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Solid Malignancies Among Etanercept-Treated Patients With Granulomatosis With Polyangiitis (Wegener's)

Long-Term Followup of a Multicenter Longitudinal Cohort

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Objective. **An association between therapeutic inhibition of tumor necrosis factor (TNF) and solid malignancies was observed during the Wegener's Granulomatosis Etanercept Trial (WGET), which included 180 patients with granulomatosis with polyangiitis (Wegener's) (GPA). The present study was conducted to determine the malignancy risk beyond the time of exposure to study therapy.**

Methods. **The occurrence and type of solid malignancies were ascertained using a standardized data form. Data collected included vital status, histologic findings, and therapeutic interventions. The Surveillance, Epidemiology, and End-Results database was used to estimate a standardized incidence rate (SIR) for solid malignancies.**

Results. **Post-trial followup data were available for 153 patients (85% of the original cohort), with a median followup time of 43 months. Fifty percent of these patients had received etanercept. There were no differences in demographic characteristics between the etanercept and placebo groups. Thirteen new solid malignancies were detected, 8 in the etanercept group and 5 in the placebo group. Compared to the general population, the risk of solid malignancies in the etanercept group was increased (SIR 3.92 [95% confidence interval 1.69–7.72]), but was not different from the risk in the placebo group compared to the general population (SIR 2.89 [95% confidence interval 0.94–6.73]). All solid malignancies occurred in patients who had been exposed to cyclophosphamide. The overall duration of disease and a history of malignancy before trial enrollment were associated with the development of malignancy during post-trial followup.**

Conclusion. **The incidence of solid malignancy remained increased during long-term followup of the WGET cohort. However, this could not be attributed solely to etanercept exposure during the trial. Anti-TNF therapy with etanercept appears to further increase the risk of malignancy observed in patients with GPA treated with cytotoxic agents and should be avoided in these patients.**

Owing to the importance of tumor necrosis factor α (TNFα) in the mechanisms of inflammation, TNFα

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blockers have been widely used for the treatment of immune-mediated chronic inflammatory diseases. However, the first property ascribed to TNFα was its ability to induce necrosis of sarcomas and other skin-transplanted cancers (1). TNFα also may play a role in immunosurveillance against cancer cells by causing cytostasis and cytolysis (2), inducing neoplastic cells to undergo apoptosis (3,4), and inhibiting tumor-associated angiogenesis (5,6). There has been a longstanding concern that TNFα blockade might facilitate the development of neoplasia de novo or the progression of premalignant and established malignant lesions by interfering with the normal physiologic effects of TNFα that control tumor growth.

The relationship between TNFα blockade treatment and malignancy has been studied in rheumatoid arthritis (RA), other inflammatory arthropathies, and Crohn's disease. However, these investigations have been complicated by the increased incidence of malignancies already observed in many of those diseases (7–14) and by possible channeling bias (i.e., patients with severe disease, who show the highest disease-associated risk of malignancy, are more likely to be treated with biologic agents than patients with milder forms of the disease) (15). TNFα blockade treatment has been linked to the development of lymphoma, notably hepatosplenic T cell lymphoma in juvenile inflammatory arthritis and Crohn's disease, which otherwise occurs only rarely (16). In contrast, the association of TNFα blockade with solid malignancies remains uncertain (16–21).

For granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA), the malignancy risk associated with TNFα blocker use has been even more difficult to estimate because of the low prevalence of these diseases and the paucity of data on TNFα blocker use in GPA and MPA. Furthermore, several reports have suggested an increased risk of both solid and hematologic malignancies in GPA and MPA per se, with estimates of global risk ranging from 1.6-fold to 18-fold compared to the general population (22–24) or to patients with other rheumatologic conditions (25,26). In the Wegener's Granulomatosis Etanercept Trial (WGET), a placebo-controlled trial in which etanercept or placebo was given in addition to standard therapy for remission induction and maintenance in GPA (27), solid malignancies were observed only among patients treated with etanercept who had also been exposed to cyclophosphamide (CYC), with an observed standardized incidence ratio (SIR) of 3.1 (95% confidence interval [95% CI 1.1–6.8]) (28). This finding led to a warning by the manufacturer of etanercept against the concomitant use of etanercept and CYC under any circumstances and against its use in conjunction with any other immununosuppressive agent for the treatment of GPA.

