



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

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– Slovenian Journal of Gastroenterology / Gastroenterolog 2024; 2: 20–23

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. We are reporting 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.

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Material and Methods. We searched our electronic database and identified 11 IBD patients who were treated with dual biologic therapy between December 2021 and November 2023. We performed a 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 a partial clinical response of luminal disease (20% had a complete response) and all of them had at least partial clinical response of extraintestinal manifestations (66.7% had a 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).

Recently a small number of IBD patients started dual biological therapy in our tertiary referral centre after carefully considering potential benefits and risks at the multidisciplinary meeting. This study aimed to report the 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 with the Department of Gastroenterology, University Medical Centre Ljubljana between December 2021 and November 2023. We assessed efficacy as judged

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

RESULTS

Patient Characteristics

Among 1142 IBD patients treated at our institution at the time of our analysis, 11 patients (0,96%) 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. The median age at diagnosis was 23 years (interquartile range 18–30 years) and the median age at the beginning of dual biologic therapy was 40 years (interquartile range 31–51 years). The median disease duration at the beginning of combination therapy was 16 years (interquartile range 10–25 years). Four patients were treated with vedolizumab and an anti-tumour 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). The median duration of combined biologic therapy was 7.5 months (interquartile range 4–12 months). No patients discontinued the treatment by the end of the observation time of this analysis.

Efficacy and Safety of Dual Biologic Therapy

Three patients had a complete response to dual biologic therapy and 3 patients had a partial response. In 2 patients combination therapy was evaluated as not successful. In 3 patients it was too soon to assess 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 biological 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: tumour 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 the clinical efficacy and safety of 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 combining 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-naïve patients with high-risk Crohn's disease. The trial lacked a 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 of biological 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 the 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. The 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 the small number of participants and retrospective study design. Another limitation is the clinical assessment of remission without endoscopic and biochemical valuation. An experienced gastroente-

rologist evaluated the clinical response. 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 from both luminal and extraintestinal manifestations of the disease. These preliminary findings require confirmation in larger trials. Prospective studies investigating the efficacy and safety of combination biologic therapy are ongoing (5).

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