Depth of remission in Crohn's disease patients seen in a referral centre : associated factors and impact on disease outcome

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Abstract

Introduction : **Our goals were to assess the prevalence of biological and tissue remission in routine practice in Crohn's disease, and to evaluate the correlation between biological or tissue remission and clinical or demographic characteristics as well as their impact on disease outcome.**

Methods : **We performed a retrospective monocenter study. Biological remission was defined by a CRP < 5 mg/l. Tissue remission was defined by the absence of ulcer at endoscopy and/or absence of signs of acute inflammation at MRI. Association with demographic, clinical and laboratory markers was studied by logistic regression models and rates of relapses, hospitalizations and surgeries were compared using the logrank test.**

Results : **Among the 263 patients included, 147 were in clinical remission ; 102/147 (69%) were in biological remission. Fifty-six patients also had morphological evaluation : 37 (66%) were in tissue remission. Biological remission was associated with older age, higher hemoglobin and lower BMI. Tissue remission was associated with older age, lower platelets count, absence of previous surgery, and the use of immunosuppressant. Time-to-relapse was significantly longer in patients with biological remission and in patients with tissue remission as compared to patients without biological or tissue remission.**

Conclusions : **Among the patients in clinical remission seen as outpatients, two thirds were either in biological and/or tissue remission. Biological and/or tissue remission was associated with a better outcome than clinical remission alone.** (Acta gastroenterol. belg., **2014**, 77, **41-46**).

Key words : Crohn's disease, endoscopy, magnetic resonance imaging, CT Scanner, C-reactive protein, deep remission.

Introduction

Crohn's disease (CD) is an inflammatory bowel disease characterized by alternative periods of remission and relapse. Remission can be judged at the clinical, biological or at the intestinal tissue level. There is no good correlation between clinical remission, biological remission and intestinal healing in CD (1). Indeed, during periods of clinical remission, endoscopic/imaging abnormalities can persist. Biomarkers such as C-reactive protein (CRP) or fecal calprotectin are better but still imperfectly correlated to tissue healing (2). Preliminary data indicate that persisting intestinal lesions despite clinical remission may lead to a higher risk of disease relapse and disease progression with worsening of tissue damage (3,4,5). The evolving concept of deep remission may include clinical but also biological remission and intestinal healing. This state could be associated with better disease outcome, with lower risk of relapse, hospitalizations and surgeries. Data from the EXTEND study indicate that with current treatment strategies, usually using anti-TNF late in the disease course, a deep remission combining clinical remission and mucosal healing can only be achieved in a minority of patients (6). This deep remission seems more frequently achieved when anti-TNF are used earlier in the disease (7). Currently, it is not precisely known what is the proportion of patients achieving such state of deep remission in routine practice, what are the factors associated with it and its influence on mid- and long-term disease outcome.

In this retrospective study we aimed at assessing the prevalence of biological and/or tissue remission in CD, in routine practice in a referral centre. Secondary objectives were to evaluate the correlation between biological and/or tissue remission and disease outcome, including relapses, hospitalizations and surgeries, and to try to find biological, clinical or demographic factors associated with it.

Patients and methods

We performed a retrospective study at the referral IBD center of Liège University Hospital in Belgium, and including patients seen at the outpatient clinic between April 2009 and April 2010. All consecutive patients seen during that period of time by two senior gastroenterologists (JB and EL) were first considered. Retrospective follow-up was then analyzed till October 2011. Protocol was accepted by University of Liège ethics committee. Among the patients seen at the outpatient IBD clinic of our hospital, we've selected a population of CD patients in clinical remission and having had a measurement of blood CRP. Some of those had also a tissue healing assessment by ileo-colonoscopy and/or intestinal MRI and/or CT-scanner within a short interval of time. Different stages of remission were compared : clinical only *vs* biological and clinical vs. tissue and clinical. Clinical remission was defined by a Harvey Bradshaw Index

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Submission date : 20/09/2013
Acceptance date : 17/11/2013

(HBI) ≤ 4 or absence of CD symptoms according to clinician judgment in the medical notes of the patient. All the patients included in our analyses were considered in clinical remission. Biological remission was defined by a CRP < 5 mg/l. Tissue remission was defined by the absence of ulcer at endoscopy and/or absence of signs of acute inflammation at magnetic resonance imaging (MRI) or CT scanner (mucosal or submucosal edema, early contrast enhancement, mucosal ulcers, fat stranding, comb sign). A relapse was defined, either by the need to change therapy due to symptoms worsening, hospitalization due to CD, endoscopic dilatation of a gastrointestinal tract stricture, or surgical procedure for the disease (including bowel resection, stoma and perianal abscess drainage). The outcome was assessed using the time-to-relapse or the time to more specific outcomes, such as hospitalization or surgery.

