Adalimumab or infliximab as monotherapy, or in combination with an immunomodulator, in the treatment of Crohn's disease

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Abbreviations

ADA: adalimumab

IFX : infliximab

IQR: Inter quartile range

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Abstract

Background : The comparative efficacy of Adalimumab (ADA) and Infliximab (IFX) in Crohn's disease and the benefit of initial combotherapy with an immunomodulator are debated. **Aim :** To assess the best anti-TNF treatment regimens in Crohn's disease. **Methods:** We included 906 biologic-naïve Crohn's disease patients (median age, 31 years [24-41]) and performed a retrospective analysis of 1284 therapeutic exposures to ADA (n=521) or IFX (n=763) between 2006 and 2015. An immunomodulator was associated during the first 4-6 months (initial combotherapy) during 706 therapeutic exposures (55%). Median duration of anti-TNF therapy was 39 months (IQR 17-67). Primary outcomes were 6-mo. and 2-yr. response rates and drug survival. Logistic regression with propensity scoring and Cox proportional hazard analysis determined variables associated with outcomes. **Results:** In first line, responses rates at 6 mo. and 2 yr. were 64% and 44% on ADA mono, 86% and 70% on ADA combo, 72% and 45% on IFX mono, and 84% and 68% on IFX combo, respectively. Differences between ADA and IFX were not significant, whereas combo was superior to monotherapy ($p<0.001$). Drug survival was longer with combotherapy vs. monotherapy (adjusted hazard ratio 2.17 [1.72-2.70]) and not significantly different between ADA and IFX. During subsequent anti-TNF exposures, IFX combotherapy fared better than other groups regarding response rates, drug survival, disease activity, hospitalizations and abdominal surgery. **Conclusion:** In this retrospective analysis of a large tertiary center cohort of Crohn's disease patients, ADA and IFX had similar efficacy as first line treatment, while initial combotherapy improved all outcome measures.

Anti-TNF agents have revolutionized the therapeutic management of Crohn's disease [1]. Infliximab (IFX) entered clinical practice at the end of the nineties and remained as the sole biologic therapeutic agent for years. The use of IFX in inflammatory diseases demonstrated immediate efficacy in a majority of patients, however, the risk of subsequent drug discontinuation due to loss of response or adverse events over time was significant. The approval of Adalimumab (ADA) in 2006 in Crohn's disease extended the therapeutic armentarium and offered a new option to patients with failure to IFX therapy. Currently, there is no head-to-head trial comparing the efficacy of ADA and IFX in Crohn's disease, and observational retrospective studies are few and limited to administrative data [2, 3]. Moreover the long term benefits and risks of combining an immunomodulator with the anti-TNF agent (combotherapy) remain a matter of debate [4], particularly regarding ADA [5, 6]. Combotherapy when given during the first months of anti-TNF administration may decrease the development of antibodies against IFX or ADA, increase response rate, and prolong drug survival [7], at the expense of an increased risk of severe infections [8], non-melanoma skin cancers [9], and T-cell lymphomas [10].

Between 2006-2014, ADA and IFX were the only authorized anti-TNF agents for the treatment of Crohn's disease in France, while the association with an immunomodulator was optional. This allowed us to compare the efficacy and tolerance of these two anti-TNF agents when given in first or second line treatment, assess their benefits in combotherapy, and determine predictors of drug survival.

MATERIALS AND METHODS

Patients

Using the MICISTA registry, a prospective cohort of all IBD patients treated at Saint-Antoine hospital (Paris, France) since 1995, we included consecutive Crohn's disease patients who received an anti-TNF agent (ADA or IFX) between January 1st 2006 and December 31st 2014. Criteria for inclusion were diagnosis of Crohn's disease according to Lennard-Jones [11] and first administration of ADA or IFX within the hereby specified study time. Patients initiating anti-TNF therapy in another academic center with prolonged follow-up in our Unit were included. We excluded patients who previously received an anti-TNF agent before 2006, patients treated elsewhere and seen for second opinion, and patients who received anti-TNF therapy primarily for rheumatologic or dermatologic diseases. The follow-up period ended on December 31, 2015.

Data collection

Data were collected from the MICISTA registry and included demographics, environmental risk factors, cumulative disease phenotype, as well as maximal disease activity, maximal treatment exposure and surgery registered on a yearly basis [12]. In addition, electronic patient charts were reviewed to assess for the dates of the first and subsequent therapeutic exposures to ADA or IFX, additional patient and disease characteristics at the onset of treatment, associated therapies (immunomodulators) and reasons for discontinuation of ADA or IFX. Any switch from an anti-TNF to another was considered as a separate therapeutic exposure. Interruptions of therapy for less than one year followed by reintroduction of the same anti-TNF agent were not taken into account. Interruptions in treatment greater than one year led to the designation of two separate therapeutic exposures. Patients were

considered on combotherapy if they received immunomodulators during at least four months during the first semester of anti-TNF treatment exposure. Early and sustained clinical responses were assessed at month 6 and 24, respectively. A patient was considered a clinical responder if clinical improvement without need for steroid maintenance was asserted by the treating physician, retrospectively assisted evaluation of Crohn's disease activity index (CDAI) [13] was <150, and the patient did not undergo surgery (abdominal or perianal) during the interval. Loss of response was defined as the presence of symptoms or evidence of disease activity after an initial improvement, as evaluated by the clinician. Adverse events were defined as any side effect leading to treatment discontinuation. Surgery was taken into account from the date of the first administration until 12 months after last administration of the anti-TNF agent. According to this definition, surgery during the first months of a subsequent exposure may be attributed to both current and prior therapeutic agents if the surgery occured within 12 months of usage of the previous agent.

