Original Article

EFFICACY OF INFLIXIMAB IN INFLAMATORY BOWEL DISEASES - A SHORT SERIES OF CLINICAL CASES

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Abstract

Background: *Crohn's disease and ulcerative colitis are chronic inflammatory conditions of unknown etiology that affect the gastrointestinal tract, each of them with certain particularities. Several therapeutical approaches have been attempted along the time, and they culminate with biological agents, with infliximab being the most used and studied.*

The aim *of the study is to identify the clinical, biological and endoscopical response after anti –TNF alpha induction treatment in a short series of patients with inflammatory bowel diseases.*

Material and method. *Four patients with well documented IBD, two with Crohn's disease and the other two with ulcerative colitis, where included for biological therapy with infliximab, based on their lack of response to conventional therapy. We analysed the outcome of every case after induction treatment consisting of three aplications of infliximab in standard regimen, 5 mg per kilogram of body weight intravenously on weeks 0, 2, and 6.*

Results.*Our data confirm the results from literature, that TNF-alpha blockage with infliximab is a reliable therapy for both Crohn's disease and ulcerative colitis, providing control of disease activity and the likelihood of obtaining a long term response in maintenance therapy..*

Keywords: *infliximab – Crohn's disease – ulcerative colitis*

Rezumat

Introducere*. Boala Crohn şi colita ulcerativă sunt entități inflamatorii cronice cu etiologie necunoscută, care afectează tractul gastrointestinal, au anumite particularități. De-a lungul timpului, au fost utilizate metode terapeutice cu agenți biologici in tratamentul acestor afecțiuni, dintre care Infliximab-ul utilizat in acest studiu.*

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Scopul *acestui studiu este de a identifica răspunsul clinic, biologic şi endoscopic, după tratamentul cu agenți anti-TNF alpha, pe o serie clinică de pacienți cu boşi inflamatorii de intestin.*

Material şi metodă. *4 pacienți diagnosticați cu IBD: 2 cu boală Crohn şi alți 2 cu colită ulcerativă, au fost supuşi terapiei biologice cu Infliximab, comparativ cu răspunsul lor la terapia convențională. Se analizează răspunsul la fiecare caz după trei aplicații de Infliximab in regim standard de 5 mg pe kg.corp, administrat intravenos.*

Rezultate*. În studiul nostru, se confirmă rezultatele din literatură şi anume, faptul că blocanții de alpha-TNF, de tip Infliximab, reprezintă o metodă terapeutică optimă pentru bolile inflamatorii intestinale, obținându-se un răspuns pe termen lung la tratament.*

Cuvinte-cheie: *Infliximab, colită ulcerativă, boala Crohn*

Introduction

Inflammatory bowel diseases represent a complex chapter of gastrointestinal disorders, owing to the incompletely known etiology and pathophysiology, the polymorphism of clinical features and the multitude and newly developed therapeutical modalities. Genetic susceptibility, luminal antigenes and enviromental triggers play a part in IBD pathogeny (1). Consequently their interaction, an immune response located in intestinal mucosa is initiated and leads to a chronic inflammatory process (2) that involves different lymphocytes populations, especially T cells. Th-1 cells characterize principally the immune reaction in Crohn's disease, while Th-2 cells are associated with ulcerative colitis.

The clinical presentation as well as the endoscopical and histological aspects show distinct features for each condition. Ulcerative colitis always involves the rectum, with inflammatory process extending to the proximal colon, up to the ileocecal valve. The lesions are typical continuous, and no skip areas of normal mucosa are detected. Left-sided disease is most frequently encountered in clinical practice (3), while severe forms of pancolitis that involve the entire colon are much less often diagnosed. Inflammation is limited to colonic mucosa and submucosa, with specific endoscopic appearance of granularity, friability and mucosal ulcerations. Unlike ulcerative colitis, Crohn's disease exhibits a segmental involvement of the entire gastrointestinal tract, from the mouth to anus, commonly the small intestine being affected. Patients with Crohn's disease present either with colonic disease, ileocolonic disease or small bowel disease in approximately equal percentages (3).

