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**ORIGINAL PAPER**

Anna Pękala [1(ABG)], David Aebisher [2(DEFG)], Piotr Pardak [1,2(BFG)], Rafał Filip [1,2(ABDFG)]

# Efficacy and safety of biosimilar IFX (CT-P13) and adalimumab in patients with active fistulizing perianal Crohn's disease naïve to anti-TNF therapy: preliminary results from the POLIBD study

[1] Department of Gastroenterology with IBD Unit, Clinical Hospital No. 2, Rzeszów, Poland
[2] Faculty of Medicine, University of Rzeszów, Rzeszów, Poland

**ABSTRACT**

**Introduction**. The development of perianal fistulas are a risk factor in colonic and rectal disease. Perianal CD treatment requires a combination of surgical and therapeutic treatments aimed to prevent septic complications, reduce fistula discharge and ultimately heal fistulas.

**Aim.** The purpose of the study was to evaluate the efficacy and safety of biosimilar IFX (CT-P13) and adalimumab in active fistulizing perianal Crohn's disease (CD) in patients from the Subcarpathian Region (South-Eastern Poland).

**Material and methods**. Thirty patients with CD with perianal fistulas naïve to anti-TNF therapy were enrolled (13 females/ 17males) ranging from 18 to 64 years of age. Twenty-one were treated with biosimilar infliximab (CT-P13), nine were treated with adalimumab (ADA). The treated patients had ileal CD (4), ileo-colonic CD (13) or colonic CD (13). All of them received standard immunosuppression with no additional steroid therapy. Response was evaluated at week 16 and 40 after the first CT-P13 dose, and 16 and 40 weeks after the first ADA dose. Remission was defined as the complete closure of all fistulas and partial response as a reduction (≥50%) in the number of draining fistulas.

**Results.** Treatment outcomes with CT-P13 and ADA were both effective and similar in the percentage of patients with perianal fistula improvement, perianal fistula remission, no effect or observed adverse events.

**Conclusion**. In patients with active fistulizing CD, both CT-P13 and ADA were effective and safe, however a slight superiority of CT-P13 was visible.

**Keywords**. adalimumab, Crohn's disease, IFX, perianal fistula

**Corresponding author:** Anna Pękala, e-mail: apekala@onet.pl

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## Introduction

The aetiology of perianal fistulas in Crohn's disease (CD) is still unclear. The presence of colonic and rectal disease represents the greatest risk factor for the development of perianal fistulas.[1] CD-associated fistulae appear as a fissure penetrating in the gut wall surrounded by granulation tissue with acute (neutrophils) and chronic (lymphocytes) inflammation. Their lumen is filled up by nuclear debris, sometimes erythrocytes.[2] The treatment of perianal CD requires a combined surgical and medical approach and should attempt to resolve and prevent septic complications, reduce fistula discharge with concurrent improvement of a patient's quality of life, and finally, the healing of fistulas. Treatment options depend on the severity of symptoms, fistula location, the number and complexity of fistula tracts, and the presence of rectal complications.

## Aim

The purpose of the study was to evaluate the efficacy and safety of biosimilar IFX (CT-P13) and adalimumab (ADA) in active fistulizing perianal Crohn's disease (CD) in patients from Subcarpathian Region (South-Eastern Poland).

## Material and methods

The human studies were approved by the Bioethical Commission of the University of Rzeszów (Resolution number 9/10/2016).

Thirty patients with CD with perianal fistulas naïve to anti-TNF therapy were enrolled (13 females/17males) ranging from 18 to 64 years of age. Twenty-one were treated with CT-P13 and nine were treated with ADA for the duration of twelve months. The treated patients had ileal CD (4), ileo-colonic CD (13) or colonic CD (13). All of them received standard immunosuppression with no additional steroid nor antibiotic therapy during biological treatment. Before including anti-TNF therapy, they received metronidazole with cyprofloxacin or other antibiotics according to the result culture of the content from the fistula for 4-6 weeks. The majority of patients in whom the inflammatory changes included the large intestine were additionally treated with mesalazine.[3]

