly Japan, Janssen, Mitsubishi Tanabe, Nippon Kayaku, Novartis, Pfizer Japan Inc, Taiho, Taisho Toyama, Takeda, Teijin, Speakers bureau: AbbVie GK., Bristol–Myers K.K., Chugai Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Astellas Pharma Inc, Diaichi Sankyo Co. Ltd., Eisai Co. Ltd., Sanofi K.K., Teijin Pharma Ltd., Takeda Pharmaceutical Co. Ltd., Novartis Pharma K.K.

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FRI0100

TOWARDS THE LOWEST EFFICACIOUS DOSE (TOLEDO): RESULTS OF A MULTICENTER NON-INFERIORITY RANDOMIZED OPEN-LABEL CONTROLLED TRIAL ASSESSING TOCILIZUMAB OR ABATACEPT INJECTION SPACING IN RHEUMATOID ARTHRITIS PATIENTS IN REMISSION

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Background: Biologic Disease Modifying Anti-Rheumatic Drugs (bDMARD) tapering is possible in rheumatoid arthritis (RA) patients in sustained remission. However, only minimal data are available on progressive tapering of non-TNF bDMARD such as tocilizumab (TCZ) or abatacept (ABA).
Objectives: The TOLEDO (Towards the Lowest Efficacious Dose) trial aimed to assess the impact on disease activity of progressive spacing of TCZ or ABA in RA patients in sustained remission compared to their maintenance at full dose.
Methods: In this multicenter open-label non-inferiority randomized controlled trial, patients fulfilling ACR-EULAR 2010 criteria for RA were included if they were 1) treated with ABA or TCZ for $\geq$ 1 year (monotherapy or in combination with csDMARD, corticosteroid allowed at a dose $\leq$ 5 mg/day), 2) in DAS28VS remission (DAS28 <2.6) for $\geq$ 6 months and 3) with no X-ray damage progression in the year before inclusion. They were randomized into 2 arms: TCZ or ABA maintenance at full dose or DAS28-driven progressive injection spacing arm adapted in which bDMARD IV or SC injections were progressively spaced out every 3 months according to a predetermined 4-step algorithm up to bDMARD discontinuation at step 4. Spacing was reversed to the previous interval in case of relapse. The primary outcome was the evolution of disease activity according to DAS44 during the 2-year follow-up, which was analyzed with a linear mixed-effect model. Relapse and durable relapse rates (respectively defined as DAS28 > 3.2, and DAS28 >3.2 not recovered at the following visit despite bDMARD escalation at previous step) were also compared between the 2 arms. Analysis were done per protocol (PP) according to a non-inferiority hypothesis (non-inferiority margin at 0.25 for DAS44 and 0.07 for relapse rates).
Results: 117 patients were randomized in Spacing arm and 116 in Maintenance arm (90 and 112 respectively for PP analysis). 165 (72.4%) patients were treated with TCZ and 63 (27.6%) with ABA. At the end of the follow-up in the Spacing arm, 12.4% of patients were able to discontinue their bDMARD (step 4), 38.9% had tapered them (step 1 to 3) and 23.9% needed to go back to initial step (step 0). In terms of disease activity, the non-inferiority of the Spacing strategy in terms of disease activity (DAS44) was not demonstrated for the whole population and the ABA subgroups: slope difference of 11% (95% CI: -9%, 32%) and 37% (95% CI: -4%, 77%) respectively. However, it was satisfied for the TCZ subgroup: slope difference 3% (95% CI: -21%, 27%) (Figure 1). Relapses (Figure 2) were more frequent in the Spacing arm: +45% (95% CI: 32%, 57%), +48% (95% CI: 24%, 71%) and +43% (95%CI: 29%, 58%) in the whole population, ABA and TCZ subgroups respectively. Durable relapses were more frequent in the Spacing arm: +10% (95%CI: 0%, 19%), 16% (95%CI: -5%, 37%) and 7% (95%CI: -3%, 16%) in the whole population, ABA and TCZ subgroups respectively, compared with Maintenance arm.
