Reasonable treatment choice in inflammatory bowel disease

Doctoral (PhD) thesis

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ABRREVIATIONS

5-ASA	5-aminosalicylic acid
ADA	adalimumab
AE	adverse event
ASUC	acute severe ulcerative colitis
AZA	azathioprine
CD	Crohn’s disease
CDAI	Crohn’s disease activity index
CI	confidence interval
CYS	cyclosporine
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
H2RA	histamine 2 receptor antagonist
IBD	inflammatory bowel disease
IFX	infliximab
MTX	methotrexate
OR	odds ratio
PPI	proton pump inhibitor
PROSPERO	International Prospective Register of Systematic Reviews
RCT	randomised controlled trial
SAE	serious adverse event
SES-CD	Simple Endoscopic Score for Crohn's Disease
TNFα	tumour necrosis factor alfa
UC	ulcerative colitis
VDZ	vedolizumab

1. INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic, inflammatory gastrointestinal diseases that are associated with relapses and remissions throughout the patient's life. There are two types of IBD, Crohn's disease (CD) and ulcerative colitis (UC).

1.1. Aetiology and aetiopathogenesis of inflammatory bowel diseases

In recent decades, the number of IBD patients has increased significantly worldwide. The global spread of IBD is likely also related to the "westernization" of diet and environment, which affects the gut microbiome and increases the risk of developing IBD in genetically susceptible individuals. In Hungary, there are approximately 25-30,000 IBD patients, and each year around 1000-1200 new cases are registered. Based on data from Veszprém, between 1997 and 2001, the incidence of IBD increased elevenfold, while its prevalence increased threefold. This growing trend also points to the fact that disease research is an extremely important area within gastroenterology.

The cause of the disease is still not completely known, however multifactorial origin is suspected. The "host factors" (innate characteristics, such as genetics, which are clearly proven by familial accumulation and abnormal functioning of the immune system), environmental effects (e.g. nutrition, smoking and microbiological factors) clearly influence the development of the disease. According to our current knowledge, chronic disease develops in genetically susceptible individuals.

Smoking is one of the most important environmental risk factors, and numerous studies have been dealing with its connection with IBD since the 1980s. Smoking (mainly reactive oxidative substances) triggers many inflammatory processes in the body through inflammatory signaling cascades [e.g. interleukin-8 or tumour necrosis factor alpha (TNFα)]. Nicotine increases mucus production in the colon, so this may play a role in its protective role in patients with UC.

1.2. Clinical characteristics of inflammatory bowel diseases

The differentiation of CD and UC is often not clear, both the general symptoms (abdominal pain, diarrhoea) and the endoscopic picture can be similar. Mucosal inflammation in CD can typically occur anywhere in the alimentary canal, mainly leaving segmentally intact parts between two affected sections (so-called "skip" lesions), affecting all mucosal layers in a transmural manner. Almost 25% of CD patients develop perianal complications and fistulas during the course of the disease. In UC, the inflammation is localized only to the large intestine and affects only the mucosa, always starting distally, extending from the rectum.

During endoscopy, the image characteristic of the two subtypes can be recognized macroscopically; deep, serpiginous ulcers like “cobblestones” drawings are visible in CD, and in UC, an erythematous, edematous bowel wall with reduced vascularity, superficial aphthae, ulcers, spontaneous bleeding, pseudopolyps, and atrophic mucosa in chronic cases. During the histological processing, we can recognize granulomas in CD and crypt abscesses in UC.

1.3. Drug therapy of inflammatory bowel diseases

In recent decades, the treatment of IBD has improved tremendously, although we cannot yet achieve a complete cure. In addition to long-term clinical remission, the goal of our current treatment is macroscopically detectable complete mucosal healing (ie. the absence of ulcers).

The latest studies aim at microscopic healing in UC and transmural healing in CD, but this is not yet considered a goal in everyday practice.

In general, locally acting 5-aminosalicylic acid (5-ASA) and/or topical steroids are administered in mild form of UC. In cases of moderately active UC and CD, systemic steroids are used to induce remission and immunomodulators are used to maintain remission. In severe cases and in patients refractory to/intolerant to steroid/immunomodulatory treatment, biological therapy is introduced. It is a general guideline that a “step-up” or “step-down” therapeutic approach can be used, gradually increasing the potency of the drugs from locally effective to systemic agents, or in more severe cases, withdrawing from systemic treatment.

From the 5-ASA agents, mesalazine and sulfasalazine are available in Hungary, the side effect profile of mesalazine is more favourable. Due to its effect on the large intestine, it is only recommended for UC patients with mild to moderate activity. Budesonide can be used in mild cases of CD involvement localized to the ileocecum. In moderate-severe cases, the administration of a systemic steroid in "per os" or intravenous form is recommended, which can be supplemented with an immunomodulator [thiopurines or methotrexate (MTX)] as needed.

The first products of biological therapies were anti-TNFα monoclonal antibodies [infliximab (IFX), adalimumab (ADA), golimumab, and certolizumab], which enable the blocking of inflammatory processes at the cellular level. Anti-TNFα agents have also been shown to be effective in inducing and maintaining clinical and endoscopic remission. Anti-TNFα drugs can be used very well in steroid-refractory and -dependent patients, however, with the use of ADA and IFX, the frequency of loss of effect within one year is 15-30%. With the development of drug therapy, other agents also appeared later. Vedolizumab (VDZ) is the first gut-selective biological therapy that appeared in the 2010s. With the inhibitory effect of α4β7-integrin, it prevents the inflow of lymphocytes into the intestine, so it has fewer side effects than anti-TNFα drugs.

1.4. Acute severe ulcerative colitis

Acute severe ulcerative colitis (ASUC) is a life-threatening condition that requires immediate treatment. It occurs in 15-25% of UC patients during their lifetime. The mortality of the disease is approx. 1%, in elderly patients it is significantly higher, around 3-4%. There are several definitions of the exact definition in the literature, of which the use of the Truelove & Witts criteria is the most accepted. According to this definition, the patient has bloody stools at least six times a day, the pulse rate is over 90/minute, the body temperature is over 37.8°C, the haemoglobin level is below 105 g/l, and the red blood cell count is more than 30 mm/hour, or C-reactive protein is higher than 30 mg/l. In the case of ASUC, institutional treatment is needed, the primary therapy is intravenous steroids, which, however, in approx. 40% of cases is ineffective. In steroid-refractory cases, total colectomy was previously recommended as second-line therapy. However, in the 1990s, the use of cyclosporine (CYS) appeared as a bowel-saving therapy and the need for colectomy could be avoided or delayed.

The use of this drug can result in rapid improvement in the patient’s state, however, many side effects may occur, such as kidney, liver, vascular or neurological damage, and the appearance of opportunistic infections is also more common. In addition, due to the narrow therapeutic serum level, frequent blood sampling is also needed during the application.

With the appearance of IFX and its rapid onset of action, it became a new alternative as a second-line therapy in cases of steroid-refractory ASUC. Some meta-analyses have found IFX treatment to be more effective than CYS for steroid-refractory ASUC. This question remains unanswered to this day, and no clear recommendation has yet been formulated in favour of any bowel saving therapy.

1.5. The use of proton pump inhibitors in inflammatory bowel disease

In recent decades, the use of proton pump inhibitors (PPI) has become extremely widespread, and they are one of the most frequently prescribed drugs worldwide. However, long-term, persistent use of PPIs can also have complications. We can detect more frequent gastrointestinal, respiratory and urinary tract infections (e.g. Clostridium difficile infection), malabsorption of vitamins B12, C, iron, magnesium and calcium, fundus gland polyps, gastric carcinoma arising on the basis of hypochlorhydria-hypergastrinemia, as well as a decrease in the anti-aggregation effect of clopidogrel platelets that can be a clinically relevant consequence. Some of these complications develop because of a decrease in gastric acid production and a change in the diversity of the gut microbiome.

