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Achievement of deep remission during scheduled maintenance therapy with TNFα-blocking agents in IBD

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Abstract

Background and aims: Deep remission, meaning clinical remission with mucosal healing (MH), with anti-tumor necrosis factor-alpha (TNF-α) agents is a new target for therapy in inflammatory bowel disease (IBD). Our aim was to study how often patients on TNF-α blocking therapy actually achieve deep remission.
Methods: The total of 252 IBD patients retrospectively included (183 Crohn's disease (CD), 62 ulcerative colitis (CU) or 7 inflammatory bowel disease unclassified-type colitis (IBDU)) received TNFα-antagonists (177 infliximab, 75 adalimumab) for at least 11 months and underwent ileocolonoscopy. We reviewed endoscopic and histological findings, clinical symptoms, C-reactive protein (CRP), and fecal calprotectin (FC) levels, and data on TNF-α blocking therapy. Defining deep remission as no clinical symptoms with endoscopic remission (the simple endoscopic score for Crohn's disease, SES-CD 0–2 or Mayo endoscopic subscore 0–1).
Results: Of the 252 patients, 168 (67%) were in clinical remission and 122 (48%) in deep remission after a median of 23 months of maintenance therapy. Of the 183 CD patients, 117

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(64%) reached clinical remission and 79 (43%) deep remission. Of the UC patients, 52 (75%) were in clinical remission and 43 (62%) in deep remission. The majority of patients in deep remission (n = 99, 81%) also had histologically inactive disease. Both median CRP and FC levels were significantly lower in patients with deep remission.
Conclusion: Reassuringly, half of the IBD patients on the TNFα-blocking maintenance therapy achieved deep remission. The majority of patients in deep remission also achieved histological remission.

1. Introduction

Inflammatory bowel diseases (IBD), Crohn's disease (CD), ulcerative colitis (UC) and inflammatory bowel disease unclassified-type colitis (IBDU) are chronic inflammatory diseases characterized by remission and exacerbations. For decades, treatment goals for IBD have been to achieve clinical response or remission and normalization of laboratory parameters.[1,2] Recently, therapeutic targets for treatment of IBD have included mucosal healing (MH) and prevention of extraintestinal complications.[2–4] MH has been defined by the International Organization of IBD (IOIBD) as the absence of friability, blood, erosions, and ulcers in all visualized segments of the mucosa.[5] Endoscopic assessment of response to therapy has only seldom been adaptable for routine clinical practice. Promising new biomarkers such as fecal calprotectin (FC) correlate closely with endoscopic and histological grading of disease activity in both UC and CD.[6–8] FC has been a useful predictor of MH, serving thus as a good noninvasive surrogate marker of MH.[6,9–11]

Like the treatment targets for IBD, the management of IBD has also changed, aiming more aggressively to MH. The anti-tumor necrosis factor-alpha (TNF-α) agents infliximab and adalimumab are the most effective therapies in IBD for induction of MH. In ACCENT I (the luminal Crohn's disease trial) infliximab maintenance therapy every 8 weeks was associated with long-term MH in about half of the CD patients undergoing endoscopy.[12] The EXTEND trial, a randomized placebo-controlled study of adalimumab induction and maintenance therapy in patients with moderate to severe ileocolonic CD, has recently shown complete MH occurring significantly more often in adalimumab-treated CD patients than in controls at week 52.[13] In UC, a randomized, double-blinded, placebo-controlled ACT1 trial demonstrated MH occurring significantly more often in the infliximab than in the placebo group.[14] In UC, the efficacy of adalimumab in inducing MH in a double-blind randomized controlled trial has been much less convincing.[15] In UC, early mucosal healing with infliximab has been associated with a lower risk for colectomy.[16] In sum MH appears to be an important therapeutic endpoint in both CD and UC and a good predictive marker for disease outcome.

