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Long-term safety study of infliximab in moderate-to-severe chronic obstructive pulmonary disease

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KEYWORDS
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Mortality risk

Summary
Rationale: There was an increased number of malignancies in infliximab-treated (5.7%) over placebo-treated (1.3%) patients in a 44-week, phase 2 clinical study of 234 patients with moderate-to-severe chronic obstructive pulmonary disease (COPD).
Objectives: To collect malignancy and mortality data from completed clinical studies of infliximab in COPD treatment.
Methods: The multicenter, observational Remicade Safety Under Long-Term Study in COPD (RESULTS COPD) collected malignancy and mortality data every six months for five years from patients who received ≥1 study-agent dose in a phase 2 study. Co-primary endpoints were the number of patients with malignancy and the number of deaths. Secondary endpoints included the number of patients with a malignancy according to malignancy type.
Results: There was a gap period between the end of the phase 2 study and the initiation of RESULTS COPD, during which six malignancies and 14 deaths were reported spontaneously for the 107 (45.7%) of 234 patients with long-term safety information. Twenty-eight patients (overall 12.0%; placebo 10.4%, infliximab 12.7%) reported malignancies, including 12 patients during RESULTS COPD. Twenty-six patients (overall 11.1%; placebo 9.1%, infliximab 12.1%) died, including nine during RESULTS COPD. Lung cancer was the most common malignancy type (placebo $n = 2$; infliximab $n = 10$).
Conclusions: The greater proportion of malignancies observed with infliximab versus placebo in a phase 2 study diminished over the long-term follow-up. Due to the observational nature,

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limited patient participation, potential reporting bias from the interim spontaneous reporting period, and unblinding of all patients, more definitive conclusions cannot be drawn.
Trial Registration Number: NCT00056264.

Introduction

Chronic obstructive pulmonary disease (COPD) is a generally progressive, not fully reversible disease that limits expiratory airflow. It results from inflammation and tissue damage and leads to tissue alterations including emphysema and/or bronchitis and fibrosis.[1,2] Symptoms of COPD include cough, sputum production, and dyspnea, which can be exacerbated with physical exertion. In addition, extrapulmonary manifestations are common.[3,4] Smoking is a causative factor of COPD[5] and increases the risk for several types of cancer.[6] The leading causes of death among patients with smoking-related COPD are lung cancer,[7–9] followed by pulmonary-related and cardiovascular causes.[10] Additional research suggests that the disease pathology in COPD and lung cancer is due to similar underlying cellular and molecular mechanisms.[11,12] In support of this, patients with COPD have an increased risk for the development of pulmonary malignancies independent of smoking status.[13–20]

Preclinical studies have suggested that tumor necrosis factor alpha (TNFα) may play a pathogenic role in COPD.[21–23] Infliximab (Janssen Biotech, Inc., Horsham, PA, United States [USA]) is a human-murine chimeric monoclonal antibody that neutralizes TNFα. In a phase 2, multicenter, double-blind, placebo-controlled study conducted in the US, 234 patients with moderate-to-severe COPD were randomized to receive intravenous infusions of either placebo, infliximab 3 mg/kg, or infliximab 5 mg/kg at weeks 0, 2, 6, 12, 18, and 24. Patients treated with infliximab showed no evidence of treatment benefit, as measured by the analysis of the primary endpoint (change from baseline from week 24 in the Chronic Respiratory Questionnaire [CRQ] total score), when compared with those who received placebo.[24] While infliximab was generally well tolerated through week 44, malignancies were reported at a higher frequency in the combined infliximab group ($n = 9$; 5.7%) than in the placebo group ($n = 1$; 1.3%). In the two published investigator-initiated studies, no malignancies were reported.[25,26] Because the actual malignancy risk is difficult to assess in clinical trials, the long-term, observational Remicade Safety Under Long-Term Study in COPD (RESULTS COPD) was conducted to collect additional information on malignancy and death risk in patients who participated in clinical studies of infliximab for the treatment of COPD.

