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TNF-α Blocker Therapy and Solid Malignancy Risk in ANCA-Associated Vasculitis

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Abstract ANCA-associated vasculitides (AAV) are small vessel systemic vasculitis syndromes associated with the potential for high morbidity and mortality. This group includes granulomatosis with polyangiitis (Wegener´s, GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (Churg-Strauss, EGPA). The standard treatment consists of a combination of glucocorticoids and potent immunosuppressant drugs. These have broad mechanisms of action as well as important adverse effects. Efforts have been made to investigate novel agents with better-defined and narrower mechanisms of action, such as biologics, including TNF-α blockers. Etanercept, a well-known TNF-α blocker evaluated for GPA in the Wegener's Granulomatosis Etanercept Trial (WGET), was associated with an increase in the development of solid malignancies in comparison to placebo during that trial period. A 5-year follow-up after the WGET trial showed a sustained increase in incidence of solid malignancies, but this could no longer be solely attributed to etanercept exposure. These studies raised concerns about the use of the family of TNF-α blockers in AAV. Here, we review the evidence about the association between therapeutic inhibition of tumor necrosis factor (TNF-α) by etanercept and other TNF-α blockers with the development of solid malignancies in GPA and other AAV.

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Introduction

The anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) are a group of autoimmune diseases with inflammation and necrosis of small and medium sized vessels in multiple organs. This group includes granulomatosis with polyangiitis (Wegener´s, GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (Churg-Strauss, EGPA). Because of many clinical similarities and their shared association with ANCA, common pathogenic mechanisms have been assumed. Conventional treatment consists of a combination of glucocorticoids and potent immunosuppressant drugs including cyclophosphamide, methotrexate, and azathioprine. These agents have broad mechanisms of action as well as significant toxicities. This has led to the investigation of novel agents with better-defined and narrower mechanisms of action, such as biologics including TNF-α blockers.

TNF-α is a molecule with many important immunoregulatory functions, including the elevation of c-reactive protein levels, the up-regulation of numerous cytokines and adhesion molecules, and the coordination of acute phase reactions, which can lead to fever, anemia, anorexia, and cachexia [1]. In the past 15 years, TNF-α blockers have become an effective therapeutic alternative for a variety of autoimmune diseases with joint, intestinal, or dermatological manifestations, allowing significant improvements in clinical outcomes and prognosis.

TNF-α blockers have also been used and investigated in a variety of systemic vasculitis syndromes including giant cell arteritis [2], Takayasu arteritis [3•], Behçet disease [4•],

and AAV [5, 6, 7•]. The use of TNF-α blockers for AAV appeared particularly compelling because several lines of evidence support a role of TNF-α in the pathogenesis of AAV. Circulating CD4(+)T cells that overproduce TNF-α as well as in situ production of TNF-α by infiltrating monocytes and renal cells in renal biopsies have been documented in patients with AAV [8]. Increased levels of urinary TNF-α during disease activity that normalize with disease remission have also been reported [9]. Moreover, most in vitro experiments that demonstrated pro-inflammatory effects of ANCA are predicated on priming of neutrophils, monocytes, or endothelial cells with TNF-α [10].

TNF-α also plays a role in the immune-surveillance against cancer. In fact, this cytokine was originally discovered as a factor responsible for the induction of hemorrhagic necrosis of sarcomas and other cancers transplanted to the skin [11]. A variety of anti-tumor mechanisms have been documented including cytostatic/cytolytic effects on transformed cell, the induction of apoptosis in neoplastic cells, or anti-angiogenic effects on tumor-associated endothelium [12, 13].

Given the described anti-tumor growth properties of TNF-α, the potential of TNF-α blockers to promote malignancies has been a concern ever since they were originally developed as therapeutic agents. Investigators and the medical community have paid close attention to the development of de novo neoplasia and to the progression of pre-malignant to established malignant lesions in patients treated with these drugs.

This article reviews the association between therapeutic inhibition of TNF-α and the development of solid malignancies in AAV with a focus on etanercept.