All patients with fistulas underwent a pelvic MRI examination, on the basis of which the abscess was excluded and the course of the fistula was depicted. All those whose anatomical conditions allowed it to have a thread or seton attached to the fistula canal (25 patients). Assignment to the treatment was not performed in random fashion, but the decision was made based on overall disease activity. Therefore, patients with higher CDAI values were assigned to treatment with CT-P13. CT-P13 was used at a dose of 5 mg per kg / body weight scheduled at 0.2 and 4 weeks in induction therapy and every 8 weeks in maintenance therapy. ADA was given as a first dose of 160 mg, 80 mg after 2 weeks and then at a dose of 40 mg every 2 weeks. Response to the treatment was evaluated at week 16 and 40 after the first CT-P13 dose, and 16 and 40 weeks after the first ADA dose. Remission was defined as the complete closure of all fistulas and partial response as a reduction (≥50%) in the number of draining fistulas. Perianal disease improvement referred to reduction fistula drainage, reduction of bleeding, pain and excretion, edema, tenderness, and surrounding redness.

Simple descriptive statistical calculations were performed with the use of Statistica version 6.0. A statistical significance threshold of $P = 0.05$ was adopted.

## Results

The basic characteristics of the study population are presented in Table 1. The efficacy of perianal fistula closure and improvement after the twelve month therapy with CT-P13 and ADA is presented in Table 2.

**Table 1.** Basic characteristics of the study population

| | |
|---|---|
| **Age** | 18-64 years |
| **Sex** | (13 females/17 males) |
| **The form of the disease / number of patients:** | ileal CD /4, ileo-colonic CD /13 colonic CD/ 13 |
| **Duration of the disease** | 1-7 years |
| **Type of anti-TNF /group size** | infliximab/21 adalimumab/ 9 |

**Table 2.** Perianal fistula closure and improvement after twelve month therapy with biosimilar infliximab (CT-P13) and adalimumab (ADA)

| *Outcome | CT-P13 | ADA |
|---|---|---|
| Perianal fistula improvement | 6 patients (28.6%) | 4 patients (44.4%) |
| Perianal fistula remission | 10 patients (47.6%) | 3 patients (33.3%) |
| No effect observed | 5 patients (23.8%) | 2 patients (22.3%) |
| Adverse events (perianal abscess) | 9%- (2 persons) | 11%- (1 person) |

* No statistical significance was observed ($p > 0.05$)

## Discussion

The perianal fistulas are an inconvenient complication of Crohn's disease (CD), significantly worsening the quality of life of patients. The risk of developing fistulas depends on disease location, being most frequent in colonic disease with rectal involvement. The cumulative incidence of perianal fistulising CD (pCD) is 12% after 1 year, and this doubles 20 years after diagnosis.[1,2] Disease lesions in the anus area in 27% of cases may be the first manifestation of the disease.[4]

Fistulas are a symptom of hollowing disease and risk factors for a more severe course of disease are: age under 40 years at the time of diagnosis, stenotic disease, involve-

ment of the upper gastrointestinal tract, need for corticosteroids on the first flare-up, lack of mucosal healing after induction of clinical remission, and smoking.[5]

Treatment of this form of the disease should be intensive from the very beginning to prevent deepening of tissue damage and abscess formation.

According to the guidelines set out in the 2014 European Society of Coloproctology Consensus, biological therapy with anti-TNFs is the gold standard for the treatment of fistulas in patients with CD.[6]

Our study assessed the efficacy of CT-P13 - biosimilar infliximab, and ADA treatment in 30 patients with active perineal disease in whom other pharmacological treatment options were exhausted. The use of IFX in this form of the disease is well established and this medicine is also used more frequently in cases of perinanal fistulas in our center, but significantly less clinical trials concern the use of ADA.

