Characteristics of Patients with Ulcerative Colitis treated at the University Medical Centre Ljubljana Slovenia – update from the UR-CARE Registry for the year 2022

Značilnosti bolnikov z ulceroznim kolitisom zdravljenih v Univerzitetnem kliničnem centru Ljubljana – poročilo iz UR-CARE registra za leto 2022

Mirjam Končan[1], David Drobne*[1,2]
[1]*Department of Internal Medicine, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia*
[2]*Department of Gastroenterology, University Medical Centre Ljubljana, Ljubljana, Slovenia*
Slovenian Journal of Digestive Diseases / Gastroenterolog 2023; 1: 13–19

***Keywords**: endoscopy, biological drugs, patient-reported outcomes, mucosal healing*

***Ključne besede**: endoskopija, biološka terapija, klinični indeksi, celjenje sluznice*

ABSTRACT

Background: The epidemiology of ulcerative colitis has not been reported in Slovenia since 2014. Therefore, there is a great need for an update of these data.

Aim: To characterize patients with ulcerative colitis treated in a large tertiary referral centre, University Medical Centre Ljubljana, Slovenia.

Methods: We performed a cross-sectional analysis using the UR-CARE Registry. The data were exported in October 2022.

Results: At the time of data extraction 932 patients with ulcerative colitis were treated at our centre (55%

IZVLEČEK

Izhodišče: Zadnjo posodobitev epidemioloških podatkov o ulceroznem kolitisu smo v Sloveniji napravili 2014. Posledično obstaja velika potreba po osvežitvi teh podatkov.

Namen: Opisati značilnosti bolnikov z ulceroznim kolitisom, zdravljenih v terciarnem centru (Univerzitetni klinični center Ljubljana, Slovenija).

Metode: Napravili smo presečno raziskavo s podatki, zbranimi preko registra UR-CARE. Izvoz podatkov smo napravili oktobra 2022.

Rezultati: V času zajema podatkov je bilo v našem centru zdravljenih 932 bolnikov z ulceroznim koli-

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

Received: 3/23/2023; Review: 4/5/2023; Accepted for publication: 4/20/2023

female). In 44% of these patients disease extension was pancolitis. Most patients were in clinical remission with a stool frequency score ≤ 1 in 419/507 (83%), a rectal bleeding score of 0 in 393/507 (78%) and a physician global assessment score ≤ 1 in 393/432 (91%) patients. Similarly, most patients were in biochemical remission with normal C-reactive protein in 141/178 (79%) and normal faecal calprotectin in 76/134 (75%) patients. However, among 189 patients with available recent endoscopic data only 113 (60%) patients had the endoscopically inactive disease (endo Mayo score 0 or 1). Most patients were treated with aminosalicylates, but *278/932* (41%) were treated with advanced therapy (inhibitors of TNF-alfa: 155/378 (41%), vedolizumab: 149/378 (39%), ustekinumab: 56/378 (15%), tofacitinib: 18/378 (5%)).

Conclusion: Most patients with ulcerative colitis enjoyed clinical remission. However, despite the high level of utilization of advanced treatment, many patients had endoscopically active disease.

Acknowledgements: We thank our study nurses Carmen Sekulić Bobnar, Tadeja Polanc and Andreja Planinc for help with data collection.

tisom (55 % žensk). Obseg bolezni je bil pri 44 % bolnikov pankolitis. Večina bolnikov je bila v klinični remisiji z dnevno frekvenco ≤ 1 pri 419/507 (83 %), z indeksom rektalne krvavitve 0 pri 393/507 (78 %) in globalno oceno zdravnika ≤ 1 pri 393/432 (91 %) bolnikih. Podobno je bilo z biokemično remisijo, saj je imelo normalen C-reaktivni protein 141/178 (79 %) ter normalen fekalni kalprotektin 76/134 (75 %) bolnikov. Po drugi strani pa je imelo le 113/189 (60 %) bolnikov endoskopsko neaktivno bolezen (endo Mayo 0 ali 1). Večina bolnikov je bila zdravljenih z aminosalicilati, 278/932 (41 %) pa je prejemalo napredno terapijo (zaviralce TNF-alfa: 155/378 (41 %), vedolizumab: 149/378 (39 %), ustekinumab: 56/378 (15 %), tofacitinib: 18/378 (5 %)).

