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A RANDOMIZED, DOUBLE-BLIND TRIAL OF ABATACEPT (CTLA4-IG) FOR THE TREATMENT OF TAKAYASU'S ARTERITIS

Carol A. Langford, MD MHS[1], **David Cuthbertson, MS**[2], **Steven R. Ytterberg, MD**[3], **Nader Khalidi, MD**[4], **Paul A. Monach, MD PhD**[5], **Simon Carette, MD**[6], **Philip Seo, MD MHS**[7], **Larry W. Moreland, MD**[8], **Michael Weisman, MD**[9], **Curry L Koening, MD**[10], **Antoine G. Sreih, MD**[11], **Robert Spiera, MD**[12], **Carol A. McAlear, MA**[11], **Kenneth J. Warrington, MD**[3], **Christian Pagnoux, MD**[6], **Kathleen McKinnon, DO**[8], **Lindsy J. Forbess, MD**[9], **Gary S. Hoffman, MD MS**[1], **Renée Borchin**[2], **Jeffrey P. Krischer, PhD**[2], **Peter A. Merkel, MD MPH**[11], and **for the Vasculitis Clinical Research Consortium**

[1]Cleveland Clinic, Cleveland, Ohio [2]University of South Florida, Tampa, Florida [3]Mayo Clinic, Rochester, Minnesota [4]St. Joseph, Hamilton, Canada [5]Boston University, Boston, Massachusetts [6]Mount Sinai Hospital, Toronto, Canada [7]John Hopkins University, Baltimore, Maryland [8]University of Pittsburgh, Pittsburgh, Pennsylvania [9]Cedars Sinai, Los Angeles, California [10]University of Utah, Salt Lake City, Utah [11]University of Pennsylvania, Philadelphia, Pennsylvania [12]Hospital for Special Surgery, New York, New York

Abstract

Objective—To compare the efficacy of abatacept to placebo for the treatment of Takayasu's arteritis (TAK).

Methods—In this multicenter trial, patients with newly-diagnosed or relapsing TAK were treated with abatacept 10 mg/kg IV on days 1, 15, 29, week 8, together with prednisone. At week 12, patients in remission underwent a double-blinded randomization to continue monthly abatacept or switch to placebo. Patients in both study arms received a standardized prednisone taper, reaching 20 mg daily at week 12 with discontinuation of prednisone at week 28 and remained on their randomized assignment until meeting criteria for early termination or until 12 months after enrollment of the last patient. The primary endpoint was duration of remission (relapse-free survival).

Results—Thirty-four eligible patients with TAK were enrolled and treated with prednisone and abatacept; 26 reached the week 12 randomization and underwent a blinded randomization to abatacept or placebo. The relapse-free survival at 12 months was 22% for those receiving abatacept and 40% for those receiving placebo (p= 0.853). Treatment with abatacept in patients with TAK enrolled in this study was not associated with a longer median duration of remission (abatacept 5.5 months, placebo 5.7 months). There was no difference in the frequency or severity of adverse events between treatment arms, including infection.

Corresponding author: Carol A. Langford, MD, MHS, Center for Vasculitis Care and Research, Cleveland Clinic, 9500 Euclid Avenue, A50, Cleveland, OH 44195, Phone: 216-445-6056, Fax: 216-445-7569, langfoc@ccf.org.

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Conclusions—In patients with TAK the addition of abatacept to a treatment regimen with prednisone did not reduce the risk of relapse.

Takayasu's arteritis (TAK) is a vasculitic disease of unknown cause that preferentially affects the aorta, its major branches, and the pulmonary arteries resulting in vascular stenoses/occlusions or aneurysms (1–9). TAK is most commonly diagnosed between the ages of 18–40 and occurs predominantly in women. Glucocorticoids have been the foundation of treatment in TAK as they improve systemic symptoms and in some studies have been found to improve blood flow through narrowed vessels (1, 10, 11). However, despite treatment with glucocorticoids, not all patients achieve remission and sustained remissions are seen in only 28–50% of patients (1, 9). Because of these concerns and the substantial morbidity of glucocorticoids, other immunosuppressive agents are frequently prescribed in TAK (12–19). However, the use of such adjunctive agents with glucocorticoids has been based solely on retrospective studies or small open-label trials. As TAK is a rare disease with an estimated incidence in the United States of 2.6 cases per million per year (2), conducting randomized trials is difficult. Therefore, it has been a high priority and unmet need in TAK to identify a safer, effective therapeutic option beyond glucocorticoids through the conduct of a randomized therapeutic trial in this disease.