Methods

Patients

All consenting patients who received at least one dose of study-agent in any of the three aforementioned interventional clinical studies of infliximab in COPD were eligible to participate in RESULTS COPD. It should be noted that of the 43 sites that participated in these three clinical studies, 19 sites (17 in the US and two in The Netherlands which conducted the investigator-initiated studies) opted not to participate in the RESULTS COPD study. All participating patients provided written informed consent before the collection of any long-term safety follow-up information. This study was conducted in accordance with the principles of the Declaration of Helsinki and all other applicable national and local laws and regulations.

Study design

This was a multicenter, long-term, observational study of the safety of infliximab treatment in patients with moderate-to-severe COPD. All consenting patients were to begin participation in RESULTS COPD for a total duration of five years of safety follow-up as soon as possible after their last safety visit in the interventional infliximab study. Because the majority of patients with COPD are smokers[5] and to investigate the increased risk in this patient population for the development of lung and/or laryngeal cancer, RESULTS COPD opted to include high resolution computed tomography (CT) chest scans (spiral preferred) at study entry and the final visit. Additionally, chest X-ray (posterior and lateral), medical history review, and physical examination (including ear, nose, and throat) were performed at study entry and the final visit. Data were collected from all patients (or next of kin) at death (date and cause) and/or malignancy (date of diagnosis and malignancy type) at six-month intervals through direct contact, medical record review, or contact with the patients' primary care physician or oncologist. Any death and/or malignancy events that occurred between the end of an interventional infliximab study and the commencement of RESULTS COPD were collected via spontaneous reporting. Information on other adverse events was not collected.

The co-primary endpoints of RESULTS COPD were the number of patients with a malignancy and the number of patients who died throughout the course of the follow-up. Secondary endpoints were the number of patients with malignancy identified by malignancy type (ie, lymphoma, head and neck cancers, lung cancer, and other), the time to death, and the time to the onset of malignancy.

Statistical analyses

The two analyzed populations in this study were all treated patients from the interventional infliximab study (NCT00056264) and all treated patients with long-term safety follow-up information (ie, patients with data spontaneously reported to the sponsor during the gap period in addition to patients who had consented to participate in RESULTS COPD). Patients were analyzed according to the treatment received during the interventional study (ie, placebo, infliximab 3 mg/kg, and infliximab 5 mg/kg). Data

from the following three periods were pooled for analysis: primary study (NCT00056264) through week 44, gap period, and RESULTS COPD through the final visit. Statistical comparisons were made between the placebo and each infliximab treatment group as well as between the placebo and combined infliximab treatment group. No formal hypothesis testing was planned; however, comparative statistics such as hazard ratios and confidence intervals (CIs) were computed. Primary endpoint analysis was conducted on all treated patients in the primary study. Hazard ratios for malignancies and deaths based on the Cox proportional hazards model (using treatment as the only covariate) and 95% confidence intervals were computed. Kaplan—Meier estimates of the cumulative incidence of deaths and malignancies were calculated.

Results

Patient data availability

Both sites of the two investigator-initiated studies declined to participate in RESULTS COPD. Of the 41 US sites that participated in the phase 2 clinical study of infliximab, 24 sites opted to participate in RESULTS COPD. Long-term safety follow-up data were available for 107 (45.7%) of 234 patients who had participated in the phase 2 interventional study (Table 1). There was a gap period between the end of the phase 2 interventional study (December 2004) and the commencement of RESULTS COPD (April 2006). Ninety-three (86.9%) of these 107 patients were alive at the start of RESULTS COPD, and 14 (13.1%) had died during the gap period. Of the remaining 127 patients who did not participate in RESULTS COPD, 9 were lost to follow-up, 33 did not consent (or withdrew consent), and 85 were treated at study sites that declined to participate.

