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Adherence to Objective Therapeutic Monitoring and Outcomes in Patients with Inflammatory Bowel Disease with Adalimumab Treatment. A Real-world Prospective Study

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ABSTRACT

Background & Aims: Objective monitoring and effective early treatment using a treat-to-target approach are key to improving therapeutic outcomes in IBD patients. This study aimed to assess adherence to objective monitoring (clinical, biomarkers, and endoscopy) and its impact on clinical outcomes.

Methods: A prospective, multicenter study included consecutive IBD patients starting on adalimumab therapy between January 2019 and December 2020. Disease activity, assessed by the Harvey-Bradshaw index (HBI), partial Mayo, C-reactive protein (CRP), fecal calprotectin (FCAL), and endoscopy were evaluated at adalimumab initiation and 3, 6, 9 and 12 months. Therapeutic drug monitoring, changes in treatment, drug sustainability, and clinical outcomes were assessed.

Results: 104 IBD patients were enrolled (78.8% CD, median age 34.3 years, disease duration 9 years). During the 12 months follow-up, high adherence to clinical activity assessment was observed in both CD (81.3%-87.7%) and UC patients (76.5-90.9%). CRP measurement decreased over time in both CD (37.3%-54.9%) and UC (29.4%-50.0%). The adherence to serial FCAL monitoring was low in CD (22.7-31.3%) and UC patients (17.6-56.0%). UC patients had higher adherence to early endoscopic assessment (<6 months) compared to CD patients (40.9% vs. 21.5%). Adherence to early combined clinical and biomarkers resulted in earlier dose optimization in CD and UC (log-rank<0.001), but drug sustainability was not different. The patients with early combined adherence had a significantly higher clinical remission rate at 1 year compared to non-adherence (70.2% vs. 29.8%, p=0.007) but no significant difference in UC patients.

Conclusions: The adherence to early objective monitoring with combined clinical and biomarkers assessment in IBD patients starting adalimumab therapy led to dose optimization and improved 1-year clinical remission in CD but did not change drug sustainability and clinical remission in UC.

Key words: adherence – monitoring– treat-to-target – dose optimization – adalimumab – inflammatory bowel disease – ulcerative colitis – Crohn's disease – fecal calprotectin.

Abbreviations: CRP: C-reactive protein; CD: Crohn's disease; FCAL: fecal calprotectin; HBI: Harvey Bradshaw index; IBD: inflammatory bowel disease; IQR: interquartile range; SAE: serious adverse event; SES-CD: Simple Endoscopic Score for Crohn's disease; STRIDE: Selecting Therapeutic Targets in Inflammatory Bowel Disease; TDM: therapeutic drug monitoring; UC: ulcerative colitis.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic progressive immune-mediated disorder of the gastrointestinal tract, including Crohn's disease (CD) and ulcerative colitis (UC). Inflammatory bowel disease impacts patients' quality of life and can result in irreversible long-term complications [1-4]. The conventional therapeutic approaches have focused on the resolution of symptoms, which probably have failed to change the natural course of the disease [5]. There is a clear discordance between clinical symptoms and active mucosal inflammation in CD and UC [6, 7].

The advancement in biological therapy and monitoring tools have introduced more means to improve long-term outcomes and increase the ability to reach beyond the conventional therapeutic goals [8]. In recent years, the treatment target in IBD has been shifted from solely symptomatic control to normalization of inflammatory objective markers with the goal of mucosal healing by adopting treat-to-target strategies as recommended

by the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) consensus [9, 10]. The composite endpoint of clinical, biomarkers and endoscopic remission should be the treatment target in both CD and UC [11]. Thus, effective disease monitoring becomes pivotal in the management of IBD. Appropriate monitoring allows physicians to establish when to optimize therapy to reach the goal of achieving and maintaining endoscopic and histologic remission [12].

In the CALM study, a randomized controlled trial of 244 patients with early, moderate to severe CD showed that timely escalation with anti-tumor necrosis factor on the basis of tight control monitoring with combined clinical symptoms and biomarkers in CD patients results in better clinical and endoscopic outcomes compared to symptom-driven decisions alone at 48 weeks [13]. In a post hoc analysis of half of the patients in the CALM trial, deep remission (clinical and endoscopic remission) at 1 year was associated with a decreased risk of disease progression (fistulas, strictures, hospitalization, and surgery) over a median time of 3 years [14]. Moreover, the tight control strategy can be more cost-effective compared with conventional clinical management [15].

