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Non-Medical Switch in Biosimilar Product Development

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Abstract

For an approved biosimilar product, it is a common practice that the provider (pharmacist or insurance company) may switch from the innovator product to the approved biosimilar product based on factors unrelated to clinical/medical consideration. In practice, it is a concern that this non-medical switch may present unreasonable risk (e.g., reduced efficacy or increase of the incidence rate of adverse events) to patients with the diseases under study. In recent years, several observational studies and a national clinical study (NOR-SWITCH) were conducted to evaluate the risk of non-medical switch from a reference product to an approved biosimilar product. The conclusions from these studies, however, may be biased and hence misleading due to lack of some scientific and/or statistical deficiencies in design and analysis of the data collected. In this article, valid study designs and appropriate statistical methods are recommended for a more accurate and reliable assessment of potential risk of medical/non-medical switch between a proposed biosimilar product and a reference product. The results can be easily extended for evaluation of the potential risk of medical/non-medical switch among multiple biosimilar products and a reference product.

Keywords: Drug interchangeability; Switching; Alternation; NOR-SWITCH; Switching design

Introduction

When an innovative biologic drug product is going off patent protection, pharmaceutical or biotechnological companies usually seek market authorization of similar biologic drug products. In 2009, the United States (US) Congress passed the Biologic Price Competition and Innovation (BPCI) Act which gave the US Food and Drug Administration (FDA) the authority to approve biosimilar products. According to the BPCI Act, a biosimilar product is a biologic product that is highly similar to an innovative biologic (reference) product not withstanding minor differences in clinically inactive components and there are no clinically meaningful differences in terms of safety, purity, and potency. A biosimilar drug can be generally used to substitute the innovative drug if it has been shown to be highly similar to the innovative drug. The FDA, however, does not indicate that (i) the approved biosimilar product and the reference product can be used interchangeably and (ii) two biosimilar products of the same innovative drug can be used interchangeably even though they are highly biosimilar to the same innovative drug.

Regarding drug interchangeability, BPCI Act indicated that a biological product is to be interchangeable with the reference product if the information submitted in the application is sufficient to show (1) that the biological product is not only biosimilar to the reference product, but also it can be expected that it will produce the same clinical result as the reference product in any given patient; and (2) that for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch. In practice, it is not possible to show same clinical result in any given patient (i.e., for every patient, we need to show that the proposed biosimilar will produce same clinical result as that of the reference product).However, it is possible to demonstrate same clinical result in any given patient with certain assurance. Along this line, the FDA circulated draft guidance on drug interchangeability for public comments [1] although thus far FDA has not yet granted approval for drug interchangeability in recent regulatory submissions.

As more biosimilar drug products become available, it is a common practice that the provider (e.g., pharmacist or insurance company) may switch from the reference product (more expensive) to an approved biosimilar product (less expensive) based on factors unrelated to clinical/medical considerations. We will refer to this switch as a non-medical switch (NMS). In practice, NMS is the switching of a patient's medicine, often at the behest of a third party, for reasons other than the patient's health and safety. Non-medical reasons for switching a patient's medicine could include (i) to increase the profits of a private insurer; (ii) to reduce costs for a government agency, or employer; and (iii) an agreement between the payer and a particular manufacturer to favor that manufacturer's product. However, it is suggested that patients and their physician should remain in control of their treatment decisions, rather than an insurer, government, pharmacy, or other third party. With this non-medical switch, it is a concern that the switch from the reference product to an approved biosimilar product may present unreasonable risk (e.g., reduced efficacy or increase of the incidence rate of adverse events) to patient population, especially for those patients who have been received the reference product at a steady and efficacious level.

In recent years, several observational studies and a national clinical study (NOR-SWITCH) were conducted to evaluate the risk of non-medical switch from a reference product to an approved biosimilar product. The conclusions from these studies, however, are somewhat biased and hence may be misleading due to some scientific and/or statistical deficiencies in design and analysis of the data collected. In this article, valid study designs and appropriate statistical methods are recommended for a more accurate and reliable assessment of potential risk of medical/non-medical switch between the proposed biosimilar product and the reference product. The results can be easily extended for evaluation of the potential risk of medical/non-medical switch among multiple biosimilar products and a reference product.

