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A RANDOMIZED, DOUBLE-BLIND TRIAL OF ABATACEPT (CTLA4-IG) FOR THE TREATMENT OF GIANT CELL ARTERITIS

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Abstract

Objective—To compare the efficacy of abatacept to placebo for giant cell arteritis (GCA).

Methods—In this multicenter trial, patients with newly-diagnosed or relapsing GCA 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 with discontinuation of prednisone at week 28. Patients 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—Forty-nine eligible patients with GCA were enrolled and treated with prednisone and abatacept; forty-one reached the week 12 randomization and underwent a blinded randomization to abatacept or placebo. Prednisone was tapered using a standardized schedule reaching 20 mg daily at week 12 with discontinuation in all patients at week 28. The relapse-free survival at 12 months was 48% for those receiving abatacept and 31% for those receiving placebo ($p=0.049$). A longer median duration of remission was seen with abatacept (9.9 months) compared to placebo (3.9 months, $p=0.023$). There was no difference in the frequency or severity of adverse events between treatment arms, including infection.

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Conclusions—In patients with GCA the addition of abatacept to a treatment regimen with prednisone reduced the risk of relapse and was not associated with a higher rate of toxicity compared to prednisone alone.

Giant cell arteritis (GCA) is a chronic granulomatous vasculitic disease of unknown cause that preferentially involves medium- and large-sized arteries, such as the carotid arteries, aorta, and their major branches (1, 2). GCA typically affects people over the age of 50 and is the most common systemic vasculitis seen in the Northern Hemisphere (3). Glucocorticoids have been recognized to effectively treat GCA with improvement in symptoms and prevention of cranial ischemic complications, including blindness (4, 5). However, glucocorticoids are associated with significant toxicity, particularly in the older patient population affected by this disease (6). This morbidity risk is further compounded by the occurrence of disease relapse in at least 70% of patients resulting in the need for long-term therapy with glucocorticoids (7). It has therefore been a high priority and unmet need in GCA to identify safer, effective therapeutic options beyond glucocorticoids.

Although the cause of GCA remains unknown, experimental data suggest that GCA is an antigen-driven disease in which activated T lymphocytes, macrophages, and dendritic cells play a critical role in the disease pathogenesis (8–11). 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 thereby inhibiting T cell activation (12–14). Abatacept is approved by the Food and Drug Administration for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis where it has been found to have a low 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 GCA, together with the favorable toxicity profile that had been seen with abatacept (15–17), a randomized trial was conducted with the objectives of investigating the efficacy and safety of abatacept in the treatment GCA.

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 GCA who had active disease within the prior 2 months. All patients met the modified American College of Rheumatology classification criteria for GCA (18) in which they were required to have 3 of 5 the following criteria with 1 of the 3 consisting of criteria 4 or 5: 1) age at disease onset of greater than 50 years, 2) new onset or new type of localized pain in the head, 3) erythrocyte sedimentation rate (ESR) of greater than 40 mm in the first hour by the Westergren method, 4) a temporal artery abnormality (i.e., temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries), 5) temporal artery or large vessel biopsy showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cell or characteristic changes of large vessel stenosis or aneurysm by arteriography. 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 live vaccination, 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.

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). 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 GCA 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 laboratories were obtained at each study visit. All patients without contraindications underwent magnetic resonance imaging of the aorta and branches at study entry. In patients found to have large-vessel involvement this imaging was repeated at 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-narcotic 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 GCA by the investigator that necessitate 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 GCA treated with prednisone was estimated to be 30% based on prior published literature (7). 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 58 patients with GCA who signed informed consent and underwent protocol screening between February 2009 and January 2014 when the study met enrollment goals (Figure 2). Nine of the 58 were not eligible and 49 patients received study drug. Eight of these 49 patients were withdrawn, relapsed, or not in remission at week 12 resulting in a randomized study population of 41 patients. The baseline and demographic features of the 41 randomized patients are listed in Table 1. Thirty-two patients had undergone a temporal artery biopsy of which 25 were positive.

Twenty patients were randomized to abatacept and 21 to placebo. Thirty four of the 41 patients met an endpoint of relapse or follow-up in remission at week 64. The 7 patients who either voluntarily withdrew or who were withdrawn by the investigator prior to week 64 were included in the analysis using their status at the last available follow-up.