The cause of TAK remains unknown, but laboratory-based data supports a critical role of activated T cells in disease pathogenesis (20). Studies of aortic tissue from patients with TAK have demonstrated that the infiltrating cells consist mainly of activated T cells (21–24) and dendritic cells in the adventitia (25). Increased expression of T cell costimulatory molecules has also been found in vascular cells and infiltrating cells at sites of inflammation in TAK (23). Abatacept is comprised of the ligand binding domain of CTLA4 plus a modified Fc domain derived from IgG1. CTLA4 binds to CD80 and CD86 with a higher avidity than CD28, thereby acting as a negative regulator of CD28-mediated T cell costimulation. By containing CTLA4, abatacept blocks the engagement of CD28 with its ligand and inhibits T cell activation (26–28). Abatacept is approved by the Food and Drug Administration for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis and has a low reported rate of toxicity with the main side-effects including hypersensitivity and infection, most commonly including upper respiratory tract infections, bronchitis, and herpes zoster.

Based upon the rationale that blockage of T cell activation might impact disease pathogenesis in TAK, together with the favorable toxicity profile that had been seen with abatacept (29–31), a randomized trial was designed and conducted with the objectives of investigating the efficacy and safety of abatacept in the treatment of TAK.

PATIENTS AND METHODS

Design Overview

The protocol for this randomized trial was written by the first and last authors in collaboration with the Steering Committee of the Vasculitis Clinical Research Consortium and the Rare Diseases Clinical Research Network Data Management and Coordinating Center (DMCC). The original study protocol and all amendments were approved by an

independent Data and Safety Monitoring Board and by the Institutional Review Board at each site. There were no significant changes made to the study methods after trial commencement. Research was carried out in compliance with the Helsinki Declaration and all patients provided written informed consent.

Setting and Participants

The trial was conducted at 11 academic medical centers and enrolled patients with newly-diagnosed or relapsing TAK who had active disease within the prior 2 months. All patients met the following modified American College of Rheumatology classification criteria for TAK (32): they were required to have arteriographic abnormalities compatible with TAK by conventional dye angiography, magnetic resonance angiography (MRA) ,or computed tomography angiography (CTA), plus at least one of the following: 1) Age at disease onset <50 years, 2) Claudication of extremities, 3) Decreased brachial artery pulse (one or both arteries), 4) Blood pressure difference of >10mm Hg between the arms, 5) Bruit over subclavian arteries or aorta. Exclusion criteria included active infection (including chronic infection, infection with the human immunodeficiency virus, hepatitis C virus, hepatitis B virus, tuberculosis), pregnancy, breast feeding, cytopenias, recent vaccination with a live agent, history of any malignant neoplasm except adequately treated basal or squamous cell carcinoma of the skin or solid tumors treated with curative therapy and disease free for at least 5 years, comorbidities that would increase the risk of study participation or that required treatment with glucocorticoids, and prior therapy with a biologic agent given within established time parameters. This included infliximab within the past 49 days, adalimumab within the past 28 days, etanercept within the past 21 days, or rituximab either within the past 12 months or greater than 12 months where there was continued B lymphocyte depletion.

Interventions

All eligible patients were treated with abatacept 10 mg/kg (500 mg for < 60 kg, 750 mg for 60–100 kg, and 1000 mg for > 100 kg) by intravenous infusion on days 1, 15, 29, and week 8 together with prednisone 40–60 mg/day followed by a standardized tapering schedule (See Supplementary Table 1). No other concurrent immunosuppressive agents were permitted during the trial. At week 12, if they were in remission, patients underwent a double-blinded randomization to switch to placebo or to continue abatacept given every 4 weeks thereafter (Figure 1). At the time of randomization, all patients were on prednisone 20 mg/day with tapering continuing after randomization such that both treatment arms discontinued prednisone at week 28. The need to increase the prednisone dose, or to restart prednisone after discontinuation, for the treatment of TAK was considered a relapse criterion.

In the absence of meeting criteria for early termination, abatacept or placebo was continued until common closing which was 12 months after enrollment of the final patient. Potential reasons for early termination included: failure to experience remission by the week 12 visit, disease relapse, pregnancy or breast feeding, development of malignancy with the exception of basal or squamous cell carcinoma of the skin that has been completely excised, grade 4 toxicity, hypersensitivity reactions to abatacept, non-compliance with study procedures, or when in the medical judgment of the physician discontinuation would be in the best interests

of the patient. Patients who experienced a relapse discontinued study drug and were treated according to best medical judgment. Following discontinuation of study drug, patients were asked to return for post-treatment visits at weeks 4, 12, and 24 after which time they were considered off study.

Randomization and Blinding

Randomization was computer generated by the DMCC in a 1:1 allocation balanced by clinical site utilizing randomly permuted blocks. Patients and all study investigators were blinded to the randomized treatment assignment.

Assessment, Outcomes and Follow-up

The assessment on which disease activity was based was obtained in a standardized manner throughout the study. A clinical history, physician examination, and laboratory tests were obtained at each study visit. All patients without contraindications underwent magnetic resonance imaging of the aorta and branches at study entry and the week 12 randomization. Large vessel imaging was then performed at every 6-month intervals and at the time of early termination/common close.

