INFLAMMATORY BOWEL DISEASE

Infliximab and newly diagnosed neoplasia in Crohn's disease: a multicentre matched pair study

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Background and aims: The widespread use of anti-tumour necrosis factor α antibody (Infliximab) in Crohn's disease (CD) raises concerns about a 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 multicentre matched pair study, 404 CD patients treated with Infliximab (CD-IFX) were matched with 404 CD patients who had never received Infliximab (CD-C). Cases and controls were matched for sex, age (±5 years), site of CD, age at diagnosis (±5 years), immunosuppressant 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 nine patients (2.22%) while among the 404 CD-C, seven patients developed neoplasia (1.73%) (odds ratio 1.33 (95% confidence interval 0.46–3.84); p = 0.40). 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 was one cholangiocarcinoma, three breast cancers, one skin cancer, one leukaemia, one laryngeal cancer, and two anal carcinomas. Among the 7/404 (1.73%) CD-C, there were three intestinal adenocarcinomas (two caecum, one rectum), one basalioma, one spinalioma, one non-Hodgkin's lymphoma, and one breast cancer. Age at diagnosis of neoplasia did not differ between groups (CD-IFX *v* CD-C: median 50 (range 40–70 years) *v* 45 (27–72); p = 0.50).
Conclusion: In our multicentre matched pair study, the frequency of a new diagnosis of neoplasia in CD patients treated with Infliximab was comparable with CD patients who had never received Infliximab.

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 tumour necrosis factor α has shown efficacy in moderate to severe[3] and fistulising CD in several controlled trials.[4] Retreatment every eight 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 evidence indicates that appropriate use of Infliximab is safe and not associated with a significantly higher risk of side effects in the short term compared with placebo.[8] A slightly higher risk of malignancies has been reported in chronic inflammation related to CD, particularly after long term use of immunosuppressants.[9–15] Newly diagnosed neoplasias 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 have investigated the frequency of a newly diagnosed neoplasia in CD patients treated with Infliximab. In order to address this issue, we investigated in a multicentre matched pair study the frequency of newly diagnosed neoplasia during follow up of CD patients treated with Infliximab, in comparison with matched CD patients never treated with Infliximab.

MATERIALS AND METHODS

Study population

This multicentre matched pair study included 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 inflammatory bowel disease (IBD) referral centres (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 the CD patients treated and not treated with Infliximab, including smoking habits,[17] are summarised in tables 1 and 2 for matched and non-matched variables, respectively.

CD patients treated with Infliximab

The Infliximab treated group included 404 active CD patients consecutively treated with Infliximab in the 11 IBD centres from April 1999 to April 2004. Follow up was completed on October 2004 (median time from Infliximab 25 months (range 6–67)). After completion of the study, each of the 404 Infliximab treated patients was matched in each centre with one CD patient who had never received Infliximab, matched according to several clinical variables detailed in the next paragraph. The indication for Infliximab was moderate

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; AZA, azathioprine; 6-MP, 6-mercaptopurine; NHL, non-Hodgkin's lymphoma; OR, odds ratio; RR, relative risk

Table 1 Characteristics of Crohn's disease patients treated with Infliximab and their Crohn's disease controls who never received Infliximab, including only matched variables

Characteristic	Infliximab treated patients (n = 404) (n (%))	Control patients (n = 404) (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%)
Other	7 (2%)	2 (1%)
Immunosuppressants	213 (53%)	218 (53%)
AZA/6-MP	203 (95%)	211 (97%)
Methotrexate	10 (5%)	7 (3%)
Duration of ISS (months)*	36 (3–160)	24 (2–120)
Patient's age (y)*	41 (13–82)	40 (14–82)
Crohn's disease duration (y)*	10 (1–62)	9 (1–34)
Follow up in each centre (months)	48 (6–396)	60 (6–384)

*Median (range).
AZA, azathioprine; 6-MP, 6-mercaptopurine; ISS, immunosuppressants.

to severe CD (CD activity index 220–400)[18]: fistulising (n = 238; 59%) or refractory/steroid dependent luminal disease (n = 166; 41%).[19] Infliximab was administered intravenously (5 mg/kg), including single or three infusions for luminal and three infusions (0, 2, and 6 weeks) for fistulising CD. 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 the time of Infliximab were immunosuppressants (n = 165; 41%), steroids (n = 117; 29%), antibiotics (ciprofloxacin or metronidazole) (n = 105; 26%), and mesalazine (n = 68; 17%).

