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Direct Retrospective Comparison of Adalimumab and Infliximab in Preventing Early Postoperative Endoscopic Recurrence After Ileocaecal Resection for Crohn's Disease: Results from the MULTIPER Database

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Abstract

Background and aims: Both adalimumab [ADA] and infliximab [IFX] seem to be effective in the prevention of early postoperative endoscopic recurrence [EPER] after ileocaecal resection in Crohn's disease [CD] patients. There is lack of data with direct comparison between the two agents in the postoperative scenario. The aim of this study was to compare the rates of EPER in patients treated with ADA and IFX after ileocaecal resection for CD.

Methods: This was a multicentre retrospective analysis of EPER rates in CD patients after ileocaecal resections, from seven referral centres in three countries. Endoscopic recurrence was defined as Rutgeerts' score ≥ i2. The patients were allocated according to treatment to two groups: ADA or IFX. The EPER rates were compared between the two treatment groups.

Results: Among the 168 patients included in the database, 96 received anti-tumour necrosis factor [TNF] agents after resection [37 in the ADA and 59 in the IFX groups] and were included in this comparative study. The groups were comparable in all baseline characteristics, mainly age, gender, previous resections, perianal CD, and mono or combination therapy. EPER was identified in 9/37 [24.32%] in the ADA group vs 16/59 [27.12%] in the IFX group [$p = 0.815$].

Conclusions: In this retrospective direct comparison between ADA and IFX therapy after ileocaecal resection, there was no significant difference between the two anti-TNF agents in terms of EPER rates. However, prospective randomised studies are needed to confirm these data and better define the role of each agent in the prevention of EPER.

Keywords: Crohn's disease; recurrence; postoperative care

1. Introduction

Resection is still an important tool in the management of ileocolic Crohn's disease [CD]. Apart from significant developments in medical therapy over past years, mainly due to the approval of and emerging experience with biological agents, surgery is still needed in a significant proportion of ileocaecal CD patients.[1] Early postoperative endoscopic recurrence [EPER] is common after resection, and can occur in up to 90% of the patients after 1 year.[2]

Ulcerations in the neo-terminal ileum usually occur before clinical symptoms and structural bowel deformation that can lead to further need for reoperations.[3,4] Therefore, early detection of inflammation close to the anastomotic site is essential in the management of postoperative CD, to promptly detect and adequately prevent or treat endoscopic recurrence.[2] Several drugs were tested with this objective, and they showed different efficacies. Metronidazole and ornidazole were proven to be effective in the prevention of EPER as compared with placebo, but significant adverse events limit their use in the long term.[5,6] Azathioprine was more effective than placebo and mesalamine in some prospective trials, mainly in patients with low risk for recurrence, and is still used worldwide with the aim to reduce EPER rates.[7,8,9]

Biological agents, mainly infliximab [IFX] and adalimumab [ADA] were also studied in prospective randomised trials in comparison with placebo, in order to prevent EPER. Regueiro *et al.* demonstrated only 9.1% of recurrence with IFX as compared with 84.6% in patients with placebo, after a follow-up period of 1 year after ileocolic resections.[10] In a small prospective trial, Armuzzi *et al.* did not find a significant difference between the use of IFX or azathioprine in 21 patients, but a tendency towards better results with the anti-TNF agent could be noted.[11] Savarino *et al.* described the superiority of ADA in preventing recurrence, as compared with azathioprine and mesalamine, in a prospective trial with 2 years of follow-up.[12] Other studies, such as the Post-Operative Crohn's Endoscopic Recurrence [POCER] trial, also proved the efficacy of tailored prevention with biological therapy, when needed, in preventing EPER prospectively.[13]

However, head-to-head comparisons between the two agents are scarce in the literature. There is only one study that compared the efficacy of ADA directly with IFX in the postoperative setting. In this pilot study, the authors found no difference between the two biological agents when evaluating endoscopic, clinical, and histological recurrence, in a small sample of 20 patients, 10 in each group, tested in an open-label design.[14]

The primary outcome of this present study was to directly compare the rates of EPER in patients treated with ADA and IFX after ileocaecal resections in CD, by means of colonoscopies performed up to 1 year after the surgical procedures, from an international multicentre database. The secondary outcome was to compare the EPER rates between patients treated with monotherapy with biological agents vs combination therapy [adding immunomodulators] after surgery.