Baseline demographics and disease characteristics

The number of patients per group was well balanced in the 107 patients who consented to participate in RESULTS COPD (placebo $n = 35$, infliximab 3 mg/kg $n = 35$, infliximab 5 mg/kg $n = 37$; Table 2). There were more males (57.0%) than females (43.0%). The majority (96.3%) of patients were white. The median age at baseline was similar across treatment groups (65—67 years). Patient baseline demographics were generally comparable between RESULTS COPD and the phase 2 interventional study. Almost half (48.6%) of the patients in RESULTS COPD had both chronic emphysema and chronic bronchitis at baseline of the primary study, whereas many patients (40.6%) in the phase 2 interventional study only had chronic emphysema at baseline. Current smokers at study entry were a smaller percentage of patients in RESULTS COPD than in the phase 2 interventional study.

Medication use

During the interventional study, the average duration of study-agent exposure in the combined infliximab treatment group was 18.6 weeks, and the median cumulative dose of infliximab received was 18.0 mg/kg in the infliximab 3 mg/kg group and 30.0 mg/kg in the infliximab 5 mg/kg group. One patient who was in the infliximab 5 mg/kg group reported a malignancy (pulmonary carcinoma) during the gap period and had received infliximab within six months of malignancy onset; this patient also died during the gap period. Only one patient, who was in the placebo group during the interventional study, was receiving commercial infliximab at RESULTS COPD study entry for another indication, although two other patients (one from the placebo group and one from the infliximab 3 mg/kg group of the interventional study) received commercial infliximab for other indications through the end of RESULTS COPD. None of these three patients had a malignancy or died during RESULTS COPD. No patients were receiving any commercial anti-TNFα therapy other than infliximab during RESULTS COPD.

Disposition

Of the 93 patients alive at RESULTS COPD study entry, 66 (71.0%) completed the study (Table 3). The remaining 27 (29.0%) patients were either lost to follow-up (15.1%), withdrew consent (5.4%), or died during the follow-up (8.6%).

Table 1 Patient status at study entry into RESULTS[a] COPD; treated patients in the primary study.

	Placebo	Infliximab			Total
		3 mg/kg	5 mg/kg	Combined	
Patients treated in phase 2 study	77	77	80	157	234
Treated patients with long-term safety follow-up information	35 (45.5)	35 (45.5)	37 (46.3)	72 (45.9)	107 (45.7)
Status at RESULTS[a] COPD study entry					
Alive	33 (42.9)	31 (40.3)	29 (36.3)	60 (38.2)	93 (39.7)
Lost to follow-up	5 (6.5)	3 (3.9)	1 (1.3)	4 (2.5)	9 (3.8)
Withdrew consent	12 (15.6)	9 (11.7)	12 (15.0)	21 (13.4)	33 (14.1)
Died	2 (2.6)	4 (5.2)	8 (10.0)	12 (7.6)	14 (6.0)
Patients not participating in RESULTS[a] COPD	25 (32.5)	30 (39.0)	30 (37.5)	60 (38.2)	85 (36.3)

Data presented as *n* *n* (%).
[a] Remicade Safety Under Long-Term Study in chronic obstructive pulmonary disease (COPD).

Table 2 Baseline demographics and disease characteristics.

	Phase 2 interventional study			RESULTS[a] COPD		
	Placebo	Infliximab		Placebo	Infliximab	
		3 mg/kg	5 mg/kg		3 mg/kg	5 mg/kg
Patients randomized in phase 2 interventional study	77	78	79	—	—	—
Patients treated in phase 2 interventional study	77	77	80	—	—	—
Patients in RESULTS[a] COPD with long-term safety follow-up information who were treated in phase 2 interventional study	—	—	—	35	35	37
Male	46 (59.7)	48 (61.5)	44 (55.7)	18 (51.4)	23 (65.7)	20 (54.1)
White	71 (92.2)	77 (98.7)	75 (94.9)	32 (91.4)	35 (100.0)	36 (97.3)
Black	5 (6.5)	1 (1.3)	4 (5.10)	3 (8.6)	0	1 (2.7)
Other	1 (1.3)	0	0	0	0	0
Ages (years)	66.0	65.0	66.0	67.0	68.0	65.0
Weight (kg)	80.9	76.9	74.0	77.3	76.4	77.2
COPD[b] type						
Chronic bronchitis	25 (32.5)	14 (17.9)	15 (19.0)	9 (25.7)	1 (2.9)	7 (18.9)
Emphysema	30 (39.0)	32 (41.0)	33 (41.8)	13 (37.1)	12 (34.3)	13 (35.1)
Both	22 (28.6)	32 (41.0)	31 (39.2)	13 (37.1)	22 (62.9)	17 (45.9)
Smoking status at study entry						
Current smoker	33 (42.9)	35 (45.5)	35 (43.8)	11 (33.3)	6 (19.4)	7 (24.1)
Former smoker	44 (57.1)	42 (54.5)	45 (56.3)	—	—	—
Median total pack- years	55	50	53	—	—	—
Median number cigarettes smoked daily	—	—	—	20.0	12.5	25.0

