Manuscript title: A review on biosimilar infliximab, CT-P13, in the treatment of inflammatory bowel disease

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A review on biosimilar infliximab, CT-P13, in the treatment of inflammatory bowel disease

Abstract

The introduction of biological agents has led to significant changes in the treatment of inflammatory bowel disease (IBD). The relatively high price of infliximab (IFX) and the expiration of the patents led to the introduction of biosimilar agents. CT-P13 was the first IFX biosimilar approved in the same indications as the reference product, however, the approval was based on randomized clinical trials conducted in patients with rheumatoid arthritis and ankylosing spondylitis. In the past 2-3 years new findings from prospective observational studies supported the short, medium and long-term clinical efficacy and safety of CT-P13 in patients with IBD. This review summarized the clinical use and efficacy of the first biosimilar IFX, CT-P13, in the treatment of IBD.

Keywords

infliximab, biosimilar, inflammatory bowel disease

Introduction

The prevalence of inflammatory bowel disease (IBD-Crohn's disease [CD], ulcerative colitis [UC]), a chronic immune-mediated inflammatory gastrointestinal disorders, is continuously increasing and places significant burden on the society and healthcare systems worldwide [1]. The introduction of biological agents has led to significant changes in the treatment of each immune-mediated disorders including IBD and improved the outcomes with the change in the natural course of the disease [2]. Infliximab (IFX) was the first biological therapy to be approved in IBD and has since been followed by other anti-tumor necrosis factor (TNF) drugs, as well as anti-integrin antibodies [3]. Many of the biologicals have recently reached or will nearly reach patent expiration. Biosimilars have been introduced with the goals to reduce financial burden of biological therapy and extend therapeutic alternatives. The IFX biosimilar CT-P13 developed by CELLTRION, Inc, Incheon, South Korea and marketed under the trade name Remsima or Inflectra was the first biosimilar licensed for use in IBD in Europe receiving approval from the European Medicines Agency (EMA) in September 2013. In April 2016, CT-P13 was also approved in IBD by the U. S. Food and Drug Administration (FDA). Since then increasing knowledge has been collected on the efficacy and safety biosimilar IFX CT-P13.

Overview of the market

Anti-TNF α therapies have been introduced more than 15 years ago for the treatment of IBD refractory or intolerant to the conventional immunomodulators. In the past few years, use of biological therapy became more and more frequent and started earlier than before in order to modify disease progression in these chronic conditions. Biological therapies induce mucosal healing and sustained clinical remission, decrease the need of hospitalizations and surgery and improve the patients' quality of life [4]. With regaining ability to work, biologicals introduced early are important for economic benefits. The ACCENT and ACT studies were the first clinical trials in CD and UC confirming the efficacy and safety of the originator IFX in IBD [5, 6]. The

ACCENT I trial randomized 573 patients with moderate to severe CD to receive IFX 5 mg/kg, IFX 10 mg/kg or placebo at weeks 2 and 6 and every 8 weeks thereafter. Remission rates at week 30 and 54 were statistically higher in patients receiving IFX 5 mg/kg and 10 mg/kg compared to placebo. In the ACT trials, randomized UC patients receiving originator IFX 5 mg/kg achieved clinical response at week 8 and 30 in 69.4% and 52.1% of patients in the ACT 1 and in 64.5% and 47.1% of patients in the ACT 2 studies [6]. In the ACT 1 trial, 45.5% maintained clinical response at week 54. The effect of anti TNF therapies in inducing and maintaining clinical and endoscopic remission in CD and UC have been further confirmed by several studies from the real life. However, the main limitation of using anti-TNF therapies is their high price. This and their patent expiration have led to the development of biosimilar agents. CT-P13 has been the first monoclonal antibody biosimilar evaluated by EMA.

