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Biosimilar Infliximab (CT-P13 Remsima™) Is Effective in The Healing of Fistulizing Crohn's Disease

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Abstract

Background: At the time, few data have been published on infliximab biosimilar's efficacy and safety in patients with Crohn's disease. Here, we describe the case of a 66-year-old man who underwent a right colectomy and multiple intestinal resections for fistulizing Crohn's disease, over the last 30 years. Since diagnosis, the patient had been treated exclusively with mesalazine. On admission, in September 2015, patient had clinical and laboratory activity and had a discharging cutaneous fistula at the right lower quadrant of the abdomen. Abdominal Ultrasonography (US) and enteric MRI with and without i.v. contrast showed presence of abdominal fluid effusion (diameter 42 mm) (Figure 1) in the right lower quadrant. This was fed by multiple entero-enteric fistulas; moreover, another fistula reached the skin. Total parenteral nutrition was started, followed by treatment with biosimilar infliximab (CT-P13 Remsima™).

Methods: We started CT-P13 Remsima™ infusion as per standard protocol (5 mg/kg at 0-2 and 6 weeks and then every 8 weeks). Patient was followed up with physical examination and blood tests at week 2, 4, 6 and 8, when an abdominal US was performed. At 6th month he underwent enteric MRI. Therapy was considered successful if diarrhea resolution, reduction of abdominal fluid effusion and closure of enterocutaneous fistula within eight weeks were achieved.

Results: At week 2, entero-cutaneous fistula was closed and patient referred diarrhea resolution. At week 8, abdomen US showed a reduction in size of abdominal fluid effusion (diameter 15 mm). Blood tests were normal. Patient did not show any adverse effects. At 6th month, patient had no symptoms, laboratory inflammatory indexes were stationary, ultrasonography was normal and enteric MRI showed a reduction in extension of the inflammatory process, the solving of fistulae and no visible fluid mass (Figure 2).

Conclusion: Biosimilar infliximab CT-P13 Remsima™ is effective in the management of a patient with fistulizing Crohn's Disease. Additional data from clinical trials are needed to confirm this finding.

Keywords: Biosimilar Drug; Crohn's Disease; Fistulizing Pattern; Fistula's Closure; Healing; Severe Disease

Introduction

Crohn's Disease (CD) is a severe chronic disease, often debilitating due to the lifelong duration and high risk of intestinal resections. It can evolve through three patterns: inflammatory-ulcerative, fibrostenosing and fistulating one. It is important to define disease's pattern because appropriate management should take into account activity, site and behaviour of disease. Fistulating CD comprises fistulae generating in the perianal area, fistulae between different intestinal loops or between intestine and another organ such as bladder or the abdominal wall. Fistula involving small bowel may determine a malnutrition state due to poor absorption or different systemic symptoms according to the specific organ affected by fistula's path. When a symptomatic or complex fistula is identified, surgical approach should be considered combined to medical therapy consisting in antibiotics (ciprofloxacin 1 g/day and metronidazole 1,5 g/day) and either Azathioprine (AZA) (first line for perianal fistulae) or Infliximab (IFX) (first line for enterocutaneous fistulae) [1]. In 2013 European Medicines Agency (EMA) approved two IFX biosimilars, copies of an original biopharmaceutical with similar biologic activity, physicochemical characteristics, efficacy and safety [2]. The lower cost of biosimilar will make biologic treatment more accessible to a wider use [3]. At the time, there are few data about efficacy in the common clinical practice. Here, we show a case of a 66-year-old man affected by fistulizing CD treated by CT-P13 RemsimaTM, an IFX biosimilar.

