

Les biosimilaires en rhumatologie: de la prescription à l'acceptation

Marc Scherlinger

▶ To cite this version:

Marc Scherlinger. Les biosimilaires en rhumatologie: de la prescription à l'acceptation. Médecine humaine et pathologie. 2018. dumas-02285201

HAL Id: dumas-02285201 https://dumas.ccsd.cnrs.fr/dumas-02285201

Submitted on 12 Sep 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Université de Bordeaux - UFR DES SIENCES MEDICALES

Année 2018 Thèse n°3196

Thèse pour l'obtention du diplôme d'État de

Docteur en Médecine

Présentée et soutenue publiquement le 16 novembre 2018

Par Marc SCHERLINGER Né le 20/01/1989 à Mulhouse

Les biosimilaires en rhumatologie : de la prescription à l'acceptation

Membres du Jury

Monsieur le Professeur Jean SIBILIA	Président
Monsieur le Professeur Thierry SCHAEVERBEKE	Directeur de thèse
Madame le Professeur Thao PHAM	Membre du Jury
Monsieur le Professeur Bruno AOUIZERATE	Membre du Jury
Monsieur le Professeur David LAHARIE	Membre du Jury

Monsieur le Professeur Thierry THOMAS......Rapporteur

Remerciements

À mon Jury et mes maîtres,

Au Professeur Jean Sibilia, pour avoir été un mentor durant tout mon parcours académique. De la découverte des doubles cursus en deuxième année, à ma thèse de médecine que vous me faites l'honneur de présider. Merci pour ces journées de consultations qui m'ont donné le goût de la rhumatologie, pour vos conseils, votre soutien, et surtout pour votre bienveillance hors du commun. J'espère me montrer à hauteur de la confiance que vous m'avez accordé.

Au Professeur Thierry Schaeverbeke, pour avoir été le directeur de cette thèse mais bien plus encore. Merci pour de m'avoir fait redécouvrir l'Aveyron, l'aligot, et la pêche à la mouche. Enfin, merci de m'avoir adopté dans la grande famille de la rhumatologie Bordelaise, de m'avoir enseigné vos connaissances mais surtout votre manière d'appréhender la médecine pour le bénéfice du patient.

Au Professeur Thao Pham, pour avoir accepté de faire partie de mon jury. Votre bienveillance et bonne humeur rend chaque conférence de rhumatologie un vrai plaisir! Votre perception et compréhension du patient atteint de rhumatisme inflammatoire est une source d'inspiration.

Au Professeur Bruno Aouizérate, pour avoir accepté de faire partie de mon jury de thèse, et ce, malgré l'épisode malheureux survenu entre votre chemise et le bac à couverts du restaurant du personnel de Charles-Perrens.

Au professeur David Laharie, pour avoir accepté de faire partie de mon jury thèse.

Au Professeur Thierry Thomas, pour avoir accepté d'être le rapporteur de ce travail de thèse.

Au Professeur Christophe Richez, qui n'a malheureusement pas pu faire partie de ce jury. Merci pour ton mentorat, tes conseils toujours avisés, de ta disponibilité tout au long de mon internat, et de ma thèse de Sciences que tu me fais l'honneur de diriger.

Au Professeur Jean-Luc Pellegrin, qui n'a malheureusement pas pu faire partie de ce jury. Merci pour votre accueil au G2, ainsi que pour ces visites passionnantes mêlant histoire de la médecine et discussions physiopathologiques.

Au Professeur Estibaliz Lazaro, pour ce stage réalisé avec toi au G2 où j'ai tant appris. Tes talents de diagnosticienne ne sont égalés que par ton humanité et ton empathie. Tu es un exemple pour moi.

Au Professeur Patrick Blanco, pour m'avoir accueilli dans son équipe, pour son enseignement de la rigueur scientifique, et surtout du fait qu'il y a 24 heures dans une journée et 7 jours dans une semaine.

Au Professeur Bernard Bannwarth, pour toutes ces visites durant mon stage en rhumatologie à Bordeaux. Merci pour ces discussions autour de la thérapeutique, et pour votre analyse toujours critique, experte et pertinente des études cliniques.

À ma famille,

Au Docteur Guy Kurtzemann, mon grand-père, pour son éducation, sa discipline et ses valeurs qui m'accompagnent encore aujourd'hui.

A ma grand-mère **Françoise**, qui est et restera ma patiente préférée. Merci pour ton éducation, tes valeurs et tes conseils toujours avisés.

À mes parents, **Claire et Patrick** qui m'ont accompagné durant toutes mes études, pour leur éducation et leurs valeurs. Merci de votre soutien indéfectible, vous qui avez même essayé de comprendre comment fonctionnait un double cursus.

À mon frère **Éric**, qui a toujours été là même si je n'ai pas été le plus facile des petits frères. À **Aurélie** sa partenaire et leur magnifique fille **Chloé**.

À mon parrain **Maurice**, pour toujours avoir le mot pour rire et pour être toujours là pour moi et pour papa...

À mes amis et collègues,

À Pierre-Olivier et Mathieu, notre trio inséparable depuis la P1, qui date maintenant de plus de dix ans ..! Merci pour votre amitié, nos rigolades, les apéros, les soirées, les vacances, les sorties sportives ... J'ai de la chance de vous avoir.

À Joseph, le plus médecin des chirurgiens que je connaisse, mon partenaire de roadtrip en mustang décapotable, de randonnée, de ski, de voyage en kimono accompagné d'un katana en bois, de pêche et de méditation zen... « Doko de katana kae mas ka ?! ».

Aux Guys, Guy François et Guy (George) Vincent, pour ces deux collocations magiques. Pour les sorties escalade avec François, les fois où j'ai essayé de courir avec (après) Vincent, pour les canards, les Suzes, les parties de raclette, le tréteau par la fenêtre, la Femme, Guy la licorne et tout le reste. D'ailleurs, vous trouvez pas que ça caille ici ? Et il est pour moi ce café ?

À mes supers colocataires durant l'internat, à Corentin pour ces burgers-bières, tes analyses politiques et tes photos humoristiques toujours de bon ton ; à Marie pour les graines; à Félix et ses galères de vélo et à Hélène pour le maquereau.

Au F.M.I.D.: Arna-ud, Kennel, Lucas, Douissard, Bimboes, Biloute, Marie et bien sûr PO et Matthieu ... la fine équipe qui a rendu mes années à Strasbourg absolument inoubliables.

Aux autres strasbourgeois qui restent dans mon cœur, Sarah Biboche, Seb K, Steeve, Léa, Charlotte, Charline, Luc et Lucas. À Marie Ruillier, ma consœur d'escalade et de bibliothèque perdue, que je compte bien retrouver! À mes deux brillants sous-colleurs, Elsa et Alexis, sans qui je ne serais sans doute pas là. À Olivier, Bastien et Guilhem, pour ces apéros toujours très intellectuels.

Aux rhumatologues. À Nicolas, Nadia et Marie-Élise pour leur présence et leurs enseignements. À mes collègues internes de rhumatologies, Fanny, Raphaëlle, Itsaso ... À Pauline H., pour sa bonne humeur perpétuelle. À toute l'équipe soignante de rhumatologie, les meilleures !!! À Patricia, la meilleure cadre du monde et notre mère à tous. À Françoise et Annick pour leur bonne humeur quotidienne qui rendait les fin de journées de stage toujours agréables.

À mes amis internistes. À Vivien et Renaud, deux perles de la médecine interne, à ne pas associer ensemble trop longtemps, sous peine de voir le niveau de l'humour ambiant chuter exponentiellement. À Guy Guillaume Vial, pour toutes ces Suzes, mais tellement plus! À Aurélie Saunier, ma super cointerne de deuxième semestre, pour ces discussions passionnantes de 6 heures à 2h du matin, et pour le 6ème café de la journée qui était peut être celui de trop.

À mes amis néphrologues. En particulier Aurore, pour les pauses glaces et les bières sans gluten ! À Hannah, pour l'échange mutuel de psychothérapie.

À mes autres amis de l'internat, Alice sans qui la réanimation n'aurait pas été aussi douce, Toto pour m'avoir fait découvrir le sud-ouest et les corridas, Caro pour le picon sur les murs, Elo, Caza, Alizée.

À mes amis du laboratoires Immunoconcept. La superbe équipe d'internes en M2, Félix, Maxime, Aurélien, Manon, Cyrielle et Gaël. Aux thésards, Nathalie, Charlotte, Paô. À Isabelle Douchet pour son accueil, ses conseils et sa bienveillance.

À mes nombreux amis du doubles cursus, au rang desquels la promotion 2009 de l'École de l'Inserm gardera toujours une place unique dans mon coeur : Sophie, Romain, Nicolas, Emilie, Sylvain et les autres. À Thomas B. doté d'une énergie hors du commun, toujours prêt à défendre les intérêts des doubles cursus. À Audrey, une future grande médecin !

Aux membres de l'AMPS, Stanislas, Ariel, Max, Erwan et tant d'autres.

Et à tous ceux que j'ai oublié de mentionner ...

Table des matières

Remerciements	.1
I. Introduction	8
II. Articles1	3
Switching from originator infliximab to biosimilar CT-P13 in real-life: The weight of patient acceptance1	
Long-term follow-up after switching from originator infliximab to its biosimilar CT-P13: the weight of nocebo effect2	20
Acceptance rate and sociological factors involved in the switch from originator to biosimilar etanercept (SB4)2	25
Switching from the bio-originators to biosimilar: is it premature to recommend this procedure?	31
Response to: 'Switching from the bio-originators to biosimilar: is it premature to recommend this procedure?' by Cantini and Benucci	32
Response to: 'Seeing the glass either half full or half empty: response to the correspondence 'Switching from the bio-originators to biosimilar: is it premature to recommend this procedure?" by Scherlinger and Schaeverbeke	
Additional response to the correspondence: 'Switching from the bio-originators to biosimilar: is it premature to recommend this procedure?' by Cantini and Bennuci	34
Les biosimilaires en France, bien en comprendre les enjeux pour bien les utiliser 3	}5
III. Discussion et Perspectives4	!2
IV. Références4	ŀ5
V. Abréviations4	!7
VI. Serment d'Hippocrate4	18

I. Introduction

La polyarthrite rhumatoïde et le groupe des spondyloarthrites appartiennent au spectre des rhumatismes inflammatoires chroniques (RIC) qui touchent environ 0,8% de la population française [1,2].

En l'absence de prise en charge thérapeutique adaptée, les RIC sont responsables de douleurs, d'un handicap et d'un retentissement sur la qualité de vie considérables pour les patients. Leur prise en charge repose essentiellement sur la pratique du « treat to target », la cible en question étant la rémission caractérisée par l'absence d'activité inflammatoire, prévenant ainsi les lésions structurales et le handicap. L'avènement des traitements biologiques (aussi appelés biothérapies ou biomédicaments) au début des années 90 a permis d'envisager la rémission comme un objectif thérapeutique.

L'infliximab (Rémicade©) a été le chef de file des biothérapies en rhumatologie. Il s'agit d'un anticorps monoclonal chimérique ciblant le tumor necrosis factor alpha (TNF-α) circulant, bloquant son activité pro-inflammatoire. Les biothérapies se distinguent des molécules chimiques classiques par le fait qu'elles possèdent une structure complexe de haut poids moléculaire, et qu'elles sont issues du vivant par des méthodes de génie génétique. Le caractère innovant, la complexité et la nouveauté des processus de production des biothérapies expliquent en partie leur coût initialement élevé, ces coûts reflétant également l'amélioration spectaculaire du service médical rendu dans des pathologies à fort besoin non satisfait au début des années 2000. Les avancées thérapeutiques dans le domaine des biothérapies ont ainsi permis, depuis plus de vingt ans, une amélioration significative de la qualité de vie des patients, du handicap

fonctionnel, ainsi que de la survie globale qui se rapproche voire rejoint celle de la population générale [3,4]. Toutefois, ces avancées thérapeutiques s'accompagnent d'un coût sociétal important, et, à l'heure où les dépenses de soins sont montrées du doigt et que la viabilité de notre système de soin est remise en question, une maitrise des dépenses liées aux médicaments semble nécessaire.

Près de vingt ans après la commercialisation du Rémicade®, son premier biosimilaire, le CT-P13 (Inflectra®, Remsima®) vient répondre à ce besoin de maitrise de coûts de santé. Un biosimilaire est un biomédicament présentant la même structure protéique et la même activité biologique que le traitement princeps. Compte-tenu de la complexité structurale des médicaments biologiques et de leurs processus de fabrication, un biosimilaire peut présenter des différences structurales minimes par rapport au princeps, notamment en terme de modifications post-traductionnelles (glycosylation, acétylation ...). Il appartient au laboratoire souhaitant commercialiser le biosimilaire de démontrer que ces différences n'impactent pas l'effet biologique du médicament. Il est cependant à noter que depuis leur mise sur le marché, les biothérapies princeps ont modifié à mainte reprise leur processus de production, induisant des altérations de ces modifications post-traductionnelles. Ainsi, on compte plus de 50 modifications du processus de fabrication du Rémicade® depuis sa mise sur le marché [5]. On peut donc considérer que nos patients sont traités par (l'équivalent de) biosimilaires depuis de nombreuses années.

Pour recevoir une autorisation de mise sur le marché (AMM) en Europe, le biosimilaire doit remplir un cahier des charges extrêmement strict imposé par l'European Medicines Agency (EMA), pour démontrer son équivalence structurale,

pharmacocinétique et pharmacodynamique [6]. En opposition aux médicaments génériques, le biomédicament doit également démontrer son équivalence en terme d'efficacité clinique, par le biais d'une étude de phase 3, le comparant directement au produit princeps. Lorsque l'équivalence clinique est démontrée dans une indication dite représentative (eg, polyarthrite rhumatoïde pour un anti-TNF), celui-ci peut recevoir l'AMM pour l'ensemble des indications du princeps, selon le principe d'extrapolation. Ce principe permettant d'économiser la démonstration (coûteuse) d'équivalence dans l'ensemble des indications, le biosimilaire est commercialisé à un prix environ 30% inférieur à celui du princeps.

L'enjeu de l'utilisation des biosimilaires réside donc dans les économies potentielles liées à leur prescription. Une étude utilisant un modèle mathématique a estimé ces économies dans 4 pays européens (France, Royaume-unis, Allemagne et Italie), à plus de 430 millions d'euros en cinq ans en prenant en compte une pénétration du biosimilaire de 40% et un prix 30% inférieur [7]. Une étude anglo-saxonne récente montre que sur l'année 2016-2017, les économies liées à la commercialisation du CT-P13 (Inflectra® et Remsima®) et du SB4 (Bénépali®) équivalaient à 36 millions de livres Sterling dont la moitié provenait d'une baisse de prix du princeps [8].

Tandis que l'ensemble des études de phase 3 évaluant l'efficacité et la tolérance des biosimilaires se sont toutes révélées rassurantes, des données sur leur prescription et leur acceptabilité en vie réelle, notamment en relai du biomédicament princeps (aussi appelé, interchangeabilité ou « switch ») manquaient. Nous avons conduit dans le service de rhumatologie de Bordeaux une étude de vie-réelle évaluant l'acceptation et la maintenance thérapeutique de l'Inflectra® chez des patients atteints de RIC

préalablement traités par Rémicade® de façon stable depuis au moins 6 mois (article 1, article original, Joint Bone Spine, novembre 2017, page 9). Nous avons montré un taux d'acceptation élevé (89%) de l'interchangeabilité entre le Rémicade® et son biosimilaire le CT-P13 (Inflectra®). Cependant, il est apparu qu'une proportion significative (44%) des patients en échec au terme du suivi ne présentaient pas d'argument objectif en faveur d'une activité du RIC, mais des symptômes douloureux subjectifs. Ces données sont en accord avec d'autres études françaises ou européennes et suggèrent un effet nocebo qui pourrait être en rapport avec une acceptation incomplète du biosimilaire [9-11]. En excluant ces patients de l'analyse, la maintenance du biosimilaire était équivalente à une cohorte historique de patients traitée par Rémicade®. De manière intéressante, une analyse des données à long terme (article 2 : lettre à l'éditeur, Annals of Rheumatic diseases, en presse, page 16) montre qu'après la phase initiale de suivi (environ 6 mois) la courbe de maintenance des patients traités par CT-P13 est strictement superposable à celle de la cohorte historique traitée par Rémicade®. Ces données suggèrent que l'effet nocebo est un événement précoce après l'interchangeabilité et que passé cette période, l'efficacité et la tolérance du CT-P13 sont comparables à celles du Rémicade®.

Dans un second travail, nous nous sommes intéressés aux déterminants de l'acceptation d'un biosimilaire de l'Enbrel® (SB4, Bénépali®) en consultation hospitalière de rhumatologie (article 3, article original, Seminars in Arthritis and Rheumatology, juin 2018, page 21). L'information prodiguée lors de la consultation pendant laquelle le biosimilaire est proposé est primordiale, et une divergence dans le discours des différents acteurs de santé (eg, pharmaciens/médecins) peut être responsable d'une méfiance du patient, d'une baisse de l'acceptation du biosimilaire voire d'un effet nocebo accru. Il semble alors évident qu'une formation du corps

médical, pharmaceutique et paramédical sont des éléments indispensables pour favoriser une diffusion optimale des biosimilaires en rhumatologie hospitalière et libérale.

Un partie du corps médical semble présenter une méfiance vis-à-vis des biosimilaires, en particulier concernant l'interchangeabilité (*articles 4,5,6,7 Lettres électroniques de Cantini et Benucci et réponses, Annals of Rheumatic Diseases, decembre 2017-mars 2018,* pages 26-30). Ces craintes sur les risques de l'interchangeabilité ne reposent à l'heure actuelle sur aucune preuve scientifique, comme l'attestent plusieurs études de grandes envergures (NOR-SWITCH, DAN-BIO) [12,13], et une méta-analyse de 90 essais évaluant l'interchangeabilité [14].

Il appartient aux rhumatologues et aux autres prescripteurs de biothérapies de se saisir de la prescription des biosimilaires au risque de voir se répéter l'histoire des génériques, la substitution étant finalement confiée au pharmacien (article 8, éditorial mandaté par la *Revue de Médecine Interne*, en presse, page 31).