2. Methods

2.1. Study design

The MULTIPER [MULTicenter International Postoperative Endoscopic Recurrence] database was a retrospective and observational cohort study that analysed EPER rates in CD patients after ileocaecal resections, from seven referral centres for the management of CD, from three countries [Brazil, Japan, and Italy].

This study was fully approved by the ethics committee of each institution involved.

2.2. Inclusion and exclusion criteria

All consecutive patients who underwent ileocaecal resection [by open or laparoscopic approach] between January 2008 and January 2013, and had ileocolonoscopies performed within 12 months after surgery, were considered in the database. From this group, only patients for whom biological therapy with either of the two anti-TNF agents [ADA or IFX] therapy was introduced within 4 weeks after surgery were included in the present analysis.

Patients who had undergone other intestinal resections secondary to CD [small bowel or segmental colonic resections, for example] or isolated strictureplasties were excluded [stricturoplasties associated with ileocaecal resections were allowed]. Patients with colonoscopies performed more than 12 months after the surgical procedure, those who were involved in other trials, those without postoperative biological therapy, and those with missing data on the charts were also excluded.

2.3. Variables analysed

General demographic characteristics [gender, age, CD phenotype, and CD duration according to the Montreal Classification] were included in the protocol. Perianal CD, smoking habit, and concomitant medications [such as steroids or immunomodulators] were also analysed. Surgical characteristics, such as the length of resected bowel, type of approach [open or laparoscopic], type of anastomosis [end-to-end or side-to-side; stapled or hand-sewn], previous resections, the need for blood transfusion, and the presence of residual CD elsewhere in the digestive tract were also studied. EPER was analysed in the first postoperative colonoscopy, which could be performed up to 12 months after surgery. We also studied early surgical complications, such as anastomotic dehiscence, sepsis, and infection in general.

2.4. Group division and definitions

After patients' identification and selection from surgical lists, electronic chart review was performed and a specific protocol with the variables of interest was completed. The included patients were then allocated to two groups, according to the biological agent used after surgery: ADA or IFX. The groups were compared as to their baseline and surgical characteristics to check homogeneity. EPER was defined as the presence of a Rutgeerts' score ≥ i2 in the neo-terminal ileum at the first postoperative colonoscopy. Anastomotic ulcers were not classified as recurrence. The rates of EPER in the two groups were then analysed and directly compared.

2.5. Statistical analysis

Statistical analysis was performed by Fisher and chi-square tests [qualitative variables], and by Student's t test and the non-parametric MannWhitney test [quantitative variables], with $p < 0.05$ considered significant.

3. Results

A total of 231 patients initially were identified and had their records accessed. Overall, 18 were excluded for missing data in the charts,

39 for having their first colonoscopy more than 12 months after the ileocaecal resection and 6 for having blinded postoperative therapy [participation in other clinical trial]. Therefore, 168 patients were initially evaluated. Among those, 72 had conventional non-biological therapy after surgery and were subsequently excluded. A total of 96 patients composed the study sample, with 59 patients on IFX and 37 on ADA. The study design and flowchart are illustrated in Figure 1.