Data presented as *n*, *n* (%), or median. 1 pack-year = 20 cigarettes smoked every day for 1 year or the equivalent.
[a] Remicade Safety Under Long-Term Study in chronic obstructive pulmonary disease (COPD).
[b] Chronic obstructive pulmonary disease.

Malignancy

Of the 234 patients treated in the phase 2 interventional infliximab study, there were 28 (12.0%) reports of malignancy. Of these patients, 10 reported a malignancy during the interventional study, 6 during the gap period, and 12 during RESULTS COPD. Although a greater percentage of patients reported a malignancy with infliximab than placebo during the phase 2 interventional study (5.7% vs. 1.3%), this imbalance appeared to diminish over time, including the gap period (1.9% vs. 3.9%) and RESULTS COPD (5.1% vs. 5.2%), respectively. The cumulative incidence of reported malignancies was similar between the placebo ($n = 8$ [10.4%]) and the infliximab 5 mg/kg ($n = 8$ [10.0%]) groups and was highest in the infliximab 3 mg/kg group ($n = 12$ [15.6%]).

The incidence of all malignancies per 100 patient-years of follow-up was 3.89 (95% CI: 1.68, 7.66) in the placebo group compared with 5.91 (95% CI: 3.05, 10.32) in the infliximab 3 mg/kg group and 4.18 (95% CI: 1.80, 8.23) in the infliximab 5 mg/kg group. Baseline age, sex, race, and COPD type did not appear to influence the proportion of patients who developed malignancies (data not shown). However, regardless of active or placebo treatment, patients who smoked $\geq$50 pack-years developed almost twice as many malignancies as patients who smoked $<$50 pack-years (14.9% vs. 8.0%).

Table 3 Patient disposition in RESULTS[a] COPD.

	Placebo	Infliximab			Total
		3 mg/kg	5 mg/kg	Combined	
Treated patients who consented to participate in RESULTS[a] COPD	33	31	29	60	93
Completed study	24 (72.7)	21 (67.7)	21 (72.4)	42 (70.0)	66 (71.0)
Terminated study	9 (27.3)	10 (32.3)	8 (27.6)	18 (30.0)	27 (29.0)
Lost to follow-up	4 (12.1)	4 (12.9)	6 (20.7)	10 (16.7)	14 (15.1)
Withdrew consent	1 (3.0)	3 (9.7)	1 (3.4)	4 (6.7)	5 (5.4)
Died	4 (12.1)	3 (9.7)	1 (3.4)	4 (6.7)	8 (8.6)

Data presented as *n* or *n* (%).
[a] Remicade Safety Under Long-Term Study in chronic obstructive pulmonary disease (COPD).