Treatment policy

The therapeutic strategy applied to our Crohn's disease patients was a step-up approach, with anti-TNF agents initiated for severe or repeated steroid-resistant flares, and following failure or intolerance to immunomodulators therapy. Our criteria favoring ADA use over IFX were initiation of treatment in the outpatient setting, compliant patient profile, limited infusion center accessibility, frequent travelers and patient's preference. We routinely combined initially an immunomodulator with an anti-TNF agent except in patients older than 70, when strictly contraindicated or intolerant. We used as immunomodulators azathioprine (2 to 2.5 mg/kg per day), mercaptopurine (1 to 1.5 mg/kg per day) and, in patients intolerant to thiopurines or EBV naïve young men, methotrexate (commonly 15 mg *per os* weekly). Prednisone or budesonide, when prescribed, were tapered during the first months of anti-

TNF therapy. In case of secondary loss of response, treatment was optimized by shortening the infusion interval, increasing the anti-TNF dose or resuming combotherapy, before switching to the other anti-TNF agent [14].

Statistical analysis

Continuous data are expressed as a median (interquartile range, IQR). Discrete data are given as percentages. Comparisons were made with Mann-Whitney test and Pearson chi-square test, respectively, as appropriate. A p value > 0.05 was considered statistically not significant (NS).

Primary outcomes were 6-mo. and 2-yr. clinical responses and drug survival. All variables collected at time of inclusion suspected to be possible predictors of clinical response and drug survival, respectively, were tested: age, gender, socioeconomic status (high or low-moderate), area of residency (within or outside Paris area), smoking status, body weight, disease duration, family history of IBD, associated joint disease, extra-intestinal manifestations, site and behavior of disease according to the Montreal Classification [15], perianal disease, recent Crohn's disease-related hospitalization, prior intestinal surgery, and modalities of drug administration (prior exposure to immunomodulators for more than 6 months, initial mono or combotherapy, ADA or IFX as first line treatment, center where the agent was first administered) were tested. Logistic regression with propensity scoring to receive either ADA, IFX, in monotherapy or combotherapy was performed to predict clinical responses. Propensity scoring included selected variables associated with different therapeutic regimens. Kaplan-Meier survival analysis was used to estimate drug survival from the date of first injection of ADA or infusion of IFX as starting point. Curves were calculated with censoring patients who stopped the anti-TNF agent intentionally. A Cox

proportional hazards regression model with a backward variable elimination procedure was used to assess the strength of the associations while controlling for possible confounding variables. Comparisons between groups were made with log rank test and Cox model. All variables with $p < 0.20$ in univariate analysis were included in the multivariate models. Logistic regression with propensity scoring was performed using the R MatchIt package software. Log rank test and Cox regression were performed using GB-stat statistical software (Silver Spring, MD, USA).

RESULTS

Nine hundred and six Crohn's disease patients were included (table 1). A total of 1284 therapeutic exposures to ADA or IFX were analyzed. There were 286 therapeutic exposures to ADA initiated as monotherapy (ADA mono), 235 to ADA combo, 292 to IFX mono, and 471 to IFX combo (Figure 1). Reasons for not using initial combotherapy included intolerance to thiopurines, intolerance to methotrexate, liver function test abnormalities, planned pregnancy, patient refusal, and physician decision. Thirty-five patients stopped immunomodulators therapy within 4 months due to intolerance and were therefore included in the monotherapy groups, as per protocol. Table 1 and table 2 compare characteristics of patients according to the type of the first and second therapeutic exposure to anti-TNF therapy, respectively. Significant differences between the groups have been noted, in particular during the first therapeutic exposure. Additionally 28 patients received other anti-TNF agents such as certolizumab pegol or golimumab. These latter exposures and other non-anti-TNF therapeutic exposures (on thalidomide, vedolizumab, or ustekinumab) were excluded. At the time of last follow up visit, 662 patients were still receiving an anti-TNF agent, 50 were receiving a non-anti-TNF biologic

agent, 129 were off biologics, 8 were deceased, and 57 were lost to follow-up. Median duration of anti-TNF therapy was 39 months (IQR 17-67).

Clinical response

Figure 2 presents the percentage of patients achieving clinical response at 6 months during 1st and subsequent therapeutic exposure to ADA or IFX according to the treatment regimen (combo or monotherapy). Irrespective of the therapeutic exposure period or anti-TNF agent used, response rates with combotherapy were significantly higher compared to monotherapy. Response rates in the combotherapy groups were similar whether patients were naïve to the immunomodulators or not. Of note, the response rates were lower during the subsequent therapeutic exposures with ADA combo and IFX mono, while patients of the IFX combo group had a better response during subsequent therapeutic exposures. There was no significant difference in the response rates according to the type of immunomodulators. Among the 442 patients receiving thiopurines, the proportion of responders was 84% vs. a response rate of 84% among the 78 patients receiving methotrexate. Based on this result, data for thiopurines and methotrexate were pooled in the following comparisons.