Introduction to compound

According to the definition of the EMA, biosimilar is a biological medicinal product that is similar to a biological medicine that has already been authorized, the so-called "reference medicinal product" [7]. The World Health Organization defines a biosimilar as a "biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product" [8]. Biosimilars may differ from the original reference drug, in particular for post-translational modifications like glycosylation, but differences are acceptable if the final molecule falls within defined "boundaries of tolerance": variations in some features of the 2 molecules are only considered important if they are clinically relevant [9, 10]. Since biologics are difficult to copy exactly due to their structural complexity and the nature of the cell culture systems used in their manufacture, biosimilars are highly similar, but not identical to their reference biologics. Therefore comprehensive comparability assessment is needed to reveal no clinically important differences are present.

Since the efficacy of the reference drug has previously been confirmed, the importance of clinical studies regarding to the approval of a biosimilar drug is significantly reduced compared to trials required for the approval of the originator. Moreover, biosimilars provide the opportunity to pharmaceutical companies to get the authorization for all the indications the originator agent has, the so-called "extrapolation" [11]. Requirements for approval of a biosimilar by the U.S. FDA, Health Canada and EMA include extensive in vitro studies demonstrating similarity to a reference biologic in terms of quality attributes, as well as nonclinical and clinical studies demonstrating comparable pharmacokinetics (PK), efficacy, safety, and immunogenicity [12].

CT-P13 was the first IFX biosimilar approved in the same indications as the reference products namely for the treatment of eight autoimmune diseases including rheumatoid arthritis (RA) and IBD through extrapolation. The biosimilar IFX CT-P13 and Remicade® have been studied in comparative clinical trials conducted in patients with RA [13-15] and ankylosing spondylitis (AS) [16-18]. In those studies, the comparison between originator IFX and CT-P13 resulted in a strong similarity profile between the two molecules.

Budget impact

Biosimilars offer discounts versus the originator prices of approximately 20–70%, thus their use will probably lead to significant cost savings and increase of access to biological therapy. However, the number of published budget impact studies is very limited compared to cost–effectiveness analyses [19]. A budget impact analysis for the introduction of Remsima across the six licensed indications in Germany, the UK, Italy, the Netherlands, and Belgium revealed that the annual cost savings resulting from the introduction of Remsima were projected to range from €2.89 million to €33.80 million. The cumulative cost savings across the five included countries and the six licensed disease areas were projected to range from €25.79 million to

€77.37 million [20]. The article by Brodszky et al. aimed to estimate the budget savings that can be generated by the use of biosimilar infliximab over the next 3 years in six Central and Eastern European countries, namely Bulgaria, the Czech Republic, Hungary, Poland, Romania, and Slovakia. According to their results when interchanging between originator and biosimilar IFX was not allowed, the introduction of biosimilar IFX resulted in €0.8, 2.6, and 4.5 million cost savings. When interchanging was allowed considerably higher budget savings revealed, €0.3 million, 7.7, and 8.9 M for the years of 1–3, respectively. Therefore, total cost savings over the 3 years were estimated to €8.0 and 16.9 million [19].

Pharmacology

Biologics are defined as active substances derived from living cells or organisms with biotechnology methods [21]. The monoclonal antibody IFX is a large (the molecular weight is approximately 149,000 Daltons), potentially unstable and immunogenic drug with complex three-dimensional structure [22]. For a biosimilar to be approved for the same indications as the originator must be comparable in terms of efficacy and safety, have similar immunogenicity and be effective for all approved indications. Extrapolation of data from one indication to another is also a pivotal aspect of biosimilar development. FDA, Health Canada and EMA have usually allowed the medical companies to perform extrapolation for all indications, thanks to comparability exercises without real clinical data for all indications [12]. During the development of CT-P13, comprehensive and extensive assessments of its physicochemical characteristics were performed [23]. The primary amino acid sequences of CT-P13 and its reference product were confirmed to be the same by several analytical methods [24]. High similarities of secondary and higher structures were also demonstrated [25]. However, when comparing glycosylation patterns between CT-P13 and the reference product, differences has been found in the level of α-fucosylated glycans, implying a potential difference in antibody-dependent cellular cytotoxicity (ADCC) [23].