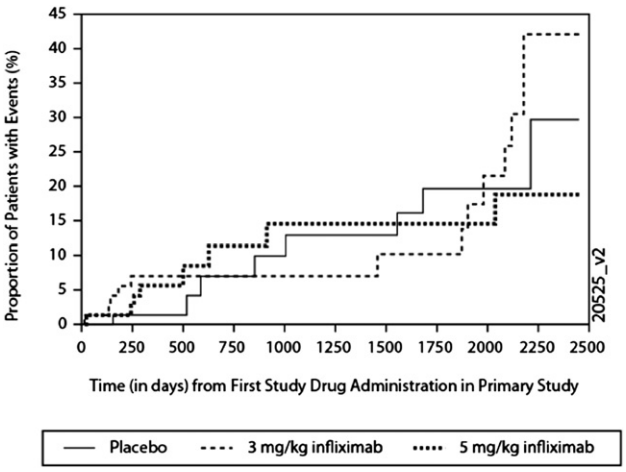

Figure 1 Kaplan–Meier estimates of the cumulative incidence of malignancy in 234 treated patients in the phase 2 interventional study.

Malignancies common in smokers (ie, lung cancer and head and neck cancers) tended to occur more often in patients treated with infliximab, whereas other malignancies tended to occur more often with placebo. However, due to the small number of cases, all confidence intervals of incidences overlapped. Lung cancer was the most common malignancy ($n = 12$; Supplementary Table E1) and occurred more often in the infliximab groups. For the entire period, two lung cancers were reported among patients treated with placebo, five among patients treated with infliximab 3 mg/kg, and five among patients treated with infliximab 5 mg/kg. Three lung cancers were reported during the 44-week randomized trial: zero, two, and one, in the placebo, infliximab 3 mg/kg, and infliximab 5 mg/kg groups, respectively. Four were reported in the gap period in only the infliximab 5 mg/kg group. In the RESULTS follow-up trial, two, three, and one patients reported lung cancer in the placebo, infliximab 3 mg/kg, and infliximab 5 mg/kg groups, respectively.

For the 234 patients treated in the phase 2 interventional study, the hazard ratio for time to malignancy for infliximab versus placebo was 1.64 (95% CI: 0.67, 4.07) for the infliximab 3 mg/kg group and 1.11 (95% CI: 0.42, 2.96) for the infliximab 5 mg/kg group. Overall, the cumulative incidence of malignancy over time was similar across all treatment groups, and no apparent differences were observed over time in the placebo and combined infliximab groups (Fig. 1) with the exception of the end of the study where more malignancies were observed in the infliximab 3 mg/kg group. The apparent disproportionate number of malignancies identified toward the end of the five-year follow-up period could be due to the protocol-recommended chest CT at the last visit leading to the detection of lung nodules, some of which were not definitively diagnosed by the end of the study. To be conservative, nodules that were suspicious for malignancy, but without biopsy confirmation, were categorized as malignancies regardless, since there would be no additional follow-up after the study was completed. The numbers of these events were two for placebo, one for infliximab 3 mg/kg, and zero for infliximab 5 mg/kg.

Death

Of the 234 patients treated in the phase 2 interventional study, 26 (11.1%) patients died: 3 during the 44-week randomized trial, 14 during the gap period, and 9 during RESULTS COPD (Table 4). A greater number of patients

Table 4 Malignancy and death.

	Placebo	Infliximab		
		3 mg/kg	5 mg/kg	Combined
Treated patients in phase 2 study	77	77	80	157
Malignancies				
Patients with ≥1 malignancies	8 (10.4)	12 (15.6)	8 (10.0)	20 (12.7)
Phase 2 study	1 (1.3)	5 (6.5)	4 (5.0)	9 (5.7)
Gap period	3 (3.9)	0	3 (3.8)	3 (1.9)
RESULTS[a] COPD	4 (5.2)	7 (9.1)	1 (1.3)	8 (5.1)
Hazard ratio (95% CI[b])[c]	—	1.64 (0.67, 4.07)	1.11 (0.42, 2.96)	1.37 (0.60, 3.12)
Incidence per 100 patient-years (95% CI)[d]	3.89 (1.68, 7.66)	5.91 (3.05, 10.32)	4.18 (1.80, 8.23)	5.07 (3.10, 7.83)
Deaths				
Patients who died	7 (9.1)	7 (9.1)	12 (15.0)	19 (12.1)
Phase 2 study	1 (1.3)	0	2 (2.5)	2 (1.3)
Gap period	2 (2.6)	4 (5.2)	8 (10.0)	12 (7.6)
RESULTS[a] COPD	4 (5.2)	3 (3.9)	2 (2.5)	5 (3.2)
Hazard ratio (95% CI[b])[c]	—	1.05 (0.37, 3.00)	1.83 (0.72, 4.66)	1.44 (0.60, 3.42)

