Efficacy of switching to infliximab in patients with Crohn's disease with loss of response to adalimumab

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Abstract

Background and study aims : **Anti-TNF monoclonal antibodies are a cornerstone in the treatment of Crohn's disease. Prospective data on switching from the subcutaneous and human adalimumab (ADM) to the intravenous and chimeric infliximab (IFX) are scarce.**

Patients and methods : **In this prospective, observational, multicentre cohort study we included 21 patients with loss of response to ADM despite at least 4 consecutive weekly injections. Clinical response (CDAI drop≥70 points) and remission (CDAI≤150) were assessed after switching from ADM to IFX after 10 weeks, 6 and 12 months. Predictive factors of response/remission, the need for therapy intensification, discontinuation and safety were investigated.**

Results : **Short-term response and remission (10 weeks) were seen in 57% and 48% respectively. Mid- and long-term clinical response and remission were achieved in 40% and 25% after 6 months and in 45% and 20% after 12 months respectively. At 12 months, 81% still were on IFX. IFX therapy intensification was needed in half of the patients at 6 months and three quarter of patients at 12 months. Undetectable ADM trough levels (despite weekly injections) were a predictive factor for short-term response and remission to IFX. About half of the patients with response at week 10 maintained response at 6 and 12 months.**

Conclusions : **Switching from ADM to IFX can be efficacious in patients with loss of response, in particular in case of undetectable ADM trough levels. The majority of patients however will need IFX therapy intensification during their first year of treatment.** (Acta Gastroenterol. belg., **2018**, 81, **15-21**).

Key words : Crohn's disease, adalimumab, infliximab, switching.

Introduction

The introduction of biologicals significantly improved the management and outcome of patients with Crohn's disease (CD). Anti-Tumor Necrosis Factor (TNF) monoclonal antibodies have proven to be efficacious for the induction and maintenance of remission in active CD (1-3).

Infliximab (IFX, a chimeric monoclonal antibody) was registered as the first anti-TNFa agent for CD in 1998, followed by adalimumab (ADM, a fully human antibody) about ten years later (4,5). Both TNF blockers induce clinical response and/or remission in about two thirds of patients. This means on the other hand that 1 in 3 patients fail to respond to anti-TNF treatment. In addition to primary non-response a subgroup of patients who initially responded will lose their response or discontinue their treatment due to intolerance (6,7).

In case of secondary failure to a first anti-TNF agent switching to a second agent is common practice. Indeed, the GAIN trial clearly showed efficacy of ADM in patients who lost response or showed intolerance to IFX (8). Moreover ADM was also able to maintain remission in patients with initial IFX failure as demonstrated in a subgroup analysis in the CHARM study (9). Elective switching from IFX to ADM during stable remission, for instance because of patients' preference for the subcutaneous administration, is however not recommended (10). The SWITCH trial showed that this strategy might be associated with a certain risk of relapse (11). In case of loss of response, therapy optimization (including dose escalation or interval shortening) is often performed as a first therapeutic option before switching to another anti-TNF agent or a molecule with another mode of action (7,12).

Since IFX was approved many years before ADM most of the studies on switching between TNFa blockers focussed upon the efficacy of ADM in IFX failures. Although routinely performed in clinical practice, prospective data on the outcome of switching to the chimeric anti-TNF (IFX) in patients who lost response or became intolerant to the humanized anti-TNF a (ADM) are scarce.

The aim of the present trial was to prospectively assess the efficacy of IFX after loss of response to ADM in patients with moderately to severely active CD in an observational cohort study.

Materials and Methods

Study Population and Data Collection

In this prospective, observational, multicentre study 21 patients with loss of response to ADM were included from 11 Belgian hospitals (6 university and 5 regional

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hospitals). All participating clinicians were member of the Belgian IBD Research and Development group (BIRD).

