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The impact of antidepressant medications on the course of inflammatory bowel diseases

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Abstract

Introduction and Objective: Inflammatory bowel diseases (IBD) and anxiety, as well as depressive disorders, can coexist. Depression may affect IBD symptoms and vice versa. The aim of our study is to determine the impact of different classes of antidepressant medications in the treatment of IBD with comorbid depressive episodes, to summarize the most commonly used therapies, and to identify the most effective practices in treating inflammatory diseases with coexisting depressive episodes.

Materials and Methods: A review of the available literature was conducted by searching the PubMed and Google Scholar databases using the following keywords: inflammatory bowel diseases, depression, antidepressants, in both English and Polish, up until July 19, 2024. To ensure the high quality of the narrative review, the SANRA scale (a scale for the quality assessment of narrative review articles) was used.

Results: Studies indicate that depressive symptoms occur in approximately 25-27.5% of patients with inflammatory bowel diseases (IBD). Treatment of depression in IBD patients often includes the use of antidepressant medications, such as selective serotonin reuptake inhibitors (SSRIs), which not only reduce depression but also exhibit anti-inflammatory effects. SSRIs may also be effective in improving patients' quality of life; however, they may cause side effects such as diarrhea and an increased risk of bleeding. In addition to SSRIs, other antidepressants, such as serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and atypical antipsychotics, are also used and may have a beneficial impact on the course of the disease.

Conclusions: In patients with IBD and comorbid depression, SSRIs are most commonly used, followed by TLPDs, SNRIs, and atypical antipsychotics. Drugs from these groups may have a beneficial effect on depressive symptoms, but also affect the course of IBD.
Further clinical studies are needed to establish precise guidelines for the use of these drugs in patients with IBD.

Keywords: inflammatory bowel disease; depression; antidepressants

Introduction: Inflammatory bowel diseases (IBD), which include Crohn's disease (CD) and ulcerative colitis (UC), significantly disrupt the daily functioning of many patients. It is noteworthy that the incidence of IBD is increasing in North America and Europe, potentially due to environmental factors such as stressful lifestyles, poorly balanced diets, or smoking (1). The pathogenesis of IBD also involves genetic and immunological factors. For example, 163 gene loci influencing the development of IBD have been described (2). At the same time, chronic inflammation impairs intestinal integrity and function (2,3). Anxiety and depressive disorders may also significantly exacerbate IBD symptoms (1). A study by J. Luo et al. (4) suggests that a genetic predisposition to depression correlates positively with an increased risk of developing IBD. Interestingly, genetic predispositions to IBD did not influence depressive symptoms. Other observational studies also suggest that depression is associated with an increased risk of developing IBD (5,6). However, the shared pathogenesis of IBD and depressive disorders remains a subject of debate and has not been fully elucidated (7,8). Depression may disrupt the gut-brain axis, negatively affecting the gut microbiome and thus exacerbating IBD symptoms (9,10,11,12).

In both depressive disorders and IBD, there is activation of the hypothalamic-pituitary-adrenal (HPA) axis and increased cortisol levels. Chronically elevated cortisol levels reduce the sensitivity of glucocorticoid receptors, potentially exacerbating intestinal inflammation and mood disorders (13,14). Concurrently, the sympathetic nervous system is activated, leading to increased secretion of catecholamines. Elevated levels of cortisol and catecholamines contribute to chronic systemic inflammation. As a result of macrophage and mast cell stimulation, the levels of pro-inflammatory cytokines such as interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF-α) increase (4,13,14). These changes affect both the severity of IBD symptoms and depression (4,15), as they increase visceral