A real-world retrospective cohort of 428 IBD patients treated with adalimumab therapy demonstrated that adherence to early combined follow-up visits resulted in earlier dose optimization and improved one-year clinical outcomes but did not change drug sustainability [16]. Although the current evidence is increasing on the role of tight control monitoring, implementing a tight treat-to-target strategy in real-world practice can be challenging [17]. Furthermore, data on prospective real-world studies on adherence to this strategy and its outcomes are scarce.

This study aimed to prospectively evaluate the adherence to serial objective monitoring with clinical symptoms, biomarkers, and endoscopic assessment and its impact on therapeutic changes, dose optimization, drug sustainability, and one-year outcomes in IBD patients with adalimumab therapy in real-world clinical practice.

METHODS

Study Design and Population

We conducted a prospective, multicenter, observational study including all consecutive adults (>18 years) with IBD, including CD and UC patients that were started on adalimumab therapy between January 1, 2019, and June 30, 2020, at the IBD center of McGill University Health Center (MUHC), Jewish General Hospital (JGH), and Centre Hospitalier Universitaire de Québec (CHUQ), Canada. IBD center is referred to the IBD center of MUHC, an academic center providing harmonized IBD-care pathway by IBD specialists, while the JGH and CHUQ are university-affiliated hospitals (non-IBD centers). Patients with indeterminate colitis were excluded. The therapeutic agent adalimumab was selected to mirror the CALM study in a real-world setting. We followed up with the patients from the date of adalimumab initiation until one year after the start of therapy.

Data Collection

Data at baseline was collected, including patients' demographic, date of diagnosis, disease duration, and previous and concomitant medical therapy, as detailed in Table I. In addition, the follow-up data were captured at 3, 6, 9, and 12 months after adalimumab initiation, including adherence to the follow-up visits, biomarkers [C-reactive protein (CRP), fecal calprotectin (FCAL)], and endoscopy, IBD disease activity based on clinical scores (Harvey Bradshaw index (HBI) for CD, Mayo score for UC), endoscopic activity [Simple Endoscopic Score for Crohn's Disease (SES-CD), endoscopic Mayo score for UC], frequency of changes in treatment including therapeutic drug monitoring (TDM), dose optimization, change of biologic therapy, immunomodulator and corticosteroid use, need for an emergency visit, hospitalization, and surgery.

Study Outcomes

The co-primary outcomes were defined as adherence to clinical follow-up visits, biomarker and endoscopic monitoring, and clinical remission rates at 1 year. The secondary outcomes were drug sustainability and the need for dose optimization.

Clinical remission was defined as an HBI < 5 in CD patients and a partial Mayo score ≤ 2 in UC patients. Clinical response was defined as a decrease ≥ 3 in either clinical activity score. Patients who discontinued adalimumab (due to treatment cessation or change to another biologic therapy) and those who underwent intestinal surgery were considered as non-response to adalimumab therapy. Moderate to severe diseases were defined as HBI > 7 in CD or partial Mayo > 4 in UC. The active endoscopic activity was defined as an SES-CD > 2 in CD and endoscopic Mayo score > 1. Patients who did not have a clinical evaluation at each follow-up visit were considered not in clinical remission.

Drug sustainability was defined as the median length to treatment discontinuation and the probability of drug retention. Clinical assessment was defined as the evaluation via a clinic visit and formal assessment by a clinical score (the components of the score must have been available to be able to calculate/approximate the clinical scores).

Combined adherence was defined as the evaluation of clinical assessment and biomarkers, either CRP or FCAL. Data analyses were stratified by type of IBD disease (CD vs. UC), patient adherence, and treatment center type (IBD center vs. non-IBD center). In addition, we assessed the changes in treatment, frequency of changes in the treatment, including therapeutic drug monitoring (TDM), dose optimization, change of biologic therapy, immunomodulator and corticosteroid use, and IBD-related emergency visit, hospitalization, and surgery.

Statistical Analysis

Baseline demographic characteristics and categorical variables were presented as frequencies with percentages and compared using χ^2 square or Fisher exact tests. Continuous variables were expressed as the median and interquartile range (IQR) and were compared using the T-test with separate variance estimates. The Kaplan–Meier was used to estimate the median time to dose adjustment and median length of treatment. Survival curves were compared by using the Log-rank test. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 20.0 (SPSS INC., Chicago, Illinois, USA).

