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What is the impact of infliximab metaoptimization on surgical rates and need-to-change therapy in real world practice for severe inflammatory bowel disease?

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UNIVERSITE GRENOBLE ALPES
FACULTE DE MEDECINE DE GRENOBLE

Année: 2017

WHAT IS THE IMPACT OF INFLIXIMAB METAOPTIMIZATION ON SURGICAL RATES AND NEED-TO-CHANGE THERAPY IN REAL WORLD PRACTICE FOR SEVERE INFLAMMATORY BOWEL DISEASE?

THESE
PRESENTEE POUR L'OBTENTION DU DOCTORAT EN MEDECINE

DIPLÔME D'ETAT

Thomas LEFEBVRE

[Données à caractère personnel]

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THESE SOUTENUE PAR : Thomas LEFEBVRE

TITRE : QUEL EST L'IMPACT DE LA METAOPTIMISATION DE L'I NFLIXIMAB SUR LE RECOURS A LA CHIRURGIE ET LES CHANGEMENTS THERAPEUTIQUES EN PRATIQUE QUOTIDIENNE DANS LES MICI SEVERES ?

CONCLUSION

Objectifs : L'intensification de l'Infliximab (IFX) ne fait actuellement pas partie des recommandations chez les patients présentant une maladie inflammatoire de l'intestin (MICI) sévère. Cependant des études rétrospectives monocentriques ont montré des taux de chirurgie précoce bien plus faibles avec intensification. Notre objectif était d'étudier l'efficacité à 1 an de l'IFX méta-optimisé (MIFX), c'est-à-dire intensifié en induction et en entretien, en comparaison à une cohorte historique traitée par le schéma standard d'IFX (SIFX), sur les taux de chirurgie et la nécessité de changer de traitement, chez les MICI hospitalisés pour poussée sévères.

Méthodes : dans cette étude monocentrique rétrospective avant/après, des patients avec maladie de Crohn (MC) et rectocolite ulcéro-hémorragique (RCUH) hospitalisés pour une poussée sévère de leur maladie ont été identifiés de 2014 à 2016 (MIFX) et de 2007 à 2014 (SIFX). Les poussées sévères étaient définies selon la classification ECCO et pour la RCUH par un score de Lichtiger >10, pour la MC par un score HBI>12 ou une maladie pénétrante, sténosante ou anopérinéale.

Résultats : 28 patients MIFX et 67 patients SIFX ont été inclus. 5/28 (17.9%) MIFX et 21/67 (31.3%) SIFX ont nécessité une chirurgie (p=0.18). Les patients MIFX avaient deux fois plus de chances de ne pas être opérés à 1an. (OR: 0.48 [IC95%: 0.16-1.42], p=0.18) . Par contre, ils nécessitaient 3 fois plus de changement de traitement à 1 an (25% vs 9%) (OR: 3.39 [IC95%: 1.02-11.22], p=0.05). On observait un taux d'infections à 1 an 2 fois plus important chez les MIFX (OR: 2.21 [IC95%: 0.61-7.95], p=0.11).

Conclusion : Ces données rétrospectives suggèrent que la méta-optimisation de l'IFX diminue la nécessité de recours à la chirurgie à 1an, sans réduire les modifications thérapeutiques à ce stade de la maladie. Une étude prospective apparait intéressante pour démontrer l'intérêt de la méta-optimisation.

VU ET PERMIS D'IMPRIMER

Grenoble, le 4/1-/17

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Pour la Présidente
et par délégation
Le Doyen de la Médecine
Pr. Jean-Paul ROMANET

PROFESSEUR J.L FAUCHERON

What is the impact of Infliximab metaoptimization on surgical rates and need-to-change-therapy in real world practice for severe Inflammatory Bowel Disease?

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ABSTRACT

Objective:

Current evidence-bases recommendations do not recommend intensified infliximab (IFX) regimens for patients with severe IBD. Nevertheless, retrospective single-centers analysis observed markedly lower early surgical rate. Our aim was to evaluate the efficacy of metaoptimized IFX (MIFX), ie combined intensified induction and maintenance regimen as compared to a standard IFX (SIFX) schedule historical cohort on 1year surgical rates and need to change therapy in severe hospitalized IBD patients

Methods:

In this retrospective single center 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 20014 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, and for CD by an Harvey Bradshaw Index (HBI) >12 and according to ECCO classification.