Figure 3 gives the percentage of patients with a clinical response at two years for first and subsequent exposures to anti-TNF therapy according to the treatment regimen (combo or monotherapy). Results were similar to those observed at six months, with a clear benefit of combotherapy over monotherapy and a better efficacy in the IFX combo group when used during subsequent rather than first therapeutic exposures.

Drug survival

The cumulative percentages of patients maintained on the first anti-TNF agent to which they were exposed are given in Figure 4. At five years, the cumulative percentage of patients remaining on their 1st anti-TNF drug was 26.4 in the ADA mono group (95% CI 17.4-37.9), 62.7 in the ADA combo group (95% CI 45.9-77.0), 40.9 in the IFX mono group (95% CI 32.4-49.9), and 67.2 in the IFX combo group (95% CI 59.7-74.0). The Kaplan Maïer curves for combotherapy were significantly different from the monotherapy curves ($p<0.0001$) whereas the curves for ADA and IFX did not differ significantly according to treatment regimen (combo and monotherapy). In multivariate analysis, combotherapy was associated with a longer drug survival during the 1st exposure to an anti-TNF with an adjusted hazard ratio of 2.17 [1.72-2.70]. Other factors associated with 1st line drug survival were male gender (adjusted hazard ratio 1.75 [1.41-2.17]), living within Paris area (adjusted hazard ratio 1.28 [1.04-1.59]), prior intestinal resection (adjusted hazard ratio 1.30 [1.01-1.67]), and when treatment was initiated at St-Antoine hospital (adjusted hazard ratio 1.52 [1.20-1.92]). Regarding the second therapeutic exposure to an anti-TNF agent, the cumulative percentage of patients remaining on this agent at five years was 23.7 in the ADA mono group (95% CI 14.4-36.5), 38.3 in the ADA combo group (95% CI 22.3-57.3), 28.9 in the IFX mono group (95% CI 11.8-55.1), and 69.2 in the IFX combo group (95% CI 21.7-94.8). The IFX combo curve was significantly different than both ADA and IFX mono curves ($p<0.001$) as well as the ADA combo curve ($p<0.01$). ADA mono and combo curves did not differ significantly.

Reasons for anti-TNF agent discontinuation

The anti-TNF agent was stopped intentionally in 63 patients (following fistula closure, pregnancy, patient decision). Reasons for unintended withdrawal were primary drug failure (188 patients), loss of response (171 patients) and adverse event (183 patients) as presented in figure 5. Most common

adverse events leading to treatment interruption were anaphylactic reactions, joint disease, psoriasis, lupus-like syndrome, and malignancy (eight patients). There were rare cases of infection leading to temporary drug removal, but not to permanent withdrawal. The proportion of patients who developed an adverse event leading to drug discontinuation was 15% in the ADA mono group, 7% in the ADA combo group, 24% in the IFX mono group, and 12% in the IFX combo group ($p<0.0001$). These percentages were similar during the first and the subsequent therapeutic exposures. When compared to monotherapy, initial combotherapy was associated with less adverse events in users of ADA ($p=0.01$) and of IFX ($p<0.0001$). Also, patients on ADA developed less adverse events compared to patients on IFX for both monotherapy ($p<0.01$) and combotherapy ($p<0.05$).

Maximal yearly disease activity and hospitalizations

Yearly disease related data was analyzed for the entire study period except for the first six months following the initiation of a new anti-TNF agent when the initial clinical response was favorable. This prevented us from registering a poor outcome that occurred prior to anti-TNF exposure when the response to the treatment was clearly favorable during a given year. The numbers of patient-years with clinically active disease and requiring hospitalization for severe Crohn's disease flare or complications (including unplanned perianal surgery) are given in Tables 3 and 4. There was a significant increase in the rate of clinically active disease in the course of subsequent therapeutic exposures compared to the 1st exposure for all treatment groups. Head to head comparisons showed that compared to monotherapy, initial combotherapy was associated with less active disease and less need for hospitalization in both users of ADA and IFX. Moreover, there was no significant differences between

ADA and IFX during the course of the first therapeutic exposure, however, patients fared better with IFX combotherapy during subsequent therapeutic exposures.

Need for abdominal surgery

Two hundred and three patients required intestinal surgery, of which 17 patients were operated on twice and three patients were operated thrice. The overall surgical rate was 5.2 per 100 patient-years. Table 3 shows the number of patients who were operated on during the first and the subsequent therapeutic exposures according to the type of initial therapy. The percentages were similar between the groups with the exception of the IFX combotherapy patients requiring less abdominal operations than those in the ADA combo group during subsequent therapeutic exposures only.

Comparison of ADA-IFX and IFX-ADA sequences

Ninety-one patients received consecutively ADA followed by IFX separated by an interval of less than one year, while 147 received IFX followed by ADA. Median duration of the sum of the two therapeutic exposures was 35 months (IQR 17-49) in patients who started with ADA and 48 months (IQR 24-72) in those who started with IFX. The incidence of intestinal surgery in the former group (5.8 per 100 patient-years) was non-statistically different to that of the later group (7.8 per 100 patient-years). The 6-mo. response rates to IFX when used as rescue treatment (i.e. second therapeutic exposure with IFX following ADA discontinuation) was 74%, versus the response rate to ADA rescue therapy of 55% ($p=0.04$). The 2-yr response rates in patients requiring IFX rescue therapy was 55% and did not significantly differ from the rate of 43% in those undergoing ADA rescue therapy. Differences in efficacy of the 2nd anti-TNF agent were particularly marked in the subgroup of patients with loss of response to the first anti-TNF agent as reason of discontinuation (n=99). In this situation, the 6-mo. and 2-yr

response rates to the anti-TNF agent used as rescue were respectively 91% and 87% with IFX vs. 61% (p=0.004) and 36% (p=0.001), with ADA.