Logistic regression models were used to measure the association between the different predefined states of remission with demographic, clinical and laboratory markers. Rates of relapses over follow-up were represented on Kaplan-Meier curves and compared with logrank test. Multivariate Cox regression models were used to explain rates of relapses with covariates. P values were considered as significant at the 5% level ($p < 0.05$). Calculations were done using SAS version 9.2 (SAS Institute, Cary, NC, USA).

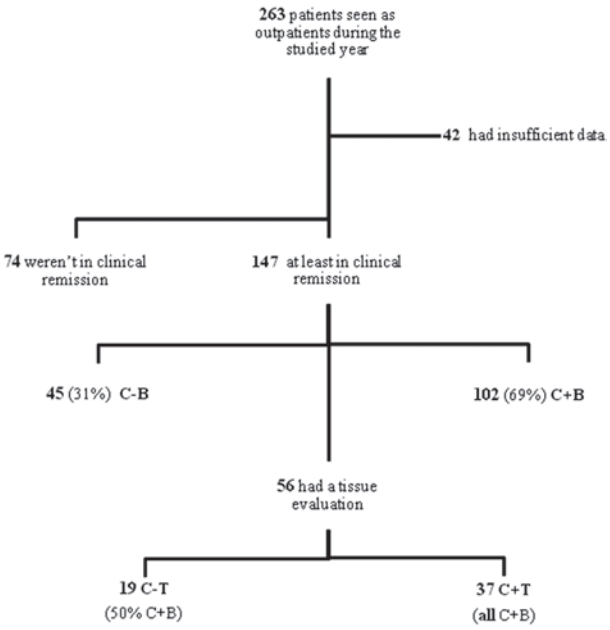

Fig. 1. — CD patients' disposition in the study. Among the 147 studied patients, 56 had endoscopic and/or MRI exploration. Among those, 37 showed mucosal (at endoscopy) and/or bowel wall (at MRI) healing and were considered in tissue remission. All of these also happened to be in biological remission.

Results

Among the 263 CD identified in outpatients track records for the considered year, 147 were at least in clinical remission (C) and had a measurement of blood CRP. The characteristics of these 147 patients are showed in table 1. Among them, 102 (69%) were in clinical and biological remission (C+B). Out of 147, only 56 patients had undergone a morphological exploration. As such kind of morphological exploration is not yet systematic in routine practice, it was only performed in a subset of patients after an agreement between the patient and physician to assess tissue healing. There was no other specific indication for this exploration and this subpopulation was not different form the global population. Among these 56 patients having had morphological evaluation (either by endoscopy (n = 35), MRI or CT (n = 21)), 37 were in clinical and tissue remission. All the patients in tissue remission were also in biological remission (C+B+T) (Fig. 1). Among the 19 patients not being in tissue remission, 10 were in biological remission.

Factors associated with biological remission (n = 147)

By univariate analysis, male gender (OR = 3.34, 95% CI = 1.53-7.32 ; p = 0.0025), older age (OR = 1.04, 95% CI = 1.01-1.07 ; p = 0.011), being a former smoker (OR = 3.58, 95% CI = 1.20-10.70 ; p = 0.022), lower platelet counts (OR = 0.13, 95% CI = 0.03-0.54 ; p = 0.049), and higher hemoglobin (OR = 2.07, 95% CI = 1.47-2.92 ; p < 0.0001) were associated with biological remission. In multivariate analysis (performed on 140/147 patients), older age (OR = 1.04, 95% CI = 1.00-1.08 ; p = 0.02), higher hemoglobin (OR = 2.16, 95% CI = 1.50-3.10 ; p < 0.0001) and lower Body Mass Index (BMI) (OR = 0.88, 95% CI = 0.81-0.98 ; p = 0.01) were associated with biological remission.