Ethical Consideration

The study was approved by the Research Ethics Board (REB) of McGill University Health care center (MUHC) under protocol REB: MP-37-2019-5042 and by the JGH Research Ethics Board under protocol REB: MEO-37-2020-1890, Montreal, Quebec, Canada. This study was conducted in compliance with regulations stated in the 1975 Declaration of Helsinki.

RESULTS

Baseline Characteristics

A total of 104 patients, 82 patients had CD, and 22 patients had UC, were started on adalimumab at the three referral hospitals. The median age at enrollment was 34.3 years, and the duration of IBD disease was 9 years. Sixty patients were followed-up at the IBD center of MUHC, and 44 patients were followed-up at non-IBD centers. The patient's baseline characteristics are shown in Table I.

At the baseline adalimumab initiation, 41.5% of CD and 63.7% of UC patients had moderate to severe disease activity. The median CRP was 5.5 mg/L (IQR: 1.7-24.2) and 5.2 mg/L (IQR: 0.6-8.1) in CD and UC patients, respectively. The median FCAL was 526 ug/g (IQR: 191-1,983) and 385 ug/g (IQR: 62-905) in CD and UC patients, respectively. The active endoscopic inflammation was found in 70.6% of CD and 81.3% of UC patients (SES-CD 6 in CD and endoscopic Mayo 3 in UC).

The concomitant systemic corticosteroid use at the time of adalimumab initiation was observed in 35.4% of CD patients and 59.1% of UC patients. The previous biological

Table I. Baseline characteristics of IBD patients with objective therapeutic monitoring

	Total n=104	Crohn's disease n=82	Ulcerative colitis n=22
Male gender, n (%)	62 (59.6)	51 (62.2)	11 (50)
Age; years, median (IQR)	34.3 (23.8-49.5)	32.5 (23.0-48.0)	41.5 (27.5-58.0)
Disease duration; years, median (IQR)	9 (3.2 -20.0)	10.0 (3.0-20.0)	7.0 (2.9-15.5)
Crohn's disease phenotype (%)			
Age at diagnosis (A1/A2/A3)	NA	22/58.5/19.5	NA
Location (L1/L2/L3)	NA	32.9/25.6/41.5	NA
Behavior (B1/B2/B3)	NA	47.6/23.2/29.3	NA
Perianal, n (%)	NA	15 (18.3)	0
Ulcerative colitis phenotype			
Extension (E1/E2/E3), %	NA	NA	9.1/31.8/59.1
Severity (S1/S2/S3), %	NA	NA	4.5/40.9/54.5
Extra-intestinal manifestations, n(%)	36 (34.6)	30 (36.6)	6 (27.3)
Previous intestinal resection, n(%)	28 (26.9)	26 (31.7)	2 (9.1)
Baseline disease activity			
Disease severity (remission/mild/moderate/severe), %	17.3/36.5/33.7/12.5	20.7/37.8/35.4/6.1	4.5/31.8/27.3/36.4
Clinical activity	NA	HBI: 7 (5-8)	pMayo: 5 (2-7)
C-reactive protein; mg/L, median (IQR)	5.4 (1.6-19.9)	5.5 (1.7-24.2)	5.2 (0.6-8.1)
Fecal calprotectin; ug/g, median (IQR)	402 (184-1,964)	526 (191-1,983)	385 (62-905)
Active fistula with drainage, n (%)	7 (6.7)	7 (8.5)	0
Active endoscopic activity, n (%) [a]	49 (73.1)	36 (70.6)	13 (81.3)
Endoscopic score, median (IQR)	NA	SES-CD: 6 (2-8)	eMayo: 3 (2-3)
Concomitant IBD medications			
5-ASA, n (%)	11 (10.6)	5 (6.1)	6 (27.3)
Systemic corticorsteroid, n (%)	42 (40.4)	29 (35.4)	13 (59.1)
Dose of corticosteroids; mg/day, median (IQR)	20.0 (12.5-30.0)	22.5 (10.0-31.2)	20 (15.0-30.0)
Immunomodulators, n (%)	13 (12.5)	12 (14.6)	1 (4.5)
Previous biologics failed, n (%)	49 (47.1)	38 (46.3)	11 (50)
1 biological	32 (30.8)	26 (31.7)	6 (27.3)
> 2 biological	17 (16.3)	12 (14.6)	5 (22.7)
Biologics exposed, n (%) [b]			
Infliximab	29 (59.2)	23 (60.5)	6 (54.5)
Vedolizumab	11 (22.4)	7 (18.4)	4 (36.4)
Ustekinumab	8 (16.3)	7 (18.4)	1 (9.1)