To further investigate the relationship between etanercept therapy and malignancy, we conducted a followup study to identify and characterize any new cases of solid malignancies that arose in the WGET cohort during the 5-year period after completion of study treatment. We report the results herein.

PATIENTS AND METHODS

The cohort of patients originally enrolled into the WGET formed the basis of this analysis. The design of the WGET, the clinical characteristics of the patients enrolled, and the treatment outcomes have been described in detail previously (27,29,30). Briefly, 180 patients who met at least 2 of the 5 modified American College of Rheumatology criteria for the classification of GPA (29,31,32) were randomized 1:1 to receive either etanercept 25 mg subcutaneously twice weekly or placebo in addition to standard remission induction and maintenance therapy for GPA. Patients were eligible for enrollment if they had active disease with a modified Birmingham Vasculitis Activity Score modified for GPA (32) of $\geq$3 as a result of newly diagnosed disease or a relapse. Patients who had been diagnosed as having a malignancy within 5 years prior to the screening for trial eligibility, except those with squamous or basal cell carcinomas of the skin or cervical carcinoma in situ who had received curative surgical therapy, were excluded from participation.

Data were obtained for this study in the context of a long-term followup study of the WGET cohort. The occurrence and the type of malignancy after the common closeout (September 2003) were ascertained by investigators in 2007–2008, using a standardized data form. Most patients continue to be followed up regularly at the original WGET site, and the information was obtained by the physician who was in direct contact with the WGET participants and/or by reviewing the medical records. If the patient was no longer being regularly followed up at the WGET site, the data form was completed by telephone interview with the patient.

The diagnosis of cancer was confirmed in all cases by reviewing the histopathologic reports. Therapy for GPA was recorded for each of these cases, focusing on type and dose of immunosuppressive agents received before and during the clinical trial, as well as after the trial closeout. Vital status at the time of last contact was recorded, including the date of death if applicable.

Descriptive statistical analyses were performed to analyze the development of malignancies during the trial, after completion of the trial (post-trial followup), and both periods combined (followup from trial entry). Exploratory analyses comparing patients who developed solid malignancies versus those who did not were performed using Pearson's chi-square test or Fisher's exact test for categorical variables, and Wilcoxon's rank sum test for continuous variables. Data were expressed as the mean $\pm$ SD or the median (range).

Using the Surveillance, Epidemiology, and End-Results (SEER) database (Surveillance Research Program, National Cancer Institute) and SEER*stat software version 6.3.6, the age- and sex-adjusted incidence rates of solid malig-