11. Articles

G Model

BONSOI-4645: No. of Pages 7

Joint Bone Spine xxx (2017) xxx-xxx



Available online at

ScienceDirect

www.sciencedirect.com

Elsevier Masson France

EM consulte www.em-consulte.com/en



Original article

Switching from originator infliximab to biosimilar CT-P13 in real-life: The weight of patient acceptance

Marc Scherlinger a,b,c,1, Vincent Germain a,b,1, Céline Labadie a,b, Thomas Barnetche a, Marie-Elise Truchetet a,b,c, Bernard Bannwarth a,b, Nadia Mehsen-Cetre a, Christophe Richez a,b,c, Thierry Schaeverbeke a,b,*, On behalf the FHU ACRONIM2



- ^a Service de rhumatologie, hôpital Pellegrin, centre hospitalier universitaire de Bordeaux, place Amélie-Raba-Léon, 33076 Bordeaux, France
- ^b Université de Bordeaux, 146, rue Léo-Saignat, 33076 Bordeaux, France ^c CNRS-UMR 5164 Immuno ConcEpT, 146, rue Léo-Saignat, 33076 Bordeaux, France

ARTICLE INFO

Article history: Accepted 25 October 2017 Available online xxx

Rheumatoid arthritis Ankylosing spondylitis Spondyloarthropathies Patient attitude to health Anti-TNF-alpha DMARDs (biologics)

ABSTRACT

Objective: To explore acceptance and retention rate of biosimilar CT-P13 after switching from originator infliximab (OI) in patients with various rheumatic diseases

Methods: Patients with stable rheumatoid arthritis (RA), ankylosing spondylitis (AS) or psoriatic arthritis (PsA) under OI were proposed to switch to CT-P13 at the same regimen. A prospective cohort of infliximabnaïve patients beginning CT-P13 and a retrospective cohort of patients treated with OI were used as controls. The primary outcome was to evaluate the retention rate of CT-P13. Secondary outcomes were the switch acceptance rate, reasons of failure and safety.

Results: Switch was proposed to 100 patients and accepted by 89 of them (63 AS, 12 PsA and 14 RA). After a median follow-up of 33 weeks, 72% of patients were still treated with CT-P13. This retention rate was significantly lower than the one found in our retrospective and prospective control cohorts: 88% and 90% respectively (*P*-value = 0.0002). Within patients who asked to be reswitched to OI, 13/25 (52%) presented clinical disease activity, one developed serum sickness and 11 (44%) presented no objective activity. A subanalysis excluding these 11 patients abrogated difference in retention rates between the 3 cohorts (P-value = 0.453). After reswitching to OI, patients without objective disease activity claimed to recover original efficacy.

Conclusions: Retention rate was lower after switching from OI to CT-P13 compared to our control cohorts. However, this difference faded after excluding patients without objective clinical activity, suggesting a reluctance of patients to the switch and a negative perception of the biosimilar.

© 2017 Published by Elsevier Masson SAS on behalf of Société française de rhumatologie.

1. Introduction

Biologic treatments, first of all TNF-inhibitors, have revolutionized the treatment of severe inflammatory rheumatic diseases with a tremendous change in disease outcomes and patient's quality of life [1]. However, the use of biological originator DMARDs (boD-MARDs) has huge financial consequences, leading to a three-fold increase in total medical costs, this increase being mainly driven by the cost of these drugs [2]. This is a major limitation for their use in emerging countries and an important concern for health insurances in developed countries [3]

Biosimilar DMARDs (bsDMARDs) offer a unique opportunity to reduce the costs in the treatment of inflammatory diseases. A prediction model of the use of biosimilar infliximab in rheumatoid arthritis (RA) in 4 European countries estimated costs reduction ranging from tens to hundreds million euros [2].

The low number of clinical trials required for the development of this biosimilar limits the information available for clinicians. Moreover, these clinical trials compare biosimilars to originator product at the time of treatment initiation. The marketing of biosimilars in rheumatology is very recent, thus data on switching from originator is still limited. However, biosimilars have been used for longer with good results in other medical specialties, as in haematology with growth factors (epoetin, filgrastim) [4], or in endocrinology with growth hormone [5]. Most clinicians are

https://doi.org/10.1016/j.jbspin.2017.10.003

1297-319X/© 2017 Published by Elsevier Masson SAS on behalf of Société française de rhumatologie.

Please cite this article in press as: Scherlinger M, et al. Switching from originator infliximab to biosimilar CT-P13 in real-life: The weight of patient acceptance. Joint Bone Spine (2017), https://doi.org/10.1016/j.jbspin.2017.10.003

^{*} Corresponding author. Service de rhumatologie, hôpital Pellegrin, centre hospitalier universitaire de Bordeaux, place Amélie-Raba-Léon, 33076 Bordeaux, France.

E-mail address: Thierry.schaeverbeke@chu-bordeaux.fr (T. Schaeverbeke).

These authors contributed equally to the work.

² On behalf of the Fédération hospitalo-universitaire ACRONIM.

M. Scherlinger et al. / Joint Bone Spine xxx (2017) xxx-xxx

reluctant to change a well-tolerated and effective treatment for a new and unknown product, therefore for a non-medical reason. Finally, although many papers have underlined the differences between biosimilars and generic drugs [6], the confusion between both kinds of drugs remains in minds for patients as well as for clinicians. Considering the poor acceptability of generics, especially in France, this confusion represents a limitation to the use of biosimilars.

We conducted a real-life study in the rheumatology department of the University Hospital of Bordeaux by systematically offering patients treated with originator infliximab (OI) to switch to CT-P13 (Inflectra®). The main goals of our study were:

- to assess the retention rate of CT-P13 in real-life setting after switching from OI;
- to compare this retention rate with the ones observed in a cohort of infliximab-naïve patients starting with CT-P13, and in a retrospective cohort of OI-treated patients.

2. Methods

2.1. Patients

Patients followed in the rheumatology department of Bordeaux University Hospital were proposed to participate in the study if:

- they presented a RA according to the 2010 ACR/EULAR criteria [7], or an ankylosing spondylitis (AS) or a psoriatic arthritis (PsA) according to the 2009 ASAS criteria [8];
- they were treated with infliximab, in monotherapy or in association with conventional synthetic DMARDs (csDMARDs), under stable infliximab treatment regimen for at least 6 months;
- the disease was controlled according to the physician opinion.

The switch was not proposed to patients with inflammatory bowel disease due to the recommendations of the French gastroenterologists society at the time of the study [9]. This cohort was prospectively followed from November 2015 to October 2016.

For comparison, two control cohorts from the same department were used:

- a cohort of infliximab-naïve patients starting anti-TNFα treatment with CT-P13;
- a retrospective cohort of patients treated with OI during the year 2013.

Prospective control cohort of infliximab-naïve patients receiving CT-P13 at initiation consisted of 29 patients among which 24 (83%) with SpA and 5 (17%) with RA. Patient characteristics are shown in Table 1.

Historic control cohort of patients treated with OI in 2013 consisted of 82 patients among which 64 (78%) with SpA and 18 (22%) with RA. Other patient characteristics are presented in Table 1.

2.2. Intervention

Patients were given oral information by the attending physician. The different practitioners reached agreement before the beginning of the study to communicate homogenous information to patients about biosimilars. The information delivered included data supporting biosimilar clinical efficacy and safety. The patients were informed before initiating the biosimilar that upon simple request, switching back to the originator would be possible. After giving oral consent, patients were switched to CT-P13 at the same treatment

regimen (dose and time interval) than previous OI. Associated treatments including csDMARDs were not modified at inclusion.

2.3. Follow-up

Usual disease activity scores were recorded at the time of infusion: DAS28-CRP for RA, BASDAI and ASDAS-CRP for AS and PsA. Objective signs of activity were defined for RA patients by a DAS28-CRP \geq 3.2 and at least one clinical synovitis [10]. For AS patients and PsA, clinical activity was defined by a BASDAI and a physician global assessment (PGA) \geq 4/10 as defined in ASAS consensus [11].

2.4. Outcomes

The primary outcome was to evaluate the retention rate of CT-P13 in the switched cohort.

The secondary outcomes were:

- the comparisons of the retention rate of CT-P13 in the switched cohort versus the historic OI cohort and the CT-P13 initiation cohort:
- the acceptance of the switch;
- · the reasons for switch failure:
- · the predictive factors of switch failure.

2.5. Statistical analysis

Quantitative variables, expressed as mean with standard deviation or median with range, were compared using a bilateral Student comparison test. Qualitative variables, expressed as proportions, were compared using a χ^2 -test, or Fisher's exact test if needed. Kaplan–Meier survival curves of retention rate were compared using a log-rank test. Multivariate analysis was conducted using a logistic regression test including all variables associated with the studied outcome with a P-value < 0.15 in the univariate analysis. A P-value less than 0.05 was considered as statistically significant.

3. Role of the funding source

Not applicable.

4. Results

4.1. Population characteristics and switch acceptance

Hundred consecutive patients treated with OI fulfilled the inclusion criteria and were proposed to participate in the study. Among them, 89 (89%) accepted to switch to CT-P13. Patient, disease and treatment characteristics are detailed in Table 1. There was no difference between patients accepting and refusing the switch in terms of age, sex, type of disease, disease duration, number of IFX infusions or concomitant csDMARD use (data not shown).

Among the 89 patients switching from OI to CT-P13, 57% (n=51/89) were men, with mean age 50.5 ± 13.3 years. Seventy-five (84%) patients had spondyloarthritis (SpA), including 63 (84%) with axial involvement and 12 (16%) with PsA. Mean BASDAI and ASDAS-CRP at baseline were $2.03 (\pm 1.88)$ and $1.38 (\pm 0.84)$ respectively.

Fourteen patients (16%) suffered from RA including 71% ACPA-positive, 86% IgM-RF positive and 79% had erosive disease. At baseline, mean DAS28-CRP was 2.14 (± 0.89) and 79% (11/14) of patients achieved EULAR remission (DAS28-CRP < 2.4).

Among this cohort of 89 patients, 47 (53%) were treated by infliximab as first line biologic whereas 42 (47%) received previously at least another biotherapy. The median dose was 5 mg/kg per

 $Please\ cite\ this\ article\ in\ press\ as:\ Scherlinger\ M,\ et\ al.\ Switching\ from\ originator\ infliximab\ to\ biosimilar\ CT-P13\ in\ real-life:\ The\ weight\ of\ patient\ acceptance.\ Joint\ Bone\ Spine\ (2017),\ https://doi.org/10.1016/j.jbspin.2017.10.003$

BONSOI-4645; No. of Pages 7

ARTICLE IN PRESS

M. Scherlinger et al. / Joint Bone Spine xxx (2017) xxx-xxx

Table 1Patient, disease and treatment characteristics in the three cohorts involved in our study.

Characteristics at inclusion	Infliximab switch population $(n=89)$	Infliximab-naïve population $(n=29)$	Infliximab historic population (n = 82)
Patient characteristics			
Age, years, mean (S.D.)	50.5 (13.3)	46.1 (11.0)	50.7 (12.3)
Male sex	51 (57%)	14 (48%)	36 (44%)
Disease characteristics			
Spondyloarthritis	75 (84%)	24 (83%)	64 (78%)
Spondyloarthritis subtype			
Axial spondyloarthritis	63 (84%)	18 (75%)	44 (69%)
Psoriatic arthritis	12 (16%)	6 (25%)	20 (31%)
History of uveitis	23 (31%)	4 (17%)	20 (31%)
HLA locus typed	62 (83%)	19 (79%)	51 (80%)
B27 positive	49 (79%)	10 (53%)	33 (65%)
Radiographic data (X-ray or MRI)	60 (80%)	28 (97%)	51 (80%)
Radiographic disease	52 (87%)	20 (71%)	44 (86%)
Associated csDMARD	42 (56%)	14 (58%)	31 (48%)
Methotrexate	39 (93%)	12 (86%)	28 (90%)
Dose, mg, median (range)	10 (5-20)	10 (10-15)	10 (5-20)
Leflunomide	3 (7%)	0	1 (3%)
Dose, mg, median (range)	20 (20-20)	NA	20 (20-20)
Salazopyrine	0	2 (14%)	3 (9%)
Dose, mg (range)	NA	2 (2-2)	2000 (500-2000)
Rheumatoid arthritis	14 (16%)	5 (17%)	18 (22%)
Rheumatoid factor positivity	12 (86%)	4 (80%)	13 (72%)
ACPA positivity	10 (71%)	4 (80%)	12 (67%)
Erosive disease	11 (79%)	2 (40%)	11 (61%)
Associated csDMARD	13 (93%)	3 (60%)	17 (94%)
Methotrexate	13 (93%)	3 (60%)	14 (78%)
Dose, mg (range)	10 (7.5-20)	15 (10-15)	12,5 (7.5-20)
Treatment characteristics			
Number of lines of biotherapy, median (range)	1 (1-4)	2 (1-7)	1 (1-4)
Disease duration, years, mean (S.D.)	16.0 (9.9)	7.7 (7.4)	13,1 (11.7)
Infliximab dose, mg/kg, median (range)	5 (3-8)	5 (3-5)	5 (3-5)
Infliximab infusion rhythm, median (range)	7 (6-12)	8 (6-8)	8 (5-11)
Number of infliximab infusions at inclusion, median (range)	39 (3-123)	NA	9 (1-92)
Disease activity			
Spondyloarthritis			
BASDAI, mean (S.D.)	2.03 (1.88)	5.21 (1.28)	3.11 (2.07)
ASDAS-CRP, mean (S.D.)	1.38 (0.84)	3.20 (0.47)	1.79 (1.06)
Rheumatoid arthritis			
DAS28-CRP, mean (S.D.)	2.14(0.89)	4.62 (0.89)	3.68 (1.82)
Remission (DAS28-CRP < 2.4)	11 (79%)	0 (0%)	5 (28%)

infusion (range: 3 to 8 mg/kg) and the median number of infliximab infusions before switch was 39 (range: 3 to 123). Mean disease duration was 16 years $(\pm\,9.9)$.

4.2. Biosimilar retention rate and reasons for switch failure

After a median follow-up of 33 weeks (range: 6 to 50), 64 (72%) patients were still treated with CT-P13 (Fig. 1). RA patients were more likely to fail after switching to CT-P13 with 57% failure (8/14) versus 23% failure (17/75) in SpA patients (*P*=0.02, Fisher's exact test).

Among SpA patients, lack of efficacy was in cause in all 17 failures among which 9 patients had a clinical worsening: 7 of them had a BASDAI and a PGA $\geq 4/10$, one had a uveitis recurrence and one had a psoriasis flare-up. Eight other patients complained to be less controlled by the biosimilar, contrasting with the lack of BASDAI score worsening and leading them to request to switch back to OI.

Among RA patients, lack of efficacy was responsible for 7/8 failures (87.5%). Four (57%) of these patients had objective signs of activity (DAS28-CRP \geq 3.2 with at least one swollen joint), while the 3 others requested to be re-treated with OI although they presented neither clinical sign of disease activity nor DAS-CRP worsening.

In total, 11 patients (12,5%) requested to switch back to OI although they did not present clinical activity defined by a worsening of disease activity scores.

In an exploratory multivariate analysis, none of the investigated criteria (patient and disease characteristics, treatment's regimen) was statistically associated with an increased likelihood of switch failure (Table 2).

4.3. Comparison of retention rate within the 3 groups

Infliximab-naïve patients starting CT-P13 had a median follow-up of 30 weeks (range: 2–53). Ol treated patients were retrospectively followed during one year.

Survival curves of treatment retention are shown in Fig. 1a for all three groups. There were significantly more failures in the switched population: 28% (25/89) than in our control groups: 10% (3/29) in the infliximab-naı̈ve population and 12% (10/82) in the retrospective OI population, as assessed by the log-rank analysis (P= 0.0002).

However, in the switched cohort, 11 patients (3 RA and 8 SpA, corresponding to 44% of failures and 12.5% of the total study population) requested to resume OI without objective clinical activity (no clinical activity defined by disease activity scores, see methods). When evaluating treatment retention according to treatment failure due to objective clinical activity worsening, the difference

Please cite this article in press as: Scherlinger M, et al. Switching from originator infliximab to biosimilar CT-P13 in real-life: The weight of patient acceptance. Joint Bone Spine (2017), https://doi.org/10.1016/j.jbspin.2017.10.003

M. Scherlinger et al. / Joint Bone Spine xxx (2017) xxx-xxx

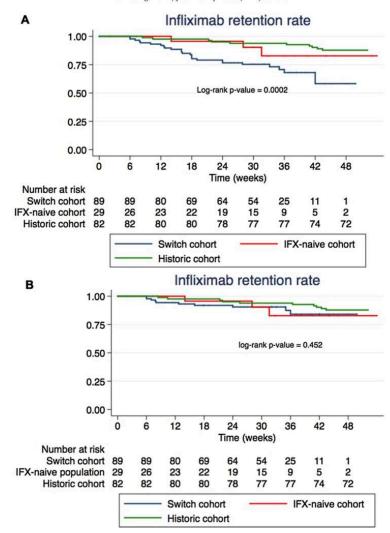


Fig. 1. Retention rate of CT-P13 among our cohorts using a Kaplan-Meier curve. A. Overall cohort retention rate for the 3 cohorts. B. Retention rate excluding patients without objective clinical activity. IFX: infliximab.

between groups became non-significant as assessed by the log-rank analysis ($\it P$ = 0.453, Fig. 1b).

4.4. Outcome after switch failure

In the SpA group, 17 patients failed the switch because of lack of efficacy; among them 15 were switched back to OI and 2 were treated by another TNF-inhibitor. Five of the 7 (71%) reswitched patients with clinical activity and all 8 patients without clinical activity were back to initial controlled state after the first infusion of OI (Fig. 2). One patient with history of uveitis had uveitis recurrence and one other had a psoriasis flare-up after switching. Both patients improved after switching back to OI together with local treatment, but developed another flare-up several months later, although re-treated with OI. These data suggest that these

flare-ups were to be expected in the natural history of their rheumatic diseases, irrespective of the switch.

In the RA patients group, all 7 patients failing the switch because of lack of efficacy were reswitched to Ol. Among these 7 patients, 4 exhibited objective activity signs, two of them being rescued by switching back to Ol with same efficacy as before the first switch, while the reswitch for Ol was ineffective for the two others, justifying a modification of the bDMARD. The 3 remaining patients presented no objective sign of disease activity. Nonetheless, they asked to be re-treated with Ol, recovering their initial state (Fig. 2).