The baseline characteristics of the patients in the two study groups are described in detail in Table 1. The groups were considered fully comparable in all variables analysed [demographic characteristics, concomitant medications before surgery, surgical characteristics, and complications]. There was also no significant difference between the groups regarding the period of the first postoperative colonoscopy (overall 6 months [1–12]; 6 [3–12] months in the ADA group vs 6 [1–12] months in the IFX patients, $p = 0.686$]. There was also no significant difference between the groups in terms of preoperative use of biologicals [overall 52.1%; 45.9% in the ADA vs 55.9% in the IFX patients, $p = 0.403$]. From the eight patients that had anastomotic dehiscence, six had temporary stomas [two of them had undergone re-anastomosis]. All these six patients had their stomas closed between 2–4 months after the first operation and had their colonoscopies performed between 10 and 12 months after the first operation, and were included in the analysis.

Regarding the main objective of this study, EPER was identified in 9/37 patients in the ADA group [24.32%] and in 16/59 patients in the IFX group [27.12%]. No significant statistical difference was found between these two groups [$p = 0.815$], which led to a conclusion that ADA and IFX lead to similar EPER rates in the management of CD. This is illustrated in Figure 2. Moreover, the EPER rates were studied in four different subgroups for each biological agent, regarding the period of the postoperative colonoscopy. As illustrated in Table 2, there was no significant difference between the agents in the four trimesters analysed after surgery. Recurrence rates were also not different between the groups regarding preoperative use of biologicals [34% in patients with and 17.4% in those without biologicals before surgery, $p = 0.102$].

Regarding concomitant immunomodulators with the biological agents, 59/96 patients were treated with biological monotherapy and 37/96 were treated with concomitant azathioprine or 6-mercaptopurine [6-MP]. Table 3 describes in detail the baseline characteristics between these two different subgroups of patients. As illustrated in Figure 3, the EPER rate in the monotherapy group was 22.03% [13/59 patients] and in the combotherapy group was 32.43% [12/37], with $p = 0.340$, showing no significant difference between these two groups.

4. Discussion

Recurrence after surgery in CD has been studied for decades, since the early 90s. At that time, Rutgeerts *et al*. published their experience with 89 patients submitted to ileocaecal resection with an interesting maximum follow-up period of 8 years.[15] That study demonstrated the natural history of postoperative recurrence in CD, and confirmed that EPER was the first to occur, in approximately 75% of the patients after 1 year. Moreover, it confirmed that endoscopic ulcers precede clinical symptoms and further need for operations, stating the importance of controlling the disease activity at an early stage to prevent flares and disability.

The rates of postoperative endoscopic recurrence are variable in the literature, from less than 10% in trials with biological therapy, reaching even up to 90% in patients without adequate postoperative treatment.[2,10,12,16] In our observational cohort, EPER occurred in approximately one-fourth of the patients treated with biological therapy after surgery in both groups, 24.32% [9/37] in the ADA group and 27.12% [16/59] in the IFX group [$p = 0.815$]. These EPER rates were considered to be higher in comparison with prospective trials performed with one or the other anti-TNF agent.

Two factorss might explain this reasonable difference. In the previous trials with biologicals, all patients had localised ileocaecal CD without residual inflammation elsewhere in the digestive tract, and 'curative' ileocaecal resection was one important inclusion criterion for those analyses. In our cohort, approximately 30% of the patients in both groups had residual disease after surgery [elsewhere