Results:

28 MIFX patients and 67 SIFX were included. Baseline demographic, clinical and biological characteristics were similar. A total of 5 of the 28 MIFX patients (17.9%) had a surgery, as compared with 21/67 SIFX (31.3%). Patients with IFX metaoptimization had almost a two-fold chance of being surgery-free at 1 year while not reaching statistical significance (OR: 0.48 [95%CI: 0.16-1.42], p=0.18). MIFX patients had a three-fold chance to change their medical therapy at 1 year (25%) as compared with

SIFX patients (9%) (OR: 3.39 [95%CI: 1.02-11.22], p=0.05). The 1year infections rate was greater in MIFX patients (OR: 2.21 [95%CI: 0.61-7.95], p=0.11).

Conclusion:

Our underpowered data suggest that an IFX metaoptimization provides benefits in relation to 1-year surgery rates, but does not reduce need for biologics at that disease stage.

KEYWORDS
Crohn's Disease; Ulcerative colitis; infliximab; intensification; severe IBD

ABBREVIATIONS

ADAbs: Antidrug Antibodies

ASUC: acute severe ulcerative colitis

CD: Crohn's disease

CDEIS: Crohn's disease Endoscopic Index of Severity

CI: confidence interval

CRP: C-reactive protein

ECCO: European Crohn's and Colitis Organization

FC: Fecal Calprotectin

HBI: Harvey Bradshaw Index

IBD: Inflammatory bowel disease

IQR: interquartile range

IFX: Infliximab

IV: intravenous

MIFX: meta-optimization of Infliximab

OR: Odds ratio

PNR: primary non response

SNR: secondary non response

SIFX: standard regimen (of Infliximab)

TDM: Therapeutic Drug monitoring

UC: ulcerative colitis

UCEIS: Ulcerative Colitis Endoscopic Index of Severity

INTRODUCTION

Inflammatory Bowel diseases (IBD) include two major entities: Ulcerative Colitis (UC) and Crohn's disease (CD). Both are chronic, progressive, disabling conditions that require lifelong medical treatment in most cases[1].

IBD have a destructive nature and can cause various complications including abscesses, fistulas, stenosis, extra intestinal manifestations, and colitis-associated neoplasia[2,3].

Most CD patients at diagnosis present with an inflammatory non-penetrating non stricturing phenotype. Complications include stricturing and possible bowel obstruction, or internal penetrating fistulas, or both, often resulting in intra-abdominal sepsis[4].

Previous reports on the natural history of CD give complication rates ranging from 48% to 52%, 5 years after diagnosis[5]. The authors of a population-based cohort study reported 20% of CD patients presented with penetrating or stricturing complications within 90 days after diagnosis and 50% with intestinal complications 20 years after diagnosis[6].

Accordingly, approximately 20%-25% UC patients present with at least one episode of severe acute exacerbation requiring hospitalization[7], and colectomy in approximately 45% of UC patients[8].

Surgery is still the cornerstone for severe CD and UC patient management, with a significant rate of IBD patients requiring hospitalization and surgery during disease follow-up[9,10].

Drug research in the field of IBD was focused on the development of biologics during the past 20 years and several anti TNF monoclonal antibodies have become available in clinical practice. However, monoclonal antibodies have limitations in term of efficacy: they are only moderately effective since there is no improvement after induction therapy in up to 30% of patients (i.e. primary non-response, PNR). Furthermore, a significant rate of patients (between 13% and 25% per year) may become non responders to Anti TNF agents over time (i.e. secondary non-response, SNR)[12,13].

In a survey of members of the Crohn's and Colitis Foundation of American Clinical Research Alliance and the International Organization for IBD, 76% of respondent indicated use of an intensified regimen for acute severe UC, either through increased infliximab (IFX) concentration (10 mg/kg per dose) and/or accelerated dosing schedule[14]. These practices are inconsistent with current evidence-based recommendations that do not support these approaches or recommend intensified regimens for patients with severe IBD. Nevertheless, the authors of retrospective single-center studies reported markedly lower early surgical rates[15]. The results of non-controlled largely retrospective series suggest considerable decrease of surgical rates with an intensified induction schedule, although a potentially increased risk of severe infections[16].

These observations underscore the uncertainty amongst the clinical community concerning IFX dosing for severe IBD patients. Lastly, one can speculate concerning the duration of IFX intensification (sole accelerated induction regimen or combined intensified induction and maintenance regimen?)

We had for aim to evaluate the efficacy of metaoptimized IFX (MIFX), i.e. combined intensified induction and maintenance regimen compared to a standard IFX

(SIFX) schedule historical cohort, in severe IBD patients hospitalized in our tertiary care center.