The principal histological feature is the transmural inflammation which involves all the four layers of the bowel, not only mucosa and submucosa like in ulcerative colitis. Rectum is inconstantly affected, but anorectal complications like abscesses and fistulas are quite common during the course of the disease. The clinical features of both diseases may overlap, but each entity has its own clinical pattern. The main symptom which dominates the clinical presentation of ulcerative colitis is bloody diarrhea. It is often accompanied by abdominal pain, rectal urgency and tenesmus (4). In majority of cases,

the course of the disease is either chronic relapsing, with flares that alternate with remission periods, either chronic continuous in a small percentage of cases or rarely, it presents as fulminant colitis. Crohn's disease exhibits a polymorphism of clinical manifestations, with diarrhea, weight loss or abdominal pain as main symptoms at the onset of the disease (5).

Also, it is important note the systemic response, more expressed in Crohn's disease comparing to ulcerative colitis, with fever, sweats, malaise, anorexia. Majority of patients develop complications like perianal fissures or fistulas, intrabdominal abscesses, fistulas with other organs (6). Extraintestinal manifestations are associated in 20-40% of patients with IBD and consist of iritis, episcleritis, arthrtis, skin reactions (7). The course of Crohn's disease is also relapsing, like ulcerative colitis, with exacerbations and remissions. Regarding laboratory findings in IBD, the presence of a flare is suggested by an inflammatory syndrome, with elevation of the erythrocyte sedimentation rate and positivity of C reactive protein. Serological testing can differentiate between the two entities, but it cannot be used as a screening procedure for diagnosing IBD (8). Perinuclear antineutrophil cytoplasmic antibodies (pANCA) have been detected in ulcerative colitis, while anti-Saccharomyces cerevisiae antibodies (ASCA) have been found in patients with Crohn's disease. The diagnosis of inflammatory bowel disease is suggested by patient's history, clinical presentation, corroborated with endoscopical or radiological findings and confirmed by histopathological examination of the mucosal samples.

The histopathological exam is a cornerstone for diagnosis, although it cannot differentiate Crohn's disease from ulcerative colitis in 15% cases, when the subjects are considered to have indeterminate colitis (9).The main goals of the treatment are induction of remission, followed by maintaining the remission, reducing the relapses and improving the patient's quality of life. Different strategies have been proposed for treating inflammatory bowel disease, based on the disease severity, extension and the presence of complications.

The management of both Crohn's disease and ulcerative colitis consist of a stepped approach, begining with a less potent drug, with adding more active agents when the disease is not controlled and either remission is not achieved or not maintained. Standard medical therapy includes variate substances that target several paths of the inflammatory processes, with induction of remission in majority of cases. 5-ASA agents are used for mild-moderate forms of Crohn's disease, with limited efficacy in maintenance therapy and also represent the mainstay of ulcerative colitis treatment (10).

Systemic steroids are potent inducers of remission in both diseases, with the newer agent budesonide, particularly indicated in ileocolonic forms of Crohn's disease. Immunosuppressant drugs like azathioprine and 6-mercaptopurine are considered steroid-sparing agents, effective in the maintenance of remission of both entities, while methotrexate may be used in induction and maintenance of remission in Crohn's disease (10). Cyclosporine was added as a rescue therapy in nonresponsive ulcerative colitis. Despite these advances in IBD treatment, a significant proportion of patients exhibit lack of therapeutical response, presenting with active disease or complications.

Biological agents, anti-TNF agents like infliximab and adalimumab represent a chance for cure the nonresponsive forms of IBD at conventional therapies. Infliximab is a

chimeric monoclonal antibody that neutralises the inflammatory effect of TNF –alpha, which is considered to have a central role in IBD pathogenesis. Used for more than 10 years in the treatment of Crohn's disease and for 5 years in ulcerative colitis, these drugs provide a certain benefit, demonstrated by healing of the mucosa, closing the fistulae and preventing strictures (11). In Crohn's disease, infliximab is indicated in moderate-severe forms, refractory to conventional treatment and in fistulizing disease, with enterocutaneous and perianal fistulas. In ulcerative colitis, infliximab induces a clinical response in moderate-severe forms that not respond at corticosteroids and thiopurines. The purpose of this study is to analyse the response to induction therapy with infliximab in a short series of four patients, two with Crohn's disease and the other two with ulcerative colitis, who were resistant at standard treatment.