All patients without objective disease activity were back to original efficacy when switched back to OI.

Overall, 82% (18/22) of patients reswitched from biosimilar to OI after switch failure due to a lack of efficacy recovered their initial state. (Fig. 2).

 $Please\ cite\ this\ article\ in\ press\ as:\ Scherlinger\ M,\ et\ al.\ Switching\ from\ originator\ infliximab\ to\ biosimilar\ CT-P13\ in\ real-life:\ The\ weight\ of\ patient\ acceptance.\ Joint\ Bone\ Spine\ (2017),\ https://doi.org/10.1016/j.jbspin.2017.10.003$

BONSOI-4645; No. of Pages 7

ARTICLE IN PRESS

M. Scherlinger et al. / Joint Bone Spine xxx (2017) xxx-xxx

Table 2Analyses of association between switch failure, patient and disease characteristics at inclusion.

	Retention population $(n = 64)$	Failure population $(n = 25)$	Univariate analysis P-value	Multivariate analysis P-value
Patient characteristics		30= 25%		
Age	49.3 (1.65)	53.5 (2.64)	NS	
Male sex	63%	44%	0.11	0.255
Disease characteristics				
Disease duration, mean (S.D.)	15.1 (1,10)	18 (2.46)	NS	
Type of disease			0.02	0.061
Rheumatoid arthritis	6	8 17		
Spondyloarthritis	58	17		
Treatment characteristics				
Number of lines of biotherapy, mean (S.D.)	1.8 (0.11)	1.8 (0.22)	NS	
Infliximab infusion rhythm,	7.6 (0.23)	7.4 (0.25)	NS	
mean (S.D.)				
Infliximab infusion dose,	4.6 (0.16)	4.2 (0.20)	NS	
mean (S.D.)				
Number of infliximab infusions, mean (S.D.)	44.7 (3.29)	54.6 (7.48)	0.10	0.053
csDMARD	59%	68%	NS	
Dose, mean (S.D.)	12.8 (0.84)	10.8 (1.29)	NS	

csDMARD; conventional synthetic disease modifying antirheumatic drug; NS; not significant; S.D.; standard deviation,

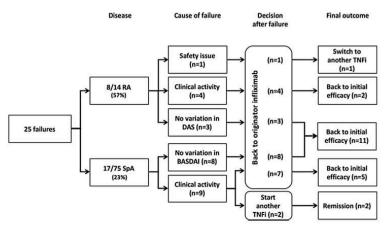


Fig. 2. Flow chart describing causes of switch failure and outcome after failure. IFX: infliximab; RA: rheumatoid arthritis; SpA: spondyloarthritis; TNFi: TNF-alpha inhibitor.

4.5. Safety

Nine patients experienced adverse events (AEs) and AEs was the cause of switch failure for one patient. Two patients reported infusion reactions (fever and chills), non-serious infections were reported by 4 patients. Two patients reported post-infusion mild headaches.

One patient with RA developed a mild serum-sickness-like disease after the third infusion of CT-P13. This infusion reaction recurred after reswitching to Ol. Infliximab was therefore definitively withdrawn and substituted with another anti-TNF α treatment with good outcome.

5. Discussion

In our cohort of patients with clinically controlled RA or SpA with OI treatment, the retention rate at a median time of 33 weeks after switching to CT-P13 was 72%. This rate was significantly lower than the one found in our two control cohorts (infliximab-naïve patients initiating CT-P13 and a historic cohort treated with OI). However, although the acceptation of CT-P13 was initially excellent, with 89% of patients accepting the switch, almost half (44%)

of the patients requesting to reswitch to OI reported a negative perception of the new treatment without any worsening of their disease activity score. After excluding patients without objective clinical activity, difference between our switch population and the control cohorts were abolished (log-rank *P*-value = 0.452). This discrepancy indicates that some patients were reluctant to the switch, despite initial acceptance.

On a total of a hundred patients who were proposed to switch, 89 accepted among which 13 failed because of objective clinical activity which is the expected rate of failure in patients treated with TNF blockers; 11 because of pain recurrence without objective findings; and one because of an AE. This means that at the end of study, 64% patients remained effectively treated with CT-P13 with a net gain of 3600€ per patient per year for the French health system (on a basis of 5 mg/kg/8 weeks for a 70kg patient, [Appendix A, document 51; see the supplementary material associated with this article online for details on calculation].

Bioequivalence was considered by health authorities following the results of two studies investigating bioclinical equivalence in RA patients for PLANETRA [12] and pharmacokinetic equivalence in AS patients for PLANETAS [13]. These two randomized double-blind studies showed similar tolerance and efficacy of CT-P13 compared

Please cite this article in press as: Scherlinger M, et al. Switching from originator infliximab to biosimilar CT-P13 in real-life: The weight of patient acceptance. Joint Bone Spine (2017), https://doi.org/10.1016/j.jbspin.2017.10.003

M. Scherlinger et al. / Joint Bone Spine xxx (2017) xxx-xxx

to OI in naïve patients after 30 weeks of treatment. In extension studies of PLANETRA [14] and PLANETAS [15], patients who received OI were switched to CT-P13 at week 52 and compared to the group receiving CT-P13 from the beginning. After an additional year of follow-up, there was no difference in terms of efficacy, tolerance and development of anti-drug antibodies (ADAb). These two studies founded the FDA and EMA approval for the use of CT-P13 and extrapolation to all OI indications.

However, more data are required for an appropriation of CT-P13 by patients and rheumatologists in daily practice. In this regard, two institutional studies have recently been published.

The Danish DANBIO registry brought data regarding 802 patients treated with OI for rheumatic disease who received nonmedical switch [16]. In Denmark, the switch was systematic for all patients receiving OI as health authorities only bought biosimilar infliximab, making OI no more available. For each patient, disease activity was compared 3 months before, at the time of the switch and 3 months after. Disease activity and flare rates remained equal during both intervals. Retention rates of the biosimilar was observed during the year following the switch. The biosimilar was withdrawn in 15% of the patients, for loss of efficacy or AEs; this rate was similar to the retention rate of OI observed in DANBIO during the year preceding the switch. To investigate the risk of inducing immunogenicity, residual infliximab concentration and anti-infliximab antibodies were assayed in 231 patients (among them 125 RA patients) before the switch, at month 3 and month 6; no difference was observed for the level of anti-infliximab antibodies at any time and infliximab concentration remained at similar level for a large majority of patients.

The NOR-SWITCH study conducted in Norway was the first, double-blind, non-inferiority phase IV study [17]. The authors randomized 481 patients with rheumatic or inflammatory bowel disease to either continue OI or to switch to CT-P13. After 52 weeks of follow-up, non-inferiority of CT-P13 over OI was demonstrated (with a 15% margin). This study also confirms the similar tolerance of the biosimilar and its originator. If the design of NOR-SWITCH is undoubtedly the best way to compare objectively the biosimilar to the originator molecule, such a study is far from the daily practice due to the selection of the patients and their blindness regarding the received treatment.

Our study much more reproduces clinical practice in countries where both originator and biosimilar drugs are available. Patients were informed of the wish of the physician to modify their treatment for non-medical reason. They had to give orally their consent, after clear information on the bioequivalence between OI and CT-P13. Patients were asked if they agreed to participate to the study and were informed that it will be possible to switch back to OI if they (or the physician) considered that the efficacy or the tolerance of the new treatment was not equivalent than with OI. The acceptance of the new treatment was therefore a major issue of the study, and the retention rate, our primary endpoint, reflects efficacy, tolerance as well as acceptance of the biosimilar. No data are available in the literature concerning patient acceptance of switching from an originator biologic to its biosimilar. In our study, although most patients had a good clinical control of their disease for years under OI, the principle of a switch for non-medical reason was initially well accepted in nearly 90 percent of the cases. Information given when proposing the switch is of primary importance, but there are many other factors, such as fears and beliefs, or poor perception of generics. During the treatment, mostly during the first couple of infusions (see survival curves Fig. 1), the subjective perception of an altered benefit of the treatment led eleven patients (12.5% of the patients who initially accepted the switch) to request to switch back to OI, although they presented no variation in their disease activity scores. This is a major concern for clinicians, health authorities and pharmaceutical companies, indicating that information on biosimilars will be a key point to promote the acceptance of switching a biodrug for a non-medical reason, that is a stylish language artifice to avoid employing the term of economic reason. Finally, it is noteworthy to notice that all these patients recovered their previous wellness by reswitching to OI.

Besides this main point on acceptance, our study provides results similar to those from DANBIO and NOR-SWITCH concerning efficacy and tolerance. First, when we focused on treatment failures based on disease activity scores and AEs, no significant difference was observed in the treatment retention rates of the switch population, the infliximab-naïve cohort and the historic cohort of patients. Concerning the safety, only one patient had to stop CT-P13 because of AEs; a mild serum-sickness-like disease[18]. The other AEs were mild and did not justify to stop the treatment or to reswitch to OI. Another question is immunogenicity, as it has been suggested that switching to biosimilar might increase the risk of immunization [19]. The immunogenicity was not investigated in our study. This question has been addressed in DANBIO and NOR-SWITCH and the production of ADAb was the same regardless the use of OI or CT-P13 [16,17]. Furthermore, two studies have shown that ADAb cross-react between OI and biosimilar infliximab [20,21]. Interestingly, most patients (82%) who were switched back to OI recovered a good efficacy, suggesting that multiple switches did not promote

Real-life experiences on the switch from an originator drug to its biosimilar for economic reasons are important for rheumatologists while the patent of many biologic DMARDs is expiring, leading to a rapid increase of the offering of biosimilars. In this respect, our work adds reassuring data to those of DANBIO and NOR-SWITCH studies concerning the efficacy and safety of the switch from OI to CT-P13; however, the main originality in our study is to emphasize the key role of patient acceptance of switching for a non-medical reason and highlights the value of the information given to patients.

Disclosure of interest

TS received honoraria as consultant from: Amgen, AbbVie, BMS, Janssen, MSD, Novartis, Pfizer, Roche Chugaï. UCB.

CR received honoraria as consultant from: Abbvie, BMS, MSD, Pfizer, Roche, UCB. BB received honoraria as consultant from Pfizer & Lilly; he received support from MSD for attending a scientific meeting

TS & CR received a research grant from Pfizer (unrelated to this work).

The other authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data (Document S1) associated with this article can be found, in the online version, at http://www.sciencedirect. com and https://doi.org/10.1016/j.jbspin.2017.10.003.

References

- Upchurch KS, Kay J. Evolution of treatment for rheumatoid arthritis. Rheumatology 2012;51:vi28-36.
 Gulácsi L, Brodszky V, Baji P, et al. Biosimilars for the management of rheumatoid arthritis: economic considerations. Expert Rev Clin Immunol 2015;11:43-52.
- Misra DP, Agarwal V, Sharma A, et al. update of the EULAR recommendations for the management of rheumatoid arthritis: a utopia beyond patients in low/middle income countries? Ann Rheum Dis 2017, http://dx.doi.org/ 10.1136/annrheumdis-2017-211446 [annrheumdis - 2017-211446].
- [5] Flodmark C-E, Lilja K, Woehling H, et al. Switching from originator to biosimilar human growth hormone using dialogue teamwork: single-center experience from Sweden. Biol Ther 2013;3:35–43.

Please cite this article in press as: Scherlinger M, et al. Switching from originator infliximab to biosimilar CT-P13 in real-life: The weight of patient acceptance. Joint Bone Spine (2017), https://doi.org/10.1016/j.jbspin.2017.10.003

BONSOI-4645; No. of Pages 7

RTICLE IN PRES

M. Scherlinger et al. / Joint Bone Spine xxx (2017) xxx-xxx

- [6] Weise M, Bielsky M-C, De Smet K, et al. Biosimilars: what clinicians should know. Blood 2012;120:5111-7.
 [7] Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62: 2500.
- [8] Rudwaleit M, van der Heijde D, Landewe R, et al. The development of Assess ment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis
- [9] SNFGE, GETAID, CREG. G., SNFGE, GETAID, CREGG. Société nationale française de gastro-entérologie (SNFGE) : information sur les inflix-imab biosimilaires 2015, http://www.snfge.org/actualite/information-sur-
- les-infliximab-biosimilaires.

 [10] Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492–509.
- [11] Braun J. First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis. Ann Rheum Dis 2006;65:316–20.
- [12] Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis 2013;72:1613-20.
- [13] ParkW, Hrycaj P, Jeka S, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis 2013;72:1605-12.

- [14] Yoo DH, Prodanovic N, Jaworski J, et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Ann Rheum Dis 2016;76:355–63 [annrheumdis – 2015-208786].
- 2015-208786].
 [15] Park W, Yoo DH, Miranda P, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. Ann Rheum Dis 2016;76:346-54 [annrheumdis - 2015-208783].

 [16] Glintborg B, Sørensen IJ, Loft AG, et al. A nationwide non-medical switch
- from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. Ann Rheum Dis 2017, http://dx.doi.org/10.1136/annrheumdis-2016-210742
- [annrheumdis 2016-210742].
 [17] Jørgensen KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double blind, non-inferiority trial. Lancet 2017, http://dx.doi.org/10.1016/S0140-6736(17)30068-5.

 [18] Scherlinger M, Schaeverbeke T, Truchetet M-E. Serum sickness-like
- disease after switching to biosimilar infliximab. Rheumatology 2017, http://dx.doi.org/10.1093/rheumatology/kex268.

 [19] Wadhwa M, Thorpe R. The challenges of immunogenicity in developing biosim-
- ilar products. IDrugs Investig Drugs J 2009;12:440–4.

 [20] Ruiz-Argüello MB, Maguregui A, Ruiz del Agua A, et al. Antibodies to infliximab in remicade-treated rheumatic patients show identical reactivity towards
- biosimilars. Ann Rheum Dis 2016;75:1693-6.

 [21] Ben-Horin S, Yavzori M, Benhar I, et al. Cross-immunogenicity: antibodies to infliximab in remicade-treated patients with IBD similarly recognise the biosimilar remsima. Gut 2016;65:1132-8.

Please cite this article in press as: Scherlinger M, et al. Switching from originator infliximab to biosimilar CT-P13 in real-life: The weight of patient acceptance. Joint Bone Spine (2017), https://doi.org/10.1016/j.jbspin.2017.10.003

Long-term follow-up after switching from originator infliximab to its biosimilar CT-P13: the weight of nocebo effect

Vincent Germain* a,b, Marc Scherlinger* a, b, c, Thomas Barnetche a, Thierry Schaeverbeke a, b, On behalf the FHU ACRONIM

Affiliations:

^a Centre Hospitalier Universitaire de Bordeaux, Service de Rhumatologie, Place Amélie Raba Léon, 33076 Bordeaux, France

^b Université de Bordeaux, 146 rue Léo Saignat, 33076 Bordeaux, France

° CNRS-UMR 5164 Immuno ConcEpT, 146 rue Léo Saignat, 33076 Bordeaux, France

On behalf of the Fédération Hospitalo-universitaire ACRONIM

* Authors contributed equally to the work

Corresponding author:

Pr Thierry Schaeverbeke

Service de rhumatologie, Hôpital Pellegrin, Place Amélie Raba Léon, 33076 Bordeaux, France

E-mail: thierry.schaeverbeke@chu-bordeaux.fr

Phone: +033 5 56 79 55 56

Fax: +033 5 56 79 60 84

Words: 593

References: 6

Keywords: DMARDs (biologic), anti-TNF-alpha, Rheumatoid arthritis, Spondyloarthritis,

patient attitude to health, nocebo effect

Acknowledgments: none.

Fundings: none to report for this study.

Disclosure of interest: TS received honoraria as consultant from: Amgen, AbbVie, BMS, Janssen, MSD, Novartis, Pfizer, Roche Chuqaï, UCB. TS received a research grant from Pfizer (unrelated to this work). The other authors report no conflicts of interests.

To date, all available data regarding the switch from bio-originator to its biosimilar are reassuring and the switch has been recommended as a shared patient-physician decision in recent consensus-based recommendations.(1) In particular, the NOR-SWITCH study, a 52-week randomized double-blind trial, strongly supports the efficacy and safety of the switch from originator infliximab (OI) to its biosimilar CT-P13 in patients with a stable disease.(2) However, long-term follow-up data are required to confirm the efficacy and safety of the switch.

In a previous real-life study, we demonstrated a high acceptance of 89% (89/100) and a 72% (64/89) retention rate after a median follow up of 33 weeks in a cohort of patients with stable rheumatic diseases switched from OI to CT-P13.(3) This retention rate was lower compared to two control cohorts: a historic cohort of 82 patients treated with OI in 2013, and a prospective cohort of 29 infliximab-naïve patients beginning CT-P13. Interestingly, 44% (11/25) of switched patients who had CT-P13 withdrawn did not present any objective disease activity (defined as BASDAI ≥4 and physician global assessment ≥4 for spondyloarthritis / DAS28-CRP ≥3.2 with ≥1 swollen joint for rheumatoid arthritis), suggesting a nocebo effect or incorrect causal attribution bias. When considering only patients with objective activity as CT-P13 failure, differences between cohorts faded, suggesting the neutrality of the switch in terms of efficacy and safety.

In the present work, our goal was to assess the long-term retention rate of CT-P13 after switching from OI, and to compare it with the retention rate observed in the historic cohort of patients treated with OI described in our previous study.(3)

In the switch cohort, 50/89 (56%) patients were still treated with CT-P13 after a median follow-up of 120 weeks (range 6 to 145). Among the 39 withdrawals, 25 (64%) patients

discontinued CT-P13 during the first period of follow-up,(3) whereas 14 (36%) patients discontinued CT-P13 later. Reasons for stopping CT-P13 belatedly were: an objective clinical worsening in 5/14 patients, non-serious safety issues in 6/14 patients (psoriatic lesions, digestive disorders, asthenia, and subjective neurological symptoms with negative extensive investigations as detailed in supplementary data) and stable remission in 3/14 patients. No case of subjective clinical worsening was observed during the second period of follow-up.