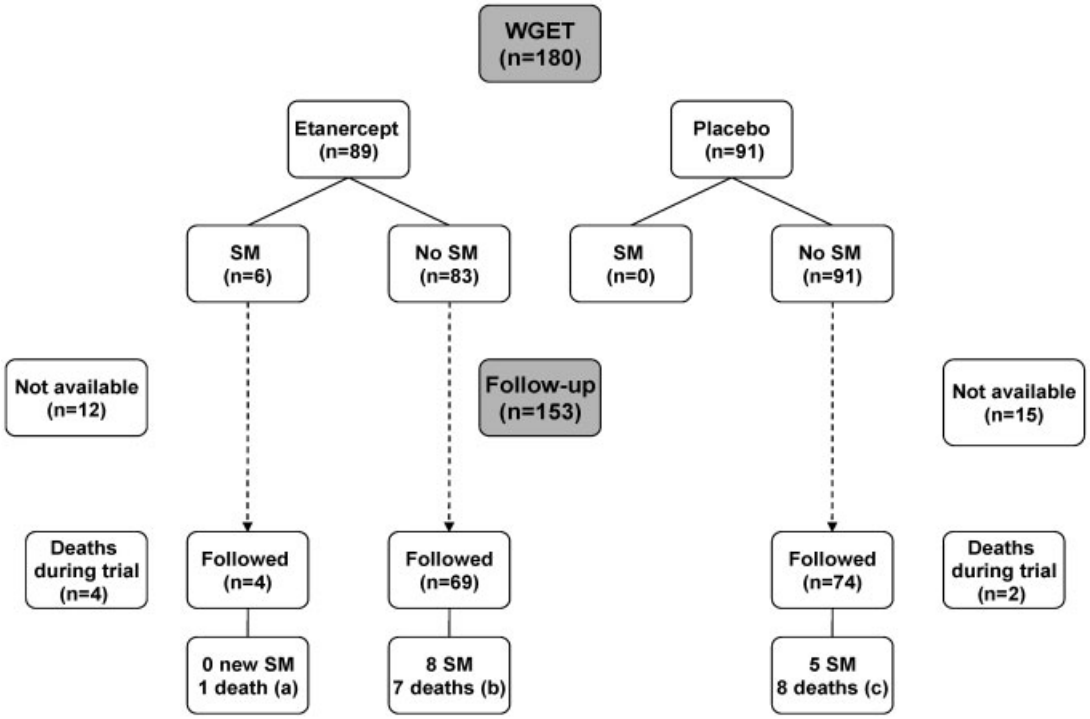

Figure 1. Schematic diagram of deaths and solid malignancies (SM) observed during followup of patients in the Wegener's Granulomatosis Etanercept Trial (WGET). a = death caused by solid malignancy diagnosed during the trial. b = deaths caused by solid malignancy diagnosed after the trial (n = 2), leukemia diagnosed after the trial (n = 1), myocardial infarction (n = 1), or indeterminate cause (n = 3). c = deaths caused by solid malignancy diagnosed after the trial (n = 2), sepsis (n = 2), renal failure (n = 1), arrhythmia (n = 1), or indeterminate cause (n = 2).

nancies in the US population between the years 2000 and 2004 (excluding leukemia, lymphoma, myeloma, and nonmelanoma skin cancers) were determined. This incidence corresponds to the expected rate of solid malignancy for the purpose of this comparison. The incidence rate for malignancies in our cohort was calculated by dividing the number of events by the total patient-years of observation (observed cases). The SIRs ([observed/expected cases] × 100) for solid malignancies with the respective 95% CIs were calculated.

The SIRs were compared between groups (etanercept versus placebo) using an approximate F test for comparing Poisson variates. With data censored at last followup for subjects without malignancies, the cumulative incidence of malignancies over time following the treatment period was also estimated (using the Kaplan-Meier method) and was compared between groups by log rank test.

RESULTS

Demographic characteristics of the patients in the cohort. Post-trial followup information was available for 153 of the 180 WGET participants (85%) (Figure 1 and Table 1). The median time of followup was 43 months from the common closeout date. Seventy-seven of these patients (50.3%) had been assigned to receive

Table 1. Demographic characteristics of the 153 GPA patients followed up after participation in the WGET*

Characteristic	Etanercept group (n = 77)	Placebo group (n = 76)	Total (n = 153)
Male sex	50 (65)	44 (58)	94 (61)
Age, mean ± SD years			
At trial enrollment	52 ± 14	49 ± 17	50 ± 15
At last contact	57 ± 14	54 ± 17	55 ± 15
Race			
White, non-Hispanic	69 (90)	72 (95)	141 (92)
Black, non-Hispanic	2 (2.5)	0 (0)	2 (1)
Hispanic	4 (5)	2 (2.5)	6 (4)
Other	2 (2.5)	2 (2.5)	4 (3)
Alive at end of present study	65 (84)	66 (87)	131 (86)
Previous history of cancer	12 (16)	5 (7)	17 (11)
Family history of cancer	15 (19)	14 (18)	29 (19)
Tobacco use			
Current use	1 (1)	1 (1)	2 (1)
Previous use	22 (29)†	10 (13)	32 (21)

* Except where indicated otherwise, values are the number (%). GPA = granulomatosis with polyangiitis (Wegener's); WGET = Wegener's Granulomatosis Etanercept Trial.
† $P = 0.015$ versus placebo group.

Table 2. Treatment assignment in the WGET, GPA disease severity, and immunosuppressive treatment in the 13 patients in whom solid malignancies were detected after completion of the WGET*