[a] Percentages were calculated in patients who had performed endoscopy within 6 months before enrollment (51 of CD and 16 UC patients); [b] percentages were calculated in patients who had been exposed to biologics.

therapies were seen in 46.3% and 50.0% of CD and UC patients. The previous exposure to infliximab, vedolizumab and ustekinumab were 59.2%, 22.4%, and 16.3%, respectively.

Adherence to the Clinical, Biological, and Endoscopic Assessment

The adherence to clinical assessment during the 12 months of follow-up in IBD patients was high, ranging between 81.3% to 87.7% in CD patients and 76.5% to 90.9% in UC patients. Both CD and UC patients had moderate adherence to serial CRP assessment, approximately 50% at 3 and 6 months, but relatively lower after 6 months of follow-up (29.4%-42.2%). However, the serial FCAL assessment adherence was low in both CD (22.7% -31.3%) and UC patients (17.6%-56%) (Fig. 1).

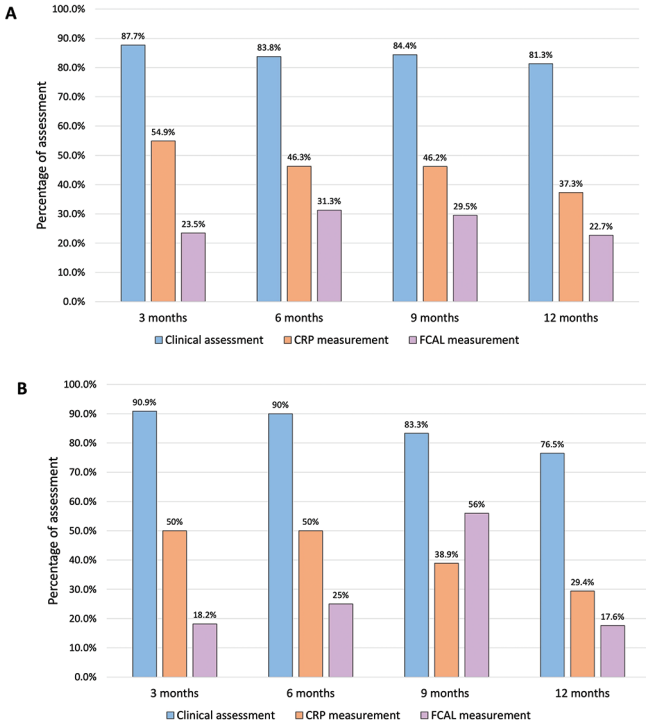

Fig. 1. Adherence to the objective monitoring, clinical and biological assessment in patients with IBD (A) Crohn's disease and (B) ulcerative colitis.

The adherence to endoscopic assessment was numerically higher in UC patients compared to CD patients (40.9% vs. 21.5% at 0-6 months, and 34.6% vs. 26.3% at 6-12 months). In patients who had early endoscopic assessment (within 6 months after initiation of adalimumab), the median time to endoscopic assessment was 14 weeks (7-19) and 21.5 weeks (10.2-23) in UC and CD patients, respectively. In addition, the adherence to endoscopic assessment after the start of adalimumab therapy was significantly higher in UC than in CD patients (50% vs. 17%, p=0.017) at the IBD center. There was no significant difference among patients treated at the non-IBD center (Fig. 2).

Patients who were followed up at the IBD center had significantly higher rates of early combined adherence to both clinical and biomarkers assessment at 3 months (71.2% vs. 27.3%, p<0.001) and at 6 months (63.8% vs. 42.9%, p=0.044) compared to the non-IBD centers (Table II).

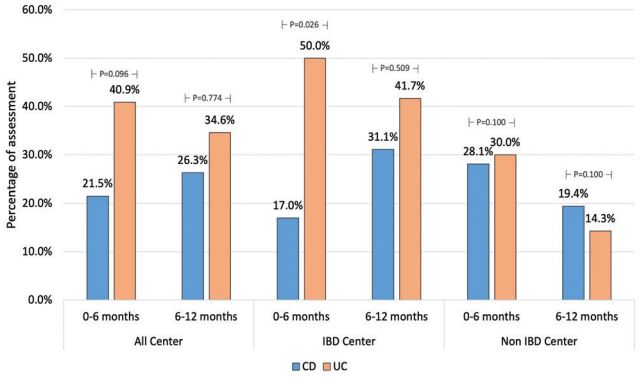

Fig. 2. Adherence to endoscopic assessment at 0-6 months and 6-12 months after the start of adalimumab therapy in IBD center and non-IBD center.

