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

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

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/17 males) 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
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. 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. 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/17 males) 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 ciprofloxacin or other antibiotics according to the result culture of the content. 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.

Table 1. Basic characteristics of the study population

<table>
<thead>
<tr>
<th>Age</th>
<th>18-64 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>(13 females/17 males)</td>
</tr>
<tr>
<td>The form of the disease / number of patients:</td>
<td>ileal CD /4, ileo-colonic CD /13, colonic CD /13</td>
</tr>
<tr>
<td>Duration of the disease</td>
<td>1-7 years</td>
</tr>
<tr>
<td>Type of anti-TNF / group</td>
<td>infliximab/21 adalimumab/9</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>*Outcome</th>
<th>CT-P13</th>
<th>ADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perianal fistula improvement</td>
<td>6 patients (28.6%)</td>
<td>4 patients (44.4%)</td>
</tr>
<tr>
<td>Perianal fistula remission</td>
<td>10 patients (47.6%)</td>
<td>3 patients (33.3%)</td>
</tr>
<tr>
<td>No effect observed</td>
<td>5 patients (23.8%)</td>
<td>2 patients (22.3%)</td>
</tr>
<tr>
<td>Adverse events (perianal abscess)</td>
<td>9% (2 persons)</td>
<td>11% (1 person)</td>
</tr>
</tbody>
</table>

* 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. Disease lesions in the anus area in 27% of cases may be the first manifestation of the disease.

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 cortico-
steroids on the first flare-up, lack of mucosal healing after
induction of clinical remission, and smoking.1

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

According to the guidelines set out in the 2014 Eu-
ropean Society of Coloproctology Consensus, biologi-
cal 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 - biosim-
ilar 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 perianal fistulas
in our center, but significantly less clinical trials concern
the use of ADA.

The efficacy of IFX in the treatment of perianal fistu-
las has been profoundly studied. In the first placebo con-
trolled trial, an induction regimen induced closure of at
least 50% of fistulas for at least 4 weeks in 56–68% of pa-
tients 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 in-
duction 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 54.6
In the CHARM trial—a 56-week phase III trial to assess the
efficacy of maintenance treatment with ADA among re-
sponders to induction treatment, a subgroup analysis in
patients with draining fistula(s) at baseline showed com-
plete fistula healing in 33% of adalimumab treated pa-
tients versus in 13% of placebo treated patients.6 An open
label extension of this trial showed reducing fistula drainage
with drainage, only after the abscess was resolved they
achieved a reduction in fistula drainage, but not fistu-
la 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 met-
ronidazole and ciprofloxacin (6 to 8 weeks) and a high
frequency 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 an-
tibiotic therapy and surgical treatment (abscess drain-
age, 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.

The surgical procedure also involved insertion of
a thread or seton into the fistula canal in order to pre-
vent 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 for-
mation.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 estab-
lished.14 In accordance with the principles of a com-
prehensive 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 high-
er fistula healing response and closure rate compared
to monotherapy.13,16 However, the results of all tests car-
ried out are not compatible, e.g. a subgroup analysis of
the ACCENT II trial found that concomitant immuno-
suppressants did not improve response rates to IFX at
1 year.17 While another recent studies suggest a clear as-
sociation between combination therapy and fistula clo-
sure, nevertheless, the gain with combination therapy is
of particular in patients with proctitis.18,19

An additional argument for combining combi-
nation therapy is to reduce the production of anti-in-
fliximab antibodies, which reduces the percentage of
secondary loss of response to treatment; in the case of
ADA, clinical trials did not show such an advan-
tage.20

According to the guidelines, all patients also re-
ceived antibiotic therapy (ciprofloxacin and metronida-
ze) 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 fistu-
la 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.

A very important element of treatment is the deter-
mination 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 clini-
cally ‘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.
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.

References