The primary endpoint was remission duration (relapse-free survival). Remission and relapse were based on the absence or presence of disease activity, respectively.

The determination of disease activity was defined by pre-established clinical and imaging criteria, where these features were not due to other causes. Clinical criteria included: a sustained fever of greater than 38°C for more than 1 week, vascular pain/tenderness producing symptoms such as carotidynia, scalp tenderness, or temporal artery abnormalities that were present for more than one day and non-fleeting, headache that was present for more than one day, non-fleeting, not fully relieved with non-opioid analgesics, and not typical for any pre-existing form of headaches the patient may have experienced, ischemic retinopathy, optic neuropathy, visual loss, tongue/jaw pain and/or claudication, transient cerebral ischemia, stroke, extremity claudication, or symptoms/signs attributed to TAK by the investigator that necessitated reinstitution or increase in glucocorticoids. Musculoskeletal symptoms or fatigue/malaise could be considered as features of active disease if they occurred in combination with an ESR of greater than 40 mm in the first hour by the Westergren method or a C-reactive protein (CRP) measurement above the laboratory normal limit. An elevation in acute phase reactants was not considered indicative of disease activity in the absence of clinically compatible disease manifestations. Imaging features of active disease were the development of new vascular stenosis or aneurysm in new vascular territories as seen by magnetic resonance, computed tomography, or conventional dye arteriography. Determination of relapse was assessed by both the site investigator and study principal investigator during the blinded phase and reaffirmed by the study team following the end of the trial. No changes were made to the outcome definitions during the course of the trial.

The secondary endpoint was toxicity. All adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (http://ctep.cancer.gov).

Study visits and data collection occurred at screening, baseline, at each infusion of study drug, at early termination/common close, and at the post-treatment visits.

Statistical Analysis and Sample Size

The 12 month relapse-free survival rate in patients with TAK treated with prednisone was estimated to be 30% based on prior published literature (9). The planned sample size for the trial of 30 randomized patients was based on an 80% probability of detecting a clinically meaningful difference between treatment arms set at a 30% improvement in the relapse-free survival utilizing a one-sided alpha of 0.1.

Kaplan-Meier curves of relapse-free survival were constructed and differences in treatment arms compared using the logrank test. The analysis of the primary outcome was based upon intent-to-treat. The secondary study endpoint was toxicity. Adverse events were collected throughout the trial and analyzed after randomization with tabulation by treatment arm. The frequency of occurrence for each event was compared for treatment differences by the Fisher's exact test.

Safety Monitoring and Stopping Guidelines

The study conduct was overseen by an independent Data and Safety Monitoring Board and the Institutional Review Board at each study site. Rules for halting new patient accrual were established prior to trial initiation and consisted of any deaths that were possibly, probably, or definitely related to the study drug or any grade 4 toxicities that were probably or definitely related to the study drug.

RESULTS

Patient population

There were 39 patients with TAK who signed informed consent and underwent protocol screening between February 2009 to January 2014 at the studies determined end-date (Figure 2). Five of the 39 were not eligible as they chose to not proceed further within the study and 34 patients received study drug. Eight of these 34 patients were withdrawn, relapsed, or not in remission at week 12 resulting in a randomized study population of 26 patients. The baseline and demographic features of the 26 randomized patients are listed in Table 1. There was no difference in baseline characteristics between study arms. Twenty-two of the 26 randomized patients were enrolled at the time of a relapse with all 4 newly-diagnosed patients being randomized to the placebo arm. There was no statistical difference in the prior use of non-glucocorticoid immunosuppressive medications between patients in the two study groups (Table 1).

Of the 26 patients, 11 patients were randomized to abatacept and 15 to placebo. Twenty-five patients met an endpoint of relapse or sustained remission at week 64. One patient randomized to abatacept was withdrawn prior to week 64 by the investigator for a comorbidity that required the long-term use of prednisone. This patient was included in the intent-to-treat analysis and was in remission at the last available follow-up.

Efficacy Assessments

In the intent-to-treat analysis of the 26 randomized patients, the relapse-free survival at 12 months was 22% for those receiving abatacept and 40% for those receiving placebo (p= 0.853) (Figure 3). There was no difference in the median duration of remission among those who received abatacept (5.5 months) compared to those who received placebo (5.7 months, p=0.125).

The relapses observed during the trial reflected typical characteristics of TAK and consisting of vascular and constitutional features (Table 2). Three patients all of who randomized to placebo met radiographic endpoints with development of a new vascular lesion in a previously unaffected territory. An elevation of ESR and/or CRP protein above normal was seen in all relapses.

Of the 8 patients who remained in remission (3 abatacept, 5 placebo), 2 declined to return for post-treatment visits (See Supplementary Table 2). One patient who had received abatacept had a relapse 12 weeks after common close. The remaining 5 patients all remained in remission during the extended follow-up period through post-treatment week 24.

