

BIOLOGIC THERAPY IN INFLAMMATORY BOWEL DISEASE - RESULTS FROM A SINGLE TERTIARY CARE CENTER IN NORTH MACEDONIA

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ABSTRACT

Medical therapies used for Inflammatory Bowel Disease (IBD) include conventional (e.g. 5-aminosalicylates, steroids, immunomodulators) and biologic (e.g. inhibitors of tumor necrosis factor – alpha, integrin inhibitors, interleukin inhibitors) medications. Biologics, due to their high cost, were unfortunately not covered by the public health insurance system in North Macedonia until 2019 and, therefore, not widely utilized for our IBD patients. In 2019, the University Clinic of Gastroenterology and Hepatology in Skopje developed a biologic therapy supply, provided by the National Health Insurance Fund, making this therapy available for a larger number of patients. This report presents the initial results of our prospective, single tertiary-care center study on the effects of biologic therapy in patients with IBD in North Macedonia. The study is focused on the evaluation of clinical outcomes after anti-tumor necrosis factor alpha (anti TNF-alpha) therapy in IBD patients with prior inadequate response to conventional medications.

Keywords: Inflammatory bowel disease, Crohn's disease, Ulcerative colitis, Biological therapy, Infliximab, Adalimumab

INTRODUCTION

Inflammatory bowel disease (IBD) represents a chronic intestinal disorder characterized by inflammation of the gastrointestinal tract. IBD comprises of two major disorders: Crohn's disease (CD) and ulcerative colitis (UC). The pathogenesis of these disorders is complex and remains incompletely understood. A complex interplay between altered immune response and genetic, microbial, and environmental factors was found to play a key role [1, 2]. Patients with IBD have a variety of symptoms involving the gastrointestinal tract (e.g. abdominal pain, diarrhea, rectal bleeding) as well as extraintestinal (e.g. oral ulcers, skin

rash, arthritis) and systemic manifestations (e.g. fever, fatigue, weight loss) [3, 4]. Early diagnosis and appropriate treatment are critical in the management of IBD and may affect the natural course of the disease. Medical therapies for IBD include conventional as well as biologic medications (e.g. inhibitors of tumor necrosis factor – alpha).

Biologic therapy, due to its high cost, was unfortunately not provided by the public health insurance system in North Macedonia until 2019. Starting in 2019, the University Clinic of Gastroenterology and Hepatology in Skopje, which serves as a public tertiary referral hospital for IBD patients

in North Macedonia, introduced biologic therapy provided by the National Health Insurance Fund. This resulted in increased availability of this therapy for our patients. However, due to budgetary limitations, biologics are initiated only in patients who fail to improve with conventional therapies.

In this report we present the initial results of our prospective study with anti-TNF-alpha therapy in North Macedonia, focusing on the effect of infliximab and adalimumab on clinical outcomes in IBD patients who had an inadequate response with conventional therapies.

Biologic therapy

Biologic therapy in IBD patients blocks proinflammatory cytokines like TNF-alpha or interleukins. TNF-alpha plays an important role in the pathogenesis of IBD and is mainly produced by activated macrophages, T-lymphocytes, and natural killer (NK) cells [5].

Overproduction of TNF-alpha was found in the intestinal mucosa of IBD patients and TNF-alpha was also found to cause trafficking of effector leukocytes, resulting in uncontrolled intestinal inflammation. [6] As such, TNF-alpha has been identified as a therapeutic target in IBD as well as in other inflammatory or autoimmune diseases [7, 8]

INFLIXIMAB

Infliximab is a chimeric monoclonal antibody that consists of murine and human antibody amino acid sequences. The primary mechanism of action is to target and neutralize TNF-alpha, but infliximab also blocks leukocyte migration and causes apoptosis of T-lymphocytes and monocytes. In 1997 Targan et al. published the first randomized controlled trial that showed infliximab to effectively induce remission in patients with Crohn's disease [9]. Subsequently, infliximab was approved for the treatment of Crohn's disease by the US Food and Drug Administration (FDA).

ACCENT 1 [10] and ACCENT 2 [11] were the two landmark studies that showed the effectiveness of infliximab as a maintenance therapy in patients with CD, while ACT1 and ACT2 were the landmark studies showing the effectiveness of infliximab in patients with UC [12].

Initially, infliximab was prescribed to patients who had an inadequate response to conventional therapy, but the therapeutic paradigm has shifted since the earlier introduction of inflix-

imab in patients with moderate to severe disease at presentation or the presence of risk factors for severe disease ("Top-down" approach). One of the main drawbacks of infliximab is its potential to cause immunogenic responses in a significant number of patients due to its complex and chimeric molecule. Formation of anti-drug antibodies (ADA) may lead to loss of response in the initially responding patients, infusion reactions and delayed hypersensitivity reactions [13, 14, 15, 16]. Co-administration of immunomodulators is the most utilized strategy to prevent development of ADA [17], but the problem of immunogenicity has also highlighted the necessity of engineering humanized and human monoclonal antibodies.

