Case Report

Adalimumab in patients with ulcerative colitis

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SUMMARY

Two patients suffering a flare of ulcerative pancolitis are reviewed. Both of them had no response to initial treatment with infliximab. The first one had lost response to it and the second one showed no initial response even after receiving increased doses of infliximab. Subsequently adalimumab subcutaneous infusions were tried. Both of the patients showed considerable clinical and laboratory remission. These two cases describe our department's experience in the use of adalimumab in ulcerative colitis patients and denote that adalimumab can bring into remission patients with severe ulcerative colitis serving as an alternative option to surgery.

Key words: adalimumab, monoclonal anibodies, inflammatory bowel disease, ulcerative colitis

INTRODUCTION

Adalimumab (Humira – Abbott Laboratories) is a recombinant human IgG1 monoclonal antibody that acts by inhibiting TNF (Tumor Necrosis Factor). It has recently been approved for use in patients with Crohn's disease.[1,2] According to our knowledge there is only one study so far having assessed the effectiveness and safety of adalimumab induction therapy in patients with ulcerative colitis.[3] The aim of our paper is to present two case reports that describe our experience in the use of this biologic agent in patients with ulcerative colitis.

MATERIALS AND METHODS

We review two patients with refractory ulcerative pancolitis. Both of them were on clinical, laboratory and endoscopic disease relapse. They first tried infliximab (Remicade) infusions on regular (5mgr/kgr) or increased (10mgr/kgr) doses without result and then adalimumab (Humira) was tried. The loading dose of adalimub was individualised (according to disease severity), followed by 40mgr every other week. The patients were reevaluated thereafter, every 2 weeks, with physical examination and laboratory investigations.

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CASE PRESENTATIONS

Two patients with ulcerative colitis, the first having previously responded but now having lost response to infliximab and the second without any response to infliximab received adalimumab, after informed consent.

The first patient was a 50 year old male and was admitted to our department because of an ulcerative colitis flare. According to his medical history the patient had been suffering from ulcerative pancolitis for the last 5 years, with frequent flares. He had a history of pyoderma gangrenosum and a year ago he had been diagnosed with CMV colitis successfully treated with ganciclovir. For the last year he was receiving infliximab (Remicade) infusions 5mgr/kgr every 8 weeks, as a monotherapy. He had been previously treated with azathioprine which was stopped a year ago because of persistent transaminasemia and had received corticosteroids several times in the past, which had provoked avascular necrosis of the femoral head.

When the patient was admitted to our department he was complaining of a one month history of bloody diarrhea, described as 10-12 loose bloody stools per day, high fever (39 C), arthralgias, anorexia (he had lost 7 kgr of his usual body weight) and anemia (5 units drop of Hct). Laboratory evaluation showed increased acute phase proteins (CRP=100 IU/ml), elevated ESR (=95 mm/hr), hypokalemia and anemia. He underwent a colonoscopy which showed edema, coarse granularity, friability and erythema of the mucosa and throughout the whole large intestine

there were several superficial erosions and ulcers. There was no histologic evidence of concurrent cytomegalovirus colitis. The clinical endoscopic and histological evidence were supportive of an ulcerative colitis flare and the patient was initially treated with increased dosage of infliximab (10mgr/kgr) every 6 weeks. Despite this, there was no significant clinical, laboratory or endoscopic response over the next three months. After discussion with the patient and his written consent, it was decided to initiate treatment with adalimumab 80mgr subcutaneously as a loading dose, followed by 40mgr every other week from week 1 (baseline). The patient was reevaluated every 2 weeks with physical examination and laboratory investigations. Following the first 4 visits (4 adalimumab infusions), the patient reported significant improvement, consisting of 2-3 non-bloody bowel movements. Currently the patient is on his 8th infusion of 40mgr every other week adalimumab, his body weight has increased to his pre therapy levels, the anemia was corrected, the inflammatory indices are normal and his colitis is in full clinical remission.

The second patient was a 39 year old male who was admitted to our hospital because of medically refractory ulcerative colitis. According to his medical history the patient had indeterminate colitis for 15 years. He was initially diagnosed as suffering from distal ulcerative colitis (proctosigmoiditis). A second colonoscopy,5 years ago, after a new disease flare, revealed pancolitis with involvement of the distal 5cm of the terminal ileum. He was then given the diagnosis of Crohn's disease and was treated with azathioprine 2,5mgr/kgr and occasionally received corticosteroids without substantial clinical improvement.

On arrival to our hospital the patient was seriously ill, having lost 30 kilograms from his usual body weight over 2 months. He was hypotensive (blood pressure 80/50mmHg), tachycardic (pulse rate 110 beats per minute) and reported 20-30 bloody bowel movements per day.

His disease was steroid dependent (he was receiving high doses of corticosteroids and his disease worsened at each effort of steroid tapering). The laboratory results showed anemia (Ht=26,6), leucopenia (WBC=1400) and increased inflammatory indices (ESR=113 mm/hr, CRP=184 IU/ml). The colonoscopy revealed continuous inflammation of the large bowel with edema, pseudopolyps, mucopurulent exudate, friability and ulcers, and with no patches of healthy tissue in between and little inflammation of the terminal ileum. The clinical features (bloody diarrhea), endoscopic evidence and histological features (cryptitis, crypt abscenses) were in favor of ulcerative pancolitis with backwash ileitis.

