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Laetitia Bastide

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UNIVERSITÉ GRENOBLE ALPES

UFR DE MÉDECINE DE GRENOBLE

Année: 2020

MID-TERM IMPACT OF INFLIXIMAB METAOPTIMIZATION ON SURGICAL RATES IN SEVERE INFLAMMATORY BOWEL DISEASE: 3-YEAR FOLLOW UP

THÈSE

PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE

Laetitia Bastide

[Données à caractère personnel]

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II. RESUME:

IMPACT A MOYEN TERME DE L'OPTIMISATION DE L'INFLIXIMAB SUR LA PRISE EN CHARGE CHIRURGICALE DES FORMES SEVERES DES MALADIES INFLAMMATOIRES CHRONIQUES DE L'INTESTIN APRES TROIS ANS DE SUIVI

Contexte: Les maladies intestinales inflammatoires provoquent des lésions digestives qui peuvent nécessiter une intervention chirurgicale dans les cas graves. Les médicaments anti-TNF réduisent les complications de ces maladies, mais certains patients résistent au traitement. Le but de ce travail était de déterminer si l'optimisation de la dose à 10 mg/kg à la semaine zéro, à la semaine 1 puis à la semaine 4 et ensuite toutes les 4 semaines réduisait la nécessité d'une intervention chirurgicale à moyen terme.

Méthode: Étude rétrospective de type avant/après monocentrique, portant sur 95 patients souffrant de DHA grave (dont 62 personnes atteintes de la maladie de Crohn, 33 de colite ulcéreuse). 46 en régime méta-optimisé (MIFX), 49 en régime standard, cohorte historique (SIFX) (5 mg/kg à la semaine 0 ; semaine 2, semaine 6 puis toutes les 8 semaines). Le critère de jugement principal était le taux de chirurgie après 3 ans de suivi.

Résultats: 15/46 (35,6%) MIFX ont été opérés, contre 21/49 (43,8%) dans le groupe SIFX, après trois ans de suivi. Les patients du groupe SIFX ont 1,6 fois plus de risque d'être opérés que ceux du groupe MIFX (OR 1,6 [95% IC : 0,633-4,255], p=0,308), mais ce résultat est non significatif.

Conclusion: Il s'agit d'une étude encourageante, mais non significative, qui montre que la méta-optimisation pourrait réduire le taux de chirurgie dans les formes graves. Un essai randomisé pourrait être intéressant pour confirmer cette tendance.

Mots clefs: formes sévères, maladies inflammatoires chroniques de l'intestin, anti TNF optimisé, chirurgie à 3 ans.

III. ABSTRACT:

MID-TERM IMPACT OF INFLIXIMAB METAOPTIMIZATION ON SURGICAL RATES IN SEVERE INFLAMMATORY BOWEL DISEASE/

3-YEAR FOLLOW-UP

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Background: severe IBD patients are prone to increased drug clearance via accelerated drug metabolism as well as excess loss through fecal excretion and may require higher doses of infliximab (IFX) to achieve appropriate pharmacokinetics and drug concentrations. Exactly how to optimize accelerated dosing strategies remains an unanswered question.

Method: Our aim was to evaluate the efficacy of meta-optimized IFX (MIFX), i.e. combined intensified induction and maintenance regimen as compared to a standard IFX (SIFX) schedule historical cohort on 3-year surgical rates. In this retrospective single-centre study, two cohorts of patients with CD and UC who were hospitalized at our single teaching hospital for an acute severe flare were identified from 2014 to 2016 (MIFX cohort) and 2007 to 2014 (SIFX cohort) were identified. Severe UC and CD were defined per clinical assessment with a Lichtiger Index > 12 for UC, a Harvey Bradshaw Index (HBI) > 12 for CD and according to ECCO classification.

Results: 15/46 (35.6%) MIFX had undergone surgery, against 21/49 (43.8%) in SIFX group, after 3 year of follow up. SIFX patients are 1.6-fold chance of not being surgery-free at 3 year than MIFX patients (OR 1.6 [95% IC: 0.633-4.255], p=0.308).

Conclusion: Our study suggests that, in our real-life practice, severe selected IBD patients with IFX meta-optimization had more persistent and higher chance of being surgery-free at the mid-term without carrying an increased risk for infection.

Key words: severe inflammatory bowel disease, Crohn's disease, Ulcerative Colitis, anti TNF therapy, dose optimisation, meta-optimization, surgery, dose de-escalation.

IV. ABBREVIATIONS:

CD: Crohn Disease

UC: Ulcerative colitis

IBD: Inflammatory Bowel Disease

UCEIS: ulcerative colitis endoscopic index of severity

ASUC: acute severe ulcerative colitis

IFX: Infliximab

ADAbs: Antidrug Antibodies

SIFX: Standard IFX group

MIFX: Meta-optimization IFX group

HBI: Harvey Bradshaw Index

OR: Odd ratio

IQR: Interquartile range

CI: Confidence Interval

TDM: therapeutic Drug monitoring

V. INTRODUCTION :

The global incidence and prevalence of Crohn's disease (CD) is increasing, with a steep increase in incidence in newly industrialized countries (1). It is associated with significant morbidity and potentially increased mortality, with a high burden of hospitalizations and surgery, decreased work productivity, and disability (2,3).

Although clinically CD is characterized by a relapsing and remitting course, subclinical inflammation often persists during periods of apparent clinical remission and leads to progressive bowel damage manifest as complications of stricture, fistula, and abscess. In population-based cohorts of CD, the majority of patients (56%–81%) have luminal inflammatory disease at diagnosis, although 5% to 25% may present with structuring or penetrating complications, but risk for surgery has decreased (4,5).