Zaključek: Večina bolnikov z ulceroznim kolitisom je bila v klinični remisiji. Po drugi strani pa je imelo veliko bolnikov še vedno endoskopsko aktivno bolezen, kljub velikemu deležu bolnikov, zdravljenih z naprednimi terapijami.

INTRODUCTION

Ulcerative colitis is a subtype of inflammatory bowel disease. This lifelong condition is characterized by inflamed colonic mucosa. Clinically it manifests with flares and remissions. Disease incidence increased in the last 20 years. The condition is more prevalent in the northern, more industrialized parts of the world [1].

In Slovenia, epidemiological data on inflammatory bowel disease have not been updated since 2014. The last report by Baraga et all. indicated that the incidence of ulcerative colitis doubled in a short period from 4.6/100 000 to 8.9/100 000 inhabitants in Slovenia. Unfortunately in this report, the characteristics of the disease such as disease severity, extent and medical treatment have not been reported [2].

This study aimed to report on disease burden and treatment patterns of patients with ulcerative colitis treated at tertiary referral inflammatory bowel disease centre of the University Medical Centre Ljubljana Slovenia by analysing prospectively collected data in the UR-CARE Registry in the year 2022.

METHODS

UR CARE Registry

In this cross-sectional study, we analysed the characteristics of all patients with ulcerative colitis treated at the University Medical Centre Ljubljana Slovenia. Patient data were extracted from the UR-CARE Registry. UR-CARE registry is European Registry used to prospectively collect patient data, such as disease demographics, disease activity, complications of disease,

treatment and similar. In this report, we included 932 patients with ulcerative colitis treated in our hospital who have had at least one visit between October 2021 and October 2022 in our outpatient unit. For the report, we extracted data from the Registry on October 15, 2022.

Data extraction

We extracted the data on the demographics of the patients, such as sex, current age, age at the time of diagnosis, duration of the disease, weight and body mass index. Values were expressed as medians with interquartile ranges. We also analysed the data on disease extension, disease activity and pharmacological therapy.

Clinical and biochemical disease activity

To assess biochemical disease activity, we extracted data on biomarkers that were available in the registry. Disease activity in ulcerative colitis is typically assessed by measuring inflammatory markers such as C-reactive protein and faecal calprotectin. In our hospital, normal C-reactive protein is less than 5 mg/l. Faecal calprotectin was measured with an immunoenzymatic assay (Calprest ELISA assay, Eurospital, Trieste, Italy). Clinical disease activity was measured using a standardised partial Mayo score. Partial Mayo score assesses 3 parameters that reflect disease activity (a higher score implicates higher disease activity) (Table 1). Partial Mayo score was measured in every patient at every outpatient unit visit by a standardized questionnaire (question on stool frequency and rectal bleeding was answered by the patient, question 'physician global assessment' was answered by the treating physician or an inflammatory bowel disease specialized nurse).

Endoscopy

Patients in our hospital have endoscopies (either full colonoscopy or rectosigmoidoscopy) performed for diagnosis and to assess the response to treatment. Endoscopic disease activity was assessed using the endoscopic Mayo score (range 0 to 3, a higher score implicates higher disease activity) (Figure 1).

Pharmacological treatment

We also extracted data on current medical treatment for patients that were treated with biologicals at the time of data extraction. At that time data on conventional treatment was not yet available, therefore these are not reported here.