Azathioprine was withheld because of leucopenia and the patient received vancomycin because of a Cl. Difficile positive stool culture. Even after successful treatment of Cl. Difficile, the patient remained in bad clinical condition and received 3 infusions of infliximab (0-2-6 week) 5mgr/kgr (the 3rd in increased dosage 10mgr/kgr). There was no significant clinical or laboratory improvement and the patient gradually developed hypoalbuminemia and hypokalemia. After discussing with the patient, he consented to starting therapy with adalimumab 160mgr on week 0, 80mgr on week 2 and then 40mgr every other week. The patient is followed up regularly every 2 weeks) and currently (after having received the 5th infusion of adalimumab) reports clinical improvement with semi-solid stools around 5 times/day, rarely small amounts of blood per rectum, having increased his weight by 6 kilograms. The laboratory results support the clinical improvement (Ht=33, CRP=9.1 IU/ml, ESR=35 mm/hr)

DISCUSSION

The use of anti-tumor necrosis factor (anti-TNF) antibodies in patients with inflammatory bowel disease has brought a revolution to the treatment of these diseases. Current medical therapy of inflammatory bowel disease follows a "step up" model anticipating anti-TNF agents as a last resort in corticosteroid – dependent or corticosteroid – refractory disease.[4] During recent years there is a tendency towards using biologic agents as a first line therapy at the first appearance – flare of the disease (top down therapy).

While in Crohn's disease there are two commercially available anti-TNF antibodies (infliximab, adalimumab), in ulcerative colitis only infliximab is approved for use.[5] However, just like in Crohn's disease, only 60-70% of patients with ulcerative colitis respond to infliximab (30-40% have no response). And even among these patients that initially respond, some loose response during maintenance therapy with infliximab (45% of patients do not achieve a 54 week remission).[5] Therefore, we need alternative therapies for these patients.

The two cases, reported in this paper, describe our department's experience in the use of adalimumab in ulcerative colitis patients. According to our recent (Feb 2009) search in medline there is no such experience described from Greece. Worldwide, there is only one open-label study having assessed the effectiveness of adalimumab in patients with ulcerative colitis.[3] According to this study only four (4) of ten (10) patients benefited from adalimumab therapy. The authors concluded that there is small advantage of adalimumab particularly in patients with mild to moderate ulcerative colitis that had lost response

or had intolerance to infliximab. Our presentation shares some similarities but has also some important differences with the aforementioned study.

First of all, both of the above cases denote that adalimumab brings into remission not only patients with mild to moderate ulcerative colitis, but also patients with serious disease. Using the Mayo Scoring system for assessment of ulcerative colitis activity (scores can range from 0 to 12, with higher scores indicating more severe disease activity) the first patient had a Mayo score 10 and the second one,12.

Secondly, adalimumab is not only useful for patients who have lost response to infliximab but also for patients who have never experienced any response to infliximab (even after receiving the first 3 infusions). The second patient of our report, even after having received 3 infusions of infliximab (the 3rd infusion in increased dosage) experienced no clinical improvement. Nonetheless, he responded, at least partially, to adalimumab (current Mayo score 8).

The two cases reported show that adalimumab may be an alternative option to surgery, for patients with medically refractory, to current available therapy, ulcerative colitis. Both patients preferred off label administration of adalimumab, rather than subtotal colectomy. Subtotal colectomy is a major surgery with serious consequences in the quality of life particularly for young patients. Besides, our second patient who may suffer from indeterminate colitis (although our department's opinion is opposite to it) with adalimumab may avoid surgery and the possibility of new post surgical flares should his colitis proves to be Crohn's disease in the future. According to our opinion most of the patients suffering from medically refractory ulcerative colitis would prefer the switch to another biologic agent rather than perform surgery. Although our follow-up period is not long enough, for the time being both of our patients have avoided surgery.

The safety issues surrounding anti-TNF therapies are of great importance. The two aforementioned patients have experienced no mild or serious adverse event. Experience from rheumatology shows that adalimumab shares the same general adverse event profiles with infliximab.[6] Our experience of two ulcerative colitis patients treated with adalimumab is minimal. However, the absence of any systemic or topical side effect is indicative of relative safety of this biologic agent in patients with ulcerative colitis.

One of the mechanisms, responsible for loosing response to infliximab (hybrid human and murine antibody), is considered to be the induction of anti-infliximab antibodies.

These antibodies develop more frequently i) when patients receive infliximab on an episodic, as needed basis, rather than on a fixed-dosage schedule and ii) when the patient doesn't receive concomitant immunomodulators, like our first patient who had stopped azathioprine therapy because of side effects.[7-8] Preexisting anti-infliximab antibodies induced by infliximab would not affect adalimumab, which remains active in the aforementioned patient.

In conclusion these two case reports provide clues that adalimumab is efficacious in patients with medically refractory ulcerative colitis. Of particular promise is the novel observation that the use of adalimumab can be of particular benefit even in the primary non responders to infliximab.

The advantage of adalimumab in patients with ulcerative colitis needs to be confirmed in randomized, double-blind, placebo-controlled trials.

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