In the next section, two commonly considered approaches for evaluation of the potential risk of non-medical switch are described. Also included in this section are some real examples (e.g., single arm observational studies and the NOR-SWITCH study) in terms of their relative merits and limitations. Section 3 outlines scientific factor and/or statistical issues that are commonly encountered when evaluating the potential risk of non-medical switch studies. Section 4 recommends several study designs and statistical methods for a valid assessment of the potential risk of medical/non-medical switch. Some concluding remarks are given in the last section.

Approaches for Evaluation of Non-medical Switch

As indicated in the previous section, although none of recent regulatory submissions have been granted FDA's approval for drug interchangeability, non-medical switch from a reference product to its approved biosimilar product enviably occurs due to certain considerations unrelated to clinical assessment/judgement. In practice, it is then of interest to evaluate whether such a switch will cause loss of efficacy and/or increase of adverse event rate. To address this issue, two approaches are commonly considered by conducting observational studies or clinical studies.

In this section, without loss of generality and for illustrational purpose, we will consider observational studies and clinical studies conducted for evaluation of the potential risk of non-medical switching of anti-TNF treatment (i.e., switch from Remicade® (reference) to Remsima™ (a proposed biosimilar product, also known as CT-P13).

Single arm observational studies

Several observational studies were conducted to evaluate the potential risk of non-medical from Remicade® (reference) to Remsima™ (test). These observational studies are summarized in (Table 1). The intention of conducting single arm observational studies for evaluation of potential risk in reduced efficacy and/or increase of adverse events due to non-medical switch is good but the conclusions may be biased and hence misleading due to the limitations of single arm observational studies. These limitations and deficiencies are outlined below.

Table 1 Reported Observational Studies
Experience Currently Limited to Celltrion's CT-P13 (Inflectra/Remsima)

	Compare vs. continued Ref. product	Switch x1 or Alternating	Sample size of Switched cohort (n)	Duration after switch
Buer L, et.al. [5] IBD	None	Single switch	143	6 mos
Sieczkowska J, et.al. [19] IBD	None	Single switch	32	8 mos
Swits L, et.al. [20] IBD	None	Single switch	83	16 wks
Kolar M, et.al. [16] IBD	None	Single switch	74	24 wks
Diaz Hernandez L, et.al. [15] IBD	None	Single switch	72	6mos
Fiorino G, et.al. [13] IBD	No: Compare vs new/ re-starts*	Single switch	97	6 mos
Glintborg B, et.al. [14] Rheum conditions	None	Single switch	647	3 mos
Nikiphorou E, et.al. [18] Rheum conditions	None	Single switch	39	11 months

Descriptive statistics rather than statistics inference

The conclusions from all of these single arm observational studies were made based on descriptive statistics and/or graphical presentations on the data collected from limited number of subjects. It is suggested confidence interval (CI) of the mean difference in primary stud endpoint (e.g., disease activity) should be obtained and sensitivity analysis should be performed before a valid statistical inference (conclusion) can be made.

Sample size justification

No sample size justifications were provided in these studies. As a result, whether the observed clinically meaningful difference truly exist or purely by chance aloe cannot be confirmed. In addition, little information regarding the variabilities associated with the reference product and the test products were provided.

Selection of non-inferiority margin

The primary objective is to show non-inferiority of CT-P13 as compared to Remicade when switch from Remicade to CT-P13 across different indications. However, different indications may have different effect sizes. It is not clear what the non-inferiority margins for specific indications are?

Evaluation of Potential Risk of Switching

In all of the studies, only single arm (R switch to T) is considered mainly because it is of interest to study the switch from R to T to determine (i) whether there is a loss of efficacy and (ii) increase of adverse events. This single arm study, however, cannot fully address switch ability between R and T. In other words, we need to address potential risk with and without such switch. That is, we need to compare (R to T) as compared to (R to R).

It should be noted that the evaluation of potential risk of switching in terms of possible reduction of efficacy and/or increase of adverse events rate in these observational studies was performed by comparing the mean responses of the primary study endpoints between the proposed biosimilar product and the innovative biological drug product. In addition to the comparison of mean responses, it is also suggested that the comparison of variabilities associated with the observed responses be made because biosimilar products are known to be sensitive to environmental factors such as light and/or temperature. A small change or variation of critical quality attributes could translate to significant change in clinical outcomes (i.e., safety and/or efficacy).