Treatment retention rates were 67% (55/82) for OI in the historic cohort after a median follow-up of 131 weeks (range 4 to 156). Survival curves of treatment retention taking all causes of withdrawals into account are shown in figure 1a. There was a statistical trend toward more withdrawals in the switch population compared to the historic cohort, as assessed by the log-rank analysis (p-value = 0.052). After excluding patients without objective clinical activity worsening, this statistical trend faded (log-rank p-value = 0.673), see figure 1b. Interestingly, infliximab retention rates were similar between the switch and the historic cohort when starting the analysis from the end of the first study as represented in figure 1c (log-rank p-value = 0.708).

These results suggest that a nocebo effect may occur in the first weeks after the switch and initially lowers the biosimilar retention rate, as already demonstrated in previous studies.(3, 4, 5) Thereafter, OI and CT-P13 retention rates appear to be identical, confirming the safety, efficacy and acceptability of the switch in the long-term. One of the strength of our study is a long term follow-up after the switch. Initial information provided before the switch appears to be crucial for biosimilar acceptance and therefore reducing the nocebo effect.(6) Patient and physician information on long-term

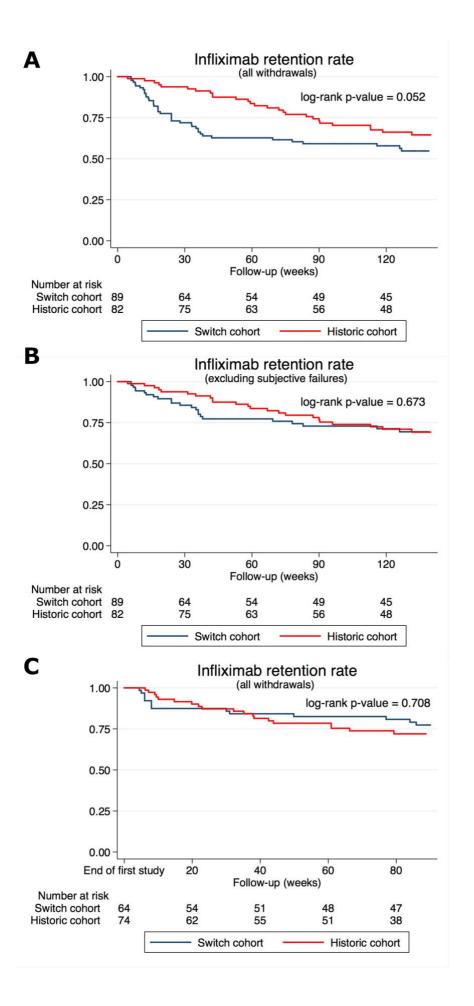
efficacy and safety of biosimilars are consequently a major need to enhance their widespread use.

References:

- 1. Kay J, Schoels MM, Dörner T, Emery P, Kvien TK, Smolen JS, et al. Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. Ann Rheum Dis. 2018 Feb;77(2):165–74.
- 2. Jørgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, Haavardsholm EA, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet Lond Engl. 2017 10;389(10086):2304–16.
- 3. Scherlinger M, Germain V, Labadie C, Barnetche T, Truchetet M-E, Bannwarth B, et al. Switching from originator infliximab to biosimilar CT-P13 in real-life: The weight of patient acceptance. Jt Bone Spine Rev Rhum. 2017 Nov 14;
- 4. Tweehuysen L, van den Bemt BJF, van Ingen IL, de Jong AJL, van der Laan WH, van den Hoogen FHJ, et al. Subjective Complaints as the Main Reason for Biosimilar Discontinuation After Open-Label Transition From Reference Infliximab to Biosimilar Infliximab. Arthritis Rheumatol Hoboken NJ. 2018 Jan;70(1):60–8.
- 5. Boone NW, Liu L, Romberg-Camps MJ, Duijsens L, Houwen C, van der Kuy PHM, et al. The nocebo effect challenges the non-medical infliximab switch in practice. Eur J Clin Pharmacol. 2018 May;74(5):655–61.
- 6. Rezk MF, Pieper B. To See or NOsee: The Debate on the Nocebo Effect and Optimizing the Use of Biosimilars. Adv Ther. 2018 Jun;35(6):749–53.

Figure legends:

- Figure 1a: Overall infliximab retention rates during complete follow-up.
- Figure 1b: Infliximab retention rates after excluding patients without objective clinical worsening during complete follow-up.
- Figure 1c: Overall infliximab retention rates from the end of the first study.



Seminars in Arthritis and Rheumatism 000 (2018) 1-6



Contents lists available at Science Direct

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit



Acceptance rate and sociological factors involved in the switch from originator to biosimilar etanercept (SB4)

Marc Scherlinger^{a,b,c,1,*}, Emmanuel Langlois^{b,c,d,1}, Vincent Germain^{a,b,1}, Thierry Schaeverbeke^{a,b,1}

- Service de Rhumatologie, Centre Hospitalier Universitaire de Bordeaux, Place Amélie Raba Léon, 33076 Bordeaux, France
- ^b Université de Bordeaux, 146 rue Léo Saignat, 33076 Bordeaux, France ^c CNRS-UMR 5164 Immuno Concept, 146 rue Léon Saignat, 33076 Bordeaux, France
- d CNRS-UMR 5516 Centre Emile Durkheim, 11 allée Ausone, 33607 Pessac Cedex France

ARTICLE INFO

ABSTRACT

Keywords: DMARDs (biologic) Patient perspective Rheumatoid arthritis Spondyloarthritis Anti-TNF

Objective: To study acceptance rate and factors influencing acceptance of the switch from originator etanercept (Enbrel®) to biosimilar etanercept (SB4, Bénépali®) in patients with rheumatic disease.

Methods: Patients with a well-controlled rheumatic disease consulting in our rheumatology department were offered the switch for SB4. After oral and written information concerning biosimilar, free choice to accept the switch was left to the patients. The main outcome was primary switch acceptance rate defined by switch acceptance during the initial consult. Real switch adherence, socio-cultural factors and beliefs influencing switch acceptance rate were retrieved during a telephonic interview at distance from the consultation.

Results: Fifty-two patients were eligible for the switch: 32 (62%) with spondyloarthritis and 20 (38%) with rheumatoid arthritis. The primary acceptance rate was 92% (48/52). Patients refusing the switch were more likely to report a bad opinion on generic drugs (100% vs 11%, p < 0.001). Other patient characteristics were roughly identical except for a statistical trend in the refusal group toward older age (61.4 vs 50.7 years, p = 0.08) and longer disease duration (26 vs 12.1 years, p = 0.05). Despite initial acceptance, two patients did not begin SB4 after receiving negative information by their regular pharmacist. Real SB4 switch rate was 85% (44/52) and 86% (38/44) of patients reported a good experience of the switch.

Conclusions: Acceptance rate of the switch from originator to biosimilar etanercept is high. Patient information, physician and pharmacist knowledge on biosimilars should be taken into account in order to improve their diffusion.

© 2018 Elsevier Inc. All rights reserved.

Introduction

The economic burden of inflammatory rheumatic diseases is high and biologic treatments represent an important part of rheumatoid arthritis (RA) direct costs [1]. Biosimilar DMARDs (bsDMARDs) offer an opportunity to reduce these costs and to improve the access to biologics in developing countries [2]. The financial issues are substantial. In the UK, the savings following the launch of infliximab and etanercept biosimilars and the price discounts of bio-originators compared to price before launch of biosimilars have been estimated to £38.8 million (€45.9 million) over two years [3

Regardless of the studies showing biosimilarity between bsDMARDs and their originator products with reassuring data on the switch [4], and despite the consensus-based recommendations

https://doi.org/10.1016/j.semarthrit.2018.07.005 0049-0172/© 2018 Elsevier Inc. All rights reserved. recently issued by an international group [5], biosimilars market remains limited in most countries where both originator and biosimilar treatments are available [6]. Among the factors limiting the switch from originator to its biosimilar for a non-medical reason, patient acceptance is of primary importance, as previously demonstrated in rheumatology settings [7,8]. Incomplete acceptance linked to a negative perception of the biosimilar may lead to a re-switch to the originator, often because of subjective complaints without worsening of disease activity scores, highly suggestive of a nocebo effect of the biosimilar [9]. At this time, little is known about factors influencing the acceptance of bsDMARDs, such as socio-cultural parameters, the confusion with generic drugs or even the lack of knowledge among health professionals. A better understanding of these factors could help us to improve the information given to patients in order to maximize the switch acceptance rate, therefore generating important savings.

We conducted a real-life study in the rheumatology department of Bordeaux university hospital by systematically offering a switch from originator etanercept (OE; Enbrel*) to biosimilar SB4

^{*} Corresponding author at: Service de rhumatologie, Hôpital Pellegrin, Place Amélie Raba Léon, 33076 Bordeaux, France.

E-mail address: marc.scherlinger@chu-bordeaux.fr (M. Scherlinger).

¹ On behalf of the Fédération Hospitalo-Universitaire ACRONIM.

M. Scherlinger et al. / Seminars in Arthritis and Rheumatism 00 (2018) 1-6

(Benepali*). The main outcome was the primary switch acceptance rate. The secondary outcomes were to evaluate real switch adherence, socio-cultural factors and fears or beliefs influencing the acceptance rate.

Patients and methods

Patients

Patients consulting in the rheumatology department of Bordeaux University Hospital between 1st May and 31 october 2017 were screened to participate in the study. They were proposed to participate if: (1) they presented a RA or a spondyloarthritis (SpA) according to the 2010 ACR/EULAR criteria and the 2009 ASAS criteria, respectively [10,11]; (2) they were treated with OE, in monotherapy or in association with conventional synthetic DMARDs (csDMARDs), under stable etanercept treatment regimen for at least 6 months; and (3) their disease was controlled according to the physician opinion.

Intervention

During a regular follow-up consultation, patients were given oral and written information on biosimilars (see translated document in supplementary material (1) and were proposed to switch for SB4 for non-medical reason. The information was provided by two rheumatology residents (MS & VG), who reached agreement before the beginning of the study to communicate homogenous information on: (1) the concept of biosimilars and the scientific evidence supporting their efficacy and their safety; (2) the physician's good opinion on biosimilars; (3) their lower price allowing savings for the health system; (4) the possibility to switch back to OE upon simple request in case of lack of efficacy or intolerance. Five to ten minutes of a thirty minutes consultation were devoted to provide information on biosimilar and to address the patient's questions. When oral consent was given, patients were switched to SB4 at the same regimen than previous OE, without any modification of associated csDMARDs or glucocorticoids.

After the initial consultation, a telephone interview was proposed to all patients, regardless of initial acceptance or refusal of the switch. All telephonic interviews were conducted by the same investigator (MS). The patients were asked a standardized set of open and closed questions concerning their socio-cultural background, their fears and beliefs, their adherence to treatments and other medical interventions (supplementary data 2). Patient experience about the switch was determined as well as the factors influencing their decision.

Outcome and follow-up

The main outcome was to assess the primary switch acceptance rate, defined by the proportion of patients accepting to switch from OE to SB4 during the initial consultation. The secondary outcomes were to evaluate the socio-cultural determinants and fears or beliefs influencing the acceptance rate, as well as the real adherence to the switch determined by reported biosimilar use. After the consultation, patients were followed prospectively until December 31st, 2017.

Statistical analysis

Quantitative variables, expressed as mean with standard deviation or median with range, were compared using a non-parametric Mann—Whitney analysis. Qualitative variables, expressed as proportions, were compared using Fisher's exact test. A p-value of less than 0.05 was considered as statistically significant.

Ethical statement

The study conforms with French ethical recommendations. For this type of sociological study, French legislation requires neither informed consent of the participant, nor independent validation of this work by an independent ethics committee.

Role of the funding source

No external funding to report for this study.

Results

Population characteristics

Fifty-two patients were included in the study between 1st May and 31st October 2017. Mean age was 51.7 ± 14.4 years and 23 (44%) were male. Twenty (38%) patients had RA and 32 (62%) had SpA including 24 axial spondyloarthritis, 4 psoriatic arthritis, 4 SAPHO syndromes and 2 reactive arthritis. Mean disease duration was 13.1 ± 11 years. At inclusion, mean DAS28-VS was 2.1 (±0.6) and mean BASDAI was 2.7 (±1.8). The patients were treated with OE for mean duration of 4.5 ± 3.3 years, and OE was the first line of biological therapy in 40 (77%) patients. Half of the patients were followed exclusively in the hospital, the other half concomitantly with a private practice rheumatologist. Other patient, disease and treatment characteristics are detailed in Table 1.

Patient reaction during the consultation

All patient accepted to receive information about biosimilars. The main questions raised by patients regarded the drug similarity in term of efficacy and safety. Many patients asked about the experience of the switch with other patients and were reassured by the existing data provided by the NOR-SWITCH and DANBIO studies [12,13].

In the subgroup of patients refusing the switch (n = 4), suspicious and defensive behavior was noted when the prospect of switching to a biosimilar was raised. These patients tended to have lower interest in biosimilar and to ask less questions on this subject (not objectively quantified).

Switch acceptance rate and outcomes

The primary switch acceptance rate (defined by switch acceptance during the initial consultation) was 92% (48/52; Fig. 1).

Table 1
Patient, disease and treatment characteristics

Characteristics at inclusion	Study cohort $(n = 52)$	
Patient characteristics		
Age, years, mean (S.D.)	51.7 (±14.4)	
Male Sex	44% (23/52)	
Disease characteristics		
Disease duration, years	13.1 (±11.0)	
Spondyloarthritis	62% (32/52)	
Axial spondyloarthritis	69% (22/32)	
BASDAI, mean	$2.7 (\pm 1.8)$	
Psoriatic arthritis	12.5% (4/32)	
Reactive arthritis	6% (2/32)	
SAPHO	12.5% (4/32)	
Rheumatoid arthritis	38% (20/52)	
DAS28-VS	$2.1 (\pm 0.6)$	
Treatment characteristics		
Number of lines of biotherapy, median (range)	1 (1-3)	
Originator etanercept use, years, mean (S.D.)	4.5 (±3.3)	
Associated csDMARD	54% (28/52)	
Shared follow-up (private practice & public hospital)	50% (26/52)	

M. Scherlinger et al. / Seminars in Arthritis and Rheumatism 00 (2018) 1-6

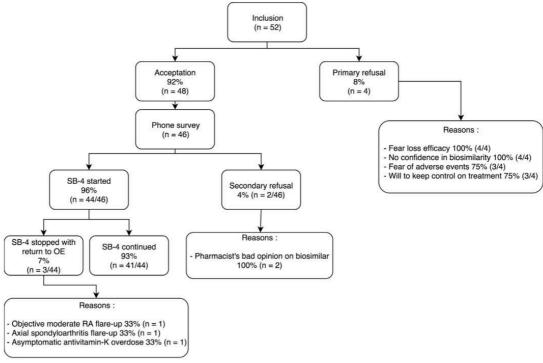


Fig. 1. Flow chat of the study.

After the consultation, 50 patients were successfully contacted and all agreed to participate in the survey. The telephone interview was not possible for two patients because of missing contact information. The telephonic survey occurred after a median of 16 weeks following the initial consultation (range 3–28 weeks).

Two patients did not begin SB4 despite their initial acceptation of the switch: for both patients, contradictory and negative information had been given by their regular pharmacist. One pharmacy continued to deliver OE although the medical prescription mentioned SB4.

After the switch, two patients developed a flare-up. One patient with RA reported increased arthralgia with moderate signs of disease activity assessed by musculoskeletal ultrasound (before switch DAS28-VS=2.1; after switch DAS28-VS=4.2), and was therefore switched back to OE. Two months after reswitching to OE, arthralgia and patient global assessment decreased to baseline but same level of objective signs of activity persisted (after OE resumption DAS28-VS=3.0); OE was continued following the patient's wish. One patient with AS reported increased axial pain with a morning stiffness lasting two hour after the switch. The BASDAI index was largely unchanged (6.0 before switch and 6.2 after switch) without C-reactive protein or erythrocyte sedimentation rate increase. In accordance to the patient wish, she was switched back to OE with good reported outcomes during a follow-up telephonic interview.

A third patient, treated with fluindione for cardiac arrhythmia requested to resume OE because of an asymptomatic increased INR above 4 which happened 10 weeks after the switch and that she attributed to SB4. Switching back to OE did not result in an improvement of the anticoagulant pharmacologic stability.

In total after the intervention, when considering missing data as failure to switch, 44 patients switched to SB4: 92% (44/48) of the patients with primary acceptance and 85% (44/52) of the total

population (Fig. 1). At the end of the follow-up, 41 patients were still treated with SB4 representing 85% (41/48) of the patients with primary acceptance, and 79% (41/52) of the total population (Fig. 1).

Factors influencing switch acceptance rate

Patients primary refusing the switch were more likely to report a bad opinion on generics: 100% (4/4) in the group refusing the switch versus 11% (5/46, p=0.001; Fisher's exact test). Other beliefs including bad opinions about vaccines or pharmaceutical industry were not associated with switch acceptance (Table 2). Patients refusing the switch had a statistical tendency to be older (61.4 vs 50.7 years, p=0.08; non-parametric Mann—Whitney test), to have a longer disease duration (26 vs 12.1 years, p=0.05) and to be treated with OE for a longer time (7.1 vs 4.3 years, p=0.24). These patients also presented non-significant trend toward a lower influenza and pneumococcal vaccines adherence (25% (1/4) vs 75% (36/48), p=0.07), as well as a lower adherence to the mandatory dermatologist and dentist annual screenings (50% (2/4) vs 81% (39/48), p=0.19).

The major concerns reported in the group primarily refusing to switch were: fear to lose efficacy of an effective and well tolerated treatment (100%, 4/4), lack of confidence in SB4 biosimilarity (100%, 4/4), fear of an adverse event related to SB4 (75%, 3/4), the will to keep control of their treatment (75%, 3/4; Fig. 1). None reported a lack of confidence in the attending physician as a cause of refusal. All these patients claimed that during the initial consult, no other argument could have convinced them to accept the switch.