Data presented as *n* or *n* (%) unless specified otherwise.
[a] Remicade Safety Under Long-Term Study in chronic obstructive pulmonary disease (COPD).
[b] Confidence interval.
[c] Based on the Cox proportional hazards model.
[d] Confidence intervals (CI) are based on an exact method.

($n = 12$ [15.0%]) in the infliximab 5 mg/kg group died compared with the infliximab 3 mg/kg and placebo groups ($n = 7$ [9.1%] each). This increase was driven largely by the number of patients who died in the infliximab 5 mg/kg group during the gap period ($n = 8$) (Fig. 2). The distribution of deaths across all groups was similar when analyzed according to age, sex, race, and COPD type at baseline (data not shown). However, irrespective of treatment group, a greater proportion of patients who smoked $\geq$50 pack-years versus <50 pack-years died (14.2% vs 7.0%, respectively).

The hazard ratio for time to death for the 234 patients treated in the phase 2 interventional study was 1.05 (95% CI: 0.37, 3.00) for the infliximab 3 mg/kg group and 1.83 (95% CI: 0.72, 4.66) for the infliximab 5 mg/kg group versus the placebo group. The incidence of deaths per patient-year was greater in the infliximab 5 mg/kg group compared with the placebo group and similar between the infliximab 3 mg/kg and placebo groups (Table 5). The cause of death was consistent with the demographics and disease comorbidities present in this population of patients with COPD.

Table 5 Summary of follow-up after first infusion: treated patients with long-term safety follow-up information.

	Placebo	Infliximab		
		3 mg/kg	5 mg/kg	Combined
Treated patients with long-term safety follow-up information	35	35	37	72
Total patient-years of follow-up	186	175	173	349
Primary study	29	27	31	59
RESULTS[a] COPD	76	73	68	141
Incidence of malignancy per patient year	0.04	0.05	0.04	0.04
Incidence of death per patient year	0.03	0.04	0.06	0.05

[a] Remicade Safety Under Long-Term Study in chronic obstructive pulmonary disease (COPD).

Discussion

The current report provides follow-up assessments for the occurrence of cancer in patients with COPD who participated in the clinical assessment of infliximab. During the 44-week clinical trial of 234 patients, ten malignancies were reported: one in the placebo group, five in the infliximab 3 mg/kg group, and four in the infliximab 5 mg/kg group. In the 17-month gap period between the studies, there were six malignancies reported: three patients who had been treated with placebo and three patients treated with infliximab 5 mg/kg. Of the 107 patients who participated in the five-year long-term follow-up, an additional nine malignancies were reported: five of 35 patients who had been treated with placebo, three of 35 patients who had been treated with infliximab 3 mg/kg, and two of 37 patients who had been treated with infliximab 5 mg/kg. Thus, the difference in the number of malignancies observed in the initial study tended to equalize over time. For the entire study period, the hazard ratio for the development of malignancy in the two infliximab groups was 1.37 (CI: 0.60—3.12). There was also a difference in the number of deaths among the infliximab-treated patients (hazard ratio 1.44 [CI: 0.60, 3.42]).