Factors associated with tissue remission (n = 56)

By univariate analysis, the absence of ANCA (OR = 0.10, 95% CI = 0.01-0.74 ; p = 0.025), a lower platelets count (OR = 0.06, 95% CI = 0.00-0.91 ; p = 0.043), a higher hemoglobin (OR = 1.97, 95% CI = 1.11-3.50 ; p = 0.020), a lower CRP (OR = 0.28, 95% CI = 0.13-0.57 ; p = 0.0006) and the use of immunosuppressive drugs (OR = 11.0, 95% CI = 1.32-91.31 ; p = 0.027) were associated with tissue remission. In multivariate analysis (performed on 54/56 patients), older age (OR = 1.08, 95% CI = 1.00-1.17 ; p = 0.03), lower platelets count (OR < 0.001, 95% CI = < 0.00-0.16 ; p = 0.008), absence of previous surgery (OR = 0.12, 95% CI = 0.02-0.85 ; p = 0.03), and the use of immunosuppressant (OR = 145.54, 95% CI = 3.42- > 999.99 ; p = 0.009) were associated with tissue remission.

Time-to-relapse according to the state of Crohn's disease remission

Time-to-relapse was significantly longer in patients with biological remission (C+B) as compared to patients

Table 1. — **Patients characteristics of the studied population (C-B and C+B; n = 147) and the subpopulation with endoscopic and/or MRI-CT assessment (C+T and C-T; n = 56). Data expressed as n (%) or mean ± SD**

		C-B (n = 45)	C+B (n = 102)		C+T (n = 37)	C-T (n = 19)	
Gender	F	34 (75.6)	49 (48.0)		19 (51.4)	9 (47.4)	
	M	11 (24.4)	53 (52.0)	**	18 (48.7)	10 (52.6)	
Age	yrs	37.1 ± 12.3	42.2 ± 13.3	*	43.4 ± 13.2	35.8 ± 13.8	
Disease duration	yrs	11.2 ± 6.76	13.3 ± 9.27		12.8 ± 9.59	9.95 ± 6.84	
BMI		25.1 ± 4.95	23.8 ± 3.68		24.3 ± 4.41	24.7 ± 4.85	
Smoking	No	21 (46.7)	34 (33.7)		16 (43.2)	7 (36.8)	
	Yes	19 (42.2)	38 (37.6)		11 (29.7)	9 (47.4)	
	ex	5 (11.1)	29 (28.7)	*	10 (27.0)	3 (15.8)	
Montreal classification							
A	1	4 (8.9)	8 (7.8)		3 (8.1)	0 (0.0)	
	2	36 (80.0)	78 (76.5)		27 (73.0)	18 (94.7)	
	3	5 (11.1)	16 (15.7)		7 (18.9)	1 (5.3)	
B	1	27 (60.0)	57 (56.4)		22 (59.5)	8 (42.1)	
	2	7 (15.6)	25 (24.8)		9 (24.3)	6 (31.6)	
	3	11 (24.4)	19 (18.8)		6 (16.2)	5 (26.3)	
L	1	10 (22.2)	33 (32.7)		14 (37.8)	5 (26.3)	
	2	10 (22.2)	19 (18.8)		5 (13.5)	2 (10.5)	
	3	20 (44.4)	43 (42.6)		15 (40.5)	7 (36.8)	
	4	1 (2.2)	2 (2.0)		1 (2.7)	1 (5.3)	
	1+4	3 (6.7)	3 (3.0)		1 (2.7)	3 (15.8)	
	3+4	1 (2.2)	1 (1.0)		1 (2.7)	1 (5.3)	
P	No	25 (55.6)	68 (66.7)		24 (64.9)	10 (52.6)	
	Yes	20 (44.4)	34 (33.3)		13 (35.1)	9 (47.4)	
Laboratory parametrers							
Platelets	10^9/L	335 ± 92.2	291 ± 94.9	**	289 ± 67.0	327 ± 68.0	*
Hemoglobin	g/dL	12.9 ± 1.09	13.9 ± 1.30	***	14.0 ± 1.06	13.1 ± 1.26	*
CRP	mg/L	12.9 ± 10.4	1.64 ± 1.28	***	1.42 ± 1.17	7.18 ± 10.1	***
Treatment							
Previous surgery		25 (55.6)	55 (53.9)		18 (48.6)	13 (68.4)	
Anti-TNF		25 (55.6)	46 (45.1)		13 (35.1)	11 (57.9)	
Mesalazine		4 (8.9)	18 (17.6)		7 (18.9)	4 (21.0)	
Topical steroids		4 (8.9)	7 (6.9)		2 (5.4)	2 (10.5)	
Immunosuppressant		14 (31.1)	34 (33.3)		14 (37.8)	1 (5.3)	*
Systemic steroids		4 (8.9)	4 (3.9)		1 (2.7)	2 (10.5)	
No treatment		1 (2.2)	8 (7.8)		4 (10.8)	1 (5.3)	