In the primary acceptance group, two subgroups of patients could be identified. A first subgroup including 70% (32/46) of patients, for which the physician good opinion on biosimilars and patient

M. Scherlinger et al. / Seminars in Arthritis and Rheumatism 00 (2018) 1-6

Table 2Differences between acceptance and refusal cohort

Characteristics at inclusion	Acceptance cohort $(n = 48)$	Refusal cohort $(n = 4)$	p-value
Patient characteristics			
Age, years, mean (S.D.)	50.7 (±14.3)	61.4(±10.3)	0.08
Male Sex	44% (21/48)	50% (2/4)	1
Disease characteristics			
Disease duration, years	12.1 (±1.4)	26 (±9.1)	0.05
Spondyloarthritis	62.5% (30/48)	50% (2/4)	0.634
Axial spondyloarthritis	70% (21/30)	50% (1/2)	
BASDAI	2.83 (±0.40)	2 (NA)	0.55
Psoriatic arthritis	10% (3/30)	50% (1/2)	
Reactive arthritis	7% (2/30)	0%	
SAPHO	13% (4/30)	0%	
Rheumatoid arthritis	37.5% (18/48)	50% (2/4)	0.634
DAS28-VS	2.13 (±0.64)	1.91 (±0.26)	0.44
Treatment characteristics			
Number of lines of biotherapy, median (range)	1 (1-3)	1 (1-2)	0.94
Originator etanercept use, years, mean (S.D.)	4.3 (±3.0)	7.1 (±5.1)	0.24
Associated csDMARD	54% (26/48)	50%(2)	1
Alternate follow-up (liberal & hospital)	48% (23/48)	75%(3)	0.61
Observance		***	
Vaccines adherence	75% (36/48)	25%(1/4)	0.07
Dermatologist/dentist follow-up adherence	81% (39/48)	50%(2/4)	0.19
Beliefs			
Bad opinion about generics	11% (5/46)	100% (4/4)	0.001
Bad opinion about pharmaceutical industry	24% (11/46)	50% (2/4)	0.28
Bad opinion about vaccines	24% (11/46)	25% (1/4)	1

confidence in their physician were the major determinants of switch acceptance. Another subgroup including 30% (14/46) of patients, for which the bsDMARD lower price was the major determinant of switch acceptance.

Patient perception of the switch

Concerning patient perception, 86% (38/44) reported a good experience of the switch. Seven patients (15%) reported feeling pressured to accept the switch.

Three patients reported a positive effect of the switch on their pain index whereas four others reported a negative effect, two of them reswitching to OE with good outcomes.

Discussion

In this study involving 52 patients with a well-controlled rheumatic disease and consulting in outpatient settings of a tertiary center, we reported a 92% primary acceptation rate of the switch from originator to biosimilar etanercept.

A 92% acceptance rate seems very high for a switch for a non-medical reason, but is close to previous studies investigating biosimilar infliximab switch (86 to 89%) [7,8]. Biosimilar acceptance rate is however higher than the one of generic drugs, including in patients with chronic diseases. For example, a work investigating generic anti-retroviral medications in French HIV patients reported an acceptance rate as low as 44% [14].

The higher acceptance rate reported in our study can be explained by several factors. First, the switch was proposed by physicians used to offering the switch and giving a positive information on biosimilars, which has been shown to increase acceptance [14]. Moreover, written information was systematically provided (supplementary material 1), which has been described to increase patient acceptance of generics drugs [14]. To note, both investigators in charge of recruiting patients and offering the switch were rheumatology residents, suggesting that senior or professorial physician status are not mandatory to reach high acceptance rate. Patients have an ambivalent view of medications: drugs symbolize the power of science and technique

in their efficacy but also represent a potential toxic compound capable of inducing severe adverse effects [15]. Because generics main object is costs limitation, they are apprehended only on the toxic side, explaining their negative perception [15]. Other common explanation of generics' negative perception are a belief of counterfeit drugs (poor quality due to lower cost), a mistrust of foreign manufacturer, and a global skepticism due for example of a history of adverse effect with generics [16]. Differences between generics and biosimilars were underlined by the investigators, thus decreasing the bad representation associated with generics. Although biosimilar follow the same cost-reduction logic than generics, the physician must emphasize that a lesser price does not translate into a lesser quality drug. Moreover, due to the frequent change in manufacturing processes of originator biologics, patients have been treated with equivalent of biosimilars for years. Educating patients on these points seem crucial to promote switch acceptance [17]. Finally, patients were informed of the possibility of a switch back to OE upon request if they considered that tolerance or efficacy was not deemed equivalent, probably improving the acceptance rate.

Health professionals' knowledge and acceptance of bsDMARDs are also crucial. During the initial consultation, information was delivered by a physician convinced of the importance of biosimilars as well as their good efficacy and safety. Physician's good opinion on biosimilar was the main reason of acceptation for 70% of patients, which is concordant with a Belgian survey involving patients with inflammatory rheumatic disease [18]. However, physician knowledge on biosimilars is sometimes scarce, thus limiting their use [18]. In two American surveys, only 40% of rheumatologists recognized that biosimilar matched efficacy and safety of the originator product. In the French BRIO study, only 64% of French rheumatologists felt capable of explaining the concept of biosimilar [19]. Finally, roughly 60% of French or American rheumatologists don't consider to switch patients receiving originator biologics, suggesting mistrust or at least, cautiousness in their use [19,20].

In our study, two patients initially accepted the switch but later reported to have continued OE despite initial acceptance after receiving negative information regarding biosimilars from their regular pharmacist. In one case, the pharmacy continued to deliver OE

although the prescription mentioned SB4 which is normally not allowed in France. The data suggest that providing physicians and pharmacists with a better knowledge of bsDMARDs might increase their acceptance, both in health care professionals and in patients, by allowing the delivery of adequate and positive information.

In patients refusing the switch, there was a statistical trend toward older age, longer disease duration and longer etanercept use. characteristics often found in case of generics refusal [21,22], Patientphysician relationship is characterized by an implicit contract concerning treatment efficacy in their condition. In patient perception, the switch might be felt as the introduction of a new (different) drug, therefore introducing uncertainty in their treatment. Uncertainty takes a major toll on RA patient's daily burden [23], and the relevance of this assumption is supported by the fact that all patients refusing the switch reported that the fear of a loss of efficacy was one of the main reason for their choice. Moreover, the switch might also introduce uncertainty in patient-physician relationship with the idea that the prescriber is taking into account treatment costs over its efficacy and patient's own benefit. In fact, costs are often secondary when considering patient's decision to accept a drug [24]. Interestingly, prescribers are able to overcome these fears and doubts by providing positive and reassuring information: in our study, 70% patients reported that physician's good opinion of the biosimilar was the main reason for their acceptance. Finally, although thorough information on biosimilar was given, all patients refusing biosimilar had a negative opinion of generics which is therefore an important prognostic factor of switch acceptance. These results suggest that providing patient with positive and reassuring information on biosimilars and underlining differences between generics and bsDMARDs are likely to increase patient acceptance.

After switching, 7% (3/43) of patients switched back to OE. Although long term maintenance rate was not the object of this study and in harmony with previously published data [7,8,13,25], a small proportion (between 5 to 15%) of patients discontinued the biosimilar in the months following the switch. After the switch, 3 patients reported a lower pain index whereas 4 reported increased pain, possibly linked to the natural process of rheumatic diseases with alternation of more and less painful periods, and once more suggesting that the nocebo effect or the incorrect causal attribution bias are at play. Almost 9 out of 10 patients reported a good switch experience irrespective of switch outcome, confirming that when properly exposed, the switch is not a traumatic event for the vast majority of patients. In the recently published Dutch BIO-SPAN study, patients with rheumatic disease accepting the switch from OE to SB4 (99% of patients accepted the switch) were followed prospectively to assess SB4 persistence rate [26]. Compared to an historical cohort of patients treated with OE, the authors found a statistically but not clinically significant lower persistence rate (90% vs 92%) and an increased incidence of subjective adverse events which are likely to be related to a nocebo effect. Interestingly, patients were randomized to receive questionnaires on expectations and beliefs in order to assess if those primed or prevented a nocebo effect, which they did not.

Biosimilar penetrance remains moderate in most developed countries where the switch has not been imposed by health authorities [6]. Yet, a 100% biosimilar market coverage is not necessarily the target to reach, which is for several reasons. First, pharmaceutical competition is one of the main driver of price reduction [27]. Secondly, a subset of refractory patient is likely to never accept the switch, irrelevant of any intervention reinforcing acceptance. Forcing the switch on these patients could be counterproductive, leading to the appearance of subjective complaints mandating a switch to another potentially still patented biologic. In France, health authorities have recently set a goal of 70% bsDMARDs use, a goal which appears to be reasonable and accessible.

This study should help to reach the target of at least 70% bsDMARDs use by highlighting the key factors improving their acceptance, specifically; improving health professionals' knowledge of bsDMARDs, delivering a thorough oral and written information on bsDMARDs to the patients, underlining the differences between biosimilars and generic drugs, and informing them of the possibility of a re-switch to the originator biologic if requested. Considering that the 2015 annual cost of Enbrel® was £408 million/year (€482 million) in the UK [28], and that the discount of the biosimilar is roughly 20%, achievement of 70% use of biosimilar etanercept would correspond to an annual cost saving of £81.6 million/year (€96.4 million).

Role of the funding source

No external funding to report for this study.

Disclosure of interest

TS received honoraria as consultant from: Amgen, AbbVie, BMS, Janssen, MSD, Novartis, Pfizer, Roche Chugaï, UCB. TS received a research grant from Pfizer (unrelated to this work).

Conflict of interest

The other authors report no conflict of interests.

Acknowledgement

Thomas Barnetche for the help concerning the ethics consideration.

References

- [1] Gulácsi L, Brodszky V, Baji P, et al. Biosimilars for the management of rheumatoid arthritis: economic considerations. Expert Rev Clin Immunol 2015;11:43–52. https://doi.org/10.1586/1744666X.2015.1090313.

 [2] Dörner T, Strand V, Cornes P, et al. The changing landscape of biosimilars in rheu-
- matology. Ann Rheum Dis 2016;75:974-82. https://doi.org/10.1136/an
- [3] Aladul MI, Fitzpatrick RW, Chapman SR. Impact of infliximab and etanercept biosimilars on biological disease-modifying antirheumatic drugs utilisation and NHS budget in the UK, BioDrugs Clin Immunother Biopharm Gene Ther 2017;31:533-44 https://doi.org/10.1007/s40259-017-0252-3
- 44. https://doi.org/10.1007/s40259-017-0252-3.
 [4] Emery P, Vencovský J, Sylwestrzak A, et al. Long-term efficacy and safety in patients with rheumatoid arthritis continuing on SB4 or switching from reference etanercept to SB4. Ann Rheum Dis 2017. https://doi.org/10.1136/annrheumdis-2017-211591. annrheumdis-2017-211591. [5] Kay J, Schoels MM, Dörner T, et al. Consensus-based recommendations for the use
- osimilars to treat rheumatological diseases. Ann Rheum Dis 2018;77:165-74. https://doi.org/10.1136/annrheumdis-2017-211937. [6] Schaeverbeke T, Pham T, Richez C, et al. Biosimilars: an opportunity. Position
- [6] Schaeverbeke T, Pham T, Richez C, et al. Biosimilars: an opportunity. Position statement of the french rheumatiology society (SFR) and inflammatory rheumatic disease club (CRI). Joint Bone Spine 2018. https://doi.org/10.1016/ji.bspin.2018.03.002. Published Online First:.
 [7] Scherlinger M, Germain V, Labadie C, et al. Switching from originator infliximab to biosimilar CT-P13 in real-life: the weight of patient acceptance. Joint Bone Spine 2017. https://doi.org/10.1016/j.jbspin.2017.10.003. Published Online First..
 [8] Tweehuysen L, van den Bemt BJF, van Ingen LL, et al. Subjective complaints as the main reason for biosimilar discontinuation after open-label transition from reference infliximals. In biosimilar diffiximals for Arthritis Rheumatal 2018; 276 60-8.
- ence infliximab to biosimilar infliximab. Arthritis Rheumatol 2018:70:60-8. 002/art.40324
- [9] Rezk MF, Pieper B. Treatment outcomes with biosimilars: be aware of the nocebo effect. Rheumatol Ther 2017;4:209–18. https://doi.org/10.1007/s40744-017-0085-z. [10] Aletaha D, Neogi T, Silman AJ, et al. Rheumatoid arthritis dassification criteria: an
- American college of rheumatology/European league against rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–81. https://doi.org/10.1002/art.27584.
 [11] Rudwaleit M, Landewe R, van der Heijde D, et al. The development of assessment
- of SpondyloArthritis international society classification criteria for axial spondy-loarthritis (Part I): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis 2009;68:770-6. https://doi.org/10.1136/
- [12] Jürgensen KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximal (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lan-
- cet 2017;389:2304–16. https://doi.org/10.1016/S0140-6736(17)30068-5.
 [13] Glintborg B, Sùrensen IJ, Loft AG, et al. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory

M. Scherlinger et al. / Seminars in Arthritis and Rheumatism 00 (2018) 1-6

- arthritis: 1-year clinical outcomes from the DANBIO registry, Ann Rheum Dis
- 2017;76:1426–31. https://doi.org/10.1136/annrheumdis-2016-210742. Jacomet C, Allavena C, Peyrol F, et al. Perception of antiretroviral generic medicines: one-day survey of HIV-infected patients and their physicians in France. PloS One 2015;10:e0117214.
- PloS Une 2015; 10:e0117214. Sarradon A, Blanc M-A, Faure M. Des usagers sceptiques face aux médicaments génériques : une approche anthropologique.. Rev Epidémiologie Santé Publique 2007;55:179–85. Article in French.
- [16] Dunne SS, Dunne CP. What do people really think of generic medicines? A systematic review and critical appraisal of literature on stakeholder perceptions of generic drugs. BMC Med 2015;13:173. https://doi.org/10.1186/s12916-015-0415-3.
- [17] Goll GL, Haavardsholm EA, Kvien TK. The confidence of rheumatologists about switching to biosimilar for their patients. Joint Bone Spine 2018. https://doi.org/ 10.1016/j.jbspin.2018.03.009. Published Online First: April. [18] van Overbeeke E, De Beleyr B, de Hoon J, et al. Perception of originator biologics and
- van Overbeeke E, De Beiegy B, de Hoon J, et al. Perception of originator biologics and biosimilars: a survey among belgian rhematoid arthritis patients and rheumatologists. BioDrugs 2017;31:447–59. https://doi.org/10.1007/s40259-017-0244-3.

 Cohen J, Bocquet F, Fayet F, Flipo R, Gaertner P, Grange L, et al. PE0105:biosimilaires en rhumatologie: information et opinions des rhumatologues hospitaliers français, résultats de l'étude BRIO. Rev Rhum 2017;84(Supplement 1):A262–332.

 Articla in Fennich.
- [20] Gibofsky A, Badawi S. Biosimilar knowledge among US rheumatologists a survey. ACR Meeting Abstracts. Available from: http://acrabstracts.org/abstract/bio-similar-knowledge-among-us-rheumatologists-a-survey/.
- [21] Shrank WH, Stedman M, Ettner SL, et al. Patient, physician, pharmacy, and pharmacy benefit design factors related to generic medication use. J Gen Intern Med 2007;22:1298–304. https://doi.org/10.1007/s11606-007-0284-3.

- [22] Decollogny A, Eggli Y, Halfon P, et al. Determinants of generic drug substitution in Switzerland. BMC Health Serv Res 2011;11:17. https://doi.org/10.1186/
- 1472-6963-11-17.
 Wiener CL. The burden of rheumatoid arthritis: tolerating the uncertainty. Soc Sci Med (1967) 1975:9:97-104
- [24] Doran E, Robertson J, Henry D. Moral hazard and prescription medicine use in Australia—the patient perspective. Soc Sci Med (1982) 2005;60:1437–43. https:// ed.2004.08.005
- dollorg 10.1016),Socscimed.2004.08.005.
 Avouac J, Moltó A, Abitbol V, et al. Systematic switch from innovator infliximab to biosimilar infliximab in inflammatory chronic diseases in daily clinical practice: the experience of cochin university hospital, Paris, France. Semin Arthritis Rheum 2018:47:741-8, https://doi.org/10.1016/j.semarthrit.2017.10.002
- [26] Tweehuysen L, Huiskes VJ, van den Bemt BJ, et al. Open-label non-mandatory transitioning from originator etanercept to biosimilar SB4: 6-month results from a controlled cohort study. Arthritis Rheumatol 2018. https://doi.org/10.1002/ art.40516. Published Online First.
- [27] Puig-Junoy J. Impact of european pharmaceutical price regulation on generic price competition: a review. PharmacoEconomics 2010;28:649–63. https://doi. org/10.2165/11535360-000000000-00000.
- [28] Prescribing Costs in Hospitals and the Community, England 2015/16 NHS Digital. Available from: http://digital.nhs.uk/catalogue/PUB22302.

Supplementary materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2018.07.005.

- 30 -

orrespondence

Switching from the bio-originators to biosimilar: is it premature to recommend this procedure?

We read with interest the recently published recommendations for the use of biosimilars in rheumatology practice. 1 However, we have some concerns regarding recommendation 6 on the efficacy and safety of switching from the originator biologic to the respective biosimilar. Considering the strong impact of the European League Against Rheumatism recommendations on real-life clinical decisions, such recommendation seems not sufficiently supported by the evidence because available data do not allow to draw definitive conclusion on the switching strategy. To date, the efficacy and safety of infliximab and etanercept biosimilars in substitution of the bio-originators have been assessed in four long-term extension reports following the blinded phase of the respective randomised controlled trials (RCTs),2 the transposition of these results to the real-life practice seems rather questionable. Indeed, patients treated in the setting of real-world practice greatly differ from those enrolled in clinical trials, as suggested by an analysis from the German Rheumatoid Arthritis: Observation of Biologic Therapy (RABBIT) registry showing that only 21%-33% of the included patients would have been eligible for RCTs.6 Also the results of the Norwegian Switch study (NOR-SWITCH) trial do not adequately support the switching strategy from infliximab originator (re-IFX) to infliximab biosimilar (bio-IFX) in patients with inflammatory rheumatic diseases because only 198 (41%) out of 481 enrolled patients had a rheumatic disorder, including 91 (18.9%) spondyloarthritis (SpA), 77 (16%) rheumatoid arthritis (RA) and 30 (6.2%) psoriatic arthritis (PsA). Consequently, the study lacks of statistical power with important repercussion on the clinical significance of the results in patients with SpA, RA and PsA. The Danish Nationwide Biologic (DANBIO) registry reported data from a large series of 802 patients with RA, SpA and PsA who were switched from re-IFX to bio-IFX.8 No negative impact of bio-IFX on the disease activity was recorded, but the retention rate was significantly lower as compared with a historical cohort of patients receiving re-IFX (86.8% vs 83.4%; P: 0.03). Similar findings have been recently observed in other clinical series from Turkey.