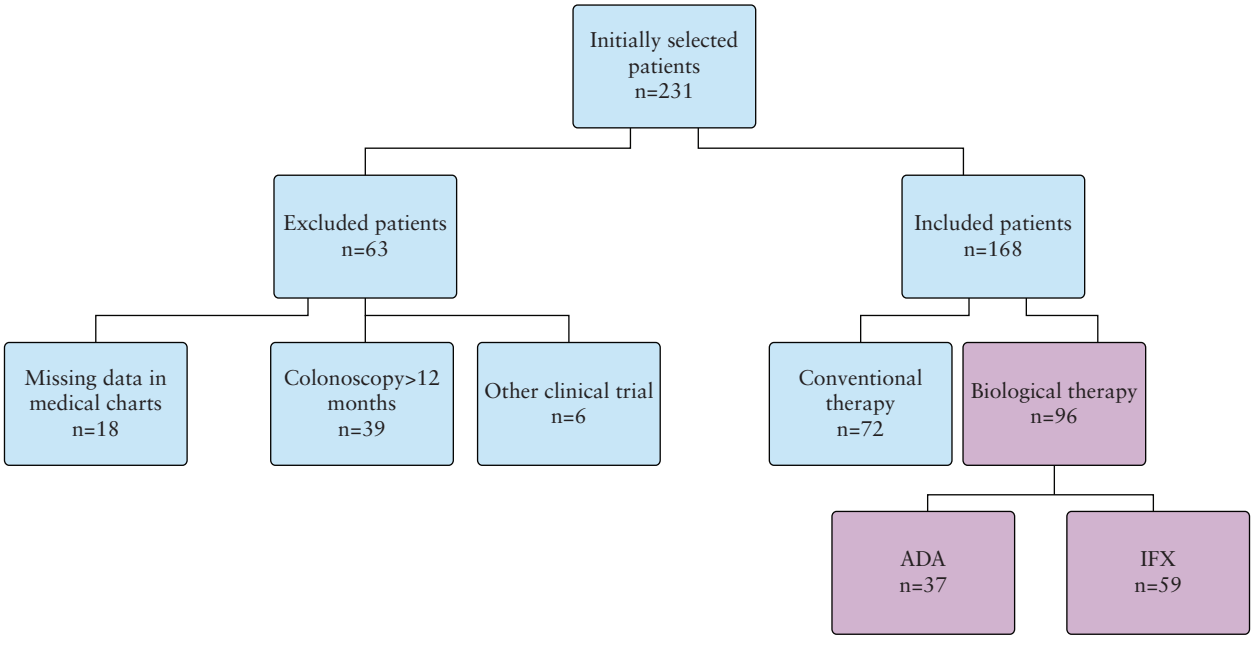

Figure 1 Study design showing exclusion criteria and definition of samples in the analyzsd groups.

Table 1. Baseline characteristics of the patients in the two groups analysed. No statistical difference was found in all variables analysed for homogeneity of the groups. Results expressed as mean ± standard deviation, median [minimum-maximum], or frequency [percent].