*p < 0.05 ; **p < 0.01 ; ***p < 0.001.

C-B = clinical remission without biological remission ; C+B = clinical and biological remission ; C-T = clinical without tissue remission ; C+T = clinical and tissue remission.

without biological remission (C-B) (median time to relapse > 30 months vs. 20 months ; p = 0.0008) (Fig. 2).

Beside the absence of biological remission, using bivariate model, the significant variables associated with a shorter time to relapse were the B2 phenotype at last visit (HR = 2.04, 95%CI : 1.14-3.65, p = 0.016), a lower hemoglobin (HR = 1.30, 95%CI : 1.04-1.63, p = 0.022), current anti-TNF treatment (HR = 1.90, 95%CI : 1.11-3.23, p = 0.018), and current systemic corticoid treatment (HR = 2.38, 95%CI : 1.11-3.23, p = 0.049).

When considering only the subset of patients with morphological assessment of tissue healing (n = 56), time-to-relapse was significantly longer in patients with tissue remission (being in this study population systematically associated with biological remission (C+B+T)), as compared to patients without tissue remission (C-T) (median time to relapse > 29 months vs. 22 months ; p = 0.0043) (Fig. 3).

Beside tissue remission, using bivariate model, no other variable was significantly associated with the time-to-relapse. In the small subgroup of patients in biological but not tissue remission (n = 10/56) the relapse rate over follow-up was 50% (5/10) as compared to 21.7% (8/37) in patients in both biological and tissue remission.

Time-to-surgery and time-to-hospitalization according to the state of remission

Biological remission tended to be associated to a lower risk of surgery (p = 0.06) but not with a lower risk of hospitalization (Fig. 4).

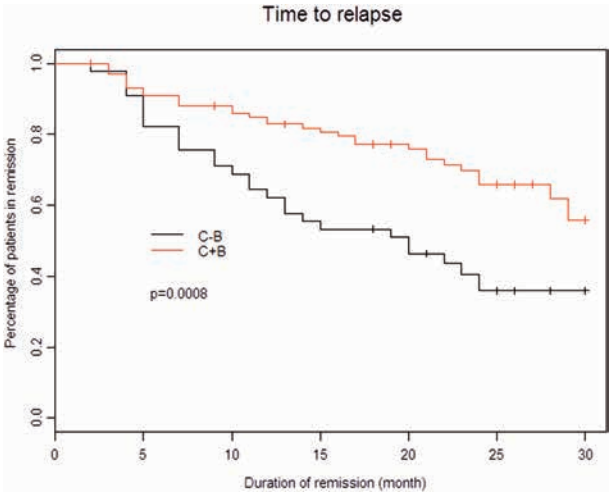

Fig. 2. — Kaplan Meier curves of time to relapse for the patients with clinical and biological remission (C+B ; n = 102) vs. patients with clinical but not biological remission (C-B ; n = 45).