Ulcerative colitis (UC) is a chronic inflammatory colonic disease with an estimated lifetime risk of hospitalization ranging from 20 to 30% (6). Estimated direct healthcare expenditures attributable to ulcerative colitis in the United States exceed $2 billion dollars, with much of that driven by treatment and hospitalization of more severe disease (7). Twenty to 30% of patients will undergo colectomy after an acute episode of ulcerative colitis, and those with persistent symptoms and signs of systemic disease despite first-line therapy have a more than 50% risk of colectomy (8,9). Both second-line medical therapies and urgent or emergent in-hospital colectomy are associated with higher risk of significant adverse events and even mortality (10).

Owing to the presence of inflamed colonic mucosa and low albumin levels, patients with severe IBD are prone to increased drug clearance via accelerated drug metabolism as well as excess loss through fecal excretion, and, therefore, these patients may require higher doses of infliximab to achieve appropriate pharmacokinetics and drug concentrations (11,12). Exactly how to optimize accelerated dosing strategies remains an unanswered question. Several retrospective cohorts have demonstrated decreased rates of colectomy with accelerated dosing (13,14).

We previously evaluated the efficacy of meta-optimised IFX (MIFX), i.e. combined intensified induction and maintenance regimen as compared with a standard IFX (SIFX) schedule historical cohort on 1-year surgical rates in severe hospitalised IBD patients (15). As our results suggested that patients with IFX meta-optimisation had a two-fold chance of being surgery-free at 1 year, our next aim was to evaluate if those clinical results were maintained over time from 1 to 3 years.

VI. PATIENTS AND METHODS:

1. Study population :

This is a before/after, retrospective study, 2 cohorts of CD and UC patients who have been hospitalized in our hospital for an acute severe flare of IBD, from September 1, 2014 to September 1 2016 (Meta optimised IFX cohort, MIFX), and September 1, 2007 to September 1, 2014 (Standard IFX cohort, the historical one), identified by their medical records, and needed an IFX start.

The severity for UC and CD was defined per clinical assessment with a Lichtiger score >12 for UC(16), and HBI > 12 for CD or according to ECCO Classification (17).

Demographics and clinical characteristics were listed (sex, age, smoking habits, year of diagnosis, anatomic distribution of inflammation and disease behaviour according to the Montreal classification) (18) [see Appendix].

We also collected retrospectively data on surgery, clinical and biochemical disease activity, and change in medication during one-year of follow-up until IFX initiation. Variables specific to MIFX use were: baseline disease severity (endoscopic, radiographic, or clinical assessments), infusions (dates, intervals, doses, premedication) and follow-up assessments (trough levels, endoscopic, radiographic, or clinical assessments).

Dose optimization IFX group (MIFX)

A meta-optimized dosing induction and maintenance regimen was adopted in our IBD unit in 2014 because of better understanding of pharmacokinetic failures (19).

From September 2014 to 2016 MIFX patients received a 10 mg/kg intravenous infusion of infliximab, then subsequent infusions, at weeks 1 and 4, and every 4 weeks thereafter until end of follow-up.

The patients were switched to a different TNF Inhibitor or another class of biological agent and/or surgery in case of IFX failure during the study.

Standard IFX group (SIFX)

SIFX patients received a 5 mg/kg intravenous infusion of infliximab at week 0, then subsequent infusions, at weeks 2 and 6, and every 8 weeks thereafter until end of follow-up, from September 2007 to 2014.

Intensifying the IFX regimen, changing to a different TNF Inhibitor or another class of biological agent, and/or surgery was decided by the managing physician in case of IFX failure.

In both groups, discontinuation of biological therapy during the follow-up in patients who have achieved combined sustained clinical and treat-to-target remission was decided by the treating physician.

2. Outcome measure:

Our primary endpoint was the 3-year surgery (colectomy for UC, intestinal and anoperineal surgeries for CD).

The secondary outcome measures included the 3-year medical therapy change rates, 1 and 2-year surgery rates, 1-month and 3-year cumulative surgery rates, 3-year dose de-escalation rate (dose reduction and lengthening of dose intervals with infliximab), 3-year dose escalation rate, cumulative infection rate at 3 year. Adverse events were graded as serious if they resulted in discontinuation of IFX, rehospitalization, surgery, or death.

Clinical remission was defined according to ECCO (17). Steroid free remission was defined as clinical remission with no use of systemic corticosteroids. Biochemical measures for both IBD included C-reactive protein (CRP) and fecal calprotectin (FC). The upper limit of normal for CRP in our institution, was ≥5 mg/L and the corresponding cut off for FC was ≥250 µg/kg. Clinical and biochemical activity was assessed at baseline, at week 12, week 24, and every three months for active disease, or every 6 months for quiescent disease.

We used the enzyme-linked immunosorbent assay (ELISA) Lisa tracker premium Theradiag for therapeutic drug monitoring (TDM) of IFX and anti-drug

antibodies (ADAbs). IFX therapeutic levels ranged between 3 and 7 µg/ml, and ADAbs to IFX >10ng/l were considered as detectable titers (20).

Non-inflammatory mechanisms for symptoms of failure during the study were excluded with biomarkers, endoscopy, and cross-sectional imaging. Opportunistic infections, Clostridium difficile and Cytomegalovirus infections were ruled out. A multidisciplinary input (gastroenterology, colorectal surgery, IBD and stoma Nurses) was used to facilitate decision-making for every severe IBD patient, on admission and during study follow-up.

