INFLIXIMAB AND NEWLY DIAGNOSED NEOPLASIA IN CROHN'S DISEASE: A MULTICENTER MATCHED-PAIR STUDY

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Key Words: Crohn's Disease**,** anti-tumour necrosis factor-α antibody, Infliximab, neoplasia, multicenter matched-pair study.

Abbreviations: CD=Crohn's Disease; IBD=Inflammatory Bowel Disease; AZA= Azathioprine; 6-MP=6-Mercaptopurine; MTX=Methotrexate; CDAI=Crohn's Disease Activity Index; NHL=Non-Hodgkin's Lymphoma

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ABSTRACT

Background and aims. The widespread use of anti-tumour necrosis factor-α antibody (Infliximab) in Crohn's Disease (CD) rises concerns about possible cancer risk in the long term. In a matched-pair study we assessed whether Infliximab is associated with an increased risk of neoplasia. **Methods.** In a multicenter matched-pair study, 404 CD patients treated with Infliximab (CD-IFX) were matched with 404 CD never receiving Infliximab (CD-C). Cases and controls were matched for sex, age (±5 years), site of CD, age at diagnosis (±5 years), immunosuppressants use and follow up. New diagnoses of neoplasia from April 1999 to October 2004 were recorded. **Results.** Among the 404 CD-IFX, neoplasia was diagnosed in 9 patients (2.22%), while among the 404 CD-C, 7 patients developed neoplasia (1.73%)(p=0.40; OR=1.33; 95% CI=0.46-3.84). The survival curve adjusted for patient-year of follow up showed no differences between CD-IFX and CD-C (p=0.90; log rank test). In the CD-IFX group, there were 1 cholangiocarcinoma, 3 breast cancers, 1 skin cancer, 1 laryngeal cancer and 2 anal carcinomas. Among the 7/404 (1.73%) CD-C, there were 3 intestinal adenocarcinomas (2 coecum, 1 rectum), 1 basalioma, 1 spinalioma, 1 NHL, 1 breast cancer. The age at diagnosis of neoplasia did not differ between groups (CD-IFX vs CD-C: median 50, range 40-70 yrs vs 45, range 27-72; p=0.50). **Conclusion.** In our multicenter matched-pair study, the frequency of a new diagnosis of neoplasia in CD patients treated with Infliximab was comparable to CD patients never receiving Infliximab.

INTRODUCTION

New treatments specifically targeting the release and/or activity of soluble mediators involved in the induction and perpetuation of the inflammatory process have been developed in Crohn's Disease (CD)[1,2]. Among these, the human-murine chimeric monoclonal antibody against tumor necrosis factor-α (TNFα) has shown in several controlled trials efficacy in moderate-to-severe [3] and fistulizing CD [4]. Retreatment every 8 weeks has also shown efficacy in maintaining remission in responsive patients [5-7]. Due to its proven efficacy, Infliximab is widely used in CD, thus rising concerns about possible side effects in the long term. Current evidences indicate that the appropriate use of Infliximab is safe, not associated with a significantly higher risk of side effects in the short-term, when compared to placebo [8]. A slightly higher risk of malignancies has been reported in chronic inflammation related to CD, particularly after the long-term use of immunosuppressants [9-15]. Newly diagnosed neoplasia have occasionally been reported in clinical trials using Infliximab in CD, with a frequency similar to that expected in the general CD population [16].
No matched-pair studies investigated the frequency of a newly diagnosed neoplasia in CD patients treated with Infliximab. In order to address this issue, we investigated in a multicenter, matched-pair study, the frequency of newly diagnosed neoplasia during the follow up of CD patients treated with Infliximab, in comparison with matched CD patients never treated with Infliximab.

MATERIALS AND METHODS

Study Population.

