Drugs of the Future 2008, 33(10): 891-896

CCC: 0377-8282/2008
DOI: 10.1358/dof.2008.033.10.1260062

Guillain-Barré syndrome

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CONTENTS

Abstract

Guillain-Barré syndrome is an immune-mediated disorder of the peripheral nervous system that manifests as a demyelinating polyneuropathy and represents one of the most common causes of acute paralysis. The causes of Guillain-Barré syndrome are still unclear, with evidence pointing towards an infectious or autoimmune origin. Here, we review the pathogenesis of this disorder, with especial emphasis on currently used and investigational pharmacological therapies.

Introduction

Named after Georges Charles Guillain and Jean-Alexandre Barré, two of the physicians who first described the characteristic elevated protein concentration but normal cell count in the cerebrospinal fluid (CSF) of patients suffering from peripheral neuropathy, this syndrome is one of the most common causes of acute paralysis in children and adults, with incidence rates of 1-2/100,000 (1, 2). Guillain-Barré syndrome was initially considered as a single disorder, but in fact includes several forms, all of which are characterized by an immune-mediated attack on peripheral nerves.

Typically, the onset of Guillain-Barré syndrome is preceded by an infection of the upper respiratory airways or the digestive tract, although surgery, trauma and parturition have also been identified in the clinical history of Guillain-Barré syndrome patients. Previous immunizations have been suggested to play a role in the etiology of Guillain-Barré syndrome, although solid evidence for this association is lacking. Clinical symptoms start with symmetrical paresthesias in distal limbs that cause weakness and that rapidly progress, reaching peak symptoms within 2-4 weeks. Sensory disturbances and pain are also common. Weakness of the diaphragm requiring mechanical ventilation may also occur. Dysfunction of the autonomic nervous system manifesting as tachycardia, or in severe forms of the disease as arrhythmias, hypertension, hypotension and gastrointestinal dysmotility, is also frequent. The treatment for Guillain-Barré syndrome consists mainly of intravenous immunoglobulin (IVIG) immunotherapy, plasma exchange and supportive care to avoid further complications and minimize the risk of mortality. Despite treatment, mortality rates are around 5% and can reach 20% for patients requiring mechanical ventilation. Recovery is usually slow, involves inpatient rehabilitation and can result in persistent disability (3).

Pathophysiology of Guillain-Barré syndrome variants

The most common clinical presentation of Guillain-Barré syndrome is acute inflammatory demyelinating polyneuropathy (AIDP), although other variants exist, such as acute motor axonal neuropathy (AMAN), primarily affecting children (4), acute sensorimotor axonal neuropathy and Miller Fisher syndrome, which shares common features with the first two.

Acute inflammatory demyelinating polyneuropathy

AIDP is the most common cause of Guillain-Barré syndrome, accounting for about 90% of cases in Europe and North America. It is characterized by a T-cell- and autoantibody-mediated attack on Schwann cells and myelin epitopes within spinal roots and peripheral nerves, associated with inflammatory infiltrates and macrophage-mediated demyelination of sensory and motor axons. Electrophysiological diagnostic testing often encounters typical features of demyelination, such as reduction of axonal conduction velocity, conduction block or temporal dispersion, as well as prolonged distal compound muscle action potential. Another distinguishing electrophysiological finding is the so-called sural-sparing pattern, which involves normal sural (lower limb) sensory nerve response, but abnormal upper limb sensory nerve conduction (3).

In most cases, AIDP develops between 1 and 3 weeks after an infection. The most frequently identified causative agent is *Campylobacter jejuni*, but

cytomegalovirus, Epstein-Barr virus and *Mycoplasma pneumoniae* have also been associated with postinfectious AIDP. These bacterial and viral agents have epitopes on their surface resembling those found on the surface of peripheral nerves. These epitopes are carbohydrate sequences, mainly gangliosides and glycolipids. In Guillain-Barré syndrome, type G immunoglobulin (IgG) antibodies generated to fight the infectious agent also bind to gangliosides on peripheral nerves, hence causing autoimmune injury. In particular, molecular mimicry between *C. jejuni* lipooligosaccharide (LOS) terminal regions and the peripheral nerve gangliosides GM1, GD1a and GQ1b has been identified, therefore triggering the production of antiganglioside autoantibodies (5, 6).