Table 2 Characteristics of Crohn's disease patients treated with Infliximab and their Crohn's disease controls who never received Infliximab, not including matched variables

Characteristic	Infliximab treated patients (n (%))	Control patients (n (%))
Crohn's disease type		
Inflammatory	146 (36%)	177 (44%)
Fistulising	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 (y)†	28 (7–80)	29 (9–81)

†Median (range).
IBD, inflammatory bowel disease.
*p = 0.042, stricturing CD in controls who had never received Infliximab versus Infliximab treated patients.
**p = 0.003, fistulising CD in Infliximab treated patients versus controls who had never received Infliximab.

Matched pair CD controls who never received infliximab

Each of the 404 patients treated with Infliximab were matched with one CD control referred to the same centre in the same study period (April 1999–October 2004) but who had never been 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 completion of the study in order to ensure that the referent population had not been exposed to Infliximab. For this purpose, at the end of the study, each CD patient treated with Infliximab was matched with one CD control who had never been treated with Infliximab, followed up in the same study period in the same centre, according to the following criteria: age ($\pm$5 years), sex, follow up period in the same centre ($\pm$5 years), immunosuppressant use (yes/no; type; duration), CD site (ileum, ileum-colon, colon, other), and CD duration ($\pm$5 years). Less than 5% of CD controls showed one of the matched variables outside the range. No CD controls had received Infliximab at any time although several clinical features were matched with CD patients receiving Infliximab. Controls were matched according to clinical variables not necessarily reflecting inherent disease aggressiveness or clinical behaviour. However, there were also a number of reasons for not using Infliximab in CD controls, including patient opinion (that is, patients refusing treatment because seriously concerned about side effects) and contraindications (abscesses, possible pregnancy, infectious diseases including TBC, concomitant disease states). Furthermore, controls included a higher percentage of patients with stricturing CD (13% *v* 5%; p = 0.042) and a lower percentage of patients with fistulising CD (43% *v* 59%; p = 0.003) than Infliximab treated CD (table 2).

Diagnosis of neoplasia

No patient had a known history of neoplasia at entrance. New diagnoses of neoplasia were made using conventional procedures in relation to specific symptoms or signs referred to 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 neoplasias were diagnosed. However, all CD patients referred to the 11 centres are enrolled in a programme 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 neoplasias were recorded during follow up together with: age at diagnosis of neoplasia, type of neoplasia, outcome (remission, death), and immunosuppressant 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, and immunosuppressant use. Differences between Infliximab treated and untreated CD patients were assessed by the χ^2 test, the Student's *t* test, or the McNemar test to compare qualitative and quantitative variables among groups. Odds ratios (OR) (95% confidence intervals (CI)) were calculated. 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

Table 3 Clinical characteristics of each of the nine Crohn's disease (CD) patients treated with Infliximab who developed neoplasia during follow up

Pt No	Sex	CD site	CD type	CD duration (y)	Type of neoplasia	Age at neoplasia diagnosis (outcome)	ISS (months)	No of infusions (schedule)	Time since IFX (months)	Time since ISS (months)
1	M	I-C	F	23	Cholangiocarcinoma	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	ND	2 on demand	6	ND
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	ND	4 on demand	15	ND
6	F	I-C	F	6	Breast cancer	40 Remission	AZA (52)	6 maintenance	33	52
7	F	C	L	13	Leukaemia	45 Lost to follow 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

ISS, immunosuppressants; IFX, Infliximab; F, female; M, male; I, ileum; C, colon; I-C, ileum-colon; C, colon; L, luminal; F, fistulising; AZA, azathioprine; Thalid, thalidomide; MTX, methotrexate; ND, not done.

newly diagnosed neoplasia in CD patients treated with Infliximab versus matched pair CD controls.

Sample size calculation implies knowledge of both the expected number of cases (that is, CD patients developing neoplasia) and the expected difference (that is, frequency of neoplasia in Infliximab treated *v* 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 study has 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 the groups were not available for sample size calculation. In order to define these two 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 who never received Infliximab, prospectively followed up in the same period.