ADALIMUMAB

Adalimumab is a fully human antibody directed to neutralize TNF-alpha. It has demonstrated clinical efficacy in the induction and maintenance of CD which was shown in the CLASSIC I [18] and CLASSIC II trials [19]. Adalimumab has been approved in the EU and US for moderate and severe CD since 2007.

Adalimumab has also demonstrated to have clinical efficacy for treatment of UC [20]. ULTRA 1 and trials found adalimumab to be more effective than a placebo in inducing and maintaining remission in patients with moderate to severe UC who did not adequately respond to conventional therapy. In 2012, Adalimumab received FDA approval for the treatment of moderate to severe ulcerative colitis and has been widely used in practice since.

Compared to chimeric monoclonal antibodies, fully human monoclonal antibodies are less frequently immunogenic. Another advantage of adalimumab is that it can be applied subcutaneously.

METHODS

Consecutive patients with moderate to severe Crohn's disease (CD) or ulcerative colitis (UC) were included in this study. To qualify for participation in the study, all patients had to be treated and have inadequate clinical response to conventional therapies including 5-ASA, glucocorticoids and immunomodulators (e.g. azathioprine).

The severity of Crohn's disease was calculated with the use of the Crohn's Disease Activity

Index (CDAI). Signs, symptoms, and history of the past 7 days were evaluated. Inclusion criterion was a CDAI score of 220-450.

For patients with UC, the disease severity was calculated with the use of the Mayo score Disease Activity Index (DAI). The Mayo score considers stool frequency, the amount of blood in stool, endoscopic appearance of colonic mucosa, and disease activity assessed by the physician. Patients with a Mayo score disease activity index of >6 or higher and endoscopic sub-score of 2 or 3 (absent vascular pattern, ulcers, spontaneous bleeding) were included in the study.

Prior to initiating the anti TNF-alpha therapy, all patients were screened for latent tuberculosis (TB) with a QuantiFERON test and chest X-ray. The screening algorithm also included laboratory serologic testing for hepatitis B, hepatitis C and HIV infections. All included patients were evaluated for a history of malignant disease and patients diagnosed or treated for malignancy within the past 5 years were not included in the study.

Infliximab was administered at a dose of 5 mg/kg intravenously at weeks 0, 2 and 6, followed by a maintenance regimen of 5 mg/kg given every 8 weeks.

Adalimumab was administered subcutaneously at a dose of 160 mg at week 0, 80 mg at week 2, followed by 40 mg given every other week.

The primary endpoint was clinical response (CR) at week 8 and was defined as a 70 points CDAI reduction from baseline for patients with CD and Mayo score DAI reduction of >3 for patients with UC.

RESULTS

Patient population

Forty-three consecutive patients fulfilled the study entry criteria and were included. The demographic and clinical characteristics of included patients are shown in Table 1.

Table 1. *Parameters of the study*

	No Cases	%
Female	16	37.2
Male	27	62.8
CD	33	76.7
UC	10	23.3

63% were male (27/43) and 37% female (16/43) ranging in age from 18-63years. Most patients (33/43, 76.7%) had CD and there were 10 patients (23.3%) with UC.

Therapeutic outcomes

Most patients (39/43, 90.6%) were assigned to treatment with infliximab and only 4 (9.4%) patients were assigned to treatment with adalimumab (Table 2.).

Table 2. *Types of drugs and number of patients treated*

Type of drug	No Cases	%
Infliximab	39	90.6
Adalimumab	4	9.4

The primary endpoint at week 8 (70 point CDAI reduction from baseline for CD; Mayo score DAI reduction of >3 for UC) was achieved in 26/33 (78.7%) patients with CD and in 8/10 (80%) patients with UC. The response rate in the CD group was 82.9% (24/29 patients) for those assigned to infliximab and 50% (2/4 patients) for those assigned to adalimumab (Table 3).

Table 3. *Clinical response in CD patients according to drugs*

CD patients	No Cases	Clinical response %
Infliximab	29	82.9% (24/29)
Adalimumab	4	50% (2/4)
Total	33	78.7%(26/33)

All 10 UC patients were assigned to treatment with infliximab with a response rate of 80% (8 pts. responded).

Safety

Apart from common minor reactions and mild symptoms with little clinical significance, such as itching and redness around the site, headache, dizziness and nausea, the treatment was well tolerated. During the first 8 weeks, no serious adverse events were seen. No patients developed serious or opportunistic infections, demyelinating neurological diseases or lymphoma; and no patients died.

DISCUSSION

In this prospective study of IBD patients with active, moderate to severe disease while receiving conventional therapies, who were treated with either infliximab or adalimumab, we found that the majority of patients achieved a clinical response or remission within 8 weeks of anti-TNF therapy initiation. These initial results of our single, tertiary-care, center study are in line with data previously reported in literature.

