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Title

Infliximab biosimilar for autoimmune rheumatological indications

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Introduction

Targeted biologic disease-modifying anti-rheumatic drugs (DMARDs) have revolutionised management of autoimmune inflammatory diseases, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), psoriasis and ankylosing spondylitis (AS). However, due to the high costs of development and production, they are expensive and cost significantly limits widespread use. After the patent on these originator medications has expired, the introduction of biosimilars at a considerably lower cost is expected to facilitate improved and earlier access to therapy and reduce the economic burden on the healthcare system. Biosimilars, while not identical to the originator, are required to show comparable pharmacology, efficacy and safety in key indications before they are made available to patients.

In partnership with Celltrion, a manufacturer of biologic medications based in South Korea, Adcock Ingram will shortly introduce the first infliximab biosimilar (CT-P13) to South Africa. CT-P13 was the first biosimilar monoclonal antibody to be approved in rheumatology and gastroenterology and is already registered in a number of countries, including the USA, European Union, Australia, Canada and Japan. The following is a review of the clinical efficacy and safety data for CT-P13 in rheumatological indications.

What is a biosimilar?

In contrast to traditional drugs, which are produced by chemical synthesis, biological medicines are complex high molecular weight proteins generated by living cells (human or animal cells, or microorganisms). Biosimilars are copies of the originator (reference) biological molecules. However, unlike generic copies of traditional medicines, and because of the highly specialised and controlled processes required for manufacture, they cannot be identical to the originator. There is inherent variability of the biological expression system and manufacturing process and every biological will display a certain degree of variability (microheterogeneity), even between different batches of the same product. Furthermore, because of changes to the manufacturing process, it is likely that biologicals available today are not identical to the same molecule when it was first introduced to patients. Nevertheless, the variability of the biosimilar should not be dissimilar to the reference product and all physiochemical and functional characteristics (e.g., molecular structure, including glycosylation, receptor binding, biological activity), and clinical efficacy and safety must be comparable.

One of the reasons for the high cost of reference biological medicines is the lengthy and rigorous process required for development and registration. This includes preclinical laboratory and animal studies; phase 1 clinical trials in healthy volunteers to assess pharmacokinetics, dosing, safety and efficacy; phase 2 studies to establish safety and efficacy in specific patient populations; and phase 3 multicentre randomised controlled trials (RCT) in large groups of patients. In comparison, biosimilars undergo an expedited regulatory and scientific process that saves time and resources and avoids unnecessary duplication. Stages in this process are (i) analytical analysis to demonstrate comparable structure, function and quality; (ii) a single randomised study to demonstrate pharmacokinetics and pharmacodynamics comparable to the reference product; and (iii) a direct clinical comparison with the reference product in a single phase 3 parallel group RCT to show comparable safety and efficacy in any indication.

Extrapolation, interchangeability, substitution, switching and the development of immunogenicity

Biological therapies are frequently used for more than one clinical indication. Prior to registration, the manufacturers of an original biological agent will be required to perform studies to demonstrate efficacy and safety in each of the clinical indications for which it has applied for registration. This is not the case for biosimilars. When biosimilarity is demonstrated in clinical studies of the biosimilar for one indication, the efficacy and safety data is extrapolated to other indications for which the reference product is already registered, avoiding the necessity of multiple RCTs for each of the indications individually. This is an area of potential concern for clinicians, but there is little evidence that this will not be successful.

Although biosimilars generally have an amino acid sequence identical to the originator, they may differ in terms of drug-p-amino acids (e.g., glycosylations or fucosilations and amino acid side chains after synthesis), which could affect three-dimensional folding and cause subtle changes in tertiary or quaternary structure. Subtle changes in the biosimilar in comparison to the original molecule may increase immunogenicity, causing reduced efficacy and increased risk of side effects.

Switching is the decision made by the treating physician to exchange one medicine to another and with the same therapeutic intent in a patient. This is done for reasons of efficacy or safety for the treatment of the patient.

Interchangeability implies that the biosimilar can be changed from one medicine to another with the

agreement or on the initiative of the prescriber. Substitution refers to the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without healthcare provider (HCP) involvement. This is done on directive from the funder, for example to reduce costs. For substitution between biologic medicines to be allowed, there must be no loss of efficacy or risk to the patient. It is therefore a more stringent requirement than demonstrating biosimilarity. In order to formally be regarded as interchangeable, manufacturers of the biosimilar would have to provide clinical trial data to support interchangeability. Substitution and interchangeability are made more complicated when one considers not only alternating between an originator and one biosimilar (and vice versa), but also between different biosimilars, or even between biological products from different classes (e.g., infliximab to rituximab).