The interaction of PPIs when used together with other drugs is also a hot topic of research. A recently published meta-analysis of patients receiving IFX therapy found a lower remission rate in patients taking PPIs than those not taking PPIs. This also leads to the conclusion that there may be many more consequences and adverse effects of long-term PPI use, which we do not yet know.

2. AIMS

1. In the course of our work, we aimed to conduct a long-term study of bowel rescue therapies in IBD patients with ASUC.

2. In steroid-refractory ASUC patients, we investigated the effectiveness of second-line CYS and IFX therapies regarding patients' colectomy-free status in a period between 1 and 10 years.

3. Adverse events, serious adverse events and mortality occurring with the applied CYS or IFX were also investigated together.

4. We aimed to analyse the remission rate of VDZ-treated IBD patients while taking PPIs.

5. We also aimed to investigate the influence of other risk factors during VDZ and PPI treatment, focusing primarily on steroid-containing drugs and smoking.

3. PATIENTS AND METHODS

3.1. Investigation of long-term drug rescue therapy in patients with steroid-refractory acute severe ulcerative colitis

We formulated our summary meta-analysis in accordance with the current international guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyse: PRISMA) and registered it in the international prospective register (International Prospective Register of Systematic Reviews: PROSPERO) (registration number: CRD42018115035).

3.1.1. Identification and search strategy of patients with steroid-refractory acute severe ulcerative colitis

In our research, we used the following databases as of May 22, 2019: PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Embase (https://www.embase.com) and Cochrane Central Register of Controlled Trials (CENTRAL) (http://www.cochranelibrary.com). During the search, we used the PICO (Patient, Intervention, Compare, Outcome) formula. The studied patient population (P) contained steroid-refractory ASUC patients who were treated with IFX (I) or CYS (C) as bowel-saving therapy. The primary outcome (O) was long-term colectomy-free survival, defined as a follow-up beyond 12 months after initiation of therapy. Adverse events (AE), serious adverse events (SAE) and mortality were examined as secondary outcomes. The definition of AE and SAE was determined in our study based on international recommendations.

3.1.2. Study selection

After running the search, we first filtered the duplicates using a reference manager program (EndNote X8, Clarivate Analytics, Philadelphia, PA, USA). Then only the controlled studies that met the following criteria were selected for the analysis: (a) adult ASUC patients (patients older than 18 years) who did not respond to intravenous or oral steroid treatment; (b) CYS or IFX was given as rescue therapy; (c) survival rate was assessed after 12 months; and (d) cytomegalovirus infection was excluded. In the use of other medications [e.g., azathioprine (AZA), 6-mercaptopurine or MTX] no restrictions were applied.

3.1.3. Data extraction, quality assessment

In our study, we collected the data related to each publication: author, year of publication, number of patients receiving IFX or CYS treatment, mean age, gender distribution, proportion of patients with extensive colitis, concomitant medication, presence of maintenance therapy, number of AE and SAE and mortality. These data were also organized according to the quality of the study (randomized or observational).

The risk of bias of the observational studies was determined according to the Newcastle-Ottawa scale (NOS). In this rating system, we used a reliable, wide-ranging quality rating system which uses stars to visualize the selection and comparability of cohorts and outcome assessment.

The quality of the selected randomized controlled trials (RCT) was evaluated using the Cochrane Risk of Bias Tool in seven topics (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, other issues). After the evaluation, low, high, and "unclear" ratings were marked with green, red, and yellow symbols.

3.1.4. Quality of evidence

In our meta-analysis, we used the GRADE system (Grading of Recommendations, Assessment, Development, and Evaluations) to assess the quality of the evidence for the main outcome endpoints. The rating ranged from very low to excellent, from higher quality RCTs to studies with low evidence.

3.2. Investigation of the relationship between proton pump inhibitor intake and relapse in patients with inflammatory bowel disease treated with vedolizumab

The Hungarian national multicentric VDZ cohort received ethical approval from the Regional and Institutional Human Biomedical Research Ethics Committee of the University of Szeged (clinical trial registration number: 99/2017-SZTE). The study protocol complies with the 2013 updated ethical guidelines of the Declaration of Helsinki. Our current observational, post hoc analysis follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) model.

3.2.1. Identification of patients

The VDZ is available in Hungary since 2016. Due to the high costs, in accordance with the financing protocol of the National Health Insurance Fund, the professional permission of a five-member Hungarian IBD committee was required for each patient to start the treatment. The Hungarian national multicentric VDZ cohort was formed from patient applications accepted between July 2016 and December 2018. The recommended induction dose was 300 mg by intravenous infusion at weeks 0, 2, and 6, followed by a maintenance infusion every 8 weeks. Clinical data were collected prospectively from adult IBD patients with moderate and severe disease activity. Concomitant immunosuppressive and corticosteroid treatment was permitted, but combination therapy with another biological agent was an exclusion criterion. A total of 240 patients (127 female and 113 male) received permission, of which 102 were diagnosed with CD and 138 with UC. Mayo and Crohn's Disease Activity Index (CDAI) clinical activity indices were recorded at weeks 0, 14 and 54. All patients underwent colonoscopy at weeks 14 and 54, when endoscopic scoring was performed using the Mayo or Simple Endoscopic Score for Crohn's Disease (SES-CD) endoscopic activity. After the induction period, based on the 14-week endoscopic and clinical score, it was decided whether the patient responded to the treatment, and whether in this case the patient could continue the VDZ maintenance treatment. The primary endpoint of the study was the achievement of short-term (week 14) and long-term (week 54) endoscopic remission. In the original study, endoscopic remission occurred significantly more often in UC than in CD during short- and long-term treatment (52.9% vs. 21.7% at week 14 and 51.4% vs. 21.2 % at week 54).

In our post hoc analysis, we collected data on PPI use retrospectively. All IBD patients were selected from the Hungarian VDZ cohort for whom we had data on PPI use. The relevant data were provided by four tertiary centers: University of Szeged; Hungarian Defense Forces Military Hospital, Budapest; János Balassa Hospital, Szekszárd and the University of Pécs. Patients with missing data (absence of CDAI, Mayo, or other endoscopic points) were excluded even if we had information about taking PPIs.

3.2.2. Analysis of the outcomes

The primary endpoints of our post hoc analysis were clinical response and clinical and endoscopic remission at 14 and 54 weeks. Clinical response was defined as a reduction of CDAI more than 100 or Mayo score more than 3 points. Clinical remission was also defined based on CDAI and Mayo score (CDAI $\leq$ 150, Mayo score $\leq$ 2). Endoscopic remission was defined based on SES-CD or endoscopic Mayo score (SES-CD $\leq$ 4, endoscopic Mayo score $\leq$ 1). As a

secondary outcome, we examined the possible connection between concomitant steroid use and smoking regarding the clinical response, remission and endoscopic remission.