Case Report

A 66-year-old man with CD was admitted to our Gastroenterology Unit for pain in middle and right abdomen side, diarrhea (about ten bowel movements/day with mucus), fever (max fever peak at 38.5°C), asthenia and weight loss: his health status and quality of life were poor. Faecal calprotectin was highly positive (218 mg/Kg; normal values < 70 mg/Kg), such as ESR (76 mm/first hour; n.v. < 14) and RCP (16,3 mg/L; n.v. < 5). In the past, the patient had had appendectomy and multiple intestinal resections (transverse colon, small bowel, caecum, the ileocecal valve, 9.84 inches of ascending colon and 7.87 inches of ileum) for recurring intestinal occlusion as complications of CD. Furthermore, bilateral perianal abscess and fistulae were identified and treated surgically through abscess drainage and wide bilateral fistulectomy. Later, two draining setons were positioned and medical treatment was started (Mesalazine Pentasa 3 g/day). During the hospitalization, an Entero-Magnetic Resonance (Entero-MR) showed multiple corpuscular fluid elements converging into an irregular mass (2.36 inches max diameter), an enterocutaneous fistula communicating with the mass, multiple complex fistulae and inflammation of surgical anastomosis, duodenum, jejunum, ileum and rectum (Figure 1).

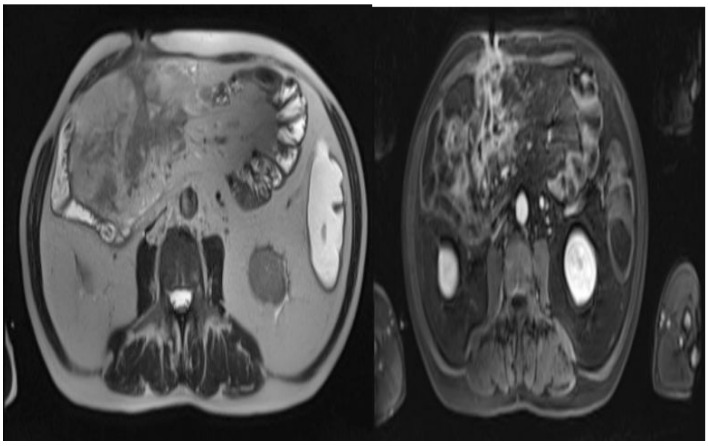

Figure 1: Axial T2-weighted TSE MR sequence (A) demonstrating inhomogeneous mass with irregular margins and peripheral fat stranding in the right abdomen that reaches the anterior right abdominal wall with a trans-muscular fistulous tract; axial T1-weighted VIBE MR sequence (B) after contrast administration showed significant and inhomogeneous contrast enhancement of the mass as well as of the mesenterial fat; of note, the mass is characterized by multiple fluid collections.

Patient started parenteral nutrition and antibiotic therapy with ciprofloxacin (1g/day) and metronidazole (1.5 g/day), after taking a sample from enterocutaneous fistula for culture that resulted negative. Fever gradually disappeared until the third day of therapy while other symptoms did not improve. An abdominal Ultrasonography (US) was performed which showed thickening of an ileal segment communicating with abdominal wall through a fistula. Also, US showed an irregular fluid collection (2.18 inches in diameter) and multiple converging fistulae (Contrast-enhanced US: hypovascular behavior, likely an abscess). All the clinical data pointed out a severe CD, due to extension of disease, symptoms and to fistulizing pattern which caused a malnutrition status; following consultation with surgeons, we started therapy with IFX biosimilar (CT-P13 RemsimaTM) 5 mg/Kg intravenous at 0-2-6 weeks and then every 8 weeks.

Results

At week two, enterocutaneous fistula was already closed and patient referred diarrhea resolution (frequency less than five/day). At the eighth week of treatment, the patient referred no abdominal pain, no bleeding, no fever, a stationary stool frequency, inflammatory indexes were normal (ESR 8 mm/first hour, RCP 2,2 mg/L, serum iron 99 ug/dL; PLT 100.000/mm3) and US showed reduction of abscess (max diam. about 0,59 inches). His quality of life slightly improved at second and eighth week of treatment since the CD was no more interfering with work and daily activities.

After three months from the first day of therapy, the stool frequency lowered to three/day, enterocutaneous fistula was still completely resolved and inflammatory indexes were within the normal range. No adverse events were observed or referred by the

patient. At sixth month, the patient had no symptom (stool frequency: less than three at day, no diarrhea; no pain, fever, asthenia or weight loss). Blood test values were within the normal range (PLT 119.000/mm; ESR 12 mm/first hour; RCP 1,7 mg/L; serum iron 81 ug/dL). US showed absence of fluid masses, thickened intestinal wall or draining fistulae, such as enteric-MRI that also pointed out a residual moderate inflammation of ileocolic anastomosis (hyperemia, low turgidity of mesenteric fat and few subcentimetric linfatic nodules) (Figure 2).