Activation of the complement system follows nerve autoantibody binding with the formation of the membrane attack complex, which ends up degrading the cytoskeleton of terminal axons and causing mitochondrial injury (3). Only a small proportion of individuals affected with *C. jejuni* infection develop Guillain-Barré syndrome, which suggests that more complex pathogenic mechanisms may be taking place. A recent study revealed that *C. jejuni* strains with a class A LOS locus are most frequently associated with Guillain-Barré syndrome. Class A locus-containing strains also presented with a polymorphism in the sialyltransferase gene *cstII,* responsible for the synthesis of GM1- and GD1a-like LOS (7). Another study pointed out the influence of the immunoglobulin kappa (KM) light chain gene in the pathophysiology of Guillain-Barré syndrome, as individuals homozygous for the KM3 allele have over a two times greater risk than heterozygous subjects for developing this disorder (8).

The involvement of the proinflammatory cytokine IL-23 in the pathophysiology of AIDP has also been suggested. Using rats with myelin-induced experimental autoimmune neuritis, an animal model for Guillain-Barré syndrome, researchers noted increased expression of the IL-23p19 subunit in sciatic nerves, which peaked just before maximum disease severity. Interestingly, IL-23p19 immunoreactivity was also found in mononuclear cells from sural nerve from patients with AIDP, which correlated with elevated IL-23p19 protein expression in CSF, in contrast to control samples in which IL-23p19 was absent (9).

Acute motor axonal neuropathy

AMAN is a purely motor subtype of Guillain-Barré syndrome that predominantly affects children and appears to be seasonal and highly correlated with *C. jejuni* enteritis. Although it is less frequent in Europe and North America, where it represents around 5-10% of cases, it is much more common in China and Japan. Inflammatory infiltrates and macrophage-mediated phagocytosis of motor axons are also typical of this syndrome (3). Although the clinical course and recovery rates are high and very similar to those of AIDP, AMAN is a pure motor axon neuropathy that presents with distinctive electrophysiological features: reduced compound motor action potential amplitudes, preserved motor nerve conduction velocities, denervation on electromyography and normal sensory nerve conduction (4). Studies have shown that AMAN patients exhibit a prolonged refractory period of transmission, leading to conduction failure in distal nerve segments (10). A potential explanation for muscle weakness in AMAN has been reported by Buchwald et al., who found that antibodies against gangliosides GM1 and GD1, often associated with AMAN, may cause presynaptic blockade of neurotransmitter release in motor nerve terminals via a reduction in depolarization-induced calcium influx (11).

Acute sensorimotor axonal neuropathy

This relatively uncommon subtype of Guillain-Barré syndrome has an acute, severe presentation featuring early axonal degeneration of motor and sensory nerve fibers, but absent demyelination (12). Electrophysiological examination usually reveals a profound reduction in compound muscle action potential and sensory nerve action potential. The resulting clinical picture involves severe paralysis, mechanical ventilation requirements and frequently incomplete recovery (3).

Miller Fisher syndrome

Miller Fisher syndrome is characterized by the triad of ophthalmoplegia, ataxia and areflexia, although other symptoms including facial or oropharyngeal weakness and CNS involvement may also be present. Serological testing typically shows antibodies to the GQ1b ganglioside in approximately 95% of Miller Fisher syndrome cases. Sensory and motor nerve conduction in extremities is usually normal or mildly impaired in Miller Fisher syndrome. However, facial compound muscle action potential amplitudes are reduced, as well as blink reflex responses. Miller Fisher syndrome has a good prognosis, with patients recovering around 6 months after disease onset (3).

Treatment

The treatment of Guillain-Barré syndrome usually involves plasma exchange therapy and immunotherapy with IVIG or immunosuppressants. Pain management is also very important, as is supportive care, especially to control symptoms of compromised respiratory function and potentially serious complications such as dysfunction of the autonomic nervous system (arrhythmias, gastrointestinal dysmotility). A summary of clinical studies discussed below is depicted in Table I.