Data from the DANBIO registry on the switching from originator etanercept (re-ETN) to biosimilar etanercept (bio-ETN) were recently presented. At the end of the follow-up period, bio-ETN was withdrawn in 129 (8.3%) out of 1548 patients who were in clinical remission prior to the switching. Confirming the different clinical characteristics of patients treated in reallife practice, despite a shorter follow-up duration of 5 months, the percentage of withdrawals was higher than in the study of Emery and colleagues (5% over 48 weeks). In this sense, the paucity of data from real life and the absence of controlled trials suggest that also recommendation 7 (evidence level 5 and degree of recommendation D) may be misleading for clinicians, who may be driven by health authorities to choices made only on an economic basis.

To conclude, in our opinion, available data from real-world clinical practice, somewhat conflicting with those of RCTs, seem to suggest that it is premature to formulate recommendations on the switching strategy from the bio-originator to its biosimilar.

Fabrizio Cantini. 1 Maurizio Benucci²

¹Department Rheumatology, Azienda USL Toscana Centro, Hospital of Prato, Prato, Italy

²Rheumatology Clinic, Azienda USL Toscana Centro, Nuovo S Giovanni di Dio Hospital, Florence, Italy

Correspondence to Dr Fabrizio Cantini, Department Rheumatology, Azienda USL Toscana Centro, Hospital of Prato, Prato 59100, Italy; fbrzcantini@gmail.com

Handling editor Josef S Smolen

Contributors FC and MB equally contributed to writing the manuscript.

Competing interests None declared.

Provenance and peer review Not commissioned; internally peer reviewed.

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.



To cite Cantini F, Benucci M. Ann Rheum Dis Published Online First: [please include Day Month Year]. doi:10.1136/annrheumdis-2017-212820

Received 9 December 2017 Accepted 15 December 2017

Ann Rheum Dis 2017;0:1. doi:10.1136/annrheumdis-2017-212820

REFERENCES

- Kay J, Schoels MM, Dörner T, et al. Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. Ann Rheum Dis 2017:annrheumdis-2017-211937.
- 2 Yoo DH, Prodanovic N, Jaworski J, et al. Efficacy and safety of CT-P13 (biosimilar infiliximab) in patients with rheumatoid arthritis: comparison between switching from reference infiliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Ann Rheum Dis 2017;76:355–63.
- 3 Park W, Yoo DH, Miranda P, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. Ann Rheum Dis 2017;76:346–54.
- 4 Emery P, Vencovský J, Sylwestrzak A, et al. Long-term efficacy and safety in patients with rheumatoid arthritis continuing on SB4 or switching from reference etanercept to SB4. Ann Rheum Dis 2017;76:1986–91.
- 5 Tanaka Y, Yamanaka H, Takeuchi T, et al. Safety and efficacy of CT-P13 in Japanese patients with rheumatoid arthritis in an extension phase or after switching from infliximab. Mod Rheumatol 2017;27:237–45.
- 6 Zink A, Strangfeld A, Schneider M, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials. Arthritis Rheum 2006;54:3399–407.
- 7 Jørgensen KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet 2017;389:2304–16.
- 8 Glintborg B, Sørensen IJ, Loft AG, et al. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. Ann Rheum Dis 2017;76:1426–31.
- 9 Yazici Y, Xiel OA, Parenti D, et al. A descriptive analysis of real-world treatment patterns of innovator infliximab (Remicade) and biosimilar infliximab in a treatment naïve Turkish rheumatologic disease population. 2017 EULAR meeting poster session RRI0211, Madrid, Spain. Ann Rheum Dis 2017;76(Suppl 2):562.
- 10 Glintborg B, Sørensen IJ, Loft AG, Esbesen J, et al. Clinical outcomes from a nationwide non-medical switch from originator to biosimilar etanercept in patients with inflammatory arthritis after 5 months follow-up. Results from the DANBIO registry. Ann Rheum Dis 2017;76(Suppl 2):553.

BMI

Ann Rheum Dis Month 2017 Vol 0 No 0

eular

Response to: 'Switching from the bio-originators to biosimilar: is it premature to recommend this procedure?' by Cantini and Benucci

In their correspondence, Cantini and Benucci¹ express their concern about the lack of real-life data supporting the switch from originator to biosimilar biological disease-modifying antirheumatic drugs, as recommended in the recently issued consensus-based recommendations.2 They argue that the Danish Nationwide Biologic (DANBIO) registry reporting real-life data showed a lower than expected retention rate after the switch to biosimilar infliximab (bio-IFX) and etanercept.34

Concerning bio-IFX, several other real-life studies have been published so far. One Dutch and one French open studies have examined real-life outcomes of the switch from originator to bio-IFX in patients with inflammatory rheumatic diseases. Both studies revealed a bio-IFX retention rate between 72% and 76%, which is lower than the expected originator IFX retention rate. Interestingly, the two studies reported that a significant proportion of patients stopping bio-IFX presented subjective complaints without any clinical sign of disease activity. In the French study, exclusion of the subgroup of patients presenting only subjective complaints (44% of dropouts) suppressed the difference in retention rate when compared with a historic cohort of original IFX (ori-IFX) treated patients. Finally, both studies allowed patients to switch back to ori-IFX. Patients presenting with subjective complaints were rescued by ori-IFX resumption, whereas those with objective symptoms were more likely to switch to another biologic.

These results strongly suggest that the lower retention rate after the switch is due to a nocebo effect,7 or an incorrect attribution bias where a random flare-up is falsely attributed to an unrelated factor (eg, the switch).

To put it in other words, if 100 patients are switched from ori-IFX to bio-IFX, roughly 70% will continue the biosimilar, 15% will present IFX failure with objective signs of activity (as expected without the switch) and 15% will develop subjective symptoms that can be rescued with ori-IFX resumption. Thus, one can see the glass half full or half empty. We prefer to see evidence that in case of switch, 70% of patients will remain treated with the biosimilar leading to substantial savings for the health system, and that the other 30% will switch back either to the originator or to another biologic.

We therefore fully support the task force guidelines including recommendation 6 stating that the switch from an originator biologic to its biosimilar appears safe and that this recommendation deserves a 1b level of evidence.

Biologics have changed the prognostic of patients with rheumatic diseases. However, this breakthrough has come with substantial costs that our health systems have difficulties to cope with. Biosimilar might be one of the solutions for this serious

issue. In the UK, considering that IFX and etanercept are estimated to cost £408 million/year (€482 million) and that biosimilar prices are on average 20% lower than originator prices, a 70% biosimilar switch rate would account for savings of 81.6 million/year (€96.4 million).8

Biosimilars have, for now, consistently shown that a lower price does not equal a lesser quality. Continuous diffusion, pharmacovigilance and research around biosimilars will allow to address the remaining questions on their use and reassure patients and physicians about their safety.

Marc Scherlinger, Thierry Schaeverbeke

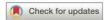
Department of Rheumatology, Centre Hospitalier Universitaire de Bordeaux,

Correspondence to Dr Marc Scherlinger, Department of Rheumatology, Centre Hospitalier Universitaire de Bordeaux, Bordeaux 33076, France; marc.scherlinger@chu-bordeaux.fr

Competing interests None declared.

Provenance and peer review Not commissioned; internally peer reviewed.

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.



To cite Scherlinger M, Schaeverbeke T. Ann Rheum Dis Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2018-213021

Received 15 January 2018 Accepted 17 January 2018

Ann Rheum Dis 2018:0:1 doi:10.1136/annrheumdis-2018-213021

- Cantini F, Benucci M. Switching from the bio-originators to biosimilar: is it premature to recommend this procedure? *Ann Rheum Dis* 2017. doi: annrheumdis-2017-212820 [Epub ahead of print: 29 Dec 2017].
- Kay J, Schoels MM, Dörner T, et al. Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. Ann Rheum Dis 2018;77:165–74.
- Glintborg B, Sørensen U, Loft AG, et al. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. Ann Rheum Dis 2017;76:1426-31.
- Glintborg B. Omerovic E. Danebod K. et al. One-year clinical outcomes in 1623 patients with inflammatory arthritis who switched from originator to biosimilar etanercept an Observational Study from the Danish Danbio Registry. ACR Meet. Abstr. 2017 http://acrabstracts.org/abstract/one-year-clinical-outcomes-in-1623-patients-within flammatory-arthritis-who-switched-from-originator-to-biosimilar-etaner cept-an-originator and the substitution of the subobservational-study-from-the-danish-danbio-registry/ (accessed 25 Dec 2017).
- Tweehuysen L, van den Bemt BJF, van Ingen IL, $et\,al.$ Subjective complaints as the main reason for biosimilar discontinuation after open-label transition from reference infliximab to biosimilar infliximab. Arthritis Rheumatol 2018;70:60–8.
 Scherlinger M, Germain V, Labadie C, et al. Switching from originator infliximab to
- biosimilar CT-P13 in real-life: the weight of patient acceptance. *Joint Bone Spine* 2017. doi: 10.1016/j.jbspin.2017.10.003 [Epub ahead of print: 14 Nov 2017].
- Rezk MF, Pieper B. Treatment outcomes with biosimilars: be aware of the nocebo effect. Rheumatol Ther 2017:4:209-18.
- NHS Digital. Prescribing costs in hospitals and the community, England 2015/16. http:// digital.nhs.uk/catalogue/PUB22302 (accessed 8 Jan 2018).

Ann Rheum Dis Month 2018 Vol 0 No 0 eular

Response to: 'Seeing the glass either half full or half empty: response to the correspondence 'Switching from the bio-originators to biosimilar: is it premature to recommend this procedure?" by Scherlinger and Schaeverbeke

We are grateful to Scherlinger and Schaeverbeke for their reply to our letter.

We would like to remind that in our letter we raised several concerns regarding the low grade of evidence supporting recommendation 6 on the switching procedure, as reported in the recently published recommendations for the use of biosimilars in rheumatology practice.²³ We believe that international recommendations should be based on solid bases, and, as underlined in our letter, by analysis of the existing literature, the evidence of such strategy in terms of efficacy, safety, retention rate and also economic advantages is poor. In particular, the colleagues focus their remarks on reduced bio-etanercept and bio-infliximab retention rates observed in the Danish Registry of Biologics (DANBIO) registry, ^{4,5} suggesting that a consistent percentage of biosimilar interruption was related to the nocebo effect. In this sense, we have at least two considerations. First, the nocebo effect is a well-known phenomenon that may negatively influence the response to therapies. However, the clinical features of nocebo effect are complex, rather undefined, not supported by adequate controlled studies, and with unavailable validated classification/diagnostic criteria, ⁶ thus making its borders rather foggy and difficult to address. Second, whatever the reason for the reduced retention rate, by contrast with the previous longterm treatment with the originators (infliximab and etanercept mean treatment duration of 6.8 years and 5.2 years, respectively), up to 30% of patients of DANBIO registry discontinued the biosimilar over a short-term follow-up.^{4,3} It should be kept in mind that the discontinuing patients were in clinical remission or low disease activity before switching, that is to say they exchanged a full glass with an empty glass.

Regarding the economic evaluation discussed by the colleagues,1 the possibility that biosimilars would be considered a solution for health systems in economic difficulty, with a saving of 81.6 million/year, in a substantial absence of specific cost-effectiveness studies, should be temporarily considered as speculative. In previously mentioned studies, there emerged an efficacy loss ranging from 8.3% to $30\%.^{4.5}$ In Italy the yearly price difference between biosimilar etanercept and the originator is €1 900.00 (€7 580.00 vs €9 480.00). Available data show that the treatment costs for patients switching from initial treatment during the first year of follow-up were higher than for patients who did not switch (€12 710.00 vs €11 332.00), with a difference of €1 378.00.7 The Incremental cost-effectiveness/quality-adjusted life year (ICER)/QALY of etanercept ranges from €15 315.00 when we consider direct and indirect costs, and up to €38 639.00 for direct costs only.8 No cost-effectiveness analysis data have been produced with SB4 biosimilar etanercept, but Yisaipu, another biosimilar of etanercept, in a model based on the PRESERVE study,9 had an estimated ICER of between \$18 324 and \$40 333 with the best strategy and \$12 735 when the dose is reduced to 25 mg in the first 9 months.

If we consider the cost of the switch for ineffectiveness and adverse events and the indirect costs of worsening QALY, we

believe that savings are weak and drug-free remission and biological dose down-titration therapeutic strategy are currently the best options to achieve cost savings.11

Fabrizio Cantini. 1 Maurizio Benucci

¹Rheumatology Department, Azienda USI, Toscana Centro, Hospital of Prato, Prato,

²Rheumatology Clinic, Azienda USL Toscana Centro, Nuovo S Giovanni di Dio Hospital, Florence, Italy

Correspondence to Dr Fabrizio Cantini, Rheumatology Department, Azienda USL Toscana Centro, Hospital of Prato, 59100 Prato PO, Italy; fbrzcantini@gmail.com

Handling editor Josef S Smolen

Contributors FC and MB equally contributed to writing the letter.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.



To cite Cantini F, Benucci M. Ann Rheum Dis Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2018-213044

Received 23 January 2018 Accepted 24 January 2018



► http://dx.doi.org/10.1136/annrheumdis-2018-213021

Ann Rheum Dis 2018;0:1. doi:10.1136/annrheumdis-2018-213044

- Scherlinger M, Schaeverbeke T. Seeing the glass either half full or half empty: response to the correspondence "Switching from the bio-originators to biosimilar: is it premature to recommend this procedure?". Ann Rheum Dis 2018.
- Cantini F, Benucci M. Switching from the bio-originators to biosimilar: is it premature to recommend this procedure? *Ann Rheum Dis* 2017. 10.1136/ annrheumdis-2017-212820. [Epub ahead of print 29 Dec 2017].
- Kay J, Schoels MM, Dörner T, et al. Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. *Ann Rheum Dis* 2018;77:165–74.
- 4 Glintborg B, Sørensen IJ, Loft AG, et al. FRI0190 Clinical outcomes from a nationwide non-medical switch from originator to biosimilar etanercept in patients with inflammatory arthritis after 5 months follow-up. results from the DANBIO registry. Ann Rheum Dis 2017:76:553-4.
- 5 Glintborg B, Sørensen IJ, Loft AG, et al. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory ritis: 1-year clinical outcomes from the DANBIO registry. *Ann Rheum Dis* 2017:76:1426-31
- Planès S, Villier C, Mallaret M. The nocebo effect of drugs. Pharmacol Res Perspect 2016:4:e00208.
- 7 Degli Esposti L, Favalli EG, Sangiorgi D, et al. Persistence, switch rates, drug consumption and costs of biological treatment of rheumatoid arthritis: ar observational study in Italy. *Clinicoecon Outcomes Res* 2017;9:9–17.
- Joensuu JT, Huoponen S, Aaltonen KJ, et al. The cost-effectiveness of biologics for the treatment of rheumatoid arthritis: a systematic review. PLoS One 2015;10:e0119683.
- 9 Smolen JS, Nash P, Durez P, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. Lancet 2013:381:918-29
- Wu B, Song Y, Leng L, et al. Treatment of moderate rheumatoid arthritis with different strategies in a health resource-limited setting: a cost-effectiveness analysis in the era of biosimilars. Clin Exp Rheumatol 2015;33:20–6.
- 11 Aletaha D, Snedecor SJ, Ektare V, et al. Clinical and economic analysis of outcomes of dose tapering or withdrawal of tumor necrosis factor-α inhibitors upon achieving stable disease activity in rheumatoid arthritis patients. Clinicoecon Outcomes Res 2017;9:451-8.

Ann Rheum Dis Month 2018 Vol 0 No 0



Correspondence

Additional response to the correspondence: 'Switching from the bio-originators to biosimilar: is it premature to recommend this procedure?' by Cantini and Bennuci

We read with great interest Cantini and Benucci's response to our letter. However, we would like to add some points to the debate

To date and to our knowledge, every single clinical trial investigating efficacy and safety of biosimilars in rheumatology using a double-blinded design has failed to report any clinical difference with the original biologic. The double-blinded controlled trial NOR-SWITCH as well as open-label extension studies such as PLANETRA investigating efficacy and safety of the switch from original to biosimilar infliximab also failed to report any difference.^{2 3} These studies unequivocally condone the grade 1b recommendation 6 regarding the efficacy and safety of the switch published in the journal.⁴

Cantini and Benucci's concern emerged from the Danish Biologic Registry (DANBIO), which reported a borderline significant lower retention rate at 1 year post-mandatory non-medical switch in the adjusted (but not the crude) analysis: 86.8% versus 83.4% (P=0.03).⁵⁶ Analysis of the literature and the work we conducted has led us to believe that the lower retention rate of the biosimilar after a switch might not be due to the biosimilar itself but rather by patient perception together with the way health authorities and physicians handle the switch.⁷

In Denmark, a national consensus led to a non-medical switch of all patients without that patient (nor physician) had any say. A non-medical switch more frequently leads to negative outcomes than medical switch, ⁸ and not taking into account patient opinion is more likely to be counterproductive. Interestingly, in a randomised study evaluating originator etanercept versus placebo in rheumatoid arthritis, 24 weeks' clinical response was lower (71.4% of ACR20 in the treated group) than in the study comparing originator and a biosimilar etanercept (86.7% and 93.3% ACR20, respectively). ⁹ 10 This suggests that the eventuality of placebo treatment affects the efficacy of the *verum* treatment. We believe that similar mechanisms are at play after offering the switch to a biosimilar. More work is needed to better understand patient perspective on biosimilars and as to how to address the switch properly. Yet, this should not refrain physicians from offering the switch, maybe at first to selected patients.

Concerning the economic considerations, we politely disagree with our colleagues since the savings will be accomplished on the proportion of patients continuing the biosimilar, which is the large majority of patients: 83.4% in DANBIO and 72% in our study. ⁵⁷ As we discussed earlier, ¹¹ the expected drop-out patients will need to be switched to another biologic or targeted synthetic disease-modifying antirheumatic drug (bDMARD or tsDMARD). The small proportion of excess drop-out (which clinical characteristics were not detailed in DANBIO) are characterised by subjective symptoms and can be rescued by originator resumption. ⁷¹² With this in mind, we hardly see how this strategy would not be generating significant savings. As for the fact that dose tapering is a cost-effective trategy in rheumatic diseases, we totally agree with our colleagues. We would, however, like to add that dose tapering can also be conducted with biosimilars, thus generating even higher savings and turning a half-full glass into a full glass.

