Biol Blood Marrow Transplant 20 (2014) 858–864

Randomized, Double-Blind, Placebo-Controlled Trial of Soluble Tumor Necrosis Factor Receptor: Enbrel (Etanercept) for the Treatment of Idiopathic Pneumonia Syndrome after Allogeneic Stem Cell Transplantation: Blood and Marrow Transplant Clinical Trials Network Protocol

Gregory A. Yanik [1,*], Mary M. Horowitz [2], Daniel J. Weisdorf [3], Brent R. Logan [2], Vincent T. Ho [4], Robert J. Soiffer [4], Shelly L. Carter [5], Juan Wu [5], John R. Wingard [6], Nancy L. Difronzo [7], James L. Ferrara [1], Sergio Giralt [8], David K. Madtes [9], Rebecca Drexler [10,11], Eric S. White [12], Kenneth R. Cooke [13]

[1] *Department of Pediatrics and Internal Medicine, Blood and Marrow Transplant Program, University of Michigan Medical Center, Ann Arbor, Michigan*
[2] *Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, Wisconsin*
[3] *Department of Internal Medicine, University of Minnesota Blood and Marrow Transplantation Program, Minneapolis, Minnesota*
[4] *Department of Hematologic Malignancies, Dana Farber Cancer Institute, Boston, Massachusetts*
[5] *The EMMES Corporation, Rockville, Maryland*
[6] *Department of Medicine, University of Florida, Gainesville, Florida*
[7] *Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland*
[8] *Department of Stem Cell Transplantation, Memorial Sloan Kettering Cancer Center, New York, New York*
[9] *Clinical Research Division, Fred Hutchinson Cancer Research Center and Division of Pulmonary and Critical Care Medicine, University of Washington, Seattle, Washington*
[10] *National Marrow Donor Program, Minneapolis, Minnesota*
[11] *Center for International Blood and Marrow Transplant Research, Minneapolis, Minnesota*
[12] *Department of Internal Medicine, Pulmonary and Critical Care Medicine, University of Michigan Medical Center, Ann Arbor, Michigan*
[13] *Department of Oncology, Sidney Kimmel Cancer Center, Johns Hopkins University, School of Medicine, Baltimore, Maryland*

Article history:
Received 2 January 2014
Accepted 28 February 2014

Key Words:
Bone marrow transplantation
IPS
TNF
Pneumonia
Pulmonary

A B S T R A C T

Idiopathic pneumonia syndrome (IPS) is a diffuse, noninfectious lung injury that occurs acutely after allogeneic hematopoietic cell transplantation (HCT). IPS-related mortality has been historically high (>50%) despite treatment with systemic corticosteroids and supportive care measures. We have now examined the role of tumor necrosis factor inhibition in a randomized, double-blind, placebo-controlled trial of corticosteroids with etanercept or placebo. Thirty-four subjects (≥18 years) with IPS after HCT were randomized to receive methylprednisolone (2 mg/kg/day) plus etanercept (0.4 mg/kg twice weekly × 4 weeks; n = 16) or placebo (n = 18). No active infections and a pathogen-negative bronchoscopy were required at study entry. Response (alive, with complete discontinuation of supplemental oxygen support) and overall survival were examined. This study, originally planned to accrue 120 patients, was terminated prematurely due to slow accrual. In the limited number of patients examined, there were no differences in response rates at day 28 of study. Ten of 16 patients (62.5% [95% confidence interval {CI}, 35.4% to 84.8%]) receiving etanercept and 12 of 18 patients (66.7% [95% CI, 41.0% to 86.7%]) receiving placebo met the day 28 response definition ($P = 1.00$). The median survival was 170 days (95% CI, 11 to 362) with etanercept versus 64 days (95% CI, 26 to 209) with placebo ($P = .51$). Among responders, the median time to discontinuation of supplemental oxygen was 9 days (etanercept) versus 7 days (placebo). Therapy was well tolerated, with 1 toxicity-related death from infectious pneumonia in the placebo arm. The treatment of IPS with corticosteroids in adult HCT recipients was associated with high early response rates (>60%) compared with historical reports, with poor overall survival. The addition of etanercept did not lead to further increases in response, although the sample size of this truncated trial preclude a definitive conclusion.

INTRODUCTION

Pulmonary complications are common after hematopoietic stem cell transplantation (HCT), occurring in nearly

Financial disclosure: See Acknowledgments on page 863.

* Correspondence and reprint requests: Gregory A. Yanik, MD, Blood and Marrow Transplant Program, 5310 Cancer Center, University of Michigan Medical Center, 1500 E. Medical Center Drive, Ann Arbor, MI 48109.
E-mail address: gyanik@umich.edu (G.A. Yanik).

1083-8791/$ – see front matter © 2014 Published by Elsevier Inc. on behalf of American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2014.02.026

50% of transplant recipients and accounting for 50% of all transplant-related deaths [1-4]. Within this context, idiopathic pneumonia syndrome (IPS) is an acute-onset, noninfectious form of lung injury that develops early post-HCT and is associated with high morbidity and mortality [5-11]. In 1993, a National Institutes of Health consensus panel proposed a broad working definition of IPS to include widespread alveolar injury in the absence of active lower respiratory tract infection after HCT [5]. The definition was updated in 2011 and further categorized the disease entities falling under the definition of IPS by the primary anatomic site of cellular damage, the interstitial tissue, vascular endothelium, or airway epithelium [11]. The diagnosis of IPS is made by the presence of multilobar infiltrates on chest radiograph and clinical signs and symptoms of respiratory distress (hypoxemia, dyspnea, rales) without infectious etiology, as determined by a negative bronchoalveolar lavage (BAL) or surgical lung biopsy. Infectious pneumonia, cardiogenic shock, acute renal insufficiency and iatrogenic fluid overload must all be excluded to ensure the diagnosis of IPS.