RESULTS

The number of patients with fistulising disease was higher in CD patients treated with Infliximab than in CD controls who never received 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). Other clinical variables were comparable between the two groups (tables 1, 2). When considering the whole group of 808 patients, including both Infliximab treated and untreated CD patients, 16 (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, nine (2.22%) had a diagnosis of neoplasia from April 1999 to October 2004. Table 3 shows the clinical features of patients who developed neoplasia. As indicated, among the 404 CD patients treated with Infliximab, the following neoplasia were diagnosed: one cholangiocarcinoma (centre 2), two anal carcinomas (centre 6; centre 8), one basalioma (centre 9), three adenocarcinomas of the breast (centre 1: $n = 2$; centre 9: $n = 1$), one laryngeal carcinoma (centre 1), and one leukaemia (centre 8). Median age of patients with neoplasia was 50 years (range 40–70), and median CD duration was 23 years (range 5–39). The outcome of neoplasia at the end of follow up was remission in five and death in three, while one patient with leukaemia was lost to follow up. 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). Median time interval between the first infusion and diagnosis of neoplasia was 18 months (range 6–45). Among nine patients with neoplasia, seven (77.7%) received immunosuppressants (azathioprine (AZA) five, thalidomide one, methotrexate one). In these seven patients, 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).

Matched pair CD controls who never received Infliximab

Among the group of 404 CD controls who never received Infliximab and were followed from April 1999, seven patients (1.73%) had a new diagnosis of neoplasia before October 2004. Table 4 indicates the clinical features of patients developing neoplasia. As shown, in CD controls the following neoplasia were diagnosed: two skin cancers (one spinalioma, one basalioma; centre 1, centre 2), one breast cancer (centre 1), one non-Hodgkin's lymphoma (NHL; centre 1), two adenocarcinoma of the caecum (centre 1, centre 7), and one adenocarcinoma of the rectum (centre 8). Median age of patients developing neoplasia was 45 years (range 27–72), and median CD duration was 12 years (range 1–27). The outcome of neoplasia at the end of follow up was remission in all seven CD controls. Among the seven patients with neoplasia, three (42.8%) received immunosuppressants

Table 4 Characteristics of each of the seven Crohn's disease control patients who never received Infliximab, who developed neoplasia during follow up

Pt No	Sex	CD site	CD type	CD duration (y)	Type of neoplasia	Age at diagnosis of neoplasia (outcome)	ISS (months)	Time since ISS
1	M	I-C	L	27	Adenocarcinoma caecum	61 Remission	ND	ND
2	F	C	L	1	Adenocarcinoma caecum	27 Remission	ND	ND
3	F	I-C	F	7	Adenocarcinoma rectum	45 Remission	ND	ND
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	ND	ND
7	F	I-C	F	12	Non-Hodgkin's lymphoma	36 Remission	AZA (48)	120

ISS, immunosuppressants; F, female; M, male; I, ileum; C, colon; I-C, ileum-colon; L, luminal; F, fistulising; AZA, azathioprine; ND, not done.

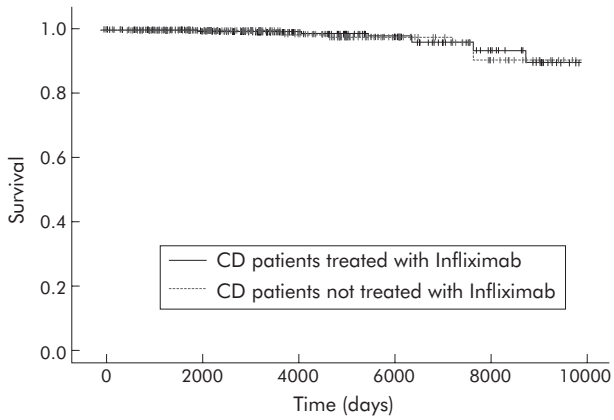

Figure 1 Survival curve for Crohn's disease (CD) patients with newly diagnosed neoplasia comparing the 404 patients treated with Infliximab (n = 404) with their 404 matched pair controls who were never treated with Infliximab (n = 404). Follow up includes CD duration (from diagnosis of CD to the last visit, expressed in number of days). As shown, no significant differences were observed between the two groups (log rank test, p = 0.90).