Predictive factors of drug survival on ADA and IFX respectively.

In this analysis, the single longest therapeutic exposure in duration per patient to an anti-TNF was considered. Results of univariate and multivariate analysis were separately performed for ADA and IFX and are given in tables 4 and 5. In the 504 patients who received ADA, the cumulative proportion of patients maintained on ADA at five years was 37.9% (95% CI, 30.7 to 46.0). Factors associated with ADA drug survival were male gender, first prescription of ADA in St-Antoine hospital, and initial combotherapy. In the 691 patients who received IFX, the cumulative proportion of patients maintained on IFX at five years was 59.5% (95% CI, 53.6 to 65.1). Factors associated with IFX drug survival were male gender, prior intestinal resection, and initial combotherapy. There was no particular factor associated with a longer drug survival with ADA compared to IFX, or vice versa.

DISCUSSION

This study demonstrated the absence of difference between ADA and IFX as first-line anti-TNF treatment in regards to clinical response and drug survival. The key factor in determining a favorable response to anti-TNF therapy was initial concomitant treatment with an immunomodulator. Also, during subsequent therapeutic exposures to an anti-TNF agent, there was a clear superiority for use of IFX in combotherapy compared to other therapeutic modalities.

Limitations of our findings are first related to its retrospective design. This observational study included a large series of consecutive patients followed-up in a single specialized gastroenterology unit applying uniform surveillance and therapeutic strategies. Of note, most of the data were collected prospectively using the MICISTA registry. During the 2006-2015 calendar period, indications for anti-TNF therapy in our patients did not change significantly, and the proportion of patients receiving anti-TNF agents remained rather stable, representing roughly 15-30% of the cohort [16] . Moreover, the choice between ADA and IFX was based in most cases on patient's preference or on practical reasons, and not related to Crohn's disease severity. Thus, we believe that the comparison between ADA and IFX is reliable. In addition, the initiation of anti-TNF as combotherapy was routine practice in our center [14], albeit ADA was in the earlier years administered more often in monotherapy. The majority of patients who received monotherapy did so because they did not tolerate immunomodulators or refused them. However, as any observational non-randomized study, there were a number of differences between the therapeutic groups, particularly for the first therapeutic exposure population. We noted that Crohn's disease activity tended to be more severe in IFX- vs. ADA-treated patients, and in those who received combo vs. monotherapy. Nevertheless propensity scoring did not significantly impact the results. Another limitation of our study was the absence of regular drug monitoring. It is unclear whether this may have jeopardized clinical response and drug survival during the course of different therapeutic exposures [17]. While IFX drug adherence was asserted at each infusion visit, there was no systematic measurement of ADA trough levels, thus compliance to ADA was not assessed. Finally, we did not analyze endoscopic or MRI changes over treatment. Actually the best marker of anatomic evolution in Crohn's disease is the need for abdominal surgery, and duration of observation was long enough to detect variability in the surgery rates between therapeutic groups.

The benefits of initial combotherapy over monotherapy were expected based on previous randomized controlled trials demonstrating the superiority of the association of IFX with azathioprine vs. IFX alone in terms of clinical response [18], maintenance of remission [19], and mucosal healing [20]. Regarding ADA, a recent meta-analysis concluded that combotherapy increases the response rate but has no clear effect on the one-year remission rate [21]. In the prospective, randomized, open-labelled DIAMOND study [6], 6-mo. response rates were similar with ADA mono and ADA combo, but endoscopic improvement at this time was significantly more frequent in the ADA combo group. In the REACT study, compared to conventional management, early combined immunosuppression was associated with a lower 2-yr occurrence of surgery, hospital admission, or serious disease-related complications [22]. In the real-world setting, many studies did confirm the increased efficacy of IFX [14, 23] and ADA [23, 24] when initially associated to immunomodulators. In the recent observational study of Singh et al. [3], there was however no apparent benefit of combo over monotherapy, but the definition of combotherapy was limited by nature of administrative data only confirming usage of an immunomodulator within 30 days before and/or after anti-TNF start date. Actually, the first six months of co-administration is the most important to prevent the decrease of IFX trough levels [25], and our clinical strategy was to favor use of combotherapy during this period. Thereafter, we routinely tried to stop the immunomodulators in accordance with Leuven's approach [26], unless there were markers of residual disease activity. It was not possible in the present study to analyze the benefit of continuing or resuming immunomodulators after the first semester because of the bias inherent to the selection of the most severe patients in this situation. Besides, it is noteworthy that benefits of initial combotherapy were observed despite the fact that patients given combotherapy were younger and had more often perianal disease. It may be extrapolated that benefits on the response rate are at the expense of more

adverse events. According to our findings, it was not the case. On the contrary the initial use of combotherapy was associated with less adverse events leading to drug discontinuation, notably allergic reactions and skin disease. Likewise, we did not observe more serious infections or malignancies with combotherapy, although this point was not specifically addressed in the present study.