Table II. Adherence to combined clinical and biomarkers assessment of IBD patients at different time points, stratified by IBD center and non-IBD centers

Follow-up (months)	IBD center N=60	Non-IBD center N=44	OR (95% CI)	p
3	42/59 (71.2%)	12/44 (27.3%)	0.152 (0.064-0.362)	<0.001
6	37/58 (63.8%)	18/42 (42.9%)	0.426(0.189-0.959)	0.044
9	25/56 (44.6%)	16/40 (40.0%)	0.827 (0.363-1.883)	0.681
12	22/55 (40.0%)	12/37 (32.4%)	0.720 (0.300-1.726)	0.514

Therapeutic Changes of Adalimumab Therapy

The frequencies of TDM and dose optimization, discontinuation of adalimumab, change to other biological therapies, and rescue therapy with systemic corticosteroids in IBD patients who had active clinical symptoms and/or elevated biomarkers are shown in Fig. 3.

In IBD patients who had disease activity and/or elevated biomarkers after starting adalimumab therapy, the need for systemic corticosteroids regarding disease activity or disease flare was observed in 16.7%, 19.5%, and 12.5% at 3, 6, and 12 months. Therapeutic drug monitoring and dose optimization of adalimumab therapy was performed at 30.6%, 22%, and 8.3% at 3, 6, and 12 months. The changes to other biological therapies were increased over follow-up time; 2.8%, 4.9%, and 20.8% at 3, 6, and 12 months, respectively. The major reason for changing biological treatment was a loss of response to adalimumab. There was no significant difference in therapeutic changes between the patients who were followed up at the IBD center versus non-IBD centers.

In clinically active CD patients, the changes to other biological therapies increase over time after six months; 3.4%, 4.0%, and 18.2% at 6, 9, and 12 months. In UC patients, the changes in treatment were observed more frequently six months after starting adalimumab. However, no IBD patients with the active disease received immunomodulators.

The percentages of treatment changes were significantly higher in patients who did not reach an optimal therapeutic response compared to patients who had reached optimal clinical response and biomarkers remission at 3 months (50%

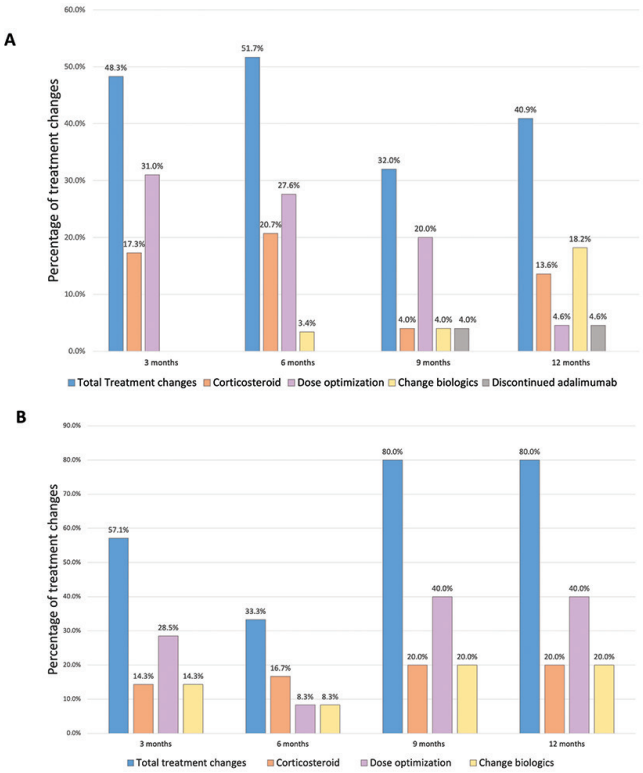

Fig. 3. Changes in treatment in IBD patients with clinical activity and/or elevated biomarkers after starting adalimumab at 3, 6, 9, and 12 months (A) Crohn's disease and (B) ulcerative colitis.

vs. 8.7%, p=0.002), 6 months (46.3% vs. 9.5%, p=0.004), 9 months (40% vs. 5.3%, p=0.008) and 12 months (45.8% vs. 0%, p=0.001) (Table III).