Of the 41 randomized patients, 7 voluntarily withdrew or were withdrawn by the investigator prior to week 64. These were included in the intent-to-treat analysis using their status at the last available follow-up. Of the 7 patients, 3 were randomized to abatacept with 1 patient who voluntarily withdrew relapsing 8 weeks after last infusion, 1 patient withdrawn by the site investigator for reason of severe infection who relapsed 6 weeks after last infusion, and 1 patient was withdrawn by site investigator who was in remission at last follow-up. Of the 4 patients randomized to placebo; 3 patients voluntarily withdrew who were all in remission at

last follow-up and 1 patient who was withdrawn for reason of malignancy who was also in remission at last follow-up.

Efficacy Assessments

In the intent-to-treat analysis of the 41 randomized patients, the relapse-free survival at 12 months was 48% for those receiving abatacept and 31% for those receiving placebo ($p=0.049$), (Figure 3). A longer median duration of remission was seen with abatacept (9.9 months) compared to placebo (3.9 months), $p=0.023$.

A covariate analysis examining those variables that statistically differed between the study arms, demonstrated that sex, age at diagnosis, and age at enrollment did not impact the study results.

The relapses that were observed during the trial reflected typical characteristics of GCA (Table 2). Only one patient experienced a cranial ischemic complication at relapse during the randomized treatment period with partial vision loss assumed to be secondary to GCA that resolved with reinstitution of glucocorticoids. Another patient experienced a branch retinal artery occlusion attributed to active GCA but this occurred during the post-treatment follow-up period 5 months after stopping abatacept and while being managed according to best medical judgment. An elevation of ESR and/or CRP protein above normal was seen in the majority of relapses.

Of the 17 patients who remained in remission (10 abatacept, 7 placebo), 3 declined to return for post-treatment visits. The other 14 patients all remained in remission during the extended follow-up period, 4 through post-treatment week 12 and 10 through post-treatment week 24 (See Supplementary Table 2). For those who reached common close in remission, the total duration of study treatment ranged from 64 to 304 weeks.

A pre-specified subset analysis was performed on the population of 34 patients who relapsed or were in remission at week 64 in which the difference between treatment arms became larger. The relapse-free survival at 12 months was 52.9% for those receiving abatacept and 23.5% for those receiving placebo ($p=0.014$).

Adverse events

Overall, 129 adverse events occurred in 35 patients, including 23 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). No deaths occurred while on study.

A total of 33 infections were reported during the trial in 20 patients. Twenty-nine infections occurred in the randomized population with 4 occurring in patients who did not undergo randomization. There was no statistical difference in the frequency of infections between treatment arms. Two infections required hospitalization and were reported as serious adverse events. Within the randomized patients, 6 infections in 4 patients occurred within the first 12 weeks. All 4 infections that occurred in the non-randomized patients developed after

discontinuation of abatacept; 2 occurring within 3 months of last drug administration and 2 occurring over 3 months later.

Of the 49 treated patients, 3 developed malignancies during the study period: a papillary urothelial transitional cell carcinoma in a patient randomized to abatacept who received the last dose of study drug week 76, an endometrial carcinoma in a patient randomized to abatacept who received the last dose of study drug week 96, and a skin squamous cell carcinoma treated with radiation therapy in a patient randomized to placebo.

DISCUSSION

Since the 1950's glucocorticoids have represented the foundation of treatment for GCA. Although effective, glucocorticoids are associated with substantial toxicity and relapse of vasculitis occurs in a high percentage of patients. Identifying other effective treatment options that may lessen the risk of relapse in GCA has been the goal of a number of previous well-designed studies (7, 19–23). Although methotrexate has arguably shown the greatest benefit, it has at most a modest effect in GCA (7, 19, 22, 23).

Abatacept was an attractive agent to investigate in patients with GCA because of the drug's favorable safety profile and mechanism of action modulating T cell activation that was hypothesized to play a role in the pathophysiology of GCA.

In this randomized withdrawal design trial, patients who achieved remission and were randomized to continue abatacept had a significantly higher rate of relapse-free survival compared to those who were randomized to placebo, providing supportive evidence of the efficacy of abatacept in this study population. This difference between groups is clinically meaningful to patients with GCA; corresponding to a prolonged duration of remission during which time they are not exposed to glucocorticoids and their potential toxicities that impact quality of life. These findings are particularly impactful given the older patient population affected by this disease, which is the most common form of primary systemic vasculitis.

In seeking to identify a less toxic treatment option in GCA, the safety of abatacept was an important aspect of this study. High-dose prednisone is associated with significant side effects and one concern was whether the addition of abatacept would increase the risk of infection or other side effects. From the comparative analysis between study arms, there was no difference in the type or severity of adverse events seen in those randomized to abatacept versus those who received placebo. There was also no signal suggesting enhanced toxicity during the first 12 weeks when all patients concurrently received high-dose glucocorticoids plus abatacept.

