Ulcerative colitis treatment : an insight into daily clinical practice

P. Bossuyt[1], F. Baert[2], J.L. Coenegrachts[3], M. De Vos[4], O. Dewit[5], M. Ferrante[6], F. Fontaine[7], F. Mana[8], J. Vandervoort[9], T. Moreels[5] : on behalf of the Belgian Inflammatory Bowel Disease Research and Development Group (BIRD)

(1) Department of Gastroenterology, Imelda GI Clinical Research, Imelda General Hospital, Bonheiden, Belgium ; (2) Department of Gastroenterology, AZ Delta, Roeselare, Belgium ; (3) Department of Gastroenterology, Jessa Ziekenhuis, Hasselt, Belgium ; (4) Department of Gastroenterology, University Hospitals Gent, Gent, Belgium ; (5) Department of Gastroenterology, UCL Saint Luc, Brussel, Belgium ; (6) Department of Gastroenterology and Hepatology, University Hospitals Leuven, KU Leuven, Leuven, Belgium ; (7) Department of Gastroenterology, Clinique Saint Joseph, Liège, Belgium ; (8) Department of Gastroenterology, UZ Brussel, Brussel, Belgium ; (9) Department of Gastroenterology, OLV Ziekenhuis, Aalst, Belgium.

Abstract

Background **: The natural history of ulcerative colitis (UC) is unpredictable. Factors associated with the need for different types of step-up therapy in UC patients failing on 5-aminosalicylic acid (5-ASA) or corticosteroids are understudied.**

Aims **: Describe step-up therapy in patients with UC the first year after failing on 5-ASA or corticosteroids.**

Methods **: A Belgian, multi-center, prospective, non-interventional observational study comprising adult UC patients failing on 5-ASA or corticosteroids and naïve to immunomodulators/ biologicals. During a 12 months follow-up, patient characteristics, demography, medical therapy, biomarkers, therapy adherence and quality of life (QoL) were assessed.**

Results **: After 1 year, 35% of the patients were on biological therapy. Use of anti-TNF differed depending on baseline treatment: corticosteroid-refractory patients (55.8%), 5-ASA refractory (20.0%), and corticosteroid-dependent (16.0%) patients ($p<0.001$). The decision to start a line of therapy was based on the Mayo combined severity but not on biomarkers like faecal calprotectin, haemoglobin, CRP, albumin, platelets, and number of extra-intestinal manifestations. At year 1, 84.2% of the patients had only mild UC or remission and a significant improvement of fatigue ($p=0.004$) and IBDQ scores ($p<0.001$) were observed implying an improved QoL.**

Conclusion **: Treatment step-up, based on clinical scores in immunomodulatory and anti-TNF naïve patients with UC, provides good clinical outcomes and QoL.** (Acta gastroenterol. belg., **2019**, 82, **365-372**).

Key words : step-up therapy, immunomodulators, anti-TNF, clinical scores.

1. Introduction

Ulcerative colitis (UC) is a chronic and debilitating immunomediated inflammatory bowel disorder arising from an inappropriate interaction between gut microbiota and environmental factors in a genetically predisposed individual (1,2). Well-established factors influencing the risk for UC are a family history of UC, previous smoking, and absence of appendectomy (3,4,5).

The natural course of UC is generally characterized by flares of (bloody) diarrhea that alternate with periods of remission, although some patients have continuous activity (6). The severity of flares and their response to treatment are difficult to predict, although the frequency of flares decreases with time (6,7).

The treatment strategy for UC is mainly based on disease severity, extent of involvement (proctitis, left-sided, extensive colitis), disease course, age at onset, and disease duration (8). It aims at inducing and maintaining clinical and endoscopic remission and providing an improved quality of life with minimal steroid exposure (9,10).

Apart from acute severe colitis, UC treatment comprises a gradual step-up approach. Aminosalicylates are baseline treatments for inducing remission in mild to moderate UC. Sequential treatments are introduced to achieve clinical and endoscopic remission. In this step-wise approach a sequence of corticosteroids, immunomodulators, biological therapies and ultimately colectomy is followed (8). Colectomy is necessary in about 20% to 30% of UC patients within 25 years after diagnosis (6).

Despite defined treatment algorithms, there are few data on current practice or adherence to treatment algorithms. There is also little data allowing prediction of treatment success in UC, especially for failing aminosalicylates and steroids.

Therefore, additional data are needed to predict treatment success and to refine the existing treatment algorithms in UC.

This prospective observational study assessed the step-up treatment in patients with UC failing on 5-aminosalicyclic acid (ASA) and/or steroids in daily practice in Belgium. The aim of this study was to assess how UC is currently being treated in Belgium, to determine whether this current practice agreed with international therapeutic guidelines (8), and to identify clinical and biochemical factors influencing therapeutic decision making.