(three AZA) for a median of 46 months (range 24–48), with a median interval between the beginning of treatment and diagnosis of neoplasia of 46 months (range 24–120).

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 differ significantly between CD patients treated with Infliximab and their matched pair CD controls (2.22% *v* 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 diagnosis of CD to the last visit), comparing Infliximab treated and untreated patients. As shown, no differences were observed between the two groups (log rank test, p = 0.90). Further indicating that Infliximab did not significantly affect the risk of neoplasia in our CD population, the RR of neoplasia adjusted for patient age was 1.35. Median age at diagnosis of neoplasia did not differ between CD patients treated with Infliximab and their matched pair CD controls (median 50 years (range 40–70) *v* 45 years (27–72); p = 0.50). Median CD duration at the time of diagnosis of neoplasia also did not differ between Infliximab treated and untreated CD patients (median 23 years (range 5–39) *v* 12 years (1–27); p = 0.18). The outcome of neoplasia among the nine Infliximab treated patients included three deaths, five remissions, and one patient lost to follow up while all seven controls who developed neoplasias were in remission at the end of follow up. Immunosuppressant use was observed in seven of nine (77.7%) patients treated with Infliximab versus three of seven (42.8%) matched pair controls (p = 0.36). Time since beginning of immunosuppressants and diagnosis of neoplasia did not differ between the two groups (Infliximab treated CD: median 40 months (range 5–144); CD controls: 46 months (24–120); p = 0.84). Duration of immunosuppressant use was also comparable between the two groups (Infliximab treated CD: median 36 months (range 4–52); CD controls: 46 months (range 24–48); p = 0.44).

DISCUSSION

CD is a chronic inflammatory condition of unknown aetiology. 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 long term use of immunosuppressants have been suggested as risk factors for neoplasia in CD.[9–16] However, the real lifetime risk of cancer in CD shows variations in different study populations, ethnic groups, and geographic areas.[9–15] No study has provided neoplasia rates adjusted for age, CD activity, or immunosuppressant duration. Although population based studies in CD suggest no increased risk of NHL,[23–25] results are conflicting.[10] 6-Mercaptopurine and AZA have been associated with NHL.[13–15] Jess *et al* reported in a cohort of 373 Danish CD patients that the lifetime risk of cancer was not increased (4.1% *v* 3.8%), although the risk of rare small bowel cancer was increased (2 *v* 0.04 expected; p = 0.001).[26] In CD, benefits appear to overwhelm risks when using immunosuppressants in the long term.[27] Newly diagnosed neoplasias have occasionally been reported in trials using Infliximab in CD[16 28] although no controlled studies have addressed the possible role of Infliximab. Rutgeerts *et al* reported a duodenal B cell lymphoma in a 61 year old patient receiving one infusion (10 mg/kg), dying from sepsis after chemotherapy.[6] A case report described newly diagnosed lymphoma in two Infliximab treated patients.[29] The ACCENT I trial reported newly diagnosed neoplasias in six of 573 patients receiving Infliximab.[5] Colombel *et al* reported nine neoplasias among 500 Infliximab treated patients although only three neoplasias were attributed to the drug.[8] The ACCENT II trial describes two rectal carcinomas in two CD patients (42 and 36 years old), among 282 patients,[7] while Ljung and colleagues reported three cancers among 191 Infliximab treated CD patients.[30]

Results from our multicentre matched pair study indicated that the prevalence of newly diagnosed neoplasia was comparable in the 808 CD patients treated or not treated with Infliximab, matched for clinical variables (2.22% *v* 1.73%; NS). This finding suggests that Infliximab is not involved in the observed nine cases of neoplasia. Supporting this concept, the 2.22% prevalence of patients with newly diagnosed neoplasia among the 404 Infliximab treated patients is comparable with 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] Median number of Infliximab infusions was comparable between patients who developed or did not develop neoplasia and median age at diagnosis of neoplasia was also comparable in the Infliximab treated and untreated patients. These observations further support the fact 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 disease severity or clinical behaviour. Patient concerns about possible adverse events, contraindications, and responsiveness to conventional drugs also accounted 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 fistulising CD (p = 0.003) than Infliximab treated patients. Among patients who developed neoplasias, the observed difference in terms of immunosuppressant use between Infliximab treated patients (7/9) and controls (3/7) was not significant. A longer follow period will further define the risk of developing neoplasia in Infliximab treated patients.

