Manuscript ID annrheumdis-2013-204164 entitled "AN OPEN-LABEL TRIAL OF ABATACEPT (CTLA4-IG) IN NON-SEVERE RELAPSING GRANULOMATOSIS WITH POLYANGIITIS (WEGENER'S)"

SUPPLEMENTARY MATERIALS

METHODS

Significant inclusion criteria

1. A diagnosis of granulomatosis with polyangiitis (GPA).

   Subjects must meet at least 2 of the 5 modified ACR criteria for the diagnosis of GPA. The modified ACR criteria are:

   a. Nasal or oral inflammation, defined as the development of painful or painless oral ulcers or purulent or bloody nasal discharge
   b. Abnormal chest radiograph, defined as the presence of nodules, fixed infiltrates, or cavities.
   c. Active urinary sediment, defined as microscopic hematuria (>5 red blood cells per high power field) or red blood cell casts
   d. Granulomatous inflammation on biopsy, defined as histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area
   e. Positive anti-neutrophil cytoplasmic antibody (ANCA) test specific for proteinase-3 measured by enzyme-linked immunoassay

2. Relapse of non-severe GPA within the past 28 days where disease activity is confined to one or more of the following sites, where the abnormal feature cannot be attributed to any cause other than GPA, and where the symptoms/signs are of such a nature that the usual

treatment would consist of the reinstitution or increase in glucocorticoids to no more than prednisone 30mg daily and/or an increase or addition of a second immunosuppressive agent other than cyclophosphamide (CYC):

- Sinonasal disease – defined by the presence of increased sinonasal symptoms together with the appearance of inflamed and/or ulcerated nasal membranes by physical examination
- Oral disease – defined by the presence of ulceration involving the oral mucosa or gingiva or salivary gland involvement
- Skin disease – defined by the presence of purpura, ulcerated, or non-ulcerated skin nodules
- Musculoskeletal disease – defined by the presence of arthritis, arthralgias, or myalgias. These features will be defined by the following characteristics – arthritis: inflammation involving one or more joints; arthralgias: the presence of joint pain without obvious swelling that is typically migratory and associated with joint stiffness; myalgias: the presence of pain and aching in the muscles. Patients who are enrolled for musculoskeletal disease alone must have had these features previously during their GPA disease course, have been known to require prednisone, and to be prednisone responsive.
- Pulmonary parenchymal disease defined as the presence of one or multiple nodules or cavities or infiltrates seen by chest computed tomography that are new or enlarging in the absence of respiratory compromise or features suggestive of alveolar hemorrhage
- Ocular disease – defined by the presence of episcleritis, uveitis, mild orbital disease, lacrimal gland inflammation

- Subglottic inflammation – defined by the presence of subglottic mucosal inflammation without significant stenosis
- Otic disease - defined as otitis media, mastoiditis
- Breast involvement – defined as breast disease previously biopsy proven as being due to GPA
- Urogenital involvement – defined as necrotizing granulomatous inflammation of the penis, urethra, vagina, cervix, or uterus
- Other disease features that meet the criteria of mild disease defined as the absence of disease that poses an immediate threat to either a critical individual organ or the patient's life, requires treatment with no more than prednisone 30mg daily, and does not require treatment with CYC.

Significant exclusion criteria

1. Presence of involvement that does not meet the criteria for non-severe disease

   Specifically this means:

   - No red blood cell casts in the urine, that are felt to be indicative of active disease.
   - No evidence of a rise in serum creatinine more than 25% above the patient's baseline that was present prior to disease relapse.
   - Pulmonary involvement must be circumscribed, such that the room air pO2 is > 70 mmHg or the room air O2 saturation by pulse oximetry is > 92%
   - No disease manifestations that would be scored as a major element in the Birmingham Vasculitis Activity Score for WG (BVAS/WG).
   - No disease may exist within any critical organ system that without the immediate institution of maximal therapy (i.e., pulse methylprednisolone and daily CYC), threatens the function of that organ and/or the patient's life