In vitro studies have demonstrated that CT-P13 and originator IFX have a comparable primary pharmacodynamic profile: CT-P13 and IFX reference product showed very similar binding affinities for soluble transmembrane TNF α and for the Fcγ receptors. They are also comparable regarding to the complement-dependent cytotoxicity and apoptotic effects against a Jurkat T-cell line expressing TNF α [17]. Some minor differences, including FcγRIIIa receptor binding, the level of α-fucosylation and some ADCC have been recorded in comparison with the originator IFX in cells overexpressing membrane TNF and by using enriched natural killer cells from CD patients with the high-affinity genotypes of the FcR [17]. However, when ADCC activity was tested by using whole blood or isolated peripheral blood mononuclear cells, the difference in fucosylation for CT-P13 and the innovator drug did not impact ADCC; therefore the clinical relevance of the observed difference in FcgRIIIa binding is questionable [26, 27]. Pharmacokinetic (PK) equivalence of CT-P13 and IFX reference product has been demonstrated in the PLANETRA and PLANETAS studies [13, 17]. PLANETRA was a randomized, double-blind, multi-center, parallel-group, Phase III study. The study was performed in RA population to demonstrate equivalent efficacy of CT-P13 and the reference drug. In the PLANETRA trial, the C_{max} and geometric means of both drugs were highly similar. PLANETAS was a randomized, double-blind, multi-center, parallel-group, Phase I study performed in the AS patient population to demonstrate the PK equivalence of CT-P13 and the reference product. The study resulted in similar efficacy and showed that steady state PK was equivalent for CT-P13 and the reference product with geometric mean ratios around 100%. Secondary PK endpoints including volume of distribution at steady state and terminal elimination half-life were also similar [16, 17]. An additional PK trial in healthy individuals was thereafter conducted between the European Union–approved and US-approved formulations of IFX originators and CT-P13 showed no difference between treatment groups in primary PK endpoints [28].

Clinical efficacy

Data on the efficacy and safety of CT-P13 came from the randomized controlled trials in rheumatic disease [13-18]. However, it was questionable whether extrapolation of data from studies on RA is appropriate for IBD and initially several national societies have raised concerns regarding the use of biosimilars in extrapolated indications [12]. Differences in the pathogenesis of rheumatic diseases and IBD, the various dosages of IFX and the different mechanism of action used in RA and IBD and the concomitant use of methotrexate and CT-P13 in the PLANETRA trial suggest that extrapolating data from rheumatology to IBD is not well established. Therefore, data from clinical studies on the comparable efficacy were extremely important to use biosimilar IFX with convictions in the real life, even if its cost-effectiveness compared to the originator is well known [29]. Recently, the overall comparability of CT-P13 and originator IFX also proved to be well maintained over the longer-term regarding to the efficacy, safety and pharmacokinetics. Data of a recently ended phase III randomized controlled trial has been presented at the latest congress of the European Crohn's and Colitis Organisation in February, 2017 and at the Digestive Disease Week congress in May 2017 [30, 31]. In the study 220 patients with CD were examined whether CT-P13 is comparable to reference IFX as determined by the Crohn's Disease Activity Index (CDAI), a measurement used to quantify the symptoms of CD patients. According to the 6 week data, similar clinical remission, CDAI-70 and CDAI-100 response rates were observed in both CT-P13 and reference IFX treatment groups [31]. A recently completed phase III study aimed to demonstrate non-inferiority in efficacy and to assess overall safety of CT-P13 compared with Remicade in patients with active CD and to assess efficacy of biosimilar IFX compared with the originator compound in CD and UC patients in remission under treatment with IFX for up to 3 months [32].