The incidence of IPS ranges from 2% to 10%, depending on patient age, degree of donor–recipient HLA match, graft type, and conditioning intensity, with a median onset 14 to 42 days post-HCT. Historically, survival has been poor, with mortality rates of 50% to 75% within 28 days of diagnosis [7-11]. The intensity of the conditioning regimen impacts the development of IPS, with a much lower incidence reported after administration of a subablative conditioning regimen [9,11]. The frequent association between IPS and acute graft-versus-host disease (GVHD) also suggests an immunologic mechanism for the syndrome, one driven by alloreactive donor T cells, pulmonary macrophages, and mediated by inflammatory cytokine production [11]. A role for tumor necrosis factor (TNF)-α in the pathogenesis of the disorder was initially suggested 15 years ago, with markedly elevated levels of TNF-α and its soluble receptors observed within the BAL fluid of affected animals and patients [1,12-14]. Preclinical models have shown that TNF-α contributes to the pathogenesis of IPS, directly by causing endothelial cell injury and apoptosis and indirectly by regulating inflammatory chemokine expression in the lung and subsequent donor leukocyte infiltration during the early stages of disease. In addition, TNF neutralization reduces the severity of IPS in murine models, further supporting a casual role for TNF-α in the pathogenesis of the disorder [11,15].

Treatment options for IPS have historically combined supportive care (supplemental oxygen, diuretics) with high-dose systemic corticosteroids. More recently, the use of TNF inhibitors was proposed, with potential benefits noted in single or limited institution studies [7,8,14]. In particular, clinical trials combining a soluble TNF binding agent (etanercept [Enbrel], Amgen Inc., Thousand Oaks, CA) with systemic corticosteroids for the management of IPS reported high response rates and improved overall survival [7,8,14]. Etanercept is a soluble dimeric binding protein consisting of 2 soluble p75 TNF receptors fused to the Fc portion of a type I immunoglobulin molecule. The agent is U.S. Food and Drug Administration approved in the management of juvenile, rheumatoid, and psoriatic arthritis; plaque psoriasis; and ankylosing spondylitis, conditions in which TNF-α is implicated in the pathogenesis. In a follow-up to early phase clinical studies, we conducted a multicenter, randomized, double-blinded, phase III trial for the treatment of adults with IPS through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) and report the results herein.

Table 1
Diagnostic Criteria for IPS

1. Evidence of widespread alveolar injury
   a. Bilateral, multilobar, or diffuse infiltrates on chest x-ray or computed tomography.
   b. $Spo_2 \leq 93\%$ on room air, or supplemental O_2 required to maintain $Spo_2 > 93\%$.
2. Absence of active lower respiratory tract infection, based on BAL assays
   a. Gram stain, fungal stain, acid fast bacilli stain
   b. Bacterial, fungal and mycobacterial cultures
   c. Viral cultures for CMV, respiratory syncytial virus, parainfluenza, adenovirus, influenza A and B
   d. *Pneumocystis jiroveci* assay (direct fluorescent antibody or cytology)

METHODS

Eligibility

Eligible patients were at least 18 years old, having received an allogeneic bone marrow, cord blood, or peripheral blood stem cell transplant within 180 days of enrollment. There were no restrictions to study entry based on underlying disease, donor source, degree of HLA match, or conditioning regimen. Eligible patients were required to meet National Institutes of Health Consensus criteria for IPS before study entry based on clinical findings, radiographic features, and BAL fluid analysis (Table 1) [5,11]. Patients with active infections, cytomegalovirus (CMV) viremia or CMV disease, a prior history of active tuberculosis, or chronic active hepatitis B or C infections were excluded from study entry. There was no restriction to entry based on hematologic, renal, or hepatic dysfunction. Patients with pulmonary edema secondary to iatrogenic fluid overload or cardiac dysfunction, as evidenced by echocardiogram or clinical findings, were ineligible. Patients were excluded if they had received >2 mg/kg/day methylprednisolone equivalent for >48 hours within 7 days of study entry or required mechanical ventilation for >168 continuous hours before study entry. Noninfectious, diffuse alveolar hemorrhage is considered a subset of IPS, and affected patients were eligible for study inclusion. The trial was registered at Clinical Trials.gov as NCT00421174.

Study Design

All patients were required to undergo bronchoscopy with BAL at study entry, with required observations specified in Table 1. Additional BAL fluid testing, including PCR assays for other bacterial, fungal, or viral or atypical pathogens, and *Pneumocystis jiroveci* pneumonia were allowed per physician discretion. The presence of mixed oral flora, "rare" *Candida*, or *Penicillium* on the BAL did not exclude a patient from study, because such findings typically reflect oral pharyngeal contamination. Transbronchial and surgical lung biopsies were not required but were allowed per physician discretion. If a BAL procedure had been obtained for any other purpose within 72 hours of study enrollment, the procedure did not need to be repeated, provided that no infectious pathogens were identified in that BAL fluid.