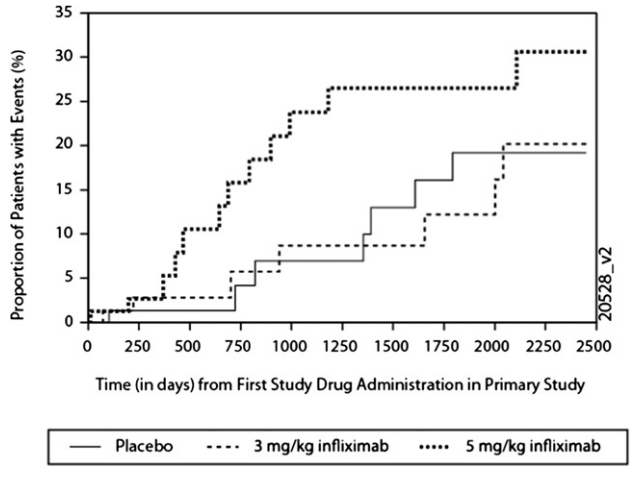

Figure 2 Kaplan—Meier estimates of the cumulative incidence of death in 234 treated patients in the phase 2 interventional study.

TNFα has been suggested to play a role in limiting cancer pathogenesis. As a result, there has been concern that anti-TNFα treatments may increase the risk of malignancy.[27,28] Infliximab, which is indicated for several conditions, including rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, and psoriatic arthritis, has been carefully monitored for the development of malignancy. Individual clinical trials, which are generally of limited duration, have reported varied results, in part due to small sample sizes. As a result, meta-analyses have been performed to determine if the use of anti-TNFα treatments increases the risk for malignancy. Bongartz et al. reported an odds ratio (OR) of 3.3 (CI: 1.2—9.1) for malignancy in an analysis of nine trials that included 5005 rheumatoid arthritis patients.[27] A more comprehensive meta-analysis was performed at the behest of the European Medicines Agency[29] and included 74 clinical trials and 22,904 patients. Data were assessed at an individual patient level, which were available due to the cooperation of all corporate sponsors. The analysis, which was conducted by an independent academic group, used several standardized definitions of incidence and prevalent malignancy and included systematic case adjudication. This analysis concluded that there was a 2.02 relative risk of nonmelanoma skin cancer (CI: 1.11—3.95) and a relative risk of 0.99 (CI: 0.61—1.68) for all other cancers. The authors concluded that the data neither refuted nor verified a short-term risk for increased cancer with anti-TNFα treatments.

Long-term assessment of cancer risk consequent to anti-TNFα treatment has been performed in several observational studies. Wolfe and Michaud, using data from the US National Data Bank for Rheumatic Diseases, reported an increased risk for nonmelanoma skin cancer (OR: 1.5, CI:

1.2—1.8) and possible melanoma (OR: 2.3, CI: 0.9—5.4), but no observed increased risk for any other cancer (OR: 1.0, CI: 0.8—1.2).[30] Using linked databases in Sweden, Askling reported no increased risk of cancer over a six-year follow-up period in more than 6000 patients with rheumatoid arthritis.[31] In contrast, a prospective observational study, reported by Mariette and colleagues, suggested an excess of lymphomas among patients with rheumatoid arthritis treated with anti-TNFα antibodies (standardized incidence ratio 2.3, CI: 1.6—3.3.[32] Diak et al. reviewed pediatric cases of malignancies reported to the Food and Drug Administration, which suggested the possibility of increased risk from anti-TNFα treatment.[33] However, differential reporting, the increased risk of malignancy associated with the underlying conditions, and selection bias for treatment initiation, confound any definite conclusions.

The current follow-up study was motivated because of the marked difference in diagnosed cancers, nine among 157 infliximab-treated patients versus one among 77 placebo patients, in a prospective 44-week clinical trial that included 24 weeks of active treatment and 20 weeks of follow-up. Plans for the study began upon recognition of the difference. Several of the participating centers declined to participate in the follow-up, as did a number of individual patients. As a result, the current follow-up study includes only 107 of the original 234 patients. Two other trials, which also evaluated the use of infliximab in COPD, had been conducted but those centers declined to participate in the current follow-up. The available data, therefore, are limited. In addition, there was a gap period between the completion of the initial trial and the current follow-up. While available information is reported, the lack of complete follow-up limits the interpretation of malignancy and mortality rates. Nevertheless, the differences in reported cancers were much less marked with the additional follow-up data. Of interest, the most prevalent cancer was lung cancer and a heavier smoking history was associated with an increased reporting of cancer, as would be expected.