IFX therapeutic levels ranged between 3 and 7 µg/l, and anti-drug antibodies to IFX >10 ng/l could be considered as detectable. We used the enzyme-linked immunosorbent assay (ELISA) Lisa tracker premium Theradiag for therapeutic drug monitoring (TDM) of IFX and anti-drug antibodies (ADAbs) (20,21).

Non inflammatory mechanisms for symptoms of failure during the study were excluded with biomarkers, endoscopy and cross-sectional imaging. Clostridium difficile, CMV and opportunistic infections were ruled out.

To facilitate decision for severe IBD patient on admission and during the follow, a multidisciplinary input was useful (gastroenterology, colorectal surgery, IBD and stoma Nurses).

3. Statistical analysis:

It was in according with the STROBE guidelines (22), univariate analysis to describe our population sample by groups and identify eventual cofounding factors, chi² to compare qualitative data, fisher test when necessary, Student's T Test or non-parametric test if quantitative data no described a Gaussian repartition.

A Kaplan-Meier curve was built when possible (with regards of proportionality assumption).

Multivariate analysis (logistic regression and cox model) (23,24) allowed to estimate the relative risks and the 95% confidence intervals (CIs), and to adjust for cofounding factors, in particular the line of biotherapy. Cox regression to account survival time, or logistic regression if the proportionality assumption was not respected.

P value <0.05 was considered significant.

Two software was used, p value (internet access) and Jamovi.

VII. RESULTS:

1. Baseline characteristics :

95 Severe IBD patients were included, 46 in MIFX group, 49 in SIFX group. The patient's demographics, clinical and laboratory features are listed in *Table1*.

The clinical parameters (age at diagnosis, type of disease, location, sex, weight), disease severity (HBI, Lichtiger Index, CD behaviour, presence of perianal disease, colitis extension), biological data (CRP, FC, albumin), and previous treatments were mostly comparable in both groups (*Table 1*). The median age at diagnosis was 25 (IQR, 19-37) for MIFX group, and 28 (IQR, 20-37) for SIFX group. The disease duration at induction was 8 years (MIFX IQR, 1-11, SIFX IQR, 2-12) for both MIFX and SIFX patients, (p=0.9). 30/46 MIFX patients (65%) and 24/49 SIFX patients (49%) were male patients (p=0.11).

There were respectively 25/46 and 37/49 CD patients in the MIFX and SIFX groups (54% and 76%, p=0.03). We found more ileocolonic and penetrating CD patients in both groups (MIFX patients: 78% and 54%, SIFX patients: 56% and 56% respectively). 9/25 (36%) MIFX and 19/37 (51%) SIFX CD patients presented with perianal disease (p=0.23).

We found 16/21 (76%) cases of pancolitis in the MIFX cohort and 8/12 (67%) in SIFX patients (p=0.69), among the UC population.

The baseline median HBI score was 10 (IQR, 8-14) in MIFX and 10 in SIFX (IQR 9-12) (p=0.87), while the median baseline Lichtiger score at induction was 14 (IQR, 13-14) in MIFX and 13 for SIFX (IQR, 12-14) (p=0.29).

The median baseline CRP was 32 mg/l (IQR, 4-49) in MIFX and 37 mg/l (IQR, 5-54) in SIFX patients (p=0.51). The median baseline albumin rate was 30 mg/L (IQR, 26-32) in MIFX patients with 31 mg/L (IQR, 26-52) in SIFX patients (p=0.24). Median baseline CF data were too scarce for analysis.

The retrospective nature of our study did not allow obtaining IFX trough nor ADAbs at baseline and during the first year of follow-up for most of our SIFX patients. We measured the IFX serum trough concentration at one-time point at least during the

follow up for 30 MIFX patients, and 33 in SIFX. Therapeutic or supra therapeutic trough concentrations were found in 22 and 24 patients at 36 months respectively. At the 3 year follow up, 1 in MIFX and 4 in SIFX had sub therapeutic IFX trough concentrations. ADAbs were detectable in 4 at 3 years for MIFX patients and 6 for the SIFX.

21/46 MIFX patients (46%) were TNF inhibitors naive, and 38/49 SIFX patients (78%) (p=0.01). 24/46 MIFX (52%) and 10/49 SIFX patients (20%) had been previously treated with 1 TNF inhibitor, while 1/46 MIFX (2%) and 1/49 SIFX patients (2%) had been previously treated with 2 TNF inhibitors. Concomitant immunosuppressive were used for most patients: 35/46 for MIFX (76%) and 35/49 for SIFX patients (71%) (p=0.61), as well as corticosteroids, and these included: 24/35 (68%) patients with azathioprine, 5/35 (14%) with methotrexate 32/35 (91%), 6/35 (0.17) for MIFX patients, while 32/35 (91%), 2/35 (5%) and 1/35) SIFX patients were treated respectively with these drugs.

12/46 MIFX patients (26%) had previously undergone surgery for IBD versus 19/49 SIFX patients (39%) (p= 0.19).

At the end of survey, 7 patients missed in MIFX group, 5 In SIFX group.

2. Outcomes:

1. Primary outcome:

15 of the 46 MIFX patients (35.6%) had undergone surgery, compared to 21/49 SIFX patients (43.8%). Indeed, patients without IFX meta-optimization had almost a 1.6-fold chance of not being surgery-free at 3 year, but this was not statistically significant (OR: 1.6 [95%CI: 0.633-4.255], p=0.308) (*Table 2 and 3*). The median time to surgery was 190 days, 210 days for MIFX patients and 130 days for SIFX patients.

After adjustment for potential confounding factors, history of previous surgery appears to be a protective factor (OR = 0.319 [95% CI: 0.108-0.938] p=0.038). Type of IBD, gender and previous anti TNF treatment did not influence results.