2. Materials and Methods

2.1 Population

This was a Belgian, multi-center, prospective, non-interventional observational study in patients with UC.

Correspondence to : Dr. Peter Bossuyt, Imelda Ziekenhuis, 9 Imeldalaan, 2820 Bonheiden, Belgium.
Peter.Bossuyt@imelda.be

Submission date : 04/02/2019
Acceptance date : 07/02/2019

The patients were enrolled between March 18th 2013 and March 13th 2015 in 17 centers. The last follow-up visit was on April 1st 2016. The study included consecutive adult patients diagnosed with UC who had failed treatment with 5-ASA or corticosteroids. The following patient categories were considered : 1) 5-ASA refractory = failing treatment with at least 2g of 5-ASA for at least 4 weeks ; (2) corticosteroid-dependent = relapse during tapering period or within 3 months after a course of steroids ; (3) corticosteroid-refractory = not responding to one week intravenous 40 mg prednisolone or 32 mg methyl prednisolone orally for 1 week.

All patients were naive to immunomodulators or biologicals and were followed for 12 months. All trial related assessments were regarded as part of common practice in Belgium. Participating investigators were members of the Belgian Inflammatory Bowel Disease Research and Development group (BIRD). The study was conducted in accordance with the Ethical principles stated in the Declaration of Helsinki 2008 and in compliance with the principles of Good Clinical Practice (GCP), according to the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline. Prior to initiation of the study at any site, the study, including the protocol (P0000 302-00), informed consent, and other study documents, was approved by an appropriate Independent Ethics Committee (IEC) of the Antwerp University Hospital and the IECs of the participating centres.

2.2 Trial assessments

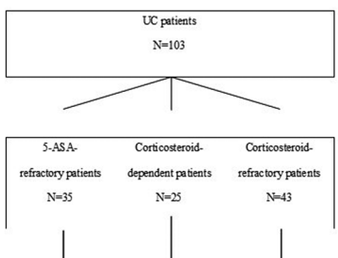
No standardised follow-up was implemented by the study protocol. Outpatient visits or hospitalisations were based on the patients' clinical evolution. Every patient contact (scheduled or unscheduled) during the 12 month of follow-up was registered in the study. At each visit, the following evaluations were performed whenever deemed necessary by the treating physician: Physical examination (weight; height only at baseline), UC-related and concomitant medications, patient demographics, clinical data based on MAYO score (10), extra-intestinal manifestations, laboratory data (faecal calprotectin, haemoglobin, C-reactive protein, albumin, platelet count), and patient questionnaires (see Supplementary data) [Visual analogue scale (VAS) for fatigue (11,12), Inflammatory Bowel Disease Questionnaire (IBDQ) (13), 8-item Morisky Medication Adherence Scale (MMAS-8) (14).

2.3 MAYO disease activity score

The full MAYO score was used to assess the UC disease activity. The total score category was defined as remission (0 to 2), mild (3 to 5), moderate (6 to 10), or severe disease (11 to 12) (10). The partial score category (without endoscopic score) was defined as remission (0 to 1), mild (2 to 4), moderate (5 to 6), or severe disease (7 to 9). MAYO combined severity was applied according to specific categories (remission, mild, moderate or severe) of the total score category if all 4 items have been scored, or the partial score category if only the 3 non-invasive items have been assessed.

2.4 Lines of therapy

Successive lines of therapy (or combinations of lines) were determined for each patient based on the list of



5-ASA-refractory patients N=35	Corticosteroid-dependent patients N=25	Corticosteroid-refractory patients N=43	All patients	Line	Therapy	Products
34 (97.1%)	35 (100%)	38 (88.4%)	97 (94.2%)	1	5-ASA	Mesalazine, sulfasalazine
32 (91.4%)	17 (68.0%)	41 (95.3%)	90 (87.4%)	2	Corticosteroids	(Methyl)prednisolone, beclomethasone diproprionate, budesonide
16 (45.7%)	17 (68.0%)	29 (67.4%)	62 (60.2%)	3	Immunomodulators	Azathioprine, 6-mercaptopurine, methotrexate, cyclosporine
7 (20.0%)	4 (16.0%)	24 (55.8%)	35 (34.0%)	4A	Anti-TNF molecules	Infliximab, adalimumab, golimumab
0 (0%)	0 (0%)	1 (2.3%)	1 (1.0%)	4B	Anti-adhesion molecule	Vedolizumab
1 (2.9%)	1 (4.0%)	3 (7.0%)	5 (4.9%)	5	Non-registered study medication	
0 (0%)	1 (4.0%)	1 (2.3%)	2 (1.9%)	6	Surgery	

Figure 1. — Use of therapy lines.