Loss of response to ADM was defined as moderately to severely active CD (220≤CDAI≤450) in combination with an elevated C-reactive protein (CRP≥5mg/L) or endoscopic or radiological evidence of disease activity occurring after at least 4 weeks of weekly injections of ADM 40mg.

Introduction of azathioprine (AZA) or mercaptopurine (MP) was allowed until 2 weeks after starting IFX and was then continued throughout the study ("combo" therapy). This 2 week interval was defined in order to allow thiopurine methyltransferase (TPMT) genotyping before starting this immunomodulator. At least a 2-week wash-out period of ADM was demanded before starting IFX. Previous treatment with IFX or certolizumab pegol was not allowed.

The following characteristics of each patient were recorded: age, sex, ethnic background, smoking habit, disease duration, age at diagnosis, disease location and behaviour (Montreal classification), prior surgery and medication (concomitant use of immunomodulators) and duration of ADM treatment (13).

IFX was administered at 5mg/kg body weight at week 0, 2 and 6 (induction) and every 8 weeks thereafter. Considering the observational design of the study (routine clinical practice), anti-TNF therapy could be optimized at the discretion of the investigator, including interval shortening and dose escalation. The decision to discontinue IFX was also left at the discretion of the treating physician. Immunomodulator dose adjustment or switch and intermittent courses of corticosteroids were recorded.

The following data were recorded: Crohn's disease activity index (CDAI), CRP, (serious) adverse events, therapy adjustments, timing and reason for IFX dose escalation or interval shortening and/or treatment discontinuation. Serious adverse events were regarded as any adverse event requiring hospitalization.

Serum samples were collected for the analysis of ADM concentrations and anti-ADM titers (ADM Ab) at screening (one week after the last ADM injection) and IFX intermediary concentrations at week 10 (4 weeks after the 3rd IFX infusion), IFX trough levels at 6 and 12 months and anti-IFX antibodies (IF Ab) at week 10 and around 6 and 12 months. The IFX trough levels around 6 and 12 months were measured just before an IFX infusion. All titers were retrospectively analysed at the end of the trial.

ADM concentrations and ADM Ab titers were quantified using in-house developed ELISAs (14, 15). IFX was quantified using the Ridascreen IFX Monitoring assay (R-Biopharm AG, Darmstadt, Germany) and IF Ab titers were quantified using an in-house developed assay (16). ADM trough levels ≥ 5 μg/mL were considered to be adequate (17, 18).

The study was approved by the ethics committees of the participating centres and all patients signed an informed consent.

Study Objectives

The primary objective was to assess clinical response and remission at week 10 after 3 infusions of IFX (week 0, 2 and 6). We defined clinical response as a drop with at least 70 points in CDAI compared to baseline. Clinical remission was defined as a CDAI score of 150 or less.

Other study objectives were: sustained clinical response (CDAI drop≥70 points compared to baseline) and mid-term clinical remission (CDAI≤150) at 6 and 12 months, the need for IFX therapy optimization (dose escalation or interval shortening) and discontinuation, safety and tolerance.

In an ancillary study we assessed for serological factors associated with clinical response and remission after switching from ADM to IFX, including CRP and serum concentrations of and antibodies against ADM (screening) and IFX (week 10, at 6 and 12 months).

Statistical Analysis

Due to the open label design of the study, statistics were mainly descriptive by the use of medians (with range) and proportions for continuous and categorical variables respectively. The observed responses, measured by the described medians and proportions were compared with data from the literature. Changes from baseline were described by differences of medians, evaluated by paired statistics (Wilcoxon Rank test). Categorical data were compared using the $\chi 2$ test. In case of missing variables, data were imputed by means or last observation carried forward was applied.

Results

Study population

A total of 21 patients were included in the study. The main characteristics are summarized in table 1. Most of the patients were women (76%) and about one fourth of the population were active smokers. Ileal involvement was present in more than 60%. Only a minority had a history of stricturing (14%) or penetrating (14%) disease. A history of perianal involvement was seen in 6 of 21 patients (29%). None of the patients had active perianal disease at inclusion.

