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An open-label trial of abatacept (CTLA4-IG) in non-severe relapsing granulomatosis with polyangiitis (Wegener's)

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Abstract

Objectives—To determine the safety and efficacy of abatacept in non-severe relapsing granulomatosis with polyangiitis (Wegener's)(GPA).

Methods—An open-label trial of intravenous abatacept was conducted in 20 patients with non-severe relapsing GPA. Prednisone up to 30 mg daily was permitted within the first 2 months, and patients on methotrexate, azathioprine, or mycophenolate mofetil continued these agents. Patients remained on study until common closing or early termination.

Results—Of the 20 patients, 18 (90%) had disease improvement, 16 (80%) achieved remission (BVAS/WG=0) at a median of 1.9 months, and 14 (70%) reached common closing. Six patients (30%) met criteria for early termination due to increased disease activity; 3 of 6 achieved remission and relapsed at a median of 8.6 months. The median duration of remission before common closing was 14.4 months, with the median duration of time on study for all patients being 12.3 months (range 2–35 months). Eleven of the 15 (73%) patients on prednisone reached 0 mg. Nine severe adverse events occurred in 7 patients, including 7 infections that were successfully treated.

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Conclusions—In this study of patients with non-severe relapsing GPA, abatacept was well tolerated and was associated with a high frequency of disease remission and prednisone discontinuation.

Granulomatosis with polyangiitis (Wegener's) (GPA) is characterised by necrotising granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotising vasculitis affecting predominantly small to medium vessels.[1] While current treatment options can induce disease remission, relapses occur in 50–70% of patients, including a high proportion of non-severe relapses.[1–8] As morbidity and damage can occur from the disease and its treatment,[89] management of non-severe relapsing disease is a significant unmet need for patients with GPA.

Abatacept is comprised of the ligand-binding domain of CTLA4 plus modified Fc domain derived from IgG1. By containing CTLA4, abatacept blocks the engagement of CD28 with its ligand, thereby inhibiting T cell activation. Based upon the rationale that blockage of T cell activation might impact GPA disease pathogenesis,[10–18] we conducted an open-label standardised trial to investigate the safety and efficacy of abatacept in non-severe relapsing GPA.

METHODS

Patients

This open-label prospective trial enrolled 20 patients, age 15 years or older, who had a non-severe relapse of GPA within 28 days prior to enrolment. Details regarding the eligibility criteria are included in the online supplementary material.

Treatment protocol

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 every 4 weeks thereafter. In the absence of meeting criteria for early termination, abatacept was continued until common closing which was 6 months after enrolment of the final patient. Following common closing, post-treatment safety visits were performed at 1, 3 and 6 months.

Patients were permitted to receive up to prednisone 30 mg daily at study entry, but by month 2, they were required to be at the same or lower prednisone dosage that they were receiving at the time that the relapse occurred. At month 2, patients who were on prednisone began a standardised prednisone taper of 1 mg each week. Patients who developed symptoms during this taper were permitted to continue or resume prednisone up to 7.5 mg daily at the discretion of the investigator.

Patients who were on methotrexate, azathioprine, or mycophenolate mofetil at the time of enrolment were continued on this therapy during the study without dosage increase. Patients receiving standard preventive regimens at enrolment, such as prophylaxis for pneumocystis infection, a bone protection programme, or folic/folinic acid for those on methotrexate, continued these medications at a consistent dosage throughout the trial.

Outcome measures

The Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) was used to assess disease activity.[19] Disease improvement was defined by a reduction of the BVAS/WG and remission as a BVAS/WG=0. Disease relapse was defined as a rise in BVAS/WG ≥1 after achieving remission. Disease worsening was defined by the occurrence of any of the following events prior to remission: the development of any major criteria in the BVAS/WG, an increase in BVAS/WG of at least 2 points above enrolment, or symptoms/signs of GPA that could not be attributed to any other cause, and that require institution of prednisone of >30 mg daily within the first 2 months. Damage was assessed using the Vasculitis Damage Index (VDI).[20] The criteria for early termination and discontinuation of study drug are described in the online supplementary materials.

Statistical analysis

The primary objective of this study was to examine the safety of abatacept in GPA with the secondary objective being to gather data on the efficacy of abatacept in patients with non-severe relapsing GPA.