After enrollment, patients were subsequently eligible for study randomization and initiation of study therapy based on results of microbial stains (Gram stain and fungal stains), completed on BAL fluid, even while the remaining BAL studies were still pending. Patients whose initial BAL microbial stains identified a potential pathogen were ineligible for study randomization. If at any point after initiation of study therapy BAL fluid analysis (cultures, stains, PCR assays) noted a likely pathogen, study therapy was discontinued at that point and not reinstituted. PCR based assays were not required, but if completed and positive, the patient was removed from study therapy. A response assessment was made at the time of therapy discontinuation and at subsequent study endpoints, and the patient was not replaced on study.

Patients were randomized to receive either etanercept plus corticosteroids (arm A) or placebo plus corticosteroids (arm B). The study therapy was subsequently initiated as long as BAL fluid microbial studies remained negative. The start of study therapy (etanercept or placebo) was defined as day 0. Corticosteroids were begun at 2 mg/kg/day methylprednisolone (or corticosteroid equivalent), with dosing based on actual body weight. Patients already receiving corticosteroids at study entry remained on corticosteroids, with their dosing adjusted to 2 mg/kg/day methylprednisolone equivalent on the day of enrollment. Intravenous corticosteroids were required for the first 3 days of study therapy, with oral dosing subsequently allowed if the patient was able to tolerate oral intake. No corticosteroid taper was allowed during the first 7 days of study therapy, with subsequent taper per physician discretion. A recommended steroid taper schedule through

day 56 was provided but not required. Patients whose oxygen requirement improved by day 7 but subsequently worsened after initiation of the corticosteroid taper were allowed to increase corticosteroid dosing to prior dosing levels.

All patients received a total of 8 etanercept or placebo doses over a 24-day period. Etanercept was administered at .4 mg/kg/dose (maximum dose 25 mg), with the initial etanercept dose given as a 30-minute i.v. infusion in 100 mL of .9 normal saline to expedite the attainment of maximal plasma levels. The initial placebo dose was administered in a similar route and dilution. Subsequent etanercept (or placebo) doses were given subcutaneously, twice weekly, for a total of 7 s.c. doses. All etanercept and placebo doses were required to be at least 72 to 96 hours apart from the prior dose. No premedication was administered. No dosage adjustments were required based on renal or hepatic function. Both subjects and investigators were blinded to study drug therapy, with no "unblinding" or crossover between study arms allowed. Other immune-suppressive agents were continued during study therapy, without dose adjustment, unless clinically indicated. Patients received antimicrobial prophylaxis according to BMT CTN guidelines or local institutional practice.

If patients developed signs of sepsis syndrome, invasive fungal infections, persistent bacteremia for >72 hours, or disseminated viral infections, study therapy was discontinued and patients were removed from the trial and not replaced on study. If a patient developed bacteremia, study therapy was held until bacteremia resolved. If more than 2 doses of study drug were missed because of persistent bacteremia despite antibiotic therapy for that organism, study therapy was discontinued and the patient was removed from the trial and not replaced. Similarly, if a patient developed CMV reactivation (by PCR or antigenemia assay), study therapy was held until CMV titers fell below the institutional cut-off for concern. If 2 or more doses of study drug were missed because of persistently elevated CMV titers, despite directed antiviral therapy, study drug was discontinued and the patient was removed from the trial and not replaced. In each scenario, patients were still followed for outcome and considered nonresponders provided they had not achieved the primary response endpoint by that time point. Patients with asymptomatic viruria were allowed to continue on therapy.

Statistical Analysis

The primary study endpoint was response to study therapy, with response defined as (1) survival to day 28 of study plus (2) discontinuation of all supplemental oxygen support for >72 consecutive hours by day 28 of study. The time to response was defined as the first of 3 consecutive days in which all supplemental oxygen support had been discontinued. Patients who subsequently required reinstitution of supplemental oxygen to achieve a $Spo_2 > 93\%$ were still deemed as responders, provided they had met the response criteria above. Patients who failed to completely withdraw from supplemental oxygen support or those who died from IPS or non-IPS–related causes by day 28 of therapy were defined as nonresponders. Patients who came off study therapy per physician or patient discretion were deemed nonresponders if they had not met the defined response criteria by the time of study withdrawal. Survival duration was defined as the interval from randomization to the date of death or last follow-up. Secondary study endpoints included response to study therapy by day 56, overall mortality, and time to discontinuation of supplemental oxygen support, measured in the number of days from study entry.

The study was designed as a phase III, double-blind, randomized, placebo-controlled, multicenter trial. Randomization between arms A and B was performed in a 1:1 ratio, using random block sizes for the 2 arms. A sample size of 60 patients per group was initially targeted, which would provide 80% power to detect an increase in the response rate from 30% to 55%, after accounting for interim analyses for efficacy and futility. Because of slow accrual, the target sample size was amended to 30 patients per arm to provide 80% power to detect an increase in the response rate from 30% to 69%, matching the effect size seen in the historical comparison [7]. The study was closed early by the Data and Safety Monitoring Board because of poor accrual, with 16 patients randomized to receive etanercept and 18 randomized to receive placebo. A post-hoc power analysis indicated that this final sample size had 80% power to detect an increase in the response rate from 30% to 81%.