Variable	Characteristic	ADA [*n*=37]	IFX [*n*=59]	*p* Value*
Age at surgery [years] SD		33.6 ± 12.1	31.1 ± 10.9	0.282
CD duration [months] min.–max.		84 [2–300]	82 [2–240]	0.137
Length of resected bowel [cm] SD		36.7 ± 26.9	33.4 ± 17.1	0.506
Gender	Female	16 [43.2]	21 [35.6]	0.521
	Male	21 [56.8]	38 [64.4]	
Montreal Classification [A]: age	A1	3 [8.1]	7 [11.9]	0.841
	A2	28 [75.7]	43 [72.9]	
	A3	6 [16.2]	9 [15.3]	
Montreal Classification [L]: CD location	L1	13 [35.1]	21 [35.6]	0.334
	L2	4 [10.8]	2 [3.4]	
	L3	20 [54.1]	36 [61]	
Montreal Classification [B]: phenotype	B1	4 [10.8]	1 [1.7]	0.144
	B2	18 [48.7]	33 [55.9]	
	B3	15 [40.5]	25 [42.4]	
Smoking	No	33 [89.2]	50 [84.8]	0.761
	Yes	4 [10.8]	9 [15.3]	
Perianal CD	No	28 [75.7]	37 [62.7]	0.262
	Yes	9 [24.3]	22 [37.3]	
Steroids at surgery	No	28 [75.7]	40 [67.8]	0.492
	Yes	9 [24.3]	19 [32.2]	
AZA/6MP	No	21 [56.8]	38 [64.4]	0.521
	Yes	16 [43.2]	21 [35.6]	
Biologicals before surgery	No	20 [54.1]	26 [44.1]	0.403
	Yes	17 [46]	33 [55.9]	
Previous resections	No	25 [67.6]	34 [57.6]	0.392
	Yes	12 [32.4]	25 [42.4]	
Isolated ileocecal resection	No	11 [29.7]	20 [33.9]	0.823
	Yes	26 [70.3]	39 [66.1]	
Blood transfusion	No	29 [90.6]	47 [88.7]	1.000
	Yes	3 [9.4]	6 [11.3]	
Residual CD after surgery	No	31 [83.8]	49 [83.1]	1.000
	Yes	6 [16.2]	10 [17]	
Type of surgery	Laparoscopic	9 [24.3]	15 [25.4]	1.000
	Conventional	28 [75.7]	44 [74.6]	
Anastomosis [technique]	Stapled	28 [75.7]	45 [76.3]	1.000
	Hand-sewn	9 [24.3]	14 [23.7]	
Anastomosis [technique]	End-to-end	11 [29.7]	12 [20.3]	0.332
	Side-to-side	26 [70.3]	47 [79.7]	
Early complications	No	29 [78.4]	52 [88.1]	0.252
	Yes	8 [21.6]	7 [11.9]	
Abdominal sepsis	No	33 [89.2]	54 [91.5]	0.730
	Yes	4 [10.8]	5 [8.5]	
Anastomotic dehiscence	No	33 [89.2]	55 [93.2]	0.707
	Yes	4 [10.8]	4 [6.8]	
Granuloma	No	19 [51.4]	25 [42.4]	0.409
	Yes	18 [48.7]	34 [57.6]	
Mono-/ combination therapy	Mono	21 [56.8]	38 [64.4]	0.521
	Combination	16 [43.2]	21 [35.6]	
Period of postoperative colonoscopy [months]		6 [3–12]	6 [1–12]	0.686

ADA, adalimumab; IFX, infliximab; CD, Crohn's disease; SD, standard deviation; 6MP, 6-mercaptopurine. '*' means statistically significant difference.

in the upper gastrointestinal tract, small bowel, colon, or perianally], which may have possibly increased the rates of EPER.

Another important prospective study in the scenario of postoperative recurrence, the POCER trial, was also recently published.[13] The main results of this study demonstrated that tailoring the management of recurrence [active arm] with a 6-months colonoscopy, presented lower endoscopic recurrence rates after 18 months than just using a fixed strategy, without the possibility of optimisation of therapy [control arm]. The rates of endoscopic recurrence at the end of the study were 49% in the active arm and 67% in the control arm, with a significant statistical difference [$p = 0.028$].[13]

The problems in comparing the results of the POCER trial with the results found in our observational study are basically related to the design of the former. In the active arm, not all patients used ADA after the operation and some of the patients had no therapy or just immunomodulators in the immediate postoperative period. Another significant factor limiting this comparison is the duration of both analyses. In the POCER trial, recurrence was evaluated after