Surgical procedures are listed in the appendix.

TABLE 2 : 3-YEARS SURGICAL RATES AS STRATIFIED BY CONFOUNDERS

						95% Confidence Interval	
	Estimate	**SE**	**Z**	**p**	**Odds ratio**	**Lower**	**Upper**
group:							
b – a	0.495	0.486	1.019	0.308	1.641	0.633	4.255
crohn:							
1 – 0	0.259	0.531	0.488	0.625	1.296	0.458	3.669
sex:							
F – M	0.118	0.460	0.255	0.798	1.125	0.456	2.772
atcd_surg:							
1 – 0	-1.143	0.551	-2.076	0.038	0.319	0.108	0.938
atcd_atnf 1-0	0.289	0.458	0.632	0.528	1.335	0.544	3.274

Legend: b=SIFX, a=MIFX, 1=Yes, 0=No, surg: surgery, atnf: anti TNF

TABLE 3: CUMULATIVES SURGERY :

		SIFX (n = 49)	MIFX (n = 46)	n	p	test
1-year, n	No	32 (65%)	36 (78%)	68	0.16	Chi2
	Yes	17 (35%)	10 (22%)	27	-	-
2-year, n	No	30 (61%)	28 (64%)	58	0.81	Chi2
	Yes	19 (39%)	16 (36%)	35	-	-
3-year, n	No	27 (56%)	27 (64%)	54	0.44	Chi2
	Yes	21 (44%)	15 (36%)	36	-	-

2. Secondary outcomes:

Switch:

MIFX patients had a three-fold chance to switch treatment at 3 year (41%) compared to SIFX patients (14%) (OR: 0.295 [95% IC: 0.0845-1.03], p = 0.055, the majority of therapeutic changes occurred during the first year of follow-up). After adjustment, we did not find any confounding factor (*Table 4 and 5*). Medical changes are listed in the appendix.

TABLE 4: 3-YEAR MEDICAL THERAPY CHANGE RATES AS STRATIFIED BY CONFOUNDERS:

						95% Confidence Interval	
	Estimate	**SE**	**Z**	**p**	**Odds ratio**	**Lower**	**Upper**
group:							
b – a	-1.222	0.637	-1.918	0.055	0.295	0.0845	1.03
crohn:							
1 – 0	-1.316	0.687	-1.914	0.056	0.268	0.0697	1.03
Sex:							
F – M	1.158	0.648	1.787	0.074	3.185	0.8937	11.35
ATCD_surg:							
1 – 0	-0.621	0.726	-0.856	0.392	0.537	0.1296	2.23
ATCD_atnf	0.606	0.521	1.164	0.245	1.834	0.6603	5.09

Legend: b=SIFX, a=MIFX, 1=Yes, 0=No, surg: surgery, atnf: anti TNF

TABLES 5: CUMULATIVE MEDICAL THERAPY CHANGE RATES

		SIFX (n = 49)	MIFX (n = 46)	n	p	test
1-year, n	No	46 (94%)	34 (74%)	80	<0.01	Chi2
	Yes	3 (6.1%)	12 (26%)	15	-	-
2-year, n	No	44 (92%)	29 (67%)	73	<0.01	Chi2
	Yes	4 (8.3%)	14 (33%)	18	-	-
3-year, n	No	38 (86%)	24 (59%)	62	<0.01	Chi2
	Yes	6 (14%)	17 (41%)	23	-	-

Dose de-escalation:

Regarding dose reduction and lengthening of dose intervals with infliximab, only 1 MIFX patient could be stepped down to standard maintenance regimen at 3 year, while 13 SIFX patients could maintain the standard regimen, the odds of receiving standard doses were ten times higher in SIFX patients. (OR: 10.3 [95 CI: 1.07-99.07] (*Table 6, 7*).

TABLE 6: 3-YEAR CONVENTIONAL POSOLOGY RECEIVED AS STRATIFIED BY CONFOUNDERS:

						95% Confidence Interval	
	Estimate	**SE**	**Z**	**p**	**Odds ratio**	**Lower**	**Upper**
group:							
b – a	2.334	1.154	2.023	0.043	10.321	1.0752	99.072
crohn:							
1 – 0	-1.286	0.978	1.315	0.188	0.276	0.0407	1.878
sex:							
F – M	0.761	0.713	1.066	0.286	2.140	0.5286	8.664
ATCD_surg:							
1 – 0	0.226	0.852	0.265	0.791	1.253	0.2361	6.654
ATCD_atnf 1 – 0	-1.588	1.086	1.462	0.144	0.204	0.0243	1.717

Legend: b=SIFX, a=MIFX, 1=Yes, 0=No, surg: surgery, atnf: anti TNF

TABLE 7 : PATIENTS STEPPED DOWN TO STANDARD MAINTENANCE REGIMEN AT 3 YEAR:

			Conventional posology		
group		**No**	**Yes**	**Total**	
MIFX	Observed	22	1	23	
	%	95.7 %	4.3 %		
SIFX	Observed	26	13	39	
		66.7 %	33.3 %		

4 MIFX patients were de-escalated during the first year (3 to 10mg/kg every 8 weeks, 1 to 5mg/kg every 8 weeks), 10 during the second year and lastly 7 during 3 year of follow up while in SIFX prealably optimised patients, a dose reduction was feasible for 3 and for 1 patients at year 2 and at year 3. (*Table 8*)

TABLE 8: NON-CUMULATIVE DE-ESCALATION RATES:

		SIFX (n = 49)	**MIFX (n = 46)**	**n**	**P**	**test**
1- year, n	No	47 (100%)	30 (88%)	77	0.028	Fisher
	Yes	**0 (0%)**	**4 (12%)**	**4**	-	-
2- year, n	No	40 (93%)	16 (62%)	56	<0.01	Fisher
	Yes	**3 (7%)**	**10 (38%)**	**13**	-	-
3- year, n	No	37 (97%)	15 (68%)	52	<0.01	Fisher
	Yes	**1 (2.6%)**	**7 (32%)**	**8**	**-**	**-**

Infliximab blood level:

IFX through levels were obviously highest in MIFX patients, 2-year levels were 11.3 µg/ml (IQR, 4.5-16), and 3-year 13µg/ml (IQR, 7-16), with year-2 levels:3.5µg/ml (IQR, 1.5-8) and year-3 levels: 6µg/ml (IQR, 2.6-8) third year in SIFX patients. Univariate analyse was logically confirmed statistically significance during both years. (p<0.01). (*Table 9*). In that retrospective cohort with few Ads available, no immunisation was recorded during the first year of follow-up. 2-year immunisation rates were slightly less frequent in 6/30 MIFX patients (20%) than in 8/27 SIFX patients (30%) (p=0.4). 6/27 (22%) MIFX and 7/31 (23%) in SIFX immunisation rates were noted during the third year (p=0.97) (*Table 10)*.

TABLE 9: INFLIXIMAB THROUGH LEVELS:

	SIFX group (n = 49)	MIFX group (n = 46)	n	p	test
2- year	3.5µg/ml (IQR, 1.5-8)	11.3 µg/ml (QR, 4.5-16),	57	**<0.01**	Mann-Whitney
3- year	6µg/ml (IQR, 2.6-8)	13µg/ml (IQR, 7-16)	60	**<0.01**	Mann-Whitney

TABLE 10: 2 AND 3-YEAR IMMUNISATION RATES:

		SIFX group (n = 49)	MIFX group (n = 46)	n	p	test
2-year n	No	19 (70%)	24 (80%)	43	0.4	Chi2
	Yes	**8 (30%)**	**6 (20%)**	**14**	-	-
3-year, n	No	24 (77%)	21 (78%)	45	0.97	Chi2
	Yes	**7 (23%)**	**6 (22%)**	13	-	-

Safety:

About infections rates:

The 3-year infection rate was greater in SIFX patients but not statistically significant (OR: 1.5 [95%CI: 0.23-9.86], (p=0.67) *(Table 11).* Infection rates were highest during the first year of follow-up, 8 (17%) in MIFX patients, as compared to 4 (8%) in SIFX patients (p=0.18); 4 in both group during second year (9% for MIFX patients, and 8% for SIFX patients, respectively) (p=1); 2 infections were reported (5%) in MIFX patients during the third year and 4 (9%) in SIFX patients. All results were not significant (p=0.55). (*Table 12*). Infections are listed in the appendix.

TABLE 11: 3-YEAR INFECTION RATE DURING THE THIRD YEAR AS STRATIFIED BY CONFOUNDERS:

						95% Confidence Interval	
	Estimate	**SE**	**Z**	**p**	**Odds ratio**	**Lower**	**Upper**
group:							
b – a	0.4147	0.956	0.4337	0.665	1.5139	0.23236	9.864
crohn:							
1 – 0	0.1133	1.379	0.0822	0.934	1.1200	0.07508	16.707
sex:							
F – M	0.1685	0.893	0.1886	0.850	1.1835	0.20547	6.817
ATCD_surg:							
1 – 0	1.1738	1.083	1.0836	0.279	3.2343	0.38703	27.028
ATCD_atnf	-0.0778	0.859	-0.0905	0.928	0.9252	0.17170	4.985
1 – 0							

Legend: b=SIFX, a=MIFX, 1=Yes, 0=No, surg: surgery, atnf: anti TNF

TABLE 12: NON-CUMULATIVE INFECTION RATES:

		SIFX (n = 49)	MIFX (n = 46)	n	p	test
1- year, n	No	45 (92%)	38 (83%)	83	0.18	Chi2
	Yes	**4 (8.2%)**	**8 (17%)**	**12**	-	-
2- year, n	No	44 (92%)	39 (91%)	83	1	Fisher
	Yes	4 (8.3%)	4 (9.3%)	8	-	-
3-year, n	No	39 (91%)	37 (95%)	76	0.68	Fisher
	Yes	**4 (9.3%)**	**2 (5.1%)**	**6**	-	-

About other adverse effects:

In MIFX group, 2 presented a lupus, 1 a severe psoriasis, 1 man suffered from uveitis, 1 a severe allergic reaction, 1 woman had her uterus removed because of dysplasia (during second year).

In SIFX, 1 prostatic neoplasia has been diagnosis after 6 months from the start of treatment, another man was operated for a baso-cellular carcinoma during second year.

VIII. DISCUSSION:

In severe IBD patients being treated with IFX, the benefit of routine administration of accelerated dosing regimens over standard dosing regimens is uncertain. Those patients have a high inflammatory burden and may develop a protein-losing enteropathy leading to an accelerated consumption and excessive faecal wasting of IFX, resulting in low serum concentrations and potentially increased risk of immunogenicity (12). Given a clear exposure–response relationship for infliximab in patients with IBD, intensive infliximab dosing regimens have been used, notably in patients with ASUC. Exactly how to optimize accelerated dosing strategies remains an unanswered question. First, there are no validated prediction models to identify patients at high risk of drug clearance, or dosing calculators to allow personalization of dosing regimens upfront, which limits inferences made from current retrospective studies.

