Izvirni znanstveni članek / *Original science article*

Dual biologic therapy in patients with inflammatory bowel disease – first experience at the Department of Gastroenterology, University Medical Centre Ljubljana and a review of the literature

Kombinirana biološka terapija pri kronični vnetni črevesni bolezni – prve izkušnje na Kliničnem oddelku za gastroenterologijo Univerzitetnega kliničnega centra Ljubljana in pregled literature

Karin Strmšek[1], David Drobne*[1,2]
[1]*Department of Gastroenterology, University Medical Centre Ljubljana, Ljubljana, Slovenia*
[2]*Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia*
Slovenian Journal of Gastroenterology / Gastroenterolog 2024; 2: 19–22

Keywords: *biological therapy, inflammatory bowel disease, combination treatment,*

Ključne besede: *biološka terapija, kronična vnetna črevesna bolezen, kombinirano zdravljenje, remisija*

ABSTRACT

Background. Dual biologic therapy is a promising treatment option for patients with inflammatory bowel disease (IBD) resistant to monotherapy or those with two indications for biologic therapy – luminal disease and extraintestinal manifestations.

Aim. Here we report first experiences with dual biologic therapy in IBD patients at the Department of Gastroenterology, University Medical Centre Ljubljana.

IZVLEČEK

Izhodišče. Kombinirana biološka terapija je privlačna terapevtska možnost pri bolnikih s kronično vnetno črevesno boleznijo (KVČB), ki so rezistentni na zdravljenje z biološkimi zdravili v monoterapiji in pri tistih, ki imajo dve indikaciji za zdravljenje – črevesno bolezen in izvenčrevesne manifestacije.

Namen. Predstavljamo prve izkušnje s kombinirano biološko terapijo pri bolnikih s KVČB na Kliničnem oddelku za gastroenterologijo Univerzitetnega kliničnega centra Ljubljana.

*assist. prof. David Drobne, MD, PhD
Department of Gastroenterology, University Medical Centre Ljubljana, Japljeva ulica 2, 1000 Ljubljana, Slovenia
Faculty of Medicine, University of Ljubljana, Vrazov trg 2, 1000 Ljubljana, Slovenia
E-mail: david.drobne@gmail.com

Received: 15/5/2024; Review: 15/6/2024; Accepted for publication: 10/7/2024

Material and Methods. We searched our electronic database, identified 11 IBD patients who were treated with dual biologic therapy between December 2021 and November 2023. We performed chart review of efficacy and safety.

Results. Partial clinical response was observed in 54,4% of patients treated with dual biologic therapy. Fifty percent of patients had at partial clinical response of luminal disease (20% had complete response) and all of them had at least partial clinical response of extraintestinal manifestations (66,7% had complete response). There were no serious adverse events.

Conclusions. Our findings suggest that dual biologic treatment is an efficient and safe option in IBD patients who failed previous biologic monotherapy or suffer from both, luminal and extraintestinal manifestations of disease.

Metode. Uporabili smo elektronsko bazo podatkov in identificirali 11 bolnikov s KVČB, ki so bili zdravljeni s kombinirano biološko terapijo v obdobju med decembrom 2021 in novembrom 2023. Zbrali smo podatke o učinkovitosti in varnosti terapije.

Rezultati. Vsaj delni klinični odgovorje imelo 54,4 % bolnikov zdravljenih s kombinirano biološko terapijo. Petdeset odstotkov bolnikov je imelo vsaj delni klinični odgovor črevesne bolezni (20 % je imelo popolni odgovor). Vsi bolniki so imeli vsaj delni klinični odgovor izvenčrevesnih manifestacij (66,7 % je imelo popolni odgovor). Hujših zapletov kombinirane terapije nismo beležili.

Zaključki. Naši izsledki kažejo, da je kombinirano biološko zdravljenje učinkovita in varna strategija zdravljenja bolnikov s KVČB, pri katerih je bilo predhodno zdravljenje z biološkimi zdravili v monoterapiji neuspešno, ter bolnikov, ki imajo tako vnetje črevesne sluznice kot izvenčrevesne manifestacije bolezni.

INTRODUCTION

Increased knowledge of the complex pathogenesis of inflammatory bowel disease has led to a broad range of approved biological agents and small-molecule therapies that target different inflammatory pathways. Despite an increase in therapeutic options still around 40% of IBD patients fail these drugs due to primary or secondary loss of response (1). Dual biologic therapy is a new and promising strategy for the management of patients with concomitant IBD and extraintestinal manifestations or in patients with medically refractory IBD. The rationale of using dual biological therapy is to combine different mechanisms of action which presumably results in more profound control of inflammation.

Data on this approach from randomised clinical trials (RCT) are lacking. Two recent RCTs that combined two biologicals provided some evidence that the short-term combination of two biological agents may lead to superior disease control than either of the agents alone in patients with ulcerative colitis (VEGA trial) and Crohn's disease (EXPLORER trial) (2,3).

During the recent years a small number of IBD patients were started on dual biological therapy in our tertiary referral centre after careful consideration of potential benefits and risks at the multidisciplinary meeting. The aim of this study was to report first experience with the efficacy and safety of dual biologic therapy in IBD patients in our tertiary care centre.

METHODS

This was a medical record–based, retrospective study of patients with IBD who were treated with ustekinumab, infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or upadacitinib in combination at the Department of Gastroenterology, University Medical Centre Ljubljana between December 2021 and November 2023. We assessed efficacy as judged

by experienced gastroenterologist (no response, partial response, complete response). We assessed efficacy of dual biological therapy on luminal disease and extraintestinal manifestations separately. We also assessed safety of dual biological therapy.