PATIENTS AND METHODS

Study population

We retrospectively studied, before/after, 2 cohorts of CD and UC patients hospitalized in our teaching hospital for an acute severe flare of IBD, from September 1, 2014 to September 1, 2016 (meta optimized IFX cohort, MIFX) and September 1, 2007 to September 1, 2014 (historical IFX cohort with a standard schedule, SIFX) identified by their medical records.

Severe UC and CD were defined per clinical assessment with a Lichtiger Index > 12 for UC[17], a Harvey Bradshaw Index (HBI) > 12 for CD[18] and/or according to ECCO classification[19,20].

We collected demographics and clinical characteristics (sex, age, smoking habits, year of diagnosis, anatomic distribution of inflammation and disease behavior according to the Montreal classification)[21] [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 (MOIFX)

A metaoptimized dosing induction and maintenance regimen was adopted in our IBD unit in 2014 because of better understanding of pharmacokinetic failures[22,23]: From September 2014 to September 2016, MOIFX 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 regimen 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 September 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.

Outcome measures

Our two primary endpoints were the 1-year surgery (colectomy for UC, intestinal and anoperineal surgeries for CD) and medical therapy change rates.

The secondary outcome measures included 1-month surgery rates, 3-month and 6-month cumulative surgery rates, rehospitalization rate at 1 year, cumulative infection rate at 1 year.

Clinical remission was defined according to ECCO[24]. 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, week 48, and at the last follow-up.
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[25].

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.

Our safety outcomes of interest were the rate of individuals developing severe infections, severe peri operative infections, infusion reactions, or serious adverse

events at 1 year. Adverse events were graded as serious if they resulted in discontinuation of IFX, rehospitalization, surgery, or death.

Statistical analysis

We used suited methods to analyze our observational controlled before-after study according to the STROBE guidelines[26]. We used a univariate analysis to describe our population sample by groups and find potential confounding factors, a chi² test to compare qualitative data (Fisher test when necessary), and Student's T test or non-parametric test (Wilcoxon test) if the distribution of data was not Gaussian for quantitative data. A Kaplan-Meier curve was built when possible (with regards of proportionality assumption).

Multivariate analyses (logistic regression and cox model) allowed to estimate relative risks and the corresponding 95% confidence intervals (CIs), and to adjust for confounding factors, in particular the line of biotherapy. Cox regression allowed to take into account survival time[27,28] but when proportionality assumption was not respected, we used logistic regression[29].

We found interaction between the MIFX group and our two main endpoints, surgery and change of biotherapy; we consequently made a separate analysis of these endpoints.

All analyses were made with STATA 11 SE (Stata Corp., College Station, TX, USA).

RESULTS

Baseline characteristics

95 severe IBD patients (62 CD and 33 UC, 54 male and 41 female patients), with a median age 34 years (IQR, 25-52) were hospitalized, and IFX was initiated. They were included in the study with a median follow-up of 12 months: 28 MIFX patients (from September 1, 2014 to September 1, 2016) and 67 SIFX (from September 1, 2007 to September 1, 2014).

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 behavior, presence of perianal disease, colitis extension), biological data (CRP, FC, albumin), and previous treatments were comparable in both groups (*Table 1*).

The median age at diagnosis was 24 years (IQR, 18.5-40.5) for MIFX patients and 26 years (IQR, 20-37) for SIFX patients (p=0.53). There were respectively 17/28 and 45/67 CD patients in the MIFX and SIFX groups (60.7% and 67.2%, p=0.55).19/28 MIFX patients (67.9%) and 35/67 SR patients (52.2%) were male patients (p=0.53). We found more ileal and penetrating CD patients in both groups (MIFX patients: 52.9% each, SIFX patients: 48.9% and 75.6% respectively). We found 9/11 (81.8%) cases of pancolitis in the MIFX cohort and (68.2%) in SIFX patients (p=0.68), among the UC population.

6/17 (35.3%) MIFX and 22/45 (48.9%) SIFX CD patients presented with perianal disease (p=0.34).

The disease duration at induction was 7 years (IQR, 2-14.5) and 3 years (IQR, 1-11) for MIFX and SIFX patients, respectively (p=0.23).

The baseline median HBI score was 10 (IQR, 9-12) in MIFX and 10 in SIFX (IQR 8-14) (p=0.87), while the median baseline Lichtiger score at induction was 13 (IQR, 12-14) in MIFX and 14 for SIFX (IQR, 13-14) (p=0.09).

The median baseline CRP was 24 mg/l (IQR, 5.5-52) in MIFX and 18 mg/l (IQR, 4-50) in SIFX patients (p=0.51). The median baseline albumin rate was 31 mg/L (IQR, 25.75-35) in MIFX with 30 mg/L (IQR, 25.5-32.5) in SIFX patients (p=0.24), and the median baseline CF levels were comparable (MIFX: 2,733µg/g (IQR, 1092-3000), SIFX: 3,000 µg/g (IQR, 815-3000), p=0.92).