Table 1. The assessment of partial Mayo score through the 3 parameters. The patient can get up to 3 points for each parameter, the total possible count is 9 points

Daily stool frequency	**Rectal bleeding**	**Physician's global assessment**
Normal ***(0 points)***	None ***(0 points)***	Very well ***(0 points)***
1–2 stools more than normal ***(1 point)***	Streaks of blood less than half times ***(1 point)***	Slightly below par ***(1 point)***
3–4 stools more than normal ***(2 points)***	Obvious blood with stools more than half times ***(2 points)***	Poor ***(2 points)***
5 or more stools than normal ***(3 points)***	Blood alone passes ***(3 points)***	Very poor ***(3 points)***

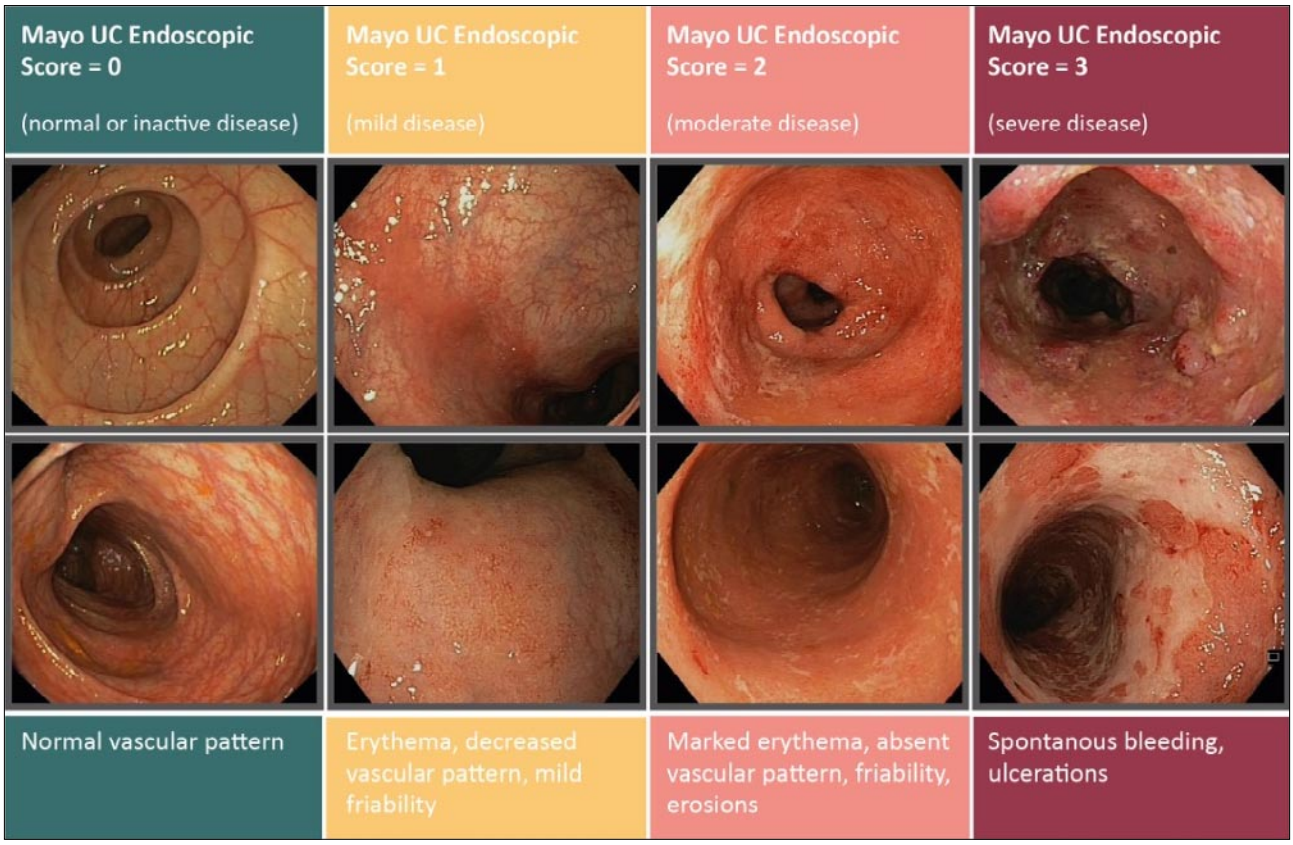

Figure 1. Endoscopic activity of ulcerative colitis (adapted from [24])

RESULTS

At the time of data extraction, 932 patients with ulcerative colitis were registered in our Inflammatory Bowel Disease unit.

