Treatment of life-threatening type I refractory coeliac disease with long-term infliximab

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Abstract

Whereas medical approach to coeliac disease is well defined, treatment of patients who fail to respond to a gluten-free diet remains still problematic. We describe the case of a 68 years DQ-2 positive male who lost response to a strict gluten-free diet after an initial response over a 3-year period. His conditions became critical despite high dose prednisone treatment. After a careful differential diagnosis, the patient was classified as having a type I refractory coeliac disease and a single infusion of infliximab at 5 mg/kg was given with excellent clinical results. However, clinical response was lost despite background therapy with azathioprine. Six months after the single infusion an induction therapy with infliximab and, thereafter, maintenance every 8 weeks was administered with excellent clinical results. Since small bowel histology recovered very slowly treatment was continued over the following 2 years with a return to near normal architecture. This case shows that anti-tumour necrosis factor treatment may be used in carefully selected patients with type I refractory coeliac disease.

Keywords: Infliximab, Refractory coeliac disease; Therapy; TNF-α

1. Introduction

Coeliac disease (CD) is an immune-mediated pathology of the small bowel characterized by atrophy to various degrees of the villi, hyperplasia of the crypts, and an increased number of intraepithelial lymphocytes (IEL) in response to gluten in genetically predisposed individuals. By definition mucosal changes of CD are fully reversible when the patients are set on a gluten-free diet.

The term refractory coeliac disease (RCD) is used when, despite a strict gluten-free diet with proved compliance and after exclusion of unwitting dietary introduction of gluten, intestinal lymphoma, ulcerative jejunitis and collagenous sprue the intestinal epithelium fails to recover [1]. RCD is categorized in two subtypes, RCD I and II, respectively, being the former characterized by a normal IEL phenotype with the expression of surface CD3 associated with surface CD8 and T-cell receptor β (TCRβ) as in classical CD. On the other hand, RCD II exhibits an abnormal IEL phenotype with the expression of intracytoplasmic CD3e, surface CD103 and the lack of CD8, CD4 and TCRαβ, together with a clonal TCR gene rearrangement. Prognosis of both subtypes is poor especially in RCD II where intestinal T-cell lymphomas occur frequently.

We report a case of RCD, treated with infliximab (IFX), initially with a single infusion and after 6 months with continuous administrations over 2 years, reversing progressively the small intestinal mucosa to near normal.
2. Case report

On February 2003 a 68 years old male patient was admitted to our hospital because of severe malnutrition and diarrhea. Five years ago he was diagnosed to have CD on the base of duodenal histology in another hospital. At that time antibodies against gliadin (AGA) and endomysium (EMA) were reported to be negative. Since diagnosis he had been on a strict gluten-free diet with a good clinical response, at least over the first 3 years. On admission his body weight was 46 kg (BMI 16.5); physical examination revealed the presence of ascites, right-sided hydrothorax and oedema of the lower limbs. Blood tests showed a reduced haemoglobin level (9.0 g/dl), low serum albumin (2.3 g/dl), a slight alteration of INR (1.56), but a normal renal function. Serology for viral hepatitis was negative. A CT scan of the abdomen evidenced the absence of enlarged mesenterial lymphnodes and a markedly reduced thickness of the small bowel wall together with the disappearance of the jejunal folds. This finding was confirmed by a radiological double-contrast small bowel follow-through.

Search for gut parasites was repeatedly negative as well as cultures for pathogens. A colonoscopy together with histologic evaluation of the mucosa was negative. Antibodies against tissue transglutaminase (tTGA) and EMA were negative despite normal IgA levels. Determination of HLA showed a DQB1*0201-DQA1*0501 genotype consistent with DQ2 positivity. On the base of distal duodenal and jejunal biopsies obtained during an upper endoscopy followed by an enteroscopy, diagnosis of refractory coeliac disease was hypothetized. Immunohistochemistry showed positivity for CD3 and surface expression of CD8 together with the absence of the TCR configuration, thus indicating a switch to lymphomatous degeneration. For abnormalities of the IEL phenotype with clonal TCR positivity for CD3 and surface expression of CD8 together with absence of the TCR configuration, thus indicating a switch to lymphomatous degeneration.

Therapy with prednisone at 1 mg/kg body weight together with enteral/parenteral nutrition was started with a good clinical response. Four weeks later azathioprine (AZA) was started at 2 mg/kg. After discharge symptoms recurred when steroids were tapered to 20 mg/day and the patients was newly admitted to our unit in May. With respect to the first admission his body weight was unchanged, he presented with 5–6 liquid stools per day and was severely asthenic. Blood tests were normal except for haemoglobin (10.5 g/dl) and serum albumin (2.8 g/dl). In consideration of the relative short therapy with AZA (3 months) and of the continuous need of high dose steroids a single infusion of IFX at 5 mg/kg e.v. was administered after obtaining informed consent. This single infusion was followed by an important clinical improvement with a weight gain of 6 kg over the following 2 months and a return to quiet normal physical activity of the patient. Steroids were tapered and stopped at 1 month after the single anti-tumour necrosis factor (TNF) infusion.