Clinical studies

For clinical studies conducted for evaluation of the potential risk of non-medical from Remicade® to Remsima™, (Table 2) lists the published results available in the literature. These clinical studies are briefly outlined below.

Table 2 Conclusions of Reported Observational Non-Medical Switching Studies of Anti-TNF Treatment

Study	Author's Main Conclusion
Buer L, et.al. [5]	Switching from Remicade® to Remsima™ was feasible and with few adverse events, including very limited antidrug antibody formation and loss of response
Sieczkowska J, et.al. [19]	Switching from IFX originator to its biosimilars seems to be a safe option in children with CD. Biosimilars after switch showed to be equally as effective as originator
Swits L, et.al. [20]	No significant change in disease activity was observed 16 weeks after switching from Remicade® to CT-P13.Two patients developed new ADA with undetectable TL during follow-up. No SAEs were observed
Kolar M, et.al. [16]	Based on our results, switching of IBD patients from original to biosimilars IFX is effective and safe. Importantly, no increase in immunogenicity was observed
Diaz Hernandez L, et.al. [15]	Switching to CT-P13 was effective in maintaining clinical remission at 6 months of treatment. No relevant AEs were observed. The use of the biosimilar supposed a cost savings in treatment
Fiorino G, et.al. [13]	No clear difference in safety was reported, however a 5-fold increase in LOR after switch and a trend towards more frequent primary failure in UC compared to CD patients was recorded. These findings should be evaluated with caution due to the short follow-up
Glintborg B, et.al. [14]	Disease activity was largely unaffected in the majority of patients 3 months after non-medical switch to biosimilar Remsima and comparable to the fluctuations observed in 3 months prior to the switch. However several patients (~6%) stopped treatment due to LOE or AE. This warrants further investigation before such a non-medical switch can be recommended
Nikiphorou E, et.al. [18]	Well tolerated in patients who maintained the treatment after 54 weeks and in patients who switched to CT-P13 after 54 weeks of IFX treatment

PLANETRA/PLANETAS studies

For the PLANETRA study [2], a total of 302 patients with RA were studied under a 2x2 crossover, i.e., (TT, RT) design. Under the (TT, RT) design, 158 patients in the TT (maintenance) group and 144 patients in the RT (switch). Patients who had completed 54 weeks of treatment were analyzed in terms of ACR20, ACR50, ACR70, immunogenicity and safety. Based on descriptive statistics, the investigators conclude that the approved biosimilar has comparable efficacy and tolerability as compared to the originator product. For PLANETAS [3], a total of 174 patients with AS (ankylosing spondylitis) were studied under a similar 2x2 crossover (TT, RT) design. Under the (TT, RT) design, 88 patients in the TT (maintenance) group and 86 patients in the RT (switch). Patients who had completed 54 weeks of treatment were analyzed in terms of ASAS20, ASAS40, and ASAS partial remission. Based on descriptive statistics, the investigators indicate that no negative effects on safety or efficacy in patients with AS were observed.

NOR-SWITCH study

A national, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of switching from innovator infliximab (Remicade®) to a biosimilar infliximab (Remsima™) for N=481 patients with one of the following diseases: ulcerative colitis (93 subjects), Crohn's disease (155 subjects), rheumatoid arthritis (78 subjects), spondyloarthritis (91 subjects), psoriatic arthritis (30 subjects), and psoriasis (35 subject). The primary study endpoint is disease worsening, which is measured based on the following criteria of individual diseases:

(1) For rheumatoid arthritis and psoriatic arthritis, increase in DAS 28 of ≥1.2 from randomization, a minimum DAS 28 score of 3.2;
(2) For spondyloarthritis, Increase in ASDAS of ≥1.1 from randomization and a minimum ASDAS of 2.1;
(3) For ulcerative colitis, increase in partial Mayo score of ≥3 points from randomization and a minimum partial Mayo score of ≥5 points;
(4) For Crohn's disease, increase in HBI of ≥4 points from randomization and a minimum HBI score of 7 points;
(5) For psoriasis, increase in PASI of ≥3 points from randomization and a minimum PASI score of 5;
(6) Based on patient and investigator consensus on disease worsening: If a patient does not fulfill the formal definition, but experiences a clinically significant worsening according to both the investigator and the patient, and which leads to a major change in treatment.