Postmarketing study

Post-marketing studies had crucial role to provide deeper insights into the efficacy and safety of CT-P13 therapy and to support its use in IBD patients. However, in most of these studies clinical efficacy was evaluated with using clinical activity scores being less sensitive than in vitro testing of comparability. Among the first real life experiences, a case series published by Kang et al. revealed clinical response and remission at 8 weeks to be 87.5 % in case of CT-P13 treatment of IFX naive patients. However, sample size was too small to allow statistical comparisons between the clinical efficacy, safety, and interchangeability of CT-P13 [33]. Jung et al. revealed clinical response and remission rates in anti-TNF naive CD patients in 90.6% and 84.4% at week 8, 95.5% and 77.3% at week 30, and 87.5% and 75.0% at week 54 [34]. In anti-TNF naive UC patients, rates of clinical response and remission were 81.0% and 38.1% at week 8, 91.3% and 47.8% at week 30, and 100% and 50.0% at week 54, respectively, while mucosal healing rates were 58.3% at week 8, 66.7% at week 30, and 66.7% at week 54. The efficacy of CT-P13 was maintained in 92.6% of CD and 66.7% of UC patients after switching from the originator to the biosimilar IFX [33]. Safety and efficacy at week 14 and 30 of CT-P13 had been confirmed in an open-label, retrospective, multicenter postmarketing study by Park et al. with remission rates of 69.2% and 59.0% in CD and 49.1% and 37% in UC [35]. The study was not powered to evaluate efficacy. The first European data came from Hungary in an observational, prospective study performed by our workgroup with the enrollment of 39 IBD patients showed an overall clinical response and remission rates at week 8 in 37.5% (partial response) and 50% of CD patients and in 20 and 66.7% of UC patients [36]. A prospective, observational study from the Czech Republic confirmed the short term efficacy of CT-P13 therapy at week 14 in 52 IBD patients with response and remission rates of 50-50% in CD and 54.5-40.9% in UC [37]. The study by Sieczkowska-Golub et al. also confirmed that the induction therapy with CT-P13 is effective in children with CD [38]. A Hungarian prospective,

multicenter, observational study evaluating 210 IBD patients showed CT-P13 to be highly effective in inducing and maintaining clinical remission and response in both CD and UC patients up to week 30 with response and remission rates of 81.4% and 53.6% of CD and 77.6% and 58.6% of UC patients at week 14. At Week 30, 67.2% of week 14 responder CD patients maintained clinical response to CT-P13 and 53.4% were in clinical remission. In UC, at week 30, 80% of week 14 responder patients maintained clinical response to CT-P13 and 68% of the patients were in clinical remission [39]. A prospective observational study performed in a single center in Norway showed that 79% of CD and 56% of UC patients achieved remission at week 14 [40]. Argüelles-Arias F *et al*. showed that 87.5 and 83.9% of CD patients switched from reference IFX to CT-P13 who was in remission at the time of the switch continued in remission, and 66.7 and 50% of naive CD patients reached remission, at months 3 and 6. In UC switched cases, 92 and 91.3% of patients in remission at the time of the switch continued in remission, at 3 and 6 months. In naive UC patients, the remission rates were 44.4 and 66.7%, at months 3 and 6 [41].

Mucosal healing after induction therapy was evaluated at first by our workgroup showing rate of mucosal healing to be 60.3% of the enrolled UC patients with complete mucosal healing in 27% of them at week 14 [42]. The recently published PROSIT-BIO study is the largest cohort of IBD patients treated with CT-P13 so far. The study evaluated the efficacy of CT-P13 in 434 patients who received treatment for at least 8 weeks. 8.1% of the patients were primary failures. After further 8, 16, and 24 weeks, the efficacy estimations were 95.7%, 86.4%, and 73.7% for naive; 97.2%, 85.2%, and 62.2% for pre-exposed to anti-TNF α; and 94.5%, 90.8%, and 78.9% for switch [43]. However, this study was not powered to discover potential differences of efficacy based on duration of withdrawal, disease activity, and use of combination therapy at the time of starting treatment with the biosimilar. The effects of switching to CT-P13 from reference IFX have been investigated in a Polish study including 39 pediatric IBD patients. In