UC medications in the stepwise treatment approach. The following lines were considered : 1) line 1 : 5-aminosalycylates ; 2) line 2: corticosteroids ; 3) line 3 : immunomodulators ; 4) line 4A : any anti-tumor necrosis factor (anti-TNF) molecule ; 5) line 4B : anti-adhesion molecule vedolizumab ; 6) line 5 : any non-registered study medication ; 7)ine 6 : surgery (Figure 1). The start of a line of therapy corresponded to the start of the first combination in which the line was used and the end corresponded to the end of the last combination in which the line was used. If between the start and end of a line a period occurred during which the line was not used, this defined a new episode. The duration of a line of therapy was calculated as the median time to discontinuation of the first course.

2.5 Statistical analysis

The statistical analysis was performed using the Statistical Analysis System (SAS) package for Windows, Version 9.2 (SAS Institute Inc., Cary, NC, USA). This was an observational study. The comparison of baseline data in the 3 patient categories (5-ASA refractory patients, corticosteroid-dependent patients, corticosteroid-refractory patients), was performed using the Kruskal-Wallis test for quantitative and ordinal variables and the Fisher Exact test for binary variables. The relation between patient questionnaire data and MAYO combined severity was analysed by means of the Spearman correlation coefficient, and the relation between treatment adherence and clinical and laboratory data by means of the Pearson correlation coefficient.

The use of lines 3 and 4A of treatment was compared in the 3 patient categories by means of the Fisher Exact test. The relation between the use of line 3 and 4A of treatment and MAYO combined severity at baseline was compared by means of the Mann-Whitney test.

Time to event variables were analysed using Kaplan-Meier survival analysis and COX proportional hazards regression. Lines 3 and 4A were compared : 1) For time

Table 1. — **Demographics and clinical patient population information**

	5-ASA refractory	Corticosteroid-dependent	Corticosteroid-refractory	All patients
Number of patients	35	25	43	103
Age (year)				
Median	40.2	39.4	38.6	40.0
Inter quartile range	29.4 to 52.0	33.4 to 52.6	30.0 to 54.7	30.0 to52.6
p-value		p= 0.939		
Gender (N, %)				
Female	19 (54.3%)	11 (44.0%)	17 (39.5%)	47 (45.6%)
Male	16 (45.7%)	14 (56.0%)	26 (60.5%)	56 (54.4%)
p-value		p= 0.425		
Smoking status (N, %)				
Never	19 (54.3%)	12 (48.0%)	17 (39.5%)	48 (46.6%)
Current	0 (0.0%)	2 (8.0%)	1 (2.3%)	3 (2.9%)
Previous	16 (45.7%)	11 (44.0%)	25 (58.1%)	52 (50.5%)
p-value		p= 0.435		
Time since diagnosis of UC (months)				
Median	17.1	31.4	12.6	17.1
Inter quartile range	3.9 to 88.2	9.1 to 112.8	3.2 to 77.9	4.4 to 84.7
p-value		p= 0.284		
Family history of UC (N, %)				
Yes	18 (51.4%)	8 (34.8%)	15 (34.9%)	41 (40.6%)
No	17 (48.6%)	15 (65.2%)	28 (65.1%)	60 (59.4%)
p-value		p= 0.282		
Most frequent family history non-UC (N, %)				
Crohn's disease	5 (14.3%)	2 (8.7%)	4 (9.3%)	11 (10.9%)
Rheumatoid arthritis	4 (11.4%)	1 (4.3%)	3 (7.0%)	8 (7.9%)
History of appendectomy (N, %)				
Yes	5 (14.3%)	2 (8.0%)	3 (7.0%)	10 (9.7%)
No	30 (85.7%)	23 (92.0%)	40 (93.0%)	93 (90.3%)
p-value		p= 0.587		
Regrouped extent of disease (N, %)				
Ulcerative proctitis	9 (26.5%)	2 (8.0%)	12 (27.9%)	23 (22.5%)
Left-sided UC	19 (55.9%)	17 (68.0%)	14 (32.6%)	50 (49.0%)
Extensive UC	6 (17.6%)	6 (24.0%)	17 (39.5%)	29 (28.4%)
p-value		p= 0.324		

UC= ulcerative colitis, N= number of patients.

to initiation of the lines using a log-rank test ; 2) For CRP and platelets at initiation of the line by the Wilcoxon test; and 3) For MAYO combined severity score at initiation of the line by means of the Cochran-Armitage Trend test. For this analysis patients initiating Lines 3 and 4A at the same time were disregarded and if both were started consecutively the first line was considered.

All statistical tests were performed two-sided, at the 5% level of significance.

3. Results

3.1 Patient demographics and clinical information

The study included 115 consecutive adult patients diagnosed with UC failing treatment with 5-ASA and/or corticosteroids. Six patients were lost to follow-up during the observation period and 6 other patients were excluded from the analysis since they were previously treated with immunomodulators. The 103 remaining patients constituted the analysis set.