When comparing clinical response, yearly disease activity, Crohn's disease-related hospitalizations, need for surgery, and drug survival between ADA and IFX as first-line anti-TNF agent, we only found significant differences associated with lesser use of combotherapy in ADA-treated patients. In contrast with the recent study of Singh et al. [3], exposure either to ADA or IFX as first-line anti-TNF agents in our cohort did not show a significant difference between subgroups treated with a monotherapy or combotherapy regimen. Although there was some trend favoring IFX this was not significant, a beta error cannot be excluded. A potential bias that may have concealed IFX superiority is the overrepresentation of the most severe cases in patients given IFX vs. ADA as first line therapy. Indeed patients hospitalized for an acute flare were more prone to be treated with IFX than with ADA and the proportion of patients with recent hospitalization was superior when IFX was chosen as first line anti-TNF agent compared to ADA. Other differences included first-line ADA users being more often women, highly educated, overweighed, having systemic symptoms. IFX first-line users were more often young males, with recent colonic and perianal disease. These factors however did not modify either response rates according to logistic regression using propensity scoring, nor did they impact drug survival.

When analyzing second-line treatments, 6-mo. and 2-yr. clinical responses, yearly disease activity, need for surgery and hospitalization rates were significantly better with IFX combotherapy compared to ADA combotherapy. Furthermore, IFX combotherapy used as second line treatment was consistently as

effective as the 1st line anti-TNF regimen, an unusual finding for a 2nd line anti-TNF treatment exposure [27]. This was not observed in the other therapeutic groups. An important difference between our study and the Mayo clinic study is that we included only anti-TNF-naïve patients, while Singh et al. potentially misclassified some patients as anti-TNF-naïve [3]. In the US Medicare database study which included new users of anti-TNF agents, there was no significant difference between IFX-treated and ADA-treated patients regarding drug survival at 26 weeks, rates of hospitalization, and need for surgery [2]. According to these results, it may be hypothesized that ADA and IFX have a similar efficacy when given as first line therapy, whereas IFX is superior to ADA as second line treatment in the subset of patients who stopped ADA because of loss of response. If one considers requirement of intestinal surgery as an appropriate marker of the overall efficacy of an anti-TNF agent, our study demonstrated similar results irrespective of the sequence of ADA-IFX exposure. Finally, multiple covariate factors were collected at time of anti-TNF initiation and tested for the potential of predicting drug survival. Predictors identified by multivariate analysis were somewhat comparable in ADA- and IFX-treated patients and no variable could discriminate when an agent should be preferred over another.

In conclusion, this study did not demonstrate relevant differences in efficacy, adverse events and drug survival between ADA and IFX in Crohn's disease, nor determined applicable criteria for choosing between ADA and IFX as the optimal first-line anti-TNF agent. Patient's preference should therefore be at the center of the discussion when choosing an anti-TNF agent, with the co-administration of an immunomodulator during the first 4-6 months of treatment as routine practice.

Table 1. Characteristics of patients at the start of the first anti-TNF therapeutic exposure according to the treatment regimen. Numbers in parentheses are percentages.

	ADA mono	ADA combo	IFX mono	IFX combo	ADA vs. IFX	mono vs. combo
No.	167	152	213	374		
Male gender	66 (40)	64(42)	110 (52)	189 (51)	0.004	NS
Age (years), median (IQR)	34 (26-43)	31 (25-41)	30 (23-43)	28 (22-41)	0.001	0.01
Crohn's disease duration (months), median (IQR)	84 (20-186)	94 (26-186)	55 (22-126)	71 (20-145)	0.01	NS
Crohn's disease location (Montréal)						
Terminal ileum (L1)	63 (38)	68 (45)	46 (22)	102 (27)		
Colon (L2)	29 (17)	20 (13)	64 (30)	112 (30)	<0.0001	NS
Ileocolon (L3)	72 (43)	63 (41)	100 (47)	157 (42)		
Upper GI (L4)	24 (14)	25 (16)	36 (17)	78 (21)	NS	NS
Crohn's disease behaviour (Montréal)	103 (62)	78 (51)	136 (64)	219 (59)		
Inflammatory (B1)					NS	NS
Stricturing (B2)	25 (15)	24 (16)	40 (19)	69 (18)		
Penetrating (B3)	39 (23)	50 (33)	37 (17)	86 (23)		
Perianal disease	67 (40)	57 (37)	81 (38)	207 (55)	0.004	0.001
Family history of IBD	34 (20)	29 (20)	47 (23)	73 (20)	NS	NS
Extra-intestinal manifestations	66 (42)	51 (35)	70 (34)	115 (31)	0.0004	NS
Associated spondyloarthropathy	17 (10)	10 (7)	10 (5)	14 (4)	0.01	NS
Current smoking	65 (39)	50 (33)	79 (38)	136 (37)	NS	NS
Overweight (BMI > 25)	41 (25)	26 (18)	32 (15)	48 (13)	0.005	NS
High socioeconomic status	50 (30)	47 (32)	52 (25)	82 (22)	0.01	NS
Living outside Paris area	86 (52)	60 (41)	102 (48)	167 (45)	NS	NS
Prior exposure to immunomodulator (> 6mo.)	90 (54)	111 (73)	127 (60)	256 (65)	NS	0.0001
Prior intestinal surgery	53 (32)	55 (36)	60 (28)	105 (28)	NS	NS
1st prescription of anti-TNF agent in St-Antoine hospital	94 (56)	134 (88)	115 (54)	281 (75)	NS	<0.0001
Any Crohn's disease-related hospitalization during the preceding six months	57 (34)	39 (26)	81 (38)	184 (49)	<0.0001	NS

Table 2. Characteristics of patients at the start of the 2nd anti-TNF therapeutic exposure according to treatment regimen. Numbers in parentheses are percentages.