This multicenter, matched-pair study includes 808 CD patients with no history of neoplasia (404 treated with Infliximab, 404 matched controls never treated with Infliximab) in regular follow up in 11 IBD referral centers (Universities: "Tor Vergata", Roma, centre 1: n=104; "La Sapienza", Roma, centre 2: n=66; "Federico II", Napoli, centre 3: n=62; GI Unit, Padova, centre 4: n=40; 2nd University, Napoli, centre 5: n=32; Hospitals: "V. Cervello", Palermo, centre 6: n=164; "S. Camillo", Roma, centre 7: n=162; "L. Sacco", Milano, centre 8: n=62; "Mauriziano", Torino centre 9: n=56; "Valduce", Como, centre 10:n=32;"San Filippo Neri", Roma, centre 11: n=28). One additional IBD centre (Policlinico "S. Orsola", Bologna) contributed to data analysis.
Clinical characteristics of CD patients treated and untreated with Infliximab, including smoking habits [17], are summarized in Table 1 and 2 for matched and not matched variables, respectively.

Table 1. Characteristics of Crohn's Disease patients treated with Infliximab and their Crohn's Disease controls never receiving Infliximab, including only matched variables.

Characteristics	Infliximab-treated patients (n=404)	Control patients (n=404)
	n. (%)	n. (%)
Sex		
Males	214 (53%)	214 (53%)
Females	190 (47%)	190 (47%)
Crohn's Disease site		
Ileum	101 (25%)	93 (23%)
Ileum-Colon	169 (42%)	175 (43%)
Colon	127 (31%)	134 (33%)
Others	7 (2%)	2 (1%)
Immunosuppressants	213 (53%)	218 (53%)
AZA/6-MP	203 (95%)	211 (97%)
Methotrexate	10 (5%)	7 (3%)
Duration of ISS (median months and range)	36 (3-160)	24 (2-120)
Patient's age (median years and range)	41 (13-82)	40 (14-82)
Crohn's Disease duration (median years and range)	10 (1-62)	9 (1-34)
Follow up in each center (median mths and range)	48 (6-396)	60 (6-384)

Abbreviations: AZA= Azathioprine; 6-MP=6-mercaptopurine; ISS= Immunosuppressants.

Table 2. Characteristics of Crohn's Disease patients treated with Infliximab and their Crohn's Disease controls never receiving Infliximab, not including matched variables.

Characteristics	Infliximab-treated patients	Control patients
	n. (%)	n. (%)
Crohn's Disease type		
Inflammatory	146 (36%)	177 (44%)
Fistulizing	238 (59%)*	175 (43%)
Stricturing	20 (5%)	52 (13%)**
Familial IBD		
No	361 (89%)	360 (89%)
Yes	43 (11%)	44 (11%)
Smoking habits		
Yes	144 (36%)	144 (36%)
No	223 (55%)	216 (53%)
Ex	37 (9%)	44 (11%)
Previous surgery		
Yes	157 (39%)	178 (44%)
No	247 (61%)	226 (56%)
Age at Crohn's Disease diagnosis		
(median years and range)	28 (7-80)	29 (9-81)

Abbreviations: IBD=Inflammatory Bowel Disease.

* p=0.003 Fistulizing CD in Infliximab-treated patients vs controls never receiving Infliximab.
** p=0.042 Stricturing CD in controls never receiving Infliximab vs Infliximab-treated patients.

CD patients treated with Infliximab

Infliximab-treated group included 404 active CD patients consecutively treated with Infliximab in the 11 IBD centers from April 1999 to April 2004. The follow up was completed on October 2004 (median time from Infliximab 25 months, range 6-67). After the completion of the study, each of the 404 Infliximab-treated patients was matched in each centre with 1 CD patient never receiving Infliximab, matched according to several clinical variables detailed in the next paragraph. Indication for Infliximab was moderate-to-severe CD (Crohn's Disease Activity Index, CDAI 220-400)[18]: fistulizing (n=238; 59%) or refractory/steroid-dependent luminal disease (n=166; 41%)[19]. Infliximab was administred e.v. (5 mg/Kg) including single or 3 infusions for luminal and 3 infusions (0,2,6 weeks) for fistulizing CD. The median number of infusions was 3 (range 1-30) according to an acute (n=225; 56%), maintenance (n=85; 21%) or "on demand" (n=94; 23%) schedule. The number of infusions was >3 in 179 CD patients (maintenance n=85; "on demand" n=94). Concomitant treatments at time of Infliximab were immunosuppressants (n=165; 41%), steroids (n=117; 29%), antibiotics (ciprofloxacine or metronidazole)(n=105; 26%), mesalazine (n=68; 17%).