Three patient categories were considered : 5-ASA refractory patients (n=35), corticosteroid-dependent patients (n=25), and corticosteroid-refractory patients (n=43).

Table 1 provides an overview of the demographics and clinical information for all patients and broken down by category. No significant differences were found between the 3 patient categories for age, gender, smoking status, time since diagnosis of UC, and family history of UC.

At inclusion, CRP level was available for 58 patients and 58.6% of them showed elevated CRP (CRP>5 mg/L). Hemoglobin and platelet count were available for 59 patients and 33.9% were anaemic (Hb<12 g/dL) and an elevated platelet count (TRC>319-450x10^9/L) was seen in 32.2%. Albuminemia was only available for 21 patients and hypoalbuminemia (albumin <32 g/L) was present in 23.8% at time of inclusion. In only 7 patients faecal calprotectin was assessed at inclusion, all of which were elevated (calprotectin >250 mg/kg).

3.2 Evolution of extent of disease and disease activity

At inclusion, the extent of disease was ulcerative proctitis for 22.6% of the patients, left-sided UC for 49.0%, and extensive UC for 28.4%. At Year 1, the extent of disease improved to 45.5% for ulcerative proctitis, 40.0% for left-sided UC, and only 14.5% for extensive UC.

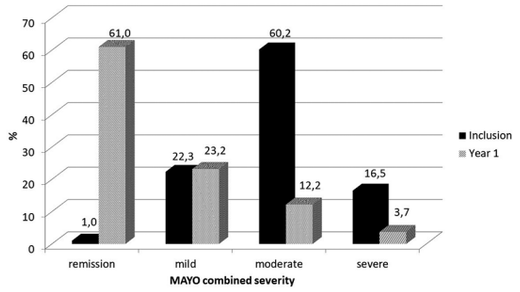


Figure 2. — MAYO combined severity at inclusion and Year 1.

At inclusion, the median MAYO disease activity was 8.0 for the total score (n= 76) and 5.0 for the partial score (n= 103). Based on the MAYO combined severity, 16.5% of the patients had severe disease, 60.2 % moderate disease, 22.3% mild disease, and 1.0% were in remission. There was no statistically significant difference in disease activity at the time of inclusion between the 3 patient categories.

At Year 1, only 3.7% of the patients had severe disease, and only 12.2 % moderate disease, whereas 23.2% had mild disease and 61.0% were in remission (Figure 2). The severity category improved for 78.0% of the patients, whereas it remained unchanged in 17.1% and worsened in 4.9%.

3.3 Treatment adherence

At inclusion, the median MMAS-8 total score was 8.0 (Interquartile range (IQR): [6.8 ; 8.0]) representing high adherence levels. At Year 1 it was still 8.0 (IQR: [7.0 ; 8.0]) (Table 2). However, at inclusion, 16.5% of the patients had low treatment adherence (MMAS-8 score <6), 30.1% had medium adherence (MMAS-8 score 6-7), and 53.4% were likely adherent (MMAS-8 score ≥8). At Year 1, these frequencies were 9.6%, 34.2%, and 56.2%, respectively. The adherence category remained

Table 2. — **Patient questionnaires at inclusion and Year 1 (median [IQR])**

	Inclusion			Year 1	
MAYO Combined Severity Category	VAS for fatigue (mm)	IBDQ	MMAS-8	VAS for fatigue (mm)	IBDQ
Remission	29.2 [29.2-29.2]	6.1 [6.1-6.1]	8.0 [8.0-8.0]	22.0 [7.3-53.0]	6.2 [5.8-6.5]
Mild disease	47.5 [27.3-53.1]	5.1 [4.8-5.8]	7.0 [6.5-8.0]	22.9 [8.0-54.0]	6.2 [5.6-6.3]
Moderate disease	48.5 [15.0-66.0]	4.4 [3.7-5.2]	8.0 [7.0-8.0]	61.0 [36.6-82.5]	3.7 [3.2-4.5]
Severe disease	68.4 [39.0-83.0]	3.6 [3.0-4.2]	7.0 [6.0-8.0]	48.0 [10.0-70.4]	5.0 [4.3-5.6]
All patients	52.0 [19.0-67.0]	4.5 [3.7-5.3]	8.0 [6.8-8.0]	30.0 [8.5-59.6]	6.0 [5.5-6.4]
r	0.265	-0.438	-0.021	0.155	-0.460
p-value	0.007	<0.001	0.835	0.193	<0.001

IQR = interquartile range, VAS = visual analogue scale, IBDQ = inflammatory bowel disease questionnaire, MMAS-8 = 8-item Morisky medication adherence scale, mm = millimeter, r = Spearman correlation coefficient

unchanged in 61.6% of the patients, it improved in 20.5% and became worse in 17.8%.