It is understandable then, when biosimilars are 'similar but not identical' and especially in the absence of clinical trials in a specific patient population, or which provide support for interchangeability or switching, that some clinicians might have concerns when considering a biosimilar for their patients.

Preclinical investigations with CT-P13

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of tumour necrosis factor-alpha (TNFα). This prevents the cytokine from binding to its receptor and thereby neutralises its biological activity. Like other IgG1 subclass antibodies, infliximab is a glycoprotein. Physicochemically, the biosimilar is highly similar to the reference molecule. It has identical primary, as well as indistinguishable higher order structures and comparable types and distributions of glycan contents. *In vitro*, it was shown to contain slightly less charge variants than the originator, primarily due to the presence of C-terminal lysine. However, the lysine is rapidly clipped inside serum *in vitro* and *in vivo*, and is therefore not considered to have any influence on the clinical efficacy and safety. Receptor binding and biological activity of CT-P13 are comparable to the reference product.

Clinical studies in rheumatology patients: PLANETAS and PLANETRA studies

The efficacy and safety of CT-P13 in a number of clinical indications, as well as interchangeability with the originator product, are supported by both a rigorous clinical trial program and real-world data.

CT-P13 was compared with reference infliximab (INX) in two 54-week, multinational, double-blind, parallel group studies in patients with active AS (Programme evaLuating the Autoimmune disease iNvEstigational drug cT-p13 in AS; PLANETAS) and in patients with active RA (PLANETRA). In these studies, patients were randomised 1:1 to receive CT-P13 or INX.

PLANETAS was a randomised, double-blind, multicentre, multinational, parallel group phase I study in which patients with active AS were randomised to 5 mg/kg CT-P13 or reference infliximab (INX) at weeks 0, 2, 6 and then every 8 weeks for 30 weeks, with an extension phase up to week 54. The pharmacokinetic profiles of CT-P13 and INX were equivalent. Efficacy endpoints, including 20% and 40% improvement response according to Assessment in Ankylosing Spondylitis International Working Group criteria (ASAS20 and ASAS40), safety outcomes, and percentage of patients testing positive for anti-drug antibodies (ADAs) were similar in the two groups (Table 1). Additional endpoints, including Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index (BASMI), chest expansion and quality of life scores were also comparable.

Table 1. Results from the PLANETAS and PLANETAS 54-week extension studies				
	30 weeks		54 weeks	
	Reference infliximab (n = 125) [a]	CT-P13 (n = 125) [a]	Reference infliximab (n = 125) [b]	CT-P13 (n = 125) [b]
ASA20	72.4%	70.5%	69.4%	67.0%
ASA40	47.4%	51.8%	49.1%	54.7%
Adverse events	63.9%	64.8%	67.2%	74.2%
Infusion reactions	4.9%	3.9%	12.3%	8.6%
Latent TB*	3.3%	3.9%	4.9%	7.0%
Anti-drug antibodies	22.5%	27.4%	23.0%	19.5%

a. Number of patients completing all visits at 30 weeks were 116 and 113 in the reference INX and CT-P13 groups, respectively.
b. Number of patients completing all visits at 54 weeks were 104 and 106 in the reference INX and CT-P13 groups, respectively.
* Latent tuberculosis (TB) as an adverse event refers to patients who originally had a negative TB test and became positive subsequently.

PLANETRA was a multinational phase III double-blind study, in which 606 patients with active RA and an inadequate response to methotrexate (MTX) were randomized (1:1) to receive CT-P13 or reference infliximab (3 mg/kg) at weeks 0, 2, 6 and then every 8 weeks to week 54 in combination with MTX (12.5-25 mg/week). Efficacy endpoints included American College of Rheumatology (ACR)20, ACR50 and ACR70 response rates, Disease Activity Score in 28 joints (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), European League Against Rheumatism (EULAR) response rates, patient-reported outcomes (pain, disease activity and physical ability) and joint damage progression. At both 30 and 54 weeks, all efficacy and safety endpoints were similar in the two groups (Table 2).