Matched-pair CD controls never receiving Infliximab

Each of the 404 patients treated with Infliximab was matched with one CD control referred to the same centre in the same study period (April 1999-October 2004), but never treated with Infliximab. Data from CD controls were recorded prospectively in each centre, according to regular follow up, but the matching was done retrospectively after the completion of the study, in order to ensure that the referent population had not been exposed to Infliximab. At this purpose, at the end of the study, each CD patient treated with Infliximab was matched with 1 CD control never treated with Infliximab, followed up in the same study period in the same centre, according to the following criteria: age (±5 years), sex, follow up period in the same centre (±5 years), immunosuppressants use (yes/no; type; duration), CD site (ileum, ileum-colon, colon, others), CD duration (±5 years). Less than 5% of CD controls showed one of the matched variables outside the range. No CD controls received Infliximab at any time, although several clinical features were matched with CD patients receiving Infliximab. Controls were indeed matched according to clinical variables not necessarily reflecting the inherent disease aggressiveness nor the clinical behaviour. However, there were also a number of reasons for not using Infliximab in CD controls, including the patients' opinion (i.e. patients refusing treatment because seriously concerned about side effects), contraindications (abscesses, possible pregnancy, infectious diseases including TBC, concomitant disease states). Furthermore, controls included a higher percentage of patients with stricturing CD (13% vs 5%; p=0.042) and a lower percentage of patients with fistulizing CD (43% vs 59%; p=0.003) than Infliximab-treated CD (Table 2).

Diagnosis of neoplasia

No patients had a known history of neoplasia at entrance. New diagnoses of neoplasia were made by using conventional procedures in relation to specific symptoms or signs referred by patients in regular follow up. No screening procedures were performed before or after entering the study in order to detect neoplasia. Therefore, only symptomatic neoplasia were diagnosed. However, all CD patients referred to the 11 centres are enrolled in a program of regular supervision for the management of CD. As a consequence, they represent a subject population undergoing regular clinical assessment and scheduled medical/hospital attendances. No cancer registry is available and the accuracy of the data was assured by clinical records of each participating centre. Newly diagnosed neoplasia were recorded during the follow up together with: age at diagnosis of neoplasia, type of neoplasia, outcome (remission, death), immunosuppressants use (yes/no, type, duration).

Statistical analysis

Statistical analysis was carried out in order to compare CD patients treated with Infliximab and their matched-pair CD controls in terms of: frequency of newly diagnosed neoplasia, age at diagnosis of neoplasia, CD duration at diagnosis of neoplasia, outcome of neoplasia (remission, death), type of neoplasia, immunosuppressants use. Differences between Infliximab-treated and untreated CD patients were assessed by the $\chi 2$ test, the Student's *t* test or the Mc Nemar test to compare qualitative and quantitative variables among groups. Odds ratios (95% confidence intervals, CI) were calculated. The Relative

Risk (RR) was assessed in relation to the patient's age (years). Cumulative survival curve was estimated by the log rank test, according to patient-years of follow up after CD diagnosis, by comparing the frequency of newly diagnosed neoplasia in CD patients treated with Infliximab versus matched-pair CD controls.
Sample size calculation implies the knowledge of both the expected number of cases (i.e. CD patients developing neoplasia) and the expected difference (i.e. frequency of neoplasia in Infliximab-treated vs untreated CD). The expected prevalence of neoplasia is poorly defined for the general CD population [9-15], and not defined for severe CD. Moreover, no studies compared the frequency of neoplasia in matched-pair CD patients treated or not with Infliximab. Therefore, both the expected number of cases and the expected difference between groups were not available for sample size calculation. In order to define these 2 parameters, in this first matched-pair study we assessed the frequency of newly diagnosed neoplasia in 404 CD patients treated with Infliximab and followed up from April 1999 to October 2004, in comparison with 404 matched-pair CD controls never receiving Infliximab, prospectively followed up in the same period.

RESULTS

The number of patients with fistulizing disease was higher in CD patients treated with Infliximab than in CD controls never receiving Infliximab (p=0.003), while the number of patients with stricturing CD was higher in CD controls than in CD patients treated with Infliximab (p=0.042) (Table 2). The other clinical variables were comparable between the two groups (Table 1 and 2). When considering the whole group of 808 patients, including both Infliximab-treated and untreated CD, 16 patients (1.98%) had a newly diagnosed neoplasia in the follow up period.