A pre-specified subset analysis was performed on the population who relapsed or were in remission at week 64; among this group of 25 patients there remained no difference between study arms (p=0.873).

Adverse events

Overall, 114 adverse events occurred in 28 patients who received study drug, including 24 serious adverse events in 15 patients. There was no difference in the frequency or severity of adverse events between treatment arms, including the rate of infection or the rate of serious adverse events (Table 3). Five of the serious adverse events occurred before week 12. One patient randomized to abatacept was hospitalized 6 times for chest pain that was determined on each occasion to be non-cardiac and non-vascular in origin. No deaths occurred during the study.

A total of 51 infections were reported during the trial in 19 patients, with 7 infections requiring hospitalization (See Supplementary Table 3). Eleven infections in 8 patients occurred within the first 12 weeks of which 2 were serious adverse events. Except for 2 infections that occurred in patients who did not undergo randomization, the remaining 49 infections developed in the randomized study population. Of these 49 infections, 13 occurred in the abatacept study arm with the remaining 36 developing in those who randomized to placebo. There was no statistical difference in the frequency of infections between treatment arms. The total infection number was strongly influenced by patients who experienced multiple infections. Three patients in the placebo arm had 5 or more infections that largely consisted of recurrent upper airways and urinary tract infections.

Of the 34 treated patients, 1 developed a malignancy during the study period, which was a breast carcinoma diagnosed shortly after the day 29 abatacept infusion.

DISCUSSION

In this trial, patients with TAK who achieved remission and were randomized to continue abatacept had a statistically similar rate of relapse-free survival compared to those who were randomized to placebo. Because a standardized prednisone taper was applied to both arms there was by definition no difference in total prednisone dose or duration between study arms. While the study results unfortunately did not provide supportive evidence of the efficacy of abatacept in this TAK study population, this is the first randomized controlled trial ever conducted in TAK and provides many important insights in conducting clinical trials in this disease and raises intriguing questions and future directions for research into this disease.

Safety was an important secondary endpoint of this study. Utilizing a study design in which all patients initially received abatacept with high-dose prednisone provided the opportunity to gain both initial efficacy data and to assess safety, particularly with regards to whether there was any increased risk of infection or other side effects. In comparing the two study arms, there was no difference in the type or severity of adverse events seen in those randomized to abatacept versus placebo and no suggestion of a high frequency of infection during the first 12 weeks. Interestingly, there were a higher overall number of infections in those randomized to placebo as compared to abatacept. In reviewing the pattern of these infections, this frequency was heavily influenced by a small number of patients who had recurrent upper airway and urinary infections. These infections can occur commonly in young patients and are likely reflective of the population affected by TAK.

This trial has several important strengths. The study was conducted by clinician investigators experienced in the care of patients with TAK and in the evaluation of such patients in research studies. Assessing disease activity in TAK is challenging and there are no well-standardized validated outcome measures for such assessments (33, 34). The definitions of disease activity used in this trial were determined collectively by the steering committee of the VCRC. These were pre-specified within the protocol and required a higher burden of evidence for those features that were the most subjective. The definitions that were used were based on both clinical and imaging parameters and reflect those that are applied by practicing physicians in the routine care of patients and all relapses were adjudicated by multiple investigators during the blinded phase. Review of the disease characteristics of all relapses (Table 2) indicates that these events were exactly the type seen in practice and include clinical manifestations fully consistent with flares of disease. The inclusion of imaging findings as a parameter of active disease and the protocol-defined schedule of advanced imaging of large arteries were another major strength and a critical feature of assessment for a disease known to have asymptomatic progression of serious vascular disease. Additionally, the use of a time-to-event analysis both provided greater power for this small sample size and is highly clinically relevant for this disease with sometimes long periods between flares.

There are several limitations to consider in assessing these results. The relatively small sample size raises the possibility that this study failed to detect a difference between treatment arms that actually exists (type II error). This study sought to detect a large

difference between study arms that would be clinically meaningful and thus a smaller difference may not have been detected. However, the results indicate that a much larger sample size would be needed to detect smaller treatment differences and the clinical utility of using a biologic agent to achieve a small benefit would be difficult to justify. Additionally, 22 of the 26 randomized patients had relapsing TAK which raises the question of whether the results were impacted by enrolling a population with a predilection for disease recurrence. However, the study population reflects the disease course of TAK where treatment for relapse would be a common and an important clinical application of any new therapeutic agent. The high frequency of relapsing patients seen in the enrolled population also demonstrates that while focusing on newly diagnosed patients in clinical trials is often considered desirable, this may not be feasible in TAK trials given the rarity of the disease and its relapsing nature.