RESULTS

Patient Characteristics

Among 1142 IBD patients treated at our institution at the time of our analysis, there were a total of 11 patients (0,96%) who were treated with dual biologic therapy. Clinical features and outcomes are summarized in Table 1. Six patients had Crohn's disease and 5 patients had ulcerative colitis. Median age at diagnosis was 23 years (interquartile range 18–30 years) and median age at the start of dual biologic therapy was 40 years (intequartile range 31–51 years). Median disease duration at the start of combination therapy was 16 years (interquartile range 10–25 years). Four patients were treated with vedolizumab and an anti–tumor necrosis factor (TNF) agent. One patient received ustekinumab with an anti-TNF agent, and 4 patients received vedolizumab with ustekinumab. Two patients were treated with vedolizumab and a Janus kinase inhibitor (JAK inhibitor). Median duration of combined biologic therapy was 7,5 months (interquartile range 4–12 months). No patients discontinued the treatment by the end of observation time of this analysis.

Efficacy and Safety of Dual Biologic Therapy

Three patients had complete response to dual biologic therapy and 3 patients had partial response. In 2 patients combination therapy was evaluated as not successful. In 3 patients it was too soon to evaluate the efficacy of the treatment, since dual biologic therapy was only recently started. We did not detect any serious complications. A female patient with many comorbidities had frequent urinary tract infections. Since she was treated with vedolizumab and adalimumab, this may be at least partly a side effect of dual biologic therapy.

Table 1. Patient Characteristics and Clinical Outcomes in Dual Biologic Therapy

Diagnosis	Age	Combination therapy				Indication			Efficacy
		Anti-integrin	Anti-TNF	Anti-IL 12/23	JAK inhibitor	Luminal	Fistula	Extraintestinal manifestations	
CD	40	vedolizumab		Ustekinumab		x	x		*
UC	56	vedolizumab	golimumab			x		x	partial
CD	67	vedolizumab	adalimumab			x	x		partial
UC	48	vedolizumab		Ustekinumab		x			NO
UC	43		golimumab	Ustekinumab				x	YES
CD	58	vedolizumab	infliximab			x	x		partial
CD	38	vedolizumab		Ustekinumab		x		x	YES
UC	35	vedolizumab		Ustekinumab		x			NO
UC	24	vedolizumab			tofacitinib	x			YES
CD	26	vedolizumab			upadacitinib	x			*
CD	19	vedolizumab	infliximab			x			*

CD: Crohn's disease, UC: ulcerative colitis, TNF: tumor necrosis factor, IL: interleukin, JAK: Janus kinase
**Combination therapy was only recently started and the efficacy assessment was not possible*

DISCUSSION

In this retrospective study, we assessed clinical efficacy and safety IBD treated with dual biologic therapy. Our main finding was that most patients benefited from this treatment. Furthermore, we did not detect any serious adverse events.

Our findings are similar to those reported in the literature. The VEGA study assessed the efficacy of the combination of guselkumab and golimumab therapy compared to guselkumab or golimumab monotherapy in patients with moderately to severely active ulcerative colitis. Thirty seven percent of patients on combination therapy achieved clinical remission and 83% clinical response at week 12 (2). The EXPLORER trial evaluated the efficacy of the combination therapy with vedolizumab, adalimumab, and methotrexate in biologic-naive patients with high-risk Crohn's disease. The trial lacked control group of patients. Nevertheless, the observed clinical remission rate was high (54,5%) with no safety signal related to the triple combination regimen (3). Our results are generally comparable with these.

An important finding in our study was that the combination biologic therapy was safe. However, it should be noted that the most commonly used biologic in combination in our population (90,9% of patients) was vedolizumab. This might explain our safety profile compared to COMBIO study, where the most frequent combination of targeted therapies in 143 patients with refractory/overlapping immune-mediated inflammatory diseases was anti-TNF agents and vedolizumab (30%), which appeared to be safe. Incidence of serious infection in this study was 4,51 per 100 person-years (95% confidence interval 2,20–8,27) and 5 combination therapies were discontinued due to adverse events (4).

Our study has important limitations. The main limitation is a very small number of participants and retrospective study design. Another limitation is clinical assessment of remission without endoscopic and biochemical assessment. Clinical response was evaluated by experienced gastroenterologist. The response to treatment was divided into three categories: no response, partial response and complete response, as assessed by an experienced gastroenterologist. Also, follow-up times were short.

In conclusion, this retrospective patient review suggests that dual biologic treatment is a valid and safe option in IBD patients who failed previous biologic monotherapy or suffer of both luminal and extraintestinal manifestations of disease. These preliminary findings require confirmation in larger trials. Prospective studies investigating efficacy and safety of combination biologic therapy are ongoing (5).

References

1. Alsoud D, Verstockt B, Fiocchi C, et al. Breaking the therapeutic ceiling in drug development in ulcerative colitis. Lancet Gastroenterol Hepatol. 2021;6:589–95.
2. Feagan BG, Sands BE, Sandborn WJ, et al. Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial. Lancet Gastroenterol Hepatol. 2023;8:307–20.
3. Colombel J-F, Ungaro RC, Sands BE, et al. Vedolizumab, Adalimumab, and Methotrexate Combination Therapy in Crohn's Disease (EXPLORER). Clin Gastroenterol Hepatol. 2023;S1542-3565(23)00746-2.
4. Guillo L, Flachaire B, Avouac J, et al. Efficacy and safety of combination targeted therapies in immune-mediated inflammatory disease: the COMBIO study. Dig Liver Dis. 2023;55:61–8.
5. A Study of Combination Therapy With Guselkumab and Golimumab in Participants With Moderately to Severely Active Ulcerative Colitis (DUET-UC). https://classic.clinicaltrials.gov/ct2/show/NCT05242484