The study was designed for testing non-inferiority of Remsima™ (biosimilar or test product) as compared to Remicade® (reference product) with a non-inferiority margin of 15% for achieving a 90% power for establishing non-inferiority assuming that 30% of subjects who receiving the reference product will occur disease worsening during 52 weeks. Based on the composite endpoint of pooled results, the investigators concluded that Remsima™ is highly similar to Remicade®. The conclusion, however, is biased and may be misleading based on the following observations. First, the use of composite endpoint of pooled results is not statistically justifiable because the variabilities associated with patients' responses for different diseases are different.

Scientific Factors and Statistical Considerations

In order to have an accurate and reliable assessment of the potential risk of non-medical switch in terms of possible reduced efficacy and/or increased incidence rate of adverse events, the following scientific factors and some statistical issues are necessarily considered during the stage of design and analysis of conducting non-medical switch studies.

Scientific factors

Selection bias (multiple diseases)

For approval of a proposed biosimilar product, regulatory agencies such as US FDA does not required clinical studies be conducted on patients with specific diseases (indications) covered by the reference product. Instead, the sponsor may conduct clinical study (studies) on patients with one disease (separate diseases) and seek for approval for all diseases with scientific justification for extrapolations of other diseases. This has posted possible selection bias especially when patients with different diseases respond to the proposed biosimilar product differently. In other words, we may show biosimilarity between the proposed biosimilar product and the reference product in some diseases but fail to show biosimilarity for other diseases. Besides, effect sizes for different diseases may be different from one disease to another. Selection bias certainly argues against the extrapolation approach with scientific justification without support of clinical data.

Confounding effects

When pooling several observational studies for a combined analysis, imbalance in demographics such as sex, age, and race and patient characteristics are commonly seen. Serious imbalance in demographics and/or patient characteristics could cause confounding effect between demographics and/or patient characteristics and the treatment effect. Consequently, the true treatment effect cannot be assessed accurately and reliably. In this case, the use of propensity score is suggested.

Study endpoint selection

For evaluation of non-medical switch, a composite endpoint by pooling the response rates across all diseases is often employed regardless (1) patients' distribution with respect to different diseases, (2) the definitions of the responders under different diseases are different, (3) the variabilities associated with the responses under different diseases may be different, (4) the effect sizes for different diseases are different, and (5) there is possible treatment-by-disease interaction. As a result, the validity for the use of composite endpoint by pooling the response rates across different diseases is questionable and hence the conclusion may be misleading.

Non-inferiority margin

In practice, non-medical switch studies are often designed as non-inferiority trials in order to demonstrate that the proposed biosimilar product is not inferior to the reference product in terms of efficacy and safety. One of the major issues is then how to select the non-inferiority margin. The selection of non-inferiority margin not only has an impact

on the sample size requirement, but also plays an important role for the success of the intended study. As mentioned earlier, effect sizes for different diseases may be different and hence non-inferiority margins for different diseases may be different. The US FDA recommends that its 2010 draft guidance on non-inferiority trial be consulted for selection of non-inferiority margin of the intended non-inferiority study. However, FDA's recommended approaches may result in different non-inferiority margins under different data sets available.

Sample size requirement

To accurately and reliably evaluate the potential risk of non-medical switch, it is suggested that statistical analysis for sample size calculation be performed to ensure that there is certain statistical assurance (e.g., sufficient power) for detecting a clinically meaningful difference (e.g., loss of efficacy, increase of incidence rate of adverse events, or risk/benefit assessment) at a pre-specified level of significance. With a limited number of subjects available, the observed clinically meaningful difference could be purely due to chance especially when there is large variability associated with the observation. Sample size should be able to adjust for potential confounding and interaction effects when pooling several studies for a combined analysis.