Plasma exchange

Plasma exchange therapy appears to be beneficial in Guillain-Barré syndrome, particularly if started in the first weeks of disease onset. According to the Quality Standards Subcommittee of the American Academy of Neurology, plasma exchange therapy should be initiated

Table I: Summary of therapeutic strategies in Guillain-Barré syndrome.

Drug	Design	Treatment	N	Conclusions/Objectives	Ref.
Intravenous immunoglobulin	Randomized Comparative	IVIG, 0.4 g/kg/d Plasma exchange, 200-250 ml/kg x 5 sessions over 7-14 d	147	IVIG was as effective as plasma exchange therapy in this randomized trial in patients with Guillain-Barré syndrome. IVIG treatment was associated with motor function improvement at 4 weeks and a reduction in time to reach main outcome measure. Fewer patients in the IVIG group experienced complications and required mechanical ventilation compared to plasma exchange.	15
	Randomized Comparative	IVIG, 0.4 g/kg/d Plasma exchange, 250 ml/kg over 8-13 d	383	IVIG was found to be equivalent to plasma exchange in reducing the amount of disability at 4 weeks after treatment in Guillain-Barré syndrome. A small but nonsignificant advantage was seen for the combined treatment compared with either treatment alone.	16
	Open	IVIG, 0.4 g/kg/d x 5d	11	IVIG was safe and effective in pediatric patients with Guillain-Barré syndrome. Adverse events due to IVIG were transient and mild.	17
	Randomized	IVIG, 1 g/kg/d x 2d No treatment IVIG, 1 g/kg/d x 2d IVIG, 0.4 g/kg/d x 2d	21 53	No differences in improvement of motor function were found between early treatment with IVIG (1 g/kg/day x 2d) or late treatment (1 g/kg/day x 2d or 0.4 g/kg/day x 2d). Faster recovery rates were observed in the early treatment group. In the late treatment study, both schedules were equally well tolerated.	19
Methylprednisolone	Randomized Double-blind	IVIG, 0.4 g/kg/d x 5d + Methylprednisolone, 500 mg/d x 5d Placebo	225	No differences in the Guillain-Barré syndrome disability score were seen with the addition of methylprednisolone treatment for 5 days within 48 h of onset of treatment with IVIG.	21
Mycophenolate mofetil	Open	IVIG, 0.4 g/kg/d + Methylprednisolone, 500 mg/d x 5d + Mycophenolate mofetil, 1000 mg/d x 6wks IVIG, 0.4 g/kg/d + Methylprednisolone, 500 mg/d x 5d	92	Addition of mycophenolate mofetil to concomitant IVIG and methyl-prednisolone therapy did not result in significant improvement in the Guillain-Barré disability score scale. Similarly, secondary outcome measures were not modified by mycophenolate mofetil treatment.	22
Interferon beta-1a	Randomized Double-blind	IVIG + IFN-beta1a, 3x/wk (22 μg x 1st wk → 44 μg x 24wks IVIG + Placebo	19	No significant differences were seen between the two groups for any of the efficacy measures.	23
Carbamazepine	Randomized Double-blind	Carbamazepine, 100 mg t.i.d. Placebo	12	In patients recovering from muscular weakness and receiving mechanical ventilation in the intensive care unit, carbamazepine 100 mg t.i.d. significantly reduced pain and sedation scores and intravenous pethidine requirements.	24
Gabapentin	Randomized, Double-blind	Gabapentin, 15 mg/kg/d Placebo	18	Gabapentin significantly decreased pain scores and the need for fentanyl used in Guillain-Barré syndrome patients admitted to the intensive care unit for mechanical ventilation support.	25

Continuation

Table I (Cont.): Summary of therapeutic strategies in Guillain-Barré syndrome.