Table 2. Results from the PLANETRA and PLANETRA 54-week extension studies				
	30 weeks		54 weeks	
	Reference infliximab (n = 304)	CT-P13 (n = 302)	Reference infliximab (n = 304)	CT-P13 (n = 302)
ACR20 [a]	69.7%	73.4%	71.3%	74.7%
ACR50 [a]	40.6%	42.3%	43.1%	43.6%
ACR70 [a]	17.9%	20.2%	19.9%	21.3%
Adverse events	60.8%	60.1%	70.3%	70.5%
Infusion reactions	8.3%	6.6%	14.3%	9.9%
Latent TB*	4.7%	4.3%	6.7%	7.3%
Anti-drug antibodies	48.2%	48.4%	36.0%	41.1%

a. Efficacy results are for the per protocol population (30 weeks: n = 251 and 248; 54 weeks: n = 216 and 225 in the reference INX and CT-P13 groups, respectively).
* Latent tuberculosis (TB) as an adverse event refers to patients who originally had a negative TB test and became positive subsequently.

To investigate the efficacy and safety of switching from INX to CT-P13 or maintaining biosimilar treatment, patients who had completed 54 weeks in PLANETAS or PLANETRA were enrolled into an open-label extension study in which all patients received CT-P13 every 8 weeks from week 62 to week 102. In PLANETAS, 88 patients were maintained on CT-P13 and 86 were switched from INX to CT-P13. In PLANETRA, 158 were maintained on CT-P13 and 144 were switched from INX to CT-P13.[11]

In both extension studies, in the switch group, efficacy was maintained from week 54 (time of last INX infusion) to week 102. In PLANETAS, ASAS20, ASAS40 and ASAS partial remission rates were similar at week 102 in the maintenance and switch groups (80.7% vs. 76.9%, 63.9% vs. 61.5%, and 19.3% vs. 23.1%, respectively). Similarly, in PLANETRA, response rates at 102 weeks were 71.7% vs 71.8% for ACR20, 48.0% vs 51.4% for ACR50 and 24.3% vs 26.1% for ACR70 in the maintenance and switch groups, respectively. In both studies, there were no significant differences between the maintenance and switch groups in any of the other efficacy outcomes. During the extension phase in PLANETRA, rates of treatment-emergent adverse events (TEAE) were comparable between maintenance and switch groups (53.5% vs. 53.8%, respectively), whereas in PLANETAS a greater proportion of switch patients experienced at least one TEAE during the extension phase (48.9% vs. 71.4%, respectively). However, rates of TEAE in PLANETAS during the main and extension studies were within the range reported in historical studies of INX and there was no indication of a change in the safety profile before and after switching.

In both PLANETAS and PLANETRA extension studies, the proportion of patients who developed ADAs was similar in the maintenance and switch groups at each time point during the extension phase. Almost all of the patients with ADAs had neutralising antibodies (Nab). The proportion of patients with NAb and the proportion of ADA-positive patients with sustained ADAs were similar between groups (Table 3).

Table 3. Proportion of patients with anti-drug antibodies at week 102 in the PLANETAS and PLANETRA CT-P13 maintenance vs. switch extension studies

	PLANETAS[10]		PLANETRA[11]	
	Maintenance group (n = 90)	Switch group (n = 84)	Maintenance group (n = 159)	Switch group (n = 143)
ADAs (% patients)	23.3%	27.4%	40.3%	44.8%
Nabs (% of ADAs)	100%	100%	100%	100%
Sustained ADAs (% of ADAs)	85.7%	88.9%	80.2%	80.4%

