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Research Article

Combination of Biologics and Small Molecules in Inflammatory Bowel Disease: New Trends in Low Doses

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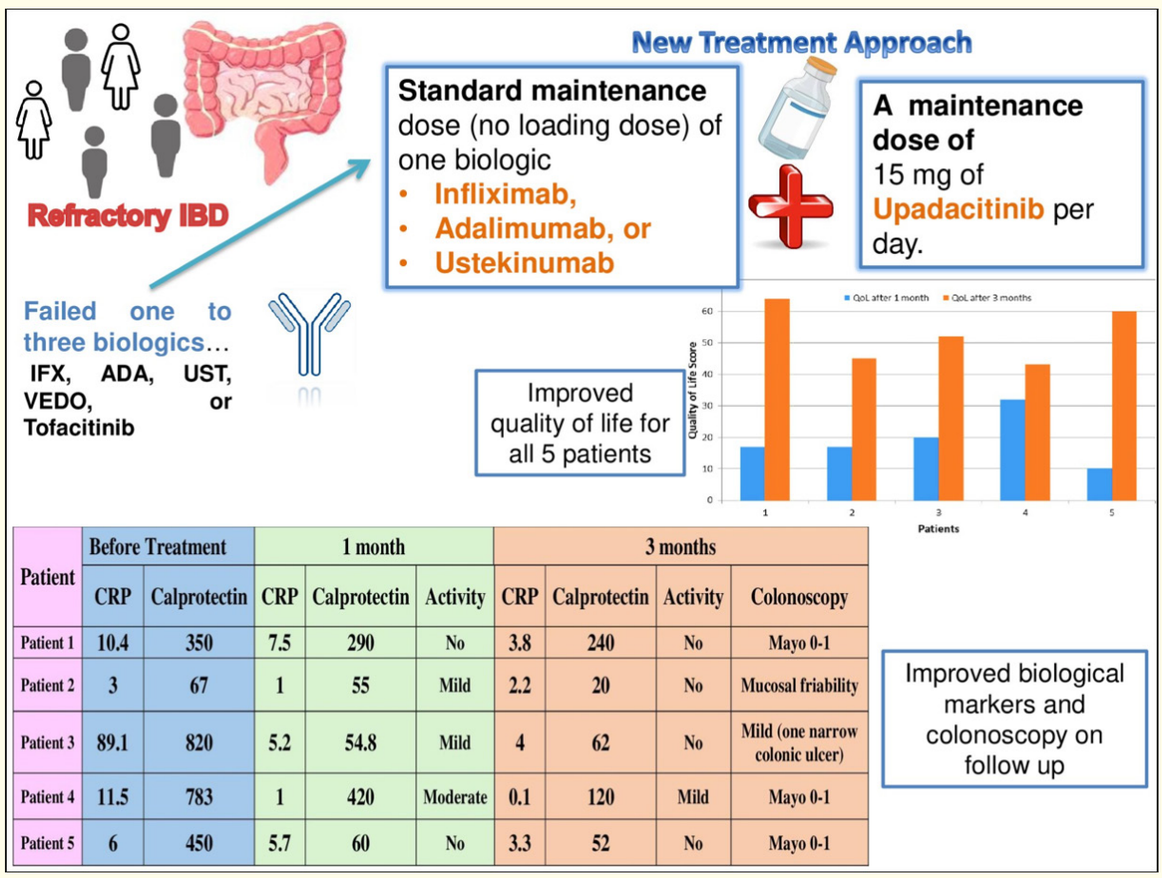
Abstract

Background: A promising approach for treating refractory IBD involves the use of a combination of two biological agents and/or small molecules. This study aimed to assess the effectiveness of low-dose combination biologic therapy for treating refractory IBD patients.

Methods: This study assessed five refractory IBD patients who previously failed one to three biologics (IFX, ADA, UST, VEDO, or tofacitinib) on standard-dose and standard-duration treatment regimens. The patients underwent clinical examination, CRP, calprotectin, colonoscopy, and quality of life evaluation. To introduce a low-dose treatment, a novel strategy was developed that combines a standard maintenance dose (no loading dose) of one biologic (Infliximab, Adalimumab, or Ustikenomab) with a maintenance dose of 15 mg of Upadacitinib per day.

Results: After one month and three months of follow-up, the patients were evaluated for clinical indices, biomarkers (CRP and calprotectin), colonoscopy, and quality of life. All patients showed rapid improvement in their disease activity, normalization of their biomarkers of disease activity, and quality of life. After three months of follow-up, the colonoscopic findings showed obvious improvement.