Risk of Malignancy Associated With TNF-α Blocker Use in Non-vasculitic Autoimmune Diseases

Currently, five TNF-α blockers (etanercept, infliximab, adalimumab, certolizumab and golimumab) are available for treatment of rheumatoid arthritis (RA), ankylosing spondylitis, juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), plaque psoriasis, and Crohn's disease. In these diseases, the relationship between TNF-α blocker use and malignancy has been studied. However, these investigations have been complicated by the increased incidence of malignancies observed in some of these underlying conditions themselves [14, 15]. Among potential mechanisms favoring the development of malignancies in these diseases are a reduction in immune-surveillance resulting from immunosuppressive therapy, the immune dysregulation associated with the underlying disease, and possible channeling bias, i.e. patients with more severe disease and greater disease-associated risk of malignancy being more frequently treated with biological agents [16, 17].

Taking these difficulties into consideration, an association with TNF-α blocker use has been suggested for hematological malignancies, especially lymphoma. In 2003, the Food and Drug Administration (FDA) reviewed all trials using the available TNF-α blockers and found an estimated relative risk for lymphoma ranging from 2.3 to 6.4 [18]. In 2006, Moreland and colleagues studied the incidence of cancer in 714 RA patients exposed to etanercept from 7 different clinical trials, and for 388 patients who continued in an open label extension study followed for 7 years. They found an increased risk of lymphoma, calculating a standardized incidence ratio (SIR) of 3.2–3.7 in the patients compared to the estimated expected rate in the global RA population [19]. More recently, the FDA alerted about an increased risk of lymphoma in children and adolescents with JIA and Crohn's disease treated with TNF-α blockers, an association not previously described with the standard treatment used in these conditions [20].

A case series of 36 patients with RA or Crohn's disease who developed lymphoma related to the use of TNF-α blockers was reported to the FDA and published in 2002 [21]. Interestingly, spontaneous regression of lymphoma was observed after discontinuation of the TNF-α blocker in 2 of these 36 patients (1 patient with type b1 thymoma who received etanercept and one patient with diffuse large cell non-Hodgkin's lymphoma who had received infliximab) [21]; this evidence was interpreted as suggesting causality.

In contrast, the association between TNF-α blocker use and non-hematologic (solid) malignancies in autoimmune diseases remains unclear. Initial reports had suggested an increased risk in RA [22], but this was not confirmed in larger studies [23].

A meta-analysis of nine large randomized, placebo-controlled trials conducted in RA with infliximab and adalimumab found a pooled odds ratio for malignancy of 3.3 (95 % CI 1.2–9.1) and detected a relationship between TNF-α blocker dose and malignancy risk [24]. This study included all types of malignancies with a predominance of solid cancers.

As etanercept was the first TNF-α blocker developed at the end of the 1990s, the risk of cancer induction by this agent has been studied extensively in chronic arthropathies including RA, PsA, and spondyloarthropathies. As for other TNF-α blockers, an association with hematologic malignancies has been described, but the estimation of risk is made difficult by the previously mentioned increased risk of malignancies, and particularly lymphoma, inherent to these autoimmune diseases themselves [15]. For solid malignancies, no evidence of association has been reported. Moreland and coworkers found that the solid malignancy rate observed in RA patients treated with etanercept was within the expected range for the general population [19]. Klareskog and colleagues studied the incidence of cancer in 549

patients with RA who received etanercept as part of a 5-year open label extension of two double-blind, placebo-controlled trials. The observed malignancy rate in that study was lower than expected for the general population [25].

Data from the pharmaceutical company exist for 10,953 adult and 696 pediatric patients across 45 etanercept clinical studies for all indications. In that report, there was no difference in exposure-adjusted rates of solid malignancies, excluding non-melanoma skin cancer, between etanercept and control arms of clinical studies. Analysis of the malignancy rate in combined controlled and uncontrolled portions of studies has demonstrated that types and rates are similar to what is expected in the general U.S. population based on the SEER database, suggesting no increased malignancy rate over time [26].