The primary intent-to-treat analysis of response to study therapy by day 28 post-randomization was conducted using Fisher's exact test due to the small sample sizes in the final dataset. Exact (Clopper-Pearson) confidence intervals (CIs) for the response rate were also obtained. Analyses of secondary endpoints of response at day 56 were done in a similar fashion. Survival was summarized using the Kaplan-Meier estimate. Time to discontinuation of oxygen, acute GVHD grades II to IV or III to IV, chronic GVHD, and relapse were described using the cumulative incidence estimate, with death as a competing risk. CIs for cumulative incidence or survival at specified time points relied on exact Clopper-Pearson intervals, because the estimates reduce to simple proportions without censoring present (1 year or earlier). Survival distributions were compared using the log-rank test, whereas cumulative incidence curves were compared using Gray's test [16]. Point-wise comparisons of survival or cumulative incidence used Fisher's exact test.

The protocol was approved by the National Heart, Lung, and Blood Institute, local institutional review boards, and required BMT CTN subcommittees. A Data and Safety Monitoring Board appointed by the National Heart, Lung, and Blood Institute reviewed toxicity data and subsequent analyses. Written informed consent was obtained from all patients (or legal guardians) before study entry. A response assessment committee, blinded to treatment assignment, reviewed all study data and determined the final assessment of eligibility, study deviations from planned therapy, and response. All evaluations were reviewed by 3 independent reviewers.

RESULTS

Thirty-seven subjects were enrolled between September 2007 and August 2011 with 34 subjects assessable for response assessment. In 2 subjects, BAL fluid collected at study entry was positive for infection, making them ineligible for randomization. Neither individual received study therapy. One patient withdrew informed consent at the time of randomization. For the remaining 34 patients, 16 were randomized to receive etanercept and 18 to placebo. Treatment arms were balanced for baseline characteristics, except for a higher frequency of transplantation for acute myelogenous leukemia on the placebo arm (50% versus 6%, $P = .02$) (Table 2). Approximately 40% of patients in both arms received a nonmyeloablative conditioning regimen. Three patients (19%) on the etanercept arm and six (33%) on the placebo arm required mechanical ventilator support at study entry ($P = .45$). There was no difference in the number of days from transplant to study entry; the median time of study entry was 17 days post-HCT in the etanercept arm versus 19 days post-transplant in the placebo arm ($P = .61$). The median Fio_2 at study entry was 40% (range, 29% to 95%), with no difference in the level of baseline supplemental oxygen support between the 2 study arms. Only 8 of 16 patients (50%) on the etanercept arm completed all 8 etanercept doses, with 6 patients (37%) receiving $\leq$ 2 doses of etanercept. Ten of 18 patients (56%) on the placebo arm received all 8 placebo doses, with only 1 of 18 patients (6%) receiving $\leq$ 2 placebo doses before study discontinuation.

Response and Survival

There was no difference in response between therapy arms, at day 28 and day 56 (Table 3). Ten of 16 patients (62.5% [95% CI, 35.4% to 84.8]) treated on the etanercept arm and 12 of 18 patients (66.7% [95% CI, 41.0% to 86.7%]) treated on the placebo arm met the day 28 response definition ($P = 1.00$). Nine of 16 patients (56.3% [95% CI, 29.9% to 80.3%]) treated on the etanercept arm and 9 of 18 patients (50.0% [95% CI, 26.0% to 74.0%]) met the day 56 response definition ($P = .74$). There were no differences in the cumulative incidence of discontinuation of supplemental oxygen between the etanercept and placebo arms ($P = .69$), with a median time to supplemental oxygen discontinuation of 9 days (etanercept) versus 7 days (placebo) among responders (Figure 1). There was no difference in response between the 2 arms based on baseline Fio_2. Eight of 11 patients (73%) on the etanercept arm and 10 of 11 patients (91%) on the placebo arm responded to study therapy when the baseline Fio_2 was $\leq$40% ($P = .59$). The intensity of the transplant conditioning regimen did not affect response, with responses seen in 10 of 14 patients (71%) who developed IPS after a nonmyeloablative regimen versus 12 of 20 (60%) after a myeloablative regimen ($P = .72$). There was no difference in response by therapy arm (etanercept versus placebo) in patients receiving nonmyeloablative transplants (71% versus 71%, $P = 1.00$). Nine of 10 patients (90%)

Table 2
Patient Demographics at Study Entry

	Etanercept	Placebo	Total	*P*
Total enrolled	18	19	37	
Total eligible	16	18	34	
Age, yr				.89
Median	47.7	46.4	46.6	
Mean	47.9	47.8	47.9	
Range	22.9-70.1	21.8-68.8	21.8-70.1	
Gender				1.00
Female	8 (50)	10 (55.6)	18 (52.9)	
Male	8 (50)	8 (44.4)	16 (47.1)	
Primary disease				.02
AML	1 (6.3)	9 (50)	10 (29.4)	
MDS	2 (12.5)	2 (11.1)	4 (11.8)	
ALL	3 (18.8)	4 (22.2)	7 (20.6)	
Lymphoma	3 (18.8)	0 (0)	3 (8.8)	
Other	6 (37.5)	2 (11.1)	8 (23.5)	
Performance status*				.55
70-90	3 (18.8)	1 (5.6)	4 (11.7)	
50-60	5 (31.3)	5 (27.8)	10 (29.4)	
<50	5 (31.3)	10 (55.5)	15 (44.1)	
Unknow	3 (18.8)	2 (11.1)	5 (14.7)	
Conditioning regimen				1.00
Myeloablative	9 (56.2)	11 (61.1)	20 (58.8)	
Nonmyeloablative	7 (43.8)	7 (38.9)	14 (41.2)	
CMV status†				.86
Positive	8 (50)	10 (55.6)	18 (52.9)	
Negative	8 (50)	7 (38.9)	15 (44.1)	
Unknown	0 (0)	1 (5.6)	1 (2.9)	
Total bilirubin‡				.93
Median	1.2	0.9	1.0	
Range	.2-18.9	.2–10.7	.2-18.9	
Creatinine§				.88
Median	1.3	1.4	1.3	
Range	.6-2.5	.4-2.9	.4-2.9	
Oxygen support‖				.37
Nasal cannula	10 (62.5)	6 (33.3)	16 (47.1)	
Face mask/Bipap	3 (18.8)	5 (27.8)	8 (23.5)	
Mechanical ventilation	2 (12.5)	6 (33.3)	8 (23.5)	
Unknown	1 (6.3)	1 (5.6)	2 (5.9)	