the CD group, 69% were in remission at the time of switching. As a limitation of the study, time of switching to IFX biosimilar during the course of therapy was heterogeneous and no data was available about trough levels or anti-drug antibody levels before switching. After a further mean follow-up period of 8 months, 88% of the patients remained in clinical remission [44]. In the prospective, observational study by Smits et al 83 IBD patients treated with the originator IFX was switched to the biosimilar agent and were followed up until 16 weeks. They found that switching did not result in significant changes of disease activity [45]. The 12-month results revealed clinical remission rates of 64% at baseline and 73% at week 52 [46]. In the study by Buer *et al.* 143 IBD patients were switched from Remicade to Remsima®. Throughout follow-up 97% of the patients remained on Remsima®. No significant changes in disease activity were observed after the switch from the originator to the biosimilar IFX [47]. In the study by Razanskaite V *et al*. patient outcomes assessed by the IBD-control Patient-Reported Outcome Measures questionnaire showed an improvement in IBD control-8 score after the switch to CT-P13 [48].

The largest study evaluating the efficacy and safety of switching from the originator to the biosimilar IFX is NOR-SWITCH, a randomised, phase IV, double-blind, parallel-group study that showed that switching from IFX originator to CT-P13 was not inferior to continued treatment with IFX originator. The study was a non-inferiority trial enrolling 482 patients with RA, spondyloarthritis, psoriatic arthritis, UC, CD, and chronic plaque psoriasis and followed for 52 weeks. Patients were randomised 1:1 to either continue originator IFX or switch to CT-P13 treatment using an unchanged dosing regimen. One hundred fifty-five patients in the full analysis set had CD, 93 had UC. However, the efficacy analysis consisted of the total eligible randomized patients who were switched from the originator IFX to CT-P13. Considering the total population, disease worsening occurred in 26% and 30% of patients in the originator and CT-P13 arms. The incidence of anti-drug antibodies detected during the study was 7% and 8%

in the originator and CT-P13 patients [49]. The findings of the NOR-SWITCH trial suggest that patients can be switched from originator IFX to biosimilar IFX which could substantially affect the use of CT-P13 and health budgets in many countries. However, the study was not powered to show non-inferiority in individual diseases. The recently published study from the Czech Republic enrolled 74 IBD patients, who were switched to biosimilar from originator and 119 naive patients newly initiated therapy with the CT-P13. Disease activity remained stable in a majority of switched patients (remission at week 0 vs. week 56: 72.2 vs.77.8%). Overall, response rates at week 14 were 92% of CD and 83% of UC patients, while response rates at week 46 were 86% in CD and 64% in UC. Half of UC patients experienced mucosal healing at week 14 and improvement of perianal disease occurred in 95% of CD at week 46 [50]. Data on long-term efficacy is limited regarding CT-P13 use in IBD. According to our unpublished data, remission rates at week 54 were 62% in CD and 65% in UC patients treated with CT-P13 [51]. Table 1 contains a summary of the postmarketing studies relating on the short, medium and long-term clinical efficacy of CT-P13 in CD and UC.

Safety and tolerability

The first position statement of ECCO on the use of biosimilars in the treatment of IBD was published in 2013 and raised some cautions on the use of biosimilars [52]. In an anonymous survey, only 24% of ECCO respondents stated that a biologic medication should be able to be approved through disease extrapolation to other disease. Sixty-seven % of IBD specialists named immunogenicity as their main concern therefore ECCO called for more data on the safety and benefit of biosimilars [53]. According to an online survey conducted among patients by Peyrin-Biroulet et al. 38% had heard about biosimilars. Only 25.2% of the respondents had no concerns about them. Forty-seven % of the responders worried about biosimilars' safety profile, 40.3% about the efficacy and 35% about the molecular basis. The survey also revealed that