2. Presence of disease activity for which the investigator would normally initiate CYC.
3. Presence of disease activity for which the investigator would normally treat the subject with a dose of prednisone > 30mg daily.
4. Treatment with CYC at the time of enrollment
5. Treatment with prednisone at a dose of > 15 mg daily at the time of relapse.
6. Evidence of active infection (includes chronic infection).
7. Subjects who are pregnant or who are nursing infants.
8. Known infection with human immunodeficiency virus (HIV), hepatitis C, or a positive hepatitis B surface antigen.
9. Cytopenia: platelet count <80,000/mm^3, absolute neutrophil count <1500/mm^3, hematocrit < 20%.
10. Renal insufficiency defined by a serum creatinine of greater than or equal to 2.0 mg/dL or creatinine clearance of less than or equal to 35 ml/min.
11. 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.
12. Receipt of an investigational agent or device within 30 days prior to enrollment
13. A live vaccination fewer than 4 weeks before enrollment
14. Presence of a positive tuberculin skin test with induration of > 5mm
15. Radiographic evidence suggestive of tuberculosis.
16. Past treatment with rituximab within the past 12 months, or past treatment with rituximab more than 12 months ago where the B lymphocyte count has not returned to normal

Criteria for Early Termination

The criteria for early termination and discontinuation of study drug included:

1. development of worsening disease

2. failure to experience improvement by month 2
3. development of disease activity within the first 2 months that required use of prednisone >30 mg daily and/or other immunosuppressive therapy
4. inability to reduce prednisone by month 2 to the same dosage that the patient was receiving at the time of relapse
5. development of disease activity after month 2 that required prednisone > 7.5 mg daily and/or other immunosuppressive therapy
6. pregnancy
7. development of malignancy with the exception of basal or squamous cell carcinoma of the skin that was completely excised
8. severe infection requiring intravenous antibiotics or hospitalization
9. grade 4 toxicity
10. hypersensitivity to abatacept

RESULTS

Patient population

At study screening, 14 patients (70%) were on maintenance therapy with either methotrexate (median dose 25 mg/week, range 15-35 mg/week), azathioprine (median dose 150mg/day, range 50-150 mg/day), or mycophenolate mofetil (median dose 2000 mg/day, range 1500-3000 mg/day), and 13 (65%) were receiving glucocorticoids.

Clinical response

A Kaplan Meier plot of the cumulative incidence of remission is shown in Supplementary Figure 1. The BVAS/WG scores in the 20 patients during the trial duration are shown in Supplementary

Figure 2. Supplementary Figure 3 illustrates individual patient profiles of time on study, time in remission, and time off prednisone.

Early termination

Six of the 20 patients met criteria for early termination. The median time to early termination was 6.0 months (range 2-10 months). All terminations were for the reason of active non-severe disease in the following organ systems: upper airway (N=4), lung (N=2), musculoskeletal (N=3), constitutional (N=2), cutaneous (N=1), and hematuria without red blood cell casts or creatinine rise (N=2). Of the 6 patients, 2 were on prednisone (7 mg/day and 12 mg/day) and 4 were on a maintenance immunosuppressive agent (mycophenolate mofetil 2000 mg/day, mycophenolate mofetil 1500mg/day, methotrexate 20 mg/week, azathioprine 50 mg/day).