hypersensitivity, intestinal permeability, microbiome translocation, and disrupt intestinal motility. At the same time, chronic inflammation and pain exacerbate depressive symptoms (16). Elevated levels of pro-inflammatory cytokines negatively impact neuronal nutrition, neurotransmitter metabolism, and increase oxidative stress (15). Chronic inflammation also intensifies the kynurenine pathway, in which tryptophan is metabolized into kynurenine rather than serotonin (the reduced levels of which exacerbate depressive symptoms) (3). Due to the shared aspects of the pathogenesis of IBD and depressive disorders, antidepressants may reduce the symptoms of CD and UC, thereby improving patient functioning (17,18). In patients with moderate to severe IBD and coexisting depression, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), atypical antipsychotics such as quetiapine, or other antidepressants such as mirtazapine may be considered (3,19). Both conditions can have a mutually negative impact; therefore, improving the well-being of IBD patients may also positively affect the alleviation of inflammatory disease symptoms (20). However, the role of antidepressants in treating depressive episodes in the course of IBD remains poorly studied. Therefore, the aim of our study is to determine the impact of different classes of antidepressants in the treatment of IBD with comorbid depressive episodes, summarize the most commonly used therapies, and identify the most effective practices in treating inflammatory diseases with coexisting depressive episodes.

Methods: A review of the available literature was conducted by searching the PubMed and Google Scholar databases using the following keywords: inflammatory bowel diseases, depression, antidepressants, in both English and Polish. Original articles, meta-analyses, and review papers published in Polish and English up until July 19, 2024, were included. To ensure the high quality of the narrative review, the SANRA scale (a scale for the quality assessment of narrative review articles) was employed (21).

Results: A meta-analysis by Luo et al. in 2021 suggests that depressive symptoms may occur in up to 25% of individuals with IBD, compared to a prevalence of 3.4% in the general population. The same study highlighted that the presence of depression increases the risk of developing IBD (4). Walker et al. in 2008, in a cohort study involving 351 patients from the United States and New Zealand, reported depression in approximately 27.5% of IBD patients. Those who experienced depressive symptoms before the onset of IBD reported a lower

quality of life and an earlier onset of IBD symptoms compared to patients without depressive disorders (22).

The Impact of Selective Serotonin Reuptake Inhibitors (SSRIs) on IBD Treatment: According to the literature, patients with IBD often suffer from mental health disorders such as depression and anxiety, leading some physicians to consider antidepressant treatment for their patients (4,23,24). Thorkelson et al. (25) in 2016 observed that SSRIs are among the most frequently chosen medications in the treatment of IBD patients with coexisting depression. SSRIs commonly used in this patient population include fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram (19).

Serotonergic neurons release serotonin in the central nervous system, while enterochromaffin cells and the mesenteric plexus are responsible for this process in the intestines (26). During intestinal inflammatory processes in IBD, serotonin levels decrease, which further exacerbates depressive symptoms. SSRIs increase serotonin levels, which may have beneficial effects in alleviating depressive symptoms in IBD patients (3). Additionally, an important aspect of SSRI therapy is its anti-inflammatory component. O'Brien et al. confirmed this by observing a significant decrease in serum C-reactive protein levels four weeks after initiating SSRI treatment in individuals with severe depressive disorders (27). The anti-inflammatory properties of SSRIs can be divided into two types based on the involved cell types. Microglial cells mediate processes dependent on the CNS, while immune cells residing in tissues or circulating in the bloodstream influence peripheral effects. It has been shown that SSRIs affect the ability of microglia to generate pro-inflammatory cytokines and free radicals, such as nitric oxide (28,29). Tynan et al. (30) found that SSRIs at standard pharmacological doses (fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram) impacted TLR, leading to reduced TNF-α production by microglia. Sertraline may also inhibit inflammation through its action on the TLR3-IRF3 pathway (31). A large study by Kristensen et al. involving 888 patients treated with SSRIs for UC or CD found that antidepressant use was associated with lower disease activity compared to those not using these medications, particularly among patients who had not previously used antidepressants before the onset of IBD. These findings suggest the potential role of SSRIs as adjunctive treatment in conventional IBD therapy (32).

Gastrointestinal disturbances are common in IBD and are also a side effect of antidepressant medications. The side effects of the aforementioned treatment are dose-dependent and usually

subside within the first few weeks of therapy. It is noteworthy that diarrhea was reported more frequently by patients using sertraline than other SSRIs (14).