The efficacy of IFX in the treatment of perianal fistulas has been profoundly studied. In the first placebo controlled trial, an induction regimen induced closure of at least 50% of fistulas for at least 4 weeks in 56–68% of patients compared with 26% treated with placebo. Closure of all fistulas was achieved in 38–55% of patients on IFX.[6] The ACCENT II trial further evaluated IFX maintenance therapy for this indication. Week 14 responders to the induction regimen were randomized to further treatment with placebo or IFX 5 mg/kg every 8 weeks and 39% of patients who received IFX maintenance therapy had complete closure of all draining fistulas at week 54.[8] In the CHARM trial—a 56-week phase III trial to assess the efficacy of maintenance treatment with ADA among responders to induction treatment, a subgroup analysis in patients with draining fistula(s) at baseline showed complete fistula healing in 33% of adalimumab treated patients versus in 13% of placebo treated patients.[9] An open label extension of this trial showed sustained healing in 90% of patients on ADA treatment at 2 years follow-up. In further open label studies, adalimumab was effective in 23–29% of patients with fistulising CD who had lost response or become intolerant to IFX.[10,11]

It is emphasized that the approach to treatment of this form of the disease should be comprehensive.

A very important element of treatment is the determination of the anatomical course and type of fistula and exclusion of abscess. In our study, all patients had a pelvic MRI scan, which is considered the preferred method that accurately visualizes the anal sphincter and the pelvic floor muscles as well as the fistula tracts and abscesses. In addition, the MRI scan can identify clinically 'silent' abscesses and luminal inflammation.[12-14]

Patients with abscesses were first treated surgically with drainage, only after the abscess was resolved they were qualified for biological therapy.

The surgical procedure also involved insertion of a thread or seton into the fistula canal in order to prevent abscess formation. This procedure was used in the majority of patients in whom the anatomical conditions allowed it.

It is believed that non-cutting seton placement is very useful in order to prevent (recurrent) abscess formation.[14] In contrast, a disadvantage of setons is that the fistula tract cannot 'close' with the seton in place. The optimal timing for seton removal is not well established.[14] In accordance with the principles of a comprehensive approach to treatment, the studied group received all the preferred methods of therapy, including immunosuppressive treatment.

Considering the studies carried out so far, anti-TNF and thiopurine combination therapy may lead to higher fistula healing response and closure rate compared to monotherapy.[5,16] However, the results of all tests carried out are not compatible, e.g. a subgroup analysis of the ACCENT II trial found that concomitant immunosuppressants did not improve response rates to IFX at 1 year.[17] While another recent studies suggest a clear association between combination therapy and fistula closure, nevertheless, the gain with combination therapy is of particular in patients with proctitis.[18,19]

An additional argument for combining combination therapy is to reduce the production of anti-infliximab antibodies, which reduces the percentage of secondary loss of response to treatment; in the case of ADA, clinical trials did not show such an advantage.[20]

According to the guidelines, all patients also received antibiotic therapy (ciprofloxacin and metronidazole) consistent with the result of culturing the content obtained from the fistula, which was carried out from 4 to 6 weeks depending on the tolerance. All patients achieved a reduction in fistula drainage, but not fistula healing; in patients in whom the time between the end of antibiotic therapy and the initiation of biological treatment was prolonged, an increase in secretion was observed.

These observations are consistent with clinical trials that evaluated the efficacy of longer treatments for metronidazole and ciprofloxacin (6 to 8 weeks) and a high frequent relapse upon discontinuation and side effects occurring was reported.[20-22] In turn, studies evaluating ciprofloxacin-combined therapy and anti-TNF drugs (IFX and ADA) showed reducing fistula drainage but not fistula healing.[23,24]

We have demonstrated that the combination of thiopurins and CT-P13 or ADA therapy preceded by antibiotic therapy and surgical treatment (abscess drainage, seton fistulae) gives slightly higher efficacy in fistula healing when IFX was used 47.6% vs. 33%. The lack of any response was noted in a similar percentage of cases, 23.8% and 22.3%, for CT-P133 and ADA, respectively.

Despite the limitation of our study, which is a relatively small number of patients and the prevalence of infliximab-treated patients, the results obtained coincide with other studies. On the basis of the analysis, the risk factor of non-response was not identified, whereas it was observed that complex and multiple perirectal fistulas were a risk factor for lack of healing but no lack of response (patients achieved a reduction in secretion by at least 50%).

## Conclusion

In patients with active fistulizing CD, both biosimilar IFX and adalimumab were effective and safe, however, a slightly better outcome with biosimilar IFX was observed. Treatment outcomes with biosimilar IFX and adalimumab were both effective and similar in the percentage of patients with perianal fistula improvement, perianal fistula remission, no effect or observed adverse events. The results obtained in this study concur with other published trials.

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