Moreover, no calculation of 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 the cancer risk in this subgroup of CD patients and it may therefore provide a useful tool for future studies addressing this relevant issue when using biologics in CD. As our findings suggest that there are no differences between Infliximab treated and untreated CD, future studies using a larger 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, three of nine Infliximab treated patients died during follow up (one cholangiocarcinoma, two anal carcinoma) while no deaths were observed among the seven controls who developed neoplasia. The observation that both cholangiocarcinoma and anal carcinoma are malignancies characterised by a poor prognosis in the general population also[31 32] may account for this finding.

A 48 year 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 long term treatment with metronidazole, suggested as a risk factor for neoplasia.[34] In the Infliximab treated group, two patients with ileocolonic CD died due to anal carcinoma (70 and 41 years old). An increased frequency of anal carcinoma has also been reported in colonic CD in patients not receiving Infliximab.[35 36] In the Infliximab treated group, neoplasia also included one laryngeal carcinoma in a 53 year old heavy smoking woman, three breast cancers (one in a 60 year old woman with a familial history of breast cancer), one skin cancer (basalioma), and one leukaemia in a 45 year old woman lost to follow up. Association between leukaemia and CD has also been reported 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 one CD control) among 808 CD patients (0.12%). Although this finding may be related to the small sample size, it should be noted that the frequency of NHL shows wide variations in CD,[10 23–25] and has also been reported as uncommon.[38 39] Moreover, the largest population based study of IBD patients from Italy showed findings comparable with our study, as NHL was found in only two of 902 IBD patients (0.22%), an in none of 231 enrolled CD patients.[40] In the CD control group, the seven newly diagnosed neoplasias included histotypes associated with CD (three colonic adenocarcinoma, two skin cancers, one NHL, one breast cancer).[23 24 26]

Taken together, results from our first multicentre matched pair study suggest that Infliximab does not increase the risk of neoplasia. Both a longer follow up period and a larger number of patients are however required in order to further address this issue. These findings may vary in different CD populations, ethnic groups, and geographic areas. Moreover, the risk/benefit balance of concomitant immunosuppressive and biological therapies in CD patients with a long history of severe chronically active disease needs further investigation.

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REFERENCES

1 **Egan LJ**, Sandborn WJ. Advances in the treatment of Crohn's disease. *Gastroenterology* 2004;**126**:1574–81.
2 **Sandborn WJ**, Targan SR. Biologic therapy for inflammatory bowel disease. *Gastroenterology*. 2002;122: 1592–608 (Erratum appears in Gastroenterology, 2002;**123**:656).
3 **Present DH**, Rutgeerts P, Targan S, *et al*. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl Med* 1999;**340**:1398–405.
4 **Targan SR**, Hanauer SB, van Deventer SJH, *et al*. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor α for Crohn's Disease. *N Engl J Med* 1997;**337**:1029–35.
5 **Hanauer SB**, Feagan BG, Lichtenstein GR, *et al*. Maintenance Infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;**359**:1541–9.
6 **Rutgeerts P**, D'Haens G, Targan S, *et al*. Efficacy and safety of retreatment with Infliximab anti-tumor necrosis factor antibody (Infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999;**117**:761–8.
7 **Sands BE**, Anderson FH, Bernstein CN, *et al*. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004;**350**:876–85.
8 **Colombel JF**, Loftus EV Jr, Tremaine WJ, *et al*. The safety profile of Infliximab in patients with Crohn's disease: the Mayo clinical experience in 500 patients. *Gastroenterology* 2004;**126**:19–31.
9 **Ekbom A**, Helmick C, Zack M, *et al*. Increased risk of large-bowel cancer in Crohn's disease with colonic involvement. *Lancet* 1990;**336**:357–9.
10 **Bernstein CN**, Blamchard JP, Kliewer R, *et al*. Cancer risk in patients with inflammatory bowel disease: a population-based study. *Cancer* 2001;**91**:854–62.
11 **Kandiel A**, Fraser AG, Korelitz BI, *et al*. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005;**54**:1121–5.
12 **Jess T**, Winther KV, Munkholm P, *et al*. Mortality and causes of death in Crohn's disease: follow-up of a population-based cohort in Copenaghen County, Denmark. *Gastroenterology* 2002;**122**:1808–14.
13 **Bouhnik Y**, Lemann M, Mary JY, *et al*. Long-term follow-up of patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. *Lancet* 1996;**347**:215–9.
14 **Dayharsh GA**, Loftus EV Jr, Sandborn WJ, *et al*. Epstein-Barr virus-positive lymphoma in patients with inflammatory bowel disease treated with azathioprine or 6-mercaptopurine. *Gastroenterology* 2002;**122**:72–7.
15 **Farrell RJ**, Ang Y, Kileen P, *et al*. Increased incidence of non-Hodgkin's lymphoma in inflammatory bowel disease patients on immunosuppressive therapy, but overall risk is low. *Gut* 2000;**47**:514–19.
16 **Sandborn WJ**, Loftus EV. Balancing the risks and benefits of infliximab in the treatment of inflammatory bowel disease. *Gut* 2004;**53**:780–2.
17 **Cottone M**, Rosselli M, Orlando A, *et al*. Smoking habitus and recurrence in Crohn's disease. *Gastroenterology* 1994;**106**:643–8.
18 **Best WR**, Becktel JM, Singleton JW. Rederived values of the eight coefficients of the Crohn's disease activity index (CDAI). *Gastroenterology* 1979;**77**:843–6.