Study arm, patient	Disease extent	Age/ sex†	Type of cancer	Time to cancer after enrollment/ closeout, months	Previous cancer/time before enrollment	Cumulative CYC use (gm)			Other treatments			Vital status at end of present study
						Before trial	During trial	After trial‡	Before trial	During trial	After trial	
Etanercept												
1	Limited	29/F	Melanoma	61/27	No	24	20	No		MTX	MTX, AZA	Alive
2	Limited	36/M	Squamous cell (tonsillar) carcinoma	52/14	No	183	No	No		MTX	MTX, AZA	Alive
3	Limited	71/M	Squamous (transitional) cell, metastatic	56/39	Bladder cancer/ 8 years	264	No	No		MTX	MTX	Dead
4	Limited	70/M	Prostate cancer	31/4	No	No	No	Yes		MTX	MTX, AZA	Alive
5	Severe	56/M	Prostate cancer	50/36	No	No	50	Yes		AZA	MTX	Alive
6	Severe	57/M	Melanoma	62/30	No	84	7	No		AZA	AZA	Alive
7	Severe	66/F	Cholangio-carcinoma	38/21	Breast cancer/ 12 years	48	7	No	AZA	MTX	MTX	Dead
8	Severe	63/M	Small bowel	78/45	Squamous skin cancer/>5 years	105	No	No	AZA	MTX	MTX, AZA	Alive
Placebo												
9	Limited	62/M	Bladder carcinoma	66/34	No	144	No	No	AZA, CSA	MTX	MTX	Alive
10	Severe	42/M	Renal cell carcinoma	49/16	No	1	24	No		AZA		Dead
11	Severe	57/M	Colon cancer	35/3	No	2.5	11.9	No		MTX, AZA		Dead
12	Severe	61/M	Prostate cancer	34/5	Melanoma/15 years	64	21	No				Alive
13	Severe	71/F	Cholangio-carcinoma	59/26	No	40	11	No		MTX	MTX, AZA	Alive

* GPA = granulomatosis with polyangiitis (Wegener's); CYC = cyclophosphamide; MTX = methotrexate; AZA = azathioprine; CSA = cyclosporin A.
† Age at the time of enrollment in the Wegener's Granulomatosis Etanercept Trial (WGET).
‡ Data on cumulative dose not available.

etanercept in the WGET and 76 (49.7%) to receive placebo. Sex distribution, age, race, vital status, previous personal or family history of cancer, or current tobacco use did not differ between the etanercept and the placebo groups; only past tobacco use was more common among patients who had received etanercept (29% versus 13%; $P = 0.015$).

Solid malignancies diagnosed since WGET closeout. Thirteen new solid malignancies, in 13 of the 153 patients (8.5%), were diagnosed during the post-trial followup period. The types of cancer and the clinical characteristics of the affected patients are summarized in Table 2. The median time to cancer diagnosis was 52 months after trial enrollment (range 31–78 months) and 26 months after the common closeout date (range 3–45 months). The 4 deaths (2 from each treatment group) that occurred during the post-trial followup all resulted from the cancer.

All of the solid malignancies diagnosed during the post-trial period occurred in patients who had received cyclophosphamide (CYC) before, during, or after the trial (n = 138). Twelve of the 13 patients had received at least 1 additional immunosuppressive agent (azathioprine, methotrexate, or cyclosporin A). The median cumulative dose of CYC was 56 gm (range 1–264) prior to enrollment and 16 gm (range 7–50) during the trial. For the post-trial period, we were able to ascertain the approximate duration of CYC exposure in the individual patients but could not quantify the cumulative doses.

Risk factors for the development of solid malignancies after WGET closeout. We compared the characteristics of the 13 patients who developed solid malignancies after the trial closeout date with those of the 140 patients who did not develop a solid malignancy (Table 3). There were no significant differences between the groups in terms of treatment assignment, age, sex, or extent of disease at trial enrollment. However, the prevalence of disease relapse at the time of trial enrollment was greater among the patients who developed solid malignancies (85% versus 54%; $P = 0.04$). This group also had a longer mean disease duration, as assessed by either time from symptom onset to trial enrollment (mean ± SD 6.4 ± 3.9 years versus 3.3 ± 4.8 years; $P = 0.001$) or time from diagnosis to trial enrollment (5.1 ± 4.4 years versus 2 ± 3.8 years; $P = 0.0006$). Similar differences were found when the times between symptom onset and end of followup or between diagnosis and end of followup were analyzed in both groups (data not shown). Importantly, the group of patients who developed a solid malignancy after trial closeout also had a higher frequency of malignancy before entering the trial (31% versus 9%; $P = 0.03$).