AML indicates acute myelogenous leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; Bipap, biphasic positive airway pressure.
Values are number of cases, with percents in parentheses, unless otherwise noted.
* Karnofsky performance status at study entry.
† Subject CMV status at time of transplant.
‡ Serum total bilirubin (mg/dL) at study entry.
§ Serum creatinine (mg/dL) at study entry.
‖ Method of supplemental oxygen support at study entry.

receiving > 2 doses of etanercept met the day 28 response criteria, with only 1 response among 6 patients (17%) receiving ≤ 2 doses of etanercept before discontinuing study therapy.

Table 3
Response and Survival

	Arm A (n = 16)	Arm B (n = 18)	*P*
Therapy	Etanercept + steroids	Placebo + steroids	
Median time to response, days	9	7	.69
Response rate, day 28, %	63	67	1.00
Response rate, day 56, %	56	50	.74
Corticosteroid dose,* day 28	0.57	0.49	.69
Median OS, days	170	64	.51
Day 28 OS, %	69	72	.82
Day 56 OS, %	63	61	.93
1-Year OS, %	23	17	.63
1-Year NRM, %	64	72	.65

OS indicates overall survival; NRM, nonrelapse mortality.
* Median corticosteroid dose (mg/kg/day, methylprednisolone equivalent) on day 28 of study.

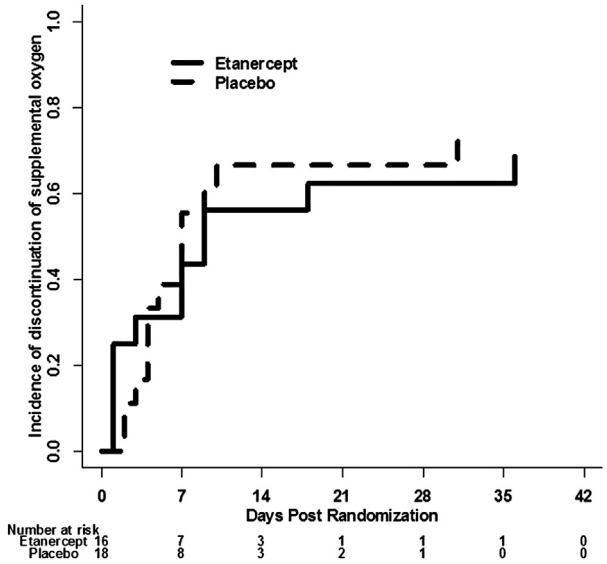

Figure 1. Time to discontinuation of supplemental oxygen support, arm A (etanercept + corticosteroids) versus arm B (placebo + corticosteroids).

Although the median survival for patients treated on the etanercept arm was 170 days (95% CI, 11 to 362) compared with 64 days (95% CI, 26 to 209) in the placebo arms, the differences in survival were not significantly different ($P = .51$) (Figure 2). Overall survival at 1 year post-therapy was 23.4% (95% CI, 6.5% to 46.3%) and 16.7% (95% CI, 4.1% to 36.5%), respectively, for the etanercept and placebo arms (not significant). With a median follow-up of 23.7 months post-randomization, 7 patients survived, 4 on the etanercept arm (25%) and 3 on the placebo arm (17%). Ten deaths occurred within the first 28 days post-randomization, 5 on each arm. For all patients, primary causes of death included graft failure (n = 1), relapse (n = 4), acute GVHD (n = 6), chronic GVHD (n = 1), progression of IPS (n = 6), infection (n = 7), and organ failure (n = 1). Six of the 7 infection-related deaths occurred in the placebo arm, with 2 of the 7 from infectious pneumonitis, both in the placebo arm. The

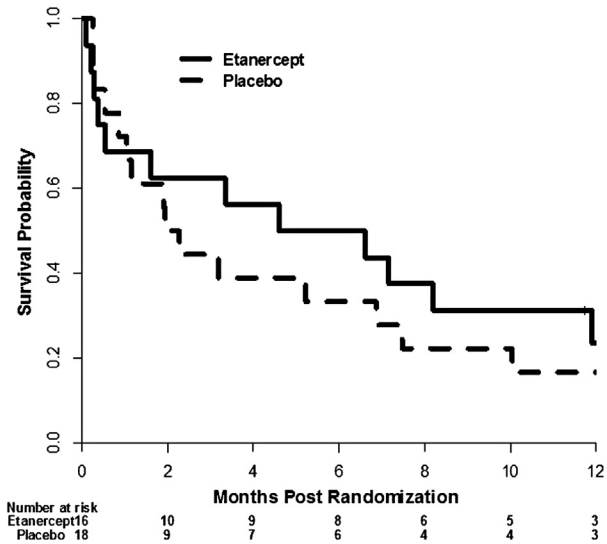

Figure 2. Overall survival by treatment arm (months post-randomization).

