

March 10, 2010

Aetna
Customer Resolution Team
PO Box 14002
Lexington, KY 40512

RE: Patient
Type of service: IVIg
Dates of service: To be determined (prior authorization)

Dear Sir or Madam:

I am writing on behalf of your insured, Patient, to request an appeal of Aetna's noncoverage decision of IVIg to treat neuromyelitis optica (NMO or Devic's disease). My HIPAA release and authorization to represent Ms. Patient in this appeal is enclosed.

In sum, this is a young patient with progressive relapsing neuromyelitis optica (NMO) which no longer is responding to steroids (prednisone or IV Solu-Medrol), immunosuppression (Imuran or CellCept), plasma exchange (plasmapheresis) or chemotherapy (rituximab). The only other treatment suggested by her doctors is IVIg. If it works, it will allow Ms. Patient to continue to live independently and productively despite her quickly progressing and debilitating NMO.

Aetna takes the position that IVIg to treat neuromyelitis optica is experimental. However, the use of IVIg in this case is supported by the medical literature. In fact, the very case Aetna cites in its Clinical Policy Bulletin no 0206 states that "Intravenous gamma globulin (IVIg) and plasma exchange are reasonable treatment options because Devic's syndrome is believed to be antibody mediated." Bakker, J, Metz L., "Devic's neuromyelitis optica treated with intravenous gamma globulin (IVIg)," *Can J Neurol Sci* 2004; 31:265-267. This same article goes on to report two cases similar to Patient's, in which IVIg not only prevented further attacks, but also showed some neurological recovery. Bakker and Metz, *supra*. Thus, even the literature cited by Aetna supports the use of IVIg in this case.

Aetna has the discretion to cover IVIg in this case based on the medical literature submitted along with extensive clinical records. Aetna should exercise this discretion in this case, in which a very young woman's life hangs in the balance, and no alternative treatments are available.

I. Ms. Patient Suffers Devastating Symptoms of NMO that Demand Treatment

Patient, who is 31, first presented with NMO symptoms in July 2003 at age 23. She reported to Dr. Doctor1 that she was experiencing "a black curtain lowering over the vision in her left eye." A 7/12/2003 spinal tap did not indicate multiple sclerosis (MS). Patient went through a five-day round of IV Solu-Medrol, after which her vision returned. (See 07/15/03 discharge summary). She then had almost three years of near remission. At that time, there was the belief that Patient had multiple sclerosis and that symptoms would return.

After about three years, Patient began to lose vision in her right eye, and after approximately one month, the vision in her left eye began to fade, as well. During that month, the optic pain became more and more severe, and ultimately, she became blind. She also was losing sensation in her legs causing her to shuffle when she walked. Other symptoms included a feeling of a tight band across her ribs, arms that always felt cold and that were sensitive to touch, as well as one leg that was really cold and one that felt as if she had seriously burnt it. She was hospitalized with relapses on seven occasions during 2006.

Given the severity of these symptoms, Doctor1 believed that Patient had NMO and referred her to the Mayo Clinic in Arizona, where Doctor2 started her on IV Solu-Medrol and immunosuppressant therapy with Imuran. Patient improved with this treatment though she never regained the vision in her right eye. In or around October 2007, Doctor2 detected liver damage in addition to the nausea and diarrhea that Patient had experienced all along. He discontinued use of Imuran and began treatment with Cellcept. Cellcept did prove to be easier on Patient's body, but it did not suppress her symptoms adequately. Patient experienced relapses that included optic nerve pain along with feelings of itching, buzzing and weakness in her legs.

In November 2008, Doctor2 ordered a round of plasmapheresis. Patient reported feeling better immediately after treatment, but there was no evidence of lasting improvement. In May 2009, Patient started chemotherapy with rituximab. Even with this therapy, she had a relapse that required hospitalization in October, a month before her second round of therapy was to begin. She did have her second round in November but this time relapsed within 3 months. She was hospitalized for a round of IV Solu-Medrol during each relapse. When out of the hospital, she has been taking oral prophylactic steroids daily.

Ms. Patient is being treated by a neurologist, an immunologist, and a gastroenterologist. In addition to NMO, she suffers from lupus and multiple side effects to the medications she has taken over the years.

Treatment to date has proven to have no lasting benefit. The only other treatment Doctor2 has recommended is IVIg. (See February, 2010 note by Dr. Doctor2 requesting authorization for IVIg therapy).