Statistical considerations

Bias and variability

In clinical research, bias and variability are related to accuracy and precision (reliability) of clinical data collected from the intended clinical study. Chow and Liu (2008) classified sources of bias and variation in clinical research into four categories: (i) expected and controllable (e.g., changes in laboratory testing procedures and/or diagnostic procedures), (ii) expected but not controllable (e.g., change in study dose and/or treatment duration), (iii) unexpected but controllable (e.g., patient non-compliance), and (iv) unexpected and not controllable (random error). In clinical research, it is not possible to avoid bias and variability in real world. Thus, it is important to identify, eliminate (remove if possible), and control the bias and variability to an acceptable limit (in the sense that it will not have a significant negative impact on the statistical inference drawn).

Baseline comparability

Baseline comparability is referred to as comparison of baseline demographics such as gender, age, weight/height, or ethnic factor and patient characteristics such as patient severity and medical history for treatment balance. In clinical research, if significant differences in patient demographics and/or patient characteristics are observed, these differences may have contaminated the treatment effect and hence they should be included in the statistical model as baseline covariates for adjustment. In other words, analysis on endpoint (post-treatment) change from baseline is recommended in order to account for treatment imbalance.

The use of propensity score

In case there is evidence of confounding effects with demographics and/or patient characteristics, it is suggested propensity score should be used to isolate the possible confounding effects for a more accurate and reliable biosimilarity assessment between the proposed biosimilar product and the reference product.

Control arm

One of major criticisms in single arm observational studies (i.e., R to T) is that there is no control arm (i.e., R to R). Without control arm, it is not possible to evaluate the potential risk of switch (i.e., R to T) because the risk should be assessed by comparing with and without switch, i.e., comparing (R to T) with (R to R). In case pooling several studies with control arm for a combined analysis, it is important to assess similarities and dissimilarities among the control arms before pooling, especially when a significant treatment-by-study interaction is observed. It is suggested that test for pool ability be performed before the data can be pooled for a combined analysis for statistical validity.

Carryover effect

Since the switch (e.g., from R to R or from R to T) occurs within individual subjects, residual effect of R at previous dosing period may carry over to the next dosing period (R or T) though there may be a sufficient length of washout between dosing periods. The carryover effects from R to R and from R to T may be different, which may have an impact on the assessment of the potential risk with/without switch. Current 2x2 crossover design such as (RR, RT) or (RT, TR) is unable to provide independent estimate of the possible carryover effect. To address the issue of carryover effect, a higher-order crossover design such as (TT, RR, RT, TR) or (RTR, TRT) may be useful.

Sensitivity analysis

Before a definite conclusion can be made, it is suggested that a clinical trial simulation in conjunction with sensitivity analysis be performed to provide a complete clinical picture of the non-medical switch. The sensitivity analysis should take the worst possible scenarios into consideration based on lower (upper) bound of a predictive confidence interval for the difference between the proposed biosimilar product and the reference product. In many case, the benefit-risk ratio should also be take into consideration.

Design and Analysis of Switching Studies

Study designs

As indicated by BPCI Act, for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product should not be greater than the risk of using the reference product without such alternation or switch. Thus, an appropriate design for switching studies should be chosen in order to address (i) the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product, (ii) the risk of using the reference product without such alternation or switch, and (iii) the relative risk between switching/alternating and without switching/alternating. Note that in the recent FDA draft guidance, switch is referred to as a single switch while alternation is referred as multiple switches.

To determine whether the proposed biosimilar product can produce the same clinical results in any given patient, a standard two-sequence, two-period crossover design, i.e., (TR, RT) is necessarily employed. In the 2x2 crossover design (TR, RT), if we replace the T in the first sequence

at the first dosing period with R, the design becomes (RR, RT), which is referred to as a hybrid parallel-crossover design (i.e., the first sequence is considered parallel and the second sequence is crossover). This hybrid parallel-crossover design with two dosing periods allows the evaluation of potential risk with and without switching, i.e., the assessment of similarity between the first sequence (switch from R to R) and the second sequence (switch from R to T) after the switch.