Marc Scherlinger, 1 Thierry Schaeverbeke2

¹Service de Rhumatologie, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France

²Université de Bordeaux, Bordeaux, France

Correspondence to Dr Marc Scherlinger, Service de Rhumatologie, Centre Hospitalier Universitaire de Bordeaux, 33000 Bordeaux, France; marc.scherlinger@chu-bordeaux.fr

Contributors MS and TS equally contributed to writing the correspondence response.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.



To cite Scherlinger M, Schaeverbeke T. Ann Rheum Dis Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2018-213342

Received 2 March 2018 Accepted 5 March 2018

Ann Rheum Dis 2018;0:1. doi:10.1136/annrheumdis-2018-213342

REFERENCES

- 1 Cantini F, Benucci M. Response to: "Seeing the glass either half full or half empty: response to the correspondence "Switching from the bio-originators to biosimilar: is it premature to recommend this procedure?" by Scherlinger and Schaeverbeke. Ann Rheum Dis 2018: 10.1136/annrheumdis-2018-213044 [Epub ahead of print 2 Feb 2018].
- 2 Jørgensen KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet 2017;389:2304–16.
- 3 Yoo DH, Prodanovic N, Jaworski J, et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Ann. Rheum Dis 2017-76:355–63.
- study. Ann Rheum Dis 2017;76:355–63.

 Kay J, Schoels MM, Dörner T, et al. Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. Ann Rheum Dis 2018;77:165–74.
- 5 Glintborg B, Sørensen IJ, Loft ÁĞ, et al. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. Ann Rheum Dis 2017;76:1426–31.
- 6 Cantini F, Benucci M. Switching from the bio-originators to biosimilar: is it premature to recommend this procedure? Ann Rheum Dis 2017: 10.1136/ apprhayumdic 2017.212820 [Epub ahead of print 29 Dec 2017]
- annrheumdis-2017-212820 [Epub ahead of print 29 Dec 2017].

 5 cherlinger M, Germain V, Labadie C, et al. Switching from originator infliximab to biosimilar CT-P13 in real-life: the weight of patient acceptance. Joint Bone Spine 2017. 10.1016/j.jbspin.2017.10.003 [Epub ahead of print 14 Nov 2017].
- 8 Nguyen E, Weeda ER, Sobieraj DM, et al. Impact of non-medical switching on clinica and economic outcomes, resource utilization and medication-taking behavior: a systematic literature review. Curr Med Res Opin 2016;32:1281–90.
- 9 Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999;340:253–9.
- 10 Matsuno H, Tomomitsu M, Hagino A, et al. Phase III, multicentre, double-blind, randomised, parallel-group study to evaluate the similarities between LBECO101 and etanercept reference product in terms of efficacy and safety in patients with active rheumatoid arthritis inadequately responding to methotrexate. Ann Rheum Dis 2017: 10.1136/annrheumdis-2017-212172 [Epub ahead of print 19 Dec 2017].
- 11 Scherlinger M, Schaeverbeke T. Response to: "Switching from the bio-originators to biosimilar: is it premature to recommend this procedure?" by Cantini and Benucci. Ann Rheum Dis 2018: 10.1136/annrheumdis-2018-213021 [Epub ahead of print 26 Jan 2018]
- 12 Tweehuysen L, van den Bemt BJF, van Ingen IL, et al. Subjective complaints as the main reason for biosimilar discontinuation after open-label transition from reference infliximab to biosimilar infliximab. Arthritis Rheumatol 2018;70:60–8.

Ann Rheum Dis Month 2018 Vol 0 No 0

eular 1

Les biosimilaires en France, bien en comprendre les enjeux pour bien les utiliser

Marc Scherlinger a,b,e, Jean-Luc Pellegrinb,c,e, Vincent Germaina,b,e, Estibaliz

Lazaro^{b,c,e}, Pierre Duffau^{b,d,e}, Thierry Schaeverbeke a, b,e pour le FHU ACRONIM

Affiliations:

^a Centre Hospitalier Universitaire de Bordeaux, Service de Rhumatologie, Hôpital

Pellegrin, Place Amélie Raba Léon, 33076 Bordeaux, France

^b Université de Bordeaux, 146 rue Léo Saignat, 33076 Bordeaux, France

^c Centre Hospitalier Universitaire de Bordeaux, Service de Médecine interne, Hôpital

Haut Levêque, Avenue Magellan, 33600 Pessac

d'Centre Hospitalier Universitaire de Bordeaux, Service de Médecine interne, Hôpital

Saint André, 1 Rue Jean Burguet, 33000 Bordeaux

e Centre de référence maladies auto-immunes et systémiques rare Est/Sud-Ouest,

CHU de Bordeaux : 33076 Bordeaux.

Correspondance:

Marc Scherlinger

Service de rhumatologie, Hôpital Pellegrin, Place Amélie Raba Léon, 33076

Bordeaux, France

e-mail: marc.scherlinger@chu-bordeaux.fr

Phone: +033 5 56 79 54 83

Fax: +033 5 56 79 60 84

Mots clés: biosimilaires ; économie de santé ; biothérapies

Liens d'intérêt:

MS, JLP et PD n'ont aucun lien d'intérêt à rapporter.

EL a reçu des honoraires en tant que consultant de : MSD, Pfizer, Roche Chugaï,

UCB

TS a reçu des honoraires en tant que consultant de : Amgen, AbbVie, Biogen, BMS, Janssen, MSD, Novartis, Pfizer, Roche Chugaï, UCB. TS a reçu une bourse de recherche de Pfizer (non liée à ce travail).

Les biothérapies ont révolutionné la prise en charge d'un certain nombre de maladies inflammatoires (rhumatismes inflammatoires, vascularites à ANCA ...), permettant d'obtenir une rémission prolongée jusqu'alors difficilement envisageable. Cette révolution thérapeutique est toutefois associée à des coûts sociétaux élevés inhérents aux prix de ces traitements. Quinze ans après la mise sur le marché d'une biothérapie, l'expiration de l'exclusivité du brevet permet la commercialisation des biosimilaires. Un biosimilaire est une biothérapie ayant la même séguence d'acides aminés que son princeps mais pouvant présenter des différences minimes en terme de structure quaternaire (glycosylation notamment) liées aux modifications post-traductionnelles. Pour recevoir une autorisation de mise sur le marché, l'industriel doit faire la démonstration de la similarité structurale du biosimilaire, de la similarité pharmacocinétique et -contrairement aux génériques- clinique par le biais d'une étude randomisée de non infériorité par rapport au biologique princeps [1]. Le nombre de biosimilaires disponibles à la prescription est en augmentation rapide. Il devient important pour les prescripteurs de biothérapies de connaître le concept de médicament biosimilaire mais également de comprendre les enjeux et les particularités de leur prescription, les patients étant eux-mêmes parfois très bien documentés [2].

Un enjeu économique

Parmi les dix traitements délivrés en ville coutant les plus chers à l'assurance maladie, on dénombre six traitements biologiques, pour un coût total de 1,451 milliards d'euros pour la seule année 2016 [3]. Ces six médicaments correspondent à deux anti-TNF alpha (adalimumab et etanercept), deux anti-angiogéniques (bevacizumab et aflibercept), l'insuline glargine et une érythropoïétine (darbepoetin alfa).

Notre formation médicale et certains défenseurs de la liberté ont fortement ancré dans notre esprit que la santé est un bien inestimable qui ne pouvait avoir de prix. Ainsi, la prise en compte par les médecins des enjeux économiques de leurs prescriptions ne saurait se faire aux dépens de la santé de leurs patients. L'avènement des biosimilaires et leur diffusion contrôlée par les agences régulatrices du médicament, sont à même de répondre aux besoins de baisse des coûts de santé tout en assurant la poursuite du meilleur traitement disponible pour nos patients, à une époque où se multiplient d'autres sollicitations très fortes des ressources du système de santé notamment en cancérologie.

Les biosimilaires actuellement disponibles présentent des prix de l'ordre de 30% inférieurs aux princeps, des prix jusqu'à 50% inférieurs ayant même été négociés dans les pays du nord de l'Europe. Avec l'arrivée d'une multitude de biosimilaires, une baisse des prix (y compris du princeps) est à prévoir selon les lois de la concurrence. Plusieurs études médico-économiques ont d'ailleurs montré l'impact positif de l'utilisation des biosimilaires sur les coûts de santé [4,5]. Cependant, malgré l'enjeu économique, un certain nombre de freins limitent encore la prescription des biosimilaires en France.

La réticence des médecins

Il existe parfois parmi les médecins une réticence à l'utilisation des biosimilaires, celleci est multifactorielle et mal étudiée. Dans une étude portant sur des rhumatologues de Belgique, les principales craintes portaient sur une moindre efficacité, un spectre différent d'effets indésirables et une moindre qualité [2]. A l'heure actuelle, il n'existe aucun argument scientifique substantiel pour alimenter ces craintes comme le montre une méta-analyse de 90 études étudiant la substitution du princeps au biosimilaire sur un total de 14.225 patients [6], ainsi que l'étude randomisée NOR-SWITCH [7]. Les craintes concernant une moindre qualité des produits biosimilaires sont essentiellement fondées sur l'idée commune qu'un produit moins cher serait nécessairement d'une moindre qualité, une telle association d'idées étant également retrouvée pour les génériques [8]. Les récentes polémiques associées aux génériques comme celle du Levothyrox© contribuent à augmenter cette défiance [9]. Les règles imposées par les agences de régulation du médicament ont cependant établi un cahier des charges visant à garantir une qualité et une sureté du produit identiques au princeps [10]. Par ailleurs, les laboratoires de biosimilaires (qui sont parfois les mêmes qui produisent une autre spécialité de biologique princeps) utilisent les même standards de production que les produits princeps et il n'y a aucun argument aujourd'hui pour suggérer le contraire.

Comme souligné par notre consœur [11], de minimes modifications du procédé de fabrication d'un traitement biologique modifient sa structure quaternaire (glycosylation notamment). Ces modifications sont-elles susceptibles de modifier l'efficacité, l'immunogénicité et le spectre d'effets indésirables de la molécule ? Si l'on se pose la question pour le biosimilaire, il n'est pas inutile de rappeler que les procédés de fabrication des biomédicaments font régulièrement l'objet de modifications parfois importantes. A titre d'exemple, depuis sa mise sur le marché en 1999, le Rémicade® a vu sa formule changer plus de 50 fois, et ce, sans qu'aucune étude clinique d'équivalence ne vienne confirmer l'absence de modification des propriétés thérapeutiques de la molécule [12]. Ainsi, les biosimilaires sont très probablement plus proches des princeps d'aujourd'hui que ne l'étaient les princeps d'il y a quinze ans... Et nos patients sont traités par (l'équivalent de) biosimilaires depuis de nombreuses années.

Il est parfois évoqué que les biosimilaires n'apportent aucune innovation [11], voire qu'ils constituent un frein à l'innovation. Plusieurs éléments vont à l'encontre de cette assertion. Premièrement, les laboratoires de biothérapie princeps ont bénéficié durant quinze ans d'un monopole leur laissant largement le temps de rentabiliser le développement de leur produit et de réinvestir en recherche et développement. La limitation de la durée d'exclusivité d'un brevet est d'ailleurs à la base même du principe d'incitation à l'innovation : la durée est suffisamment longue pour garantir un fort retour sur investissement, et la limite temporelle impose aux laboratoires de réinvestir dans l'innovation pour rester sur des niveaux de marge bénéficiaire élevés en produisant de nouvelles molécules originales. Enfin, on constate qu'un grand nombre de laboratoire de biologiques princeps investissent dans le domaine des biosimilaires, ce qui démontre que la commercialisation d'un biosimilaire reste une opération rentable. Dernier point, les biosimilaires peuvent apporter des innovations au bénéfice du patient comme par exemple un stylo injecteur moins douloureux ou une formule provoquant un plus faible nombre de réactions au site d'injection [13].

Il existe deux situations très différentes d'utilisation du biosimilaire : en initiation ou en substitution (ou interchangeabilité) du biologique princeps. L'utilisation d'un biosimilaire en cas d'initiation ne pose pas de problème particulier et devrait être privilégiée pour des raisons économiques. Chez un patient déjà traité par un biologique princeps, la substitution par un biosimilaire est l'objet de nombreux débats [14–17]. L'instruction de la direction générale de l'offre de soin (DGOS) du 3 août 2017 assure

que la prescription d'un biosimilaire peut être réalisée à tout moment d'un traitement biologique et qu'une substitution par un biosimilaire « induit la même obligation d'information du patient ou de traçabilité que les médicaments biologiques de référence, mais aucune obligation supplémentaire » [18].

Proposer à un patient une substitution par un biosimilaire pour raison non médicale (un euphémisme signifiant raison économique) est un acte médical à part entière nécessitant un temps et des explications conséquentes de la part du médecin. Des recommandations d'un groupe international publiées dans le journal de l'EULAR encouragent d'ailleurs leur utilisation en substitution d'un traitement princeps dans le cadre d'une décision partagée avec le patient [19]. La perception de cette modification thérapeutique, influencée par de nombreux facteurs, détermine l'acceptation du biosimilaire et, en toute vraisemblance, explique le ressenti d'une efficacité moindre chez certains patients.

La perception des patients

La perception de la substitution au biosimilaire est influencée par un certain nombre de facteurs externes (eg, opinion *a priori* du patient sur les biosimilaires, préoccupation vis-à-vis des coûts de santé...) et interne à la consultation (explications et réassurance du médecin, présence de documentation écrite, champs lexical et langage non verbal utilisés ...).

La prescription d'un traitement chez un malade atteint d'une pathologie chronique est percue comme un contrat réalisé avec son médecin. Le patient met dans les mains du praticien sa santé et accepte la prise d'une thérapeutique lui étant inconnue. Les médicaments sont appréhendés de façon ambivalente par les patients : ils représentent le fruit de la Science et de la Technique, susceptibles d'apporter l'effet thérapeutique escompté [20]. Ils représentent également une molécule étrangère potentiellement toxique et susceptible d'induire des effets néfastes [20]. Les biosimilaires prescrits en substitution d'un princeps, c'est-à-dire lorsque la maladie est déjà contrôlée, sont par conséquent considérés uniquement du coté potentiellement toxique. Enfin, il en résulte parfois une incompréhension de la part du patient : le médecin modifiant ce contrat en introduisant une « nouvelle » molécule alors que la maladie est déjà contrôlée. Le patient peut alors être amené (à tort) à se demander si son praticien ne serait pas prêt à lui proposer une prise en charge sub-optimale dans le but de réaliser des économies. Les politiques incitatives récemment proposées apportant un gain financier au service prescripteur (qui seront détaillées plus bas) pourraient par ailleurs participer à ce sentiment.

La communication au patient d'une information claire et rassurante est un élément clé dans l'acte thérapeutique d'introduction d'un biosimilaire [21]. L'accompagnement de l'information orale par une information écrite améliore la qualité et l'efficacité du message [8]. Comme souligné par une étude française récente, il est également indispensable d'apporter une formation des intervenants non-médicaux (pharmaciens, paramédicaux) car une discordance dans les discours de différents professionnels de santé peut induire un sentiment de méfiance chez le patient [21].

Malgré une information optimale et l'acceptation d'une transition au biosimilaire, plusieurs études de vie réelle des patients atteints de rhumatismes inflammatoires rapportent l'apparition de symptômes douloureux, en l'absence de signe objectif d'activité de la maladie [22,23]. Compte tenu du fait que ces études étaient réalisées

en ouvert et surtout de l'absence de tels symptômes dans les études menées en double-aveugle [7,24,25], ces symptômes ont été mis sur le compte d'un effet *nocebo* des biosimilaires [26]. Il est estimé que cet effet *nocebo* est lié à une acceptation incomplète du biosimilaire et concerne environ 15% des patients substitués au biosimilaire [23]. De nombreux facteurs comprenant la pathologie sous-jacente, les caractéristiques des patients mais également le discours médical peuvent participer à cet effet *nocebo* [27]. Ce potentiel effet *nocebo* ne doit pas décourager les médecins à proposer un biosimilaire en substitution, une reprise du biologique princeps permettant en règle le retour à l'état initial [23]. Des stratégies de prise en charge de ces effets *nocebo* (traitement symptomatique, réassurance, wait and see) pourraient en outre améliorer la maintenance des biosimilaires dans ce sous-groupe (minoritaire) de patients.

La pénétration des biosimilaires en France et les mesures incitatives

La pénétration des biosimilaires en France reste faible par rapport à ses voisins européens : à six mois de la mise du premier anti-TNF biosimilaire sous-cutané (étanercept biosimilaire), sa pénétration en France était de 3% contre 19% en Allemagne et 31.6% au Royaume-Unis [28]. Plusieurs raisons peuvent être invoquées à l'inertie de l'utilisation des biosimilaires en France. Il s'agit principalement du manque d'information, la réticence des médecins ou patients et l'absence initiale de politique incitative à leur prescription.

Début 2018, une instruction publiée par la direction générale de l'offre de soin (DGOS) a mis en place un dispositif financier incitatif en faveur des établissements de santé qui prescrivent des biosimilaires au titre des prescriptions hospitalières réalisées en ville (PHEV) dans le cadre d'un contrat d'amélioration de la qualité et de l'efficience des soins (CAQES) [29]. Pour chaque biosimilaire prescrit (en initiation ou en substitution), l'établissement de santé se voit reverser 20% de l'écart de prix entre les deux spécialités, soit 30 euros par mois de traitement pour l'étanercept.

L'échec de la politique de diffusion des génériques où les autorités ont choisi d'inciter financièrement les pharmaciens à effectuer la substitution doit servir de leçon pour les biosimilaires. Le paradigme proposé est de profiter du renouvellement annuel de la prescription initiale hospitalière (PIH) pour que les biosimilaires soient utilisés en substitution des originaux, au bénéfice des établissements de soins (et bien sûr, de la collectivité). Il faut cependant noter que ce renouvellement de PIH n'est, dans la grande majorité des cas, pas réalisé par le spécialiste traitant. Compte-tenu de l'importance de la perception du patient sur l'efficacité et la maintenance thérapeutique biosimilaire. nous pensons qu'il est indispensable l'interniste/rhumatologue traitant au centre du processus de prescription du biosimilaire, surtout en cas de substitution d'un biologique princeps. Les dispositifs incitatifs devraient donc cibler le spécialiste traitant (souvent libéral) au même titre que les structures hospitalières.