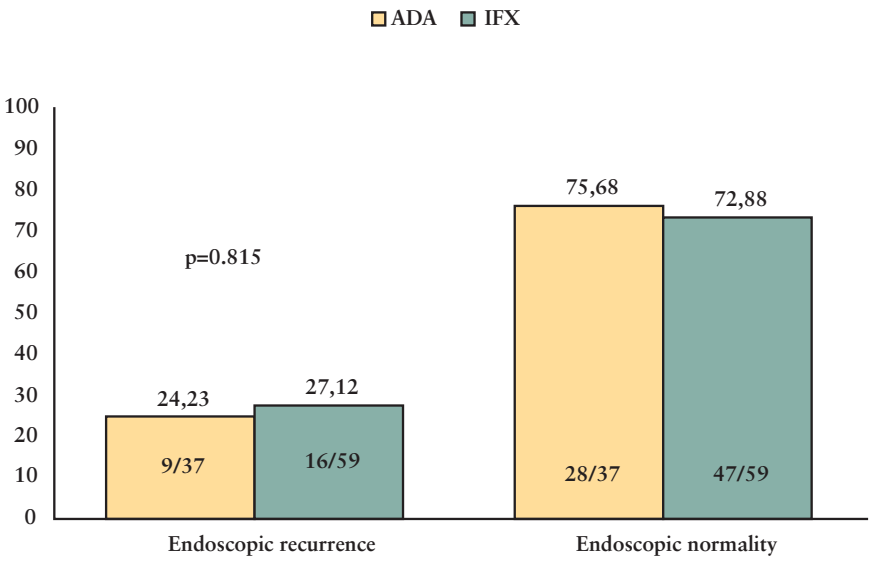

Figure 2. Main results of the study. Comparison of endoscopic recurrence rates between the ADA and IFX groups. No statistical difference in terms of EPER rates was found between the groups [$p = 0.815$].

Table 2. Early postoperative endoscopic recurrence rates between the groups in different periods [trimesters] of the postoperative colonoscopy. There was no significant difference between the groups [$p = 0.644$].

Period [months]	1–3	4–6	7–9	10–12	Total
ADA	0 [0%]	4 [44.4%]	2 [22.2%]	3 [33.4%]	9/37 [100%]
IFX	1 [6.3%]	9 [56.4%]	3 [18.8%]	3 [18.8%]	16/59 [100%]

ADA, adalimumab; IFX, infliximab.

18 months, whereas our results were based on a first colonoscopy performed up to 12 months after the ileocaecal resection, or even performed earlier on in the postoperative setting. It is known that recurrence rates have a tendency to be higher, the longer the postoperative period after which endoscopic evaluation is done. Therefore, it seems that in the active arm of the POCER trial, a mixture of both biological [ADA] and conventional treatments might be the cause of increased rates of endoscopic recurrence.

In a recent publication, Tursi *et al.* described an initial series of 20 patients, prospectively followed, using IFX and ADA after ileocaecal resection. They compared the rates of endoscopic, clinical, and histological recurrence after 1 year between the groups, with 10 patients treated with each biological agent.[14] In this interesting pilot open-labelled study, the authors found no difference between patients using ADA or IFX in the postoperative setting, in terms of endoscopic [10% vs 20%; $p = 0.14$], clinical [10% in both groups; $p = 1.0$], and histological activity [20% vs 30%; $p = 0.11$], respectively.

This was the only study previously published in the literature that aimed at a comparison between the two agents in terms of EPER, the same primary objective as in our present retrospective analysis.[14] Although using different methodologies, both studies reached the same conclusion: the absence of difference in terms of efficacy between ADA and IFX in the prevention of EPER. The above-mentioned study was performed prospectively, with unblinded randomization, and strict inclusion criteria.[14] The authors also performed central reading of the colonoscopies' video recordings, which also might have reduced the bias. However, the sample size of their study may be relatively small to detect a significant difference.

On the other hand, our study, even being retrospective and multicentric, also demonstrated the same results. Within the limitations of an observational cohort analysis, our study's quality is based on the sample of patients [96 in total, with 37 in the ADA and 59 in the IFX groups, the wider to date in terms of direct comparison]. Moreover, the baseline characteristics of the patients were completely and fully comparable between the groups, demonstrating the strength of our results. Indeed, comparison of EPER rates between our cohort and the above-mentioned study by Tursi *et al.*[14] would not be completely possible, mainly on account of different populations and methods. In our cohort, a significant proportion of included patients had open surgery, young age at surgery, residual CD, and longer CD duration. At the same time, even with the above-mentioned limitations, our study was less restrictive in inclusion criteria and may therefore better reflect real-life results. Even with those differences, in the IFX group of the study by Tursi *et al.* they found 20% of EPER, a similar number to our approximately 25% of patients in the two groups analysed.