5 nonpulmonary infectious deaths included bacterial (n = 3), viral (n = 1), and fungal (n = 1). There were no differences in causes of death between the 2 arms ($P = .87$). Four of 16 patients (25%) on the etanercept arm and 2 of 18 patients (11%) on the placebo died from progression of IPS ($P = .36$).

Toxicity and Adverse Events

Ten patients on the etanercept arm (63%) and 18 patients on the placebo arm (100%) reported at least 1 grade 3 to 5 toxicity between days 0 and 56 of therapy ($P = .006$) (Table 4). There were nonsignificant but higher incidences of dyspnea, hypoxia, somnolence, hemorrhagic cystitis, mucositis/stomatitis, and abnormal hepatic transaminases reported between days 0 and 56 on the placebo arm, compared with the etanercept arm. The most commonly reported grades 3 to 5 events were hypoxia (56% frequency on the etanercept arm and 89% on the placebo arm) and dyspnea (50% on the etanercept arm and 83% on the placebo arm). Three patients on the etanercept arm and 2 patients on the placebo arm relapsed. The cumulative incidence of relapse at 1 year from study entry was 14.3% (95% CI, 1.8% to 42.8%) versus 11.8% (95% CI, 1.5% to 36.4%) for the etanercept and placebo arms respectively ($P = 1.00$).

Infectious complications (pulmonary and nonpulmonary) developed in 19 of 34 patients (56%) within 56 days of study entry (Table 5). There was a slightly greater incidence of CMV infections in the placebo arm compared with the etanercept arm (33% versus 13%, $P = .23$). Invasive aspergillus infections developed in 4 patients, 2 per arm, including aspergillus pneumonitis (2 cases), soft tissue infection (1 case), and fungemia (1 case). Two additional fungal infections occurred, both from *Candida* species, on the etanercept arm. Overall, infectious pneumonia occurred in 4 patients on the etanercept arm (25%) and 4 patients on the placebo arm (22%) during the study period.

Graft-versus-Host Disease

Five patients (31.2% [95% CI, 11.0% to 58.7%]) on the etanercept arm and 8 patients on the placebo arm (44.4% [95% CI, 21.5% to 69.2%]) developed grades II to IV acute GVHD within 56 days of study entry ($P = .50$). The incidences of grades III to IV GVHD were also similar, with 4 patients on the etanercept arm (25.0% [95% CI, 7.3% to 52.4%]) and 5 patients on the placebo arm (27.8% [95% CI, 9.7% to 53.5%]) developing grades III to IV GVHD during study ($P = 1.00$). The median time from diagnosis of IPS to onset of acute GVHD was 7 days in both the etanercept and placebo arms. Two patients on the etanercept arm developed chronic GVHD within 1 year from study entry (12.5% [95% CI, 1.6% to 38.4%]), whereas no patients on the placebo arm developed chronic GVHD within that time period (0% [95% CI, 0 to 18.5%]; $P = .21$).

Table 4
Noninfectious Complications: Grades 3-5 Events

Toxicity	Etanercept (n = 16)	Placebo (n = 18)	Total (N = 34)
Renal	4 (25)	3 (17)	7 (21)
Hepatic	7 (44)	14 (78)	21 (62)
Cardiac	1 (6)	2 (11)	3 (9)
CNS	2 (13)	6 (33)	8 (24)

CNS indicates central nervous system.
Values are number of cases, with percents in parentheses.

Table 5
Infectious Complications*

	Etanercept (n = 16)	Placebo (n = 18)	Total (N = 34)
Infections (patients)†	10 (63)	9 (50)	19 (56)
Infections (events)‡	20	32	52
Bacterial	9	21	30
Viral	7	10	17
Fungal	4	2	6

Values are number of cases, with percents in parentheses.
* Infectious events in which a pathogen was documented. Excludes febrile events without a defined pathogen.
† Total number of patients who developed an infectious complication between days 0 and 56.
‡ Total number of infectious events between days 0 and 56.

Corticosteroid Requirements

All 34 patients were treated with systemic corticosteroids with methylprednisolone at 2 mg/kg/day on day 0, with taper allowed after day 7. There was no difference in corticosteroid requirement between the etanercept and placebo arms, at both day 14 and day 28 of study. By day 14, the median corticosteroid dose was .94 mg/kg/day (range, .56 to 1.92) for the etanercept arm versus 1.00 mg/kg/day (range, .25 to 2.21) for the placebo arm ($P = .96$). By day 28, the median corticosteroid dose was .57 mg/kg/day (range, 0 to 2.0) and .49 mg/kg/day (range, .03 to 1.04) for the etanercept and placebo arms, respectively ($P = .69$).