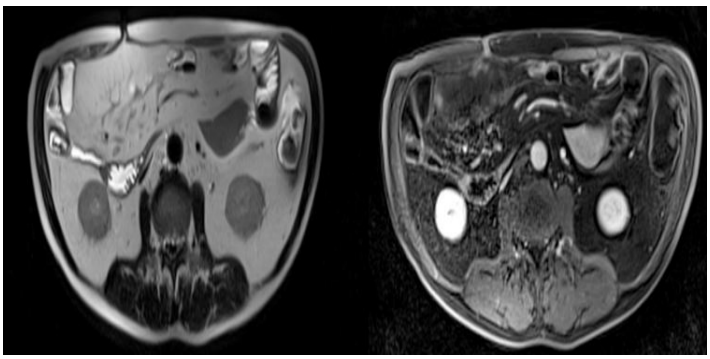

Figure 2: Post-treatment axial T2-weighted TSE MR sequence (A) demonstrating complete disappearance of the mass with only residual irregularity of the right anterior abdominal wall profile; post-treatment axial T1-weighted VIBE MR sequence (B) after contrast administration showed only faint contrast enhancement of the trans-muscular fistulous tract of the right anterior abdominal wall.

Discussion

Fistulating CD is a complex clinical condition which often needs a multidisciplinary approach, both surgical and pharmacological. Symptoms can be various according to specific organs involved in the fistula's path: malabsorption in enteroenteric fistulae; dysuria, fecaluria or urinary infections for entero-urinary fistulae; external drainage in enterocutaneous or gynecological fistulas [1,4]. The pharmacological treatment of fistulating CD consists of AZA, and IFX therapy [1]; Present et al proved enterocutaneous fistulas' healing by using IFX (5 mg/kg 68% of patients, 10 mg/kg 56% of patients) and a median length of time of three months without reopening [5,6]. Another study, ACCENT II Trial, about rectovaginal fistulae found a 69% of response to induction therapy with IFX (5 mg/kg) at week 14 (195/306 patients) [7]. After response to induction therapy phase, maintenance of response can be gained through IFX infusion every 8 weeks [8]. Hospitalizations and surgery procedures are less needed if a maintenance therapy with IFX is estabilished [9]. In November 2013, as innovator IFX's patent expired, the European Medicines Agency (EMA) approved a biosimilar formulation of IFX, known as CT-P13, which is marketed under the trade names Remsima and Inflectra. The term biosimilar has been defined by the World Health Organization as "A biotherapeutic product that is similar in efficacy, safety and quality to the reference product" [10,11]. Biological products are large molecules created using recombinant DNA but step-to-step process is known only to the manifacturer.2 Indeed, manufacturing processes may be variable across manufacturers, that could be basic to determinate safety and efficacy of a biosimilar drug. It is clear that biosimilar drug is not considered a generic version of the innovator biologic one [12,13].

The most important benefit is the reduction of costs, Ashok Jha et al. considered the budget impact of using biosimilar IFX for Autoimmune Diseases in 1-year period and they estimated budget savings of € 45.13 million in European countries [14]. Clearly it is needed to assure that biosimilars are really "Similar" to innovator IFX in the common clinical practice and, at the time, data are still few. CT-P13 is manufactured using the same human/mouse cell hybrid clone technology as IFX [15]. The first trial comparing CT-P13 and IFX was the phase 1 PLANETAS trial, which involved 250 patients with Ankylosing Spondylitis (AS). It was a biosimilarity study planned to show pharmacokinetic equivalence and to compare efficacy and safety of CT-P13 and IFX. Their endpoints included ASAS20 and ASAS 40 (two criteria for evaluation of AS clinical response to therapy, commonly used for treatments' efficacy assessment trials). ASAS20 responses were evaluated about 62.6 and 70.5% at weeks 14 and 30, respectively, for patients treated with CT-P13 and 64.8 and 72.4%, respectively, for patients treated with IFX. Serum levels of antibodies (Ab) to IFX and CT-P13 were comparable as it was the safety profile [16].