Patient characteristics

Both sexes were affected almost equally with 55% of the patients being women and 45% men. The median age of the patients was 46 years (interquartile range (IQR) 35-60 years). The median age at the time of the diagnosis of ulcerative colitis was 33 years (IQR 23–46 years). Family history data on inflammatory bowel disease were available for 781/932 (84%) patients. Of these 9% had a positive family history of inflammatory bowel disease. Data on smoking were available for 771/932 (83%) patients. Nine per cent were active smokers, and 23% were former smokers. Body weight data were available for 450/932 (48%) patients. Median body weight was 74 kg (IQR 64-85 kg), median body mass index was 24.6 (IQR 21.8-28.2).

Clinical and biochemical disease activity

Clinical disease activity as assessed by partial Mayo score is shown in Table 2.

Daily stool frequency and rectal bleeding data were available for 507/932 (54%) patients. Physician's global assessment data were available for 432/932 (46%) patients.

Data on C-reactive protein was available for 178/932 (19%) patients. This was normal in 79% of patients. Faecal calprotectin measurements were available for 134/932 (14%) patients. Faecal calprotectin was below 100 mg/kg (consistent with biochemical remission) in 57% of patients.

Endoscopy

Data on maximal disease extension were available for most patients from patient documentation. In the majority of patients, the disease affected the left side

Table 2. Clinical disease activity (partial Mayo score)

Daily stool frequency	**Normal**	**1-2 stools more than normal**	**3-4 stools more than normal**	**5 or more than normal**
	306 *(60%)*	113 *(22%)*	49 *(10%)*	39 *(8%)*
Rectal bleeding	**None**	**Streaks of blood less than half time**	**Obvious blood with stool more than half times**	**Blood alone passes**
	393 *(78%)*	71 *(14%)*	40 *(7.4%)*	3 *(0.6%)*
Physician's global assessment	**Very well**	**Slightly below par**	**Poor**	**Very poor**
	317 *(73%)*	76 *(18%)*	34 *(8%)*	5 *(1%)*

of the colon (sigma and rectum). The specific data for each segment of the colon are shown in Figure 2.

Among 189 patients with available recent endoscopic data only 113 (60%) patients had the endoscopically inactive disease (endo Mayo score 0 or 1), and other patients had the active disease (endo Mayo score ≥ 2).

Current biological treatment

Among 932 patients with ulcerative colitis 378 patients (41%) were receiving biological treatment. Among these, 155/378 (41%) patients were treated with TNF-alfa inhibitors, 149/378 (39%) with anti-integrin vedolizumab, 56/378 (15%) with IL-12/23 inhibitor uste-