Relationship between treatment assignment and risk of solid malignancy during WGET followup. Table 4 shows the observed and expected number of patients with solid malignancy and the calculated SIRs for the etanercept and placebo groups. The analysis is presented for 3 periods: the trial period (from enrollment until the common closeout in September 2003), the post-trial period (from common closeout until last visit or death, representing the focus of the present study), and the overall period (trial and post-trial periods combined). During the trial, the frequency of solid malignancies was higher in the etanercept group than in the placebo group (7% versus 0%; $P = 0.01$) (28). However, during the post-trial period, the frequency of solid malignancies was not different between the etanercept and placebo groups (10% versus 7%; $P = 0.39$), although the frequency was numerically higher in the etanercept group. When the 2 periods were combined, the overall frequency of solid malignancies from time of trial enrollment remained higher in the etanercept group (18%) compared to the placebo group (7%) ($P = 0.03$).

To account for variations in age, sex, and duration of followup, SIRs were calculated for each treatment group and period (Table 4). For the trial period, the SIR for solid malignancies in the etanercept group was 3.8 (95% CI 1.39–8.26), compared to 0 (95% CI 0–3.63) in the placebo group. These values differ numerically from those previously reported (SIR in etanercept group 3.12 [95% CI 1.15–6.8]) (28) because the reference population was extended for the present analysis to include the last year with available data in the SEER database. For the post-trial period, the SIR for solid malignancies in the etanercept group was not significantly different from that in the placebo group (3.92 [95% CI 1.69–7.72] and 2.89 [95% CI 0.94–6.73], respectively; $P = 0.597$). For the combined period, the SIR was 3.76 (95% CI 2.05–6.31) in the etanercept group and 1.71 (95% CI 0.56–3.99) in the placebo group ($P = 0.117$). A time-to-event analysis comparing treatment groups confirmed that the occurrence of malignancies post-trial did not differ between treatment arms ($P = 0.44$).

We also evaluated whether exposure to other TNF blockers had an effect on the malignancy rate. Sixteen patients (8 in each WGET treatment group) received infliximab after discontinuation of experimental therapy. One of these patients, assigned to the placebo group, developed a solid malignancy that was previously reported (27). We reanalyzed the SIRs in 2 ways: 1) by excluding from analysis all 16 patients

Table 3. Baseline characteristics of the GPA patients who did and those who did not develop solid malignancies after WGET closeout (September 2003)*

	Solid malignancy (n = 13)	No solid malignancy (n = 140)	P†
Treatment assignment			0.40
Etanercept	8 (10)	69 (90)	
Placebo	5 (7)	71 (93)	
Age, mean ± SD years	57 ± 13	50 ± 16	0.07
Male/female	10 (77)/3 (23)	84 (60)/56 (40)	0.37
Limited/severe disease	5 (38)/8 (62)	42 (30)/98 (70)	0.54
Age at onset of vasculitis symptoms, mean ± SD years	51 ± 13	46 ± 16	0.26
Relapsing disease	11 (85)	75 (54)	0.04
Duration since symptom onset, mean ± SD years	6.4 ± 3.9	3.3 ± 4.8	0.001
Duration since diagnosis, mean ± SD years	5.1 ± 4.4	2 ± 3.8	0.0006
History of cancer before trial‡	4 (31)	12 (9)	0.03
Family history of cancer	0 (0)	29 (21)	0.13
Current tobacco use	0 (0)	5 (4)	1.0
Prior treatment with immunosuppressive drugs	11 (85)	80 (57)	0.08
Ever treated for GPA	13 (100)	125 (89)	0.37
CYC treatment (daily or intermittent)			
Ever used§	13 (100)	125 (89)	0.4
During WGET	8 (62)	113 (81)	0.13
MTX treatment (oral or SC or IM)			
Ever used§	9 (69)	82 (59)	0.56
During WGET	11 (85)	110 (79)	1.0
AZA treatment			
Ever used§	7 (54)	49 (35)	0.23
During WGET	4 (31)	45 (32)	1.0

* Except where indicated otherwise, values are the number (%). "Baseline" refers to the time of enrollment in the WGET. SC = subcutaneous; IM = intramuscular (see Table 2 for other definitions).
† By chi-square or Fisher's exact test for categorical data, and by Wilcoxon's rank sum test for continuous data.
‡ In the solid malignancy group, bladder cancer (1 patient), breast cancer (1 patient), melanoma and basal cell carcinoma (1 patient), and skin cancer (1 patient). In the no solid malignancy group, basal cell carcinoma (4 patients), colon cancer (3 patients), breast cancer (1 patient), lymphoma (1 patient), precancerous or cancerous skin lesion (1 patient), prostate cancer (1 patient), and rectal and skin cancer (1 patient).
§ Before trial enrollment, during trial, or after trial.