Second, most observational studies are limited by selective use of intensive dosing regimens in patients with inadequate response to standard induction dose, resulting in confounding by disease severity: severe IBD Patients treated with intensive regimens generally had higher CRP and lower albumin levels, with more severe endoscopic activity compared to patients treated with standard dosing regimens. Third, there are no clinical trials comparing different IFX dosing regimens in severe IBD patients. Five observational studies compared outcomes in patients hospitalized with severe IBD being treated with different IFX regimens (13,14,25–27). In these studies, intensive dosing was defined as either shortened interval between IFX doses) and/or induction with higher dose (10 mg/kg) either upfront or at time of dose stacking. Across studies, there was no standard protocol to determine which infliximab regimen to use when, but rather most decisions were at the discretion of the treating physician. Dose stacking was performed based on inadequate response to initial regimen, rather than being predetermined. On meta-analysis of these 5 studies with 515 patients, there was no difference in short-term risk of colectomy between intensive infliximab dosing regimen vs standard infliximab dosing regimen (RR, 1.61; 95% CI, 0.74– 3.52), with considerable heterogeneity (28). However, in 2 studies, upfront induction with higher dose (10 mg/kg IFX) was superior to dose stacking with standard doses (5 mg/kg), with lower risk of colectomy (RR, 0.24; 95% CI, 0.08–0.68).

After considering these studies, we were prompted to implement a before/after study to try to establish a potential role for both accelerated induction and accelerated maintenance regimen. We report our 3-year results with combined intensified IFX induction and maintenance (at a monthly interval following the 3 double-dose induction regimen). Our study was retrospective and observational without randomization and blinding, so there were a number of potential biases. Nevertheless, it did include 95 patients with severe IBD and the 2 induction and maintenance groups were well-matched for baseline characteristics.

Our primary endpoints included the need for surgery at 3 year: we found that there was a 1.6 -fold risk not to be surgery-free in SIFX patients, (OR 1.6 [IC 0.633-4.255] p=0.308). Key issues can explain those non-significant surgical results: we had a challenging highly selected population including more severe IBD patients, with high risk factors for surgery in both groups; there were more advanced cases of CD, more colonic location, more cases of pancolitis in the UC patients, with longer duration of disease, and a lot of these patients had been previously given an anti TNF agent. Our results were not modified by the type of IBD, CD or UC. We have an underpowered heterogeneous small cohort of patients, with both UC and CD, and our results should be considered with caution. Since our study was retrospective in nature, we were not able to proactively follow the IFX trough levels of each patient, but several retrospective cohort studies have shown an association between IFX serum concentrations and clinical and endoscopic outcomes (29,30). Based on these observations, the concept of therapeutic drug monitoring (TDM) was introduced. Higher IFX levels and absence of antibodies to IFX are associated with better outcomes: an author recently reported a significant association between serum IFX levels and rates of fistula healing and fistula closures in CD patients (31). In that severe IBD setting, TDM with dose adjustment based on weekly serum IFX could be contributive, but thresholds before week 2 have yet to be defined (32). In that setting, Point-of-care assays, which are analytical devices that provide clinically relevant information without the need for a core clinical laboratory, show great promise in improving TDM (33). Another recent study shows that higher IFX level in CD patients was associated with biological remission especially in patients with CD (34).

Therapeutic changes were more frequent in MIFX group than in SIFX group, this was an expected result, dose escalation was possible for SIFX group if residual dose was not obtained, is a possible strategy for PNR or LOR if IFX level is low (35), according the study of Kamperidis and al (36). An explanation for this result came from the fact than more patients in the MIFX group had already been treated with anti TNF, and some study revealed that having a first line anti TNF treatment and having stop because of a non-response increases the risk of non-response to the second anti TNF.

Regarding our safety outcome, we found a 1.5-fold infection rate increase in our SIFX patients at 3 year. There is indeed no consistent association between intensive infliximab dosing regimens, possibly leading to higher infliximab drug concentrations, and serious adverse events. Association between preoperative infliximab and postoperative complications in a subset of patients who undergo colectomy is also inconsistent (37–39). Nonetheless as we previously reported (13), the 1-year infection rate was higher in MIFX patients, which suggests, caution and increased vigilance when prescribing IFX dose intensification at the beginning in severe IBD patients who already present with a high overall burden of complications (notably bacterial translocations in malnourished patients). Undoubtedly, the safety biological therapy is a key issue for clinicians, but the risk of drug-related adverse events must be balanced against the harmful effects of losing disease control in those highly severe patients. In this context, we addressed discontinuation of biological therapy in our patients who have achieved sustained clinical remission. Although the probability of de-escalating MIFX patients appears disappointingly low, a number of reasons could explain those results: notwithstanding the retrospective nature of our study, without complete endoscopic nor IFX PK analysis, MIFX patients are not suitable candidates for de-escalation, as they carry the majority of poor prognostic features, previous challenging disease course, and markers of active disease, enhancing the difficulty to step-down their IFX regimen. A personalised approach to de-escalation of therapy is essential, as currently patients cannot be precisely stratified into appropriate treatment pathways (40).

The use of molecular profiling to identify predictive biomarkers of disease course and treatment response is now of considerable research interest (41,42). In addition to HLA-DQA1*05 (43), a number of other polymorphisms predict development of anti-drug antibodies, suggesting an additional benefit to determining a personalised gene expression signature for patients with IBD (44).