4. RESULTS

4.1. Investigation of long-term drug rescue therapy in patients with steroid-refractory acute severe ulcerative colitis

4.1.1. Selection of patients with acute severe steroid-refractory ulcerative colitis

With our search strategy, we identified a total of 731 publications from the 4 investigated databases, and two more from the reference list of the found articles. After excluding duplicates, 594 studies remained, of which 565 were excluded based on title and abstract. We reviewed the full text of the remaining 29 studies and excluded a further 10 for the following reasons: 3 studies included only short-term data, one did not include colectomy rate and timing, and two were uncontrolled studies. In another two studies, the number of patients treated with CYS and IFX was not reported, in one case patients received both therapies, and in one case patients with Crohn's colitis were included. Thus, 19 studies remained, but four more were also excluded due to the likelihood of overlapping patient population. Finally, 15 studies remained that met all criteria and were thus included in the meta-analysis (Figure 1).

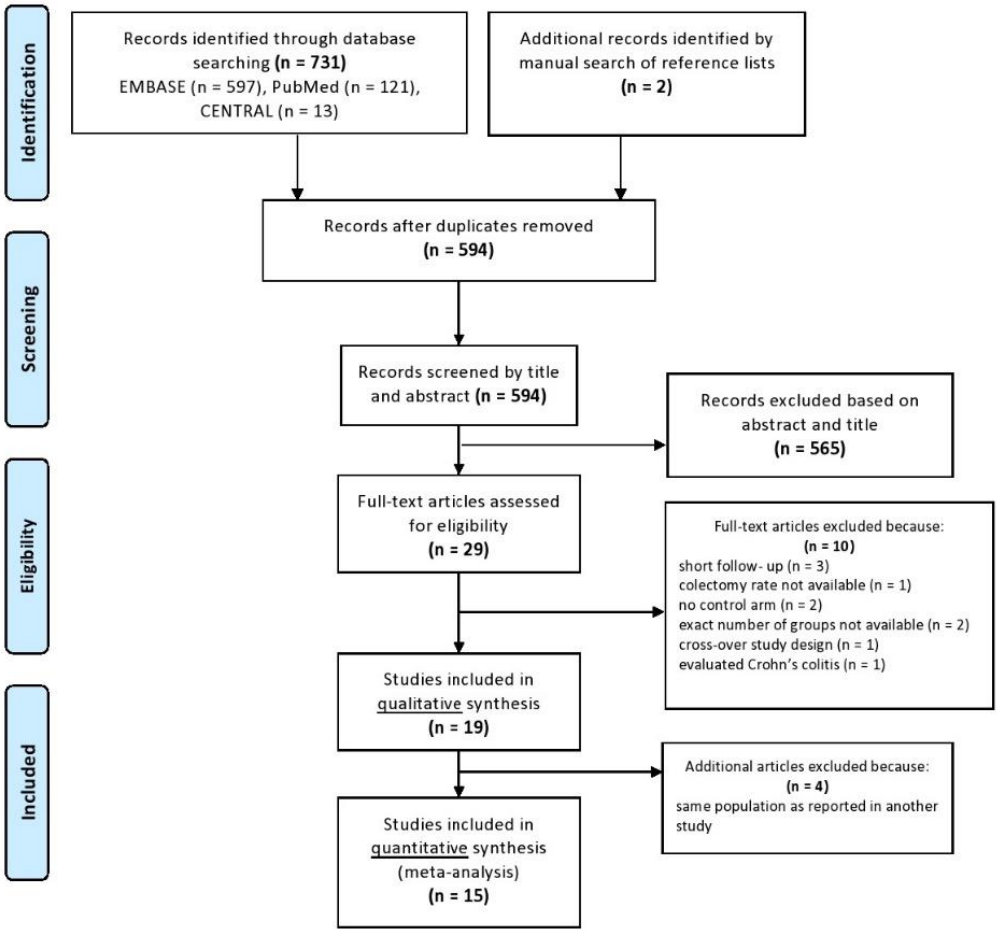

Figure 1. PRISMA flow-chart

4.1.2. Characteristics of the patient population

The studies we analyzed were published between 2004 and 2018, and the follow-up period ranged from at least 1 year to 10 years. Three of the 15 studies were RCTs, the remaining 12 studies were cohort studies. Our population consisted of a total of 1,607 steroid-refractory ASUC patients, of which 879 (54.7%) received CYS and 728 (45.3%) received IFX treatment. The Truelove and Witts criteria and the Lichtiger and Mayo scores were used to determine the definition. Three studies were only available as conference abstracts. In most studies, the standard 2 mg/kg/day intravenous CYS scheme was used, oral CYS was used for remission induction in only two studies. After the parallel introduction of oral CYS, AZA maintenance therapy was continued in all studies. The patients received the standard dose of IFX 5 mg/kg body weight in multiple intravenous infusions (weeks 0, 2 and 6) according to the induction protocol. Only two studies reported a single IFX infusion. In the IFX-treated groups, AZA was the most frequently used maintenance drug, although recent studies have continued the administration of IFX. Since safety data were not available during long-term follow-up in RCTs, we used the CYSIF study and the AEs reported in the original study in our meta-analysis.

4.1.3. Long-term colectomy-free survival

A total of fifteen, eight, five and one studies reported on the colectomy-free survival rate at 1, 3, 5 and 10 years. In the first three years, the colectomy-free survival rate was higher in patients treated with IFX compared to those treated with CYS (OR=1.59, 95% CI: 1.11-2.29, p=0.012 in the first year; OR =1.57, 95% CI: 1.14-2.18, p=0.006 in the second year, and OR=1.75, 95% CI: 1.08-2.84, p=0.024 in the third year, with moderate heterogeneity in the studies I^2=44.3%, p=0.033; I^2=0.0%, p=0.74 and I^2=42.6%, p=0.093) (Figure 2).