	ADA mono	ADA combo	IFX mono	IFX combo	ADA vs. IFX	mono vs. combo
No.	103	76	60	70		
Male gender	44 (43)	26 (34)	25 (42)	28 (40)	NS	NS
Age (years), median (IQR)	32 (25-45)	28 (21-35)	34 (26-44)	30 (26-38)	NS	0.008
Crohn's disease duration (months), median (IQR)	83 (44-145)	81 (37-139)	78 (41-166)	88 (40-148)	NS	NS
Delay from starting 1st anti-TNF (months), median (IQR)	20 (13-34)	17 (10-33)	19 (9-35)	18 (9-37)	NS	NS
IFX as prior anti-TNF agent	100 (97)	76 (100)	14 (23)	14 (20)	<0.0001	NS
Crohn's disease location (Montréal)						
Terminal ileum (L1)	31 (30)	13 (17)	26 (43)	26 (37)		
Colon (L2)	30 (29)	25 (33)	15 (25)	13 (19)	0.01	NS
Ileocolon (L3)	41 (40)	36 (47)	18 (30)	30 (43)		
Upper GI (L4)	18 (17)	17 (22)	3 (5)	13 (19)	NS	NS
Crohn's disease behavior (Montréal)						
Inflammatory (B1)	64 (62)	45 (59)	40 (67)	40 (57)		
Stricturing (B2)	20 (19)	15 (20)	9 (15)	10 (14)	NS	NS
Penetrating (B3)	19 (18)	16 (21)	11 (18)	20 (29)		
Perianal disease	50 (49)	42 (55)	25 (42)	39 (56)	NS	NS
Family history of IBD	23 (23)	14 (19)	13 (22)	15 (21)	NS	NS
Extra-intestinal manifestations	49 (49)	28 (37)	27 (49)	24 (36)	NS	0.05
Associated spondyloarthropathy	9 (9)	3 (4)	5 (8)	4 (6)	NS	NS
Current smoking	45 (45)	20 (26)	27 (46)	28 (40)	NS	0.04
Overweight (BMI > 25)	14 (14)	6 (8)	20 (34)	13 (19)	0.002	NS
High socioeconomic status	23 (23)	21 (28)	10 (17)	16 (24)	NS	NS
Living outside Paris area	57 (56)	29 (39)	38 (64)	31 (44)	NS	0.003
Prior intestinal surgery	36 (35)	25 (33)	24 (40)	22 (31)	NS	NS
Any Crohn's disease -related hospitalization during the preceding six months	31 (30)	32 (42)	23 (38)	24 (34)	NS	NS

Anti-TNF in second line was prescribed in all cases in St-Antoine hospital

Table 3. Yearly disease activity and Crohn's disease -related hospitalization according to first and subsequent therapeutic exposures

	First therapeutic exposure		Subsequent therapeutic exposures		P (1st vs. subsequent)
Patient-years with clinically active disease					
	No. patient-years	Clinically active disease	No. patient-years	Clinically active disease	
ADA mono	394	181 (46%)	262	154 (59%)	0.002
ADA combo	383	106 (28%)*	162	83 (51%)	<0.001
IFX mono	580	235 (41%)	96	51 (53%)	0.027
IFX combo	1263	398 (32%)*	68	40 (37%)*†	<0.001
Patient-years with hospitalization					
	No. patient-years	Hospitalization	No. patient-years	Hospitalization	
ADA mono	394	72 (18%)	262	57 (22%)	NS
ADA combo	383	36 (9%)*	162	37 (23%)	<0.001
IFX mono	580	87 (15%)	96	26 (27%)	0.005
IFX combo	1263	132 (10%)*	108	10 (9%)*†	NS

* P<0.01 vs. respective mono

† p<0.01 vs. ADA combo

Table 4. Abdominal surgery (intestinal resection, stricturoplasty, stoma) according to first and subsequent therapeutic exposures

	First therapeutic exposure			Subsequent therapeutic exposures			
	No. patient-years*	No. Intestinal surgery	Rate per 100 patient-years	No. patient-years*	No. Intestinal surgery	Rate per 100 patient-years	P (1st vs. subsequent)
ADA mono	576	39	6.8	391	30	7.8	NS
ADA combo	519	21	4.0	230	26	11.4	0.0003
IFX mono	835	52	6.2	189	19	10.1	NS
IFX combo	1676	81	4.8	221	12	5.4†	NS

* duration of therapeutic exposure to ADA or IFX + 12 months following discontinuation

† P<0.05 vs. ADA

Other comparisons did not show significant differences (p>0.05)

Table 5. Predictors of drug survival in patients treated with ADA. Only variables entering the Cox model (log rank p<0.20) are presented

	Log rank	Cox	adjusted HR (95% CI)
Male	0.04	0.02	1.39 (1.05-1.82)
High socioeconomic status	0.003	NS	
Living outside Paris area	0.11	NS	
Current smoking	0.13	NS	
Long disease duration	0.20	NS	
Ileal location (L1)	0.04	NS	
Perianal disease	0.06	NS	
Intestinal stricture (B2)	0.05	NS	
Intestinal perforation (B3)	0.19	NS	
Prior intestinal surgery	0.05	NS	
1st prescription of ADA in St-Antoine hospital	<0.001	<0.001	2.04 (1.56-2.63)
ADA prescribed in 2nd line	0.01	NS	
6-mo. combotherapy with an immunomodulator	<0.001	<0.001	1.89 (1.41-2.50)