Finally, a meta-analysis of nine etanercept trials conducted in RA found no statistical difference between groups, with a hazard radio of 1.84 (95 % CI 0.79–4.28) for the etanercept group compared to the control group. This study focused solely on solid malignancies [27••].

Taken together, the evidence confirms that the use of TNF- α blockers for the described chronic non-vasculitic autoimmune diseases is associated with an increased risk of lymphoma. However, for solid malignancies, the pooled evidence is not consistent for the different TNF-α blockers: for etanercept, there seems to be no significantly increased risk for solid malignancies, whereas when infliximab and adalimumab are analyzed together, an increased risk becomes apparent.

Risk of Malignancy Associated With TNF-α Blocker Use in ANCA-Associated Vasculitis

Risk of Malignancy in Patients With AAV

An inherent increased risk of both solid and hematologic malignancies in AAV per se has been suggested by several, but not all, studies, with estimates of global risk ranging from 1.6- to 18-fold compared to the general population [28–31], or in relation to patients with other rheumatologic conditions [31, 32]. However, whether this risk is inherent to the disease or related to its treatment is difficult to determine for several reasons. First, the prevalence of AAV is low [33]. Second, patient survival without treatment is very short [34]. Third, treatment with the alkylating agent cyclophosphamide, which has well-documented carcinogenic properties, has been the standard of care for the majority of patients until very recently [35].

The differences in estimated risk of cancer seem to be related, in part, to study designs. In studies comparing incidence of solid malignancies in AAV with healthy populations as reference and using risk estimates based on incidence, Westman and coworkers reported a standardized morbidity ratio, SMR, of 1.6 (95 % CI 0.9–2.7) [29], and Knight and colleagues, a standardized incidence ratio, SIR, of 2.0 ([95 % CI 1.7–2.5] [30] (Fig. 1). However, in studies using estimates based on frequency rather than incidence, higher figures are found, such as in the articles by Tatsis and coworkers, who reported an odds ratio (OR) of 18 (95 % CI 2.3–140) [32], or by Pankhurst and colleagues, who found a relative risk (RR) for solid malignancies of 6.0 (95 % CI 3.7–9.7) [31].

Various mechanisms have been proposed, including fortuitous association, paraneoplastic etiology, and immunosuppressive or carcinogenic effects of the prescribed drugs [36]. Whether the pathophysiology of vasculitis per se confers a malignancy risk remains unclear and doubtful. For giant cell arteritis, which is not customarily treated with cyclophosphamide, no increased malignancy risk has been found [37].

Risk of Solid Malignancy Associated With Etanercept Use in GPA

The safety of etanercept therapy in GPA was evaluated in a 6- month open-label pilot trial [38]. In this study, etanercept 25 mg subcutaneously twice weekly was combined with standard treatment. A total of 20 patients were treated for 6 months. No malignancies were observed (Table 1), and the safety profile was deemed acceptable [38]. Based on that preliminary evidence, the "Wegener`s Granulomatosis Etanercept Trial" (WGET) was designed as a randomized, placebo-controlled, double-masked trial in which etanercept or placebo were given in addition to standard therapy for remission induction and maintenance in GPA [39]. In this

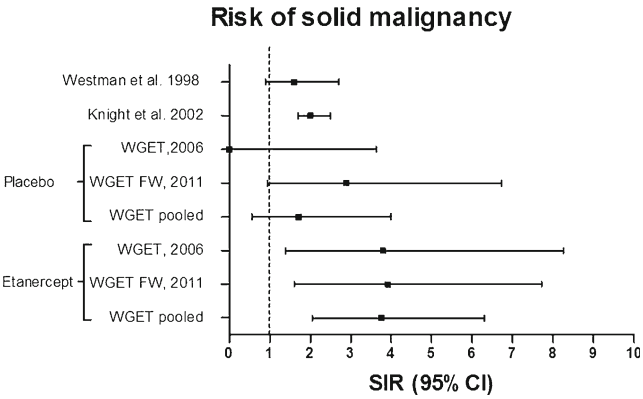

Fig. 1 Risk of solid malignancy associated with etanercept use in GPA. The risk of solid malignancies in GPA patients is presented. Only articles with risk based on SIR (standardized incidence ratio) are included. Standard therapy used in studies of Westman, Knight or placebo group in WGET and WGET FW is compared to etanercept. (Data from Westman et al. [29], Knight et al. [30], WGET [6], and WGET FW [40••]; WGET pooled data correspond to pooled data from references [6] and [40••])