Conclusion: The introduction of a combination of biological and small molecules at standard maintenance doses (no loading doses) is an interesting concept with potential benefits, as it provides rapid and effective management of refractory IBD patients and improved quality of life.



Patient	Before Treatment		1 month			3 months			
	CRP	Calprotectin	CRP	Calprotectin	Activity	CRP	Calprotectin	Activity	Colonoscopy
Patient 1	10.4	350	7.5	290	No	3.8	240	No	Mayo 0-1
Patient 2	3	67	1	55	Mild	2.2	20	No	Mucosal friability
Patient 3	89.1	820	5.2	54.8	Mild	4	62	No	Mild (one narrow colonic ulcer)
Patient 4	11.5	783	1	420	Moderate	0.1	120	Mild	Mayo 0-1
Patient 5	6	450	5.7	60	No	3.3	52	No	Mayo 0-1

Figure a

Keywords: Biologics; Combination Therapy; Small Molecule Drugs

Introduction

IBD comprises Crohn's disease (CD) and ulcerative colitis (UC) and is characterized by a heterogeneous presentation and widely variable clinical course. The therapeutic targets are to provoke and maintain remission [1]. The basis for current modern IBD treatment algorithms includes data supporting the efficiency of combination therapy, activation as a feasible treatment, and the necessity of early treatment of high-risk patients [2]. Treatment with a single drug is typically insufficient for the long-term induction of remission; this may be partially explained by the phenotypic variety in clinical presentations and the presence of many cytokine patterns. A growing body of research suggests that dual-targeted therapy may hold promise for overcoming current IBD treatments [3]. Combination therapy has been suggested to improve treatment outcomes and is superior to monotherapy in terms of remission induction and maintenance because it produces a synergistic benefit [4,8]. Multiple biologics can be combined to maximize efficacy while also limiting side effects in patients with incomplete responses to standard therapeutic approaches [5,6]. The combination of immunosuppressants and other biological therapies is safe and effective [7]. Nevertheless, combining two biological agents and small molecules into one treatment (full loading and maintenance standard dose of Upadacitinib and Ustekinumab). may be a good option for patients with both extraintestinal symptoms and concurrent IBD, as well as for those with medically resistant IBD who have no other viable options. They have reduced adverse effects (mild respiratory symptoms and nausea) and improved targeted efficiency to achieve optimal disease control [8-10]. This study aimed to evaluate the efficacy and safety of combination biologic therapy and small molecules at low doses for treating refractory IBD patients.

Methods

We included five patients with medically refractory luminal illness related IBD, 3 males and 2 females, whose ages ranged from 23 to 37 years. Clinical examinations were conducted on patients who had not responded to one to three biologics (IFX, ADA, UST, VEDO, or tofacitinib) on conventional dose and duration treatment regimens. CRP, calprotectin, and quality of life were evaluated, and colonoscopy was performed. A low-dose treatment that combines a maintenance dose of 15 mg of upadacitinib per day with a standard maintenance dose (no loading dose) of one biologic (Infliximab, Adalimumab, or Ustikenomab), either as a starting point for treatment with both medications or as add-on therapy, was introduced.

The patients were recruited from the IBD Clinic at the National Institute of Hepatology and Tropical Medicine (NHTMRI). Ethical approval was obtained from the NHTMRI Research Ethics Committee (number 11-2022).