exposed to infliximab, and 2) by reclassifying the infliximab-exposed patients from the placebo group to the etanercept group. Neither analysis resulted in a meaningful change in the SIRs or a significant difference in the malignancy rates between TNF blocker–exposed versus nonexposed patients, for any of the observation periods (data not shown).

DISCUSSION

This long-term followup study of the WGET cohort showed that in comparison to the general population, the increased risk of solid malignancies observed in the etanercept group during the trial persisted during post-trial followup. However, in contrast to the trial

Table 4. Frequency of observed and expected solid malignancy events, and SIRs*

	Solid malignancies, etanercept group			Solid malignancies, placebo group			*P*, etanercept vs. placebo	
Followup period (median duration)	No. observed	No. expected	SIR (95% CI)	No. observed	No. expected	SIR (95% CI)	Frequency of malignancy†	SIR‡
Trial (30 months)	6	1.58	3.80 (1.39–8.26)	0	1.02	0 (0–3.63)	0.01	0.03
Post-trial (43 months)	8	2.04	3.92 (1.6–7.72)	5	1.73	2.89 (0.94–6.73)	0.39	0.60
From trial entry (64 months)	14	3.73	3.76 (2.05–6.31)	5	2.92	1.71 (0.56–3.99)	0.03	0.12

* SIRs = standardized incidence ratios; 95% CI = 95% confidence interval.
† By Fisher's exact test.
‡ By F test.

period, solid malignancies were also observed in the placebo group during post-trial followup. Furthermore, there was no significant difference in SIRs between the etanercept and placebo groups. Other factors associated with the development of solid malignancies in the WGET cohort were recognized, particularly the duration of disease and history of malignancy prior to trial enrollment. This suggests that after discontinuation of etanercept, the malignancy risk conferred by this agent in GPA reverts back to the increased baseline risk inherent to the disease and its treatment. As the duration of disease is linked to duration of therapy and all solid malignancies that occurred in this cohort developed after CYC exposure, our results further highlight the need for safer treatment regimens, especially ones that reduce or eliminate exposure to CYC.

During the time period of the WGET, all solid malignancies that developed occurred in the etanercept group (28). In contrast, new malignancies observed during the post-trial followup were diagnosed in patients from both treatment arms (Table 4). The risk of solid malignancies remained significantly increased for patients in the etanercept group compared with risk in the general population (based on the SEER database). However, the relative risk in the placebo group compared to the general population was of similar magnitude. Thus, with longer time from exposure to etanercept, other risk factors become relatively more important.

In our study, the SIR for solid malignancies in the etanercept group during the followup from trial entry (trial and post-trial period) was 3.76 (95% CI 2.05–6.31), an estimated risk that was higher than the risks among non–TNF blockade–treated patients with antineutrophil cytoplasmic antibody–associated vasculitis reported by Westman et al (standardized morbidity ratio 1.6 [95% CI 0.9–2.7]) (23), Knight et al (SIR 2.0 [95% CI 1.7–2.5]) (24), and Faurschou et al (SIR 2.1 [95% CI 1.5–2.7]) (33). The risk observed in these 3 earlier studies was similar to the SIR in the placebo group of the WGET cohort (1.71 [95% CI 0.56–3.99]). These earlier studies are comparable to ours in that they also used healthy populations as the reference and determined risk estimates based on incidence. In contrast, our estimate of risk was lower than those reported by Tatsis et al (odds ratio 18 [95% CI 2.3–140]) (25) and Pankhurst et al (relative risk 6.0 [95% 3.7–9.7]) (26). The latter 2 studies are not as easily comparable to ours because their reference populations consisted of patients with autoimmune diseases (systemic lupus erythematous and RA, respectively) rather than healthy populations, and their estimates were based on the frequency of solid malignancies in the studied groups, rather than the incidence. In the context of this literature, the SIRs observed in our study suggest that etanercept boosts the already increased background risk of malignancies in patients with GPA for the duration of exposure to etanercept, but not much beyond the time of exposure.