No significant correlation was found between MMAS-8 total score and MAYO combined severity at inclusion (p=0.835) nor at Year 1 (p=0.723).

However, based on the data at Year 1, significant inverse correlations were found between MMAS-8 total score and VAS for fatigue (r=-0.247; p=0.012), and between MMAS-8 total score and number of extra-intestinal symptoms (r=-0.216; p=0.029), which means that patients with more fatigue and more extra-intestinal manifestations were less adherent. No significant correlations were found between MMAS-8 total score and faecal calprotectin, haemoglobin, CRP, platelets, albumin, MAYO score, and number of corticosteroid courses during the study.

3.4 Patient questionnaires

A positive correlation was found between VAS for fatigue and MAYO combined severity at inclusion (r=0.265; p=0.007), but not at Year 1, probably related to the fact that more patients were in remission at Year 1. Moreover, the median VAS score for fatigue significantly improved during the study period: from 52.0 mm (IQR : [19.0 ; 67.0]) to 30.0 mm (IQR : [8.5 ; 59.6]) (p=0.004). An inverse correlation was found between IBDQ total score and MAYO combined severity both at inclusion (r= -0.438 ; p=<0.001) and at Year 1 (r= -0.460 ; p=<0.001) which means that patients with a more severe state of the disease had a lower quality of life, both at the beginning and at the end of the study period. However, total IBDQ score significantly improved during the study period: from 4.5 (IQR : [3.7 ; 5.3]) to 6.0 (IQR : [5.5 ; 6.4]) (p<0.001).

3.5 Lines of therapy

The vast majority of the patients (94.2%) used 5-ASA at any time during the study. Furthermore, 87.4% used corticosteroids, 60.2% immunomodulators (Line 3), 34.0% anti-TNF therapy (Line 4A), 1.0% used vedolizumab (Line 4B), 4.9% any non-registered study medication and 1.9% had surgery (Figure 1). Of the 87.4% of patients who received corticosteroids during the study, 68.0% had 1 course, 11.7% two courses, and 7.8% three courses.

Anti-TNF therapy was mostly used by baseline corticosteroid-refractory patients (55.8%), followed by 5-ASA refractory (20.0%) and corticosteroid-dependent patients (16.0%) (p<0.001). For the use of immunomodulators no difference was found between the 3 patient categories (p=0.107) (Table 3).

Anti-TNF therapy was used by 8.7% of the patients who presented mild disease at inclusion, 40.3% with moderate disease, and 47.1% with severe disease (p=0.025). Immunomodulator use at any time during the study was independent of severity of the disease at baseline (p=0.337). Considering the type of anti-TNF medication (n=35), 51.4% of the patients used infliximab during the study, 22.9% adalimumab, 14.3% golimumab, and 11.4% used different types of anti-TNF sequentially.

Of the 35 patients (34%) on anti-TNF at any time during the study, 19 (54.3%) were on combination therapy (anti-TNF and immunomodulators), 11 (31.4%) on monotherapy, and 5 (14.3%) used immunomodulators and anti-TNF sequentially but never concomitantly. Combination therapy was predominantly used in corticosteroid-refractory patients (p=0.002) (Table 3).

The median time to initiation of immunomodulators and anti-TNF therapy after inclusion was 1 day (95% CI: [0.0; 10.0]) and 55 days (95% CI: [29.0; 140.0]), respectively. The median treatment duration of immunomodulators was 253 days for corticosteroid-dependent patients. It could not be calculated for the other patient categories due to too short follow-up data.

In univariate analysis, the time to discontinuation of immunomodulators was significantly associated with MAYO partial score within 30 days before treatment switch (p=0.046), smoking status (p=0.034), and history of appendectomy (p=0.009). In a stepwise multivariate analysis it appeared that MAYO partial score and history of appendectomy were significant independent prognostic factors of shorter duration of immunomodulatory therapy

Table 3. — **Overview of the use of immunomodulators and anti-TNF therapy at any time during the study by patient category**

	5-ASA refractory (N=35)	Corticosteroid-dependent (N=25)	Corticosteroid-refractory (N=43)	All patients (N=103)
Number of patients (%)				
Line 3 ever used	16 (45.7)	17 (68.0)	29 (67.4)	62 (60.2)
Line 4A ever used	7 (20.0)	4 (16.0)	24 (55.8)	35 (34.0)
Line 3 and not Line 4A	13 (37.1)	15 (60.0)	10 (23.3)	38 (36.9)
Line 4A and not Line 3	4 (11.4)	2 (8.0)	5 (11.6)	11 (10.7)
Lines 3 and 4A ever used concomitantly	2 (5.7)	2 (8.0)	15 (34.9)	19 (18.4)
Lines 3 and 4A never concomitantly	1 (2.9)	0 (0.0)	4 (9.3)	5 (4.9)
Median [95% CI] of time to initiation of therapy line (months)				
Line 3	10.5 [0–49]	0.0 [0.-1]	0.0 [0-22]	1.0 [0-10]
Lines 4A	97.0 [17-262]	33.5 [0-148]	57.5 [2-181]	55.0 [29-140]

Line 3 = immunomodulators, Line 4A = anti-TNF therapy, N = number of patients, CI = confidence interval.