This was the first-ever randomized trial to be performed in TAK and in conducting this study, a great deal was learned about the challenges of performing a sufficiently powered trial in this disease. TAK is one of the least common forms of primary systemic vasculitis. Even with the dedicated participation of centers that have an established referral base for patients with vasculitis, enrollment required perseverance and careful planning. Patients with TAK are eager investigational partners who want to identify treatment options beyond glucocorticoids, as evidenced in our trial in which only 1 patient withdrew before randomization and no others prior to being observed on study for 64 weeks. Nonetheless, family and work responsibilities faced by the young population in which this disease occurs can make it more difficult for them to participate in clinical trials, particularly studies that involve frequent visits over the extended time course necessary to reach study endpoints in this form of vasculitis.

The results from this trial also pose interesting questions regarding where TAK may fit within the spectrum of large-vessel vasculitis. In giant cell arteritis (GCA), a randomized trial examining abatacept that was conducted by this same investigator group using an identical design, found that abatacept combined with glucocorticoids resulted in a longer duration of relapse-free survival than treatment with prednisone alone (35). GCA and TAK share many common features in both being large-vessel granulomatous vasculitides that can have similar arterial distributions (36, 37) and laboratory-based studies have supported both as being antigen-drive diseases (38, 39). It is an ongoing question whether GCA and TAK are unique entities or if they represent part of a single clinical spectrum (36). The divergence in therapeutic efficacy seen in these parallel trials provides strong evidence of the need to continue scientific investigations to better understand the underlying immunologic nature of these diseases, which in turn may guide therapeutic strategies.

In conclusion, this study found that in patients with TAK, abatacept combined with glucocorticoids did not provide a longer duration of relapse-free survival than treatment with prednisone alone. This trial demonstrated the ability to conduct rigorous randomized trials in TAK and provided knowledge of, and insight into, strategies to aid the conduct of future comparative trials in this disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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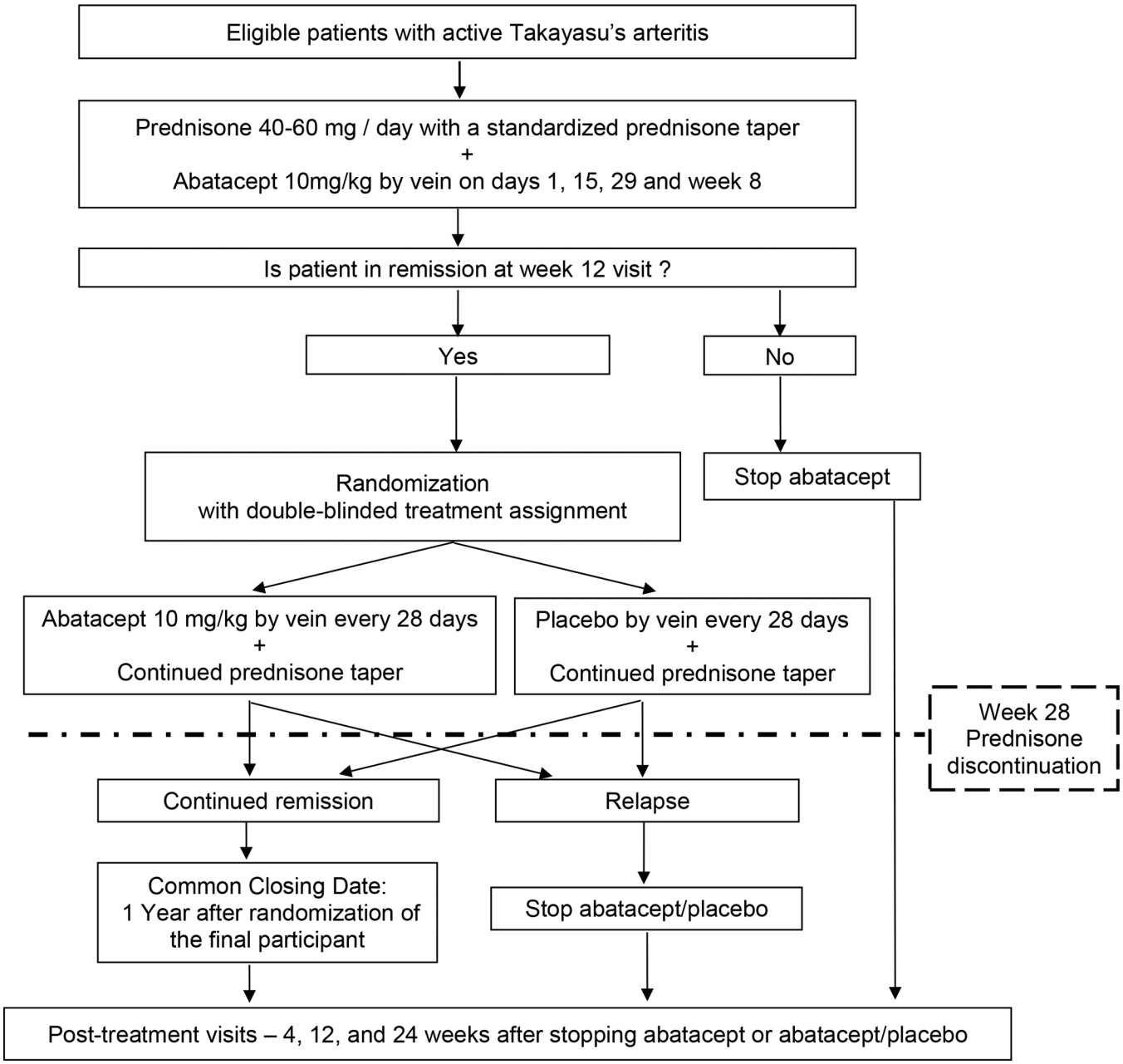

Figure 1.
A randomized trial of abatacept in Takayasu's arteritis – study diagram.