The retrospective nature of our study did not allow obtaining IFX trough nor ADAbs at baseline and during 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 26/28 MIFX patients. Therapeutic or supra therapeutic trough concentrations were found in 19/25, 7/8, and 12/12 patients at 3months, 6 months, and 12 months respectively. At the 3 month and 6 month follow up, 1 out of 8 patients and 1 out of 8 had sub therapeutic IFX trough concentrations. ADAbs were detectable in 3 out of 25 patients at 3 months but in none of the patients during the end of follow up.

13/28 MIFX patients (46.4%) were TNF inhibitors naive, and 46/67 SIFX patients (68.7%) (p=0.04). 14/28 MIFX (50%) and 20/67 SIFX patients (29.8%) had been previously treated with 1 TNF inhibitor, while 1/28 MIFX (3.6%) and 1/67SIFX patients (1.5%) had been previously treated with 2 TNF inhibitors.

21/28 MIFX patients (75%) versus 55/67 SIFX patients (82.1%) (p 0.57) had received previous treatment (aminosalycilates, corticosteroids, immunosuppressive drugs, TNF inhibitors, Vedolizumab, Ustekinumab).

Concomitant immunosuppressive agents were used for most patients: 22/28 for MIFX (78.6%) and 48/67 for SIFX patients (71.6%) (p=0.48), as well as corticosteroids, and these included: 14/22 patients with Azathioprine (63.6%), 3/22 with Mercaptopurine (13.6%), and 5/22 with Methotrexate (22.8%) for MIFX patients while 42/48 (87.5%), 4/48 (8.3%) and 2/48 (4.2%) SIFX patients were treated respectively with these drugs. 7/28 MIFX patients (25%) had previously undergone surgery for IBD versus 24/67 SIFX patients (35.8%) (p= 0.31).

Outcomes

First primary endpoint: 5 of the 28 MIFX patients (17.9%) had undergone surgery, compared to 21/67 SIFX patients (31.3%). Indeed, patients with IFX metaoptimization had almost a two-fold chance of being surgery-free at 1 year, but this was not statistically significant (OR: 0.48 [95%CI: 0.16-1.42], p=0.18) (*Table 2*). The median time to surgery was 116 days, 76 days for MIFX patients and 210 days for SIFX patients.

Second primary outcome: MIFX patients had a three-fold chance to switch treatment at 1 year (25%) compared to Sifx patients (9%) (OR: 3.39 [95%CI: 1.02-11.22], p=0.05). Our SIFX population included more anti TNF antagonist naive patients, hence we made an adjustment based on that covariable, but the results were not modified (*Table 2*).

Secondary endpoints:

1/28 (3.6%) MIFX and 5/67 (7.5%) SIFX patients had undergone surgery (p=0.66) at one month (very early evaluation). None of the MIFX group with active perianal CD at baseline required surgery while 5/22 SIFX patients underwent perianal surgery.

The cumulative rehospitalization rate at 1 year was 42.9% for MIFX patients versus 40.3% for SIFX patients (OR: 1.11 [95%CI: 0.5-2.83], (p=0.82). Most of these hospitalizations were due to an IBD flare.

The cumulative surgery, treatment switch, hospitalization, and steroid-free clinical remission rates at 3, 6, and 12 months are listed in *Table 3*. The cumulative rates of steroid free clinical remission after 1 year in MIFX and SIFX patients were 53.6% and 44.7% respectively (p=0.61).

The following surgical procedures were performed:

- MIFX patients (n=5): subtotal colectomies (n=3), ileocecal resection (n=1), segmental bowel resection (n=1).
- SIFX patients (n=21): 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.

7 MIFX patients underwent an out of class switch: 5/7 (71.4%) were switched to Vedolizumab and 2/7 (28.6%) to Ustekinumab.

8 SIFX patients were switched: 4/8 to Vedolizumab (50%), 1/8 to Ustekinumab (12.5%), 1/8 to Golimumab (12.5%), and 2/8 to Adalimumab (25%).

Safety

The 95 patients included in our analysis received a median of 14 IFX infusions during the follow up for MIFX patients (IQR, 13-14), and 10 infusions for SIFX patients (IQR, 9-10). 2 presented with adverse reactions to infusion, 1 in each group, requiring IFX discontinuation and switch to another biologic therapy.