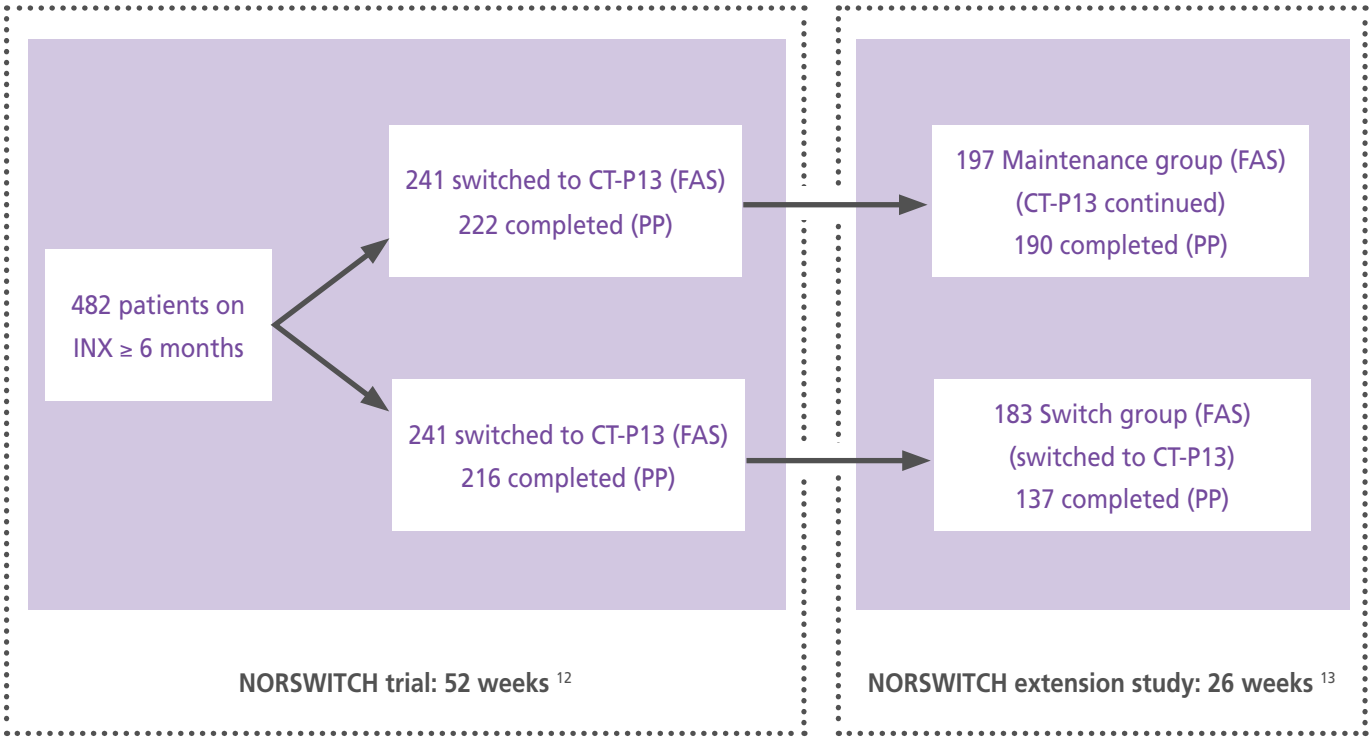
In summary, the PLANETAS and PLANETRA studies demonstrated that in patients with AS and patients with RA receiving MTX, CT-P13 had comparable long-term efficacy and safety to reference infliximab and switching from reference infliximab to CT-P13 was not associated with any detrimental effects on efficacy, safety or immunogenicity. Furthermore, CT-P13 remained efficacious and well tolerated during 2 years of treatment.

Switching from originator infliximab to CT-P13: The NORSWITCH studies

The NORSWITCH study was a randomised, non-inferiority, double-blind, phase 4 trial to evaluate efficacy, safety and immunogenicity of CT-P13 after switching from the originator infliximab.[12] Four hundred and eighty two adult patients who had been treated with INX in a hospital setting for at least 6 months were randomised to continue with INX or to switch to CT-P13 at the same dose as before for 52 weeks. In the overall population, the indications for INX included Crohn's disease (32%), ulcerative colitis (19%), spondyloarthritis (19%), RA (16%), psoriatic arthritis (6%) and chronic plaque psoriasis (7%). The primary outcome was disease worsening at 52 weeks, with a prespecified non-inferiority margin of 15%. Secondary outcomes included disease-specific patient-reported outcome measures. Results at 52 weeks (Table 4) confirmed that switching to CT-P13 was not inferior to continued treatment with INX and was not associated with any safety concerns. Patient reported outcomes, and frequencies of adverse events and serious adverse events were similar between the two groups and no unexpected adverse events occurred during the study. Serum drug concentrations and occurrence of ADAs were similar in the two groups throughout the duration of the study.

Follow-up in the NORSWITCH trial was extended for a further 26 weeks in an open-label extension study.[13] In this study, consenting patients who had completed 52 weeks of the NORSWITCH trial were either switched from INX to CT-P13 (switch group), or maintained on CT-P13 (Fig. 1). The total group comprised 380 patients of whom 33% had Crohn's disease, 21% ulcerative colitis, 18% spondyloarthritis, 15% RA, 5% psoriatic arthritis and 8% chronic plaque psoriasis. At the end of the study, there were no differences between patients who were maintained on CT-P13 and patients who switched from INX to CT-P13 (Table 4).