In the study conducted by Targan et. al. [9] 81% and 50% of CD patients treated with 5mg/kg infliximab had a clinical response at weeks 4 and 12, respectively. The ACCENT I study conducted in CD patients treated with 5 mg/kg infliximab found a response rate of 58% at week 2 and 50% at week 30. In our study the rate of clinical response at week 8 for CD patients treated with 5mg/kg infliximab was 82.9% .

In the current study, there were only 4 CD patients treated with adalimumab. Two of the 4 patients (50%) had a clinical response at week 8 which was comparable with the results from the CLASSIC I and II trials, where 56% of CD patients treated with adalimumab achieved clinical response at week 4 (defined as a decrease from baseline in the CDAI score of 70 points). In the CLASSIC II trial, this response at week 8 was maintained in 90% of those patients.

All 10 patients with UC in the current study were treated with 5mg/kg infliximab and showed a response rate of 80% at week 8. Comparably, ACT 1 and ACT 2 studies showed response rates at week 8 of 69% and 64%, respectively, in UC patients treated with the same infliximab dose.

We defined clinical response as the primary endpoint even though the STRIDE panel recommends both clinical and endoscopic remission as therapeutic goals in IBD trials [21, 22]. However, since we did not have alternative medical therapies to offer, clinical response was selected and regarded as a realistic achievable goal.

The ratio of CD to UC patients in our study was 33 to 10. This is not in line with the ratio of IBD diagnoses that we encounter in our daily practice (nor in line with ratio of diagnoses at our IBD database) but since patients with severe UC have the option of surgery as “definitive treatment”, biologic therapy was more often offered to patients with severe CD.

Although treatment with biologic therapy for IBD started in North Macedonia almost two decades ago this is the first study assessing the efficacy of anti-TNF medications in North Macedonia. In 2004, a patient with CD was first treated with infliximab, within a research study performed at the Clinic of Gastroenterology and Hepatology in Skopje. In 2008, the first patient with UC was treated with infliximab. The Clinic of Gastroenterology and Hepatology in Skopje is a referral center for patients with IBD from the region and provides care for approximately 1,500 IBD patients (as of December 2022 our database includes 642 CD and 923 UC patients.). Unfortunately, due to limited supply, it was not possible to utilize biologic therapy on a consistent basis until 2019. In this period, the majority of our patients were treated with conventional therapies and/or surgery, whereas biologic therapy was available only for patients able to cover related expenses on their own or had private health insurance. This resulted in limited literature from our institution on this topic that includes case reports. Studies with biologics, however, could not be conducted due to the small number of treated patients.

Despite these difficulties, the availability of biologic therapies at the Clinic of Gastroenterology and Hepatology has significantly improved since 2019.

The introduction of anti TNF-alpha medications enabled us to achieve a clinical response in a significant proportion of our IBD patients, reduce the use of glucocorticoids, and likely improve overall outcomes in these patients. However, due to expected loss of response to anti-TNF therapy in some of these patients (the rate of secondary non-responders to anti-TNF therapy within one year is reported at 30-40%) [23, 24] a further increase in the spectrum of modern therapies available at our Clinic will be crucial to increase patients' chances of having a better and steroid-free control of their disease.

CONCLUSION

In summary, this study shows that in patients with moderate to severe CD and UC, who inadequately responded to conventional therapy, initiation of anti TNF-alpha medications achieved satisfying rates of clinical response with an excellent safety profile. Our results are comparable

with reported effectiveness and safety of anti-TNF therapy from large, multicenter, randomized-controlled studies. Continued follow-up of studied patient group will allow evaluation of the longer-term effects and safety profile of anti TNF-alpha therapy, when utilized as maintenance treatment for patients with IBD.

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Резиме

БИОЛОШКА ТЕРАПИЈА КАЈ ВОСПАЛИТЕЛНИ ЦРЕВНИ ЗАБОЛУВАЊА – РЕЗУЛТАТИ ОД ЕДИНИЧЕН ТЕРЦИЕРЕН ЗДРАВСТВЕН ЦЕНТАР ВО РС МАКЕДОНИЈА

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Медикаментозниот третман на воспалителните цревни заболувања (ВЦЗ) опфаќа конвенционална и биолошка терапија. Биолошката терапија поради високата цена на чинење не беше достапна за осигурениците на Фондот за здравствено осигурување (ФЗО) на РС Македонија сè до 2019 година. Од 2019 година Универзитетската клиника за гастроентерохепатологија почна да ги лекува пациентите со ВЦЗ со биолошка терапија на товар на ФЗО, со што биолошката терапија стана достапна за поширок круг пациенти. Ги прикажуваме првите резултати од нашата проспективна студија со биолошка терапија кај пациенти со ВЦЗ. Фокусот на студијата е процена на терапискиот одговор на анти TNF- α лековите кај пациенти со ВЦЗ и претходен неадекватен одговор на конвенционална терапија.

Клучни зборови: воспалителни цревни заболувања, Кронава болест, улцерозен колит, биолошка терапија, инфликсимаб, адалимумаб