Material and method

Crohn's disease cases

Case 1

A 44-year-old woman, with heredo-collateral history of inflammatory bowel disease was diagnosed with Crohn's disease in 2001, based on clinical, endoscopical and histological aspects. Considering the data from patient's records, the involvement of the gastrointetsinal tract at that time was limited to the colon. She started a therapy based on 5-ASA agents, salazopyrin at a dose of 4 grams per day, without obtaining an adequate control of symptoms, adding then corticotherapy in standard doses. The course of the disease was marked by achieving clinical and endoscopical remission while on prednisone, with flare development when the dose was tapered. In addition, the patient presented a rectovaginal fistula, expressed by intermittent passage of stool through vagina. The presence of fistula was radiologically documented and antibiotic treatment was initiated at that time. The patient came to our attention in 2009, for bloody diarrhea associated with colicky abdominal pain located predominantly in inferior abdomen. She denied fever, stool passage through vagina recently. The current treatment consisted of salazopyrin 4 grams/day and 10 mg prednisone. Under such circumstances, taking into account the previous history of the inflammatory bowel disease, we considered the patient to be corticodependent. Physical examination shows a pale, underweight female patient with mild abdominal tenderness. The remainder of the examination was unremarkable. The laboratory panel showed moderate inflammatory syndrome with elevated erythrocyte sedimentation rate (60mm/h) and C-reactive protein (38 mg/L) and also mild anemia (Hb -10.2 g/dl). Viral testing was negative for hepatitis viruses and HIV. Tuberculin test was negative, too. Stool samples were negative for infectious microorganisms. Colonoscopy revealed segmental colitis within the entire colon, with multiple, superficial and deep ulcers of variate caliber, terminal ileum was macroscopically normal; mucosal samples for histopathological examination were taken. Skip areas were interposed with affected areas, given the typical cobblestone appearance of the colonic mucosa. Histology confirmed the diagnosis of Crohn's disease, showing transmural inflammatory infiltrate composed of lymphocytes and macrophages, aggregates of macrophages, without any evidence of well-developed granuloma (Figure 1).

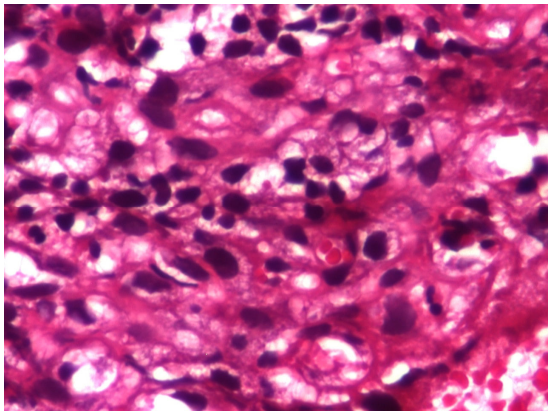

Figure 1. Glandular epithelium of small intestine with regenerative lesions, inflammatory infiltrate and stasis. H-E stain, 40x

Upper digestive endoscopy completed the examination of the digestive tract and revealed no pathological findings. The paraclinical survey included an imagistic exam, an abdominal CT scanning which did not evidence intraabdominal abscesses or fistulas. At that moment, the calculated Crohn's disease activity index was 321 (CDAI score), which means a moderate flare. The patient was started on induction therapy with infliximab, 5 mg per body weight, on repeated infusions at 2 and 6 weeks which led to improvement of symptoms. The patient described soft stools without blood and only minimal abdominal pain. A complete evaluation of the clinical, biological and endoscopical response was performed after the third infusion of infliximab. Besides the clinical benefit, it was noted the improvement of the inflammatory syndrome and also of the colonic lesions, with visible mucosal healing and only shallow small ulcerations.