Conclusion: The TOLEDO trial generally failed to demonstrate the non-inferiority of the proposed tapering strategy in comparison to maintenance at full dose. However, the non-inferiority was satisfied in terms of disease activity for the TCZ subgroup.
Disclosure of Interests: Joanna KEDRA: None declared, Philippe Dieudé: None declared, Hubert MAROTTE: None declared, Alexandre Lafourcade: None declared, Emilie Ducourau Speakers bureau: BMS and Abbvie, Thierry Schaeverbeke: None declared, Aleth Perdriger: None declared, Martin SOUBRIER: None declared, Jacques Morel: None declared, Arnaud Constantin: None declared, Emmanuelle Dernis: None declared, Valérie Royant: None declared, Jean-Hugues Salmon Speakers bureau: Janssen Novartis, Thao Pham Speakers bureau: Lilly, Novartis, Jacques-Eric Gottenberg Grant/research support from: Bristol-Myers Squibb, Grant/research support from: Bristol-Myers Squibb, Consultant for: Bristol-Myers Squibb, Lilly, Pfizer, Sanofi-Genzyme, UCB Pharma, Consultant for: Bristol-Myers Squibb, Eli Lilly, UCB, Sanofi-Genzyme, Pfizer, Edouard Pertuiset: None declared, maxime dougados Grant/research support from: Eli Lilly and Company, Pfizer, AbbVie, and UCB Pharma, Consultant for: Eli Lilly and Company, Pfizer, AbbVie, and UCB Pharma, Valerie Devauchelle-Pensec Grant/research support from: Roche-Chugai, Speakers bureau: MSD, BMS, UCB, Roche, Philippe Gaudin Speakers bureau: Roche, Chugai, BMS, Abbvie, Servier, Pfizer, MSD, UCB, ESAOTE, Genévrier, Janssen, Novartis, Lilly, Biogen, Amge, Gregoire CORMIER: None declared, Philippe Goupille: None declared, Xavier Mariette Grant/research support from: Servier, Consultant for: AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Pfizer, UCB Pharma, Francis Berenbaum: None declared, Didier Alcaix: None declared, SID AHMED ROUIDI: None declared, Jean-Marie Berthelot: None declared, Agnès Monnier: None declared, Christine Piroth: None declared, Frederic Lioté Grant/research support from: institutional grants from Grunenthal, Ipsen Pharma/Menarini, Novartis, SOBI for the European Crystal Network Workshops, Consultant for: Grunenthal, Novartis, Vincent Goeb: None declared, Cecile Gaujoux-Viala Consultant for: Speaking and/or consulting fees from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Gilead, Janssen, Merck-Serono, Medac, Nordic Pharma, Novartis, Pfizer, Roche, Sandoz, Sanofi and UCB Pharma., Speakers bureau: Speaking and/or consulting fees from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Gilead, Janssen, Merck-Serono, Medac, Nordic Pharma, Novartis, Pfizer, Roche, Sandoz, Sanofi and UCB Pharma., Isabelle CHARY VALCKENAERE: None declared, David Hajage: None declared, Florence Tubach Grant/research support from: Financial compensation received from MSD on a pro-rota basis for participation in Scientific Committee meetings and functions for this study, Bruno Fautrel Grant/research support from: AbbVie, Lilly, MSD, Pfizer, Consultant for: AbbVie, Biogen, BMS, Celgene, Janssen, Lilly, Medac, MSD, NORDIC Pharma, Novartis, Pfizer, Roche, Sanofi-Aventis, Sanofi Genzyme, SOBI, UCB