As a standardized prednisone taper was applied to both arms and all patients reached a prednisone dose of 20 mg/day at randomization and were off prednisone at week 28, there was by definition no difference in prednisone dose or duration between study arms. This schedule was similar to ones previously utilized in clinical trials of GCA and it allowed sufficient time before the primary endpoint analysis to assess the impact of the study drug without prednisone.

A number of factors strengthen these results. This trial was conducted by clinician investigators experienced in the care of patients with GCA and clinical trials, which provided an enhanced ability to evaluate parameters of disease activity as well as monitor for toxicity in these older patients. The choice of a double-blind randomized withdrawal design was attractive for several reasons. Because there had been no prior experience with abatacept in GCA or the use of abatacept combined with high-dose prednisone, this design in which all patients initially received abatacept with high-dose prednisone provided an ideal opportunity to gain initial efficacy data and to assess safety that would be relevant to clinical practice.

This study has some limitations to consider. One of the greatest investigational and clinical challenges in GCA is that there remains no definitive indicator for disease activity and assessment of remission and relapse is based on clinical and imaging parameters. The definitions of disease activity used in this trial were pre-specified within the protocol and required a higher burden of evidence for those features that were the most subjective. Moreover, the definitions that were used were based on those that are applied by practicing physicians and utilized parameters commonly assessed in the routine care of patients. Review of the disease characteristics of all relapses were adjudicated by both the site investigator and study principal investigator during the blinded phase and by the study team following the end of the trial with no changes in outcome assessment being made after unblinding. The features of active disease at the time of relapses were convincing in both arms and provide strong support for the method of assessment of remission/active disease used in this study.

Despite the small sample size, the difference in relapse-free survival between treatment arms was statistically and clinically significant. In addition, a benefit associated with abatacept exceeding the clinically meaningful difference predefined in the study design, was found in a secondary analysis of those with relapse or remission at 64 weeks, further strengthening these findings.

Although the small sample size could also potentially impact the role of confounding variables within the study, the influence of individual GCA characteristics on treatment response remains unclear. The study was not powered to demonstrate differences between specific features such that any findings from the analysis of individual variables could be inaccurate and misleading. The planned design to look for a large difference between study arms that was felt to be clinically meaningful diminishes the impact that any unknown confounding variables could have had on the study findings.

This study also provides useful insights into the currently available measures of disease activity in GCA. ESR and CRP are commonly-used biomarkers in GCA but a rise in these markers did not accompany every relapse, including in the setting of otherwise compelling features of disease activity, an observation previously noted (24). These observations reflect the need for ongoing investigation of clinical, laboratory, and imaging biomarkers as well as patient-reported outcomes to better assess disease activity in GCA (25, 26).

Although reduction in relapse would hopefully result in a reduction of overall medication-related morbidity, this trial does not allow conclusions to be drawn as to whether abatacept reduces the risk of glucocorticoid-related toxicity in GCA. It is also important to recognize that abatacept was used as an adjunctive treatment with standard prednisone in this trial and no conclusions should be reached regarding the effect of abatacept for the treatment of active GCA independent of glucocorticoids.

The ongoing development of novel agents that target specific immunologic components will continue to provide exciting opportunities for novel therapies in GCA. Tocilizumab, an interleukin-6 receptor blocker, has also been proposed as an adjunctive treatment for GCA (27, 28), including in a phase 3 trial currently underway (29). Every agent possesses a unique side-effect profile which may make it contraindicated for certain patients. Continuing to investigate promising therapeutic options in GCA remains vitally important.

In conclusion, this study demonstrated that treatment of GCA with abatacept combined with glucocorticoids results in a longer duration of relapse-free survival than treatment with prednisone alone and is well tolerated. In the older patient population impacted by GCA, this potential for a glucocorticoid-sparing option is clinically important and meaningful.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
A randomized trial of abatacept in giant cell 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.
Kaplan-Meier plots of relapse-free survival following randomization.