Hatamnejad et al. indicated that SSRI use is associated with an increased risk of bleeding, particularly during the first month of use. SSRI inhibition of the serotonin transporter may affect platelet function, leading to increased blood loss at the site of injury (24). Similarly, Abajo et al. (33) in a 1999 population-based case-control study demonstrated that upper gastrointestinal bleeding can occur as an adverse effect of SSRI therapy in IBD patients. The incidence rate of this complication was estimated at 1 case per 8,000 prescriptions or 1 case per 1,300 patients. Additionally, SSRIs used concurrently with aspirin may further increase bleeding risk due to the inhibition of cytochrome P450 (34). Mesalazine, also known as 5-aminosalicylic acid (5-ASA), is the preferred therapeutic option for IBD. Mesalazine is an effective, safe, and well-tolerated drug for mild to moderate UC. Since it is a derivative of salicylic acid and has similar effects to aspirin, it may also increase the risk of bleeding when used with SSRIs (24).

The most commonly reported side effects of SSRIs include sleep disturbances, sexual dysfunction, and weight gain. The most concerning effects are usually observed during long-term use (over 6 months) (35,36). Sleep disturbances, including sleep apnea, may contribute to cyclic reductions in intestinal oxygen partial pressure gradients, potentially resulting in prolonged periods of hypoxia, which can adversely affect the microbiome. Imbalances in gut microbiota can lead to intestinal inflammation, which in turn may exacerbate IBD symptoms (24,37). However, other studies suggest that SSRIs may be used in the treatment of sleep apnea (38).

The Impact of Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) on IBD Treatment

In a 2016 systematic review by Thorkelson et al. (25), it was noted that approximately 1% of patients with ulcerative colitis (UC) were treated with SNRIs. These medications were used both to alleviate symptoms of depression and anxiety, and to reduce pain intensity. In a 2012 systematic review, Srinath et al. (39) demonstrated that abdominal pain, a common symptom in patients with IBD, negatively impacts patient well-being and quality of life. In a 2022 randomized clinical trial, Liang et al. (40) indicated that SNRIs have a positive effect on the quality of life of patients with IBD who also suffer from depression or anxiety. Forty-five

patients were randomly assigned to either the treatment group, which received venlafaxine at a dose of 150 mg daily, or the placebo group. The patients were then observed for six months. The results of this study indicate that venlafaxine effectively improves quality of life, alleviates depressive and anxiety symptoms, improves the CDAI (Crohn's Disease Activity Index) and Mayo scores (for assessing UC activity), and reduces CRP levels, ESR (erythrocyte sedimentation rate), and TNF-α in the blood. Similarly, in a 2015 randomized double-blind trial, Daghaghzadeh et al. (41) showed that SNRIs have a positive effect on the quality of life of patients with IBD who also suffer from depression or anxiety, and they also reduce pain associated with IBD. The study involved 44 IBD patients, 35 of whom completed the study, with 17 receiving duloxetine and 18 receiving a placebo. After 12 weeks of duloxetine treatment, patients showed improved quality of life, reduced severity of depressive and anxiety symptoms, as well as IBD symptoms (including pain and diarrhea frequency). Thorkelson et al. (25), Liang et al. (40), and Daghaghzadeh et al. (41) noted that adverse effects of SNRI treatment include dizziness, nausea, palpitations, and insomnia, leading some patients to discontinue treatment. Baldwin and Papakostas (42), in 2006, suggested that duloxetine is not recommended for patients experiencing drowsiness and fatigue, whereas venlafaxine is neutral with respect to these issues. Bailey et al. (43), in a 2006 analysis of seven clinical trials, observed that patients taking duloxetine frequently experienced constipation as a side effect. Colombel, Shin, and Gibson (44), in a 2019 analysis, suggested that IBD patients suffering from diarrhea should take medications that reduce intestinal motility, with duloxetine being one such potential medication (41). However, the most important consideration is the individualization of medication choice based on patient needs.

The Impact of Tricyclic Antidepressants (TCAs) on IBD Treatment

In a 2016 systematic review, Thorkelson et al. (25) noted that 2% of patients with UC used TCAs. The indications for TCA therapy include depression, anxiety, and insomnia in IBD patients. TCAs are the second most commonly chosen class of antidepressants in the treatment of IBD, but their use has declined due to numerous side effects. TCAs include medications such as amitriptyline, dothiepin, prothiaden, doxepin, imipramine, nortriptyline—though in Poland, only amitriptyline, doxepin, opipramol, and clomipramine are available (45,46). In a 2012 review, Srinath et al. (39) reported that 60% of CD patients and 30% of UC patients experience chronic abdominal pain and diarrhea. Low doses of TCAs may be helpful in alleviating functional abdominal pain in IBD patients. Smiley et al. (47) from the Poursina

