Off-Label Drug Uses

Immune Globulin Intravenous: Myasthenia Gravis (Acute Exacerbation)

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

BACKGROUND

Myasthenia gravis, an autoimmune neuromuscular disease, is characterized by fluctuating weakness and fatigue of voluntary muscle. The usual cause of myasthenia gravis is the production of autoantibodies against the acetylcholine receptor and receptor-associated proteins at the neuromuscular junction. An acute exacerbation of the disease can be a life-threatening complication that causes swallowing impairment or respiratory failure. Treatment options for myasthenia gravis include symptomatic treatment (eg, anticholinesterase agents), long-term immunosuppressive therapy (eg, corticosteroids), and rapid immunomodulating treatments. Thymectomy has proven beneficial to increase the probability of remission and improvement in patients with thymomas and in those younger than 60 years of age with generalized myasthenia.¹

PATIENT POPULATION

Adult and adolescent patients with myasthenia gravis.

DOSAGE AND DURATION

Adjunctive therapy: 2 g/kg per treatment course, administered in divided doses over 2 to 5 consecutive days (eg, 400 mg/kg/day for 5 days).²⁻⁴ A single

dose of 1 g/kg may have similar efficacy to 1 g/kg given on 2 consecutive days.⁵

RESULTS

Controlled trials demonstrate the efficacy of short-term immune globulin IV (1 to 5 days) in the management of acute exacerbation of moderate to severe myasthenia gravis.³⁻⁵

Guidelines from the American Academy of Neurology (AAN), European Federation of Neurological Societies (EFNS), and the IVIG Hematology and Neurology Expert Panel recommend the use of immune globulin IV as adjunctive therapy for the treatment of acute exacerbation of myasthenia gravis based on controlled trials and expert consensus. These guidelines also do not recommend or state that evidence is insufficient evidence to recommend use of immune globulin IV as maintenance therapy for chronic myasthenia gravis.^{2,6,7}

Guidelines

American Academy of Neurology

According to an evidence-based AAN guideline on the use of intravenous immunoglobulin in the treatment of neuromuscular disorders, immune globulin IV is probably effective for treating myasthenia

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gravis. This recommendation is based on studies involving primarily moderate or severe disease. Benefits and risks should be weighed in patients with mild disease. There is insufficient evidence to compare the efficacy of immune globulin IV and plasmapheresis in treating myasthenia gravis.⁷

European Federation of Neurological Societies

According to EFNS consensus guidelines for the treatment of autoimmune neuromuscular transmission disorders, anticholinesterase agents are considered first-line therapy in the management of myasthenia gravis for most patients based on low-level evidence (class IV) but are considered as good practice. In severe cases, plasma exchange is recommended to induce remission or in preparation for surgery (level B recommendation). Immune globulin IV and plasma exchange are considered effective for the treatment of acute exacerbations of myasthenia gravis based on data from controlled trials and a Cochrane review (level A recommendation). Immunosuppressives should be considered in cases of progressive myasthenia gravis.¹ An earlier consensus guideline by EFNS regarding the use of immune globulin IV in neurological diseases states that immune globulin IV is an effective treatment for acute exacerbations of myasthenia gravis and for short-term treatment of severe myasthenia gravis (level A recommendation). In addition, immune globulin IV is considered similar to plasma exchange for efficacy. There is insufficient evidence to recommend immune globulin IV for maintenance therapy of chronic myasthenia gravis.⁶

IVIG Hematology and Neurology Expert Panel

In a consensus guideline regarding the use of immune globulin IV in neurological conditions, immune globulin IV is recommended as a treatment option for patients with severe exacerbations of adult or juvenile myasthenia gravis or myasthenia crisis. In addition, immune globulin IV may be considered an option to stabilize disease in patients prior to surgery. Immune globulin IV is not recommended as maintenance therapy of chronic disease. Based on consensus by the expert panel, the recommended total dosage is 2 g/kg given in divided doses over 2 to 5 days.²

Controlled Trials

Comparative trial: Immune globulin IV vs plasma exchange

In a double-blind trial, 84 adult patients with moderate to severe myasthenia gravis and worsen-

ing weakness were randomized to receive immune globulin IV (1 g/kg/day for 2 consecutive days) or plasma exchange every other day for 5 exchanges. Patients continued other treatments for myasthenia gravis during the study. The primary outcome was the mean change in Quantitative Myasthenia Gravis Score (QMGS) from baseline to day 14. Eighty patients were assessed on day 14. An intent-to-treat analysis documented a significant improvement in QMGS at day 14 (decrease of 4 points) for the entire group ($P < .0001$) without significant differences between the immune globulin IV and plasma exchange groups (3.2 vs 4.7, respectively; $P = .13$). There was also no difference between the 2 groups in the number of responders defined as at least a 3.5-point change in QMGS (51% vs 57%; $P = .5$). Persistence of treatment effect was similar in both groups. The authors concluded that immune globulin IV and plasma exchange have comparable efficacy in the patients with moderate to severe myasthenia gravis with worsening weakness.³