Table 1

Baseline clinical and demographic features of the 41 randomized patients

		Abatacept N=20	Placebo N=21	
		N (%)	N (%)	p-value
Patient demographics				
Age at enrollment (years), median (range)		63.5 (57.3–80.1)	71.5 (54.3–86.6)	0.052
Age at diagnosis (years), median (range)		62.4 (53.6–80.1)	70.5 (52.4–86.6)	0.043
Sex	Female	16 (80%)	21 (100%)	0.048
	Male	4 (20%)	0 (0%)	-
Diagnosis category at enrollment	Newly-diagnosed	12 (60%)	11 (52%)	0.62
	Relapsing	8 (40%)	10 (48%)	-
Disease duration (years), median (range)		0.15 (0–13.3)	0.31 (0–6.9)	0.77
Race	Asian	0 (0%)	1 (5%)	1.00
	Black/ African-American	1 (5%)	1 (5%)	-
	Caucasian	19 (95%)	19 (91%)	-
TA biopsy performed		15 (75%)	17 (81%)	0.72
TA biopsy positive (of those performed)		12 (80%)	13 (77%)	1.00
Active disease characteristics at enrollment				
Vascular pain or tenderness		8 (40%)	10 (48%)	0.62
Headache		12 (60%)	13 (62%)	0.90
Ischemic retinopathy or visual loss		1 (5%)	1 (5%)	1.00
Tongue/jaw pain or claudication		10 (50%)	9 (43%)	0.65
Extremity claudication		3 (15%)	6 (29%)	0.45
Musculoskeletal symptoms		6 (30%)	5 (24%)	0.65
Malaise/fatigue + ESR/CRP elevation		7 (35%)	10 (48%)	0.41
New vascular stenosis or aneurysm		2 (10%)	3 (14%)	1.00
Other features attributed to GCA		5 (25%)	3 (14%)	0.45

Abbreviations: CRP: C reactive protein; ESR: erythrocyte sedimentation rate; GCA: giant cell arteritis; TA: temporal artery

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	Headache, scalp pain, PMR, dizziness	14	0.2	0	28
2	Jaw/tongue claudication, hoarseness	35	39.9	0	24
3	Headache, PMR, malaise	43	9.9	0	28
4	Malaise	48	80.6	0	24
5	Headache, scalp pain	17	17.3	20	12
6	Headache, partial visual loss	8	1.2	0	28
7	Headache, diplopia, night sweats, sensory neuropathy, malaise	10	0.3	10	52
8	PMR, arthralgias	49	32.4	3	20
9	PMR, arthralgias (occurred 6 weeks after last infusion)	10	5.6	0	48
10	PMR, arthralgias, myalgias (occurred 8 weeks after last infusion)	14	3.0	0	28
PLACEBO					
1	Headache, temporal artery tenderness, jaw/tongue claudication	30	1.1	7	20
2	Headache, scalp pain, PMR	36	10.0	0	28
3	Headache, jaw/tongue claudication, malaise	66	71.3	0	24
4	Headache, PMR, arthralgia	33	6.0	1	24
5	Headache, temporal artery tenderness, jaw/tongue claudication	44	10.0	0	64
6	Headache, scalp pain, PMR, malaise	36	3.0	0	24
7	Weight loss, fever, arthralgia, arthritis, malaise	14	0.2	20	12
8	Scalp pain, jaw/tongue claudication, PMR, malaise	75	29.2	0	24
9	Headache, PMR, arthralgia	40	0.8	0	36
10	PMR	31	27.8	0	32
11	Bilateral upper extremity claudication	17	11.8	9	16
12	PMR, arthralgia, fatigue, malaise	39	28.2	0	24
13	New large vessel stenosis	63	33.1	4	24
14	Headache, temporal artery tenderness, jaw/tongue claudication	23	91.2	1	24

Abbreviations: CRP; C reactive protein; ESR; erythrocyte sedimentation rate; PMR; polymyalgia rheumatica

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Table 3

Serious adverse events. Summary of 23 events in 15 patients.

	Non-randomized N=8	Abatacept N=20	Placebo N=21	p-value
Diarrhea (3 months after abatacept)	1	-	-	-
Syncope, melena (3 months after abatacept)	1	-	-	-
Urinary tract infection (4 months after abatacept)	1	-	-	-
Deep venous thrombosis (6 months after abatacept)	1	-	-	-
Anticoagulation hematoma (6 months after abatacept)	1	-	-	-
Herpes zoster	-	1	-	0.487
Squamous cell carcinoma skin	-	-	1	1.000
Diarrhea/dehydration	-	1	-	0.487
Diverticulitis	-	1	-	0.487
Hyperglycemia	-	-	1	1.000
Spinal surgery	-	-	1	1.000
Syncope	-	-	1	1.000
Branch retinal artery occlusion	-	1	-	0.487
Partial vision loss	-	1	-	0.487
Retinal detachment	-	1	-	0.487
Narcotic withdrawal	-	-	1	1.000
Chronic obstructive pulmonary disease	-	-	1	1.000
Dyspnea	-	-	1	1.000
Transitional cell carcinoma	-	1	-	0.487
Endometrial carcinoma	-	1	-	0.487
Urine electrolyte disturbance	-	-	1	1.000
Knee replacement	-	1	-	0.487
Deep venous thrombosis after knee replacement	-	1	-	0.487