Study safety and adverse events

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). During protocol development, the study team identified selected adverse events for priority analysis including: infections, infusion reactions, cytopenias, transaminase elevations, gastrointestinal side effects, skin reactions and malignancies. This study was approved by the institutional review board at each site. Onsite monitoring was performed throughout the trial by the Data Management and Coordinating Center with study oversight by an independent data and safety monitoring board.

RESULTS

Patient population

Twenty patients were enrolled in this study over a period of 28 months. The baseline and demographic features of these patients are listed in table 1.

Clinical response

The efficacy endpoints are summarised in table 2, with further details in the online supplementary materials.

Fourteen of 20 patients (70%) remained on study until common closing, with six meeting criteria for early termination. All terminations were for the reason of active disease. The median BVAS/WG at early termination was 3 (range 2–4) and there was no severe active disease. Of these six patients, four were not on prednisone, with the other two patients being on prednisone 7 mg and 12 mg daily. Three of the six met criteria for relapse having achieved remission prior to early termination. Of the remaining three patients, two (10%) had disease worsening, with one first having disease improvement followed by worsening.

Glucocorticoid reduction

A total of 15 patients received prednisone within the first 2 months, 13 of whom were receiving glucocorticoids at the time of enrolment. Eleven of these 15 patients (73%) were able to come off prednisone of which eight remained off until common closing. Overall, 11 of 20 were in remission and off of prednisone at common closing, and had been off for a median of 13.6 months (range 4–30 months). Of the remaining nine patients, six were those patients who discontinued study drug because of active disease, one was a patient who improved but did not meet criteria for remission, and two patients achieved and maintained remission until common closing, but remained on prednisone 5 mg daily.

Toxicity

Table 3 summarises the main adverse events that occurred on study. Further information is provided in the online supplementary materials.

DISCUSSION

Despite advances in the treatment of GPA, relapse remains a frequent occurrence often associated with cumulative organ damage and the need for long-term glucocorticoids. With its favourable safety profile in rheumatoid arthritis and potential to modulate T cell activation, abatacept is an attractive agent to investigate in patients with GPA with non-severe disease.

The findings from our prospective study of 20 patients with non-severe relapsing GPA treated with abatacept are compelling and provide a signal supporting therapeutic efficacy of abatacept in non-severe GPA. In this study population who had longstanding relapsing disease, 90% improved on abatacept, 80% experienced disease remission, 70% remained on study until common closing, and 10 of 15 on prednisone were able to discontinue glucocorticoids. While efficacy cannot be definitely determined from a small open-label study, several characteristics of this population provided strengths in assessing the signal for efficacy. Most patients in the study cohort had long-standing disease with prior relapses despite significant immunosuppressive therapy, and had already incurred organ damage. This cohort is reflective of the chronic course commonly seen in GPA and is also a group for which recurrent relapse would be readily expected to occur in the face of an ineffective therapy.

The nature, frequency and severity of adverse events, and specifically infections, were comparable to what has been observed in other therapeutic trials of GPA. As would be expected in GPA, upper airways infections represented the most common infection seen during the trial. All infections were successfully treated and none mandated study treatment termination.

An important aspect of this trial was its concentration on relapsing non-severe disease. With over 50% of patients with GPA experiencing relapse, there is a need for studies that address the challenges faced by these patients. As a greater understanding has been gained about GPA, there has been an appreciation of the differing spectrum of disease severity.[4] That this trial focused on non-severe disease is in keeping with the evolution of therapeutic

investigation in GPA, whereby treatment decisions have increasingly become based on specific disease and patient factors.

This study has some limitations, including the small sample size and uncontrolled design. Although the allowance of prednisone early in the course of the study may have impacted initial response, the requirement to be back to the prior dose by month 2 together with the extended duration of follow-up would have minimised the influence of this agent on remission maintenance. Continuation of methotrexate, azathioprine and mycophenolate mofetil for those who were on these agents at enrolment could also have represented a confounding variable, but as no increase in dose was permitted, their actions were unlikely to have resulted in the study findings. This also prevented any problems due to treatment withdrawal, and allowed the efficacy of abatacept as adjuvant therapy to be assessed. These results cannot be generalised to all GPA patients, and as severe disease was excluded from this trial, no conclusions can be reached regarding the efficacy of abatacept in this setting.

