

EDITORIAL

Switching from originator biological agents to biosimilars: what is the evidence and what are the issues?

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INTRODUCTION

Biological disease-modifying antirheumatic drugs (bDMARDs) have revolutionised the therapeutic management of inflammatory rheumatic diseases with dramatic clinical improvement and reduction in systemic inflammation in arthritis on the one hand, and slower joint degradation (in rheumatoid arthritis (RA) and psoriatic arthritis) on the other hand. These drugs are able to induce clinical remission and *in fine* strongly improve patient quality of life. Due to their high levels of efficacy, bDMARDs are widely used in chronic arthritic conditions with a strong increase in treatment costs. The recent expiry of patents for the first bDMARDs such as tumour necrosis factor (TNF) inhibitors has led to developments in biosimilar (bs) DMARDs.^{1 2} The European Medicines Agency (EMA) has approved bsDMARDs of infliximab (with CT-P13 produced by Celltrion and commercialised as Remsima or Inflectra, and SB2 produced by Samsung Bioepis and commercialised as Flixabi) and SB4, a bsDMARD of etanercept (Benepali by Samsung Bioepis). With these new agents, the reduction in cost treatment in Europe between now and 2020 was estimated at between €11 and €33 billion.³

Since bsDMARDs were introduced to the market, many questions emerged about their use in routine practice.^{4 5} Indeed, the issue of changing from biological originator (bo) DMARDs to its/their bsDMARDs is open to debate despite a systematic switch for all patients receiving boDMARDs in some countries. Here, we review the different concerns that may be raised when switching from a reference biopharmaceutical to its/their bsDMARDs and consider the pros and cons of switching in clinical practice. We focus the discussion on TNF inhibitors in rheumatic inflammatory disorders.

Development of a biosimilar: the challenges

The development of bsDMARDs had to follow rigorous and comprehensive comparability specifications in order to assume and prove biosimilarity to its boDMARD according to official medicine agency guidelines. Specifically, a bsDMARD had to demonstrate similar characteristics in terms of structure, biological activity, efficacy and safety profiles to its boDMARD. The EMA has thus approved around 20 biosimilar products between 2006 and 2015.^{1 4} Medicine agencies also allow extrapolation principle.⁵ After showing clinical similarities for one indication, the bsDMARD is approved for all other indications previously obtained by its boDMARD. CT-P13, which is already available in daily practice, was assessed with a phase III study in RA and with a phase I study in ankylosing spondylitis (AS).^{6 7} Due to a lack of data on Crohn's disease and associated discrepancies in few bioassays, extrapolation was not initially accepted for CT-P13 in Canada for Crohn's disease. However, health Canadian authorities approved extrapolation of CT-P13 in inflammatory bowel diseases after additional data provided. Extrapolation is generally accepted by the rheumatologists, because many studies were performed in the field of rheumatology. On the contrary, gastroenterologists and dermatologists are more bored to use a bsDMARD in their respective indications. The next challenge is substitution or interchangeability from the boDMARDs to its/their bsDMARDs and is still open to debate. Indeed, the interchangeable property was not specifically analysed during the clinical development of CT-P13 or other anti-TNF bs. Only replacements from the boDMARDs to the bsDMARDs were assessed during the open-label phase of CT-P13 or SB2. However, one of the etanercept bsDMARDs was evaluated in patients with psoriasis with multiple

switches from the boDMARD to the bsDMARD.⁸ Substitution is the term applied for the replacement of a prescribed branded drug by a different form of the same active substance mainly performed by the pharmacist without physician involvement. Interchangeability supposes that the bsDMARDs can be alternated with the boDMARDs without any loss of efficacy or change in risk of adverse events and without increased immunogenicity risk. One preliminary question is who should decide that a biopharmaceutical may be substitutable and/or interchangeable? This question remains to be answered and could lead to a strong reduction in the cost.

What are the reasons for switching?

Independent of these relevant questions and their potential consequences, it is important to remember that besides changing a boDMARD to its biosimilar, switching from one bDMARD to another one is currently performed to control disease activity and can be necessary in different clinical settings: in the case of loss of response to one biological agent (primary or secondary insufficient response or loss of response); when an adverse event occurs; when immunogenicity is associated with clinical loss of response or side effects; when adherence to the treatment is not optimal; or due to a choice made by the patient and/or the physician.⁹ For instance, data from the NOR-DMARD registry indicated that switching from one TNF inhibitor to another restored clinical response in patients with AS.¹⁰ Conversely, a systematic switch when low disease activity was observed was not suitable. For instance, in Crohn's disease, there was a loss of tolerance and a high rate of discontinuation of adalimumab when infliximab was replaced with adalimumab in patients with stable disease as compared with patients who remained on infliximab.¹¹