The patients had active CD at time of inclusion (CDAI ranging from 226 to 413) despite dose optimization of ADM (at least 4 consecutive, weekly injections of 40mg until 1 week before screening). Median time from diagnosis to ADM treatment was 1.5 years (range 0-30 years). All 21 patients had initially responded to the induction therapy with ADM and were therefore defined as having loss of response. The median of ADM

Table 1. — **Study population characteristics**

Variables	**N = 21**
Median (range) age	34 (19-69) years
Gender Male Female	 5 (24%) 16 (76%)
Smoking Active Ex-smoker Non-smoker	 5 (24%) 5 (24%) 11 (52%)
Median (range) disease duration	3 (1-33) years
Median (range) age at diagnosis ≤ 16 y (A1) 17-40 y (A2) > 40 y (A3)	23 (14-67) years 2 (10%) 15 (71%) 4 (19%)
Location Ileum (L1) Colon (L2) Ileocolon (L3) + Upper GI tract (L4)	 3 (14%) 8 (38%) 10 (48%) 1 (5%)
Behavior Non-stricturing, non-penetrating (B1) Stricturing (B2) Penetrating (B3)	 15 (71%) 3 (14%) 3 (14%)
Perianal disease (P) at inclusion	0 (0%)
CD related surgery	4 (19%)
Median (range) ADM therapy duration	23 (6-60) months
Steroids at baseline	5 (24%)
Immunomodulators (combo) AZA/6MP MTX	10 (48%) 7 (33%) 3 (14%)
Median (range) CDAI at baseline	276 (226-413)
Median (range) CRP at baseline	23 (2-127) mg/L

ADM = adalimumab, AZA = azathioprine, MP = mercaptopurine, MTX = methotrexate, CDAI = Crohn's disease activity index, CRP = C-reactive protein.

treatment duration was 23 months, ranging from 6 to 60 months. The number of weekly ADM injections ranged from 4 to 52 (median 13.5 weeks).

At the end of ADM treatment, 4 patients concomitantly used azathioprine or mercaptopurine and 3 patients were on methotrexate. All these patients continued their immunomodulator after starting with IFX. In addition, 3 patients were started on combo therapy with azathioprine within the first 2 weeks of the study (as allowed by the study protocol). In total, 10 patients started the study with "combo" therapy (48%).

Clinical remission/response

After starting IFX, approximately half of the patients (n = 10, 48%) were in clinical remission at short term (week 10). Clinical response was seen in 12 out of 21 patients (57%) (Fig. 1). Short term response was absent in 43% of patients.

CDAI scores at 6 and 12 months were missing in one patient. In the remaining 20 patients remission and clinical response (all without immunomodulatory adjustment or corticosteroids) at 6 months dropped to 25% (n = 5) and 40% (n = 8) respectively. At 12 months, remission and clinical response were observed in 20% (n = 4) and 45% (n = 9) respectively.

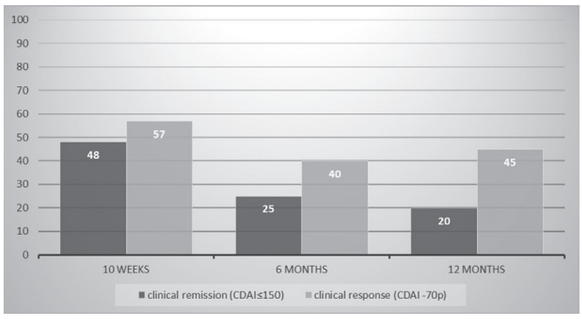

Fig. 1. — Clinical remission and response (with or without IFX therapy optimization). CDAI = Crohn's disease activity index.