Non-severe relapses occur commonly in patients with GPA and are associated with substantial damage and morbidity. In this study, abatacept was well tolerated and led to disease remission and prednisone discontinuation in a high percentage of patients. These findings suggest that abatacept warrants further study as a treatment option for patients who have non-severe relapsing GPA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline clinical and demographic features of the patients

Variable	Value at study entry
Age (range)	45 years (17–73 years)
Female/male	9/11
cANCA/anti-PR3, n (%)	16 (80%)
pANCA/anti-MPO, n (%)	2 (10%)
Biopsy performed for diagnosis	17 (85%)
GPA disease duration, median (range)	100 months (5–326 months)
BVAS/WG, median (range)	3.0 (1–6)
VDI, median (range)	3.0 (0–7)

Organ involvement, n (%)	Before study entry (ever) (%)	Active disease at study entry (%)
Constitutional	17 (85)	6 (30)
Ear, nose, throat	20 (100)	18 (90)
Bloody nasal discharge/crusting/ulcer		14
Sinus involvement		14
Conductive hearing loss		2
Subglottic inflammation		2
Musculoskeletal	15 (75)	10 (50)
Arthralgias/arthritis		9
Myalgias		1
Cutaneous	12 (60)	8 (40)
Purpura		4
Skin nodules		3
Rash		1
Mucous membranes	5 (25)	1 (5)
Lung	14 (70)	6 (30)
Nodule/cavity		4
Infiltrate		1
Endobronchial disease		1
Kidney	8 (40)	0
Eye	6 (30)	0
Nerve	4 (20)	1 (5)

Medication usage, n (%)	Before study entry (ever)	At entry and during trial
Cyclophosphamide intermittent	4 (20)	0
Cyclophosphamide daily	11 (55)	0
Azathioprine	10 (50)	3 (15)
Methotrexate	15 (75)	7 (35)
Mycophenolate mofetil	5 (25)	4 (20)
Etanercept	1 (5)	0
Infliximab	1 (5)	0

Medication usage, n (%)	Before study entry (ever)	At entry and during trial
Rituximab	5 (25)	0
Plasmapheresis	1 (5)	0
Trimethoprim/sulfamethoxazole*	6 (30)	0
Intravenous immunoglobulin	1 (5)	0
Glucocorticoids	20 (100)	Entry 13 (65), During 15 (75)

* Defined as a dose of trimethoprim 800 mg/sulfamethoxazole 160 mg twice a day (does not include doses as used for pneumocystis prophylaxis).

BVAS/WG, Birmingham Vasculitis Activity Score for Wegener's Granulomatosis; cANCA, cytoplasmic antineutrophil cytoplasmic antibodies; GPA, granulomatosis with polyangiitis (Wegener's); MPO, myeloperoxidase; pANCA, perinuclear antineutrophil cytoplasmic antibodies; PR3, proteinase 3; VDI, Vasculitis Damage Index.

Table 2

Summary of efficacy endpoints

Parameter	n (%)
Disease improvement	18 (90)
Remission (BVAS/WG=0)	16 (80)
Relapse	3 (19)
Reached common closing	14 (70)

Parameter	Median	Range
Time from entry to remission (months)	1.9	1–19
Time from remission to relapse (months)	6.7	5–9
Time on study before common closing/early termination	12.3	2–35
Remission duration before common closing (months)	14.4	4–20
VDI at common closing/early termination	3.0	0–7

BVAS/WG, Birmingham Vasculitis Activity Score for Wegener's Granulomatosis; VDI, Vasculitis Damage Index.

Table 3

Adverse events

Serious adverse events (n=9)	# Events	# Patients	Possibly, probably, or definitely related
Infection	7	6	4
Dental	1	1	1
Ocular	2	2	2
Lung (pneumonia)	2	1	1
Upper airways	1	1	0
Gastrointestinal	1	1	0
Hospitalization for subglottic stenosis dilation	2	1	0
Overall adverse events (n=92)			
Infection	35	14	27
Upper airways	12	9	10
Infusion related (systemic)	9	1	9
Infusion related (intravenous site reaction)	2	1	2
Cytopenia	5	4	1
Neutropenia	2	2	0
Lymphopenia	1	1	1
Anemia	2	2	0
Transaminase elevation	0	0	–
Gastrointestinal side effects	0	0	–
Malignancy	0	0	–