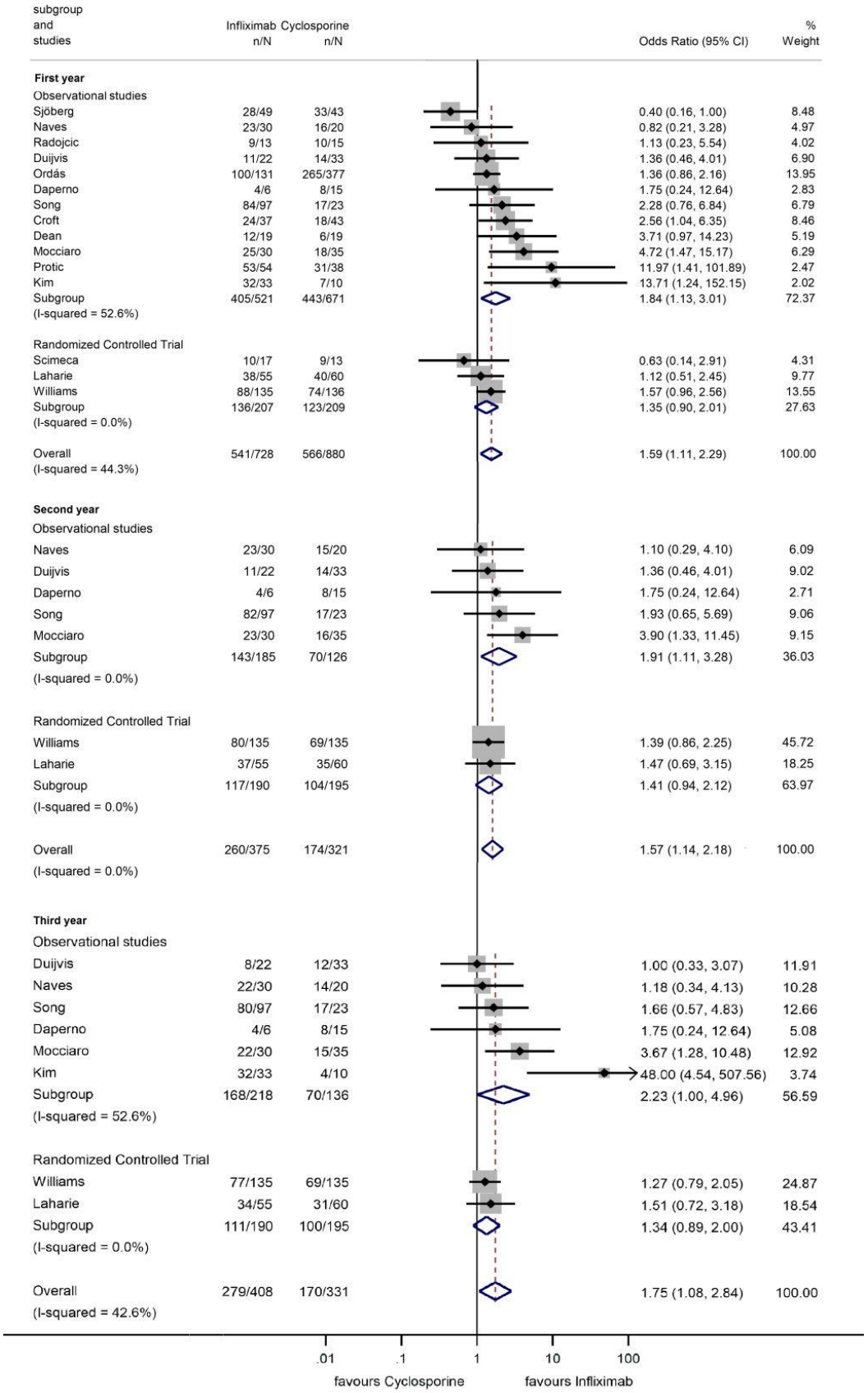

Figure 2. The odds ratio of colectomy-free survival rate in the first, second and third year in steroid-refractory acute, severe ulcerative colitis with infliximab and cyclosporine treatment

From the fourth year of follow-up, no significant difference was found in the colectomy-free rate between the two treatment groups (Figure 3).

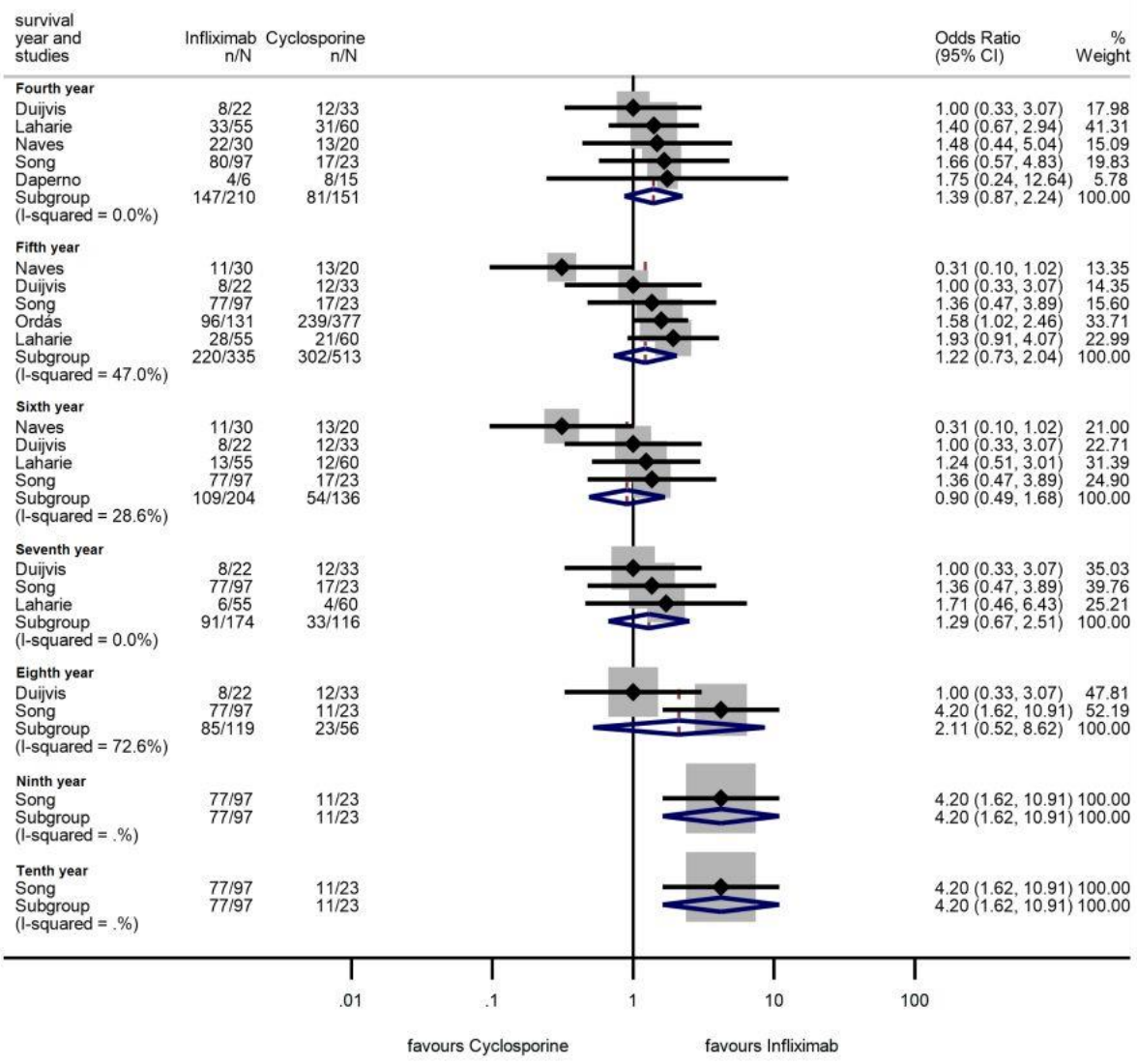

Figure 3. Colectomy-free survival rate in 4-10 years after infliximab and cyclosporine treatment in steroid-refractory acute, severe ulcerative colitis

After nine and ten years of follow-up, only one small, retrospective study remained in the analysis, where colectomy-free survival rate was higher with IFX than with CYS.

However, separating the data from the RCTs showed that the significant difference was only visible when observational studies were included (in the case of observational studies, OR=1.84, 95% CI: 1.13-3.01, p=0.015 in the first year; OR=1.91, 95% CI: 1.11–3.28, p=0.020 in the second year, and OR=2.23, 95% CI: 1.00–4.96, p=0.049 in the third year ; for RCTs, OR=1.35, 95% CI: 0.90–2.01, p=0.143 in the first year; OR=1.41, 95% CI: 0.94–2.12, p= 0.096 in the second year; and OR=1.34, 95% CI: 0.89–2.00, p=0.157 in the third year) (Figure 2). Heterogeneity remained significant in the analysis from observational studies but was negligible when only RCTs were considered (in the first year, I^2=52.6%, p=0.016 and I^2=0.0%, p=0.466, respectively).

Based on our rigorous and consistent classification, the GRADE quality of evidence for 1-, 3-, 5-, and 10-year colectomy-free survival rates was found to be low in subgroups of RCTs, and very low when non-randomized studies were also included.

4.1.4. Adverse events

Seven studies evaluated AEs. 67 (18.1%) side effects were reported for CYS and 72 (18.9%) for IFX. The pooled OR for events was 0.93 (95% CI: 0.45-1.92, *p*=0.847), showing no significant difference between groups (Figure 4).