Case 2

We present other case of Crohn's disease, this time a male patient of 33 years old, diagnosed in 2001 on clinical, endoscopical and histological basis. The course of the disease was relapsing, under standard therapy with 5-ASA agents and intermittent oral corticosteroids, with incomplete clinical improvement. He presented in october 2009 with symptoms consistent with a moderate flare of the disease: bloody loose stools, diffuse abdominal pain not related to defecation and weight loss, under mesalazine 4 grams per day and prednisone in tapered dose of 20mg/day. We stated for corticodependence, taking into account the previous medical history and the response to the treatment. The patient was afebrile, but ill-appearing, thin, with mild palor and diffuse abdominal tenderness. Extraintestinal manifestations were absent. Laboratory studies evidenced an inflammatory syndrome with high serum concentration of C-reactive protein (32 mg/L) and mild normocytic, normochromic anemia (Hb-10.2 g/dl). Viral markers assessment and coprocultures for infectious microorganisms were negative. Tuberculin test showed hyperergia and the patient received tuberculosis chemoprophylaxis for 2 months. Total colonoscopy including terminal ileum inspection demonstrated a typical aspect of Crohn's disease, with cobblestone mucosal pattern, serpiginous ulcers, aphtous

ulcerations in terminal ileum, confirmed by histopathological examination (Figure 2a, 2b).

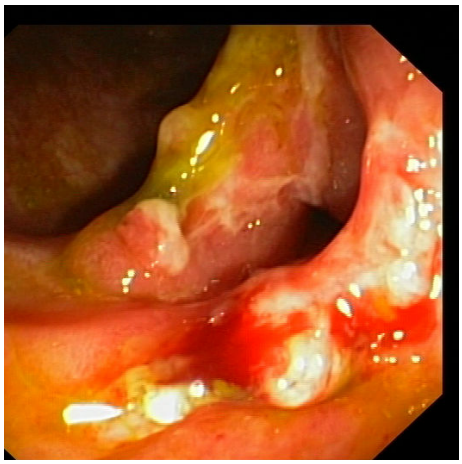

Figure 2a. Afthous ulcerations in terminal ileum

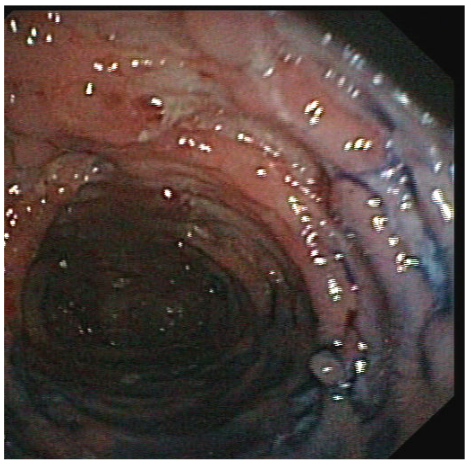

Figure 2b. Cobblestone mucosal pattern in descendent colon

Upper digestive tract is not involved in the inflammatory process. We also performed an abdominal CT scan in order to rule out the presence of complications like intraabdominal abscesses or fistulas. We calculated the Crohn's disease activity index as 366, which was consistent for a moderate Crohn's disease, with ileocolonic extension, without strictures or fistulas. Under such circumstances, we considered adequate initiation of the biological therapy with infliximab at standard dose of 5 mg per body weight, in three induction applications at 2 and 6 weeks following the initial dose. The clinical improvement developed rapidly, with soft stools without blood and minimal abdominal pain. Biological picture illustrated normalizing of the systemic inflammatory syndrome and colonoscopy performed after the third infusion of infliximab showed marked improvement of the colitis.

Ulcerative colitis cases

Case 1

A 63-year-old male patient came to our attention 3 years ago for bowel disturbances, consisted of loose stools with blood and mucus mixed, abdominal discomfort located in left flanc, ameliorated by defecation and intermittent rectal bleeding. We raised the suspicion of ulcerative colitis, which was then confirmed by endoscopical and histological examination. Colonoscopy revealed erythematous mucosa, with friability, absent vascular pattern, friability and microulcerations, changes that emerge from the anal verge up to transverse colon. The aspect sustained the diagnosis of extensive left sided colitis. The first therapeutic option was mesalazine, 4 grams per day which proved no efficacy with lack of clinical response. Then oral corticotherapy was considered, obtaining disease control with reduced number of stools and no signs of blood. The course of the disease was chronically continuous, with development of symptoms when