CD patients treated with Infliximab

Among the 404 CD patients treated with Infliximab, 9 (2.22%) had a diagnosis of neoplasia from April 1999 to October 2004. Table 3 shows the clinical features of patients developing neoplasia. As indicated, among the 404 CD patients treated with Infliximab, the following neoplasia were diagnosed: 1 cholangiocarcinoma (centre 2), 2 anal carcinoma (centre 6; centre 8), 1 basalioma (centre 9), 3 adenocarcinoma of the breast (centre 1: n=2; centre 9: n=1), 1 laryngeal carcinoma (centre 1) and 1 leukemia (centre 8). The median age of patients with neoplasia was 50 years (range 40-70), and the median CD duration was 23 years (range 5-39). The outcome of neoplasia at the end of the follow up was remission in 5 and death in 3, while 1 patient with leukemia was lost at the follow up. The median number of Infliximab infusions in patients developing neoplasia was 4 (range 2-11), comparable with the median of 3 infusions in patients not developing neoplasia (range 1-30). The median time interval between the first infusion and diagnosis of neoplasia was 18 months (range 6-45). Among the 9 patients with neoplasia, 7 (77.7%) received immunosuppressants (AZA 5, thalidomide 1, MTX 1). In these 7 patients, the median time interval between beginning of immunosuppressants and diagnosis of neoplasia was 40 months (range 5-144), with a median treatment duration of 36 months (range 4-52).

Table 3. Clinical characteristics of each of the 9 Crohn's Disease (CD) patients treated with Infliximab developing neoplasia during the follow up.

Pt.	Sex	CD Site	CD type	CD Duration (years)	Type of neoplasia	Age at neoplasia diagnosis (outcome)	ISS (mths)	No. of Infusions (schedule)	Time since IFX (mo)	Time since ISS (mo
1.	M	I-C	F	23	Cholangio-carcinoma	48 Deceased	AZA (5)	3 acute	6	5
2.	F	I-C	L	23	Anal carcinoma	70 Deceased	Thalid. (4)	9 on demand	45	96
3.	F	I-C	F	24	Anal carcinoma	41 Deceased	n.d.	2 on demand	6	n.d.
4.	F	C	L	39	Breast cancer	50 Remission	MTX (36)	6 on demand	24	36
5.	F	I	L	39	Breast cancer	60 Remission	n.d.	4 on demand	15	n.d.
6.	F	I-C	F	6	Breast cancer	40 Remission	AZA (52)	6 maintenance	33	52
7.	F	C	L	13	Leukemia	45 Lost f.up	AZA (24)	4 maintenance	12	144
8.	M	I	L	18	Basalioma	61 Remission	AZA (36)	11 maintenance	18	24
9.	F	I-C	F	5	Laryngeal carcinoma	53 Remission	AZA (48)	2 on demand	38	40

Abbreviations: ISS=Immunosuppressants;IFX=Infliximab; F=Female; M=Male; I=Ileum; C=Colon; I-C=Ileum-Colon;C=Colon;L=Luminal;F=Fistulizing;AZA=Azathioprine ;6-MP=6-mercaptopurine.

Matched-pair CD controls never receiving Infliximab

Among the group of 404 CD controls never receiving Infliximab and followed from April 1999, 7 patients (1.73%) had a new diagnosis of neoplasia within October 2004. Table 4 indicates the clinical features of patients developing neoplasia. As shown, in CD controls the following neoplasia were diagnosed: 2 skin cancers (1 spinalioma, 1 basalioma) (centre 1,centre 2), 1 breast cancer (centre 1), 1 non-Hodgkin's lymphoma (NHL)(centre 1), 2 adenocarcinoma of the coecum (centre 1, centre 7), adenocarcinoma of the rectum (centre 8). The median age of patients developing neoplasia was 45 years (range 27-72), and the median CD duration was 12 years (range 1-27). The outcome of neoplasia at the end of the follow up was remission in all 7 CD controls. Among the 7 patients with neoplasia, 3 (42.8%) received immunosuppressants (3 AZA) for a median of 46 months (range 24-48), with a median interval between beginning of treatment and diagnosis of neoplasia of 46 months (range 24-120).