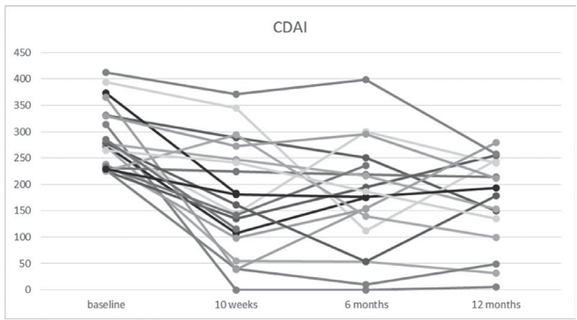

Fig. 2. — CDAI scores. CDAI = Crohn's disease activity index.

At the end of the study, 17 of 21 patients (81%) of patients were still on IFX. In one patient IFX was stopped within the first 6 months, 3 additional patients stopped between 6 and 12 months. The reasons for discontinuation were a delayed infusion reaction (arthralgia), 2 flares of CD and an ileocaecal resection (because of intractable disease), despite IFX therapy optimization. Remarkably, all 4 patients who needed to discontinue their treatment with IFX had been in clinical remission at week 10.

The median CDAI dropped from 276 at baseline to 161 at week 10 (P<0.001), 176 at 6 months (P<0.001) and 186 at 12 months (P = 0.001). The individual CDAI scores and their evolution over time are demonstrated in figure 2.

Therapy adjustment

As demonstrated before, mid-term remission and response rates were 25% and 40% at 6 months and 20% and 45% at 12 months respectively. The majority of these patients however needed an IFX therapy intensification (interval shortening or dose increase) in order to maintain their remission or response. At 6 months, IFX therapy adjustments were seen in 10 out of 21 patients (48%) (Fig. 3). After 12 months of IFX treatment only 5 of the patients (24%) never had a therapy intensification. Four of these 5 patients still had a clinical response, one patient was in remission.

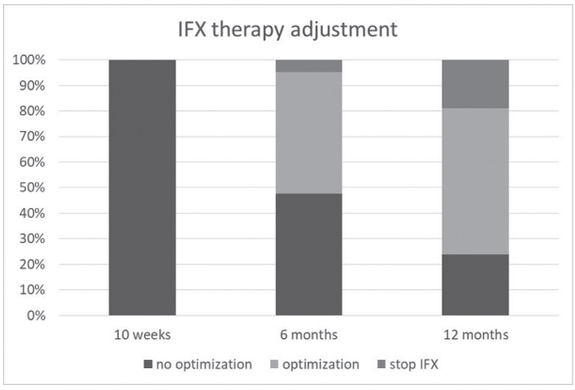

Fig. 3. — Infliximab therapy intensification. IFX = infliximab, intensification = interval shortening or dose increase

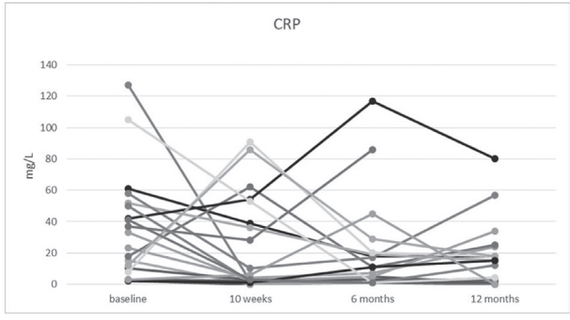

Fig. 4. — CRP evolution. CRP = C-reactive protein

Overall, immunomodulatory therapy (AZA, MP or MTX) was started, changed or switched in 6 patients (29%) during the study. An intermittent course of corticosteroids was given in 4 patients (19%). Six out of the 7 patients with one or both of these treatment adjustments remained on IFX throughout the study.

Prognostic factors

After starting IFX, the median CRP level dropped from 23 mg/L to 4 mg/L at week 10 (P = 0.1), 7 mg/L at 6 months (P = 0.1) and 13.5 mg/L at 12 months (P = 0.25). We found no correlation between the CRP level at baseline and the short term response to IFX. The individual CRP trends in the study population are demonstrated in figure 4.