Table III. Percentages of IBD patients who underwent therapy change, stratified by clinical response and biomarkers remission

Follow-up (months)	Combined clinical response and normalized biomarkers *	No clinical response or elevated biomarkers *	OR (95% CI)	p
3	2/23 (8.7%)	18/36 (50.0%)	0.095 (0.019-0.467)	0.002
6	2/21 (9.5%)	19/41 (46.3%)	0.122 (0.025-0.592)	0.004
9	1/19 (5.3%)	12/30 (40.0%)	0.083 (0.010-0.710)	0.008
12	0/19 (0%)	11/24 (45.8%)	NA	0.001

* Percentage included only patients who remained in adalimumab therapy and had assessed both clinical activity and biomarkers.

Clinical Outcomes of Patients with Objective Monitoring

The clinical remission rate at one year was significantly higher in CD patients with early combined adherence compared to non-adherence (70.2% vs. 29.8%, p=0.007) but did not differ in UC patients.

In the patients who remained on adalimumab and were followed, the clinical remission rates were 70.3%, 75.7%, 79.3% in CD patients, and 75.0%, 58.8%, and 83.3% in UC patients at 3, 6, 12 months, respectively.

In patients who had active endoscopic inflammation at baseline, endoscopic remission was achieved in 46.2% and 44.4% at 6 and 12 months in CD, and 25% and 33% at 6 and 12 months in UC patients.

Additionally, IBD-related emergency visits (23.2% vs. 9.1%), hospitalization (15.9% vs. 4.5%), and need for intestinal surgery (31.7% vs. 4.5%) were likely to occur more frequently in CD than in UC patients during 1-year follow-up, but with no significant difference between patients with and without early combined adherence.

Drug Sustainability and Dose Adjustment

The Kaplan Meier curves of the drug sustainability of adalimumab therapy in the IBD patients stratified by type of disease (CD and UC) and adherence to early combined clinical and biomarkers at 3 and 6 months are shown in Fig. 4. The probability of remaining on adalimumab therapy was significantly higher in CD compared to UC patients (log-rank=0.004). However, drug sustainability was not different in patients with and without early combined adherence after the start of adalimumab therapy (log-rank=0.330).

Patients with early combined adherence at 3 and 6 months had significantly earlier dose optimization of adalimumab in both CD and UC patients (log-rank<0.001) (Fig. 5). The Median duration of dose adjustment after the start of adalimumab therapy was 20 weeks (12.0-52.0).

Serious Adverse Events and Drug Discontinuation

Adalimumab-related serious adverse events (SAEs) were observed in 5 patients; 3 (2 patients with CD and 1 UC) reported dermatitis and/or severe skin reaction. Two patients with CD developed infections, recurrent urinary tract infection and recurrent perianal abscesses. Of those five patients, four patients stopped adalimumab treatment regarding the SAEs.

DISCUSSION

In this multicenter, prospective study, we evaluated adherence to objective monitoring by adopting a treat-to-target strategy in IBD patients in real-world practice. The clinical activity was frequently assessed in patients starting adalimumab therapy at regular intervals. C-reactive protein was measured in about half of the patients at the early follow-up visits but decreased over time. However, serial FCAL monitoring was a suboptimal assessment in both CD and UC. The UC patients had higher adherence rates to early endoscopic assessment compared to CD patients, especially patients who were followed at the IBD center. The drug sustainability of adalimumab therapy was higher in CD than in UC patients. Adherence to early combined clinical and biomarkers assessment resulted in earlier dose optimization and improved 1-year clinical remission in CD patients, but drug sustainability was not different.