IX. CONCLUSION:

Our study suggests that, in our real-life practice, severe selected IBD patients with IFX meta-optimisation had more persistent and higher chance of being surgery-free at the mid-term without carrying an increased risk for infection. Although prospective studies are needed to address the questions of accelerated induction, it is clear that many centres are currently using 10-mg/kg dosing initially for severe IBD with proactive drug concentration monitoring, to determine timing of administration of subsequent doses.

X. ANNEXES:

TABLE 1: BASELINE CHARACTERISTICS:

	SIFX (n=49)	MIFX (n=46)	p=
Gender			
Male	24 (49%)	30 (65%)	0,11
Female	25 (51%)	16 35%)	
RCUH	12 (24%)	21 (46%)	0,03
CROHN	37 (76%)	25 (54%)	0,03
Age at diagnosis median	28 (20-37)	24,5 (19-39)	0,63
Disease duration at induction (years)	8 (1-11)	8 (2-12)	0,9
Weight (kg)	67 (55-75)	67 (55,5-75)	0,91
CRP at induction median (mg/l)	32 (4-42)	37 (5-54)	0,51
Albumin at induction median (mg/L)	30 (27-34)	30 (24-35)	0,75
CD location,	/37	/25	
L1	11(30%)	8 (32%)	0,85
L2	6 (16%)	3 (12%)	0,73
L3	20 (54%)	14 (56%)	0,44
L4	0	0	1
CD behavior	/37	/25	
B1	3(8%)	5 (20%)	0,25
B2	5 (12)	6 (24%)	0,33
B3	29 (78¨%)	14 (56%)	0,06
pCD	19 (51%)	9 (36%)	0,23
UC Pancolitis	8 (67%)	16 (76%)	0,69
Median HBI at induction	10 (9-14)	10 (9-12)	
Lichtiger	13,6 (13-14)	12,9 (12-14)	0,29
Previous surgery	19 (39%)	12 (26%)	0,19
Prior medication	38 (78%)	38 (83%)	0,54
TNF inhibitor naïve	38 (78%)	21 (46%)	0,01
Concomitant immunsuppressive drugs	35 (71%)	35 (76%)	0,61

(L1: ileon, L2: colonic, L3 ileon and colonic, L4: upper location

B1: inflammatory, B2: stenosing, B3: pentrating, pCD: perineal Crohn disease)

XI. APPENDIX:

Surgical procedures:

- MIFX patients:

*at 1 year (n=9): subtotal colectomies (n=4), ileocecal resection (n=4), segmental bowel resection (n=1).

*at 2 year (n=5): subtotal colectomies (n=3), segmental bowel resection (n=1), perianal surgery for abscess (n=1).

*at 3 year (n=1): ileo-caecal resection

- SIFX patients

* at 1 year(n=17): subtotal colectomies(n=4), ileocecal resections (n=6), 3 segmental colonic resections (n=3), 3 total colectomies (n=3) and perianal surgeries, (n= 5), all for perianal abscesses.

* at 2 year (n=4): ileo-caecal resections.

*at 3 year (n=1): perianal surgery for perianal abscess.

Medical therapy changes:

-MIFX patients:

*at 1 year (n=12): 12 MIFX patients underwent an out of class switch: 9/12 (75%) were switched to Vedolizumab and 3/12 (25%) to Ustekinumab.

*at 2 year (n=4): 2 patients were switched to adalimumab secondary non response, one for immunisation), 1 to ustekinumab and one to filgotinib (both for secondary non response).

*at 3 year (n=1): 1 patient was switched to vedolizumab (secondary non response)

-SIFX patients:

* at 1 year(n=3): 3 SIFX patients were switched, 1 to Vedolizumab (secondary non response), 1 to Golimumab (loss of response), and the last one to Adalimumab (immunisation).

* at 2 year (n=1): 1 patient was switched to vedolizumab (secondary non response)

*at 3 year (n=2): 2 SIFX patients underwent an out of class switch, 1 was switched to adalimumab (lupus) and one to vedolizumab (loss of response)

Infections:

- MIFX patients

*at 1 year (n=8): clostridium difficile infection (n=2), CMV surinfection (n=1), bacterial translocation (n=1), central venous infection (n=1), 1 angina (n=1), pneumocystosis(n=1), non-severe dental abscess(n=1).

*at 2 year (n=4): post-operative peritonitis (n=1), Whipple disease (n=1), zoster (n=1), central venous infection (n=1)

*at 3 year (n=2): bronchitis (n=1), angina (n=1)

-SIFX patients:

* at 1year(n=4): CMV infection, complicated by activated macrophagic syndrome (n=1); prostatitis (n=1) Sinusitis (1), 1 ileal abscess (n=1).

* at 2 year (n=4): aspergillosis (n=1), leptospirosis (n=1), cervix staphylocoque aureus colonisation (n=1), recurrent cystitis (n=1).

*at 3 year (n=4): pneumonia (n=1), ileal abscess (n=1), prostatitis (n=1), angina (n=1).

Other safety outcomes of interest:

- MIFX patients: lupus 2), severe psoriasis (1), uveitis (1), anaphylactic reaction (1), uterine dysplasia (1).

-SIFX patients: prostatic neoplasia (1), baso-cellular carcinoma (1).