In clinical practice, TNF-α blocking therapy may be withdrawn for several reasons such as primary nonresponsiveness, fear of long-term side-effects, or concerns about pregnancy and about cost. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID) studied the risk for relapse following withdrawal of infliximab therapy in CD patients with long-standing remission. They showed that among CD patients in stable remission at the time of withdrawal of infliximab therapy, up to half relapsed within one or two years. Importantly, that study showed that patients at low risk for relapse could be determined by use of a combination of clinical and biological markers, and in those relapsing, re-treatment with infliximab was effective and well tolerated.[17]

Although TNF-α blocking therapy has been used in clinical practice for over a decade, only little data have appeared on the prevalence of concomitant clinical remission and MH during maintenance therapy with anti-TNF-α agents. Recently, in CD the term deep remission has been applied to patients on immunomodulators or TNF-α blocking therapy or both who have no clinical symptoms and no objective signs of inflammation (defined as Crohn's disease activity index [CDAI < 150] and endoscopic remission).[13] In UC or IBDU, no such definition exists.

Our aim was to study how often deep remission can actually be achieved in IBD patients on TNF-α blocking therapy in everyday clinical practice. In addition, we evaluated the achievement of histological remission.

2. Materials and methods

2.1. Patients and treatment

Eight gastroenterological units in various parts of Finland participated (Helsinki (2), Espoo, Vantaa, Hyvinkää, Tampere, Turku, and Oulu). Data were collected retrospectively for all UC, CD, and IBDU patients treated for at least 11 months with a scheduled TNFα-blocking therapy and undergoing ileocolonoscopy during 2010 and 2011. The total was 252 patients with IBD (183 patients with CD, 62 with UC, and 7 with IBDU). Because of its small size, the subgroup IBDU with 7 is herein included in the UC group. The majority (145, 79%) of the patients with CD were treated for luminal CD, and 37 (20%) patients for fistulizing CD. In two patients with pediatric CD onset, the main indication for TNFα-blocking therapy had been delayed growth. Of UC or IBDU patients, 31 (45%) had a steroid-refractory disease and 38 (55%) had steroid-dependent disease.

2.2. Clinical and endoscopic assessment of disease activity

Clinical disease activity was assessed by the physicians' global assessment (PGA) scores: 0 for nonsymptomatic patients and 1 for patients with gastrointestinal symptoms indicating with active IBD. Scoring of endoscopic findings took place in participating units as routine clinical practice. Endoscopic

findings were scored according to the simple endoscopic score for Crohn's disease (SES-CD),[18] and in UC according to the Mayo endoscopic score.[19] An SES-CD 0 to 2 was defined as remission, 3 to 6 as mildly active disease, 7 to 15 as moderately active disease, and ≥16 as severely active disease.[20] For the Mayo endoscopic subscore, endoscopic findings were scored as normal (0), mild (1), moderate (2), or severe (3); a subscore of 0 to 1 meant remission and a subscore of ≥2 active disease.[21] In this study we defined deep remission as no clinical symptoms (PGA=0) with concomitant endoscopic remission (SES-CD 0–2 or Mayo endoscopic subscore 0–1).

2.3. Histological assessment of disease activity

During the ileocolonoscopy, random biopsy specimens were taken from the ileum, the right, transverse, and left colon, and the rectum. We graded histological findings according to the most severely diseased areas: 0=normal and 1=active inflammation.

2.4. Laboratory measurements

Data on FC concentrations and C-reactive protein (CRP) values were those measured at the time of the ileocolonoscopies. The values considered as normal for FC were <100 μg/g[22] and <3 mg/l for CRP.

2.5. Statistical analysis

For data analyses we used the PASW (Predictive Analytics Software) Statistics 18 for Windows software (IBM Company, Chicago, IL, USA). The Mann–Whitney U-test served to test differences between independent variables. The Chi square test was used to find out differences between categorical variables. Significance was set at $p<0.05$.