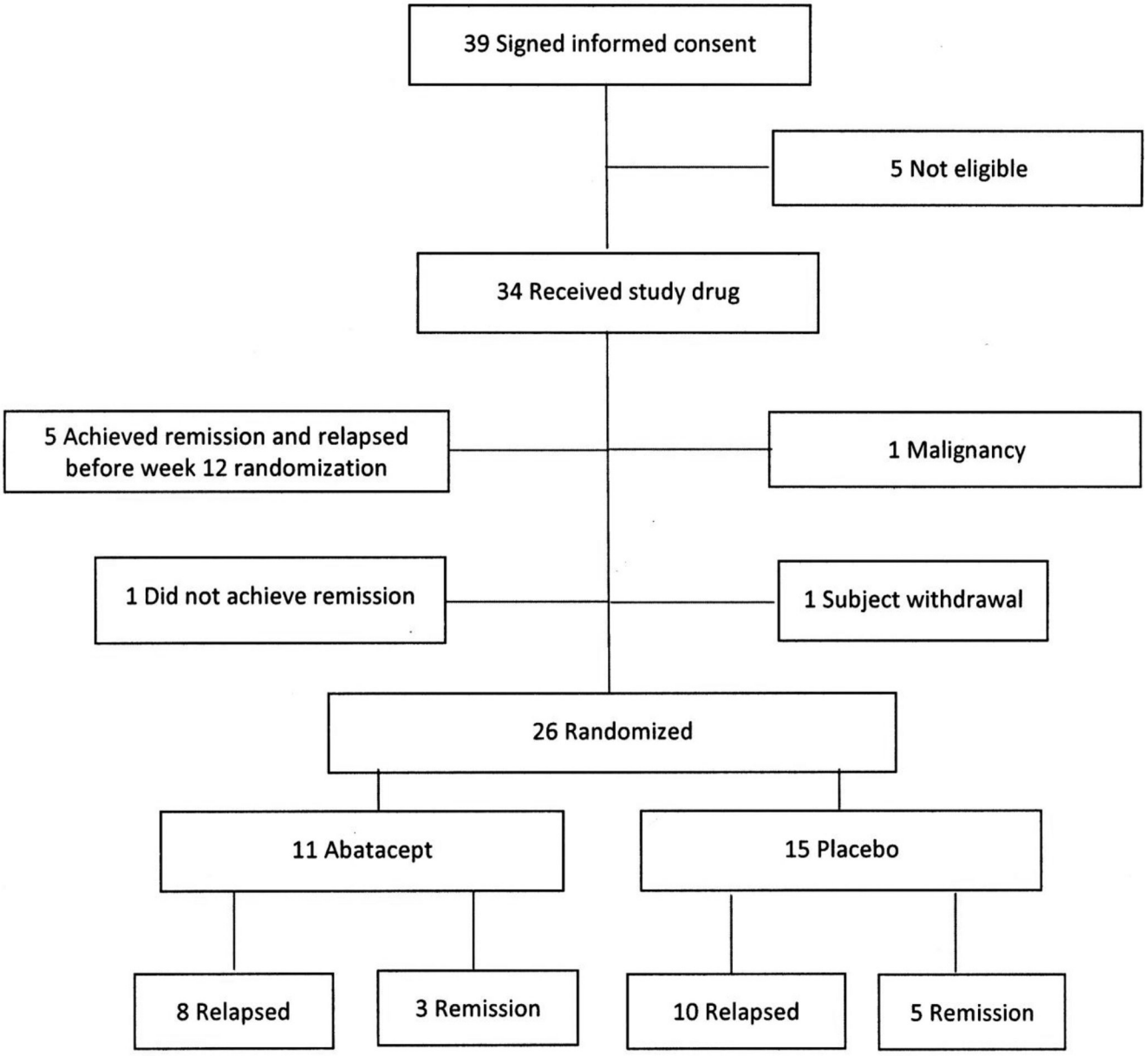

Figure 2.

Randomization assignment at week 12.

All patients were initially treated with abatacept and prednisone. At week 12, those in remission underwent a blinded randomization at a 1:1 ratio to receive placebo or to continue abatacept. All randomized patients were included in the intent-to-treat analysis.