Table 4. Characteristics of each of the 7 Crohn's Disease control patients never receiving Infliximab, developing neoplasia during the follow-up.

Pt.	Sex	CD site	CD Type	CD Duration (years)	Type of neoplasia	Age at diagnosis of neoplasia (outcome)	ISS (mo)	Time since ISS
1.	M	I-C	L	27	Adenocarcinoma coecum	61 Remission	n.d.	n.d.
2.	F	C	L	1	Adenocarcinoma coecum	27 Remission	n.d.	n.d.
3.	F	I-C	F	7	Adenocarcinoma rectum	45 Remission	n.d.	n.d.
4.	M	I	F	22	Spinalioma	33 Remission	AZA (46)	46
5.	F	I-C	L	12	Basalioma	58 Remission	AZA (24)	24
6.	F	I-C	F	13	Breast cancer	72 Remission	n.d.	n.d.
7.	F	I-C	F	12	Non-Hodgkin's Lymphoma	36 Remission	AZA (48)	120

Abbreviations: ISS=Immunosuppressants;IFX=Infliximab; F=Female; M=Male; I=Ileum; C=Colon; I-C=Ileum-Colon; L=Luminal; F=Fistulizing; AZA=Azathioprine; 6-MP=6-mercaptopurine ; n.d.= not done.

Comparisons between Infliximab-treated CD patients and their matched-pair CD controls

The frequency of newly diagnosed neoplasia in the follow up period did not significantly differ between CD patients treated with Infliximab and their matched-pair CD controls (2.22% vs 1.73%; p=0.40; OR=1.33; 95% CI=0.46-3.84). Figure 1 shows the survival curve of CD patients with newly diagnosed neoplasia adjusted for patient-year of CD duration (from the diagnosis of CD to the last visit), comparing Infliximab-treated and untreated patients. As shown, no differences were observed between the 2 groups (log rank test p=0.90). Further indicating that Infliximab did not significantly affect the risk of neoplasia in our CD population, the relative risk (RR) of neoplasia adjusted for patient's age was 1.35. The median age at the diagnosis of neoplasia did not differ between CD patients treated with Infliximab and their matched-pair CD controls (years: median 50, range 40-70 vs median 45, range 27-72; p=0.50). The median CD duration at time of diagnosis of neoplasia also did not differ between Infliximab-treated and untreated CD patients (years: median 23, range 5–39 vs median 12, range 1-27; p=0.18). The outcome of neoplasia among the 9 Infliximab-treated patients included 3 deaths, 5 remissions and 1 patient lost at the follow up, while all the 7 controls developing neoplasia were in remission at the end of the follow up. Immunosuppressants use was observed in 7 out of 9 (77.7%) patients treated with Infliximab versus 3 out of 7 (42.8%) matched-pair controls (p=0.36). Time since beginning of immunosuppressants and diagnosis of neoplasia did not differ between the 2 groups (Infliximab-treated CD: median 40 months,

range 5-144; CD controls: 46 months, range 24-120; p=0.84). Duration of immunosuppressants use was also comparable between the 2 groups (Infliximab-treated CD: median 36 months, range 4-52; CD controls: median 46 months, range 24-48; p=0.44).

DISCUSSION

CD is a chronic inflammatory condition of unknown etiology. The role of macrophage and T-cell activation in tissue damage [20-22] gave rise to the widespread use of immunomodulatory drugs in CD. Both chronic inflammation and the long term use of immunosuppressants have been suggested as risk factors for neoplasia in CD [9-16]. However, the real life-time risk of cancer in CD shows variations in different study populations, ethnic groups and geographic areas [9-15]. No studies provide neoplasia rates adjusted for age, CD activity and immunosuppressants duration. Although population-based studies in CD suggest no increased risk of NHL [23-25], results are conflicting [10]. 6-MP and AZA have been associated with NHL [13-15]. Munkholm *et al*. reported in a cohort of 373 Danish CD patients that the life-time risk of cancer is not increased (4.1% vs 3.8%), although the risk of rare small bowel cancer is increased (2 vs the 0.04 expected; p=0.001) [26]. In CD, benefits appears to overwhelm risks when using immunosuppressants in the long-term [27]. Newly diagnosed neoplasia have occasionally been reported in trials using Infliximab in CD [16, 28], although no controlled studies addressed the possible role of Infliximab. Rutgeerts *et al.* firstly reported a duodenal B-cell lymphoma in a 61 year old patient receiving one infusion (10 mg/Kg), dying for sepsis after chemotherapy [6]. A case-report described newly diagnosed lymphoma in 2 Infliximab-treated patients [29]. The ACCENT I trial reports newly diagnosed neoplasia in 6 out of 573 patients receiving Infliximab [5]. Colombel *et al.* reported 9 neoplasia among 500 Infliximab-treated patients, although only 3 neoplasia were attributed to the drug [8]. The ACCENT II trial describes 2 rectal carcinoma in 2 CD patients (42 and 36 years old), among 282 patients [7], while Ljung *et al.* reported 3 cancers among 191 Infliximab-treated CD patients [30].