19 **Gasche C**, Scholmerich J, Brynskov J, *et al*. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology. Vienna 1998. *Inflamm Bowel Dis* 2000;**6**:8–15.
20 **Fiocchi C**. Inflammatory bowel disease: etiology and pathogenesis. *Gastroenterology* 1998;**115**:182–205.
21 **Monteleone G**, Monteleone I, Fina D, *et al*. Interleukin-21 enhances T-helper cell type I signalling and interferon-γ production in Crohn's disease. *Gastreonterology* 2005;**128**:687–94.
22 **Monteleone G**, Biancone L, Marasco R, *et al*. Interleukin 12 is expressed and actively released by Crohn's disease intestinal lamina propria mononuclear cells. *Gastroenterology* 1997;**112**:1169–78.
23 **Persson PG**, Karlen P, Bernell O, *et al*. Crohn's disease and cancer: a population-based cohort study. *Gastroenterology* 1994;**107**:1675–9.
24 **Ekbom A**, Helmick C, Zack M, *et al*. Extracolonic malignancies in inflammatory bowel disease. *Cancer* 1991;**67**:2015–19.
25 **Lewis JD**, Bilker WB, Brensinger C, *et al*. Inflammatory bowel disease is not associated with an increased risk of lymphoma. *Gastroenterology* 2001;**121**:1080–7.
26 **Jess T**, Winther KV, Munkholm P, *et al*. Intestinal and extra-intestinal cancer in Crohn's Disease: follow-up of a population-based cohort in Copenaghen County, Denmark. *Aliment Pharmacol Ther* 2004;**19**:287–93.
27 **Lemann M**, Mary JY, Colombel JF, *et al*. A randomised double-blind controlled withdrawal in Crohn's disease patients in long term remission on azathioprine. *Gastroenterology* 2005;**128**:1812–18.
28 **Fiocchi C**. Closing fistulas in Crohn's Disease—should the accent be on maintenance or safety? *N Engl J Med* 2004;**350**:934–6.
29 **Bickston SJ**, Lichtenstein GR, Arseneau KO, *et al*. The relationship between Infliximab treatment and lymphoma in Crohn's disease. *Gastroenterology* 1999;**117**:1433–7.
30 **Ljung T**, Karlen P, Schmidt D, *et al*. Infliximab in inflammatory bowel disease: clinical outcome in a population based cohort from Stockholm County. *Gut* 2004;**53**:849–53.
31 **Sirica AE**. Cholangiocarcinoma: molecular targeting strategies for chemoprevention and therapy. *Hepatology* 2005;**41**:5–15.
32 **Gervasoni JE Jr**, Wanebo HJ. Cancers of the anal canal and anal margin. *Cancer Invest* 2003;**21**:452–64.
33 **Altaee MY**, Johnson PJ, Farrant JM, *et al*. Etiologic and clinical characteristics of peripheral and hilar cholangiocarcinoma. *Cancer* 1991;**68**:2051–5.
34 **Krause JR**, Ayuyang HQ, Ellis LD. Occurrence of three cases of carcinoma in individuals with Crohn's disease treated with metronidazole. *Am J Gastroenterol* 1985;**80**:978–82.
35 **Somerville KW**, Langman MJ, Da Cruz DJ, *et al*. Malignant transformation of anal skin tags in Crohn's disease. *Gut* 1984;**25**:1124–5.
36 **Sjodhal RI**, Myrelid P, Soderholm JD. Anal and rectal cancer in Crohn's disease. *Colorectal Dis* 2003;**5**:490–5.
37 **Askling J**, Brandt L, Lapidus A, *et al*. Risk of haematopoietic cancer in patients with inflammatory bowel disease. *Gut* 2005;**54**:617–22.
38 **Bickston SJ**, Lichtenstein GR, Arseneau KO, *et al*. The relationship between infliximab treatment and lymphoma in Crohn's disease. *Gastroenterology* 1999;**117**:1433–7.
39 **Loftus EV Jr**, Tremaine WJ, Habermann TM, *et al*. Risk of lymphoma in inflammatory bowel disease. *Am J Gastroenterol* 2000;**95**:2308–12.
40 **Palli D**, Trallori G, Bagnoli S, *et al*. Hodgkin's disease risk is increased in patients with ulcerative colitis. *Gastroenterology* 2000;**119**:647–53.