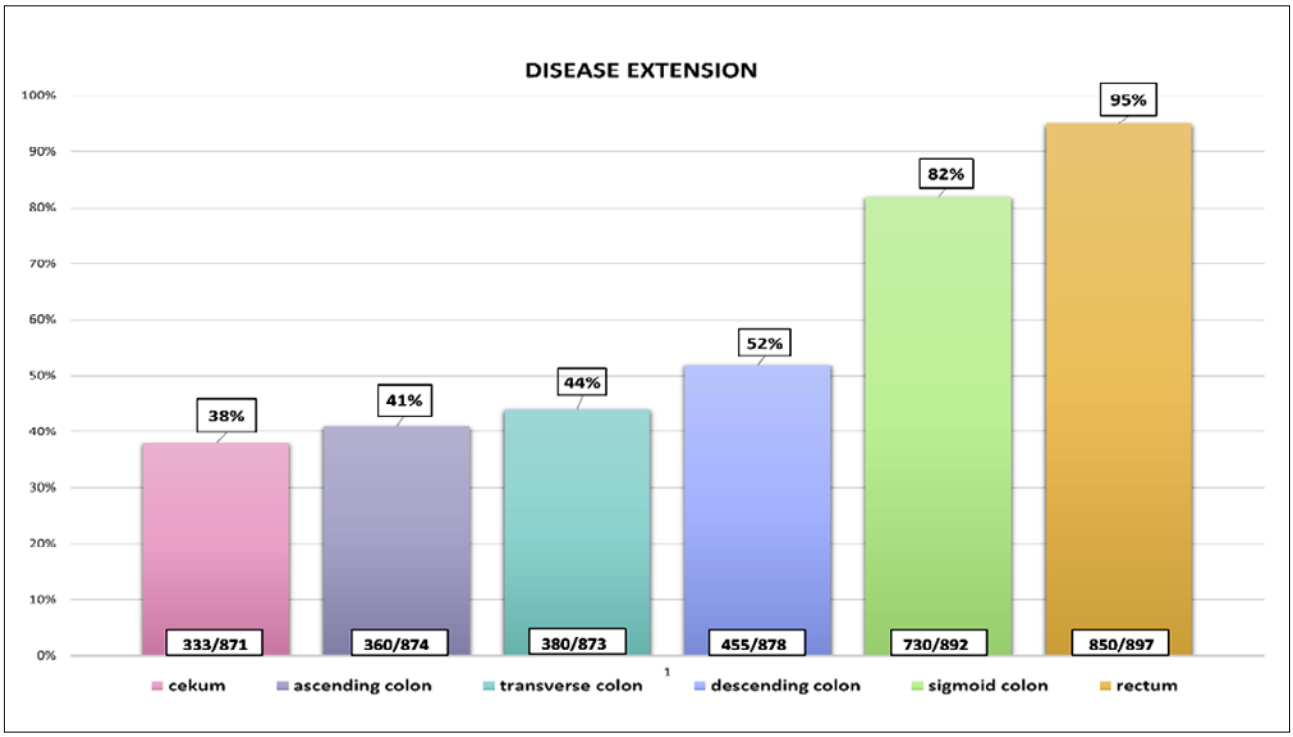

Figure 2. Disease extension in patients with ulcerative colitis

kinumab and 18/378 patients (5%) were treated with Janus kinase inhibitor tofacitinib.

DISCUSSION

In this study, we report on the phenotype and treatment patterns of patients with ulcerative colitis treated in a large tertiary referral centre. Therefore, it is not surprising that more than one-half of patients had pancolitis. Also, 41% of patients were treated with advanced therapies reflecting a resistant patient population. In general, disease control was adequate as most patients were enjoying clinical remission.

The characteristic of patients in our study is similar to those reported by other [1.3-5]. Of note, the proportion of patients with pancolitis was high, but we attributed this to the fact that our centre is a tertiary referral centre.

The majority of our patients were enjoying clinical remission. Remission rates in our cohort are generally in line with some other studies across the world [3-6]. In a Danish population study around 50% of patients were in remission at any time [7]. In another Danish study, 77% of patients with ulcerative colitis were in clinical remission [6]. Complete normalization of stool frequency was observed in only 60% of our patients. This suggests that structural changes to the bowel wall or functional disorders might drive symptom burden also after the elimination of inflammation by different treatments. However, a stool frequency score of 1 or less was present in most patients, thus the quality of life of our patients was still high. We, however, failed to record data on faecal urgency, an evolving treatment target that seems to play a major role in the quality of life of patients with ulcerative colitis [8].