No severe perioperative serious infection, nor serious adverse event were noted in MIFX patients 1 month after surgery, while in the SIFX group, 1 patient presented with a severe adverse event (colonic necrosis with colostomy disinsertion) requiring a second surgery, and 3 cases of post-operative ileus were treated medically. Finally, 1 SIFX patient presented with intra-abdominal sepsis due to a post-operative abscess requiring IV antibiotics.

At one year, 5 MIFX and 6 SIFX had presented with an infection (*Table 4*). The 1-year infection rate was greater in MIFX patients but not statistically significant (OR: 2.21 [95%CI: 0.61-7.95], p=0.22). One MIFX patient was hospitalized in the Intensive Care Unit for a severe case of Pneumocystis pneumonia, and another MIFX patient was hospitalized for a pulmonary embolism; one SIFX patient developed a macrophage activation syndrome induced by a Cytomegalovirus infection.

No deaths were observed.

DISCUSSION

IBD (CD and UC) are chronic relapsing disorders with a progressive and destructive nature that can cause various conditions including for CD stenosis, abscesses, fistulas[2]. A significant improvement in medical treatment has been made over the last 20 years, with the widespread use of immunomodulators and the addition of biologics to the IBD armamentarium, especially anti TNF.

No decrease in the rates of obstructive severe CD complications and surgeries has been recorded in the global population despite the increased use of anti TNF therapy over the past decades [10,30,31].

Severe flares of UC are associated with a considerable rate of morbidity, and a mortality rate of approximately 1% for ASUC[32].

Available biologics are moderately effective since there is no improvement with anti TNF for up to 30% of patients (i.e. PNR)[33]. Furthermore, a significant rate of patients, 20%/year, may develop SNR[13,34].

Even if biologics have revolutionized our approach to the treatment of severe CD and UC, and are clearly a success story in the history of IBD, there is always a need for new management strategies to improve outcomes, and especially surgical rates. Although the authors of early randomized controlled trials have failed to establish the role of IFX in the management of ASUC, the authors of more recent studies have reported its efficacy and IFX has become the most frequently used salvage therapy in clinical practice as in severe CD[35,36].

The role of the other anti TNF agents for ASUC and hospitalized severe CD patients remains to be determined. Indeed, in those cases, intravenous IFX appears to be the

most effective and thus a suitable therapy, due to its rapid action[37]. For the same reason, Vedolizumab, a slow-acting drug, cannot be recommended in those settings.

The rational for an intensified IFX dosing regimen in severe IBD comes from pharmacokinetic mechanisms that influence IFX clearance rates. High inflammatory burden results in elevated amounts of TNF which serve as a sink for IFX, and result in the formation of immune complexes[38]. Phagocytosis and proteolytic degradation of the immune complexes is facilitated by an increase in the number of phagocytic mononuclear cells[39]. A severely damaged mucosal barrier results in efflux of IFX in the colonic lumen and fecal loss of the drug[23].

An increased clearance of IFX leads to low serum drug concentrations which may enhance immunogenicity and facilitate the formation of anti-drug antibodies due to loss of high zone temperance[40].

Many authors have reported an association between IBD severity and IFX failure, suggesting that a conventional dose insufficiently targets the inflammation associated with severe IBD[16]. The efficacy of an intensified dosing strategy with 10mg/kg of IFX has not been prospectively evaluated in ASUC or severe CD. Nonetheless, doses of 10mg/kg have been investigated in chronic CD and UC[41,42,43]. Further evaluation of a more intensive dosing regimen in severe IBD settings is needed.

Some recent reports have indicated that an accelerated IFX dosing regimen could decrease colectomy rates in patients with highly active diseases. The authors of a single-center retrospective study analyzed the outcome in 50 ASUC: 35 patients were treated with SIFX infusions at week 0, 2, and 6, and 15 patients received an accelerating dosing with 3 induction doses of IFX administered within 3-4 weeks. The responders were given 8-weekly maintenance IFX doses. The early colectomy rate

during IFX induction was shown to be significantly lower in the group that had received an accelerated induction regimen -7% (1/15) and 37% (13/35), p=0.039. However, colectomy rates were similar in both groups at the 2-year follow-up[15].

The authors of another retrospective study compared outcomes in patients who had received intensified IFX with patients who had received standard dosing. No difference was observed between the 2 groups in surgical rates at 3 or 12 months. However, intensified dosing in that study was selectively administered to patients with higher CRP for whom an increased rate of surgical management was expected[44].

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 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 in the study. Nevertheless, it did include 95 patients with severe IBD and the 2 induction and maintenance groups were well-matched for baseline characteristics.