There is ample epidemiologic evidence and mechanistic experimental support linking chronic inflammation to the development of cancer (34). For autoimmune disease in general, it has been speculated that both immune dysregulation inherent to the underlying disease and the reduction of immunosurveillance caused by immunosuppressive therapy promote malignancy (35,36). An association between duration of RA and risk of malignancy (lymphoma) has long been suspected, and evidence linking the malignancy risk to disease activity and severity of RA has emerged (11,37–40).

There is currently no clear evidence that vasculitis per se confers an increased risk of malignancy. Among patients with giant cell (temporal) arteritis, which is not treated with CYC, no increased malignancy risk was found (41). In GPA, the development of urothelial malignancies has been clearly linked to therapy with CYC, and one recent epidemiologic study showed that the overall cancer risk in GPA is linked to the cumulative CYC exposure (33,42). Of note, in the present study at least 10 of the 13 patients who developed solid malignancies after trial closeout had received >36 gm of CYC (Table 2), a cumulative dose that has been identified as critical for the development of malignancies in GPA (42).

In our cohort, duration of disease and history of previous malignancy emerged as risk factors for the development of solid malignancy. The greater number of different cytotoxic drugs used and greater cumulative CYC exposure in the group of patients with solid malignancies did not reach statistical significance when compared to those who did not develop malignancy (Table 3). However, these factors cannot be separated from disease duration.

The risk of cancer induction by etanercept has been studied extensively in chronic arthropathies, in which the drug has been used widely. An association with hematologic malignancies has been suggested, but estimation of the risk is difficult as these autoimmune diseases by themselves have an increased risk of malignancy (especially lymphomas) (12,43,44). In contrast, no etanercept-associated risk of solid malignancy has been found to date in other autoimmune diseases (45,46). However, unlike patients with GPA, patients with RA or other arthropathies are usually not treated with CYC.

The malignancies observed in the WGET cohort include a variety of histopathologic types and organs of origin. The fact that 3 of the 19 solid malignancies diagnosed after enrollment in the WGET (2 in patients from the etanercept group and 1 in a patient from the placebo group) were cholangiocarcinomas is an unexpected finding, owing to the rarity of this neoplasm in the general population.

Our study has several important strengths. The study cohort consisted of well-characterized patients with a single disease, GPA. The exclusion of patients who had a solid malignancy within 5 years prior to enrollment, as well as the temporal relationship between the diagnosis of GPA and the development of cancer, make it unlikely that the vasculitis was a paraneoplastic phenomenon in any of the patients (47). The demographic and clinical characteristics were similar in the etanercept and placebo groups. Finally, the clinicians caring for the study participants were aware of the possible malignancy risk conferred by randomization to receive treatment with etanercept (28) and of the increased malignancy risk among patients with GPA, and consequently these patients were monitored closely, making it unlikely that any solid malignancies were missed in this cohort.

The study also has limitations. First, followup information could be obtained for only 85% of the original cohort, possibly introducing some bias. However, the balance in the number of patients originally assigned to receive etanercept versus those assigned to receive placebo was maintained, and the high rate of followup likely preserved the balance of risk factors between the 2 groups (27). Second, the information obtained during post-trial followup is less complete than that obtained under the strict trial protocol; however, it remains unlikely that any cancers were missed unless they were asymptomatic. Third, the small number of observed solid malignancies precluded a multivariate analysis of risk factors contributing to malignancy development.

In conclusion, the long-term post-trial followup of the patients in the WGET cohort confirms that patients with GPA are at increased risk for solid malignancies. The increased risk in the etanercept group compared to the general population observed during the trial remained unchanged during post-trial followup. However, in contrast to the trial period, this increased risk observed during post-trial followup could no longer be attributed to an effect of etanercept, owing to the lack of a significant difference in the frequency of malignancies between the active treatment and placebo groups. Rather, the increased risk for solid malignancy during post-trial followup of this cohort seems to be related to disease duration and history of previous malignancy. Because of the potential interaction between anti-TNF therapy and high CYC exposure in the development of malignancy and the lack of demonstrable efficacy of this regimen in GPA, it is reasonable to avoid the use of etanercept in patients with GPA, particularly those with a history of chronic relapsing disease, CYC exposure, or previous malignancy.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Specks had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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