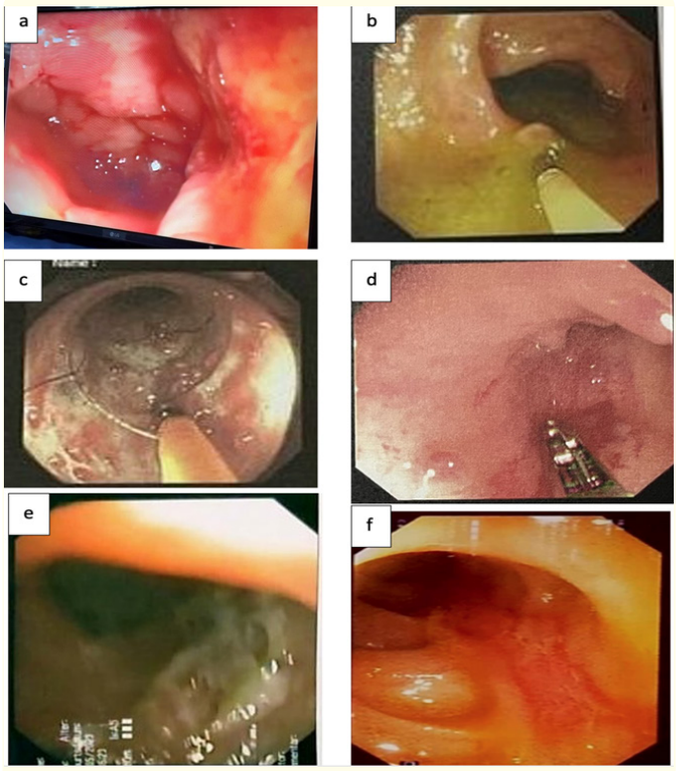


Figure 1: (a): Case 1 before treatment severe UC (Mayo score 3), (b): Case 1 after combination therapy (Mayo score 0-1), (C): Case 2 before treatment showing linear ulcerations, (d): Case 2 after treatment with friable mucosa and no ulcerations, (e): Case 3 before treatment [Severe CD] showing multiple deep colonic ulcerations, f: Case 3 after combination therapy revealed one narrow linear superficial ulcer.

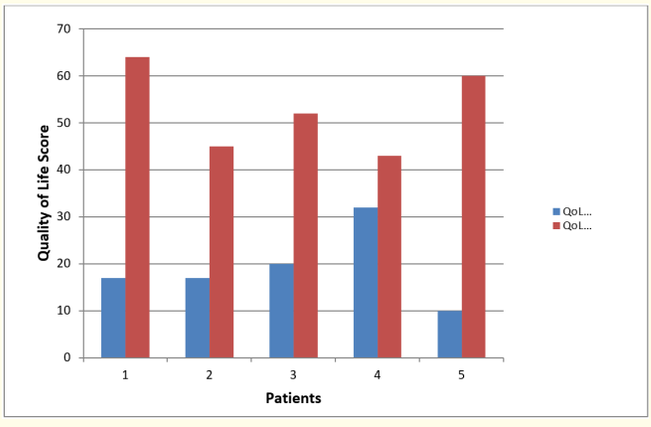


Figure 2: The quality of life after one month and after 3 months of treatment.

Patient	Age	Gender	IBD	Before treatment				Biologic Failure	Combination therapy	After 1 month of treatment				After 3 months of treatment			
				CRP	Calprotectin	colonoscopy	Activity			CRP	Calprotectin	Activity	Side effects	CRP	Calprotectin	Colonoscopy	Activity
1	23	M	UC (Extensive colitis)	10.4	350	Mayo 3	severe	IFX for 48 weeks	UST and Upa	7.5	290	no	Fatigue and Abdominal Pain	3.8	240	Mayo 0-1	no
2	21	M	CD (Partial colectomy)	3	67	Mucosal ulcerations	mild	ADA for 24 weeks	ADA and Upa	1	55	mild	Fatigue and Abdominal Pain	2.2	20	Mucosal friability	no
3	30	F	CD	89.1	820	Severe (multiple deep colonic ulceration)	severe	Goli, UST Vedo for 46 weeks	IFX and Upa	5.2	54.8	mild	_	4	62	Mild (one narrow colonic ulcer)	no
4	30	F	UC (Extensive colitis)	11.5	783	Mayo 3	severe	IFX, Tofa, UST for 46 weeks	ADA and Upa	1	420	moderate	_	0.1	120	Mayo 0-1	mild
5	37	M	UC (Total colectomy)	6	450	Mayo 2-3	moderate	IFX for12 weeks	IFX and Upa	5.7	60	no	Fatigue and Abdominal Pain	3.3	52	Mayo 0-1	no

Table 1: Clinical data of patients before and after one and three months of treatment.

Results

Patient characteristics included those who failed one to three biologics (IFX, ADA, UST, VEDO, or tofacitinib) using standard dose and duration treatment regimens (Table 1). Two patients had previously undergone surgery. One patient with CD underwent surgery (ileostomy and right hemicolectomy), one patient with severe UC (posttotal colectomy and ileostomy), and 3 patients with CD with severe colonic effects. None of the patients responded to combination therapy. The other two patients had severe active colitis. Colonoscopy was performed for all patients before treatment and after 3 months of treatment (Figure 1).

This research led to the design of a novel method for low-dose treatment involving the combination of a standard maintenance dose (no loading dose) of one biologic (infliximab, adalimumab, or Ustekinumab) and a maintenance dose of a small molecule (upadacitinib) 15 mg daily, whether given as add-on therapy or starting treatment with both medications (Table 1). The patients were followed after one month with clinical indices and biomarkers (CRP and calprotectin) and after 3 months with biomarkers and colonoscopy (Figure 1). After one month, quality of life was assessed with a valid scoring system [11] (Figure 2). Clinical response was assessed by using Crohn's disease patient-reported outcome signs and symptoms (CD-PRO/SS) (5). Two factors were analyzed: (1) bowel signs and symptoms, which included several bowel movements (BMs), BMs mostly or completely liquid, and the urge to have BMs right away; and (2) abdominal symptoms, which included pain in the belly, bloating, and passing gas. The clinical response for UC patients was evaluated using the partial Mayo score. Treatment-related adverse events were assessed throughout combined therapy [12].