Eight studies reported SAEs such as opportunistic infections, sepsis, anaphylactic reaction, hepato- and nephrotoxicity (Figure 4). 103 (15.5%) SAEs were reported for CYS and 71 (15.3%) for IFX. The rate of SAEs was not increased with IFX compared to CYS (OR=1.27, 95% CI: 0.86-1.89, *p*=0.236); although in subgroup analysis of observational studies, IFX was associated with higher SAE (OR=1.80, 95% CI: 1.17-2.79, *p*=0.008). However, in the three RCTs, no statistically significant difference could be detected between the two groups (OR=0.81, 95% CI: 0.47-1.41, p=0.461), the data proved to be homogeneous (I^2=0.0 %, *p*=0.712; I^2=0.0%, *p*=0.781 and I^2=7.2%, *p*=0.374).

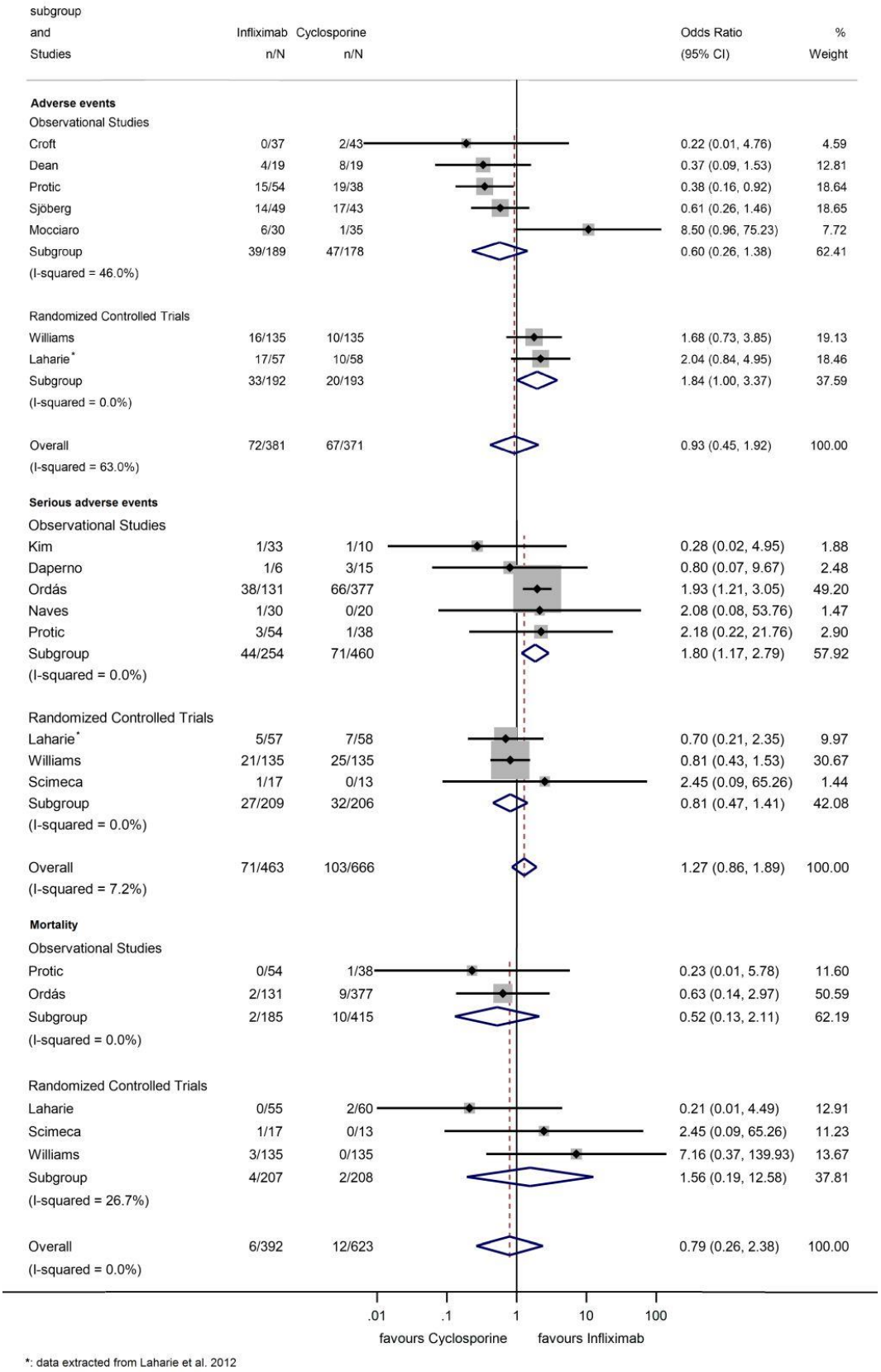

Figure 4. Comparison of odds ratios of adverse, serious adverse events and mortality in infliximab and cyclosporine treatment in steroid-refractory acute severe ulcerative colitis

There was no significant difference in mortality between treatment groups (OR=0.79, 95% CI: 0.26-2.38, p=0.678; I^2=0.0%, p=0.411) (Figure 4).

GRADE assessment of safety outcomes showed low-quality evidence for RCTs and very low-quality evidence for non-randomized trials.

4.1.5. Risk of bias assessment

In the RCTs, the studies by Williams and Laharie had the lowest risk of bias. As these were open trials, participants and staff were not blinded, however, the outcome assessment in Williams' study was blinded. Since Scimeca's study was only published as a conference abstract, we marked almost all sections as "unclear" risk of bias.

Among the observational studies, studies by Croft, Kim, Mocciaro, Naves and Song had the lowest risk of bias, while Protic's study proved to have the highest risk. The representativeness of the affected cohort and the selection of the unaffected cohort were considered high-risk in several studies. In the study by Daperno, Protic, and Radojcic, no comparisons were made between groups with respect to age, sex, and extent of disease (Figure 5).