2.6. Ethical statement

Because this study was a retrospective review of patients' medical records, no application for ethics committee was needed. Research study permission number 195/2009 was received from the Department of Medicine, Helsinki University Central Hospital.

3. Results

Patient characteristics are listed in Table 1. Of 252 patients, 177 (70%) received infliximab (CD n=109, UC n=68) and 75 (30%) adalimumab (CD n=74, UC n=1). At the time of ileocolonoscopy, 183 (73%) patient received combination therapy (Table 1). The median time to treat was 23 months (range 11–147) from induction of TNFα-blocking therapy to ileocolonoscopy. Table 2 shows endoscopic activity indices, FC and CRP levels at ileocolonoscopy.

Table 1 Patient characteristics.

Characteristic	Crohn's disease (n=183)	Ulcerative colitis (n=62)	Inflammatory bowel disease unclassified type colitis (n=7)
Age at onset (median, range)	21 (2–57)	25 (8–72)	18 (17–65)
Age at induction (median, range)	32 (12–69)	31 (13–75)	27 (22–68)
Gender (female/male)	85/98	25/37	2/5
Disease duration (median, range)	8 (0–33)	5 (0–34)	5 (0–9)
Disease behavior (Mb Crohn)			
Inflammatory (B1)	86		
Stricturing (B2)	45		
Penetrating (B3)	20		
B1±perianal disease	11		
B2±perianal disease	13		
B3±perianal disease	8		
Disease location			
Ileum (L1)	14		
Colon (L2)	55		
		Proctitis 0 Left colon 17	
		Extensive colitis 45	7
Ileocolon (L3)	106		
L1+upper GI	2		
L2+upper GI	2		
L3+upper GI	4		
TNFα-blocking therapy			
Infliximab	109	61	7
Adalimumab	74	1	
Concomitant immunomodulators			
Azathioprine	93 (51%)	41 (66%)	6 (86%)
6-mercaptopurine	15 (8%)	10 (10%)	
Methotrexate	18 (10%)	6 (6%)	

3.1. Deep remission

At ileocolonoscopy, 168 (67%) patients of 252 were in clinical remission and 122 (48%) in deep remission. Of 183 CD patients, 116 (63%) achieved clinical remission and 79 (43%) deep remission. Of UC patients, 52 (75%) achieved clinical remission and 43 (62%) deep remission. The clinical remission rate in CD ranged from 50% to 85% and in UC from 33% to 100%, and the deep remission rate in CD ranged from 25% to 71% and in UC from 33% to 100% among clinics. No significant difference appeared as to achieving clinical remission between CD and UC patients ($p=0.072$). UC patients achieved deep remission significantly more often than did CD patients ($p=0.007$).

There emerged a significant difference in CRP level between those 122 in deep remission (median<3 mg/l, range <3 to 103) and those 130 with clinically or endoscopically active disease (median 3 mg/l, range 0–83, $p<0.0001$).

Table 2 Endoscopic activity indices, fecal calprotectin and CRP levels at time of ileocolonoscopy.

	All patients (n=252)	CD patients in deep remission (n=79)	CD patients with active disease (n=104)	p value	UC patients in deep remission (n=43)	UC patients with active disease (n=26)	p value
SES-CD	2 (0–24, n=183)\	0 (0–2, n=79)	5 (0–24, n=104)	p<0.001			
Endoscopic Mayo subscore\	0 (0–3, n=69)				0 (0–1, n=43)	2 (1–3, n=26)	p<0.001
Fecal calprotectin	78 (1–4190, n=163)	54 (6–722, n=40)	251 (6–2534, n=67)	p<0.001	50 (1–500, n=39)	519 (13–4190, n=18)	p<0.001
CRP	<3 (0–103, n=252)	<3 (1–103, n=79)	3 (0–83, n=67)	p<0.001	3 (0–32, n=26)	<3 (0–24, n=43)	p=0.001

Values presented as median (range).
CD, Crohn's disease; UC, ulcerative colitis; SES-CD, simple endoscopic score for Crohn's disease, CRP; C-reactive protein.