II. Use of IVIg Is Supported by the Medical Literature

Aetna has denied coverage of IVIg for NMO on the ground that it is experimental or investigational. In some sense, every treatment for NMO is experimental. Again quoting the same article cited in Aetna Clinical Policy Bulletin no 0206, Bakker and Metz state that, "Despite evidence that prognosis is generally poor, treatment guidelines do not exist."

Bakker and Metz, *supra*. Wiles, et al explain that "The relative rarity of some of the disorders means that good randomized control trials will be difficult to deliver." Wiles CM *et al*. "Intravenous immunoglobulin in neurological disease: a specialist review." *J Neurol Neurosurg Psychiatry*. 2002 Apr; 72(4): 440-8. However, this is not an argument for denying all other forms of treatment. A trial of IVIg is supported by the medical literature.

First, as recognized in Aetna's policy on IVIg, IVIg is an entirely accepted treatment of other demyelinating diseases such as relapsing remitting multiple sclerosis, as well as other neurological diseases causing symptoms similar to those Ms. Patient is experiencing, like Guillain-Barre syndrome. Aetna Clinical Policy Bulletin no. 0206. In addition, IVIg is often used to treat a whole host of immune-related diseases like systemic lupus erythematosus (which Patient also has), and immune related blistering diseases; indeed, the list of accepted uses is quite long, and dances all around the fringes of NMO. The anti-inflammatory effects of IVIg make it an obvious choice for many of these inflammatory, auto-immune diseases. Nimmerjahn, et al., "The anti-inflammatory activity of IGG: the intravenous IgG paradox," *J. Exp Med* 2007 Jan 22; 204(1): 11-15. "The frequent concurrence of a variety of autoantibodies and connective tissue disorders suggests that [NMO] is an autoimmune disorder. . . . This would favor treatments commonly used for antibody mediated disorders such as IVIG or plasma exchange." Bakker and Metz, *supra*. The entirely accepted use of IVIg for these somewhat overlapping illnesses supports the use of IVIg in this case.

NMO is a devastating, progressive illness. "Neuromyelitis optica (NMO, Devic's syndrome is characterized by concurrence of optic neuritis and transverse myelitis." Wingerchuk, D and Weinshenker, B "Neuromyelitis optica." *Current Treatment Options in Neurology* 2008; 10:55-66. "Devic's disease is an inflammatory disease of the central nervous system in which there are episodes of inflammation and damage to the myelin....that almost exclusively affect the optic (eye) nerves and spinal cord. It usually causes temporary blindness, occasionally permanent, in one or both eyes. It can also lead to varying degrees of weakness or paralysis in the legs or arms, loss of sensation, and/or bladder and bowel dysfunction from spinal cord damage. The major risk to patients is severe damage to the upper spinal cord, which can lead to inability to breathe on one's own." Transverse Myelitis Association page "Devic's Disease" http://www.myelitis.org/devics_disease.htm (accessed March 5, 2010). "Most attacks in NMO are moderately or severely disabling; remissions are often incomplete and neurologic disability accumulates in a step-wise fashion. . . . However it is beyond question that attacks of NMO are generally more severe than those seen in MS and disability is acquired earlier than in relapsing remitting MS." Jacob, A and Boggild, M. "Neuromyelitis optica." *Ann Indian Acad Neurol* 2007; 10: 231-239.

Several neurologists have reported success in treating NMO with IVIg. Li, Y et al found that their patient "excellently responded to IVIg while methylprednisolone pulse therapy was not effective." Li, Y et al. "Reversible stenosis of large cerebral arteries in a patient with combined Sjorgren's syndrome and neuromyelitis optica spectrum disorder." *Rheumatol Int* 2008; 28: 1277-1280. They go on to say that "In NMO and NMO spectrum disorder, IVIg may be a good option for the treatment at the acute stage." Li et al, *supra*.

Okada et al report another patient with a history much like Patient's who also improved dramatically. Their patient developed symptoms at age 32. She was treated first with Beta interferon. After three relapses they tried azathioprine. She experienced two more relapses by the age of 40 under that treatment. At age 40 they started her on IVIG treatments. "Since monthly IVIG was started at age 40... **she has never had a relapse**

for more than 4 years." (emphasis added). They concluded that "IVIG seems to be effective for NMO, because NMO pathogenesis has been suggested to mediate humoral immunity involving AQP4 antibody..." Okada, K et al, "Intermittent intravenous immunoglobulin successfully prevents relapses of neuromyelitis optica." *Japanese Society of Internal Medicine* 2007.