Table 1 Reported solid malignancies in studies of etanercept for AAV

Type of TNF blocker	Year of study	No. of cases AAV/total	Diagnosis (*n*)	Disease duration (months)	CYC use	Cancer type	Follow-up (months)	Control group	Ref.
Etanercept	2001	20/20	GPA (20)	63	12	0	6	No	[38]
	2006	180/180, 89 etanercept 91 placebo	GPA (180)	48	70	Colon adenocarcinoma (2) Cholangiocarcinoma (1) Renal-cell carcinoma (1) Breast carcinoma (1) Liposarcoma (1)	27	Yes	[6]
	2011	153/153 77 etanercept 76 placebo	GPA (153)	81	69	Melanoma (2) Prostate cancer (2) Tonsillar carcinoma (1) Squamous cell metastatic (1)[a] Cholangiocarcinoma (1) Small bowel (1)	43	Yes	[40••]

AAV ANCA-associated vasculitis; GPA granulomatosis with polyangiitis (ex Wegener´s granulomatosis); *MPA* microscopic polyangiitis; *EGPA* eosinophilic granulomatosis with polyangiitis (ex Churg-Strauss syndrome), *CYC* cyclophosphamide; *NA* no data available

[a] A recidivant bladder carcinoma

study, 6 solid malignancies were observed after a median follow-up of 27 months. All these occurred in the group of patients receiving etanercept, (etanercept group: $n=6$, placebo group: $n=0$ group; $p=0.01$). When compared to the incidence of malignancies in a gender- and age-matched normal population in the National Institutes of Health Surveillance Epidemiology and End Results (SEER) database, 1.9 solid malignancies would have been expected, resulting in an observed SIR of 3.8 (95 % CI 1.39–8.26) [6, 40••]. Concordantly, the cancer SIR of the placebo group in this trial cohort was 0 (95 % CI 0–3.63) [6, 40••] (Fig. 1).

The initial results observed in the WGET cohort prompted a long-term follow-up study designed to identify and characterize new cases of solid malignancies that occurred during 5 years following completion of study treatment, and to determine whether the increased risk of malignancies observed in the etanercept group was sustained over time [40••]. In this study, 153 patients (85 % of the original cohort) were evaluated with a median follow-up of 43 months post-trial; 50 % of these patients received etanercept during the study [40••]. In this post-trial follow-up, new solid malignancies were diagnosed in both treatment arms. The higher risk of solid malignancies among patients treated with etanercept compared to those who received placebo observed during the original trial period did not persist after termination of etanercept therapy. Thirteen new solid malignancies were detected (etanercept group: $n=8$; placebo group: $n=5$; $p=0.39$). However, the risk of solid malignancies in the etanercept group remained increased compared to the general population, with a SIR of 3.92 (95 % CI 1.69–7.72), but was not different ($p=0.6$) from that of the placebo group, with a SIR of 2.89 (95 % CI 0.94–6.73] (Fig. 1).

In the analysis of the combined follow-up (trial and post-trial periods), the total number of solid malignancies in the patients originally assigned to etanercept was 14, with a SIR related to the general population of 3.76 (95 % CI 2.05–6.31). As indicated previously, the comparison of this estimate with other studies must consider the study design. Thus, the SIR was higher than the reported estimate for patients with AAV without exposure to TNF-α blockers evaluated in comparable studies (normal population as a reference and with estimates based incidence) [29, 30], but lower than those reported in studies with reference populations that included patients with autoimmune diseases and estimates that were based on prevalence [31, 32].