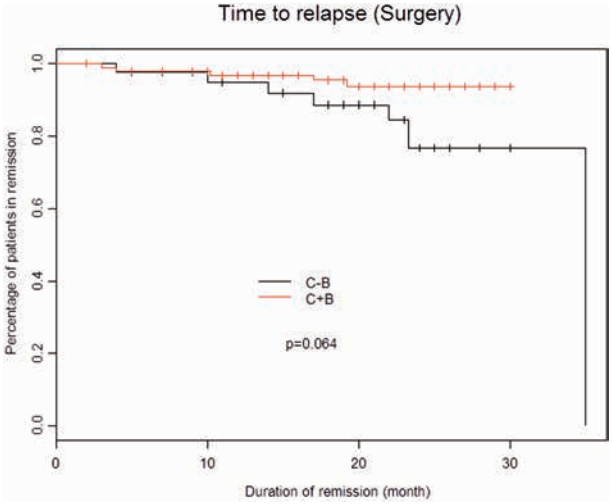

Fig. 3. — Kaplan Meier curves of the time to relapse in patients with clinical and tissue remission (C+T ; n = 37) vs. patients with clinical but not tissue remission (C-T ; n = 19). The 37 patients with clinical and tissue remission (C+T) happened to be also in biological remission (C+B+T).

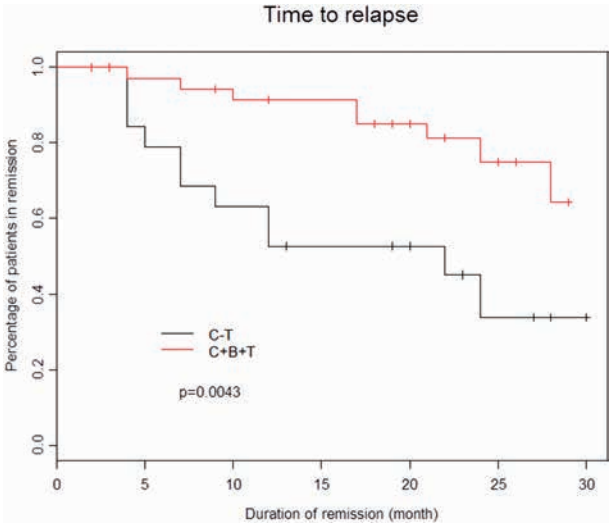

Fig. 4. — Kaplan Meier curves of the time to surgical resection in patients with clinical and biological remission (C+B ; n = 102) vs. patients with clinical but not biological remission (C-B ; n = 45).

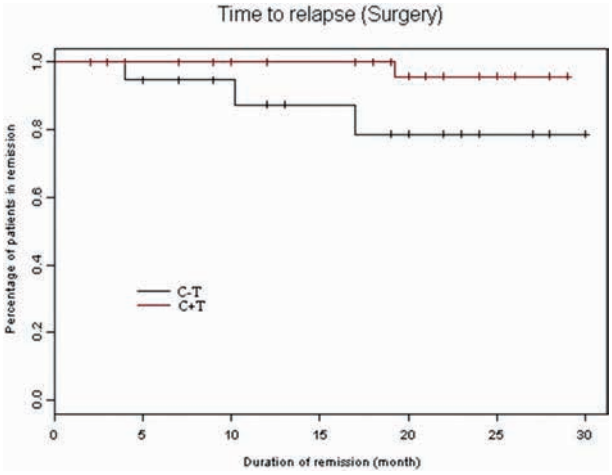

Fig. 5. — Kaplan Meier curves of the time to surgical resection in patients with clinical and tissue remission (C+T ; n = 37) vs. patients with clinical but not tissue remission (C-T ; n = 19). The 37 patients with clinical and tissue remission (C+T) happened to be also in biological remission (C+B+T).

Tissue remission (here systematically associated with biological remission) was associated to a lower risk of surgery (p = 0.04) but not of hospitalization (Fig. 5).

Discussion

Among the patients seen as outpatients, in clinical remission, in our center in 2009, we found a proportion of two thirds who were in biological and/or tissue remission. This state of remission beyond clinical symptoms was associated with better outcome including less relapses and less surgeries.