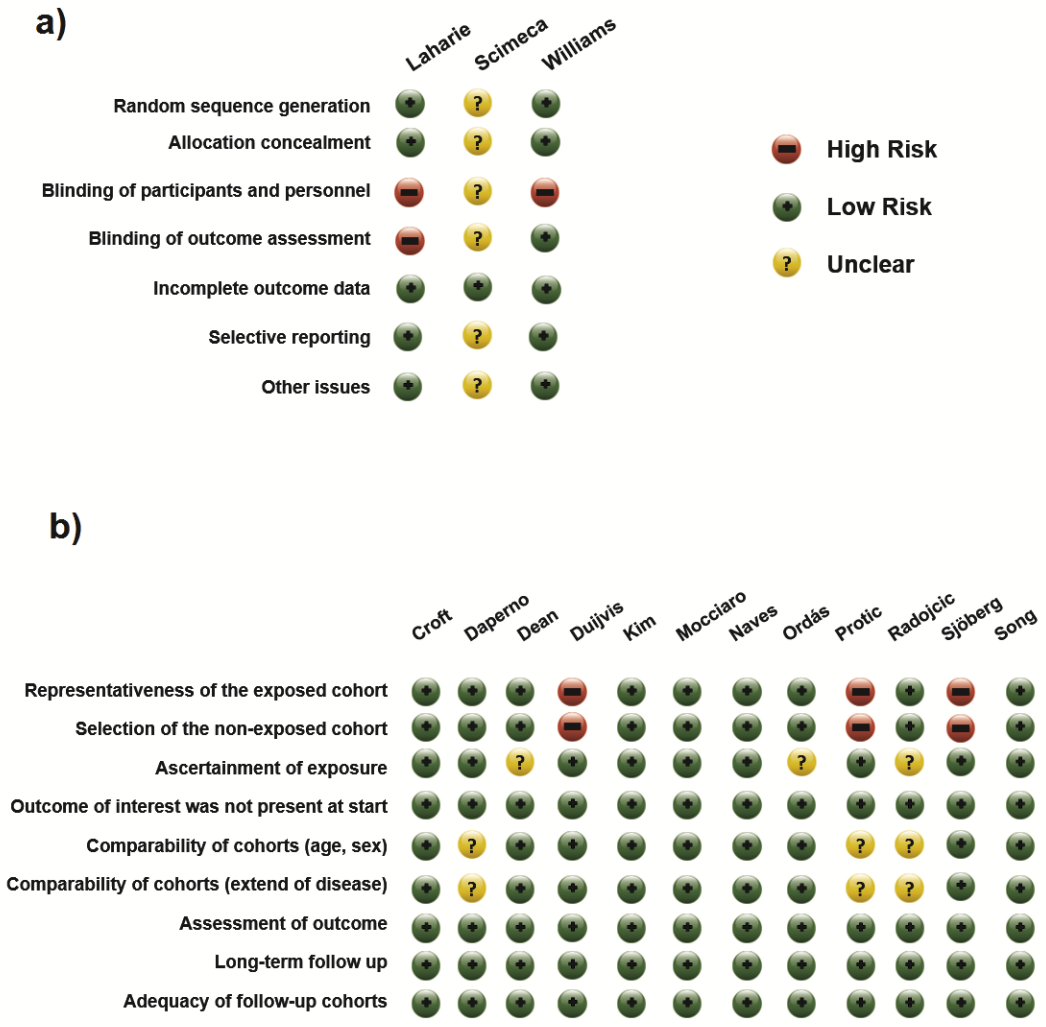

Figure 5. Risk of bias in (a) RCTs and in (b) non-randomized studies.

4.2. Examination of the relationship between proton pump inhibitor intake and relapse in patients with inflammatory bowel disease treated with vedolizumab

4.2.1. Selection of vedolizumab-treated inflammatory bowel patients depending on proton pump inhibitor intake

Between 2016 and 2018, 240 patients received permission for VDZ treatment in Hungary. During patient selection, we excluded 130 patients based on missing PPI data, and another 2 patients due to missing endoscopic and CDAI subscores. Thus, 108 patients remained in our cohort for the final analysis with data on PPI use.

In the VDZ–PPI cohort, 46 (43%) patients were diagnosed with CD and 62 (57%) with UC. The average age at the time of diagnosis was 41±17 years. Only 15% of patients were active smokers.

At week 14, 105 and 100 patients had adequate data for clinical remission/response and endoscopic remission, respectively. At week 54, data were available for 75 patients in clinical response, 79 in clinical remission, and 71 in endoscopic remission.

4.2.2. Results of the examination of patients receiving vedolizumab and proton pump inhibitor treatment

In our cohort, 60 (56%) patients were taking PPI and 48 (44%) were not receiving. PPIs prescribed to the patients were pantoprazole in 47 cases (78%), esomeprazole in 7 cases (12%), and omeprazole and lansoprazole in 1 case each (2-2%), and in 4 patients (6%) there was no data available on the PPI about its type. When investigating the indications for PPI use, the following results were obtained: in 9 cases, the patients took it for GERD and in 42 cases for the prevention of ulcers, but in 9 cases we did not find a clear indication. Overall, 77% of patients used steroids simultaneously.

We found no significant difference between PPI users and non-users during VDZ therapy regarding clinical and endoscopic remission at 14 and 54 weeks. Analyzing the CD and UC subgroups separately, there were also no differences between the two study groups.

However, VDZ-treated non-smoking IBD patients had a significantly higher rate of clinical response at week 14 than smoking patients (Figure 6), particularly in those who did not receive a PPI compared with those receiving concomitant PPI treatment. with patients (81% vs. 53%, p=0.041 and 92% vs. 74%, p=0.029) (Figure 7).

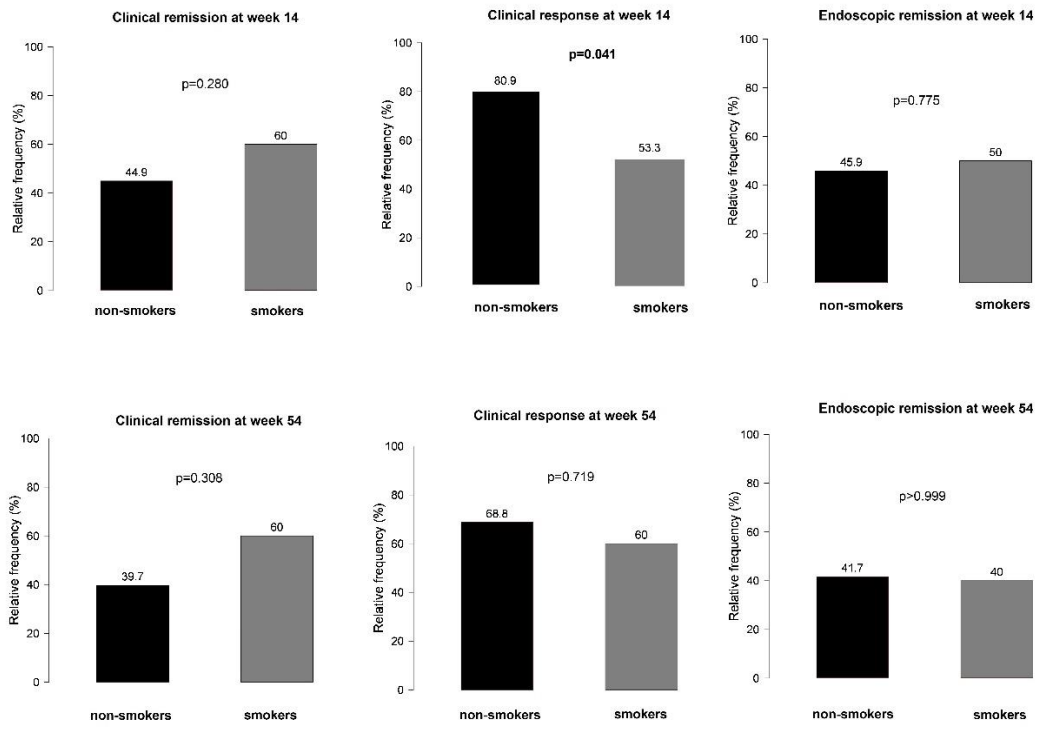

Figure 6. Effect of smoking on clinical response, clinical and endoscopic remission outcomes in patients treated with vedolizumab