Regarding the secondary outcome of our study, no difference was found between patients under monotherapy with biologicals vs combination therapy with these agents and immunomodulators. The groups were not fully comparable in baseline characteristics, as seen in Table 3. We did not analyse those rates between the two different agents, as reduced subgroups of patients with small numbers could lead to a type II error. No study in the literature had previously looked at a comparison between these two different strategies postoperatively. Still, differences between ADA and IFX in combination with immunomodulators compose a hot topic for discussion at the present date, not only in the postoperative setting but also in the management of luminal CD.

Table 3. Baseline characteristics of patients treated with mono- or combination therapy. Patients in combotherapy had longer disease duration, less residual disease, more stapled anastomoses, and less granulomas in the specimens. Results expressed as mean ± standard deviation (SD), median [minimum-maximum], or frequency [percent].

Variable	Characteristic	Mono [*n*=59]	Combo [*n*=37]	*p*-Value*
Age [years] with SD		33.4 ± 11.1	29.9 ± 11.6	0.150
CD duration [months] min-max		64 [2–300]	108 [2–240]	0.030*
Specimen extension [cm] with SD		33.7 ± 15.1	36.2 ± 28.9	0.617
Gender	Female	22 [37.3]	15 [40.5]	0.830
	Male	37 [62.7]	22 [59.5]	
Montreal Classification [A]: age	A1	3 [5.1]	7 [18.9]	0.042*
	A2	44 [74.6]	27 [73]	
	A3	12 [20.3]	3 [8.1]	
Montreal Classification [L]: CD location	L1	22 [37.3]	12 [32.4]	0.336
	L2	2 [3.4]	4 [10.8]	
	L3	35 [59.3]	21 [56.8]	
Montreal Classification [B]: phenotype	B1	2 [3.4]	3 [8.1]	0.551
	B2	31 [52.5]	20 [54.1]	
	B3	26 [44.1]	14 [37.8]	
Smoking	No	52 [88.1]	31 [83.8]	0.555
	Yes	7 [11.9]	6 [16.2]	
Perianal CD	No	38 [64.4]	27 [73]	0.502
	Yes	21 [35.6]	10 [27]	
Steroids	No	38 [64.4]	30 [81.1]	0.107
	Yes	21 [35.6]	7 [18.9]	
Biologicals before surgery	No	33 [55.9]	13 [35.1]	0.060
	Yes	26 [44.1]	24 [64.9]	
Previous resections for CD	No	39 [66.1]	20 [54.1]	0.284
	Yes	20 [33.9]	17 [45.9]	
Isolated ileocecal resection	No	24 [40.7]	7 [18.9]	0.043*
	Yes	35 [59.3]	30 [81.1]	
Blood transfusion on admission	No	44 [91.7]	32 [86.5]	0.494
	Yes	4 [8.3]	5 [13.5]	
Residual macroscopic CD after surgery	No	49 [83.1]	31 [83.8]	1.000
	Yes	10 [16.9]	6 [16.2]	
Type of surgery	Laparoscopic	17 [28.8]	7 [18.9]	0.338
	Conventional	42 [71.2]	30 [81.1]	
Anastomosis [technique]	Stapled	39 [66.1]	34 [91.9]	0.006*
	Hand-sewn	20 [33.9]	3 [8.1]	
Anastomosis [technique]	End-to-end	18 [30.5]	5 [13.5]	0.085
	Side-to-side	41 [69.5]	32 [86.5]	
Early complications [30 days]	No	50 [84.7]	31 [83.8]	1.000
	Yes	9 [15.3]	6 [16.2]	
Abdominal sepsis	No	54 [91.5]	33 [89.2]	0.730
	Yes	5 [8.5]	4 [10.8]	
Anastomotic dehiscence	No	53 [89.8]	35 [94.6]	0.480
	Yes	6 [10.2]	2 [5.4]	
Granulomas in the specimen	No	22 [37.3]	22 [59.5]	0.038*
	Yes	37 [62.7]	15 [40.5]	
Type of biological after surgery	ADA	21 [35.6]	16 [43.2]	0.521
	IFX	38 [64.4]	21 [56.8]	

ADA, adalimumab; IFX, infliximab; CD, Crohn's disease; SD, standard deviation. '*' means statistically significant difference.