Drug	Design	Treatment	N	Conclusions/Objectives	Ref.
Gabapentin	Randomized, Double-blind Placebo	Gabapentin, 300 mg t.i.d x 7d Carbamazepine, 100 mg t.i.d. x 7d	36	Gabapentin-treated patients exhibited lower median NPRS (Numeric Pain Rating Scale) scores in comparison to carbamazepine and placebo, as well as significantly reduced fentanyl use. Sedation scores were similar in both treatment groups. No adverse effects were reported during the study period.	26
4-Aminopyridine	Randomized, Double-blind	4-Aminopyridine, 30 mg/d Placebo	NR	This study assessed the safety and efficacy of the potassium channel blocker 4-aminopyridine in Guillain-Barré syndrome. Primary outcome measures included improvement in the ASIA (American Spinal Injury Association) motor score at 8 and 19 weeks and improvement in the Functional Independence Measure motor scale at 8 and 19 weeks.	28

NR, not reported.

within 4 and 2 weeks of symptom onset in nonambulatory and ambulatory patients, respectively, time frames that ensure a faster recovery (13). Plasma exchange is usually administered repeatedly as one plasma volume of 50 ml/kg, thus reaching a total plasma volume of 200-250 ml/kg exchanged over 7-10 days. Plasma exchange therapy is not devoid of potential side effects like bleeding, hypotension, hypocalcemia, coagulation problems, sepsis and complications derived from poor venous access (14).

IVIG

Encouraged by the previous efficacy of IVIG in patients with chronic inflammatory polyneuropathy, van der Meche et al. conducted a clinical trial to examine whether IVIG provided the same benefit as plasma exchange therapy (15). In this study, 147 patients with Guillain-Barré syndrome for less than 2 weeks and who were not able to walk 10 m independently were randomized to receive plasma exchange therapy (n = 73) at 200-250 ml/kg in 5 sessions within 7-14 days or 0.4 g/kg/day IVIG (n = 74), which were started as soon as possible after randomization. The primary outcome measure was improvement in the degree of motor function, which was assessed using a 7-point functional scale and a more detailed score using the Medical Research Council scale that evaluated six bilateral muscle groups. IVIG was equally effective as plasma exchange therapy in causing improvement by one or more functional grades after 4 weeks and significantly reduced the time to improvement by one functional grade from 41 days for plasma exchange to 27 days for IVIG. In addition, IVIG therapy was associated with a lower incidence of a requirement for mechanical ventilation and complications. A larger clinical trial with a similar design confirmed these initial results and found that the combination of both therapies did not provide additional benefit (16).

IVIG treatment was also found to be safe and effective in children with Guillain-Barré syndrome, a patient group in which IVIG represents a safer alternative than plasma exchange. An open-label trial by the Study Group for Pediatric Guillain-Barré Syndrome assessed the efficacy of IVIG 0.4 g/kg/day for 5 consecutive days in 11 children under 15 years of age fulfilling the criteria for moderate or severe Guillain-Barré syndrome on the Hughes' functional grade scale and with onset of neuropathic symptoms in the previous 4 weeks (17). After 4 weeks of treatment, 81.8% of patients showed improvement by one or more grades and 63.6% by two or more. The median time to improvement by at least one grade was 10 days. Four patients experienced adverse events associated with IVIG treatment that were mild and transient. Researchers compared results of this trial to a previous retrospective study (18), which found that IVIG was more effective than supportive treatment alone. Both studies showed a comparable change in the proportion of improvement in functional scores with IVIG treatment.

In an additional randomized study in 95 pediatric patients with Guillain-Barré syndrome, patients were distributed into two substudies that assessed the efficacy of early and late IVIG treatment (19). Children who were still able to walk unaided for 5 m or more were randomized to receive IVIG 1 g/kg/day for 2 days or no treatment. Alternatively, children who needed assistance to walk 5 m were randomized to IVIG 1 g/kg/day for 2 days or IVIG 0.4 g/kg/day for 5 days. Early treatment was not associated with an improvement in disease severity compared to late treatment, but it was associated with faster motor recovery. In those randomized to late treatment, no differences were observed between the treatment schedules, which were equally well tolerated, with transient and mild adverse events.

Immunosuppressants

Corticosteroids have been used for the treatment of Guillain-Barré syndrome, although no efficacy has been observed in randomized clinical trials. A meta-analysis

that included 6 clinical studies (N = 587) showed no significant differences in disability grade between patients receiving or not receiving corticosteroids (20). Furthermore, the addition of i.v. methylprednisolone (500 mg/day) to patients who had been receiving standard treatment with IVIG (0.4 g/kg/day) for 5 days did not modify the patients' outcome in a randomized, double-blind, placebo-controlled trial that involved 225 patients with Guillain-Barré syndrome (21).

