Original Work

Efficacy of Tocilizumab in Reducing Steroid Requirements in Giant Cell Arteritis (GCA) at a Veterans Hospital

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Abstract

Objective: Giant Cell Arteritis (GCA) is a form of vasculitis involving large and medium-sized arteries, commonly affecting the cranial branches of the carotid arteries with the mainstay of therapy being glucocorticoids. In 2017, the FDA approved tocilizumab as a glucocorticoid-sparing agent for GCA. The purpose of this review was to evaluate the efficacy and safety of tocilizumab therapy in patients with GCA, and its efficacy in aiding in glucocorticoid de-escalation at a veterans' hospital.

Methods: A retrospective chart review was performed for patients at the William S. Middleton Memorial Veterans Hospital with prescriptions for tocilizumab for GCA from May 2017 to May 2019.

Results: Laboratory monitoring was appropriate for each patient in accordance with monitoring recommendations, with no instances of significant abnormal changes. Tocilizumab therapy was interrupted in one patient due to illness and in another due to a planned procedure. Tocilizumab therapy was discontinued in one patient diagnosed with prostate cancer who also showed remission of GCA and in another patient who chose to discontinue therapy after 33 months of therapy. All patients were able to be tapered off glucocorticoids while on tocilizumab.

Conclusions: Tocilizumab dosed weekly and every other week led to glucocorticoid-free remission of GCA at 52 weeks in the available literature. This review showed similar results, with the majority of patients having been glucocorticoid-free after approximately 15 months of treatment with tocilizumab.

Giant Cell Arteritis (GCA) is a form of vasculitis involving large- and medium-sized arteries, commonly affecting the cranial branches of the carotid arteries. GCA most commonly occurs in patients who are 50 years old or older. While there is no definitive diagnostic test for GCA, it is typically diagnosed by temporal artery biopsy and/or imaging, within the context of a suggestive clinical presentation. Symptoms of GCA can commonly include headaches, fevers, fatigue, weight loss, and jaw pain. One of the more severe manifestations is blindness, which is considered a medical emergency.[1] Lab data such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) often help with differential diagnosis; however, these are not diagnostic.[2]

Prompt treatment of this disease is imperative, particularly when visual manifestations are experienced, with the mainstay of therapy being chronic glucocorticoids.[3] Given the concern for potential adverse effects with long-term glucocorticoid therapy, glucocorticoid-sparing agents should be considered to facilitate tapering when possible. In 2017, the FDA approved tocilizumab as a glucocorticoid-sparing agent for GCA.

Tocilizumab (Actemra®, Genentech, Inc) is an interleukin-6 (IL-6) receptor antagonist that is FDA-approved for the treatment of rheumatoid arthritis (RA), giant cell arteritis (GCA), polyarticular and systemic juvenile idiopathic arthritis, and cytokine release syndrome.

Inflammatory stimuli induce endogenous IL-6 among other immunological responses, and tocilizumab inhibits these receptors, which leads to decreased cytokine and acute phase reactants.[4] Tocilizumab should not be used in patients who have already been prescribed another biologic disease-modifying antirheumatic drug (DMARD); who have active infections or untreated hepatitis B, latent tuberculosis, coccidioidomycosis or histoplasmosis; whose baseline absolute neutrophil count (ANC) is less than 2,000/mm^3; whose baseline platelet count is less than 100,000/mm^3; and/or whose baseline alanine transaminase (ALT) and/or aspartate transaminase (AST) is greater than 1.5 times the upper limit of normal. Live or live-attenuated vaccines should not be given during treatment with tocilizumab.[5]