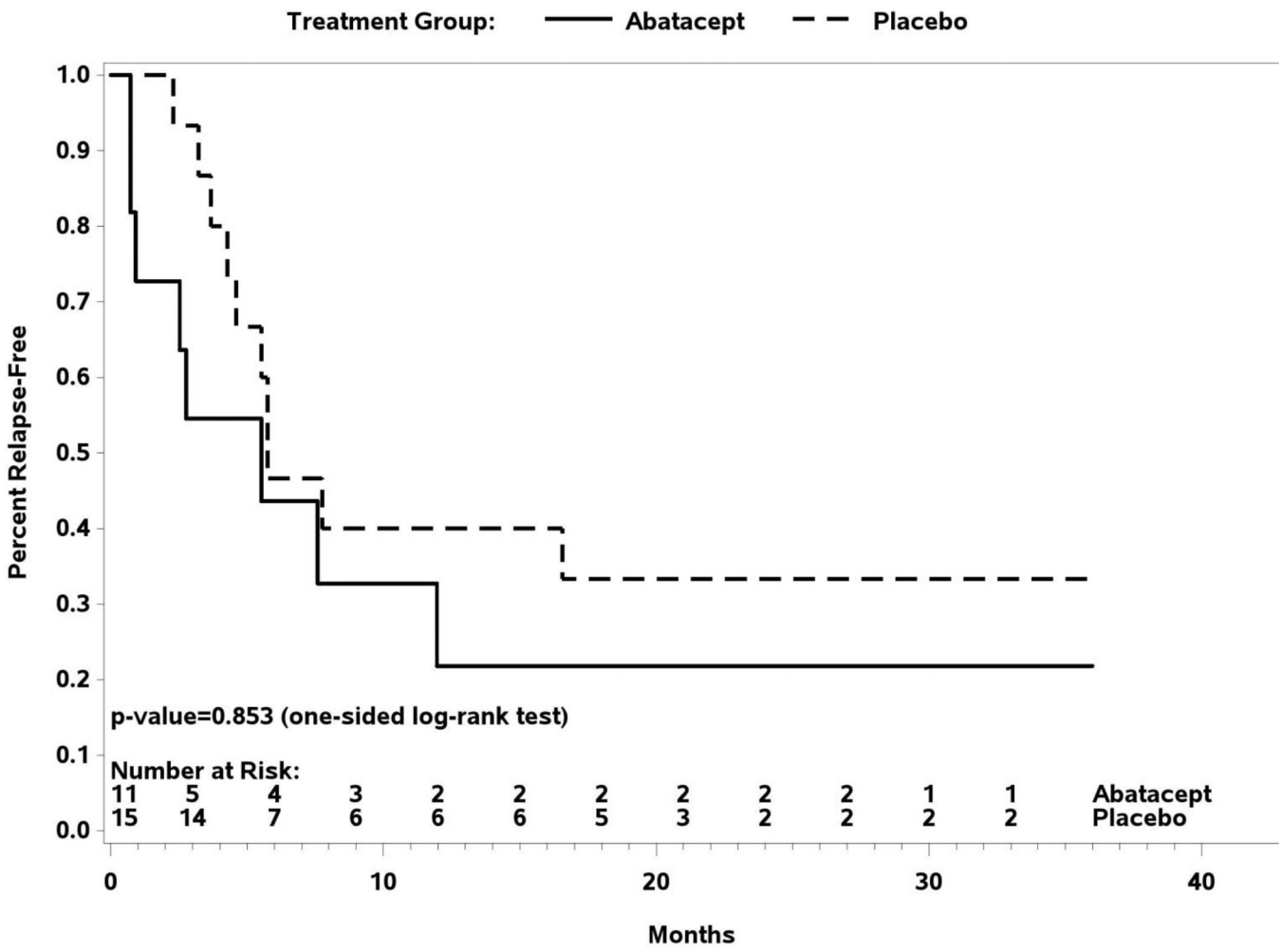

Figure 3.
Relapse-free survival following randomization.