Hakim Research Institute conducted a randomized clinical trial in 2008 involving 50 patients with mild to moderate UC. The treatment group, which received imipramine, included 52% of patients, while 48% received a placebo. Throughout the study, patients on imipramine tolerated the drug well, with only one patient with mild prostate enlargement experiencing urinary retention after two weeks of treatment. Imipramine reduced the severity of anxiety and stress in UC patients, and the study suggests that it also reduced the severity of the disease and UC symptoms. In a 2012 study, Srinath et al. mentioned desipramine, which has a beneficial effect on treating functional abdominal pain in IBD patients (39). Mikocka-Walus et al., in a 2007 survey of 18 gastroenterologists, listed medications successfully used in the treatment of pain and intestinal hypersensitivity, including amitriptyline, dothiepin, prothiaden, doxepin, imipramine, and nortriptyline (48).

Thorkelson, Bielefeldt, and Szigethy reported that TCA side effects include sedation, a lowered seizure threshold, and weight gain. TCAs also affect the gastrointestinal tract, causing constipation and xerostomia. TCA overdose can be fatal (25). Peretti, Judge, and Hindmarch noted that TCA use has declined in recent years due to the availability of newer antidepressants with better safety and efficacy profiles (49).

The Impact of Atypical Antipsychotics or Other Antidepressants on IBD Treatment

Hall et al. (19) in 2018 described atypical antipsychotics and other antidepressants, such as mirtazapine, bupropion, and phenelzine, as potentially promising therapeutic options for treating CD and other forms of IBD. Mikocka-Walus et al.'s 2006 research suggests that these drugs, known primarily for their effects on the nervous system and mood, may also have beneficial effects on the course of inflammatory bowel diseases through anti-inflammatory and immunomodulatory properties (50).

The Impact of Mirtazapine, a Noradrenergic and Specific Serotonergic Antidepressant (NaSSA), on IBD Treatment

Mirtazapine, a tetracyclic antidepressant, acts on various receptors, including serotonergic and noradrenergic receptors (25). A systematic review by Mikocka-Walus et al. suggests that mirtazapine may increase TNF-α levels, so its use in treating depression in CD patients is avoided (50). A 2016 systematic review by Thorkelson et al. highlighted that mirtazapine is generally well tolerated, but it often causes weight gain. However, it has significantly fewer

gastrointestinal side effects than other classes of antidepressants (SSRIs, SNRIs, TCAs), including reduced nausea and no induction of liver isoenzymes. It also does not have significant clinically relevant interactions with other drugs (25).

The Impact of Bupropion, a Selective Norepinephrine and Dopamine Reuptake Inhibitor, on IBD Treatment

In a clinical study, Moreira observed that bupropion affects the dopaminergic and noradrenergic systems by inhibiting the reuptake of these neurotransmitters (51). In a 2006 mouse study, Brustolim et al. demonstrated that bupropion not only improves mood but also exhibits anti-inflammatory effects by lowering levels of TNF-α, interferon-gamma (IFN-γ), and interleukin-1 (IL-1) (52). Research by Kane et al. (2003) and Kast (2003) on adult CD patients indicated that bupropion positively affects both depression and the reduction of CD activity (53)(54). In a meta-analysis, Mikocka-Walus et al. observed that bupropion use leads to reduced TNF-α levels, a key cytokine associated with the inflammatory process in CD. As a result, patients treated with bupropion experienced long-term remission of the disease (50).

The results of a 2022 clinical trial by Hashash et al. involving 232 CD patients suggest that bupropion may help patients with high levels of fatigue and emotional dysregulation. The study examined the effect of bupropion on this group of patients in correlation with the aforementioned symptoms (55). A systematic review by Graff et al. highlighted that sexual dysfunction, which is a common side effect of antidepressants, can significantly worsen the mental state of IBD patients. However, bupropion minimally impacts sexual dysfunction compared to other antidepressants, which led to discontinuation of other antidepressant therapies in favor of bupropion in some IBD patients. Additionally, it alleviates sexual dysfunction caused by side effects of SSRIs and SNRIs. Moreover, bupropion does not cause sedation or weight gain. The most common side effects include dry mouth, nausea, headache, dizziness, tinnitus, increased sweating, and urination (14). Bupropion may exacerbate insomnia due to catecholamine activity stimulation (56). Bupropion is a strong enzyme inhibitor and can increase plasma levels of several drugs, including other antidepressants, antiarrhythmics, and antipsychotics (25,57).