The initial findings of PLANETAS were further confirmed in a large phase III randomized, double-blind, multicentre trial: PLANETRA. In this study, patients with active Rheumatoid Arthritis (RA), who were refractory to Methotrexate (MTX) treatment, received 3 mg/kg of CT-P13 (n=302) or IFX (n=304), both in association to MTX (12.5-25 mg/week) and folic acid. Clinical efficacy, pharmacokinetic profile, safety and immunogenicity were comparable between IFX and CT-P13. The primary endpoint (ASAS20 ± 15% at week 30) was achieved by 60.9 and 58.6% of patients in the CT-P13 and IFX groups respectively. Adverse events (mild to moderate intensity) were observed in 181 (60.1%) CT-P13-treated patients and 183 (60.8%) IFX-treated patients, while infusion-related reactions occurred in 6.6 and 8.3% of these patients, respectively [17]. A prospective observational study performed in a single center in Norway demonstrated the effectiveness of CT-P13 in moderate to severe disease, after failure of other treatments (steroids, AZA, etc): 79% of CD and 56% of Ulcerative Colitis (UC) patients achieved remission at week 14. Patients with CD (n = 46) or UC (n = 32) received CT-P13 (5 mg/kg) by intravenous infusion at weeks 0, 2, and 6. Moreover, at week 14 it was observed a significant reduction of serum CRP levels compared with baseline in CD patients (4.9 mg/l [2.4-7.4] vs 22.5 mg/l [11.3-33.7], p = 0.006;) and UC patients (9.6 mg/l [4.0-15.2] vs 36.8 mg/l [18.0-55.7], p = 0.012). Same results for fecal calprotectin levels were also observed (CD patients: 214 mg/kg [53-374] vs 1148 mg/kg [756-1540], p = 0.0002; UC patients: 857 mg/kg [458-

1255] vs 2582 mg/kg [2016-3147], p = 0.0001) [18].

In our case, patient was affected by a complex fistulating Crohn's disease (severe activity), since he had a deep abdomen abscess with multiple fistulas and an enterocutaneous fistula; the CD compromised patient's quality of life, interfering with work and daily activities. According to ECCO Statements (9J- 9K), we began therapy by using antibiotics and IFX (RemsimaTM) 5mg/kg at 0-2-6 weeks because of the failure of previous surgery procedures and presence of an enterocutaneous fistula (that usually requires IFX) [1]. Response was already satisfactory at week 2 with to diarrhea resolution and closure of the abdomen wall fistula. At week 8, patient was asymptomatic and abdominal abscess significantly reduced in size: since the second week, patient's quality of life slightly improved. Patient underwent maintenance therapy with biosimilar IFX (RemsimaTM) every 8 weeks and at the sixth month he had no abscess or fistula at US and enteric-MRI showed a definite reduction in inflammation, while confirming absence of fluid masses or significant fistulae. During the whole period of observation, no adverse events were noticed. The health status totally changed since the introduction of biosimilar IFX (expecially the malnutrition status, indeed at follow-up checks no more asthenia or weight loss were observed) and enteric-MR images were significantly different before and after the biological therapy; the absence of symptoms, fluid mass or draining fistulae granted a good quality of life to our patient, achieving the main goal of a treatment. The fistulizing CD is hard to treat, patients often undergo surgery, with possible complications on short and long term; the percentage of response to drugs is about half of patients though. We used a biosimilar drug, gaining a clinical, laboratory and imaging healing, with same efficacy and safety of the "Originator" one: this suggests that we could try using a biologic therapy instead of early surgery in fistulizing CD and use a biosimilar drug, expecting a complete healing, no adverse effect and efficacy over time [19,20].

This conduct may lead to economy saving and overcome the most problematic features of this kind of drugs: their cost and their accessibility to patients.

Conclusions

Biosimilar IFX (CT-P13 RemsimaTM) is effective and safe in the treatment of fistulating Crohn's disease. Large case series are necessary to confirm this preliminary observation.

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