Table 4. — **Time to failure/discontinuation of immunomodulator therapy**

Cox proportional Hazards regression	Hazard ratio	95% Wald CI	p-value
Univariate regression			
Age	1.017	[0.995-1.040]	0.122
Gender	0.917	[0.424-1.985]	0.826
Smoking status	2.468	[1.069-5.701]	0.034
Marital status	2.240	[0.844-5.948]	0.105
VAS for fatigue at baseline	1.002	[0.987-1.016]	0.833
Faecal calprotectin at baseline	1.000	[0.997-1.002]	0.786
Haemoglobin at baseline	1.000	[0.987-1.023]	0.974
CRP at baseline	1.000	[0.991-1.009]	0.999
Albumine at baseline	1.237	[0.951-1.607]	0.112
Platelets at baseline	0.997	[0.992-1.001]	0.161
Number of days not able to perform normal activity since last treatment change (*)	0.990	[0.971-1.010]	0.322
MAYO partial score at baseline	0.907	[0.739-1.113]	0.351
MAYO partial score (*)	1.192	[1.003-1.417]	0.046
CRP (*)	1.001	[0.992-1.009]	0.906
Other immune related pathologies	0.805	[0.241-2.684]	0.724
History of appendectomy	3.403	[1.350-8.577]	0.009
Any extra-intestinal symptoms	2.570	[0.967-6.833]	0.058
Montreal classification Left-sided UC versus extensive UC or pancolitis Proctosigmoiditis versus extensive UC or pancolitis	 0.464 0.717	 [0.183-1.174] [0.276-1.866]	 0.105 0.495
Multivariate regression			
History of appendectomy	4.663	[1.429-15.218]	0.011
MAYO partial score (*)	1.234	[1.030-1.479]	0.023

CI = confidence interval, (*) = parameter evaluated at the last visit within 30 days before the treatment switch.

(p=0.023 and p=0.011, respectively) (Table 4). The analysis of time to discontinuation of the first course of anti-TNF therapy using Cox proportional hazards showed no significant prognostic factors.

At the start of a treatment course of immunomodulators patients (n=59) had a mean VAS for fatigue of 44.4 mm (SD: 27.4), whereas it was increased up to 59.3 mm (SD: 21.7) at the start of a course of anti-TNF therapy (n=27).

No statistical differences were found in levels of faecal calprotectin, haemoglobin, CRP, albumin, platelets, and in the number of extra-intestinal manifestations at the start of both therapy lines. Also, no statistical difference was found between the number of days not able to perform normal daily activity or the indication for surgical treatment at the start of both therapy lines since inclusion.

When a course of immunomodulators was started, 30.0% of the patients had a MAYO combined severity category of remission/mild disease, 60.0%, had moderate disease, and 10.0% had severe disease. However, at the start of an anti-TNF treatment course, 7.6% had mild disease, 46.2% had moderate disease, and 46.2% had severe disease, showing a statistically significant difference between the 2 therapy lines (p=0.008), which indicates that immunomodulators were initiated in case of mild to moderate disease and anti-TNF therapy was mainly initiated in case of moderate to severe disease.

4. Discussion

We studied the step-up treatment of patients with UC failing on 5-ASA and/or steroids in daily practice.

The European Crohn and Colitis Organization (ECCO) guidelines on the management of UC recommend therapy based on severity and extent of disease, prior response to therapy and quality of life indices (8). A sequential step-up treatment with 5-ASA, corticosteroids and immunomodulators constitutes the conventional therapy. If this conventional therapy fails after 3 months of treatment biologicals are added to induce or maintain sustained remission.

In this study, after 1 year 35% of all patients were on biological therapy. In these patients we observed a rapid step-up approach with a median time to initiation of biological treatment of less than two months. As expected, anti-TNF treatment was mostly used by corticosteroid-refractory patients (55.8%), followed by 5-ASA refractory (20.0%), and corticosteroid-dependent (16.0%) patients while no difference was found between the 3 patient categories for the use of immunomodulators during the study. This illustrates that anti-TNF treatment is becoming more popular, whereas use of conventional immunomodulators in UC is declining. From the complete cohort only 18.4% used combination therapy (immunomodulators and anti-TNF), mainly

corticosteroid-refractory patients. Combination therapy seems underused in daily clinical practice, with only half of the patients having co-treatment with IMM during anti-TNF use.