Statistical analysis

At the planning stage ofnon-medical clinical trials, under the study design, appropriate statistical methods should be developed under the null interval hypothesis of dis-similarity for achieving a desired power for establishment of biosimilarity between a proposed biosimilar and the reference product. At a pre-specified level of significance. Power calculation for sample size should be performed under the alternative interval hypothesis of similarity at a pre-specified level of significance. It should be noted that we intend to reject the null hypothesis of dis-similarity and conclude the similarity between the proposed biosimilar product and the reference product. Since switching study designs with single switch or multiple switches (i.e., 2 switches or three switches) are special cases of a complete N-of-1 crossover trial design, statistical analysis can be performed using statistical methods described in the previous section.

Concluding Remarks

The potential risk of non-medical switch in terms of loss of efficacy and/or increase of the incidence rate of adverse reactions or adverse events need to be carefully evaluated based on relevant clinical endpoints. Single arm non-medical switch observational studies do not provide substantial evidence regarding the safety and efficacy of the proposed biosimilar product when switch from the reference product to the proposed biosimilar product.

NOR-SWITCH clinical studies attempted to evaluate the potential risk of non-medical switch from the reference product to an approved biosimilar product across various indications (diseases) of the reference product. The intention is good. However, there are several scientific and/or statistical deficiencies in design and analysis of the collected data. As a result, the conclusion made is biased and somewhat misleading.

As discussed in the previous section, in practice, there are three types of hybrid parallel-crossover designs that are commonly used for addressing drug interchangeability in terms of potential risk of switching and alternation. These three types of designs include the parallel plus 2x2 crossover design, the parallel plus 2x3 crossover design and the parallel plus 2x4 crossover design. These study designs are special cases of a complete N-of-1 design with 2, 3, and 4 dosing periods, respectively. Valid study designs and appropriate statistical methods are strongly recommended for a more accurate and reliable assessment of the potential risk of medical/non-medical switch for consumers' protection.

Note that the recent FDA draft guidance does not address the question of non-medical switch post-approval. However, this issue has been raised and discussed at the ODAC meeting for review of two biosimilar regulatory submissions (i.e., Avastin biosimilar sponsored by Amgen and Herceptin biosimilar sponsored by Mylan) held on July 13th 2017 in Silver Spring, Maryland. Despite the lack of any FDA-approved interchangeable biosimilars, 26 states, including Puerto Rico, now have interchangeable biosimilar laws in place that restrict substitution.

Table 3.Summary of Clinical Studies for Non-medical Switch

Study	Study Type	Indication	Treatment	Efficacy	Safety	ADA
PLANETAS extension	OL 102-wk follow-up	AS	N=174 (of original 250 randomized): • 88 continued (CT-P13 to CT-P13) • 86 switched (IFX to CT-P13)	ASAS20, ASAS40 and ASAS partial remission rates were similar between groups	Proportion of pts with ≥ TEAE: • 48.9%continuers • 71.4% switchers • Mainly owing to fewer mild and moderate AEs	ADAs detected wk 54: • 22.2% continuers • 26.2% switchers ADAs detected Wk 102: • 23.3% continuers • 27.4% switchers
PLANETRA extension	OL 102-wk	RA	N=302 (of original 606 randomized): • 158 continued (CT-P13 to CT-P13 • 144 switched (IFX to CT-P13)	ACR20/50/70 response rates were maintained and similar in each group	Proportion of pts with ≥ AE or SAE: • Comparable between groups • 53.5% continuers • 53.8% switchers	ADA-positive pts comparable at Wk 54: • 49.1% continuers • 48.3% switchers Also at Wk 102: • 40.3% continuers • 44.8% continuers
NOR-Switch	1-sided transition	RA,SpA, PsA,UC, CD,Ps	Pts receiving IFX: • Switch to CT-P13(same dose and frequency) • Or remain on IFX	TBD: Disease worsening based on disease-specific assessment scores	TBD	TBD

Table 4. A Complete N-of-1 Randomized Trial Design with Four Periods

Group	Period I	Period II	Period III	Period IV
1	R	R	R	R
2	R	R	R	T
3	R	R	T	R
4	R	R	T	T
5	R	T	R	R
6	R	T	R	T
7	R	T	T	R
8	R	T	T	T
9	T	R	R	R
10	T	R	R	T
11	T	R	T	R
12	T	R	T	T
13	T	T	R	R
14	T	T	R	T
15	T	T	T	R
16	T	T	T	T