Tocilizumab's effect on inflammatory markers has been shown to occur in as little as two weeks after initiation. Given its immunosuppressive properties, tocilizumab can increase the risk for infections and malignancies; serious warnings include activation of latent tuberculosis, invasive fungal infections, and bacterial and viral

infections. Safety recommendations for screening prior to and monitoring during tocilizumab therapy for GCA include testing for tuberculosis and hepatitis B prior to initiating therapy; monitoring neutrophils and platelets at baseline and at 4 to 8 weeks after the start of therapy and every 3 months thereafter; testing ALT, AST, and total bilirubin at baseline, then every 4 to 8 weeks after the start of therapy for the first 6 months and every 3 months thereafter; and obtaining a lipid panel at baseline and at 4 to 8 weeks following the start of therapy, then as recommended by current prescribing guidelines. All patients should be monitored for signs and symptoms of infection and of central nervous system demyelinating disorders.[4]

For patients with GCA, the FDA-approved standard tocilizumab dosing is a 162 mg subcutaneous injection, once weekly or once every other week, based on clinical considerations.[4] The efficacy and safety of tocilizumab 162 mg once weekly has been supported by a placebo-controlled study in 251 patients with GCA. This study concluded that tocilizumab, combined with a 26-week steroid taper, was superior to placebo when looking at the primary outcome of sustained, glucocorticoid-free remission at 52 weeks.[6]

At the William S. Middleton Memorial Veterans Hospital, there is a specialty rheumatology clinic staffed by rheumatologists; a clinical pharmacy specialist and pharmacy residents; and resident and fellow physicians. On average, at the time of data collection for this review, about 30% of the prescriptions for tocilizumab at this facility were prescribed for GCA. Given the high cost of this medication in the setting of limited literature and recent FDA approval for this indication, this review was conducted to evaluate the efficacy and safety of tocilizumab therapy in patients with GCA, and its success in helping with glucocorticoid de-escalation at this facility.

Methods

A retrospective chart review was performed for seven patients at the William S. Middleton Memorial Veterans Hospital with recent prescriptions for tocilizumab for GCA at the time of data collection. This evaluation was determined not to meet the federal definition of research and IRB review was not required per the University of Wisconsin-Madison Health Sciences IRB Not Research Determination Decision Tool. Baseline characteristics collected included patient demographics, tocilizumab start date and initial dose, and glucocorticoid dose at the time of tocilizumab start. The identified outcomes included time to glucocorticoid discontinuation; duration of tocilizumab treatment; and any clinically significant changes in neutrophils, platelets, liver transaminases, ESR, and CRP during therapy.

TABLE 1. Baseline Characteristics

Characteristic	*Value*
Mean age ± SD upon initiation	69 ± 4.5 years
Gender	100% Male
Race	• 86% White (n=6) • 14% Native Hawaiian or Other Pacific Islander (n=1)

SD: standard deviation

TABLE 2. Patient Outcomes

Characteristic	*Value*
Time to glucocorticoid discontinuation after start of tocilizumab	• 24 months (n=1) • 15 months (n=3) • 14 months (n=1) • 12 months (n=1) • 11 months (n=1)
Tocilizumab interrupted or discontinued	• 2 of 7 patients discontinued therapy (29%) • 2 of 7 patients interrupted therapy (29%)

Results

Seven patients were identified with recent prescriptions for tocilizumab for GCA. As shown in Table 1, all patients were males, with an average age of 69. Laboratory monitoring was appropriate for each patient in accordance with monitoring recommendations,[5] with no instances of significant abnormal changes. One patient had evidence of increased liver transaminases while on 8 mg/kg IV once monthly dosing, and upon holding the dose of tocilizumab, the enzymes normalized and tocilizumab was able to be restarted at a lower dose of 4 mg/kg IV once monthly with no further complications. No other patients experienced significant adverse drug reactions.

As shown in Table 2, tocilizumab therapy was interrupted for two patients. One interrupted therapy for a gastrointestinal illness, which led to two doses of tocilizumab being held. This patient held another dose of tocilizumab two months later after presenting to the emergency department to rule-out a deep vein thrombosis. This patient was on 8 mg/kg IV dosing and able to restart at a 4 mg/kg dose with no further complications. The second patient interrupted therapy due to a scheduled surgical procedure. Tocilizumab 162 mg subcutaneous injection was held for two weeks prior to and following surgery, then restarted with no documented complications.