DISCUSSION

The current study was designed to examine the impact of a soluble TNF binding protein, etanercept, when given in conjunction with systemic corticosteroids in the management of IPS in adult HCT recipients. Although BMT CTN0403 fell far short of anticipated accrual, with inadequate power and sample size to make definitive conclusions, specific aspects of the protocol are still valuable for consideration. Historically, early response and overall survival have been poor (<50%) when IPS was treated with systemic corticosteroids plus supportive care measures alone. In the past decade, significant improvements in day 28 survival (>70%) were reported in 2 limited institution studies combining etanercept with systemic corticosteroids [7,8]. In the current study, the day 28 response (67%) and survival (72%) noted in the corticosteroid (plus placebo) arm greatly exceeded historical reports using corticosteroids as primary management (Table 6), whereas 1-year survival remained poor (16.7%).

Has IPS changed over the past 2 decades? The statistical plan for BMT CTN0403 was based on historical data from the University of Michigan Medical Center (1996 to 2002) in which IPS occurred in 9.0% of transplants, a median 15 days

Table 6
Corticosteroid Therapy for IPS: Historical Controls vs. Arm B, CTN 0403

	Michigan [7] (N = 59)	Penn [8] (N = 22)	CTN 0403 Arm B (n = 18)
Therapy	Steroids	Steroids	Steroids + placebo
Median time to response, days	14	16	7
Response rate, %	30	18	67
Median OS, days	15	NS	64
Day 28 OS, %	33	36	72
OS,* %	6	9	17

OS indicates overall survival.
* OS at day 100 for the Michigan cohort and at 1 year for Penn and CTN 0403 Arm B cohorts.

post-transplant, with a day 28 survival of 33% when treated with corticosteroids plus supportive care. This incidence of IPS was supported by data from the Center for International Blood and Marrow Transplant Research during a similar time period. However, significant differences in supportive care practices, conditioning regimen intensity, the frequency of performing BAL, and the ability to isolate pathogens on a BAL have occurred over the past decade. With molecular-based assays for a wide variety of pathogens now in common use, the potential exists that IPS identified in the 1990s may not be identified as such now. Additionally, the use of reduced-intensity conditioning has increased significantly over this same time period, with 41.1% of patients on BMT CTN0403 treated after receiving reduced-intensity regimen. By comparison, none of the historical control subjects in the University of Michigan IPS database received reduced-intensity conditioning. The intensity of the conditioning regimen has been postulated to impact the incidence of IPS, with significantly lower rates of IPS seen with reduced intensity [9]. Could the intensity of the conditioning regimen also impact response to therapy once IPS develops? As such, are there subjects for whom corticosteroids alone are sufficient to treat IPS without the addition of a TNF inhibitor (etanercept)? Conversely, are their subjects with IPS who are more likely to benefit from the addition of TNF-α inhibition?

Although our trial was not designed to answer either of these questions, the expression of TNF-α and its surrogate markers, stratified by regimen intensity and IPS severity, is currently being examined on BAL fluid and plasma of study subjects and may help to elucidate these issues. Moreover, we recently identified a set of IPS-associated proteins that revealed distinct similarities between IPS in humans and animal models and could predict at the time of HCT patients who progressed to IPS and who respond to etanercept therapy [17]. Patients predisposed to over-express TNF-α in response to immunologic stress (ie, high TNF-α secretors) may be more likely to benefit from strategies that neutralize this protein. Current strategies to assay TNF-α levels in real time from affected patients is now being examined at various centers and may ultimately be beneficial in optimizing therapy.

BMT CTN0403 was initially designed to enroll 120 patients, 60 per arm. Accrual fell far short of projected expectations, with only 34 (28%) of a targeted 120 subjects enrolled. Given slow accrual, the statistical design was subsequently amended to enroll 60 patients, 30 per arm. Other amendments to increase accrual included extending the eligibility from IPS developing within 120 days to IPS developing within 180 days post-transplant and modifying enrollment criteria so that bronchoscopy and BAL were no longer required for patients developing IPS within 30 days post-transplant. On-study surveys were tracked during the study course, investigating factors that impacted potential accrual. Reported factors included (1) investigator bias (pro or con) regarding the test agent (etanercept), (2) investigator reluctance to perform a BAL in critically ill patients, and, most importantly, (3) a much lower incidence of IPS than originally anticipated. The critical nature of the patient population was evident, with 8 of 34 patients (24%) requiring mechanical ventilation at baseline and an additional 6 patients requiring $>$ 40% supplemental oxygen support (non-ventilated) at baseline. Importantly, nearly 40% of patients treated on the etanercept arm discontinued study therapy after receiving 2 (or fewer) doses of etanercept, in several cases because of investigator reluctance to continue "blinded" therapy. Response rates were poor in this group of patients, compared with those receiving $>$ 2 doses of etanercept. Ultimately, a patient was more likely to continue therapy if he or she was were stable or improving early in the treatment course, rather than not improving. This study highlights both the difficulties in performing phase III trials in critically ill patients and the merits of including a contemporaneous control group in a clinical trial.

In summary, the treatment of IPS with corticosteroids in adult HCT recipients was associated with high early response rates (>60%) when compared with historical reports. The addition of etanercept did not lead to further increases in response, although the small sample size of this truncated trial precludes a definitive conclusion. Etanercept administration was not associated with increased toxicity, incidence of opportunistic infection, or risk of relapse when compared with placebo controls. Although early response rates were high in both arms, long-term outcomes remain unacceptably poor in this patient population, underscoring the continued need for novel therapeutic options.