References

1. FDA (2017) FDA Draft Guidance on Interchangeability of a Biosimilar with a Reference Biological Product. US Food and Drug Administration, Silver Spring, Maryland.
2. Yoo DH, Prodanovic N, Jaworski J, Miranda P, Ramiterre E, et al. (2017) 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 76: 355-363.
3. Park W, Yoo DH, Miranda P, Brzosko M, Wiland P, et al. (2017) 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 76: 346-354.
4. BPCI (2009) Biologic Price Competition and Innovation Act, Passed by the United States Congress.
5. Buer LCT, Moum BA, Cvancarova M, Warren DJ, Medhus AW, et al. (2016) Switching from Remicade to Remsima is safe and feasible: a prospective, open-label study. J Crohns Colitis 11: 297-304.
6. Chow SC, Endrenyi L, Lachenbruch PA, Yang LY, Chi E (2011) Scientific factors for assessing biosimilarity and drug interchangeability of follow-on Biologics. Biosimilars 1: 13-26.
7. Chow SC (2011) Quantitative evaluation of bioequivalence/ biosimilarity. J Bioequiv Availab, S1-002:1-8.
8. Chow SC (2013) Biosimilars: Design and Analysis of Follow-on Biologics, Chapman and Hall/CRC Press, Taylor & Francis, New York 444.
9. Chow SC, Song FY, Cui C (2017) On hybrid parallel-crossover designs for assessing Drug interchangeability of biosimilar products. J Biopharm Stat 27: 265-271.
10. Chow SC, Song FY, Chen M (2016) Some thoughts on drug interchangeability. J Biopharm Stat. 26: 178-186.
11. Chow SC, Xu H, Endrenyi L, Song FY (2015) A New Scaled Criterion for Drug Interchangeability, Chinese Journal of Pharmaceutical Analysis 35: 844-848.
12. FDA (2015) Guidance on Scientific considerations in demonstrating biosimilarity to a reference product. The United States Food and Drug Administration, Silver Spring, Maryland, USA.
13. Fiorino G, Manetti N, Armuzzi A, Orlando A, Variola A, et al. (2016) The PROSIT-BIO cohort of the IG-IBD: a prospective observational study of patients with inflammatory bowel disease treated with infliximab biosimilars. Inflamm Bowel Dis 23: 233-243.
14. Glintborg B (2016) Three months' clinical outcomes from a nationwide non-medical switch from originator ro biosimilar infliximab in patients with inflammatory arthritis. Presented at EULAR 2016. Annal Rheum Dis 75: 142.
15. Hernandez LD, Gonzalez GER, Gonzalez MV, Diaz CYR, Hernandez FP, et al. (2016) Poster presentations: Clinical: Therapy & Observation.
16. Kolar M, Duricova D, Brotlk M, Hruba V, and Lukas M, et al. (2016) Switching of patients with inflammatory bowel disease from original infliximab (Remicade) to biosimilariunfliximab (Remsima) is effective and safe. Presented at IFX & IFX Biosimilars.
17. LøvikGoll G (2016) NOR-SWITCH study: A randomized, double-blind, parallel-group study to evaluate the safety and efficacy of switching from innovator infliximab to biosimilar infliximab compared with maintained treatment with innovator infliximab in patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis,ulcerative colitis, Crohn's disease and chronic plaque psoriasis. Clinical Trials.

18. Nikiphorou E, Kautiainen H, Hannonen P, Asikainen J, Kokko A (2015). Clinical effectiveness of CT-P13 (infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data, Expert Opin Biol Ther 15: 1677-1683.

19. Sieczkowska J, Jarzebicka D, Banaszkiewicz A, Plocek A, Gawronska A (2016) Switching between infliximab originator and biosimilar in paediatric patients with inflammatory bowel disease. Preliminary observation. J Crohns Colitis 10: 127-132.

20. Smits L, Deriks J, de Jong JDD, van Esch A, and Hoentjen F (2016) Elective switching from Remicade to biosimilar CT-P13 in inflammatory bowel disease patients: a prospective observational cohort study. Presented at IFX & IFX Biosimilars.