As shown in Table 2, tocilizumab therapy was discontinued in two patients. One patient was diagnosed with prostate cancer after 19 months of therapy and had shown remission of GCA, leading to drug discontinuation. The other patient had chosen to self-discontinue tocilizumab after 33 months of therapy. Four months after the last injection of tocilizumab, the patient's inflammatory markers had increased; however, there was no documented evidence of disease relapse. At the time of this review, the remaining patients were on tocilizumab

TABLE 3. Tocilizumab Prescribing Trends

Characteristic	Value
Tocilizumab Initiation Dose	• 4 mg/kg IV once monthly (n=3) • 162 mg SQ once weekly (n=4)
Maintenance Dose at Time of Data Review	• 162 mg SQ once weekly (n=2) • 162 mg SQ once every 2 weeks (n=5)
Glucocorticoid initial dose (upon tocilizumab initiation)	• 20 mg once daily (n=4) • 30 mg twice daily (n=1) • 35 mg once daily (n=1) • 80 mg once daily (n=1)

IV: intravenous; SQ: subcutaneous

followed by a Veterans Administration (VA) rheumatology service.

Regarding efficacy of tocilizumab, the patient mentioned above whose therapy was interrupted showed a significant increase in CRP and ESR after two held doses. Their ESR increased from 17 mg/dL to 71 mg/dL, with an increase in CRP from 0.5 mm/hr to 7.98 mm/hr. After resuming therapy, one dose of tocilizumab led to normalization of the inflammatory markers. Another patient started therapy with their CRP and ESR at 8.63 mm/hr and 40 mg/dL, respectively; after one dose of subcutaneous tocilizumab, inflammatory markers decreased significantly to undetectable and 4 mg/dL, respectively. A third patient presented with an extremely elevated ESR at 105 mm/hr and after two doses of IV tocilizumab, the levels decreased to 95 mm/hr and then 23 mm/hr. The ESR continued to decrease with each consecutive dose until it eventually normalized.

All patients were able to taper off glucocorticoids while on tocilizumab with an average time to discontinuation of 15 months after tocilizumab start.

Discussion

The results show that tocilizumab therapy was both well-tolerated and efficacious, in line with what available literature has shown. As noted in Table 3, there were differences in the dosing and administration of tocilizumab upon initiation. Three patients were initiated on IV tocilizumab based on literature supporting its use, prior to the subcutaneous dose being studied.[7] The FDA announced its approval on May 22, 2017, and these patients were all transitioned to the FDA-approved subcutaneous dosing.

Although all data showed positive outcomes, this review does not come without limitations. One limitation is the small sample size of patients on this therapy for the treatment of GCA, given that this is a newer indication for tocilizumab. Another limitation of this review is the fact that adverse reactions to tocilizumab were not observed. While this is a positive finding, it also proves difficult to generalize the outcomes to a larger population where adverse effects might be more apparent. Given the retrospective nature of this review, and the fact that it is a snapshot in time, another limitation is the inability to assess the rate of disease recurrence after discontinuation of tocilizumab. While a significant improvement in lab surrogate markers (ESR, CRP) was evident with this therapy, the clinical significance of these surrogate changes on the progression of the GCA itself is unknown.

Conclusions

Tocilizumab dosed weekly and every other week has led to glucocorticoid-free remission of GCA at 52 weeks in the available literature. This review showed similar results, with the majority of patients having been glucocorticoid-free after approximately 15 months of treatment with tocilizumab. Based on the results of the review, tocilizumab can be considered as a therapy option for patients diagnosed with GCA on glucocorticoid maintenance therapy, who experience disease-flare during a steroid taper. Given the limited data showing a correlation between surrogate lab markers and GCA progression, it is important to continue to monitor patient symptoms and not solely rely on ESR and CRP to determine disease remission. Additionally, it is important to have a discussion with each patient regarding risks versus benefits of continuing tocilizumab therapy after 52 weeks, given that future studies are needed to determine the safety and efficacy of tocilizumab beyond 52 weeks for this indication.

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