Bakker and Metz reported two patients where "Monthly IVIG was associated with **complete cessation of relapses** and significantly **improved neurological status** over one year of treatment." (Emphasis added). Bakker and Metz, *supra*.

The above cited cases apply to patients specifically with NMO. Since NMO is a disease that includes transverse myelitis (TM) along with optic neuritis, good results in treating TM with IVIg would indicate that good results could also be obtained in treating NMO. There is, in fact, such evidence. A quick summary follows.

Marchioni, et al. found that several forms of myelitis "showed a good response to intravenous immunoglobulin (IVIg) after steroid treatment failure." E. Marchioni, et al., "Effectiveness of intravenous immunoglobulin treatment in adult patients with steroid-resistant monophasic or recurrent acute disseminated encephalomyelitis," *J. Neurol* 2002; 249:100-104. IVIg has proven to be effective in treating TM accompanied by mixed connective tissue disease. S. Bhinder, et al., "Transverse myelitis, a rare neurological manifestation of mixed connective tissue disease – a case report and a review of literature," *Clin Rheumatol* 2007; 26: 445-447. And IVIg along with IV methylprednisolone was effective in treating a severe case of TM in a child. LF Fonseca, et al., "Early-onset acute transverse myelitis following hepatitis B vaccination and respiratory infection: case report," *Arch Neuropsychiatr* 2003; 61(2A):265-268. Finally, a large study showed that, although IVIg alone was not more effective than steroids or plasma exchange, plasma exchange followed by IVIg is quite effective in treating TM. H. Murai, et al., "Effect of immunotherapy in myelitis with atopic diathesis," *J. Neurol Sci* 2004; 227: 39-47.

[NOTE – Transverse Myelitis Abstracts are found in Transverse Myelitis section]

In another similar disease – optic neuritis – when steroids are refractory, IVIg has produced the desired results. Tselis, et al., "Treatment of corticosteroid refractory optic neuritis in multiple sclerosis patients with intravenous immunoglobulin," *European J. of Neuro* 2008; 15:1163-1167.

Time is very much of the essence for treating NMO. "It is important to prevent relapses of NMO as early from the disease onset as possible, because NMO has frequent relapses of fulminant optic neuritis and acute myelitis resulting in severe neurological sequelae." Okada, *supra*. "Relapses should be treated aggressively" Bakker and Metz, *supra*. "The sooner you can treat the patient with IVIg the better the results The longer you wait to treat with IVIg the longer it will take for IVIg to work." Chronic inflammatory demyelinating polyneuropathy IVIG Information Page, "What is IVIG (Intra Venous Immune Globulin) 20 Facts." <http://www.cidpusa.org/P/ivig.htm> (accessed March 5, 2010.) Ms. Patient's case is now progressing rapidly with symptoms – optic pain, blurring vision, weakness in her legs– that have become increasingly severe, disabling and more frequent. Since the only other treatments suggested for NMO – steroids,

plasmapheresis, and chemotherapy – have been tried and failed, Aetna should allow a trial of IVIg in an effort to stem the progression of this disease.

Without the IVIg, we know that her condition will worsen and, as is the case in NMO patients who are not treated, she will develop some degree of paralysis and become totally blind. In short, since everything that has been tried has failed, and everything that has not been tried would be considered experimental by Aetna, the literal application of Aetna's policy regarding IVIg would mean denying Ms. Patient any treatment at all. This is unacceptable. Ms. Patient is 31 years old. If IVIg were to work, she would retain her ability to work and engage in the activities of daily living.

In sum, there is ample medical literature to support the use of IVIg in treating steroid-resistant NMO. Therefore, the noncoverage decision should be reversed.

III. Conclusion

In sum, IVIg should be covered. Steroid therapy worked once then failed. Immunosuppression worked for a while then failed. Plasmapheresis alone has been tried and failed. Rituximab has been tried and is failing. Without effective treatment, Ms. Patient's medical bills for rehabilitation, physical therapy, and other needs will skyrocket far beyond the cost of IVIg. Thus, it is in both Aetna's interest and Ms. Patient's to try IVIg therapy.

Of course, if you would like any additional information, please do not hesitate to contact me. Thank you.

Sincerely,

Patient or representative