The pharmacokinetic data influencing IFX clearance was gender, associated with a faster clearance in male patients, bodyweight (faster clearance in patients with high bodyweight but also with a bodyweight ≤40kgs)[45]. It was not different between MIFX and SIFX patients as CRP, FC, and Albumin. We looked for the presence of ADAbs in our 2 study drug regimens concerning IFX immunogenicity, when the data was available, but data was missing in the historical SIFX cohort.

Our primary endpoints included the need for surgery and the need to switch out of IFX at 1 year: we found that there was a two-fold chance to decrease surgery rates and a

three-fold chance to increase therapy changes in our MIFX patients respectively, but the difference did not reach statistical difference for surgery. Our SIFX surgical surgery rate though correlated well with the 1-year colectomy rates for ASUC or the 1-year surgical rates for severe CD[46,47]. Some 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 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. It is now known that the best time to optimize dosing is early in the course of IBD [48].

Of course, we have an underpowered heterogeneous small cohort of patients, with both UC and CD, and our results should be considered with caution, but we felt it really reflected our day-to-day real world clinical practice.

Secondly, we do not know if the dose increase used for our MIFX patients was the optimal one. Only the 10mg/kg dose was shown to decrease the need for colectomy during 54 weeks in the two placebo-controlled trials comparing IFX to placebo[49], but patients presented with moderate to severe UC. Furthermore, since our study was retrospective, we were not able to follow the trough levels of each patient, but it is known that the IFX dose-exposure relationship may better predict trough concentrations and clinical outcomes[50,51].There is also growing evidence that 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[52].

The 10mg/kg dose increase and intensified dosing used for our MIFX patients were perhaps too suboptimal due to the pharmacokinetics of IFX failure and disease

severity. In that severe IBD setting, therapeutic drug monitoring with dose adjustment based on weekly serum IFX could be contributive[53], but thresholds before week 2 have yet to be defined[23].

Moreover, our treatment strategy, as every dose intensification strategy, is obviously very expensive, and anti TNF agents, which are also extensively used for a number of other chronic inflammatory diseases, now constitute one of the greatest medical expenditures in western countries[54]. Managing SNR by an algorithm based on serum IFX and IFX antibody levels has been shown to be more effective than an intensified regimen; the basis for this difference is the lower costs generated by avoiding inappropriate use of drugs, without any apparent negative consequence for clinical efficacy[55].

Using IFX fecal loss as a predictor of outcome is also an interesting concept although the reference study was conducted in a small population, which may be susceptible to measurement error[23].

Finally, the mucosal levels of IFX could become increasingly relevant in our clinical scenario, since high mucosal TNF in conjunction with low mucosal anti TNF has been shown to correlate with endoscopically active IBD, whereas higher serum and low mucosal levels also appear to predict mucosal disease activity[56].

Lastly, the failure to induce response or remission in our severe IBD patients indicates that other inflammatory (i.e. non-anti TNF driven) pathways may be dominant in these patients. Our growing understanding of the immunopathogenesis of IBD has opened new perspectives for the development of targeted therapies. Indeed, emerging novel, and easily administered therapeutics may be viable candidates for the

management of severe IBD, such as small molecules including Janus Kinases Inhibitors, antisense oligonucleotides against SMAD7 m RNA, or inhibitors of leucocytes trafficking to intestinal sites of inflammation (e.g., sphingosine-1-phosphate receptor modulators), all of which have not been studied in severe IBD yet[57,58,59].

Our underpowered data suggests that an IFX metaoptimization provides benefits in relation to early (as shown by other authors[15]) and 1-year surgery rates. This suggests that even if metaoptimization does not reduce the long-term need for IBD surgery, there is potential for turning an emergency into a less life-threatening and severe disease, with more efficacy to control the disease with newer treatments which were not available at the time for the historical SIFX cohort.

Regarding our safety outcome, we found a 2-fold infection rate increase in our MIFX patients. There is little evidence indicating that patients treated with higher doses of IFX or those with greater drug exposure are at an increased risk of adverse-effects such as severe infection. In the TREAT registry, which prospectively evaluated more than 6,000 patients exposed to IFX, no increased safety signal was observed at 5 years in patients who had received dose escalation from 5mg/kg to 10 mg/kg[60]. In addition, an association between IFX dose and increased risk of severe infections was identified in a retrospective analysis of CD patients who had received high-dose IFX therapy[61]. We did not observe any early perioperative severe infections in our MIFX patients and found 1 out of 5 severe infections at one year (Pneumocystis pneumonia). Most of our patients were under combotherapy. Our data, although limited, suggests caution and increased vigilance when prescribing IFX dose intensification in severe IBD patients who already present with a high overall burden of complications.