Results from our first multicenter matched-pair study indicate that the prevalence of newly diagnosed neoplasia was comparable in the 808 CD patients treated or untreated with Infliximab, matched for clinical variables (2.22% vs 1.73%; p=n.s.). This finding suggests that Infliximab is not involved in the observed 9 cases of neoplasia. Supporting this concept, the 2.22% prevalence of patients with newly diagnosed neoplasia among the 404 Infliximab-treated patients is comparable to the reported 1.4% prevalence of neoplasia in the general CD population [16]. The overall 1.98% frequency of neoplasia among the 808 patients is also comparable with the reported frequency in the general CD population [16]. The median number of Infliximab infusions was comparable between patients developing or not neoplasia and the median age at diagnosis of neoplasia was also comparable in the Infliximab-treated and untreated patients. These observations further support that in our CD population Infliximab appeared not to influence newly diagnosed neoplasia. Control patients never received Infliximab, as they were matched according to several clinical variables not necessarily reflecting the disease severity nor clinical behaviour. Patients' concerns about possible adverse events, contraindications and responsiveness to conventional drugs also account for not using Infliximab in CD

controls. Moreover, controls included a higher percentage of patients with stricturing CD (p=0.042) and a lower percentage of patients with fistulizing CD (p=0.003) than Infliximab-treated patients. Among patients developing neoplasia, the observed difference in terms of immunosuppressants use between Infliximab-treated patients (7 out of 9) and controls (3 out of 7) was not significant. A longer follow period will further define the risk of developing neoplasia in Infliximab-treated patients. Moreover, no calculation of the sample size was possible, as no data were available regarding both the expected frequency of neoplasia in severe CD patients requiring Infliximab, and the expected differences between Infliximab-treated and untreated patients in terms of newly diagnosed neoplasia. Thus, our study provides the first available data on the magnitude of cancer risk in this subgroup of CD patients and it may therefore provide useful tools for future studies addressing this relevant issue when using biologics in CD. As present findings suggest that no differences are expected between Infliximab-treated and -untreated CD, future studies using a higher number of patients should be planned in order to confirm the absence (rather than the presence) of a significant difference between Infliximab-treated and untreated patients in terms of risk of developing neoplasia. Among patients developing neoplasia, 3 out of the 9 Infliximab-treated patients deceased during the follow up (1 cholangiocarcinoma, 2 anal carcinoma), while no deaths were observed among the 7 controls developing neoplasia. The observation that both cholangiocarcinoma and anal carcinoma are malignancies characterized by a bad prognosis also in the general population [31,32] may account for this finding. A 48 years old man treated with Infliximab died due to cholangiocarcinoma. Although CD has been associated with cholangiocarcinoma [33], this patient had no known history of sclerosing cholangitis and he also received a long-term treatment with metronidazole, suggested as a risk factor for neoplasia [34]. In the Infliximab-treated group, 2 patients with ileocolonic CD died due to anal carcinoma (70 and 41 years old). An increased frequency of anal carcinoma has been reported in colonic CD, also in patients not receiving Infliximab [35,36]. In the Infliximab-treated group, neoplasia also included 1 laryngeal carcinoma in a 53-years old heavy-smoker woman, 3 breast cancers (1 in a 60-years old woman with a familial history of breast cancer), 1 skin cancer (basalioma) and 1 leukemia in a 45 years old woman lost at the follow up. Association between leukemia and CD has been reported also in patients not receiving Infliximab [37]. Association between Infliximab and NHL has also been suggested [16]. In our study, only one case of NHL was detected (in 1 CD control) among the 808 CD patients (0.12%). Although this finding may also be related to a small sample size, it seems worthwhile to note that the frequency of NHL shows wide variations in CD [10,23-25], being also reported as uncommon [38,39]. Moreover, the largest population-based study of IBD patients from Italy showed findings comparable to our study, as NHL was found only in 2 out of 902 IBD patients (0.22%), an in none of the 231 enrolled CD patients [40]. In the CD control group, the 7 newly diagnosed neoplasia included histotypes associated with CD (3 colonic adenocarcinoma, 2 skin cancers, 1 NHL, 1 breast cancer)[23,24,26].