The addition of the immunosuppressive agent mycophenolate mofetil to IVIG and methylprednisolone treatment has also been investigated with similar results. In an open-label study (N = 92), simultaneous treatment with IVIG (0.4 g/kg/day) and methylprednisolone (500 mg/day) for 5 days and mycophenolate mofetil (1000 mg/day) for 6 weeks showed no differences in the primary endpoint (improvement by one or more grades in the Guillain-Barré syndrome disability score) compared to combined IVIG and methylprednisolone treatment. Similarly, secondary outcome measures relating to long-term effects were not affected by mycophenolate mofetil treatment (22).

Another attempt to enhance the improvement achieved with IVIG treatment involved the use of the immunoregulatory molecule interferon beta-1a (IFN-beta1a), which was previously demonstrated to be beneficial in an animal model of Guillain-Barré syndrome (experimental autoimmune neuritis). Pritchard et al. evaluated the efficacy of s.c. treatment with IFN-beta1a 3 times weekly (22 μg for the first week and then 44 μg for 24 weeks or until improvement to disability grade 2) in addition to IVIG and compared to placebo in 19 nonambulatory patients. No significant differences were seen between the two groups for any of the efficacy measures (23).

Treatment of pain

In addition to muscular weakness and other neuromuscular symptoms, pain is characteristic of Guillain-Barré syndrome. The most commonly reported types of pain are deep, aching back and lower limb pain and dysesthetic limb pain. Pain is common and can be very intense in patients in the recovery phase of muscle weakness (3). While opioids are used to treat Guillain-Barré syndrome-associated pain, their known adverse effects (dependence, tolerance, sedation, respiratory depression and constipation) have prompted the search for safer options. The antiepileptic carbamazepine, which is the first-line treatment for trigeminal neuralgia, has been investigated as an adjuvant therapy for pain management in Guillain-Barré syndrome.

In a prospective, double-blind study,12 patients recovering from muscular weakness and receiving pressure support ventilation in the intensive care unit (ICU) were randomized to receive carbamazepine (100 mg t.i.d.) or placebo following a crossover design. The use of i.v. pethidine (0.5-1 mg/kg) was allowed if the pain score was moderate, severe or intolerable (pain score > 2). During the days treated with carbamazepine, patients displayed lower pain and sedation scores and markedly reduced pethidine requirements (24).

Gabapentin is another anticonvulsant used in the treatment of neuropathic pain syndromes that has been tested in Guillain-Barré syndrome with similar results to carbamazepine. Results from a randomized, double-blind clinical study in 18 ICU patients under mechanical ventilation support showed a significant decrease in pain scores with the use of gabapentin (15 mg/kg/day) compared to placebo. In addition, there was a significant reduction in fentanyl needs in gabapentin-treated patients (25).

A subsequent study comparing gabapentin and carbamazepine in Guillain-Barré patients in the ICU carried out by the same research group revealed that gabapentin may be more effective than carbamazepine for decreasing pain and fentanyl consumption (26). In this study, 36 patients were randomized to receive gabapentin 300 mg, carbamazepine 100 mg or placebo 3 times a day for 1 week and fentanyl 2 μg/kg was given on demand. Gabapentin-treated patients exhibited lower median NPRS (Numeric Pain Rating Scale) scores in comparison to carbamazepine and placebo, as well as significantly reduced fentanyl use. Sedation scores were similar in both treatment groups. No adverse effects were reported during the study period.

The potential utility of methylprednisolone for pain management in Guillain-Barré syndrome has also been investigated, but no significant effect on the presence and intensity of pain has been observed (27).

Other agents

The U.S. Food and Drug Administration (FDA) Office of Orphan Products Development recently completed a randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of the potassium channel blocker 4-aminopyridine (4-AP) in patients with Guillain-Barré syndrome (28). The rationale for this study was based on the ability of 4-AP to block potassium channels, thus potentially improving nerve conduction across partially demyelinated axons and therefore ameliorating motor performance for walking and other activities of daily living.

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