En conclusion, l'ensemble des données disponibles convergent en faveur d'une efficacité et d'une sureté comparables entre biosimilaires et biologiques princeps, que cela soit en initiation ou en substitution. Les enjeux économiques et sociétaux liés à leur utilisation sont majeurs et il appartient aux prescripteurs de s'approprier leur usage pour en garantir la meilleure utilisation au bénéfice des patients et de la collectivité.

Références:

- [1] Weise M, Bielsky M-C, De Smet K, Ehmann F, Ekman N, Giezen TJ, et al. Biosimilars: what clinicians should know. Blood 2012;120:5111–7. doi:10.1182/blood-2012-04-425744.
- [2] van Overbeeke E, De Beleyr B, de Hoon J, Westhovens R, Huys I. Perception of Originator Biologics and Biosimilars: A Survey Among Belgian Rheumatoid Arthritis Patients and Rheumatologists. BioDrugs 2017;31:447–59. doi:10.1007/s40259-017-0244-3.
- [3] Open Medic: base complète sur les dépenses de médicaments interrégimes Data.gouv.fr n.d. /fr/datasets/open-medic-base-complete-sur-les-depenses-demedicaments-interregimes/ (accessed June 27, 2018).
- [4] Gulácsi L, Brodszky V, Baji P, Kim H, Kim SY, Cho YY, et al. Biosimilars for the management of rheumatoid arthritis: economic considerations. Expert Rev Clin Immunol 2015;11:43–52. doi:10.1586/1744666X.2015.1090313.
- [5] Aladul MI, Fitzpatrick RW, Chapman SR. Impact of Infliximab and Etanercept Biosimilars on Biological Disease-Modifying Antirheumatic Drugs Utilisation and NHS Budget in the UK. BioDrugs Clin Immunother Biopharm Gene Ther 2017;31:533–44. doi:10.1007/s40259-017-0252-3.
- [6] Cohen HP, Blauvelt A, Rifkin RM, Danese S, Gokhale SB, Woollett G. Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes. Drugs 2018;78:463–78. doi:10.1007/s40265-018-0881-y.
- [7] Jørgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, Haavardsholm EA, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, doubleblind, non-inferiority trial. The Lancet 2017;389:2304–16. doi:10.1016/S0140-6736(17)30068-5.
- [8] Jacomet C, Allavena C, Peyrol F, Pereira B, Joubert LM, Bagheri H, et al. Perception of antiretroviral generic medicines: one-day survey of HIV-infected patients and their physicians in France. PloS One 2015;10:e0117214.
- [9] Wémeau J-L, Ladsous M. [Lévothyrox®: The teachings of a senseless polemic]. Presse Medicale Paris Fr 1983 2017;46:887–9. doi:10.1016/j.lpm.2017.10.015.
- [10] World Health Organization. GUIDELINES ON EVALUATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS (SBPs) n.d.
- [11] Chapelon-Abric C. Les biosimilaires en Médecine Interne : bien les connaître pour bien les prescrire. Rev Médecine Interne 2018. doi:10.1016/j.revmed.2018.04.005.
- [12] Vezér B, Buzás Z, Sebeszta M, Zrubka Z. Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents. Curr Med Res Opin 2016;32:829–34. doi:10.1185/03007995.2016.1145579.
- [13] Girolomoni G, Feldman SR, Emery P, Ghil J, Keum JW, Cheong SY, et al. Comparison of injection site reactions between the etanercept biosimilar SB4 and the reference etanercept in patients with rheumatoid arthritis from a Phase III study. Br J Dermatol 2017.
- [14] Cantini F, Benucci M. Switching from the bio-originators to biosimilar: is it premature to recommend this procedure? Ann Rheum Dis 2017:annrheumdis-2017-212820. doi:10.1136/annrheumdis-2017-212820.
- [15] Scherlinger M, Schaeverbeke T. Response to: 'Switching from the bio-originators to biosimilar: is it premature to recommend this procedure?' by Cantini and Benucci. Ann Rheum Dis 2018;annrheumdis-2018-213021, doi:10.1136/annrheumdis-2018-213021.
- [16] Cantini F, Benucci M. Response to: 'Seeing the glass either half full or half empty: response to the correspondence 'Switching from the bio-originators to biosimilar: is it premature to recommend this procedure?' by Scherlinger and Schaeverbeke. Ann Rheum Dis 2018:annrheumdis-2018-213044. doi:10.1136/annrheumdis-2018-213044.

- [17] Scherlinger M, Schaeverbeke T. Additional response to the correspondence: 'Switching from the bio-originators to biosimilar: is it premature to recommend this procedure?' by Cantini and Bennuci. Ann Rheum Dis 2018:annrheumdis-2018-213342. doi:10.1136/annrheumdis-2018-213342.
- [18]DGOS, DSS, DGS. INSTRUCTION N° DGOS/PF2/DSS/1C/DGS/PP2/CNAMTS/2017/244 du 3 août 2017 relative aux médicaments biologiques, à leurs similaires ou « biosimilaires », et à l'interchangeabilité en cours des traitements 2017.
- [19] Kay J, Schoels MM, Dörner T, Emery P, Kvien TK, Smolen JS, et al. Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. Ann Rheum Dis 2018;77:165–74. doi:10.1136/annrheumdis-2017-211937.
- [20] Sarradon A, Blanc M-A, Faure M. Des usagers sceptiques face aux médicaments génériques : une approche anthropologique. Epidemiol Public Health Rev Epidémiologie Santé Publique 2007:55:179–85.
- [21] Scherlinger M, Langlois E, Germain V. Acceptance Rate And Sociological Factors Involved In The Switch From Originator To Biosimilar Etanercept (SB4). Semin Arthritis Rheum 2018. doi:10.1016/j.semarthrit.2018.07.005.
- [22] Tweehuysen L, van den Bemt BJF, van Ingen IL, de Jong AJL, van der Laan WH, van den Hoogen FHJ, et al. Subjective Complaints as the Main Reason for Biosimilar Discontinuation After Open-Label Transition From Reference Infliximab to Biosimilar Infliximab. Arthritis Rheumatol 2018;70:60–8. doi:10.1002/art.40324.
- [23] Scherlinger M, Germain V, Labadie C, Barnetche T, Truchetet M-E, Bannwarth B, et al. Switching from originator infliximab to biosimilar CT-P13 in real-life: the weight of patient acceptance. Joint Bone Spine 2017. doi:10.1016/j.jbspin.2017.10.003.
- [24] Park W, Yoo DH, Miranda P, Brzosko M, Wiland P, Gutierrez-Ureña S, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. Ann Rheum Dis 2016:annrheumdis-2015-208783. doi:10.1136/annrheumdis-2015-208783.
- [25]Yoo DH, Prodanovic N, Jaworski J, Miranda P, Ramiterre E, Lanzon A, et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Ann Rheum Dis 2016:annrheumdis-2015-208786. doi:10.1136/annrheumdis-2015-208786.
- [26] Rezk MF, Pieper B. Treatment Outcomes with Biosimilars: Be Aware of the Nocebo Effect. Rheumatol Ther 2017;4:209–18. doi:10.1007/s40744-017-0085-z.
- [27] Mouly S, Bergmann J-F, Molimard M. L'effet Nocebo: particularités et conséquences pour le clinicien. Rev Médecine Interne 2018;39:315–20. doi:10.1016/j.revmed.2018.02.021.
- [28] IMS. The Impact of Biosimilar Competition in Europe 2017.
- [29] Direction Générale de l'Offre de Soins. INSTRUCTION N° DSS/1C/DGOS/PF2/2018/42 du 19 février 2018 relative à l'incitation à la prescription hospitalière de médicaments biologiques similaires, lorsqu'ils sont délivrés en ville n.d. http://circulaires.legifrance.gouv.fr/index.php?action=afficherCirculaire&hit=1&r=43152 (accessed June 11, 2018).

III. Discussions et Perspectives

Malgré l'intérêt économique et la sureté de l'utilisation des biosimilaires, il existe un retard à leur diffusion en France comparé aux autres pays d'Europe, notamment par rapport aux pays où des mesures incitatives à leur prescription ont été mises en place [15]. Actuellement, un objectif de 70% d'utilisation de biosimilaires a été fixé, ce qui semble être une cible mesurée et atteignable [16].

Début 2018, une instruction publiée par la direction générale de l'offre de soins (DGOS) a mis en place un dispositif financier incitatif en faveur des établissements de santé qui prescrivent des biosimilaires au titre des prescriptions hospitalières exécutées en ville (PHEV) dans le cadre d'un contrat d'amélioration de la qualité et de l'efficience des soins (CAQES) [16]. Pour chaque biosimilaire prescrit (en initiation ou en substitution), l'établissement de santé se voit reverser 20% de l'écart de prix entre les deux spécialités, soit 30 euros par mois de traitement pour l'étanercept.

En dehors de ces mesures incitatives, une formation de l'ensemble des professionnels de santé à la présentation d'une information positive et rassurante sur les biosimilaires semble indispensable pour promouvoir leur acceptation [17]. En effet, le langage verbal (champs lexical utilisé, arguments choisis...) et le langage non verbal (posture ouverte ou non ...) par le médecin, influent sur la perception du traitement par le patient, ce qui conditionne son acceptation [18]. La délivrance d'une information individualisée aux croyances et attentes du patient pourraient également améliorer l'acceptation. La délivrance simultanée d'une information écrite a démontré un effet bénéfique sur l'acceptation des traitements, notamment dans le domaine des

génériques, et devrait donc être encouragée [17]. Les patients recherchant souvent des informations sur internet y compris sur les biosimilaires (communication personnelle), la mise en place d'un site internet fournissant des informations adaptées à destination des patients semble souhaitable.

En dehors des mesures favorisant l'acceptation des biosimilaires, le développement de stratégies de prise en charge des patients présentant un effet *nocebo* est nécessaire car ils correspondent à 5 à 15% des patients interchangés. Deux options pourraient être discutées : 1) un retour systématique au biologique princeps assurant un retour à l'état initial; 2) des stratégies de réassurance et de traitement symptomatique (wait and see) [19]. À l'heure actuelle, ces stratégies n'ont pas été comparées. Cependant, compte-tenu du faible nombre relatif de patients développant cet effet *nocebo* et surtout de l'effet positif sur l'acceptation de la connaissance *a priori* d'une possibilité de retour au princeps, nous avons jusqu'à présent privilégié la première solution.

D'ores et déjà, la politique d'utilisation large des biosimilaires menée dans le service de rhumatologie du CHU de Bordeaux a porté ses fruits, avec une pénétrance dans la région Nouvelle-Aquitaine mesurée à 23.2%, contre 18.2% sur le reste de la France fin 2016 [20]. Dans la continuité de cette politique, un nouveau travail va être mené en collaboration avec l'agence régionale de santé (ARS) et l'observatoire du médicament, des dispositifs médicaux et de l'innovation thérapeutique (OMEDIT). L'objectif principal est d'évaluer l'influence sur la prescription de biosimilaires d'un dispositif plaçant le rhumatologue traitant (le plus souvent libéral) au centre d'un processus de décision

partagé avec le patient, tout en valorisant cet acte thérapeutique sur le plan financier (via le développement professionnel continu (DPC)).

En effet, les mesures incitatives proposées jusqu'alors ne visent que les services hospitaliers. Ces établissements profitent du renouvellement annuel de la prescription initiale hospitalière (PIH) pour interchanger les patients, même si la majorité d'entre eux sont suivis par un rhumatologue libéral. L'absence d'implication du rhumatologue libéral dans la décision d'interchangeabilité est à même d'induire une frustration voire une défiance vis-à-vis du rhumatologue hospitalier. Nos résultats montrent qu'une information contradictoire provenant de différents professionnels de santé (*eg*, rhumatologue hospitalier et libéral) peut induire un sentiment de méfiance limitant l'acceptation et qu'une acceptation incomplète peut mener à un effet *nocebo*, diminuant ainsi la maintenance thérapeutique du biosimilaire. Par conséquent, nous prédisons qu'une implication forte des praticiens libéraux, permettra de renforcer l'acceptation et une utilisation prolongée des biosimilaires en rhumatologie.

IV. Références

- [1] Minichiello E, Semerano L, Boissier M-C. Incidence, prévalence et sévérité de la polyarthrite rhumatoïde au XXI e siècle. Rev Rhum Monogr 2017;84:303–10. doi:10.1016/j.monrhu.2017.07.002.
- [2] Rat A-C. Épidémiologie de la spondyloarthrite au xxie siècle. Rev Rhum Monogr 2014;81:225–9. doi:10.1016/j.monrhu.2014.05.001.
- [3] Dadoun S, Zeboulon-Ktorza N, Combescure C, Elhai M, Rozenberg S, Gossec L, et al. Mortality in rheumatoid arthritis over the last fifty years: Systematic review and meta-analysis. Joint Bone Spine 2013;80:29–33. doi:10.1016/j.jbspin.2012.02.005.
- [4] Poppelaars PBM, Tuyl LHD van, Boers M. OP0015 Mortality of the cobra early rheumatoid arthritis trial cohort after 23 years follow up. Ann Rheum Dis 2018;77:57–57. doi:10.1136/annrheumdis-2018-eular.3675.
- [5] Vezér B, Buzás Z, Sebeszta M, Zrubka Z. Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents. Curr Med Res Opin 2016;32:829–34. doi:10.1185/03007995.2016.1145579.
- [6] European Medicines Agency Multidisciplinary Similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues n.d. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_ content_001382.jsp&mid=WC0b01ac058002958c (accessed September 8, 2018).
- [7] Gulácsi L, Brodszky V, Baji P, Kim H, Kim SY, Cho YY, et al. Biosimilars for the management of rheumatoid arthritis: economic considerations. Expert Rev Clin Immunol 2015;11:43–52. doi:10.1586/1744666X.2015.1090313.
- [8] Aladul MI, Fitzpatrick RW, Chapman SR. Impact of Infliximab and Etanercept Biosimilars on Biological Disease-Modifying Antirheumatic Drugs Utilisation and NHS Budget in the UK. BioDrugs Clin Immunother Biopharm Gene Ther 2017;31:533–44. doi:10.1007/s40259-017-0252-3.
- [9] Tweehuysen L, van den Bemt BJF, van Ingen IL, de Jong AJL, van der Laan WH, van den Hoogen FHJ, et al. Subjective Complaints as the Main Reason for Biosimilar Discontinuation After Open-Label Transition From Reference Infliximab to Biosimilar Infliximab. Arthritis Rheumatol 2018;70:60–8. doi:10.1002/art.40324.
- [10] Avouac J, Moltó A, Abitbol V, Etcheto A, Salcion A, Gutermann L, et al. Systematic switch from innovator infliximab to biosimilar infliximab in inflammatory chronic diseases in daily clinical practice: The experience of Cochin University Hospital, Paris, France. Semin Arthritis Rheum 2018;47:741–8. doi:10.1016/j.semarthrit.2017.10.002.

- [11] Rezk MF, Pieper B. Treatment Outcomes with Biosimilars: Be Aware of the Nocebo Effect. Rheumatol Ther 2017;4:209–18. doi:10.1007/s40744-017-0085-z.
- [12] Jørgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, Haavardsholm EA, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. The Lancet 2017;389:2304–16. doi:10.1016/S0140-6736(17)30068-5.
- [13] Glintborg B, Sørensen IJ, Loft AG, Lindegaard H, Linauskas A, Hendricks O, et al. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. Ann Rheum Dis 2017;76:1426–31. doi:10.1136/annrheumdis-2016-210742.
- [14] Cohen HP, Blauvelt A, Rifkin RM, Danese S, Gokhale SB, Woollett G. Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes. Drugs 2018;78:463–78. doi:10.1007/s40265-018-0881-y.
- [15] IMS. The Impact of Biosimilar Competition in Europe 2017.
- [16] Direction Générale de l'Offre de Soins. INSTRUCTION N° DSS/1C/DGOS/PF2/2018/42 du 19 février 2018 relative à l'incitation à la prescription hospitalière de médicaments biologiques similaires, lorsqu'ils sont délivrés en ville n.d. http://circulaires.legifrance.gouv.fr/index.php?action=afficherCirculaire&hit=1&r=4 3152 (accessed June 11, 2018).
- [17] Jacomet C, Allavena C, Peyrol F, Pereira B, Joubert LM, Bagheri H, et al. Perception of antiretroviral generic medicines: one-day survey of HIV-infected patients and their physicians in France. PloS One 2015;10:e0117214.
- [18] van Netten JJ, Francis A, Morphet A, Fortington LV, Postema K, Williams A. Communication techniques for improved acceptance and adherence with therapeutic footwear. Prosthet Orthot Int 2017;41:201–4. doi:10.1177/0309364616650080.
- [19] Pouillon L, Socha M, Demore B, Thilly N, Abitbol V, Danese S, et al. The nocebo effect: a clinical challenge in the era of biosimilars. Expert Rev Clin Immunol 2018:1–11. doi:10.1080/1744666X.2018.1512406.
- [20] Les médicaments biosimilaires : données de la Nouvelle-Aquitaine, journée régionale de l'OMEDIT Nouvelle-Aquitaine juin 2017. http://www.omedit-aquitaine.fr/sites/omedit.drupal7.aquisante.priv/files/54/52_-_presentation_biosimilaires_omedit.pdf n.d.

V. Abbréviations

AMM, autorisation de mise sur le marché

ARS, agence régionale de santé

CAQES, contrat d'amélioration de la qualité et de l'efficience des soins

DGOS, direction générale de l'offre de soin

OMEDIT, observatoire du médicament, des dispositifs médicaux et de l'innovation thérapeutique

PHEV, prescription hospitalière exécutées en ville

PIH, prescription initiale hospitalière

RIC, rhumatisme inflammatoire chronique

TNF-α, tumor necrosis factor - alpha

VI. Serment d'Hippocrate

Au moment d'être admis à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré et méprisé si j'y manque.