The Mayo score remains an import evaluation tool in clinical practice. The decision to start a specific line of therapy is based on the patients' Mayo score (partial or total). It was shown that the start of anti-TNF therapy correlated well with moderate to severe disease while the start of immunomodulators with mild to moderate disease.

Despite of recent ECCO guidelines, this cohort showed that biomarkers like faecal calprotectin, haemoglobin, CRP, albumin, platelets, and number of extra-intestinal manifestations, although widely available in the participating centers, were not the drivers of treatment decisions since they are underused and no difference was seen between initiation of immunomodulators and anti-TNF. For example, the use of faecal calprotectin was negligible (7%) in therapeutic decision making. Currently, faecal calprotectin testing is not reimbursed and therefore underused. Nevertheless, its importance as a non-invasive and objective measure of disease activity that can be monitored during follow-up has been shown previously (2).

The accelerated stepwise approach led to good clinical outcomes at 1 year, with 84.2% of the patients having only mild UC or remission. Furthermore, a significant improvement of fatigue (VAS: 47.2 mm to 34.1 mm) and IBDQ scores (4.5 to 6.0) were observed during the study period implying an improved quality of life. This is in line with the study of Knowles *et al*. (15) which showed that QoL was significantly poorer for IBD individuals with active disease relative to when it was quiescent. However, the observed improvement of fatigue is not in line with the reported long-term presence of fatigue in literature (16).

This study has some limitations. Since this is an observational study without any prior defined treatment strategy, no conclusion can be drawn on a specific outcome linked to a specific treatment though the primary aim was to describe the daily clinical practice in these specific patient cohorts. Secondly, the follow-up period of the study is only one year, hence long term outcomes are not available, but the high clinical remission rate at one year suggests a long term effect of the treatment decisions.

In conclusion, an accelerated step-up approach in patients with UC failing on 5-ASA or steroids leads to a good clinical outcome at 1 year with high remission rates and significant improvements in fatigue and quality of life. Immunomodulators are initiated early in patients flaring on 5-ASA or steroids, and up to 34% will be on anti-TNF treatment within 1 year, with corticosteroid-refractory patients having the highest exposure. Combination therapy is not used very often in daily clinical practice. The gradual step-up and the acceleration of the therapy are based on clinical scores guides, not on serological biomarkers or faecal calprotectin levels.

5. Acknowledgements

The authors thank the patients and their caregivers in addition to the investigators (Members of the Belgian Inflammatory Bowel Disease Research and Development Group) and their teams who participated in this study: De Mayer Marc, Rahier Jean-Francois, Louis Edouard, D'Heygere Francois, Caenepeel Philip, de Suray Nicolas, Coche JC, Abdo El Nawar, and Delen Stefan. The authors acknowledge An Verloes, from Data Investigation Company Europe (DICE NV), for medical writing and editorial assistance in preparing this manuscript for publication based on the authors' input and direction. All costs associated with the development of this manuscript were funded by MSD Belgium.

6. Funding

This work was supported through an unrestricted MSD Belgium, who funded this study and manuscript.

Peter Bossuyt: Speakers and advisory fee : MSD, Genetech Roche, Takeda, AbbVie, Mundipharma, Janssen, Dr. Falk Pharma; Grants: Janssen, Mundipharma and AbbVie.

Filip Baert : Speakers fee: AbbVie, Falk, Ferring, Janssen, Pfizer, Takeda; Grant: MSD ; Grant for department: AbbVie, Chiesi, Roche, Ipsen; Consultancy: Ferring, Janssen, Mundipharma, MSD, Pfizer, Takeda, Celgene ; CEO of IBDIM as of October 2018.

Jean-Louis Coenegrachts : no conflict of interest.

Martine De Vos : no conflict of interest.

Olivier Dewit : no conflict of interest.

Marc Ferrante : Research grant: Janssen, Takeda ; Consultancy : Abbvie, Boehringer-Ingelheim, Ferring, Janssen, Mitsubishi Tanabe, MSD, Pfizer, Takeda ; Speakers fee : Abbvie, Boehringer-Ingelheim, Chiesi, Ferring, Janssen, Lamepro, Mitsubishi Tanabe, MSD, Pfizer, Takeda Tillotts, Tramedico, Zeria.

Fernard Fontaine : no conflict of interest.

Fazia Mana : Grant from AbbVie.

Jo Vandervoort : no conflict of interest.

Tom Moreels : Speakers fee from Olympus, ERBE, MSD.