Placebo-controlled trials

In a randomized, double-blind, placebo-controlled, multicenter trial, 173 consecutive patients (age range, 15-85 years) with acute exacerbation of myasthenia gravis were randomized to receive immune globulin IV in 2 dosage regimens. Immune globulin IV was administered as 1 g/kg on day 1 with placebo on day 2 (group 1) or as 1 g/kg/day for 2 consecutive days (group 2). Patients continued treatment with immunosuppressives during the study; anticholinesterase agents were provided as needed. The primary outcome was change in the myasthenic muscular score (MMS) from baseline to day 15. Secondary endpoints included time course of MMS change and response rate (response defined as a 20-point or more increase in MMS), time to treatment response, absolute difference in forced vital capacity and serum anti-AChR antibody levels from baseline to day 15, and the need for mechanical ventilation or nasogastric tube during the study period (15 days). On day 15, the mean change in MMS from baseline was 15.49 points (95% CI, 12.09-18.9 points; $P < .001$) in group 1 and 19.33 points (95% CI, 15.82-22.85 points; $P < .001$) in group 2. In subanalysis, there was no evidence of a time-treatment effect in mean MMS changes or response rates. The 2 groups were similar for response rates (55% vs 60%; $P = .48$), median time to response (13.5 vs 12 days; $P = .48$), and all other secondary endpoints assessed. A

total of 138 clinical adverse events were observed in 75 patients with a similar mean cumulative incidence documented in both groups (40.48 vs 46.59; $P = .39$). The most frequently cited reactions included fever (11.9% vs 14.8%) and headaches (13.1% vs 22.7%). The authors concluded that there was no significant difference between the 2 immune globulin IV dosage regimens in the treatment of acute exacerbation of myasthenia gravis.⁵

In a randomized, double-blind, placebo-controlled trial, 51 adult patients with myasthenia gravis and worsening weakness were randomized to receive either immune globulin IV (1 g/kg/day) or placebo (IV dextrose 5%) for 2 days. A total of 23 patients had mild disease (QMGS < 10.5) and 28 had moderate to severe disease (QMGS > 10.5). Other treatment for myasthenia gravis was continued during the study without changes to these regimens. The primary outcome was change in the QMGS from baseline to day 14. A significant improvement in the QMGS was observed in the immune globulin IV group compared with the placebo group for days 0 to 14 (mean change, -2.54 vs -0.89; $P = .047$) but not for days 0 to 28 (-3 vs -1.19; $P = .055$) or days 14 to 28 (-0.46 vs -0.3; $P = .823$). When patients were stratified by disease severity, those with moderate to severe disease and treated with immune globulin IV had significant improvements in QMGS on day 14 compared to placebo (-4.1 vs -0.71; $P = .01$). In contrast, there was no difference between the 2 groups for patients with mild disease (-0.97 vs -0.86; $P = .914$). The postintervention status measure (day 14) demonstrated that improvement was noted in 25% and 6% of the immune globulin IV and placebo-treated patients, respectively ($P < .004$). No serious adverse events occurred; headache was the most frequently reported event (75% vs 19%, respectively; $P < .001$).⁴

SAFETY

Refer to package labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

Systemic reactions with an incidence of 3% to 15% are typically self-limiting and of mild to moderate severity.² The most common adverse reactions noted with treatment included headache, nausea, malaise, myalgia, arthralgias, chills, and fever. Acute renal failure, aseptic meningitis, and arterial or

venous thrombosis are other major adverse reactions associated with immune globulin IV therapy.

THERAPY CONSIDERATIONS

Controlled trials demonstrate the efficacy of short-term immune globulin IV (1 to 5 days) in the management of acute exacerbation of moderate to severe myasthenia gravis.

Guidelines from the AAN, EFNS, and the IVIG Hematology and Neurology Expert Panel recommend the use of immune globulin IV as adjunctive therapy for the treatment of acute exacerbation of myasthenia gravis based on controlled trials and expert consensus. These guidelines also do not recommend or state that evidence is insufficient to recommend use of immune globulin IV as maintenance therapy for chronic myasthenia gravis.

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