The CALM trial showed that timely escalation with an anti-TNF therapy based on clinical symptoms combined with biomarkers in biologics-naïve patients with early CD resulted in better outcomes than conventional care based on symptoms alone [13]. This present study demonstrated that adherence to early combined clinical and biomarkers assessment improved clinical remission at 1 year in patients with CD. It is important to note that the average duration of IBD disease within our

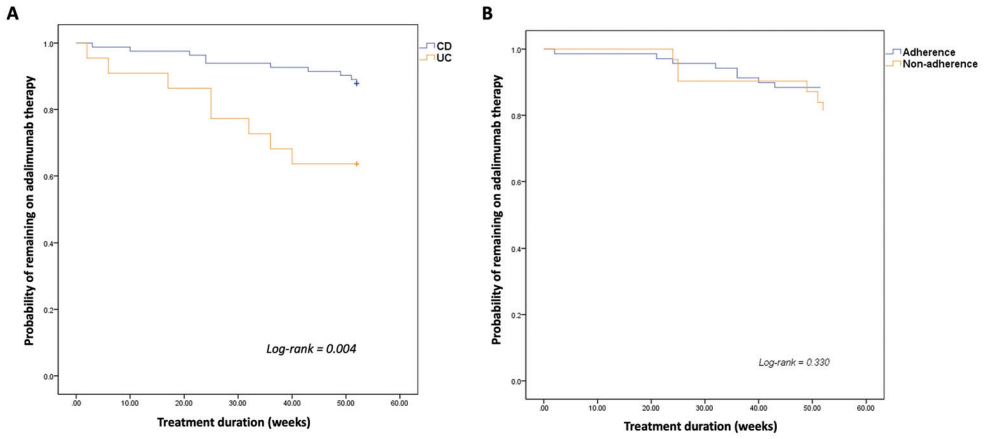

Fig. 4. Drug sustainability of adalimumab therapy stratified by (A) type of disease (CD vs. UC) and (B) adherence to early combined objective monitoring, clinical and biomarkers at 3 and 6 months after starting adalimumab therapy (adherence vs. non-adherence).

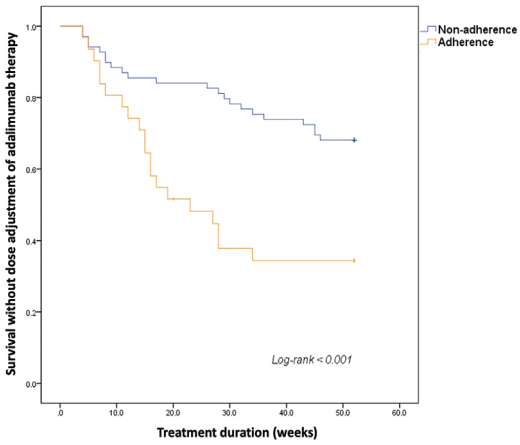

Fig. 5. Dose optimization of adalimumab therapy stratified by adherence to early combined objective monitoring, clinical and biomarkers at 3 and 6 months after starting adalimumab therapy.

population was much longer compared to the CALM study (9 vs. 0.9 years in CALM). Moreover, approximately 50% of patients in this study had failed other biological therapies prior to adalimumab treatment, suggesting that tight-control disease monitoring may affect the long-term disease outcomes in CD patients, even in patients with longer disease duration. However, our study did not find the early objective monitoring on a 1-year clinical remission in UC patients beneficial. In contrast to data on CD, there is an absence of solid evidence supporting the benefit of tight control management on long-term outcomes in UC [18].

We demonstrated that adherence to early assessment in combined clinical and biomarkers at 3 and 6 months after the start of adalimumab was associated with earlier dose optimization but did not affect overall drug sustainability. Interestingly, biologics sustainability was determined by IBD subtypes. Patients with CD had a higher probability of long-term drug sustainability than UC patients. This is potentially due to UC patients having a higher proportion of severe disease activity (UC 36.4% vs. CD 6.1%) and concomitant steroid use compared to CD patients (59.1% vs. 35.4%) at the time of adalimumab initiation, which can influence the response to treatment [19]. The previous retrospective IBD cohort indicated sustainability of biologic therapy is less in UC than in CD patients and is not strongly determined by prior biologic exposure [20].

In real-life clinical practice, the ultimate timing and frequency of serial objective monitoring can vary depending on a different phase of disease activity, severity, and IBD phenotype. Many of the monitoring tools are intrusive to patients, expensive to perform, and carry a significant administrative burden on health care teams. As such, not all patients should be monitored with the same intensity [21]. In this present study, the clinical activity and CRP monitoring occurred more frequently in the first 3 months and less after 6 months, but FCAL measurement occurred less in the first 3 months and increased frequency at 6-9 months after starting adalimumab therapy. Although, FCAL level is a better predictor for detecting endoscopic mucosal healing and clinical relapse than CRP [22-25], serial FCAL monitoring was a suboptimal assessment and remained challenging in clinical practice. In accordance with the reported rates in our study, a retrospective cohort also showed that only 35% of IBD patients performed the FCAL tests [26]. The main reason for non-adherence was forgetfulness and difficulty in sample collection [26, 27]. The endoscopic assessment was performed more frequently and earlier in UC patients than in CD patients, in line with the STRIDE recommendations that endoscopic assessment should be performed at 3-6 months after the start of therapy in UC patients and after 6-9 months in CD patients to decide on further treatment changes [9, 10. 28].