The attenuation in the difference in cancers with follow-up does not eliminate the possibility that infliximab could contribute to the emergence of cancer. However, such an effect was not observed in the meta-analyses of clinical studies reported by Askling[29] or by Bongartz.[27] Wolfe specifically assessed lung cancers in a US-based observational study and reported an odds ratio of 1.1 (CI: 0.7—1.8) for 112 lung cancers observed among 8627 patients.[30] All of these studies included patients who differ in important ways from the patients in the current trial. Many may have been smokers, as smoking is a risk factor for rheumatoid arthritis.[34] Moreover, a number may have had COPD, although this was not reported. However, smoking is a major risk factor for lung cancer, and among smokers, the presence of COPD increases the risk. Thus, the current study population is likely at much greater risk for lung cancer than the patients in previous analyses of cancer risk following anti-TNFα therapy. It should be noted that the continued smoking in patients with COPD has been associated with an increased risk of lung cancer and mortality from lung cancer.[8] In this and other studies, there was little difference in risk in the first 5 years after cessation, but an increased risk of lung cancer is present for up to 15 years after smoking cessation. Although in the primary phase 2 interventional study, the incidence of "current smoking" at the time of randomization was balanced among the 3 groups, there was an imbalance, with slightly lower percentage of current smokers in the infliximab groups, during the follow-up study. Despite this, there were numerically more subjects with lung cancer in the two infliximab groups. Whether infliximab might alter the risk of emergent cigarette smoke-induced cancers, therefore, cannot be resolved from the available data.

Anti-TNFα therapy has proven effective for several chronic inflammatory conditions. There are a number of mechanisms by which TNFα could contribute to the pathogenesis of COPD. The current study presents long-term follow-up of patients with COPD who participated in a phase 2 randomized clinical trial evaluating infliximab at doses effective in rheumatoid arthritis. No clinical benefits were observed in any of the primary or secondary endpoints. It is possible, however, that TNFα may play a role in a specific subset of COPD patients or at a specific time in the course of the disease. For example, the hypotheses that anti-TNFα therapy may have a therapeutic benefit among patients with COPD who are cachectic or who have very high levels of circulating TNFα remain untested. The current report provides additional information on the potential for adverse effects of infliximab. As such, it can help inform the patient of the potential risks that need to be assessed against any potential benefits. Whether similar concerns would apply to other anti-inflammatory treatments that may target mechanistic pathways shared with TNFα is unknown, but should be a concern leading to careful prospective monitoring.

In summary, the current study provides additional observational information on a group of patients with COPD who participated in a trial evaluating infliximab. The originally observed excess of malignancies in the infliximab-treated groups was less prominent among those in whom long-term follow-up was obtained. The excess malignancies were most marked for lung cancers. Whether this represents an increase in emergent cancers during infliximab treatment cannot be ascertained. The potential for anti-TNFα treatment to contribute to cancer risk should be considered in the design of future trials targeting TNFα and related pathways for the treatment of COPD.

Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki and all other applicable national and local laws and regulations.

Support

This study was funded by Janssen Research & Development, LLC.

Author contribution

Concept and Design: SIR, SF, KHL, ESB; Development of methodology: SIR, SF, PA, KHL, ESB; Acquisition of data: SIR; Analysis and interpretation of data: SIR, SF, PA, KHL, ESB; Writing, review and/or revision of the manuscript: SIR,

SF, PA, KHL, ESB; Administrative, technical, or material support: SF, PA; Study supervision: SIR, ESB.

Conflicts of interest statement

Susan Flavin, Prasheen Agarwal, Kim Hung Lo, and Elliot S. Barnathan are or were employees of Janssen Research & Development, LLC, and own(ed) stock in Johnson & Johnson, of which Janssen is a subsidiary.

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Appendix A. Supplementary material

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