The drug concentrations and antibody titers and their relation to response/remission are summarized in table 2A and 2B.

At baseline, ADM trough levels were adequate (≥ 5 μg/mL) in 8 of 17 patients, sub-therapeutic (0.3-5 μg/mL) in 3 patients and undetectable (<0.3 μg/mL) in 7 patients. Serum was missing at baseline in 3 patients. Short-term response was seen in 5 of 7 patients (71%) with undetectable ADM trough levels whereas in only 3 of 8 patients (38%) with adequate ADM trough levels (P = 0.2). There was no correlation between the ADM trough level at screening and the response or remission at 6 and 12 months.

Remarkably, response and remission rates were not influenced by IFX trough levels. Several patients showed response or remission with low (<3 μg/mL) or even undetectable (<0.1 μg/mL) trough levels. Two out of 3 patients with IF Ab at week 26 had a clinical response (in the absence of other maintenance treatments). Low or very low levels of IFX were not always accompanied by the presence of IF Ab. On the other hand, high serum levels of IFX were not clearly predictive for response or remission. In general, trough levels seemed very fluctuating over time. Of three patients with IF Ab at 6 months, 1 patient had an adequate trough level at 12 months. In the other 2 patients these antibodies could not be demonstrated anymore at the end of the study (despite low trough levels). Of the 4 patients with ADM Ab at baseline, only 1 patient also developed IF Ab during the trial.

There was no correlation between "combo" therapy at the start of the study and short- or long-term response or remission nor on IFX serum concentrations or the development of IF Ab.

About half of the 12 patients with response at week 10 maintained their response at 6 months (6/12, 50%) and 12 months (5/12, 42%). On the other hand, 6 out of 8 patients (75%) with response at 6 months and 5 out of 9 patients (56%) at 12 months already showed response at week 10.

Safety data

A total of 13 serious adverse events (SAEs) were reported in 6 patients (29%). The reasons for these 13 hospitalizations (as reported by the investigators) are summarized in table 3. All but 1 SAE resolved without sequelae. One patient was still hospitalized for a flare of CD at the end of the study. As mentioned above, 4 patients discontinued IFX treatment due to a SAE.

Of these 6 patients, none showed response or remission at week 26, 1 patient had a response at week 52 (no remission). This last patient was hospitalized because of an episode of obstruction for which he needed an adhesiolysis.

Discussion

Anti-TNF monoclonal antibodies are efficacious in two thirds of patients with active CD. About half of these patients however will experience a loss of response (secondary failure) or intolerance over time (6,8,19). In case therapy intensification (dose increase and/or interval shortening) is not (longer) successful, switching to another anti-TNF agent is common practice (12,20-22). However, prospective outcome data on switching from the human anti-TNF agent ADM to its chimeric counterpart IFX are very scarce.

In our prospective, multicentre, observational cohort study we observed a short-term clinical remission and response at week 10 in nearly 50% and 60% of

Table 2A. — **Short-term outcome, trough levels and anti-drug antibodies**

Patient	ADM	ADM Ab	WEEK 10				Combo
			Remission	Response	IFX	IFX Ab	
1	7,5				9,9		
2	<0,3	yes	x	x	7		AZA
3	<0,3	yes	x	x	15,6		AZA
4	5,2		x	x	1,1		MTX
5	<0,3	yes			ND		
6	<0,3	yes	x	x	5,3		
7	5,3				0,4	no	
8	ND		x	x	10		MTX
9	5				ND		MP
10	<0,3	no	x	x	1,6		
11	1,3			x	<0,1	no	MP
12	13,5		x	x	5,1		AZA
13	5,9		x	x	29,6		
14	3,4		x	x	2,7		
15	ND			x	6,9		
16	ND				ND		
17	7,6				27,2		AZA
18	4,2				39,7		
19	5,2				9,8		
20	<0,3	no			20,3		MTX
21	<0,3	no	x	x	38		AZA

ADM = adalimumab serum concentration, ADM Ab = anti-adalimumab antibody titer, IFX = infliximab serum concentration, IFAb = anti-infliximab antibody titer, combo = combination therapy (biological + immunomodulator), Resp = response, Rem = remission, Adequate ADM≥5μg/mL, adequate IFX≥3μg/mL.