20.9% of the respondents would be against the idea of interchangeability if the patient was not aware [54]. A second survey amongst ECCO members in 2016 reflected a major changing regarding biosimilar use and 28.8% of survey respondents reported they were 'totally confident' prescribing biosimilar medications compared to 5% according to the previous survey [55]. The updated ECCO position statement showed a significant shift in attitude from the previous one and agreed on that switching from the originator to a biosimilar in patients with IBD is acceptable and adverse events and loss of response cannot be expected to be overcome with a biosimilar of the same molecule [56]. Data on safety and tolerability coming from the real life studies had main importance in the acceptance of CT-P13 in the treatment of IBD. In the PLANETRA trial conducted in RA patients, treatment-emergent adverse events (TEAEs) were reported in 35.2% and 35.9% of the subjects. Regarding immunogenicity, anti-drug antibodies (ADAs) were detected in comparable proportions of patients receiving CT-P13 (25.4 and 48.4%) and reference product (25.8 and 48.2%) at weeks 14 and 30 and overall, CT-P13 and originator IFX had similar safety profiles. TEAEs were reported in 60.1% and 60.8% of patients receiving CT-P13 and reference drug [13]. In the PLANETAS study adverse events in the CT-P13 and IFX originator groups were reported in 64.8% and 63.9% of the subjects, respectively, while infusion reactions occurred in 3.9% and 4.9% of the cases. In the CT-P13 group, ADAs were detected in 9.1% and 27.4% of patients at weeks 14 and 30, respectively. In the reference drug group, ADAs were detected in 11% and 22.5% of the patients at weeks 14 and 30 [17]. The cross-immunogenicity of the biosimilar IFX Remsima® with the originator drug Remicade has been examined in the study published by Ben-Horin et al. [57]. All 69 positive anti-Remicade IBD sera were shown to be cross-reactive with Remsima. Anti-Remicade antibodies inhibit similarly Remsima and Remicade TNF-α binding capacity. Regarding to IBD studies, Park et al. revealed TEAEs in 10% of the enrolled IBD patients being mainly mild-to-moderate in severity [35]. Our study of 18 CD and 21 UC patients revealed a mild arthralgia in 1 CD

patients and an anaphylactic reaction after the second infusion of CT-P13 in a UC patient with high ADA levels and previously treated with the originator IFX [36]. In the Norwegian study by Jahnsen *et al.*, infusion reaction occurred in 1 CD and 1 UC patients, rate of adverse event was 2.2% and 3.1% in CD and UC [40]. The studies from Poland revealed that safety profile is similar to that reported for the reference IFX and adverse event rate did not differ significantly either in CD or in UC before and after the switch from IFX to CT-P13 [38, 44]. The Hungarian multicenter study revealed adverse events in 17.1% of all patients. Infusion reactions occurred in 6.7% of CT-P13 treated patients, 71.4% of them had previously received the originator IFX. Infusion reactions occurred in a significantly higher proportion of patients with previous IFX exposure compared with naive patients [39]. Smits et al published adverse events in 29% of the patients after switching [45]. The study by Buer *et al.* revealed adverse events in 6.8% of UC and 14% of CD patients after switching to the biosimilar IFX. Rate of infusion reaction was 0.7% [47]. In the PROSIT-BIO cohort, serious adverse events were reported in 12.1% of the IBD patients, 6.9% of them were infusion-related reactions [43]. However, infusion reactions were significantly more frequent in patients pre-exposed to infliximab than to other anti TNF-α. The NOR-SWITCH study revealed an incidence of ADAs as being 7% and 8% in the originator and CT-P13 patients, respectively. The frequency of adverse events was similar between groups: for serious adverse events, 10% for IFX originator vs. 9% for CT-P13; for overall adverse events, 70% vs. 68%; and for adverse events leading to discontinuation, 4% vs. 3%, respectively [49]. The multicenter, prospective study examining the rate, the characteristics and the predictors of infusion reactions developed in CT-P13-treated Hungarian and Czech IBD patients revealed infusion reactions to occur in 7.3% of all the enrolled patients. 35.7% of patients developing infusion reaction were anti TNF naive. Anti-CT-P13 antibody was proved in 32.6% of patients with infusion reaction and 4.1% of subjects without any reaction during treatment. Our results suppose a lower immunogenicity of the biosimilar in CD and similar rates

and characteristics of infusion reaction with the originator [58]. Table 1 contains a summary of the postmarketing studies relating on the safety profile of CT-P13 in CD and UC.