In total, 140 patients had normal CRP levels (<3 mg/l). In this group, 94 (67%) were also in deep remission. FC measurements were available for 163 patients. Median FC level was significantly lower for the 79 in deep remission compared to the 84 others (50 μg/g, range 1–722 vs. 288 μg/g, range 6–4190, p<0.0001). FC was normal (<100 μg/g) in 88 patients. In deep remission, 63 (72%) patients had normal FC levels, but in the active disease group, FC was normal only in 16 (21%) (p<0.0001).

Of patients in deep remission 51% (n=93) received combination therapy (azathioprine n=71, 6-mercaptopurine n=13, methotrexate n=9). In infliximab group 79% were on combination therapy (azathioprine n=109, 6-mercaptopurine n=17, methotrexate n=14) and in adalimumab group 57% (azathioprine n=31, 6-mercaptopurine n=4, methotrexate n=8). When comparing combination therapy and monotherapy in inducing deep remission, no significant differences were found (all patients p=0.214, CD group p=0.845, UC group p=0.107). Of CD patients 46% (50 of 109) in the infliximab group and 39% (29 of 74) in the adalimumab group achieved deep remission. On the contrary, of UC patients receiving infliximab, up to 63% (43 of 68) achieved deep remission. The study population being heterogeneous, no direct comparison between the two regiments could be made.

After the ileocolonoscopy, based on clinical judgment, for 43% (53 of 122) among patients in deep remission, TNFα-blocking therapy was withdrawn. In all these 53 patients, discontinuation of TNFα-blocking therapies was tried for the first time. For the other 69 patients (57%), TNFα-blocking therapy was continued for various reasons (Table 3).

3.2. Histological remission

Of the 122 patients in deep remission, 99 (81%) also had histologically inactive disease (39% of all patients). Of all CD patients in deep remission, 75% were also in histological remission, whereas in UC, the rate was 93% (p=0.001). Concomitant histological remission in CD patients with deep remission occurred in 59 (32%) patients. Of UC patients, 40 (58%) were in clinical, endoscopic, and histological remission. In the infliximab group, 36% (39 of 109) CD patients and 59% (36 of 61) UC patients, and in the adalimumab group 27% (20/74) of CD patients achieved clinical, endoscopic, and histological remission.

4. Discussion

This study demonstrates that during scheduled TNFα-blocking therapy in everyday clinical practice, 43% of CD patients and 62% of UC patients can achieve deep remission. Furthermore, of patients on scheduled TNFα-blocking therapy, 39% achieved concomitant clinical, endoscopic, and histological remission. To the best of our knowledge, this is the first study to demonstrate the achievement of clinical and deep remission rates based on nationwide data on the effect of TNFα-blocking therapy in everyday clinical practice judged by clinical symptoms and endoscopic findings providing important information for the use of TNFα-blocking agents.

We earlier demonstrated that after one year of scheduled maintenance therapy, two-thirds of endoscopic anti-TNF induction responders could be in endoscopic remission.[23]

Table 3 Reasons for continuing TNFα-blocking therapy among our patients in deep remission.

	n = 69
Retreatment	19
Concomitant rheumatoid disease	4
Only effective medication	15
High fecal calprotectin level	6
History of severe disease	19
Fistulating disease	6