The Impact of Phenelzine, a Monoamine Oxidase Inhibitor (MAOI), on IBD Treatment

Kast (1998) refers to the effect of phenelzine use in a 33-year-old female patient with CD and coexisting depression. Phenelzine, as a monoamine oxidase inhibitor (MAOI), acts by increasing the concentration of neurotransmitters such as dopamine, norepinephrine and serotonin and can induce remission of CD symptoms and thus improve intestinal barrier function. Seven days after starting phenelzine (15 mg three times daily) in a patient with CD, the number of watery bowel movements decreased from 10 to 3-4 per day. In addition, the previously severe abdominal cramps subsided. One month later, the dose was increased to 30 mg three times daily and thus the depressive symptoms decreased and the abdominal discomfort disappeared. At the same time, the patient started to defecate properly without the presence of painful abdominal cramps (58). Mikocka-Walus et al. also describe that the effects of phenelzine can provide relief of IBD symptoms by reducing disease activity and reducing inflammatory processes. One of the side effects is the possibility of hypertensive breakthrough during phenelzine use (50).

Effect of S-ketamine on the treatment of IBD.

In a randomised controlled trial of 2023. Zhang et al. suggest that S-ketamine has anti-inflammatory and immunomodulatory effects by reducing levels of pro-inflammatory cytokines such as IL-6 and TNF-α, which may benefit patients with IBD(59). Kiraly et al. in 2017, in a clinical trial on 33 patients with drug-resistant depression, reported that intravenous administration of S-ketamine was followed by a decrease in levels of the cytokines Il-6, G-CSF and Il-1alpha, after four hours. A reduction in inflammation was observed(60). Additionally, Zhou et al. in 2018 conducted a study on the effect of ketamine administration in patients with major depressive disorder (MDD). They showed that 24 hours after ketamine administration (0.5 mg/kg), MDD patients experienced a reduction in depressive symptoms, accompanied by an increase in KYNA levels and KYNA/KYN ratio. The kinurenin (KP) pathway plays an important role in the pathogenesis of depression. This is because it converts tryptophan to kinurenine (KYN) under the influence of indoleamine 2,3-dioxygenase (IDO). KYN can be converted to kirunic acid (KYNA), which has neuroprotective and anti-inflammatory properties, or to quinolinic acid (QUIN), which has neurotoxic properties (61). In a 2021 systematic review, Chen et al. noted that overactivation of IDO in the body and brain due to chronic inflammation accelerates KP pathway metabolism. This leads to overproduction of QUIN and reduction of KYNA in the brain. QUIN neurotoxicity negatively affects glial cells and neurons, contributing to inflammation-related depression. KYNA, on

the other hand, has been shown to have neuroprotective effects, and the ratio of KYNA to QUIN may serve as an indicator of neuroprotection(62). Getachew et al. in 2018 described the positive effects of ketamine on gut microbiota composition. The researchers administered ketamine intraperitoneally to a group of adult rats. The feces collected for seven days served as a microbiome source to analyze the strains of bacterial microflora in the gastrointestinal tract. They concluded that reduced levels of Lactobacillus and Turicibacter in the gut microbiota could exacerbate depressive symptoms. Applied ketamine, on the other hand, increased the abundance of Lactobacillus, Turicibacter and Sarcina in the rat microbiota, while reducing opportunistic bacteria such as Mucispirillum, which may contribute to inflammatory bowel disease (63). Zhang et al. 2023 in a randomized prospective study showed that S-ketamine may also have an analgesic effect in CD. They described a reduction in pain intensity in a 124-person study group after bowel resection surgery for CD with associated depressive symptoms. This is a relatively new form of therapy that has shown promising results in alleviating depressive and physical symptoms associated with IBD. However, further studies are needed to fully understand the efficacy and safety of long-term use of S-ketamine in the patient population (59).