Three months later the patient was newly admitted because of profound weakness of the lower limbs, weight loss and diarrhea while on azathioprine monotherapy.

Given the good response to the single anti-TNF infusion a therapeutic strategy with IFX in analogy to Crohn’s disease treatment was proposed and discussed with the patient and his relatives. Therapy was started on December 2003 with an induction schedule at point 0, and 2 and 6 weeks later, and a subsequent maintenance treatment every 8 weeks. The clinical response was excellent with a weight gain over the following year of 12 kg (final BMI 23.2). The patient underwent repeated upper endoscopies (every 6 months) with biopsies of the distal duodenum and one examination of the whole small bowel by capsule endoscopy (14 months later) in order to exclude lymphomatous degeneration. Every examination was macroscopically consistent with mild CD, but showed continuous histological improvement (Fig. 1). After completing the first year of therapy, anti-TNF treatment was reduced to one infusion every 12 weeks with continuing histological improvement. Anti-TNF therapy was stopped at 24 months while maintaining azathioprine.

3. Discussion

We describe the third patient in literature treated with IFX with the difference to former reports [2,16] that our patient despite an excellent response to a single infusion relapsed after a few months and, therefore, a continuous treatment was chosen.

In gastroenterology IFX has been introduced as therapy for adult and paediatric Crohn’s disease, refractory to conventional therapies [3,4] and, recently, its efficacy has been shown also in ulcerative colitis [5,6].

IFX is a chimeric human/mouse antibody that neutralizes circulating and membrane bound TNF. Moreover, a dose-dependent apoptosis-inducing effect on peripheral blood (PB) monocytes from healthy volunteers and patients with Crohn’s disease by activation of caspase-8, 9 and 3, independently from Fas has been shown [7]. Subsequently it has been demonstrated that IFX induces apoptosis of lamina propria T cells in vivo [8] and in vitro [9].

Knowledge about refractory or non-responsive CD is still evolving and, consequently, therapy of this disorder is yet poorly defined. Only in the past 10 years, research on this topic has made important progress, which in turn has led to new data in literature on therapy of this potentially life-threatening pathology.

So, Cellier et al. [10] reported on 21 patients treated with different approaches including prednisolone in association with or followed by azathioprine, methotrexate or cyclosporine A. Forty-three percent died during a mean follow-up of 6.7 years due to severe malnutrition or development of lymphoma. The majority of these patients, however, at the time of the data collection were found positive for abnormalities of the IEL phenotype with clonal TCRy configuration, thus indicating a switch to lymphomatous degeneration.
A first approach with biologics was reported by the same group [14] using interleukin-10 (IL-10) over 3 months. The primary endpoint, improvement of gut histology at 3 months, was met by only 2 out of 10 patients, while histology remained unchanged in 5 or even deteriorated in 1 subject. Two patients dropped because of side effects, i.e. nausea and thrombocytopenia.

In a prospective open labelled trial, Maurino et al. [15] described seven patients with RCD treated with prednisone and azathioprine. Two out of these seven patients did not respond to therapy and died. Despite a monoclonal TCR-γ gene rearrangement was observed in five patients, no one developed lymphoma during the study period. In the same year Abdulkarim et al. [16] described a mixed RCD population of nine patients, five of them with associated pathologies such as ulcerative jejunitis, lymphocytic or collagenous colitis. One of the patients with pure RCD was treated with IFX and prednisone obtaining remission.

In a subsequently published study by Goerres et al. [17] patients were divided in two well-defined subgroups, RCD type I and type II respectively, treated both with prednisone and azathioprine over 1 year. Clinical outcome of these two subtypes were strikingly different with a 100% survival in RCD type I and 88% of deaths mainly due to lymphoma development in RCD type II. Histologic evaluation in RCD type I patients after 1 year of therapy showed a normalization in 40%, an improvement with still abnormal architecture in 30%, and persistence of an abnormal mucosa despite clinical improvement in another 30%. The authors concluded that combination therapy with AZA and prednisone was promising in RCD type I and superior to former approaches published the same group, i.e. cyclosporine A and IL-10 [11, 14].

In conclusion, we describe the third patient in literature treated with IFX for RCD. This case shows that TNF-α plays a role in the pathogenesis of CD and anti-TNF treatment may be used in carefully selected patients after exclusion of lymphoma and under a close clinical and endoscopic follow-up.

Conflict of interest statement
None declared.

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References