Table 1

Baseline clinical and demographic features of the 26 randomized patients

	Abatacept N=11	Placebo N=15	
	N (%)	N (%)	p-value
Patient demographics			
Age at enrollment (years), median (range)	30.2 (18.9–58.9)	28.6 (19.5–57.0)	0.92
Age at diagnosis (years), median (range)	25.1 (16.9–52.2)	28.5 (15.9–56.9)	0.47
Sex			
Female	9 (82%)	13 (87%)	1.00
Male	2 (18%)	2 (13%)	-
Diagnosis category at enrollment			
Newly diagnosed	0 (0%)	4 (27%)	0.11
Relapsing	11 (100%)	11 (73%)	-
Disease duration (years), median (range)	5.1 (0.4–19.0)	0.91 (0–17.0)	0.10
Race			
Asian	1 (9%)	3 (20%)	0.35
Black or African-American	1 (9%)	0 (0%)	-
Caucasian	8 (73%)	12 (80%)	-
Unknown/not reported	1 (9%)	0 (0%)	-
Active disease characteristics at enrollment			
Sustained fever of > 38° C for > 1 week	0 (0%)	1 (7%)	1.00
Vascular pain or tenderness	2 (18%)	3 (20%)	1.00
Headache	2 (18%)	3 (20%)	1.00
Ischemic retinopathy or visual loss	0 (0%)	1 (7%)	1.00
Tongue/jaw pain or claudication	1 (9%)	1 (7%)	1.00
Extremity claudication	5 (46%)	9 (60%)	0.46
Musculoskeletal symptoms	4 (36%)	5 (33%)	1.00
Malaise/fatigue + ESR > 40 mm/hour	6 (55%)	6 (40%)	0.46
New vascular stenosis or aneurysm	4 (36%)	7 (47%)	0.70
Other features attributed to TAK	1 (9%)	3 (20%)	0.61
Prior non-glucocorticoid immunosuppressive treatment			
Adalimumab	2 (18%)	2 (13%)	1.00
Azathioprine	2 (18%)	3 (20%)	1.00
Cyclosporine	1 (9%)	1 (7%)	1.00
Cyclophosphamide-daily	0 (0%)	1 (7%)	1.00
Cyclophosphamide-intravenous	1 (9%)	0 (0%)	0.42
Etanercept	0 (0%)	2 (13%)	0.49
Infliximab	4 (36%)	1 (7%)	0.13
Leflunomide	1 (9%)	0 (0%)	0.42

	Abatacept N=11	**Placebo N=15**	
	N (%)	**N (%)**	**p-value**
Methotrexate	9 (82%)	8 (53%)	0.22
Mycophenolate	2 (18%)	2 (13%)	1.00
Tacrolimus	0 (0%)	1 (7%)	1.00

ESR: erythrocyte sedimentation rate; TAK: Takayasu's arteritis

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Table 2

Description of disease relapses in the abatacept and placebo study arms.

Disease Features at relapse		ESR mm/hr	CRP mg/dl	Prednisone Dose at relapse (mg)	Last infusion (week)
ABATACEPT					
1	Leg extremity claudication, malaise	74	9.5	15	12
2	Arthralgias, malaise	92	90.9	0	60
3	Arthralgias, skin lesions	52	12.3	4	20
4	Arthralgias, erythema nodosum	98	99.2	0	32
5	Leg claudication, headache, malaise	30	116.0	9	20
6	Carotidynia, jaw/tongue claudication, leg claudication	41	20.7	15	12
7	Arthralgias, malaise, fatigue, myalgias	44	60.1	12.5	16
8	Carotidynia, fatigue, malaise	25	33.6	0	44
PLACEBO					
1	Vascular back pain	76	9.6	7	20
2	New vascular stenosis	53	3.2	0	36
3	Arthralgias, malaise, myalgias	43	50.8	0	84
4	Headache, scalp pain, arthralgias, arthritis, artery pain, malaise	33	2.6	0	28
5	Pericarditis, myalgias, malaise	50	1.6	0	32
6	New vascular stenosis	31	20.9	0	32
7	Headache, carotidynia	80	69.8	0	32
8	Jaw/tongue claudication, blurred vision, dizziness	ND	ND	6	24
9	Leg claudication, arthralgia, mesenteric ischemia, melena, malaise	30	15.4	1	24
10	New vascular stenosis, venous thrombosis	129	9.2	0	44

CRP: C reactive protein; ESR: erythrocyte sedimentation rate, ND: not done

Table 3

Serious adverse events. Summary of 24 events in 15 patients.

	Non-randomized (N=8) 3 events	**Abatacept (N=11) 12 events**	**Placebo (N=15) 9 events**
Ischemic colitis (occurred during screening) *	-	-	1
Ischemic colitis *	-	-	1
Rectal bleeding	-	-	1
Possible pyelonephritis	-	1	-
Pyelonephritis *	-	-	1
Chest pain of unclear etiology	-	-	1
Epiglottitis	-	-	1
Appendicitis	-	-	1
Nausea/vomiting/diarrhea due to possible infection	-	-	1
Severe headache due to migraine	-	1	-
Chest pain non-cardiac (6 events in one patient)	-	1	-
Chest pain non- cardiac	-	1	-
Chest pain non- cardiac	-	1	-
Chest pain non- cardiac	-	1	-
Chest pain non- cardiac	-	1	-
Chest pain non- cardiac	-	1	-
Dyspnea/dysphagia due to gastroesophageal reflux	-	-	1
Arterial thrombosis following angioplasty	-	1	-
Skin site infection from thrombectomy	-	1	-
Duodenal ulcer	-	1	-
Elective aortic surgery	-	1	-
Elective aorto-bi-iliac bypass	1	-	-
Deep venous thrombosis *	1	-	-
Possible urinary tract infection *	1	-	-

* occurred within the first 12 weeks