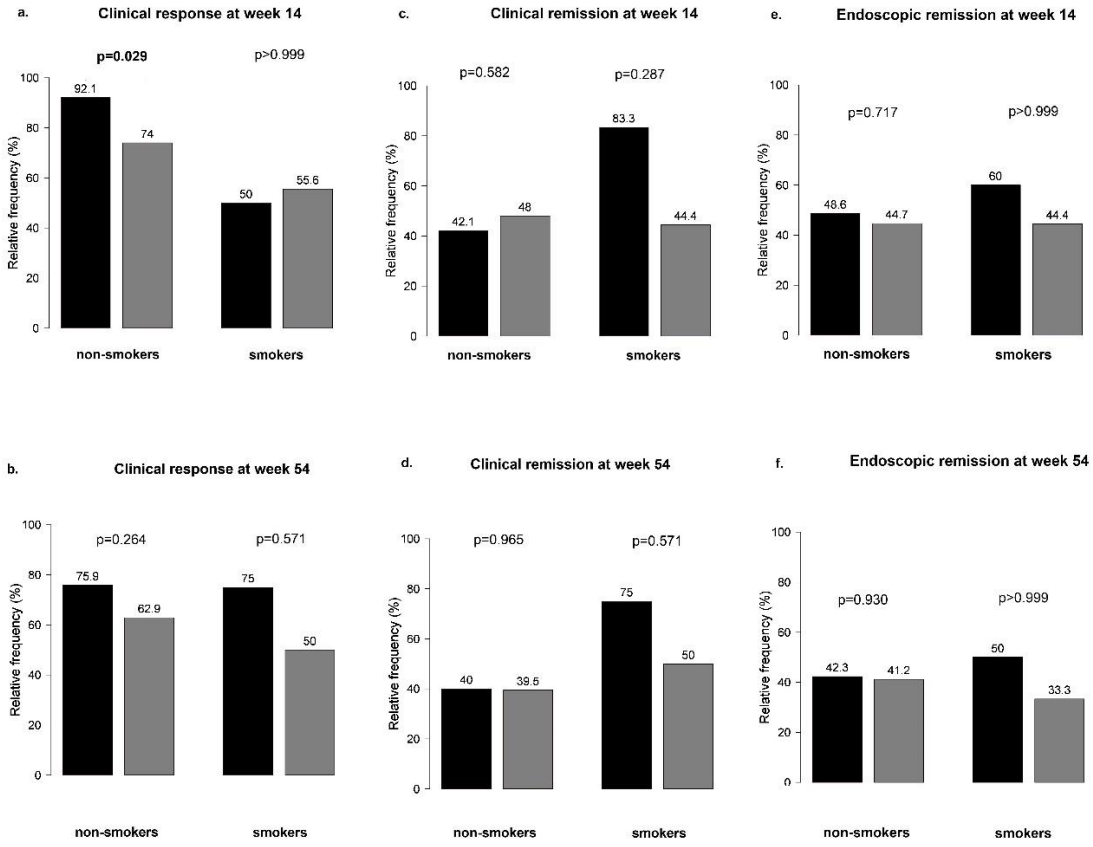

Figure 7. Influence of proton pump inhibitor therapy in smokers and non-smokers treated with vedolizumab: (a,b) clinical response at weeks 14 and 54; (c,d) clinical remission at weeks 14 and 54; (e,f) endoscopic remission at weeks 14 and 54; **black bar:** patients without PPI; **grey bar:** patients with PPI.

No other significant differences were found between smokers and non-smokers regarding PPI use.

Examining steroid use, we found no significant differences overall in the main outcome endpoints at weeks 14 and 54. Further dividing the patients receiving steroid treatment based on PPI intake, a higher rate of patients not receiving PPI treatment achieved a clinical response at week 14 than patients receiving PPI treatment (95% vs. 67%, p=0.005) (Figure 8).

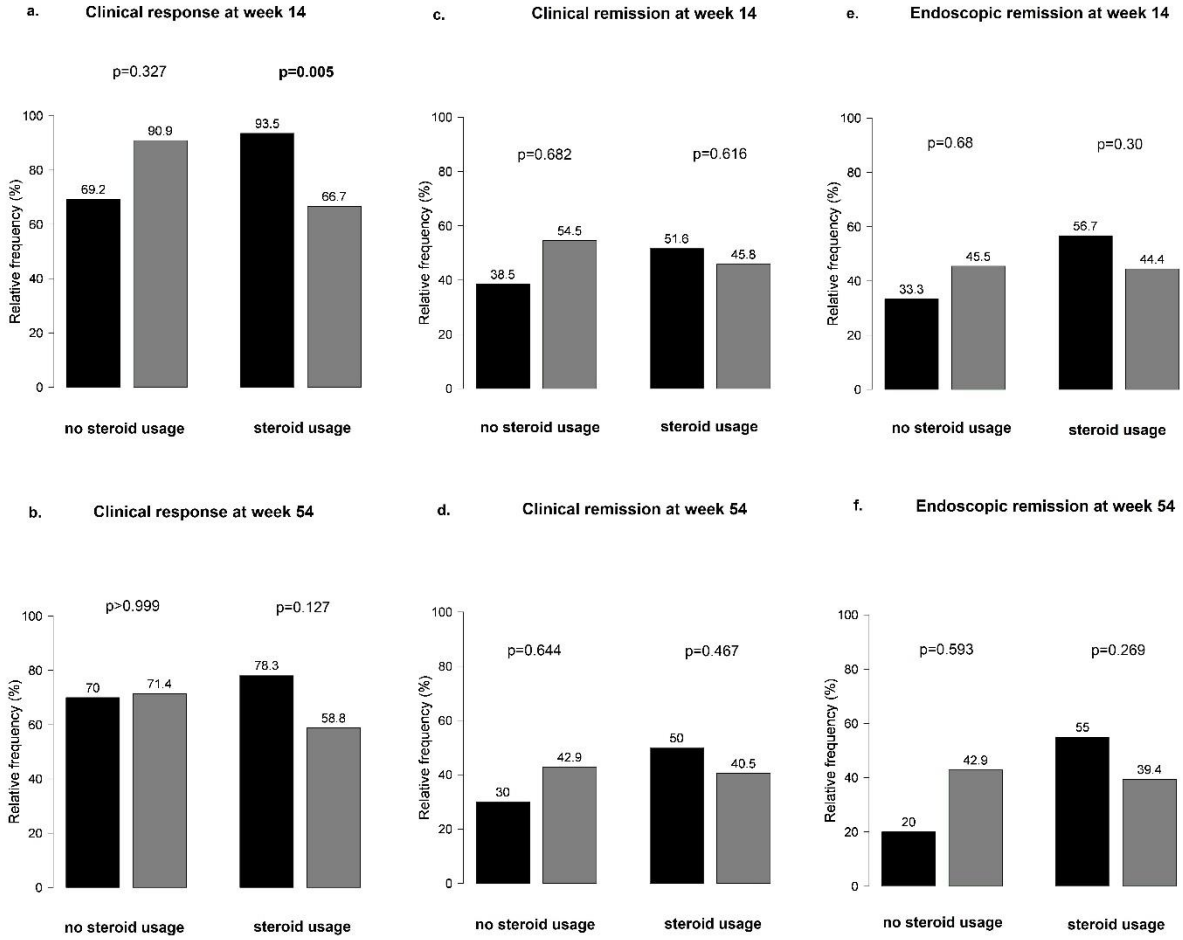

Figure 8. Patients receiving steroid treatment stratified by proton pump inhibitor co-treatment: (a,b) clinical response at weeks 14 and 54; (c,d) clinical remission at weeks 14 and 5; (e,f) endoscopic remission at weeks 14 and 54; **black bar:** patients without PPI; **grey bar:** patients with PPI

5. DISCUSSION

Inflammatory bowel diseases are important topic in gastroenterology due to their globally increasing incidence. The growing amount of knowledge and experience in relation to drug therapy also raises many questions. In patients with UC, an acute severe relapse is a life-threatening condition, and in some cases may lead to complete colon removal. To avoid this, promising data are available on the use of CYS or IFX as bowel-saving therapy, however, no comparative data from a large patient population is yet available regarding the long-term outcome. The use and interaction of PPIs with biological therapy in patients with IBD is also an important issue, as PPIs are one of the most used drugs. New biological therapies, such as gut-selective VDZ, have not yet been analyzed with the interaction with PPIs.