Taken together, results from our first multicenter matched-pair study suggest that Infliximab does not to increase the risk of neoplasia. Both a longer follow up period and a higher number of patients are however required in order to further address this issue. Present findings may also show variations in different CD populations, ethnic groups and geographic areas. Moreover, the risk/benefit balance of concomitant immunosuppressive

and biologic therapies in CD patients with a long history of severe, chronically active disease needs further investigations.

Ethics Approval
The study was approved by the Ethic Committee of the proposing centre (centre 1).

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Competing interest statement
All authors have no competing interests.

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Legend for the Figure

Figure 1
Survival curve for CD patients with newly diagnosed neoplasia comparing the 404 patients treated with Infliximab (continuous black line)(n=404) with their 404 matched-pair controls never treated with Infliximab (dotted grey line)(n=404). The follow up includes CD duration (from the diagnosis of CD to the last visit, expressed in number of days). As shown, no significant differences were observed between the two groups (log rank test p=0.90).

APPENDIX

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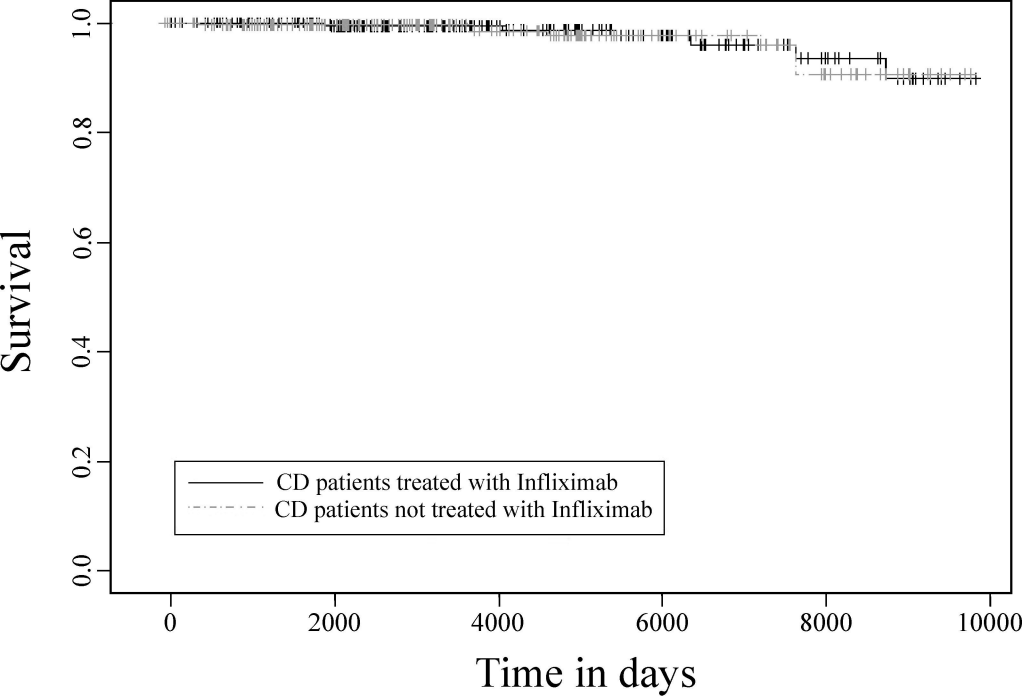
Survival
1.0
0.8
0.6
0.4
0.2
0.0
CD patients treated with Infliximab
CD patients not treated with Infliximab
0
2000
4000
6000
8000
10000
Time in days