IMMUNOGENICITY

One major concern with interchangeability of bDMARDs is immunogenicity.^{4 9 12} Indeed, it is well known that bDMARDs, especially monoclonal antibodies, may induce antidrug antibodies (ADAb). Immunogenicity to bDMARDs in inflammatory diseases is a complex phenomenon that is influenced by several factors including patient characteristics (body mass index, for instance), the disease itself and its pathophysiological-associated mechanisms, the administered drug dosage and circulating through levels, the associated drugs and especially concomitant use of conventional synthetic DMARDs such as methotrexate.¹³ ADAb development is associated with a reduced therapeutic response and/or injection-related events. Production of bDMARDs may generate post-translational modifications that can induce heterogeneity of the expressed protein, which can contribute to its immunogenicity. Consequently, modifications introduced during the manufacturing process of bsDMARDs could induce subtle small changes compared with boDMARDs and trigger an immune response with

ADAb induction. Strong data on the immunogenicity of a bsDMARD are thus required and are included in the development programme of each bsDMARDs.

Switch of a boDMARD to its biosimilar: what are the clinical data?

The first report of switching from originator infliximab to CT-P13 in clinical practice was described in patients with established rheumatic diseases, with a maintenance of the clinical efficacy after a median period of 11 months following the switch¹⁴ (table 1).

Switches in clinical trials

CT-P13 was approved by EMA on 20 September 2013. This approval was based on two clinical trials comparing CT-P13 with the infliximab originator. It consisted of a phase I PLANETAS study in AS and a phase III PLANETRA study in RA^{6 7} with a double-blinded period of 12 months. In the PLANETRA extension study, patients who participated in the 1 year initial study were given an additional year of treatment. Of the 302 patients who completed the pivotal trial, 155 were maintained under CT-P13 (maintenance group) and 144 were switched from infliximab reference to CT-P13. At week 102, the American College of Rheumatology 20 (ACR20), ACR50 and ACR70 rates of response were similar between each group (table 1). In addition, the proportion of patients with ADAb was also comparable between groups.¹⁵ The same transition study was performed in the PLANETAS study. Of the 174 patients who completed that study, 88 kept CT-P13, while 86 were switched from infliximab reference to CT-P13 during the extension phase. Again, the clinical response (ASAS20 response) was comparable throughout the follow-up until week 102. Development of ADAb was also similar in both groups¹⁶ (table 1). Other observational studies of patients switching from infliximab reference to CT-P13 were performed in patients with inflammatory bowel diseases and showed maintenance of clinical efficacy with similar safety profile (reviewed in reference⁹).

SB2 is another bsDMARDs of infliximab approved by the EMA on 1 April 2016. The 52-week results of phase III study have been published previously.¹⁷ A phase III transition study has been conducted to evaluate the efficacy and safety of patients with RA who switched from reference infliximab to SB2. In this randomised, double-blind, transition study at week 52, 94 patients from infliximab were transitioned to SB2, 101 patients continued infliximab and 201 from the initial SB2 arm continued to receive SB2. Patients were followed up until week 78. The clinical efficacy as evaluated by disease activity score 28 joints (DAS28) was sustained and comparable between the three treatment groups as well as the safety profile. Of note, there was no difference in the rates of newly developed ADAb between the different arms (table 1).¹⁸

Etanercept is the second bDMARD to have a bsDMARD, with the SB4 approved by EMA on 14 January 2016. The phase III randomised trial comparing SB4 with its reference product in patients with RA demonstrated the

Table 1 Randomised clinical trials, extension studies and observational studies of switching from originator TNF- α inhibitors to biosimilars in inflammatory rheumatic diseases.