The prevalence of deep remission defined by the occurrence of both clinical and biological remission and/or intestinal tissue healing has not been broadly studied in routine practice in CD. In a prospectively recruited cohort of CD patients in clinical remission under combination therapy with infliximab and immunosuppressants, more than ¾ were also in biological remission (defined by a hsCRP < 5 mg/l) and more than 2/3 were in mucosal healing (defined either by the absence of ulcer or a CDEIS < 3) (5). This is very close to what we observed, in a relatively similar population since around 80% of our patients were treated with anti-TNF and/or immuno-

suppressants. The proportion of deep remission may be much lower in patients treated with corticosteroids (1), in more severe patients, or patients not responding optimally to anti-TNF and/or immunosuppressants. In a population-based study from Norway, including CD cases diagnosed in the early nineties, before the era of anti-TNF, only 38% were in mucosal healing one year after the diagnosis (4). Steroid treatment was associated with a lower rate of mucosal healing. In a recently published controlled trials comparing adalimumab to placebo for the induction and maintenance of mucosal healing in CD, only around 20% of the patients achieved such level of remission including clinical remission and mucosal healing (6).

Biological remission is known to be associated with an older age (8). Low platelet count and a higher hemoglobin concentration have already been associated with good outcome in CD including a low risk of developing severe disease and lower risk of relapse (5,9,10). In a post-hoc analysis of the EXTEND trial, it was also associated with mucosal healing (7). A more surprising association may be the one between biological remission and low BMI. Despite low BMI is usually associated with uncontrolled CD, particularly affecting the small bowel, a relatively low BMI (albeit far above the levels associated with malnutrition) could thus be associated with a lower systemic inflammatory burden, among the patients who are in clinical remission. The association between mesenteric fat and inflammation is well known and some authors have showed an association between higher BMI and bad prognosis in CD (11). Furthermore the CRP production by mesenteric fat itself in the setting of CD may partly explain this observation (12). Indeed, due to this local production, patients with increased mesenteric fat may more seldom achieve a normalization of their CRP concentration.

Factors independently associated with tissue remission were older older age, lower platelets count, absence of previous surgery, and the use of immunosuppressant. Older age and platelet count were also associated with biological remission. As highlighted here-above, the association with a lower platelet count was already showed in the EXTEND trial, although in that study, an older age was associated with a lower rate of mucosal healing (7). Several studies have shown the potential of immunosuppressants to achieve mucosal healing although it has been showed to be lower than with anti-TNF (13,14). The fact that we found an association with immunosuppressant and not with anti-TNF may reflect a bias in the treatment of our patients. Most severe cases, particularly immunosuppressant refractory cases are treated with anti-TNF and the achievement of a tissue healing in those patients is difficult as highlighted in the EXTEND trial. On the contrary, the patients who remain under immunosuppressant treatment are most probably the good responders to these drugs. In those patients with an adequate response to immunosuppressants, the rate of mucosal healing has been showed around 75% (13).

Time to relapse was significantly longer in patients with biological remission as compared to patients without biological remission. This has already been published in several studies a while ago (15,16). The elevation of a broad range of blood inflammatory markers, including CRP, IL6, sIL2R and ESR has been consistently associated with an increased risk of relapse. In the present study, biological remission also tended to be associated with a lower risk of surgery but not with a lower risk of hospitalization.

Time to relapse was also significantly longer in patients with tissue remission, as previously showed in the long-term follow up of controlled trials (3). Tissue remission was also associated to a lower risk of surgery ($p = 0.04$) but not of hospitalization. This association with a lower rate of surgery was already found in a population-based study from Norway (4) and in another cohort of patients treated with infliximab in a tertiary referral centre (17).

Our study presents limitations. It is a retrospective monocentre study. Clinical remission or relapse were established either based on a HBI available in patients' notes or on a simple qualitative assessment by the clinician. Fecal calprotectin was not routinely used in those patients to confirm biological remission. No endoscopic or MRI score was prospectively calculated. The subgroup of patients being in biological remission but not in tissue remission was too small to draw any definitive conclusion about the added value of tissue remission over isolated biological remission to improve disease outcome. Nevertheless, the proportion of relapse in patients with biological but no tissue remission was numerically higher than in patients with combined biological and tissue remission. Likewise the impact of combined biological and tissue remission on the time-to-surgery seemed statistically more significant than the one of simple biological remission.

In conclusion, among patients in clinical remission, seen as outpatient in a referral centre, only one third is not in biological and/or tissue remission. Nevertheless, those patients are important to identify because they are at higher risk of relapse and more importantly, of surgery.

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