Based on these data, one could hypothesize that the use of etanercept enhances an inherent increased background risk for malignancies in patients with GPA treated with conventional immunosuppressive therapy. This underlying risk seems to become relatively more important as the distance from the etanercept exposure increases.

Concomitant Risk Factors for Solid Malignancy in the WGET Cohort

The comparison of the solid malignancy risk associated with TNF-α blockers in vasculitis to that of other autoimmune diseases would be incomplete without the consideration of other potential confounding risk factors. In the WGET cohort, univariate analysis identified the following factors in association with the development of solid malignancies: a history of cancer prior to enrollment and the duration of GPA.

Four patients in the WGET cohort, who developed a solid malignancy, had a history of previous remote cancer, despite the 5-year exclusion criterion for neoplasia. All these cancers presumably had been cured long before trial enrollment. In two cases, the investigators thought the malignancies represented a recurrence of the preceding cancers: a metastatic liposarcoma occurring during the trial and a metastatic urothelial cell carcinoma diagnosed during the follow-up after trial termination in a patient with previously treated bladder cancer. The recurrence of a previous malignancy or the progression of pre-cancerous lesions has been described for mycosis fungoides (cutaneous T cell lymphomas) in patients treated with TNF-blockers [41].

The duration of GPA was associated with the occurrence of solid malignancies in the WGET cohort. A relationship between the duration of the disease and risk of malignancy has also been observed in other autoimmune diseases including RA; yet this relationship remains controversial and is difficult to separate from activity or severity of the disease itself [14]. Possible confounding factors related to longer disease duration, such as older age, the greater number of different immunosuppressant drugs used, or higher cumulative CYC exposure in the group of patients with solid malignancies, did not reach statistical significance in the WGET analysis.

Yet, all the WGET trial subjects who developed solid cancers, either during the original study period or during follow-up, had been exposed to cyclophosphamide. Cyclophosphamide exposure is one important difference between GPA and other autoimmune diseases such as RA, JRA, PsA, or psoriasis that are usually not treated with cyclophosphamide, and in which no risk of solid malignancies has been documented to date in association with etanercept use. Cyclophosphamide exposure is strongly associated with the development of malignancies in GPA, especially bladder carcinoma [42].

Risk of Solid Malignancy With Infliximab and Other TNF-α Blockers Use in AAV

Data about malignancy risk associated with other TNF-α blockers in AAV is scarce. This has several reasons. First, published studies conducted with TNF-α blockers other than etanercept in AAV consisted of small cohorts, and follow-up has been short [5, 40••, 43–50, 51••, 52, 53]. Second, as the WGET had provided no evidence of efficacy of etanercept for GPA, but rather raised malignancy concerns, and rituximab emerged as a more promising effective agent for the control of refractory disease, enthusiasm for TNF- α blocker therapy in AAV waned quickly.

As there are differences in mechanisms by which various TNF-α blockers exert their effects, which are thought to explain observed differences in therapeutic responses, some authors have proposed that there may also be differences in malignancy promoting potential between the various agents [27••]. At the molecular level, it is well known that infliximab differs from etanercept in structure and affinity to TNF-α [54], and, more importantly, it does not inhibit the anti-tumor molecule lymphotoxin α, whereas etanercept does [27••].

To date, only two cases reported of solid malignancies related to infliximab use have been reported in AAV (Table 2). The first case was a patient who developed a carcinoid of the bronchus in at 16 months follow-up of 6 GPA patients treated with infliximab in 2002, reported by Lamprecht and coworkers [44]. The second case was detected in the follow-up of the WGET cohort. Seventeen of the original WGET participants had received infliximab as part of their vasculitis therapy after trial completion (original arm assignment: etanercept $n=8$; placebo: $n=9$; unpublished data). Of these, one patient who was assigned to the placebo arm during the trial developed a renal cell carcinoma 14 months after completion

Table 2 Reported solid malignancies in studies of infliximab or adalimumab for AAV