Table 2B. — **Long-term outcome, trough levels and anti-drug antibodies**

		WEEK 10		MONTH 6				W10 – M6	MONTH 12				M6 – M12
Patient	Combo	Rem	Resp	Rem	Resp	IFX	IF Ab	↑ IFX	Rem	Resp	IFX	IF Ab	↑ IFX
1					x	<0,1	yes	x			5,5		x
2	AZA	x	x	x	x	1,8		x	x	x	>48		x
3	AZA	x	x	x	x	5			x	x	20		x
4	MTX	x	x			ND		x	STOP IFX	STOP IFX	STOP IFX		
5						2,1		x			<0,1	yes	x
6		x	x		x	5,6		x	STOP IFX	STOP IFX	STOP IFX		
7						8,3		x			1,7		
8	MTX	x	x			ND					ND		
9	MP					43,9				x	1,9		
10		x	x	x	x	<0,1	yes		x	x	0,2	no	
11	MP		x	No CDAI	No CDAI	ND		x	No CDAI	No CDAI	ND		
12	AZA	x	x			<0,1	yes	x			0,1	no	x
13		x	x		x	3,3				x	3,4		
14		x	x			15,7		x	STOP IFX	STOP IFX	STOP IFX		
15			x	x	x	5				x	9,7		x
16				x	x	4,1		x	x	x	12		x
17	AZA					27,6				x	28,4		x
18						19,1					10,6		x
19						3					2,5		x
20	MTX					11				x	2,7		
21	AZA	x	x	STOP IFX	STOP IFX	STOP IFX			STOP IFX	STOP IFX	STOP IFX		

Rem = remission, Resp = response, IFX = infliximab trough level, IF Ab : anti-infliximab antibody titer, IFX = infliximab therapy intensification.

Table 3. — **Serious adverse events (hospitalizations)**

SAEs	# SAEs (n = 13)	# patients (n = 6)
CD flare	5	2
Sepsis (bacteroides fragilis/aggregatibacter)	1	1
Abdominal pain unrelated to CD	3	2
Pneumonia	1	1
Delayed IFX infusion reaction	1	1
Obstruction (adhesiolysis)	1	1
Abscess right iliac fossa/CD worsening	1	1

patients respectively after switching from ADM to IFX because of loss of response. Patients with primary non-response to ADM were excluded from the study. At 6 and 12 months, remission was present in 25% and 20% respectively whereas 40% and 45% of patient still showed a clinical response. Response at week 10 seemed somehow predictive for sustained response since the majority of patients with response at 6 and 12 months already had short-term response (75% and 56% respectively). On the other hand, about half of the patients with short-term response maintained this response at 6 and 12 months.

A small retrospective cohort study looked at the effectiveness of IFX after ADM (23). Five patients with loss of response to ADM were included. Three of them achieved short-term remission, the other 2 patients had partial response (at week 4). There were no long-term results available. A prospective French study of Roblin et al investigated loss of response to ADM in 82 patients and the effects of ADM interval shortening (weekly injections) and switching to IFX (24). Overall, clinical remission at 6 months was achieved in 31% of 52 patients after switching from ADM to IFX (24). In an open label trial with ADM after loss of response or intolerance to IFX, Sandborn et al showed similar results as in our cohort with clinical response and remission at week 12 in 29% and 59% respectively (25). Looking at systematic reviews, remission rates after switching from IFX to ADM for loss of response vary from 12 to 67% during induction and 29 to 72% during maintenance therapy. Clinical response ranged from 29 to 83% during induction and 31 to 59% during maintenance (20,26,27).