tapering the dose of predisone under 20 mg was tempted, classifying the patient as corticodepent. At the moment, the patient presented with similar symptoms as mentioned above, being on current medication with 5-ASA agents and low doses of prednisone. Clinical examination shows a pale patient, normal weight, with mild abdominal tenderness in the left flanc. Laboratory studies reveal a moderate inflammatory syndrome with high plasmatic concentration of C-reactive protein and elevated erythrocyte sedimentation rate. Repeated colonoscopy demonstrated similar changes to those discovered when the disease was first diagnosed, consisting of erythema, friability and patchy mucosal bleeding over the last 50 cm of the colon; the lesions are uniformed distributed throughout the affected bowel, without areas of normal mucosa in-between (Figure 3a, 3b).

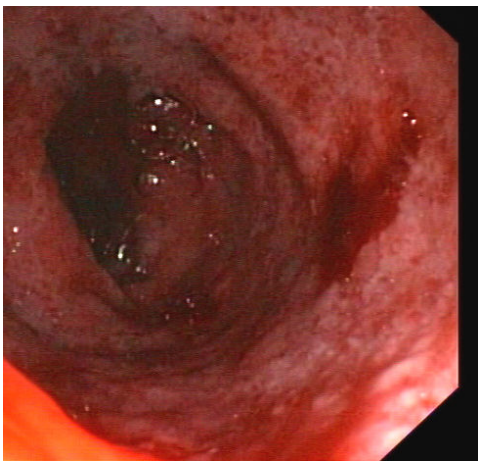

Figure 3a. Ulcerative colitis – Endoscopic appearance

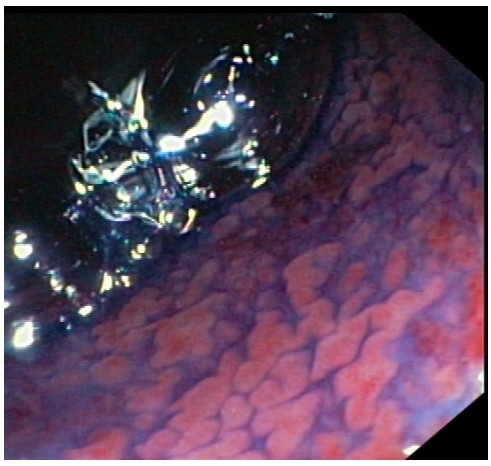

Figure 3b. Ulcerative colitis – chromoendoscopy with indigocarmin 0.2%

Histopathological examination confirmed the diagnosis and showed typically features of ulcerative colitis, like infiltration of the mucosa and submucosa with neutrophils, crypt abscesses and criptic distorsion. Given the incomplete response to the first-line therapeutic agents together with the development of corticodependence, we considered necessary to start biological therapy with infliximab in standard doses, which is the induction therapy with infusions at 2 and 6 weeks. The clinical response appeared promptly, with decreasing the number of stools and improving the quality of life; we also noted a reduction of serum values of inflammation markers. Control colonoscopy detected mucosal healing with slight decrease of the mucosal vascular pattern.

Case 2

The patient we report is 49-years old and exhibits a long history of ulcerative colitis, a chronic continuous form, with the onset of the disease 8 years ago. Clinical presentation was typical for proctosigmoiditis with bloody diarrhea, intermittent rectal bleeding, tenesmus and rectal urgency. Extraintestinal manifestations were absent. The colonoscopy performed at that time detected specific features for ulcerative colitis, while

the histological examination completed the survey and confirmed the diagnosis. Standard treatment was initiated with systemic and topical 5-aminosalicylates, with slight improvement of symptoms. As the disease worsen, corticosteroids were considered necessary for induction of remission. Prompt relief of symptoms was obtained, but with clinical recurrence when prednison was reduced under the dose of 20 mg per day. Given the continuous pattern and the lack of complete response, immunossupresive therapy with azathioprine 1.5 mg per body weight was started in September 2009, maintaining initially high corticoid doses and then tapering it off over a 2-month period. The patient was admitted in december 2009 with 8 to 10 bloody bowel movements per day, abdominal cramping and rectal urgency, being under current therapy with imuran 150 mg per day and mesalazine 4 grams daily. Routine laboratory tests identified a moderate inflammatory syndrome. Colonoscopy assessment evidenced loss of the normal vascular pattern beginning from the anal verge, continuous, mucosal erythema with mild friability, multiple superficial ulcerations over the last 40 cm of the colon. The changes were consistent with ulcerative colitis, confirmed by the histological evaluation (Figure 4).