Reference study	Patients (n)	Disease	Reference product/ biosimilar	Primary endpoint	Clinical results	Immunogenicity (presence of ADAb)
Nlkiphorou ¹⁴	39	RA (38%) AS and ReA (39%) PsA (18%) JIA (5%)	IFX/CT-P13	PROs (HAQ, pain, fatigue and morning stiffness) Disease activity (VAS patient)	Patient symptoms and disease activity were similar during IFX and CT-P13.	ND
PLANETRA Extension study ¹⁵	302 Maintenance: 158 Switch IFX originator to CT-P13: 144	RA	IFX/CT-P13	ACR20 at week 102	Maintenance: 71.7% Switch: 71.8%	Maintenance: 40.3% Switch: 44.8%
PLANETAS Extension study ¹⁶	174 Maintenance CT-P13: 88 Switch IFX originator to CT-P13: 86	AS	IFX/CT-P13	ASAS20 week 102	Maintenance group: 80.7% Switch group: 76.9%	Maintenance: 23.3% Switch: 27.4%
SB4 extension study ²⁰	245 Maintenance SB4: 126 Switch originator to SB4: 119	RA	ETA/SB4	ACR20 week 100	Maintenance group: 80% Switch group: 80%	ND
SB2 transition study ¹⁸	Switch IFX to SB2: 94 Maintenance SB2: 101 Maintenance IFX: 201	RA	IFX/SB2	Change in DAS28 at week 78	Comparable change between the three groups	Switch IFX to SB2: 14.6 Maintenance SB2: 14.1 Maintenance IFX: 14.9
SB5 transition study ²¹	Maintenance SB5: 254 Switch ADL to SB5: 125 Maintenance ADL: 129	RA	ADL/SB5	ACR20 week 42	Maintenance SB5: 76.9 Switch ADL to SB5: 81.1 Maintenance ADL: 71.2	Maintenance SB5: 15.7 Switch ADL to SB5: 16.8 Maintenance ADL: 18.3
NOR-SWITCH ²²	481 Maintenance originator IFX: 241 Switch: 240	RA: 77 SpA: 91 PsA: 30 Other (CD, UC, Pso): 283	IFX/CT-P13	Worsening of the disease according to specific clinical endpoint	Maintenance: 26.2% Switch: 29.6%	Maintenance: 7.1% Switch: 7.9%
DANBIO ²³	768 All switch	RA: 364 SpA: 256 PsA: 119 Other: 29	IFX/CT-13	Disease flare at month 3	Unchanged disease and flare 3 months prior to versus 3 months after switch	No difference of ADAb positivity between baseline and at 6 months after switching

Continued

Table 1 Continued

Reference study	Patients (n)	Disease	Reference product/ biosimilar	Primary endpoint	Clinical results	Immunogenicity (presence of ADAb)
DANBIO ²⁴	1548	RA: 891 SpA: 322 PsA: 335	ETA/SB4	Disease flare at month 3	Unchanged disease and incidence of flare prior versus after switch	ND

ACR20, American College of Rheumatology 20; ADL, adalimumab; ADAb, antidrug antibodies; AS, ankylosing spondylitis; ASAS20, Assessment in Ankylosing Spondylitis; CD, Crohn's disease; DAS28, disease activity score 28 joints; DANBIO, a nationwide registry of biological therapies in Denmark; HAQ, Health Assessment Questionnaire; IFX, infliximab; ETA, etanercept; JIA, juvenile idiopathic arthritis; ND, not determined; NOR-SWITCH, Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab; PLANETRA, 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; PLANETAS, 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; PRO, patient-reported outcome; PsA, psoriatic arthritis; Psoriasis; RA, rheumatoid arthritis; ReA, reactive arthritis; SpA, spondyloarthritis; TNF- α , tumour necrosis factor- α ; UC, ulcerative colitis; VAS, Visual Analogue Scale.

similarity of SB4 to its boDMARD in terms of efficacy and safety, with surprisingly a lower immunogenicity profile at week 24.¹⁹ After 52 weeks of treatment with etanercept or SB4 during this randomised, double-blind period, the patients were enrolled into an extension phase for 48 additional weeks. Of the 596 patients enrolled in the double-blind study, 126 were maintained on SB4 and 119 were switched from etanercept reference to SB4. Efficacy in terms of ACR20 response was similar between the groups at week 100 (table 1). Other clinical endpoints (changes in DAS28, clinical disease activity index (CDAI) and simplified disease activity index (SDAI), low disease activity, and remission) were also similar between the two groups, as well as radiographical progression.²⁰

SB5 is a bsDMARD of a third anti-TNF, adalimumab. The results of the phase III study are not currently published, and this bsDMARD is not currently approved by medical agencies. After the 24-week, randomised, double-blind phase, patients entered into a transition period from week 24 to week 52. After the double-blind phase, 254 patients continued to receive SB5, 125 switched from adalimumab to SB5, while 129 kept adalimumab. The clinical response as evaluated by the ACR20 response was sustained and did not differ between the three groups. Safety and immunogenicity were also comparable in the different treatment arms (table 1).²¹