According to the definition of remission [9-14] the majority of our patients were in clinical remission defined as stool frequency stool ≤1 combined with a rectal bleeding score of 0. This is reassuring since the correlation of clinical remission to endoscopic improvement is good [15]. Our remission rates reflect real-life study design since these are typically higher than those observed in clinical trials that use more stringent criteria [5, 10, 14, 16-19].

Sixty per cent of our patients achieved endoscopic improvement defined as a Mayo endoscopic score of ≤1. This reflects patient selection for endoscopy as predominantly patients with symptoms suggestive of active disease were considered for endoscopy. Still, endoscopic improvement rates were similar to those observed in clinical trials [20]. Conversely, biomarkers are part of the routine work-up of patients in our unit. Because of this, we believe that clinical scores in this cross-sectional analysis better reflect the disease activity of our cohort than endoscopy.

The majority of patients had normal C-reactive protein, consistent with disease remission. However C-reactive protein is not a reliable marker of disease activity in ulcerative colitis [21]. Roughly half of the patients in our study had elevated faecal calprotectin values. Since faecal calprotectin is part of the routine assessment of patients at our outpatient unit, we believe that this estimation of the disease activity of our cohort is valid. This reflects the huge therapeutic gap in the management of patients with ulcerative colitis.

Utilization of biologicals among our patients with ulcerative colitis was high, but in line with rates reported in Western Europe and the United States of America [22]. This reflects excellent access to biologicals in Slovenia, where all biologicals are available for the treatment of ulcerative colitis. However, the percentage of patients treated with tofacitinib was low. This could be due to the safety issues reported recently [23].

In summary, a significant proportion of patients with ulcerative colitis in Slovenia suffer from active disease, despite the high access to advanced treatments. This reflects the therapeutic gap that needs to be addressed in drug development.