Type of TNF blocker	Year of study	No. of cases AAV/total	Diagnosis (*n*)	Disease duration (months)	CYC use	Cancer type (*n*)	Follow-up (months)	Control group	Ref.
Infliximab	2002	7/10	GPA (7)	109		0	6	No	[46]
	2002	3/14	GPA (3)	NA		0	NA	No	[47]
	2002	6/6	GPA (3), MPA (3)	42	NA	0	3	No	[45]
	2002	6/6	GPA (6)	72	6	0	12	No	[43]
	2002	6/6	GPA (6)			Carcinoid of the bronchus (1)	16–26	No	[44][a]
	2004	32	GPA (19), MPA (13)	17	22	[Lymphoma (1)]	18	No	[5]
	2004	1	GPA	30	1	0	4	No	[48]
	2005	1	GPA	5	1	0	5	No	[49]
	2008	1	GPA	8	1	0	25	No	[50]
	2010	1	GPA	7	1	0	24	No	[52]
	2010	1/32	GPA	NA	1	0	NA	No	[53]
Adalimumab	2011	17[b]/153	GPA (17)	ND	ND	Renal cell carcinoma (1)	14	No	[40••]
	2010	14/14	GPA (9),MPA (5)	"new"	14	0	20	No	[7•]

AAV ANCA-associated vasculitis; *GPA* granulomatosis with polyangiitis (ex Wegener´s granulomatosis); *MPA* microscopic polyangiitis; *EGPA* eosinophilic granulomatosis with polyangiitis (ex Churg-Strauss syndrome), *CYC* cyclophosphamide; *NA* no data available

[a] This report (ref 44) corresponds to the follow-up of the previous study (ref 43)

[b] 17 cases received Infliximab (WGET cohort follow-up)

of protocolized study therapy and after infliximab therapy [40••]. One lymphoma was reported in a study of 32 patients with AAV after 18 months of follow-up (Table 2).

Because of limited or absent evidence related to the use of adalimumab, golimumab, or certolizumab in AAV, the malignancy risk associated with these agents cannot be assessed [7•, 55•]. However, as newer TNF-α blockers are more extensively used in chronic inflammatory diseases in general, and potentially in AAV in the clinical practice, the individual toxicity profiles and malignancy risks associated with individual agents should be scrutinized closely [20]. In view of the studies evaluating TNF-α blockers other than etanercept in AAV or other systemic vasculitides [7•, 51••], continued long-term monitoring of the association between TNF-α blockers and malignancies in AAV is indicated.

Type of Malignancies and Prognosis

The malignancies described in patients with AAV treated with etanercept or infliximab use include a variety of histopathological types and organ systems of origin. However, a predominance of involvement of the digestive system was observed, with 5 of the 16 solid malignancies reported with etanercept or infliximab (colon adenocarcinoma: $n=2$; cholangiocarcinoma: $n=2$; small bowel: $n=1$). This was followed by 3 cases originating in the urinary system (renal-cell carcinoma: $n=2$; bladder carcinoma; $n=1$). Interestingly, only one of the cases presented with a bladder carcinoma (presented as metastatic squamous cell carcinoma), a neoplasia strongly associated with cumulative cyclophosphamide use (Tables 1 and 2).

Conclusions

An increased risk of solid malignancies related to TNF-α blockers in AAV has been observed with etanercept during its use in the WGET trial. However, the long-term follow-up of that cohort showed that the increased risk conferred by the addition of etanercept to cyclophosphamide during the trial does not persist for years following discontinuation of etanercept. Few data exist for other TNF-α blockers as these agents are not widely used in AAV. Disease duration, which is a factor that cannot be clearly separated from cyclophosphamide exposure, as well as a previous history of malignancy of any type, are potential concomitant risk factors for solid malignancy.

Based on these data, etanercept should be avoided in patients with AAV, particularly in cases with long-standing relapsing disease history, cyclophosphamide exposure, and previous history of malignancy. There are no data about other TNF-α blockers in AAV that would allow any kind of risk assessment, but there is no compelling reason for use of TNF-α blockers in AAV either.

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