Table 6. Predictors of drug survival in patients treated with IFX. Only variables entering the Cox model (log rank p<0.20) are presented

	Log rank	Cox	adjusted HR (95% CI)
Male	<0.001	<0.001	1.96 (1.52-2.56)
High socioeconomic status	0.02	NS	
Living outside Paris area	<0.001	NS	
Long disease duration	0.01	NS	
Extra-intestinal manifestations	0.002	NS	
Perianal disease	0.07	NS	
Intestinal stricture (B2)	0.07	NS	
Intestinal perforation (B3)	0.03	NS	
Prior intestinal surgery	0.01	0.007	1.49 (1.11-1.89)
Prior exposure to immunomodulators (>6mo.)	0.17	NS	
1st prescription of IFX in St-Antoine hospital	0.10	NS	
6-mo. combotherapy with an immunomodulator	<0.001	<0.001	2.00 (1.56-2.56)

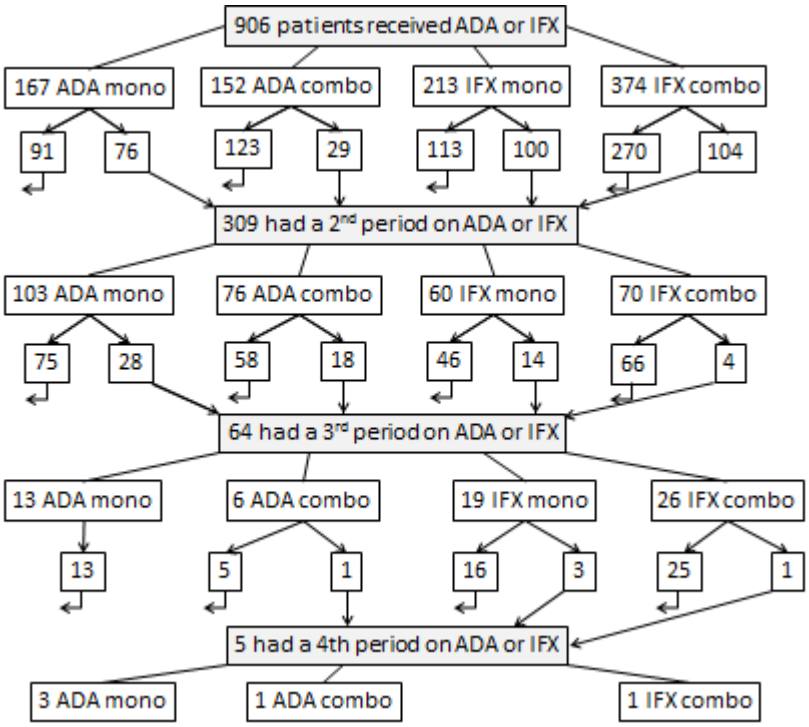

Figure 1. Flow chart of the anti-TNF therapeutic exposures. Patients who stopped the same treatment for more than one year were counted in two different squares. The curved arrow indicates the continuation of treatment till last news.

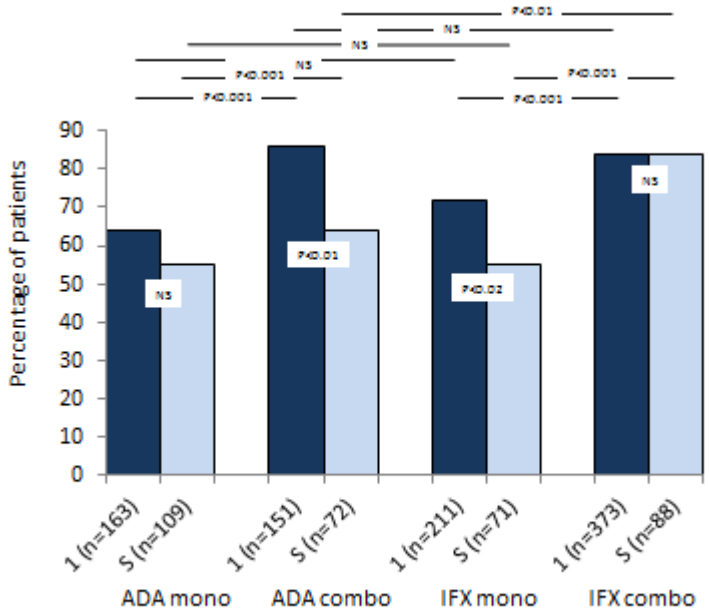

Figure 2. 6-month response rates for 1st (1) and subsequent (S) therapeutic exposures to anti-TNF according to initial treatment regimen.