CONCLUSION

Our study results suggest that patients with IFX metaoptimization have a two-fold chance of being surgery-free at one year, and a three-fold chance to switch IFX at the one-year follow-up. Despite its limitations, our results stress the need for challenging multicenter randomized prospective trials comparing IFX dosing regimens with a more personalized approach to dosing. Such trials may then reveal a better understanding of metaoptimization and open doors to help identify both predictors of response and new targets to optimally manage severe IBD in this novel era of personalized medicine.

Table 1 - Demographics, Clinical and Laboratory features of 95 severe IBD patients stratified by IFX metaoptimization

	MIFX (n = 28)	SIFX (n= 67)	p value
Gender **male** **female**	 19 (67.9%) 9 (32.1%)	 35 (52.2%) 32 (47.8)	0.16
Age at diagnosis (y) median (IQR)	24 (18.5-40.5)	26 (20-37)	0.53
Disease duration at induction (y) median (IQR)	7 (2-14.5)	3 (1-11)	0.23
Weight (kg)	62.5 (55.5-74)	68 (55-76)	0.40
Ulcerative colitis, no (%)	11 (39.3)	22 (32.8)	0.55
Crohn's disease, no (%)	17 (60.7)	45 (67.2)	0.55
CRP at induction (mg/L) median (IQR)	24 (5.5-52)	18 (4-50)	0.51
Albumin at induction (g/L) median (IQR)	31 (25.75-35)	30 (25.5-32.5)	0.24
Fecal Calprotectin (µg/g) median (IQR)	2,733 (1,092-3,000)	3,000 (815-3,000)	0.92
CD Location, no (%)			
L1	9/17 (52.9%)	22/45(48.9%)	0.78
L2	1/17 (5.9%)	5/45 (11.1%)	1
L3	6/17 (35.3%)	17/45 (37.8%)	0.86
L4	0/17 (0%)	0/45 (0%)	1
CD behavior, no (%)			
B1	4/17 (23.5%)	4/45 (8.9%)	0.20
B2	7/17 (41.1%)	20/45 (44.5%)	0.82
B3	9/17 (52.9%)	34/45 (75.6%)	0.08
pCD	6/17 (35.3%)	22/45 (48.9%)	0.34
UC Pancolitis, no (%)	9/11 (81.8%)	15/22 (68.2%)	0.68
HBI at induction (CD), no (%) median (IQR)	10 (9-12)	10 (8-14)	0.87
Lichtiger Index at induction (UC), no (%) median (IQR)	13 (11-14)	14 (13-14)	0.09
Previous surgery , no (%)	7 (25%)	24 (35.8%)	0.31
Prior medication, no (%)	21 (75%)	55 (92.1%)	0.62
TNF inhibitor naïve, no (%)	13 (46.4%)	46 (68.7%)	0.04
Concomitant immunosuppressive drugs no (%)	22 (78.6%)	48 (71.6%)	0.48

Table 2 - 1 Year MIFX Outcomes measures stratified by prior TNF antagonist use

	Odds ratio (95% confidence interval)	**"TNF inhibitor naive"**
Surgery	0.48 (0.16-1.42)	0.48 (0.16-1.47)
Switch	3.39 (1.02-11.22)	2.66 (0.77-9.23)
Infections	2.21 (0.61-7.95)	2.99 (0.78-11.53)
Hospitalization	1.11 (0.50-2.83)	1.15 (0.46-2.88)
Clinical remission	1.42 (0.59-3.45)	1.59 (0.53-3.97)

Table 3 - Cumulative surgery, therapy changes, hospitalization and steroid-free clinical remission rates at 3, 6, and 12 months in MIFX and SIFX groups

	MIFX	SIFX	P
Surgery rate			
3 months	**4/28 (14.3%)**	**6/67 (9%)**	0.33
6 months	**5/28 (17.9%)**	**10/67 (14.9%)**	0.76
12 months	**5/28 (17.9%)**	**21/67 (31.3%)**	0.18
Therapy changes			
3 months	4/28 (14.3%)	3/67 (4.5%)	0.19
6 months	5/28 (17.9%)	4/67 (6%)	0.12
12 months	7/28 (25%)	6/67 (9%)	0.05
Hospitalizations rate			
3 months	7/28 (25%)	18/67 (26.9%)	0.85
6 months	11/28 (39.3%)	20/67 (29.9%)	0.37
12 months	12/28 (42.9%)	27/67 (40.3%)	0.82
Steroid free remission			
3 months	12/28 (42.8%)	28/67 (41.2%)	0.92
6 months	14/28 (50%)	33/67 (49.2%)	0.95
12 months	15/28 (53.6%)	30/67 (44.7%)	0.61