Regulatory affairs

IFX biosimilar was approved by the EMA under the trade name Remsima® in September 2013 and launched in Europe in early 2015. The US FDA approved Celltrion's CT-P13 in April 2016 under the trade name Inflectra™. CT-P13 is now approved in more than 79 (as of January 2017) countries including the US, Canada, Japan and throughout Europe [59]. In May 2016 SB2 (Flixabi®) was the second biosimilar to infliximab receiving marketing authorization in Europe. The efficacy of SB2 was evaluated in a randomized double-blind, multinational phase III trial in adult patients with moderate to severe rheumatoid arthritis despite methotrexate therapy [60]. During the 24-week switching period of the study efficacy was sustained as indicated by similar response rates across treatment groups [61]. Currently, >20 other biosimilars to infliximab and adalimumab are in the development pipeline. Generally, clinicians need to decide about switching from the reference biologic agent to a biosimilar. However, in the future, they will probably need to also consider a switch in the opposite direction (reverse-switch), or from one biosimilar to another (cross-switch) which may express concerns about the interchangeability if the drugs in this form [62]. The follow-up study of NOR-SWITCH will add useful information about the safety and efficacy of reverse-switch.

Conclusion

Biosimilars represent an opportunity to reduce healthcare costs and increase access to biologicals in several countries. Cost savings associated with the use of CT-P13 across all indications were studied in five European countries from the beginning of 2015 to the first half of 2016. According to the data presented at the 12th Congress of ECCO, total cost savings

observed for Germany, Italy, Spain and the UK amounted to €32.4 million and the findings suggest that this could allow an additional 5,428 patients a year access to this important biologic therapy. There were no cost savings in France, as the price of biosimilar and reference IFX were the same, however despite this; use of CT-P13 has gradually increased in this country [63]. As access to biologicals, these highly effective therapeutic options broaden, the wider they will be used and as their significant clinical benefits, more patients will be able to receive more effective therapy earlier in their disease. The changes in the current pyramidal paradigm of therapy will give way to individualized therapeutic planning.

Executive summary

The introduction of biological agents has led to significant changes in the treatment of IBD with improving the outcomes of the patients. The relatively high price of IFX, the first biological therapy approved in IBD, and the expiration of the patents led to the introduction of biosimilar agents.

Introduction to compound

CT-P13 was the first IFX biosimilar approved in the same indications as the reference products. The approval of the biosimilar IFX was based on randomized clinical trials conducted in patients with RA and AS.

Pharmacokinetic properties

PK equivalence of CT-P13 and IFX reference product has been first demonstrated in AS and RA patients. An additional PK trial in healthy individuals showed no difference thereafter between the European Union–approved and US-approved formulations of IFX originators and CT-P13 treatment groups in primary PK endpoints.

Efficacy and safety profile

Efficacy and safety of CT-P13 has been initially evaluated in rheumatologic diseases, where it has demonstrated its equivalency in terms of efficacy and safety compared to the original IFX. However, in the past 2-3 years, many data have raised from prospective observational studies supporting the short, medium and long-term clinical efficacy and safety of CT-P13 in patients with IBD, including those who switched from the originator IFX.

Regulatory affairs

IFX biosimilar was approved by the EMA under the trade name Remsima® in September 2013 and launched in Europe in early 2015. The US FDA approved Celltrion's CT-P13 in April 2016 under the trade name Inflectra™.

Conclusion

The biosimilar IFX CT-P13 is already available in many countries for IBD. Clinical studies did not find significant difference in terms of efficacy, safety and immunogenicity of CT-P13 in IBD, moreover, switching of IBD patients from original to biosimilar IFX also proved to be effective and safe. The increasing number of publications on the biosimilar medications in IBD will support the use of CT-P13 in this indication in patients who may not have been able to afford biologic therapy previously.

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** This is an important study demonstrating the equivalent efficacy of CT-P13 to originator infliximab with a comparable pharmacokinetic profile and immunogenicity in patients with rheumatoid arthritis.

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