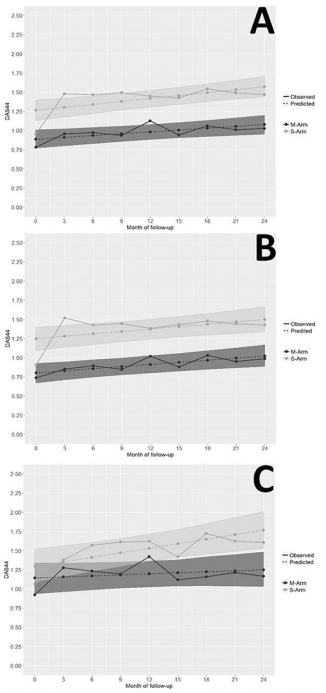

Figure 1: evolution of DAS44 in overall groups (A), TCZ patients (B) and ABA patients (C), and between Maintenance arm (M-arm) and Spacing arm (S-arm)

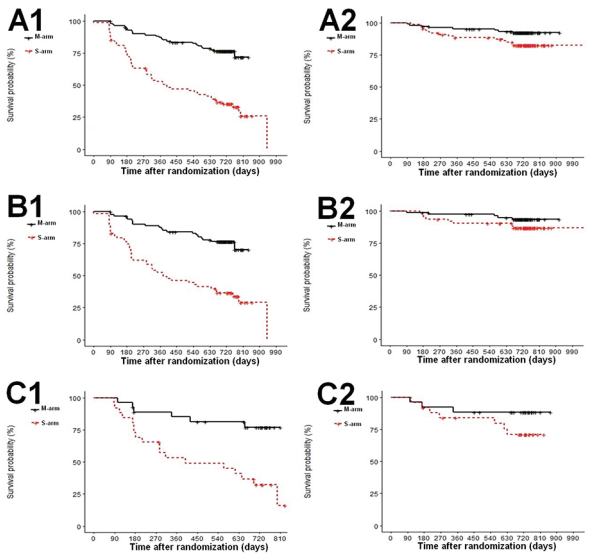

Figure 2: relapse-free (1) and durable relapse-free (2) survival in overall (A), TCZ (B), and ABA (C) populations and between Maintenance arm (M-arm) and Spacing arm (S-arm)

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FRI0101

NON-MEDICAL SWITCHING FROM ORIGINATOR TO BIOSIMILAR ETANERCEPT – NO EVIDENCE FOR A RELEVANT NOCEBO EFFECT – A RETROSPECTIVE ANALYSIS OF REAL-LIFE DATA

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Background: Real-world data about switching patients from originator product to a biosimilars are important to assess and to document the outcome of switches in clinical practice in order to confirm the low risk of major problems. It has been hypothesized that lack of efficacy and adverse drug events (ADEs) upon switching from reference biologics to biosimilar products are related to the nocebo effect [1].

Objectives: To evaluate the effectiveness and safety of systematic non-medical switching from innovator etanercept to biosimilar etanercept SB4 in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) or axial spondyloarthritis (axSpA) in a real-life setting based on different information strategies before switching.

Methods: Data of all adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) or axial spondyloarthritis (axSpA) who had received innovator etanercept and were switched in our specialized center from innovator to biosimilar etanercept for economic reasons were retrospectively analysed. Whether or not patients were informed about the switch was left to the discretion of the treating physician. Disease activity and function were regularly assessed, and any changes were recorded in two consecutive visits at week 12 and 24. The scores documented at week 12 week after switching were taken as primary outcome. AEs were documented.

Results: A total of 84 patients were included (44 RA, 25 axSpA and 15 PsA patients), 24 of which had received information about switching (28.5%). The scores at week 12 of both, disease activity and function, remained rather unchanged (Table 1). Whether patients had been informed about switching or not did not influence outcomes or AE. The retention rate of the biosimilar was 96.4% (n=81) at week 12 and 87.6% (n=71) at week 24 (Figure 1). While 7 patients were lost to follow-up, 6 patients discontinued due to inefficacy or AE, including one malignant melanoma. Overall, 18 AEs were reported in 10 patients (12%). In 3 patients (3.6%) who had 5 AEs in the first 12 weeks the innovator was successfully re-administered.

Conclusion: Systematic switch from innovator to biosimilar etanercept was not associated with changes in disease activity or function in all three indications within 12 weeks. This was independent of information on the switch transmitted to the patients.

Table 1. Patient characteristics

	Assessment	Baseline (n=84)	Follow-up 12 weeks (n=81)	Follow-up 24 weeks (n=74)
RA	DAS28	3,1 (1,4)	2,8 (1,0)	3,1 (1,3)
	HAQ	1,2 (0,7)	1,3 (0,7)	1,3 (0,7)
	CRP (mg/dl)	0,5 (0,6)	0,6 (0,8)	0,7 (0,9)
PsA	DAS28	2,9 (1,4)	1,9 (1,4)	2,8 (1,5)
	HAQ	0,8 (0,5))	0,9 (0,9)	0,9 (0,9)
	CRP (mg/dl)	0,4 (0,5)	0,6 (0,6)	0,6 (0,5)
axSpA	BASDAI	4,8 (2,5)	5,0 (2,5)	4,7 (2,4)
	ASDAS	2,6 (1,3)	2,7 (0,9)	2,7 (0,8)
	BASFI	5,3 (2,7)	5,5 (2,7)	4,9 (2,8

*Values are mean ± standard deviation

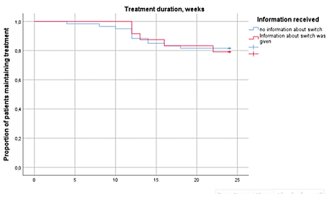

Figure 1. Retention of biosimilar stratified for patients with and without information.

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REFERENCE:

[1] Kristensen, L.E., et al., *Non-pharmacological Effects in Switching Medication: The Nocebo Effect in Switching from Originator to Biosimilar Agent*. BioDrugs, 2018. 32(5): p. 397-404.

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