The patients who started treatment and followed up at the IBD center were more likely to have earlier adherence to combined clinical and biomarkers monitoring in the first 3 and 6 months compared to patients who had follow-up at non-IBD centers. However, there is no difference in changes in treatment and clinical remission between patients who were treated and followed up at the IBD center and non-IBD center. This present study confirmed the results from our previous retrospective cohort that the objective monitoring

strategies can be implacable to either IBD-expert center or community hospital as a standard of care in IBD patients, allowing individual flexibility, and harmonized care across health care providers [16].

The strengths of this present study are the prospective assessment of the objective monitoring, including clinical, biomarkers, and endoscopic monitoring in real-world clinical practices and its impact on clinical outcomes from both a tertiary referral IBD center and community hospitals. In addition, this study included consecutive IBD patients comprising recent and longstanding IBD diagnosis with a well-defined geographical area. Nonetheless, this study has some limitations. Firstly, despite a prospective study, we could not control for confounders, including the patients' reasons for non-compliance and non-clinical reasons for a change of treatment. Second, the study was interrupted by the COVID-19 pandemic during the end of the study, which resulted in underestimated adherence to follow-up regarding a limited number of patients at the outpatient clinic, blood investigation, and endoscopic evaluation. However, we provided remote telemedicine and a rapid assessed IBD clinic for follow-up patients at the IBD center during the pandemic to maintain disease monitoring.

CONCLUSIONS

The adherence to early objective monitoring with combined clinical and biomarkers assessment in IBD patients treated with adalimumab therapy led to earlier dose optimization and improved clinical remission in CD but did not change drug sustainability and clinical remission in UC. Clinical and CRP measurements were frequently assessed in the patients starting adalimumab therapy. However, serial fecal calprotectin monitoring was a suboptimal assessment in this real-world clinical practice. Patients who were followed at the IBD center had a higher rate of early combined adherence but no difference in treatment changes and clinical remission.

Conflicts of interest: P.W. has been a speaker and/or advisory board member: Takeda, Pfizer, Janssen, Ferring, A. Menerini, and MSD. P.A.G. has been a speaker for AbbVie, Takeda, Fresenius, and Ferring. J.W. has been consultant for Abbvie. A.C. has been a speaker and advisory board member for Abbvie, Janssen, Takeda, Pfizer, Ferring, and Shire. T.B. has been a speaker or advisory board member for Takeda, Janssen, Abbvie, Merck, Pfizer, Pendopharm, Ferring, Shire, Sandoz, BMS, and Roche. G.W. has been a speaker and/or advisory board member for AbbVie, Janssen, Pfizer, Shire and Takeda. W.A. has been a speaker for Janssen, Prometheus, Dynacare, Takeda, and AbbVie Theradiag. A.B. has been a member of Advisory Boards: Abbvie, Pfizer, Takeda, Janssen, Merck; Speaker's bureau: Abbvie, Janssen, Takeda, Pfizer. P.L.L. has been a speaker and/or advisory board member for AbbVie, Arena, Falk Pharma GmbH, Ferring, Genetech, Janssen, Kyowa Hakko Kirin Pharma, Mitsubishi Tanabe Pharma Corporation, MSD, Pfizer, Roche, Shire, Takeda, and Tillots, and has received unrestricted research grants from AbbVie, MSD, and Pfizer. E.G., A.A.K., G.D.H., and M.B. declare no conflict of interests.

Authors' contribution: P.W. and P.L.L. contributed to the conception and study's designed. P.W., P.A.G., and E.G. collected data. P.W. and P.L.L. performed the analyses and interpretation of the data. P.W. drafted the initial manuscript. P.W., P.A.G., A.A.K., G.D.H., A.C., J.W., M.B., T.B., W.A., G.W., A.B. and P.L.L. contributed to revising the manuscript for intellectual content. All of the authors have read and approved the published version of the manuscript.

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