All our patients showed rapid improvement in disease activity, normalization of their biomarkers of disease activity, and improvement in quality of life. After 3 months of follow-up, the colonoscopic findings showed obvious improvement, which paved the way for reconstruction for CD and UC patients. None of our patients experienced any serious side effects; however, only 3 out of 5 patients complained of mild symptoms, such as fatigue and mild abdominal pain, in the first few days after starting the regimen.

Discussion

Intestinal obstruction is the most common side effect of the small intestine in CD patients. Up to 35% of CD patients in population-based studies initially exhibit colonic obstruction [13]. In this study, one CD patient underwent ileostomy and right hemicolectomy because of a previous colonic obstruction. Repetitive dilation may be less necessary if combined therapy is used following endoscopic dilation [14]. Most UC patients have a mild-to-moderate disease course, although 10% to 15% of individuals may experience an aggressive disease course, and approximately half of patients may need to be hospitalized due to severe disease activity [15]. Colectomy, end ileostomy, and rectal stump closure are common surgical treatments for ulcerative colitis (UC) in the era of biological therapy, with a postoperative complication rate of 27.7% [16]. One of our UC patients presented with post total colectomy and ileostomy with preservation of the rectal stump. Thirty percent of ulcerative colitis patients develop the severe form. In approximately 13% of these patients, the standard treatment is emergency colectomy, ileostomy, and rectal stump creation [17]. Moreover, patient 3 with CD presented with severe colonic effects. This report included patients who received standard doses of monobiologic therapies (IFX, ADA, UST, VEDO, or tofacitinib) but had persistent, uncontrolled disease activity at the time of inclusion.

A novel strategy for the introduction of a low-dose treatment that combines a maintenance dosage of one biologic (Infliximab, adalimumab, or Ustekinumab) at a standard level (no loading dose) with a maintenance dose of a small molecule (Upadacitinib) of 15 mg per day was given to patients. Even though our cohort's condition was severe, the 5 patients showed symptomatic improvement according to the CD-PRO/SS and partial Mayo subscore within one month, indicating a reduction in the need for steroid medication. In three of the patients, there was a significant improvement in quality of life along with weight gain. This finding is similar to those of Solitino., *et al*. and Wetwittayakhlang., *et al*. [7,18]. The patients demonstrated complete cessation of steroid medication after three months. Two of our patients were able to undergo reconstructive surgery as a result of the colonoscopy results, which indicated mucosal improvement in all of our patients ranging from severe to mild. The safety and effectiveness of alternative treatments, including biologics, in various stricturing situations have been reported to decrease intestinal damage and disease progression, further preventing the need for surgery [19-20]. Only three patients experienced mild side effects, such as fatigue and mild abdominal pain, within the first few days after beginning therapy. This is consistent with the results of Mikaml., *et al*. [21]. Following one month of combination therapy, all clinical and serologic parameters improved significantly, and there were no major infections that required hospitalization or intravenous therapy. Safety and adverse events were also evaluated. In addition to being less expensive, the combination maintenance dosage regimen did not exhibit any significant side effects [10]. These findings, despite their modest sample size, imply that combining biologics with various modes of action could be a safe and useful treatment option for IBD. Lower costs and minimal adverse effects result from using both medications at maintenance levels rather than loading them [22]. Adding more, a recent literature discussing the results of combination biologics (full loading and maintenance standard doses regimen) in treating IBD pa-

tients reports different range of side effects from mild to serious according to the type of combination biologics used in the study [8]. Although patients respond differently to different medications,It is important to note that tailoring treatment based on individual needs and responses remains crucial [23]. Consequently, the appropriate dosage, the duration of the administration, the suitable timing for checking the clinical and laboratory outcome, as well as the treatment side-effects is the subject of intense clinical research shortly [8].

Our study is the first to use a combination of biologics and small molecules in treating inflammatory bowel disease at low doses and to study its effect on disease activity and patient quality of life.

Conclusions

The introduction of a combination of biological and small molecules of standard maintenance doses (no loading doses) is an interesting concept with potential benefits, as it has shown rapid and effective management of refractory IBD patients and improved quality of life. More studies on such combinations are necessary to determine whether there is any synergistic effect of these two medications and to determine the best combination regimen and the lowest effective doses with the least side effects.

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