Table 4 - Early post-operative adverse effects and 1-year infections rate

	MIFX	**SIFX**
Early post-operative adverse effects	none	n=5 - colonic necrosis, with colostomy disinsertion (surgical recovery), n=1 -post-operative ileus (medical treatment), n=3 -intra-abdominal abscess (IV antibiotics, no surgical recovery), n=1
Infections rate at 1yr	n = 5 -severe Pneumocystis pneumonia n=1 -Clostridium difficile infection, n=1 - CMV infection, n=1 - throat infection, n=1 - whitlow, n=1	n= 6 -severe CMV primary infection with macrophage activation syndrome, n=1 - Clostridium difficile infection, n=2 - sinusitis, n=1 - dental abscesses, n=2

APPENDIX

In CD, according to the Montreal classification[21], inflammatory lesions can be isolated from terminal ileum (L1: ileum), or colon (L2: colonic), or both (L3: ileocolonic). Upper location is L4.

CD phenotypes can be non-stricturing non-penetrating (B1), stricturing (B2), or penetrating (B3).

In UC, inflammation can be limited to the rectum (E1: ulcerative proctitis), to a proportion of colorectum distal to the splenic flexure (E2: left sided UC) or extended to proximal colon above the splenic flexure (E3: extensive UC).

Stricturing CD was defined by the occurrence of constant luminal narrowing demonstrated on radiologic or endoscopic methods with pre stenotic dilation and/or obstructive signs and symptoms without the presence of penetrating disease[62].

Penetrating CD was based on the occurrence of intraabdominal inflammatory masses, abscesses ad/or fistula[63].

Active perianal CD was defined as complex perianal fistula. All patients underwent clinical examinations, magnetic resonance imaging to classify the type of fistula and also endoscopy for the evaluation of rectal inflammation. Complex fistulas were defined as high (high hyper sphincteric, high trans sphincteric, supra sphincteric or extra sphincteric), with either multiple external openings associated with such pain or fluctuation to suggest a perianal abscess, or with a rectovaginal fistula or anorectal stricture. The therapeutic management of perianal CD was decided by the managing physician but fistula tracks were systematically treated by curettage, irrigation with saline and apposition of loose setons to facilitate drainage. The seton was removed

after IFX induction if sepsis was not present. If there was no response the seton was left in place.

Patients with CD were clinically identified according to Harvey Bradshaw Index (HBI)[18], an index comprising four domains reflecting signs and symptoms of CD.

Clinical activity in patients with UC was assessed by the Lichtiger index[17] ranging from 0 to 21, and the Partial Mayo Score (PMS) ranging from 0 to 3[64].

ASUC is defined by ≥ 6 bloody stools/ pulse > 90 bpm or temperature > 37.8°C or Haemoglobin < 10.5 g/dl or CRP> 30 mg/l (adapted from Truelove & Witts criteria)[65].

For UC, the Ulcerative Colitis Endoscopic Index of Severity (UCEIS)[66] ranging from 0 to 8 was recorded. Endoscopic remission was defined by UCEIS 0 and endoscopic response by a decrease in UCEIS ≥2 according to international consensus[67].

For CD, the CDEIS (Crohn's disease Endoscopic Index of Severity) was calculated for the definition of endoscopic remission and for the definition of endoscopic response in CD according to international consensus[68]. Endoscopic remission was defined by CDEIS<3, and endoscopic response by a decrease in CDEIS >50%.

Radiological parietal healing was defined according to the local site radiologist and all of the patients had a baseline radiologic assessment demonstrating severe active disease as a reference.

Because of its retrospective design, we were unable to consistently obtain an UCEIS, a CDEIS and a radiologic evaluation for all of our IBD patients.

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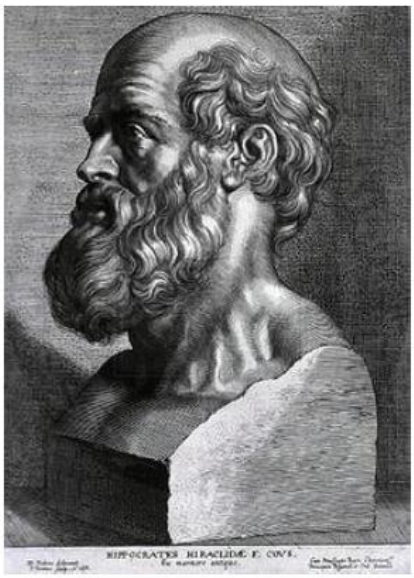

SERMENT D'HIPPOCRATE

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 donnerais 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.