Glucocorticoid Reduction

A total of 15 patients received prednisone within the first 2 months, 13 of whom were receiving glucocorticoids at the time of enrollment. The maximum prednisone doses within the first 2 months were 30 mg (N=3), 20 mg (N=4), 12-15 mg (N=2), 10 mg (N=4), 7.5 mg (N=1), 5 mg (N=1) with 6 having a dose increase within the first 2 months. In examining the features associated with higher prednisone doses of 20-30 mg daily use within the first 2 months, the most predominant organ feature was lung involvement and of the 6 patients with active lung disease, 5 received these higher prednisone doses. There was also a tendency for patients treated with higher prednisone doses to have active disease involving more organ systems. Of the 7 patients who received prednisone 20-30 mg daily 2 had a BVAS/WG=6, 1 BVAS/WG=5, 2 BVAS/WG=4, 1 BVAS/WG=3, 1 BVAS/WG=2. By month 2, all but one patient who by definition had disease worsening, was at the same or lower prednisone dose as they were on at the time of the enrollment relapse. After month 2, no patient who remained on study was put back on prednisone or had a prednisone dosage increase.

Experience in patients on longterm glucocorticoids

Fourteen patients had received glucocorticoids within the year prior to study entry. Of these 14, the prednisone dosage ranged from 0-60 mg daily with a total 12 month cumulative dose ranging from 1120-7300 mg/12 months. Ten of these 14 patients (71%) who had received long-term glucocorticoids were able to come off prednisone during the study with 7 of the 14 remaining off prednisone through study end.

Damage

At enrollment, the median VDI score was 3.0 (range 0-7) in the 20 patients with the median score at common closing /early termination being 3.0 (range 0-7). Only 3 patients had an increase in VDI score throughout the course of the trial: a 1 point increase due to visual decline at month 15, a 1 point increase due to muscle weakness at month 9, and a 2 point increase due to chronic nasal crusting and septal perforation at month 6.

Toxicity

Nine serious adverse were seen in 7 patients, consisting of 2 hospitalizations in one patient following dilation of GPA-related subglottic stenosis from scarring and 7 infections. Of these infections, 3 occurred during the post-treatment safety observation period after abatacept had been discontinued and included hospitalizations for gastroenteritis, sinusitis, and bacterial pneumonia. Of the remaining 4 infections, one was a dental abscess requiring operative intervention deemed an important medical event by the site investigator in a patient also on azathioprine, one was hospitalization for dacryocystitis with rapid response to intravenous antibiotics, one was endophthalmitis in a patient with a corneal transplant deemed an important medical event by the site investigator, and one was hospitalization for pneumonia in a patient also on mycophenolate moftetil.

Overall, 92 adverse events occurred in 17 patients, which included 35 infections in 14 patients. Nine of these 14 patients were on a concomitant immunosuppressive agent (5 methotrexate, 2 azathioprine, 2 mycophenolate mofetil), 3 were not on a concomitant immunosuppressive, and 2 developed infections during the post-treatment safety period. Of the 6 patients who did not develop an infection, 5 were on a concomitant immunosuppressive. Of the 35 infections, 12 (34%) involved of the upper airways. There was one episode of localized herpes zoster and one patient with a positive sputum culture for *Mycobacterium avium intracellulare,* although this was felt to be a case of colonization and not a pathogenic infection requiring anti-microbial treatment. There were no infections with Pneumocystis, cytomegalovirus, or other opportunistic pathogens. Eleven grade 1 infusion-related events occurred in 2 patients with one patient experiencing mild systemic symptoms during 9 infusions and one patient having redness localized to the intravenous insertion site during 2 infusions. Five episodes of hemocytopenia were seen in 4 patients, of which 3 events were linked to a concomitant immunosuppressive agent. One patient developed leucopenia and anemia attributed to mycophenloate mofetil resulting in dose reduction, one patient developed leucopenia attributed to azathioprine resulting in dose reduction, one patient not on a concomitant immunosuppressive developed transient anemia that resolved, and one patient on methotrexate had lymphopenia, likely influenced by prednisone. No malignancies developed during this trial.

Supplementary Figure 1.

Kaplan Meier plot demonstrating the cumulative incidence of remission.

Supplementary Figure 2.

The BVAS/WG scores in the 20 patients followed over the trial duration (in months).

Supplementary Figure 3.

Individual patient profiles of time on study, time in remission, and time off prednisone.