At the end of our study (12 months) 17 of 21 patients (81%) still were on IFX. Four patients discontinued their treatment with IFX due to a delayed hypersensitivity reaction, a flare of their disease or surgery. Six patients who were not considered to have remission or response on IFX regained somehow symptom control after a dose increase or switch of immunomodulator or an intermittent course of steroids.

At 6 months half of our patients already needed a therapy intensification whereas at 12 months only one quarter of the patients never had a dose increase or interval shortening. In general, therapy optimization can be seen in about half of the patients on IFX (28,29).

Trough levels of ADM at screening seemed to be predictive for a short-term response or remission. In case of undetectable ADM trough levels 71% achieved remission at week 10 compared to 38% in patients with adequate trough levels (≥ 5μg/mL). This correlates with the study of Roblin et al where low ADM trough levels with anti-ADM antibodies were considered to be a good indication for switching to IFX. In these patients remission at 6 months was achieved in 80% as opposed to 7% in patients with high ADM trough levels (≥ 5μg/mL) (24). In the latter, according to these results switching to another drug class should be considered. In case of low ADM trough levels without anti-ADM antibodies therapy optimization (interval shortening) clearly remains the first choice before switching to IFX (24).

The predictive effect of IFX trough levels and antibodies to IFX on the clinical outcome of this treatment has been explored in several studies (30-32). Moreover, there is a growing interest in the clinical utility of these tests for therapy optimization (therapeutic drug monitoring) (33). However, we found no clear correlation between the serum concentrations of IFX at week 10 (intermediary levels) and 6 and 12 months (trough levels) and the response and remission rates in our cohort of 21 patients. Furthermore, these trough levels seemed quite fluctuant and anti-IFX antibodies were even transient in some patients. This was also seen in a study from Leuven where antibodies against IFX were transient in 28% of patients (34).

Combination therapy of IFX with immunomodulators ("combo") has shown to be correlated with better outcome than IFX alone (30). Furthermore, combining both medications reduced the risk for anti-drug antibody formation. Neither response or remission rates nor IFX trough levels or anti-IFX antibodies were influenced by combo therapy in our study.

In total, 13 SAEs (hospitalizations) were recorded in 6 patients (29%). Eventually, 4 of these patients needed to discontinue their treatment with infliximab (19%). In their systematic review with meta-analysis, Gisbert et al found mild to moderate AEs in up to 81% and SAEs in 0-21% of patients receiving a second anti-TNF agent after failure of a first one (20). Most of these SAEs were gastrointestinal disorders and infections as it was also the case in our cohort. The authors reported withdrawal of anti-TNF treatment in up to 20% of patients.

We need to take into account some limitations interpreting our results. First of all, statistics in this observational cohort study are mainly descriptive due to the relative small population. The decision to intensify or discontinue IFX was not standardised but left at the discretion of the treating physician. Furthermore drug serum concentrations and anti-drug antibodies were retrospectively analysed at the end of the study whereas currently these tests are more and more used in clinical practice for real therapeutic drug monitoring. Unfortunately, serum samples were missing in 20-25% of patients at 6 and 12 months. Our study was performed before the era of vedolizumab and

ustekinumab. Probably some of these patients would otherwise have been switched earlier to vedolizumab or ustekinumab instead of further optimizing IFX treatment with or without immunomodulatory dose adjustment or corticosteroids. Finally we did not have endoscopic data or faecal calprotectin levels at our disposal in order to further evaluate the response or remission in our patients.

In conclusion, our prospective data confirm the usefulness of switching to IFX in patients with loss of response to ADM, including optimization to weekly administration, especially in patients with undetectable ADM trough levels. Three fourths of the patients however will need an IFX therapy intensification during the first year of treatment. Nevertheless, this strategy can be effective at both the short- and long-term and might be considered before deciding on other therapeutic options like vedolizumab, ustekinumab or surgery.

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