Switches in routine practice

Data about switching TNF inhibitors in real practice are now available. NOR-SWITCH (ClinicalTrials.gov NCT02148640) is the first trial that investigated the effect of switching originator infliximab to CT-P13 at country level, in Norway.²² This was a randomised, double-blind, non-inferiority, phase IV trial funded by the Norwegian government. Patients with RA, axial or peripheral spondyloarthritis, Crohn's disease, ulcerative colitis or plaque psoriasis treated by originator infliximab with a stable disease for at least 6 months were enrolled. Then, patients were randomised to continue with infliximab originator or were switched to CT-P13. The primary endpoint was worsening of disease during follow-up of 52 weeks according to composite measures specific to each disease. In the 481 patients enrolled, the rate of disease worsening was comparable between the maintenance group and the switch group: 26.2% and 29.6% (table 1). In addition, the incidence of ADAb was similar in each group. Additional valuable information came from the Danish nationwide biological registry (DANBIO). According to national guidelines, all the patients with inflammatory rheumatic diseases treated in routine care by originator infliximab were switched to CT-P13.²³ Data on efficacy, safety and immunogenicity were then monitored. Disease activity was recorded and compared at different time points, including before switching, at the time of the switch and 3 months later, allowing disease flares to be evaluated in 768 patients. Infliximab originator was given for a mean period of 6.6 years. Disease activity and disease flare remained unchanged 3 months prior to

the switch versus 3 months after the switch. At the last visit at 12 months, disease activity was stable. Treatment adherence was similar between the different inflammatory rheumatic diseases. CT-P13 was stopped in 15% of patients between the switch and the end of follow-up due to loss of efficacy in half of them. Immunogenicity assessed by the rate of ADAb positivity was comparable between inclusion visits and at 6 months. Similar results were reported in this registry when switching etanercept originator to its bs SB4²⁴ (table 1).

What are the issues when switching a boDMARD to a bsDMARD?

Overall, data on the effects of switch in the field of biologics are accumulating and provided valuable insights on efficacy, safety and immunogenicity with bsDMARDs. Extension studies evaluating the transition from originators (infliximab, etanercept or adalimumab) to their respective bsDMARDs (CT-P13 or SB2, SB4 and SB5, respectively) are reassuring as are data from switch studies in patients receiving infliximab or etanercept in routine care. The follow-up in the long-term extension/transition studies, in the NOR-SWITCH trial and in the Danish registry, was sufficient to detect an effect on efficacy, safety and immunogenicity of the bsDMARDs. Regulatory agencies (the EMA and the Food and Drug Administration (FDA)) have not currently taken a view on automatic substitution and have no authority to designate a biosimilar to be automatically substitutable. In addition, the EMA did not designate biosimilar as interchangeable, and this decision is under the authority of each national agency. Therefore, each country follows its own recommendations. In general, substitution is not made by pharmacists. Thus, the current and most careful view of treating physicians is to propose a bsDMARD when initiating a TNF inhibitor. Conversely, not all physicians are prone to systematically switching a boDMARD to its bsDMARD, especially in patients with stable disease. Due to immunogenicity concerns, repetitive or reverse switches (repeat changes between a reference product and its bsDMARD) are also not recommended. Another situation is the switch from one reference bDMARD to a first bsDMARD and then to another of the same reference drug or cross-switching (for instance to move from reference infliximab to CT-P13 and then to SB2). Indeed, data are currently lacking about these two situations and are thus required before adopting such a treatment strategy. All in all, we are lacking clear recommendations from official regulatory agencies as well as from scientific organisations. The FDA published guidance for industry, giving the information needed to support a demonstration of interchangeability for bsDMARDs.²⁵ In France, the national medicine agency stated that interchangeability between two bDMARDs may be proposed subject to certain conditions: the patient must be clearly informed; he may benefit from appropriate clinical surveillance; and biodrug traceability must be

guaranteed.²⁶ The European League Against Rheumatism (EULAR) mentioned the use of bsDMARDs in its recommendations for the treatment of RA.²⁷ In parallel, the EULAR committee published a position paper on the issues that patients need to consider with bsDMARDs. This paper is a reminder that as for all medicines, patients must receive clear information on this drug class and need to be able to make a fully informed decision about whether to take a bDMARD or a bsDMARD.²⁸ For inflammatory bowel diseases, data on switching from originator to CT-P13 showed the same results as observed in RA, that is, maintenance of clinical efficacy under the bsDMARD and no special safety signal or higher immunogenicity rates.⁸ Thus, the European Crohn's Colitis Organisation proposed that switching from originator to biosimilar is acceptable, but it did not recommend multiple switching nor reverse switch or cross-switching.²⁹

CONCLUSION

Future studies are required to confirm the preliminary—not alarming—results on the safety and efficacy of switching from originator TNF inhibitors to their biosimilars. A clear position from medicine agencies as well as data from postmarketing surveillance and registries would certainly be appreciated from both the treating physicians and their patients in order to provide additional confidence in these lower cost medications. In addition, information on bsDMARDs given to the patients must be clear and transparent and must include the reasons for a non-medical switch, such as financial savings.

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