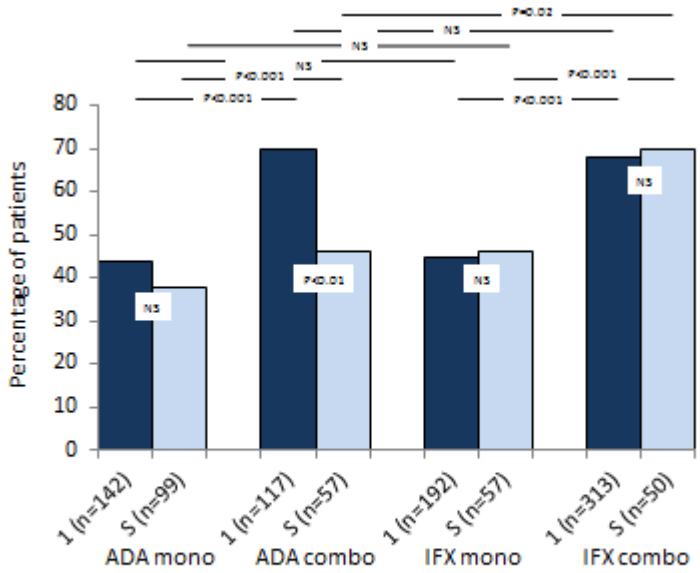

Figure 3. 2-year response rates for 1st (1) and subsequent (S) therapeutic exposures to anti-TNF according to initial treatment regimen

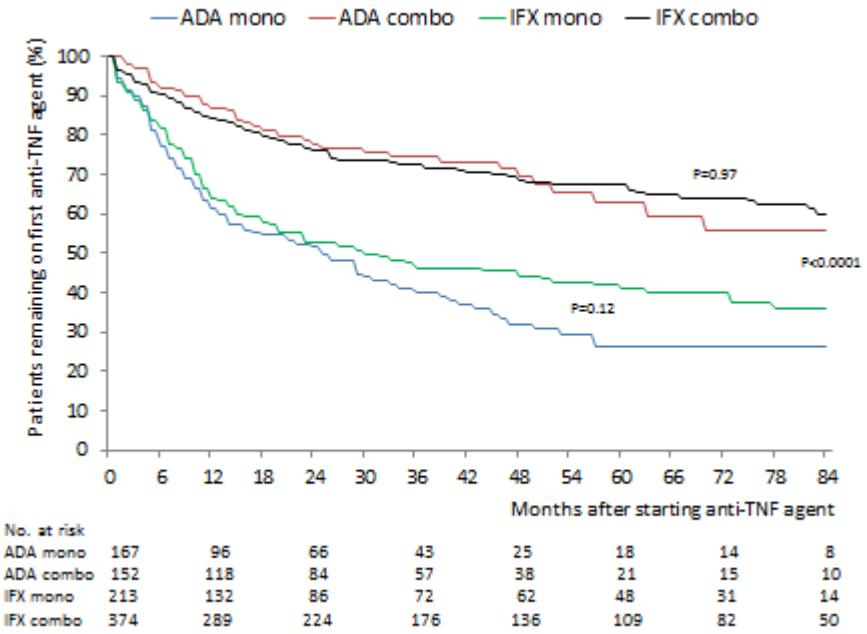

Figure 4. Drug survival curves according to initial first-line treatment regimen

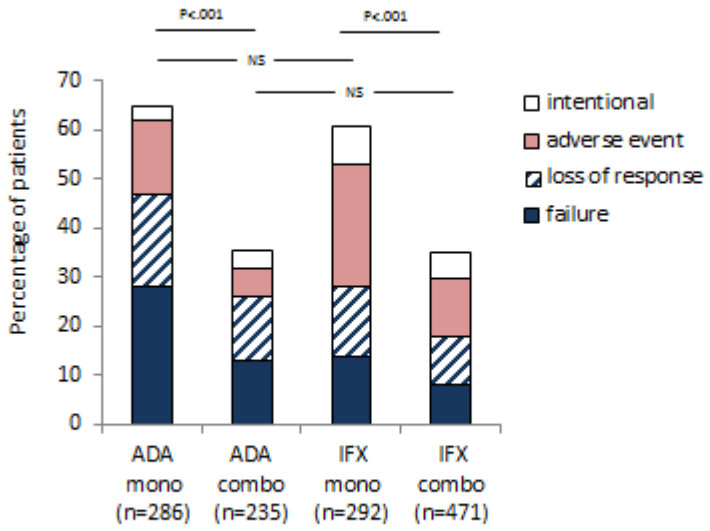

Figure 5. Percentage of patients stopping anti-TNF therapy and main reason for discontinuation according to initial therapeutic exposure (first and subsequent therapeutic exposures are pooled)

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Author's declaration of personal interests:

Jacques Cosnes has served as a speaker for Abbvie and Falk Foundation and an advisory board member for VIFOR PHARMA. Harry Sokol has received consulting fees from Danone, Enterome, Maat pharma, Merck-MSD, Roche, Gilead, Astellas and speaker fees from Abbvie, Takeda, Astellas, Cobas. Andrew Wisniewski has served as a speaker for Abbvie. Laurent Beaugerie has received consulting fees from Abbott and Janssen, lecture fees from Abbott, Abbvie, Janssen, MSD and Ferring Pharmaceuticals, and research support from Abbott, Biocodex and Ferring Pharmaceuticals. Philippe Seksik has received consulting fees from Abbvie, Merck-MSD and Biocodex, and grants from Biocodex. Other authors declare no conflict.

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Authorship statement

Jacques Cosnes is the guarantor of the article.

Jacques Cosnes designed the study, collected the data, performed the statistical analysis, and wrote the paper.

Kevin Perez performed the propensity analysis.

Philippe Seksik participated to the study design.

Other contributors were involved in patients care.

All authors approved the final version of the manuscript