Figure 1. The NORSWITCH and NORSWITCH extension studies[13]



FAS: full analysis set; PP: per protocol set

Table 4. Results from the NORSWITCH and NORSWITCH extension studies				
	NORSWITCH Week 52 [12]		NORSWITCH Extension Week 78 [13]	
	INX	CT-P13	Maintenance group	Switch group
Disease worsening [a]	26%	30%*	16.8%	11.6%
Disease remission [a]	61%	61%	61.1%	67.6%
Suspected unexpected serious adverse reaction [b]	0%	0%	0%	0%
Serious AE [b]	10%	9%	7%	4%
AE [b]	70%	68%	44%	40%
AE leading to study discontinuation [b]	4%	3%	1%	0.5%
Infusion-related reaction [b]	4%	2%	2%	1%
ADA [b,c]	7%	8%	2.5% [d]	2.2% [d]

a. Per protocol set; b. Full analysis set; c. Excludes patients with detectable ADA at baseline; d. New ADA observed during weeks 52 to 78.
AE: adverse events; ADA: antidrug antibodies

* Adjusted treatment difference -4·4% (95%CI -12.7 to 3.9).

In summary, the NORSWITCH studies confirm that switching from the originator infliximab to CT-P13 is safe and efficacious and supports switching from INX to CT-P13 for non-medical reasons.

Real World experience

The DANBIO Registry

Despite results from clinical trials, because of the non-identical nature of biosimilars with respect to the originator, clinicians often retain concerns about quality, efficacy, safety and immunogenicity and might be reluctant to switch their own patients to a biosimilar. In order to evaluate whether these concerns are justified, data were analysed from the DANBIO registry, a nationwide quality registry covering more than 95% of adults with rheumatic diseases treated in routine care with biological DMARDs in Denmark.[14] Because it was considerably less expensive, in 2015 a national guideline in this country dictated that all patients treated with INX should be switched to CT-P13 (i.e., non-medical switch). Disease activities were compared 3 months before and after switch and changes over time were calculated. Crude and adjusted retention rates were compared with a historic cohort of patients treated with INX. Data were analysed from 802 patients (403 RA, 120 PsA and 279 axial spondyloarthritis) with a mean follow-up duration of 413 days. The mean duration of prior treatment with INX was 6.8 years. After switching, disease activity remained unchanged in the majority of patients, and there were no clinically meaningful changes in disease activity or flare rates in comparison to before the switch.

Although one-year crude retention rate was not different, compared to the historic INX cohort, the adjusted absolute retention rate was slightly lower in the CT-P13 cohort (86.8% vs. 83.4%, respectively; p = 0.03). Of the patients who discontinued CT-P13, 54% did so due to lack of effect and 28% consequent to adverse events. Retention rates across diagnoses were comparable and retention was longer in patients with more than 5 years previous treatment with INX.

In summary, this study confirmed in a large cohort of real-life patients with inflammatory arthritis who had previously been treated with INX for more than 6 years that switch to CT-P13 has no negative impact on disease activity. No new safety signals were detected for CT-P13.

Observational data from Korea

An observational study in Korea evaluated the effectiveness and safety of CT-P13 in patients under routine care.[15] It included 940 biologic-naïve patients (400 with RA, 531 with AS, 3 with PsA and 6 with plaque psoriasis) and 338 patients who had been switched from another anti-TNF agents (108 with RA, 228 with AS and 2 with plaque psoriasis). Adverse events were collected over 6 months. During follow-up, the proportion of patients with RA or AS who achieved remission and the proportion of patients with RA who achieved each disease category by Disease Activity Score in 28 joints (DAS28) was similar in the naïve and switch groups (Table 5). In the biologic-naïve AS group, the proportion of patients who achieved BASDAI 20/50/70 response gradually increased from week 6 (98%, 76% and 28%, respectively) up to week 24 or 30 (97%, 85%, 50%, respectively). TEAEs and serious AEs (SAE) are listed in Table 6.