The CHARM (Crohn's disease trial of the fully Human antibody Adalimumab for Remission Maintenance) study of adalimumab demonstrated a steroid-free clinical remission rate at week 56 for 29% of the patients, and also fewer hospitalizations and surgery.[24] That study lacks endoscopic data. According to the EXTEND trial, deep remission, defined as a combination of clinical remission (CDAI < 150) and complete MH, was achievable in some 19% of patients by week 52.[13] Compared to adalimumab studies, the ACCENT 1 endoscopic substudy demonstrated a higher MH rate in patients on scheduled infliximab therapy at 54 weeks.[12] Lichtenstein et al.[25,26] demonstrated that patients achieving MH on maintenance therapy with infliximab, experienced fewer hospitalizations and surgery and a better quality of life. Moreover, Schnitzler et al.[27] showed in a large cohort study that in patients with scheduled infliximab treatment, MH was associated with fewer complications and better long-term outcome. The SONIC (Study Of biologic and Immunomodulator Naïve Patients In Crohn's Disease) study showed a steroid-free clinical remission rate at week 26 of 44%.[28] Baert et al.[29] demonstrated that complete MH can lead to significantly higher steroid-free remission rates in patients with early-stage CD for as long as 4 years after start of therapy. In UC, the data on long-term outcome of TNFα-blocking therapy is based mainly on the ACT 1 trial. Scheduled maintenance therapy with infliximab 5 mg/kg resulted in MH in about 46% of patients by week 54.[14] The results of our trial resemble those described earlier. In CD, up to 46% in the infliximab group and 39% in the adalimumab group achieved deep remission. In UC, up to 63% of patients on infliximab maintenance therapy were in deep remission at the time of the ileocolonoscopy. The clinical remission rates were higher. In the infliximab group, 66% CD patients and 77% UC-patients achieved clinical remission, whereas in the adalimumab group, 60% CD patients achieved clinical remission. The data whether adalimumab-patients were naïve to biological therapies were unfortunately not available.

British guidelines for management of IBD in adults recommend an attempt at withdrawal from therapy for all patients in stable clinical remission.[30] In our study, after ileocolonoscopy, a total of 43% patients discontinued TNFα-blocking therapy in deep remission. The GETAID group's study showed that even in remission, defined as CDAI ≤ 150, relapse rate after withdrawing TNFα-blocking therapy was up to 50% in 1–2 years.[17] A. Molazahi et al.[31] demonstrated in their study published this far only as an abstract that up to 24% of their patients in CD and 30% of patients in UC stopped the medication during steroid-free remission. Their remission rates were 61% in CD and 75% in UC at one year after discontinuation of the TNFα-blocking therapy, and were 50% in all patients at a respective median of 680 and 1334 days. For CD patients on infliximab monotherapy, the factors associated with a high probability of relapse after stopping infliximab are short remission, endoscopically active disease, high markers of inflammation (S-CRP or platelet count), inadequate infliximab trough levels, and earlier intestinal operations.[32] In our study, discontinuation of TNFα-blocking therapy was no option in about half of the patients in deep remission, either because of a failed earlier discontinuation attempt, history of very severe disease, or no other effective medication to maintain remission. More studies are necessary to clarify the options of discontinuation of the TNFα-blocking therapy, before we can clearly determine in whom TNFα-blocking therapy can be safely stopped.

Our study has several limitations. The patient group was heterogeneous, with both CD and UC patients included regardless of localization, behavior, or duration of disease. The induction doses of both infliximab and adalimumab varied, especially at the beginning of the study period, due to local variation in protocols. We included only patients who had responded to TNF-blocking therapy sufficiently to continue with scheduled maintenance for at least 11 months. This may overestimate the efficacy of biological therapies due to endoscopy-based case selection. Furthermore, the study population included only those maintenance therapy patients that underwent ileocolonoscopy during the study period. As we had gathered our data retrospectively, clinical disease activity was assessed by the PGA rather than being based on any validated score. Finally, the endoscopic scoring was done by several experienced endoscopists, making some interobserver variability in the scoring system possible. Despite these limitations, we believe that this study reflects well the real-life situation in clinical practice.

In conclusion, deep remission may be achievable in roughly half of IBD patients on TNFα-blocking maintenance therapy. A considerable number of our patients had concomitant histologically inactive disease. Only for about half of our patients was discontinuation of TNF-blocking medication considered reasonable after achievement of deep remission.

Conflict of interest

The authors declared no financial conflict of interest.

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