Conclusions

Studies indicate that symptoms of depressive disorders may be present in 25-27.5% of patients with IBD (4,22). One of the most commonly used antidepressants in patients with IBD and co-occurring depression are SSRIs (19), which have anti-inflammatory effects (27-31) and allow serotonin levels to increase (3,26). This results in lower rates of disease activity in patients with IBD (32), reducing the severity of depression, anxiety, while improving various areas of quality of life (41). In patients with IBD, SSRIs can cause a variety of side effects that are dose-dependent, but usually decrease within the first few weeks of therapy (14). SSRIs used in patients with IBD also increase the risk of bleeding, particularly in the first month of use (24,33,34). The risk of bleeding is further increased by concomitant use of aspirin (34) and mesalazine (24). The most common side effects of SSRIs are sleep disturbances, sexual dysfunction and weight gain (24,35,36,37,38).

SNRIs are used relatively infrequently in patients with IBD (25). Most commonly, SNRIs are used in the course of IBD to alleviate symptoms of depression, anxiety, and to reduce inflammation, pain and the severity of IBD symptoms (including the frequency of diarrhea)

(25,40,41). This may have a positive impact on patients' quality of life (39,40,41). The most commonly cited side effects of SNRIs are dizziness, nausea, palpitations, insomnia (25,40,41) and constipation in the case of duloxetine (43). Duloxetine is not recommended for patients with drowsiness and fatigue (42). TCAs are the second most commonly chosen group of antidepressants for the treatment of IBD, but the use of this group of drugs is increasingly being abandoned due to its numerous side effects (25). In patients with IBD, TLPD group drugs are used for co-occurring depression, anxiety and insomnia (25). Findings suggest that TLPDs can reduce disease severity and effectively control IBD symptoms. Conversely, the use of low doses of these drugs may help to relieve functional abdominal pain in patients with IBD (25,39,48). The most common side effects of TLPD drugs are sedation, decreased seizure threshold, weight gain, constipation and xerostomia (25).

Atypical antipsychotics are a potentially promising therapeutic option for the treatment of CD and other forms of IBD(19). These drugs exhibit anti-inflammatory and immunomodulatory properties with positive effects on the course of IBD (50). Mirtazapine appears to have pro-inflammatory effects and is therefore not recommended in CD with co-morbid depression. Although it has significantly fewer gastrointestinal side effects than the other antidepressant groups (SSRIs, SNRIs, TLPDs), it reduces nausea and does not induce hepatic isoenzymes (25,50). Bupropion has mood-enhancing, anti-inflammatory effects(50,51,52), has antidepressant effects and reduces disease activity in CD (50,53). Bupropion also reduces high levels of fatigue and emotional dysregulation in patients with CD (55). The most common side effects of bupropion are dry mouth, nausea, headache, dizziness, tinnitus, increased sweating and urination and insomnia (56). Bupropion also has numerous drug interactions (25,57).

Phenelzine can improve intestinal barrier function, induce a reduction in disease activity and even remission of CD symptoms (50,58). Phenelzine use is associated with a risk of hypertensive breakthrough (50).

Findings indicate that S-Ketamine also has anti-inflammatory and immunomodulatory properties, also leading to positive effects on the composition of the gut microbiota of IBD patients (59,60,62,63,64). S-ketamine may also reduce the severity of pain in CD (59).

Studies indicate that SSRIs, SNRIs, TLPDs, atypical antidepressants and other antidepressants have applications in the treatment of IBD, not only with co-occurring depressive symptoms.

Due to the wide adverse effects of drugs from these groups, it is important to take into account the clinical condition of the patient and use them in a personalized manner. There also seems to be a need for an interdisciplinary approach when selecting treatment for patients with IBD and co-occurring depression, involving collaboration between a gastroenterologist and a psychiatrist. Research is needed to improve knowledge of the common pathogenesis of IBD and depression, and the correlation between the two diseases. There is a lack of high-quality randomized trials to determine in which group of IBD patients the above-mentioned drugs should be included and at what doses. However, more high-quality multicentre studies are needed to establish precise guidelines for the use of these drug groups in patients with IBD.

Author's contribution

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