Table 5. Clinical remission in the Korean Observational Study [15]*

		Naive		Switch	
	Criterion	Baseline	Post-baseline	Baseline	Post-baseline
RA	DAS28-ESR	0/181 (0%)	24/182 (13.2%)	0/25 (0.0%)	5/25 (20.0%)
	DAS28-CRP	0/180 (0.0%)	43/179 (24.0%)	2/25 (8.0%)	6/24 (25.0%)
AS	BASDAI	2/292 (0.7%)	199/292 (68.2%)	112/209 (53.6%)	150/210 (71.4%)

* Clinical remission defined as DAS28≤2.6 in RA and BASDAI<3 in AS.

Table 6. Treatment-emergent and serious adverse events in the Korean Observational Study[15]

	AE	AE related to CT-P13	SAE	SAE related to CT-P13	Infusion-related reactions
RA (n=400)	49.5%	18.3%	13.0%	3.8%	7.0%
AS (n=531)	34.5%	12.1%	2.6%	1.1%	2.1%

The observational data were clinically consistent with historical efficacy and safety data and reaffirm that in everyday clinical practice, CT-P13 was efficacious and well tolerated and may provide a useful alternative to other anti-TNFα agents.

Persistence with biosimilar therapy: BIO-SWITCH and the nocebo effect

The Biosimilar Infliximab Options, Strengths and Weaknesses of Infliximab Treatment Change (BIO-SWITCH) study aimed to prospectively investigate clinical outcomes in patients who switched from infliximab originator to CT-P13 in everyday rheumatological practice in the Netherlands.[16] Patients who were currently being treated with INX were given the option to switch to CT-P13. Those who agreed started CT-P13 at the same dose at the next infusion. In total, 192 patients (75 with RA, 50 with PsA and 67 with AS) were switched to CTP-13 and were followed up for 6 months. Nineteen patients who declined the switch acted as a control group. In general, efficacy markers, infliximab trough levels, ADA levels and safety remained stable after the switch, showing that INX can be switched to CT-P13 without clinical compromise in the majority of patients. However, surprisingly, 24% of patients discontinued CT-P13 due to perceived lack of effect (n=26), AE (n=11), or a combination thereof (n=10). Of the 32 reported AEs, 78% could be categorised as subjective health complaints. Indeed, just prior to discontinuation of CT-P13, both DAS28-CRP and BASDAI were increased relative to baseline. The increase in the DAS28-CRP was caused by significant increases in the subjective assessment criteria (tender joint count and patient's global assessment of disease activity), but not objective criteria (swollen joint count and CRP). Of the 37 patients who discontinued CT-P13, 37 restarted INX, 7 switched to another biologic drug and 3 continued without biologic drugs.

The reason for the high rate of discontinuation is not clear. However, it is postulated that doubts and concerns about the effectiveness and safety of switching from the original to a biosimilar may have negatively influenced the patient's subjective experience (the nocebo effect), leading to higher drug discontinuation than expected.[16] In that case, since both patients and physicians were aware of the switch, incorrect causal attribution (i.e., attributing symptoms to the biosimilar) would be likely to prompt transition back to INX.

The study highlights the importance of the relationship between clinician and patient and clear communication to improve awareness and knowledge about the biosimilar. Patients with concerns about the efficacy and safety of a biosimilar need to be reassured. Education and access to a helpline during the transition can enhance acceptance of the biosimilar and reduce the nocebo effect.[17] In the absence of objective evidence of worsening disease, discussion of the nocebo effect and adopting a 'wait and see' approach before restarting the reference drug may be a more prudent response to subjective health complaints.[16]

In a similar prospective study, 45 patients agreed to switch from INX to CT-P13 and prior to switch, were educated using the Dutch Association of Hospital Pharmacists (NVZA) toolbox Biosimilars, which is a practical guide for successful implementation of biosimilars in daily practice. The persistence rate at approximately 2 years was 87%.[17] Almost all of the patients (96%) were satisfied with the information provided, and this might have contributed to the high rate of persistence.

Conclusion

The introduction of biosimilars is expected to significantly increase access to effective therapy for patients with rheumatological autoimmune disease, with considerable cost savings to the healthcare system. RCTS, observational cohort studies and real-world experience show that there are no efficacy or safety concerns when initiating biologic therapy with CT-P13, or when switching from INX to CT-P13 in patients already in stable remission. However, in order to optimise treatment persistence, efficacy, safety and patient satisfaction, it is important to improve patients' awareness about biosimilars through education and provision of up-to-date information.

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