References

1. Mak WY, Zhao M, Ng SC, *et al.* The epidemiology of inflammatory bowel disease: East meets west. *J Gastroenterol Hepatol* 2020; 35:380-9. doi:10.1111/jgh.14872.
2. Baraga D, Cvetko T, Ferkolj I. Epidemiology of patients with inflammatory bowel disease in general practice. *Gastroenterolog* 2014; 1:10-7.
3. Gibson PR, Vaizey C, Black CM, *et al.* Relationship between disease severity and quality of life and assessment of health care utilization and cost for ulcerative colitis in Australia: A cross-sectional, observational study. *J Crohns Colitis* 2014; 8:598-606. doi:10.1016/j.crohns.2013.11.017.
4. Solberg IC, Lygren I, Jahnsen J, *et al.* Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). *Scand J Gastroenterol* 2009; 44:431-40. doi:10.1080/00365520802600961.
5. Armuzzi A, Tarallo M, Lucas J, *et al.* The association between disease activity and patient-reported outcomes in patients with moderate-to-severe ulcerative colitis in the United States and Europe. *BMC Gastroenterol* 2020; 20:18. doi:10.1186/s12876-020-1164-0.
6. Burisch J. Occurrence, course and prognosis during the first year of disease in a European population-based inception cohort.
7. Langholz E, Munkholm P, Davidsen M, *et al.* The course of ulcerative colitis: Analysis of changes in disease activity over years. *Gastroenterology* 1994; 107:3-11. doi:10.1016/0016-5085(94)90054-X.
8. Fiorino G, Danese S, Giacobazzi G, *et al.* Medical therapy versus surgery in moderate-to-severe ulcerative colitis. *Dig Liver Dis* 2021; 53:403-8. doi:10.1016/j.dld.2020.09.022.
9. Ungaro R, Mehandru S, Allen PB, *et al.* Ulcerative colitis. *The Lancet* 2017; 389:1756-70. doi:10.1016/S0140-6736(16)32126-2.
10. Jharap B, Sandborn WJ, Reinisch W, *et al.* Randomised clinical study: discrepancies between patient reported outcomes and endoscopic appearance in moderate to severe ulcerative colitis. *Aliment Pharmacol Ther* 2015; 42:1082-92. doi:10.1111/apt.13387.
11. de Groof EJ, Rossen NGM, van Rhijn BD, *et al.* The burden of disease and increasing prevalence of inflammatory bowel disease in a population-based cohort in the Netherlands: *Eur J Gastroenterol Hepatol* 2016; 28:1065-72. doi:10.1097/MEG.0000000000000660.
12. Fluxá D, Simian D, Flores L, *et al.* Clinical, endoscopic and histological correlation and measures of association in ulcerative colitis: Correlation in ulcerative colitis. *J Dig Dis* 2017; 18:634-41. doi:10.1111/1751-2980.12546.
13. Perrig K, Krupka N, Jordi SBU, *et al.* Effectiveness of golimumab in patients with ulcerative colitis: results of a real-life study in Switzerland. *Ther Adv Gastroenterol* 2022; 15:17562848221074188. doi:10.1177/17562848221074188.
14. Muñoz-Villafranca C, Ortiz de Zarate J, Arreba P, *et al.* Adalimumab treatment of anti-TNF-naïve patients with ulcerative colitis: Deep remission and response factors. *Dig Liver Dis* 2018; 50:812-9. doi:10.1016/j.dld.2018.03.007.
15. Golovics PA, Gonczi L, Reinglas J, *et al.* Patient-Reported Outcome and Clinical Scores Are Equally Accurate in Predicting Mucosal Healing in Ulcerative Colitis: A Prospective Study. *Dig Dis Sci* 2022; 67:3089-95. doi:10.1007/s10620-021-07178-w.
16. Thunberg J, Björkqvist O, Hedin CRH, *et al.* Ustekinumab treatment in ulcerative colitis: Real world data from the Swedish inflammatory bowel disease quality register. *United Eur Gastroenterol J* 2022; 10:631-9. doi:10.1002/ueg2.12275.
17. Van Assche G, Peyrin-Biroulet L, Sturm A, *et al.* The burden of disease and patient-reported outcomes in patients with moderate to severe ulcerative colitis in the last 12 months – Multicenter European cohort study. *Dig Liver Dis* 2016; 48:592-600. doi:10.1016/j.dld.2016.01.011.
18. Sandborn WJ, van Assche G, Reinisch W, *et al.* Adalimumab Induces and Maintains Clinical Remission in Patients with Moderate-to-Severe Ulcerative Colitis. *Gastroenterology* 2012; 142:257-265.e3. doi:10.1053/j.gastro.2011.10.032.
19. Chaparro M, Garre A, Iborra M, *et al.* Effectiveness and safety of ustekinumab in ulcerative colitis: Real-world evidence from the ENEIDA registry. *J Crohns Colitis* 2021; jjab070. doi:10.1093/ecco-jcc/jjab070.
20. O'Connor A, Ford AC. Poor Correlation Between Patient-reported and Endoscopic Components of the Mayo Score in Ulcerative Colitis. *Gastroenterology* 2016; 150:1037-9. doi:10.1053/j.gastro.2016.02.054.
21. Chang S, Malter L, Hudesman D. Disease monitoring in inflammatory bowel disease. *World J Gastroenterol WJG* 2015; 21:11246-59. doi:10.3748/wjg.v21.i40.11246.
22. Armuzzi A, Tarallo M, Lucas J, *et al.* The association between disease activity and patient-reported outcomes in patients with moderate-to-severe ulcerative colitis in the United States and Europe. *BMC Gastroenterol* 2020; 20:18. doi:10.1186/s12876-020-1164-0.
23. Ytterberg SR, Bhatt DL, Mikuls TR, *et al.* Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. *N Engl J Med* 2022; 386:316-26. doi:10.1056/NEJMoa2109927.
24. Surgery in Inflammatory Bowel Disease. https://pure.uva.nl/ws/files/49602043/General_introduction_and_outline_of_the_thesis.pdf (accessed 12 Feb 2023).