7. References

1. ANANTHAKRISHNAN A. Epidemiology and risk factors for IBD. *Nat. Rev. Gastroenterol. Hepatol.*, 2015, **12** : 205-17.
2. MAGRO F., GIONCHETTIE P., ELIAKIM R., ARDIZZONE S., ARMUZZI A., BARREIRO-DE ACOSTA M. *et al.* Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. *J Crohns Colitis*, 2017, **11** : 649-70.
3. HIGUCHI L.M., KHALILI H., CHAN A.T., RICHTER J.M., BOUSVAROS A., FUCHS C.S. A prospective study of cigarette smoking and the risk of inflammatory bowel disease in woman. *Am. J. Gatroenterol*., 2012, **107** : 1399-1406.
4. ABEGUNDE A.T., MUHAMMAD B.H., BHATTI O. *et al.* Environmental risk factors for inflammatory bowel diseases: Evidence based literature review. *World J. Gastroenterol.,* 2016, **22** : 6296-317.

5. SAHAMI S., KOOIJ I.A., MEIJER S.L., VAN DEN BRINK G.R., BUSKENS CJ., TE VELDE A.A. The link between the appendix and ulcerative colitis: clinical relevance and potential immunological mechanisms. *Am J. Gastroenterol.,* 2016, **111** : 163-69.
6. COSNES J., GOWER-ROUSSEAU C., SEKSIK P., CORTOT A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology,* 2011, **140** : 1785-94.
7. BOLGE S.C., WATERS H., PIECH C.T. Self-reported frequency and severity of disease flares, disease perception, and flare treatments in patients with ulcerative colitis: results of a national internet-based survey. *Clin. Ther.,* 2010, **32** : 238-45.
8. HARBORD M., EILIAKIM R., BETTENWORTH D., KARMIRIS K., KATSANOS K., KUPYLOV U. *et al*. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. *J. Crohns Colitis*, 2017 ,**11** : 769-84.
9. KORNBLUTH A., SACHAR D.B. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am. J. Gastroenterol.,* 2011**, 105** : 501-23.
10. PEYRIN-BIROULET L, SANDBORN W, SANDS BE, REINISH W., BEMELMAN W, BRYANT RV. *et al*. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining therapeutic goals for treat-to-target. *Am. J. Gastroenterol.,* 2015 ,**110** : 1324-38.
11. SCHROEDER K.W., TREMAINE W.J., ILSTRUP D.M. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N. Engl. J. Med.,* 1987, **317** : 1625-9.
12. COLANGELO K., HAIG S., BONNER A., ZELENIETZ C., POPE J. Self-reported flaring varies during the menstrual cycle in systemic lupus erythematosus compared with rheumatoid arthritis and fibromyalgia. *Rheumatology (Oxford),* 2010, **50** : 703-8.
13). TREHARNE G.J., LYONS A.C., HALE E.D., GOODCHILD C.E., BOOTH D.A., KITAS G.D. Predictors of fatigue over 1 year among people with rheumatoid arthritis. *Psychol. Health Med.,* 2008, **13** : 494-504.
14. GUYATT G., MITCHELL A., IRVINE E.J., SINGER J., WILLIAMS N., GOODACRE R. *et al*. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology*, 1989, **96** : 804-10.
15. KANE S., BECKER B., HARMSEN W.S., KURINA A., MORISKY D.E., ZINSMEISTER A.R. Use of a screening tool to determine nonadherent behavior in inflammatory bowel disease. *Am. J. Gastroenterol.,* 2012, **107** : 154-60.
16. KNOWLES S.R., KEEFER L., WILDING H., HEWITT C., GRAFF L.A., MIKOCKA-WALUS A. Quality of Life in Inflammatory Bowel Disease: A Systematci Review and Meta-analyses – Part II. *Inflamm. Bowel. Dis.,* 2018, **24** : 966-76.
17. GRAFF L.A., CLARA I., WALKER J.R. , LIX L., CARR R., MILLER N. *et al*. Changes in fatigue over 2 years are associated with activity of inflammatory bowel disease and psychological factors. *Clin. Gastroenterol. Hepatol.,* 2013, **11** : 1140-46.

8. Supplementary data

Visual analogue scale (VAS) : A horizontal Likert scale used to evaluate the degree of fatigue experienced by the patients, and ranging from 0 (no fatigue) to 10 (extremely tired) (12,13).

IBDQ : An interviewer administered, disease-specific questionnaire consisting of 32 items, divided into 4 domains: Bowel symptoms, emotional function, systemic symptoms, and social function, each ranging between 1 (worst function) and 7 (best function) (14). The IBDQ total score is 32 times the sum of the available scores divided by their number. The scores for the 4 domains (=scale scores) were calculated in the same way.

MMAS-8 : A structured self-report measure of medi-cation-taking behaviour consisting of 7 yes/no questions and one 5-point ordinal scale (15). The total score is the sum of the eight scores. When 1 or 2 items were missing, the missing items were substituted by the median score of all respondents over all visits. If more than 2 were missing the total score was missing. The total score category was defined as likely to be adherent (=8), medium adherence ($\geq$ 6 and <8), and low adherence (< 6).