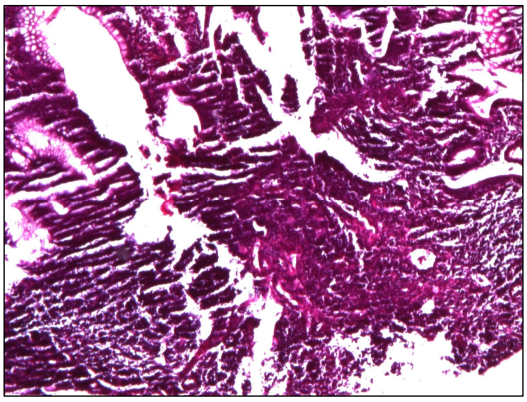

Figure 4. Histopathological aspect of an abcess within the lamina propria in nonspecific colitis condition. H-E stain, 4x

Taking into account the lack of response to conventional treatment, including immunossupresants, we attempted biological therapy with infliximab in induction regimen of 5 mg per body weight at 0, 2, 6 weeks. In addition, the patient received tuberculosis chemoprophylaxis one month before starting the biological therapy, given the positivity of the tuberculin testing. The clinical response developed rapidly, the patient's symptoms substantially improved, stool frequency had decreased to 3 times daily, with only minimal blood loss and mild abdominal cramping. Colonoscopy performed after the third infusion showed improvement of the mucosal lesions without ulcerations and friability.

Discussions

Inflammatory bowel diseases are chronic relapsing disorders, with important morbidity and life-long complications. Choosing the right medication is challenging for each physician, because once remission obtained, it should be maintain over time in order to prevent the development of flairs and to improve the quality of life. The goal of the treatment is on one hand to achieve clinical response with decreasing the number of bowel movements and stools without blood, to improve the abdominal pain and other symptoms, and on the other hand to obtain the resolution of the inflammatory syndrome

and endoscopic remission. It has been demonstrated that mucosal healing is of great significance because besides expressing remission, it represents a predictor for reducing the risk of cancer development in patients with ulcerative colitis (12, 13).

The management of both ulcerative colitis and Crohn's disease involves a multistep approach, depending on the disease severity and gastrointestinal extension. Severe forms of disease do not respond to 5-ASA agents, leading to start corticotherapy or even immunosuppressive drugs. A main disadvantage of cortizone is the likelihood to develop corticodependence or corticoresistance and also notable adverse events. Establishing the right moment for starting infliximab therapy for induction of remission, favourably influences the disease course and leads to better outcomes.

In case of patients with Crohn's disease who did not respond to standard therapy or who develop corticodependence, biological therapy with TNK alpha blockers remains a logical approach. As we describe above, both patients with Crohn's disease achieved initially a clinical response, which was then followed by resolution of systemic inflammatory syndrome and mucosal healing demonstrated by colonoscopy.

Our patients with ulcerative colitis present a slight improvement of symptoms after conventional treatment with 5-ASA, being necessary to add on one hand corticotherapy in order to induce remission and on the other hand, immunosuppresive agents as a maintenance treatment. Unfortunately, despite achieving clinical response after the maximal dose of prednison, both patients develop cortidependence, with symptoms exacerbation when the dose was reduced. TNF – blockage provided a significant benefit after three infusions, with marked clinical improvement.

The limitation of treatment with TNF – alpha blockers is related to adverse events like upper-respiratory-tract infections particularly tuberculosis, infusion-related reactions, development of antibodies against infliximab (14, 15).

Analyzing the data presented, we can conclude that the induction regimen of three doses of 5 mg per body weight of infliximab is clearly associated with clinical and biological response and also with mucosal healing at endoscopic assessment.

The patients reported above should be assigned for maintenance treatment with infliximab because, according to data from literature, those patients who have a response to induction therapy are likely to achieve a sustained response to continued maintenance treatment (16).

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