Our study had some evident limitations that need to be considered in the interpretation of its results. First, the methodological features of a retrospective multicentre and observational analysis, without a fixed protocol, could have led to some bias, even if the databases in the single institutions were prospectively maintained. The absence of a a fixed date for performing the colonoscopies [for example, 6 months for every patient] could have also been a counfounding factor, even if the range was restricted up to only 12 months. However, the fully comparable groups in all the baseline characteristics and in the main risk factors for recurrence may overcome this bias and make the results solid. In this retrospective study, the sample size calculation was not done based on a primary statistical endpoint. This was another limitation of our study. In future, a randomised trial with sample size justification should be conducted to confirm the results obtained in the present analysis.

In summary, in this restrospective multicentre and observational analysis, with the largest sample to date in terms of direct comparison, no difference was found between ADA and IFX in the prevention of EPER rates after ileocaecal resection. There was also no difference between mono- and combination therapy [with this agents added to by immunomodulators] in preventing endoscopic recurrence. These conclusions could be confirmed by a double-blind prospective trial with a similar design.

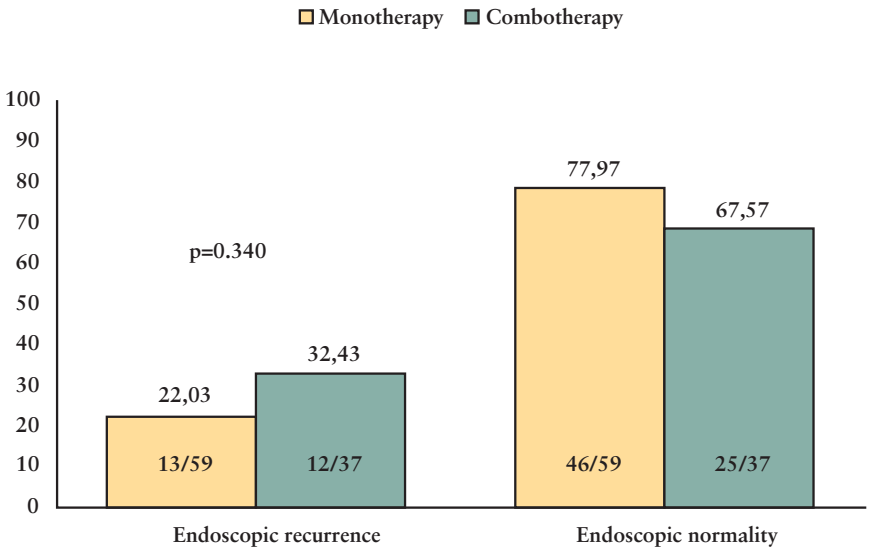

Figure 3. Comparison between mono- vs combination therapy regarding early postoperative endoscopic recurrence [EPER] rates. No significant statistical difference was found between the two groups [$p = 0.340$].

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PK, TY, FVT, AY, and AS designed the study. All authors did data collection and gave scientific contribution to the study design and discussion. MO did the statistical analysis. PK, TY, and AS drafted the article. All authors read and approved the final version of the manuscript.

Conflicts of Interest

PK: Abbvie, Astrazeneca, Ferring, Janssen-Cilag, Pfizer, and Takeda. TY: no disclosure. SD: Merck Sharp & Dohme, Schering Plough, AstraZeneca, Abbvie, Takeda, UCB Pharma, and Ferring. YS: Abbvie. FT: Abbvie, Janssen-Cilag, and Celltrion. IA: Abbvie and Janssen-Cilag. RSH: Abbvie. IFB, RNS, LK, MO, MS, AY, KT, and AS: no disclosure.

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