EDITOR'S QUIZ: GI SNAPSHOT

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Answer

From question on page 196

This patient suffered from yellow nail syndrome with intestinal lymphangiectasia, which is a very rare condition. Treatment of these patients is mainly symptomatic but localised lymphangiectasia in the small intestine would potentially be curable with surgical resection. Therefore, the extent of lymphangiectasia was determined by use of capsule endoscopy, a novel and efficient method to visualise the small intestine.

Capsule endoscopy showed swollen mucosa with thick and short villi covered with opalescent "milky" fluid throughout the small intestine (fig 2). Importantly, capsule endoscopy revealed that the lymphangiectasia was generalised throughout the small intestine, which excluded this patient from surgery. Biopsies taken from the proximal small intestine showed short and widened villi and lymphangiectasia (fig 3). Thus capsule endoscopy may be decisive in the management of patients with yellow nail syndrome and protein loosing enteropathy.

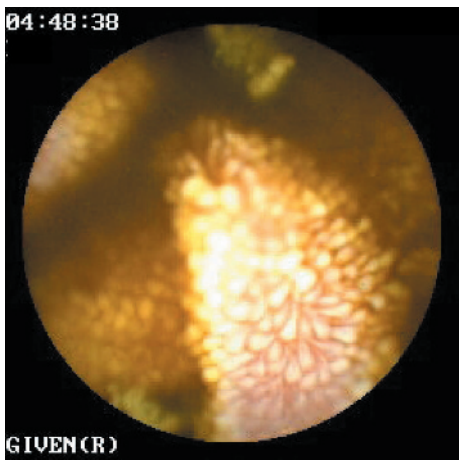

Figure 2 Capsule endoscopic image showing swollen mucosa with thick, short, and whitish villi and intraluminal opalescent "milky" fluid in the jejunum.

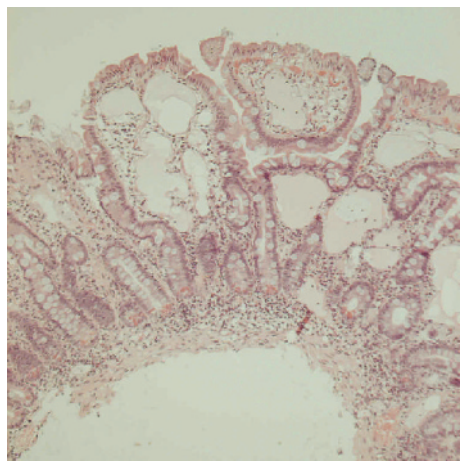

Figure 3 Microphotograph of duodenal biopsy showing dilated lymphatics in the lamina propria consistent with intestinal lymphangiectasia.