XII. CONCLUSION

THÈSE SOUTENUE PAR : Laetitia Bastide : Lac

TITRE :

MID-TERM IMPACT OF INFLIXIMAB METAOPTIMIZATION ON SURGICAL RATES IN SEVERE INFLAMMATORY BOWEL DISEASE/ 3-YEAR FOLLOW-UP

CONCLUSION : Les maladies inflammatoires de l'intestin sont des maladies chroniques (MICI), plus fréquentes dans les pays riches et qui concernent environ 250 000 personnes en France. Environ 50 % des personnes atteintes de la maladie de Crohn présentent des complications chirurgicales après 20 ans d'évolution de la maladie. Dans la population souffrant de RCH, 20 % sont concernés par une exacerbation aiguë sévère, et près de 30 % des personnes souffrant de RCH nécessitent une colectomie.
Les anti-TNF constituent la première molécule moderne dans l'arsenal thérapeutique des MICI, et ont montré leur efficacité dans les essais cliniques sur la diminution de l'usage des corticoïdes, et la diminution du taux de chirurgie. Ceci n'est pas confirmé par toutes les études de vraie vie, notamment dans les populations atteintes par des formes sévères de MICI.
L'objet de ce travail est de rechercher si, dans les formes graves et par rapport au schéma classique, l'optimisation d'emblée de l'Infliximab à 10 mg/kg avec une induction accélérée (une injection semaine 0, semaine 1 et semaine 4) puis en entretien toutes les 4 semaines pourrait diminuer le taux de prise en charge chirurgicale après 3 ans de suivi.
Le groupe contrôle bénéficie du schéma standard du traitement par Infliximab, à savoir une dose de 5 mg/kg, avec un schéma d'induction classique, une injection à semaine 0, semaine 2 et semaine 6 puis un schéma d'entretien classique, une dose de 5 mg/kg toutes les 8 semaines.
Dans notre étude monocentrique de type avant/après, l'optimisation montre une diminution du taux de prise en charge chirurgicale durant ces 3 ans de suivi, mais qui n'est pas significative.
Cette étude présente des biais, elle est rétrospective, monocentrique. D'autres études s'avèrent indispensables afin de discuter cette tendance, mais également d'identifier les patients pour qui cette optimisation pourrait s'avérer être la prise en charge la mieux adaptée.

VU ET PERMIS D'IMPRIMER
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Professeur Decaens, pour ton savoir vivre, ta bonne humeur et tes connaissances, Professeurs Leroy et Zarski, en hépatologie.

Marie Noelle Agnès et Bleuenn: le passage au 7 C a été rude mais j'en garde un excellent souvenir, de superbes visites et je l'espère de bonnes bases en hepato, merci beaucoup Agnès pour ton dynamisme et ton envie d'apprendre à chaque interne externe.

Merci à Aurelie, qui est toujours là pour trouver une solution, merci à Gael, et ses petites blagues, Victoire que l'on voit moins hélas.

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A Chambéry, qu'est-ce qu'on se marre, merci pour votre compréhension, j'ai bien conscience que nous ne sommes pas toujours le duo d'internes le plus facile du fait de cette période de transition. Merci de nous faire répéter nos diapo la veille des présentations, Justine, je te souhaite de profiter ++++ des mois à venir, loin du travail, et de ta boite mail…. Aude, vivement qu'on aille boire une bière !

Merci à l'équipe voironnaise de m'avoir permis de toucher un endoscope pour la première fois de ma vie, merci à Isabelle pour la formation endoscopique de qualité.

A toutes les infirmières du 7ème : merci pour tout ce que vous faites pour les patients, pour votre investissement, merci à Yves, le chat noir, Seb Jeremy, Margaux, Sandie, Sana, Marion, Cindy, Amelie forment ou formaient le noyau dur de l'équipe. Sans oublier l'équipe d'endoscopie qui supporte avec nous la sonnerie horrible du téléphone.

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Loic : quels moments stressants nous avons partagé, merci d'avoir tenu le choc !

SABINE : je te remercie de me guider dans ma vie de tous les jours à Chambery, d'être passée référente dans l'organisation temporelle de ma thèse, et de partager tous ces cafés dans ce bureau si mal rangé à ce qu'on dit. Je te souhaite tout le meilleur à Annecy !

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Thomas : Toto la rigueur, tes avis tranchés me manqueront à Saint Etienne, je me referai le discours de Raffarin quand j'aurai le temps.

Sophie et Juliette: une belle découverte, Juju, spécial remerciement pour ces 6 mois à Annecy, pour ce confinement partagé avec toi, j'espère que ton projet va aboutir, sans que tu n'aies besoin de contacter Olivier…… Embrassez vos boys de ma part!

Sylvain, la bonne humeur, humour cinglant, à toutes ces verres partagés et ces cigarettes fumées.

Marion la sportive de l'équipe, probablement celle qui a la vie la plus équilibrée d'entre nous. Peut-être qu'on se recroisera à st e. Bonne dispo

Pauline Fabien Alia et Victoria: joli quatuor qui m'aura bien fait marrer, Merci à Fabien d'avoir soutenu Alex lors des rencontres entre gastro. Profitez bien de ces 5 années d'internat.

Passons à la vie perso :

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UFR de Médecine
UNIVERSITÉ Grenoble Alpes

Doyen de la Faculté : **Pr. Patrice MORAND**

Année 2019-2020

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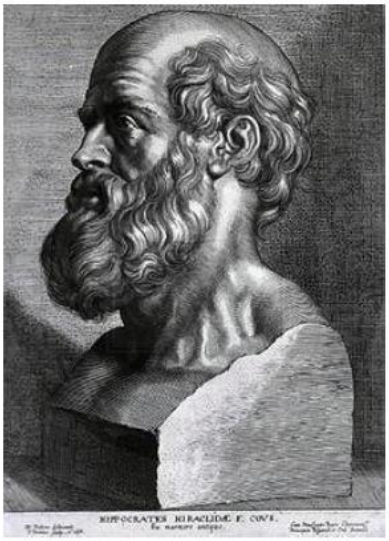

SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.