ACKNOWLEDGMENTS

The authors thank the staff and administration from the following BMT CTN participating centers: the University of Michigan Medical Center (Ann Arbor, MI), Case Western University (Cleveland, OH), University of Florida College of Medicine (Gainesville, FL), Dana Farber Cancer Institute (Boston, MA), University of Minnesota (Minneapolis, MN), University of Nebraska Medical Center (Omaha, NB), Duke University Medical Center (Durham, NC), Johns Hopkins University (Baltimore, MD), Fred Hutchinson Cancer Research Center (Seattle, WA), Indiana University Medical Center (Indianapolis, IN), Mayo Clinic (Rochester, MN), Oregon Health and Science University (Portland, OR), Memorial Sloan Kettering Cancer Center (New York, NY), University of Pennsylvania Cancer Center (Philadelphia, PA), and University of Texas/MD Anderson Cancer Research Center (Houston, TX). The authors thank Ms. Jennierose D'Elia and Mr. Eric Balsey from the EMMES Corporation for their technical expertise in data management and clinical trial coordination and Nancy Poland from the National Marrow Donor Program (Minneapolis, MN) for her assistance.

Financial disclosure: Support for this study was provided by grant U10HL069294 from the National Heart, Lung, and Blood Institute and the National Cancer Institute, The Leukemia and Lymphoma Society (to K.R.C.), and the Burroughs Welcome Fund (to K.R.C.). Immunex Corporation, a wholly owned subsidiary of Amgen Inc., provided study drug and central pharmacy support for the trial.

Conflict of interest statement: There are no conflicts of interest to report.

REFERENCES

1. Clark JG, Madtes DK, Martin TR, et al. Idiopathic pneumonia after bone marrow transplantation: cytokine activation and lipopolysaccharide amplification in the bronchoalveolar compartment. *Crit Care Med*. 1999;27:1800-1806.
2. Kantrow SP, Hackman RC, Boeckh M, et al. Idiopathic pneumonia syndrome: changing spectrum of lung injury after marrow transplantation. *Transplantation*. 1997;63:1079-1086.
3. Chien JW, Duncan S, Williams KM, Pavletic SZ. Bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation-an increasingly recognized manifestation of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2010;16:S106-S114.
4. Shannon VR, Andersson BS, Lei X, et al. Utility of early versus late fiberoptic bronchoscopy in the evaluation of new pulmonary infiltrates

following hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2010;45:647-655.
5. Clark JG, Hansen JA, Hertz MI, et al. NHLBI workshop summary. Idiopathic pneumonia syndrome after bone marrow transplantation. *Am Rev Respir Dis*. 1993;147:1601-1606.
6. Crawford SW, Hackman RC. Clinical course of idiopathic pneumonia after bone marrow transplantation. *Am Rev Respir Dis*. 1993;147:1393-1400.
7. Yanik GA, Ho VT, Levine JE, et al. The impact of soluble tumor necrosis factor receptor etanercept on the treatment of idiopathic pneumonia syndrome after allogeneic hematopoietic stem cell transplantation. *Blood*. 2008;112:3073-3081.
8. Tizon R, Frey N, Heitjan DF, et al. High-dose corticosteroids with or without etanercept for the treatment of idiopathic pneumonia syndrome after allo-SCT. *Bone Marrow Transplant*. 2012;47:1332-1337.
9. Fukuda T, Hackman RC, Guthrie KA, et al. Risks and outcomes of idiopathic pneumonia syndrome after nonmyeloablative and conventional conditioning regimens for allogeneic hematopoietic stem cell transplantation. *Blood*. 2003;102:2777-2785.
10. Sakaguchi H, Takahashi Y, Watanabe N, et al. Incidence, clinical features, and risk factors of idiopathic pneumonia syndrome following hematopoietic stem cell transplantation in children. *Pediatr Blood Cancer*. 2012;58:780-784.
11. Panoskaltsis-Mortari A, Griese M, Madtes DK, et al. An official American Thoracic Society research statement: noninfectious lung injury after hematopoietic stem cell transplantation: idiopathic pneumonia syndrome. *Am J Respir Crit Care Med*. 2011;183:1262-1279.
12. Cooke KR, Kobzik L, Martin TR, et al. An experimental model of idiopathic pneumonia syndrome after bone marrow transplantation. I. The roles of minor H antigens and endotoxin. *Blood*. 1996;88:3230-3239.
13. Cooke KR, Hill GR, Gerbitz A, et al. Hyporesponsiveness of donor cells to lipopolysaccharide stimulation reduces the severity of experimental idiopathic pneumonia syndrome: potential role for a gut-lung axis of inflammation. *J Immunol*. 2000;165:6612-6619.
14. Yanik G, Hellerstedt B, Custer J, et al. Etanercept (Enbrel) administration for idiopathic pneumonia syndrome after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2002;8:395-400.
15. Cooke KR, Hill GR, Gerbitz A, et al. Tumor necrosis factor-alpha neutralization reduces lung injury after experimental allogeneic bone marrow transplantation. *Transplantation*. 2000;70:272-279.
16. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat*. 1988;16:1141-1154.
17. Schlatzer DM, Dazard JE, Ewing RM, et al. Human biomarker discovery and predictive models for disease progression for idiopathic pneumonia syndrome following allogeneic stem cell transplantation. *Mol Cell Proteomics*. 2012; http://dx.doi.org/10.1074/mcp.M111.015479.