In my scientific work, I was the first to examine the bowel rescue therapy of patients with ASUC. ASUC is a life-threatening condition that needs to be treated in tertiary centers within and multidisciplinary care. In patients with ineffective first-line parenteral steroid therapy, CYS or IFX can be given as gut-saving drug therapy. There are several studies in the literature in one-year follow-up, but no long-term results are available. In our meta-analysis, we examined RCTs and observational studies with long-term results (longer than 1 year). The results showed a significantly higher colectomy-free rate in the first three years with the use of IFX, but this result was not observed from the fourth year onwards. In addition, we examined the results based on the type of included studies, separately RCTs and observational studies. Based on this, there was only a noticeable difference in IFX in the observational studies, but not in the RCTs. In the analysis of secondary endpoints, such as AE, SAE and mortality, we did not find a significant difference between the two drugs.

The strength of our meta-analysis is that it investigates a large patient population, and it is the first to report a long-term, 10-year follow-up. The quality of the evidence was assessed for each outcome based on the GRADE method.

However, it should be noted that our meta-analysis has several limitations. Most of the included studies are non-randomized, retrospective studies. In addition, the use of maintenance therapy was not unified in the studies, so this could also have influenced the results obtained. In two of the RCTs, we found a documented “therapy switch” in some patients from IFX to CYS and vice versa as third-line therapy. This may also have affected the effect of the drug and the long-term outcome. We also included a conference abstract, and we found incomplete information in many cases, which could increase the chance of possible errors. We differed from the research plan initially registered in PROSPERO in a point that we examined the long-term outcomes not only in a five-year interval, but also after ten years. Finally, AE and SAE were not clearly defined everywhere.

During the drug therapy of IBD patients, there is a question of what interactions occur when other drugs are used in addition to biological therapy. One of the most frequently prescribed drugs in the world are PPIs, thus the long-term complications have come to the fore in recent decades. In our post hoc analysis of the Hungarian VDZ register, we found that in certain subgroups, the remission achieved with VDZ can be influenced by taking PPIs. Non-smoking patients treated with VDZ and PPIs were less likely to develop a clinical response at week 14 than patients not taking PPIs. In addition, we observed less clinical response at week 14 in steroid-treated patients who also used a PPI.

Previous studies have also confirmed that the use of PPIs in patients with IBD may not result in a favourable effect, presumably related to reduced acid production. In H2RA users, a significant difference could only be detected in CD patients, and in PPI users in both CD and UC patients. In the background of the correlations, other studies also shed light on the cause

of reduced acid production, as we find similar results in the literature even with H2RA, which has a different mechanism of action. In a large cohort study of thousands of patients, the use of H2RA doubled the risk of hospitalization, especially in CD patients.

In recent years, more and more studies have examined the effectiveness of biological therapy in addition to PPIs and the achieved remission rate. The studies covering a large number of patients came to the conclusion that taking PPIs is related to a decrease in the remission rate in patients treated with IFX, and even during the study, at the week 30 and 54, a significantly lower remission rate was obtained in patients taking PPIs than in patients not taking PPIs.

We can better understand the cause of adverse results associated with taking acid secretion inhibitors by analyzing the microbiome. Reduced acid production changes the composition of the intestinal microbiome and reduces the diversity of bacterial species. During the long-term use of PPIs, the diversity of the microbiome decreases, due to the increased pH in the stomach, enteric infections, such as Clostridium infection, may develop.

For these reasons, the routine use of prophylactic PPIs should be considered, even in steroid-treated patients. There is currently no evidence about this in the literature, however, in the absence of a clear indication, the "cost-benefit" ratio must be taken into account when prescribing the drug, knowing the many known long-term complications of PPIs. According to the English National Health Service, the use of PPIs in addition to steroids is only recommended if the patient has a high risk of gastrointestinal bleeding. Such factors include, for example, old age, previous gastroduodenal ulcer and its complications, severe comorbidity, and the presence of other drug therapy, such as taking anticoagulants or regular non-steroidal anti-inflammatory drugs. If the patient does not have these factors, steroid treatment can also be used without PPI therapy. In our case, the patients of IBD usually belong to the younger age group, typically 20-30 years old, who rarely have the afore mentioned risk factors.

Smoking is a well-known risk factor for CD, it clearly increases the risk of relapse and the appearance of postoperative recurrence. In smoking patients, a clear pattern can be detected in the reduction of diversity in the microbiome. We assume that the combined effect of smoking and microbial changes caused by PPIs may prevail during VDZ treatment in IBD. Quitting smoking can contribute to a better outcome of the disease.

The strength of our post hoc analysis is that we obtained the data from a real cohort. In addition, this is the first study reporting the effect of PPI treatment in IBD patients treated with VDZ.

We must also mention some weaknesses of our research work. Due to the relatively small number of patients, the statistics may be biased. Due to the post hoc data analysis, the clear indication of PPI use (e.g. gastroprotection, gastroesophageal reflux disease) and upper gastrointestinal symptoms could not be properly recorded.

In summary, with our work on IBD patients, we can help choosing the right therapy in everyday practice. It is a particularly difficult task to treat ASUC and choose the right therapy at the right time to avoid colectomy. By analysing drug interactions, we pointed out that PPI treatment given without indication and considered harmless can hinder the effectiveness of biological treatment. Long-term use of PPIs can lead to the development of side effects, so careful consideration and a clear indication are always recommended before prescribing.

6. THESES

- In our study, we were the first to collect data about the long-term colectomy-free survival of patients with ASUC used CYS and IFX as bowel saving treatment.

- In the overall analysis of RCTs and observational studies, in the first three years the colectomy-free survival rate was higher in IFX-treated patients than in CYS-treated patients. This difference disappeared after the fourth year. When analysing data from only RCTs, we did not find a clearly significant difference between the use of CYS and IFX in ASUC in terms of long-term outcome.

- There was no difference in AE, SAE and mortality in IFX and CYS bowel salvage treatments in patients with ASUC.

- Further studies with a large number of patients are needed in order to be able to formulate a recommendation in second-line bowel rescue treatments.

- In our cohort study, we found no significant difference between PPI users and non-users during VDZ therapy regarding clinical and endoscopic remission at weeks 14 and 54.

- In the subgroup analysis, however, concomitant PPI therapy negatively affected the clinical response in smokers and in steroid users in VDZ-treated IBD patients.

- Based on our results, the use of PPIs is not recommended in steroid-taking IBD patients with no risk factors.

8. PUBLICATIONS

8.1. Publications supporting the dissertation

Kata Szemes, Alexandra Soós, Péter Hegyi, Nelli Farkas, Adrienn Erős, Bálint Erőss, Emese Mezősi, Zsolt Szakács, Katalin Márta, Patrícia Sarlós. Comparable Long-Term Outcomes of Cyclosporine and Infliximab in Patients With Steroid-Refractory Acute Severe Ulcerative Colitis: A Meta-Analysis. Front Med (Lausanne). 2020 Jan 21;6:338.
Q1, IF: 3,9

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Q1, IF: 4,7 (2022)

Impact factor of publicated papers supporting the dissertation: **8.6**

Impact factor of publicated papers: **44.185**

Citation: **245**

8.2. Other publications

Patrícia Sarlós, **Kata Szemes**, Péter Hegyi, András Garami, Imre Szabó, Anita Illés, Margit Solymár, Erika Pétervári, Áron Vincze, Gabriella Pár, Judit Bajor, József Czimmer, Orsolya Huszár, Péter Varju, Nelli Farkas. Steroid but not Biological Therapy Elevates the risk of Venous Thromboembolic Events in Inflammatory Bowel Disease: A Meta-Analysis. J. Crohns Colitis. 2018 Mar 28;12(4):489-498. Review. **Q1/D1, IF:7,82**

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8.3. Citable abstracts

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