

CLINICAL RESPONSE TO INTRAVENOUS IMMUNOGLOBULIN IN ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

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Abstract

Immunoglobulin pharmaceutical preparations are sterile concentrated antibodies. Intravenous immunoglobulin (IV Ig) exerts its effect through modulation of expression and function of Fc receptors, interference with complement activation and the cytokine network, provision of anti-idiotypic antibodies, modulation of T and B cell activation. The efficacy of IV Ig has been proved to be grade A recommendation for the Guillain-Barré Syndrome (GBS) and chronic inflammatory demyelinating polyneuropathies. GBS is an acute inflammatory disorder of the peripheral nervous system thought to be due to autoimmunity. This etiology led to our study where we investigated the timing, course and clinical characteristics of the response to intravenous immunoglobulin. We examined retrospectively the records of 69 patients with GBS. Every patient received 0.4g/kg body weight immunoglobulin, for 5 days, every 4 weeks for up to 20 weeks. The data revealed that more participants responded after the second courses of IV Ig treatment. Treatment with intravenous immunoglobulin in the first two weeks from symptoms onset has proved efficient in shortening recovery time in patients with GBS.

Rezumat

Preparatele farmaceutice cu imunoglobuline sunt concentrate sterile de anticorpi. Imunoglobulinele intravenoase (IgIV) își exercită efectul prin modularea expresiei și funcției receptorilor Fc, interferența cu activarea complementului și a rețelei de citokine, furnizarea de anticorpi anti-idiotipici și modularea activării celulelor T și B. IgIV au nivel de recomandare A, dovedindu-și eficacitatea pentru sindromul Guillain-Barré și polineuropatiile inflamatorii cronice demielinizante. Sindromul Guillain-Barré este o afecțiune inflamatorie acută a sistemului nervos periferic considerat a fi de origine autoimună. Această etiologie a condus la studiul nostru, în care am investigat timpul, evoluția clinică și răspunsul la imunoglobulinele intravenoase. Am examinat retrospectiv un număr de 69 pacienți cu sindrom Guillain-Barré. Fiecare pacient a primit 0,4 g/kgc de imunoglobuline, timp de 5 zile, la fiecare 4 săptămâni până la 20 săptămâni. Datele au arătat că mai mulți participanți au răspuns după a doua cură de tratament cu IgIV. Tratamentul intravenos cu imunoglobuline în primele 2 săptămâni de la debutul simptomatologiei, s-a dovedit eficient pentru scurtarea timpului de recuperare a pacienților cu sindrom Guillain-Barré.

Keywords: Intravenous immunoglobulin, mechanisms of action, Guillain-Barré Syndrom

Introduction

Immunoglobulin preparations were first used therapeutically in the 1950s for primary immunodeficiency disorders. Meanwhile, monomeric suspensions of IgG suitable for intravenous use were developed and now have become an important treatment option in autoimmune and acute inflammatory conditions [1].

Immunoglobulin preparations are sterile concentrated protein solutions derived from pooled plasma of over one thousand blood donors. They contain specific antibodies (immune globulins) proportionally to the infectious and immunization experience of the population whose plasma was used for their preparation [3].

The precise mechanism of action by which IV Ig exerts its immunomodulatory effects is not clearly understood but there are studies that show how IV Ig has multiple activities such as: complement activation, receptor blockade, microbial and toxin inhibition, modulating cytokine production [2, 7, 12].

The efficacy of IV Ig in the management of patients with specific autoimmune-mediated neuromuscular diseases has been established in controlled clinical trials and proved to be grade A recommendation (is established as an effective treatment after at least one Class I study or two second class studies consistent and compelling), level Ia evidence for the Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathies [1, 2, 10].

Guillain-Barré Syndrome (GBS) is an acute-onset, immune mediated disorder of the peripheral nervous system and a major cause of acute neuromuscular paralysis. The reported incidence rates for GBS are 1 to 2 per 100 000 throughout the world. GBS is equally common in men and women and can occur at any age [5, 11]. It is a clinical syndrome whose pathological substrate may be acute inflammatory demyelinating polyradiculoneuropathy (AIDP) or acute axonal motor or motor and sensory axonal neuropathy [6]. AIDP is much more common than axonal forms in Western world. Experimental evidence implicates autoantibodies to gangliosides as the cause of the axonal subgroups of GBS [13]. These autoantibodies may be generated by the immune response to an infective organism, such as *Campylobacter jejuni*, viral illnesses, cross-reacting with epitopes on the axon [14]. This proposed autoimmune aetiology led to our study where we investigated the timing, course and clinical characteristics of the response to intravenous immunoglobulin in AIDP. The goals of this therapy are to prevent complication or retard their progression and optimize quality of life expectancy.

Materials and Methods

In the neurology department of “Colentina Hospital” from Bucharest, Romania, we developed a study on patients diagnosed with GBS between January 2010 - July 2011 in order to establish the efficacy of immunoglobulin treatment. We examined retrospectively the records of 69 patients with GBS, of which 27 women and 42 men, aged 28-62 years old

who presented to the hospital within 4 weeks from the onset of symptoms. We divided them in 2 groups: group A (40 patients) who received treatment with IV Ig in the first 14 days from symptoms onset, and group B (29 patients) who received treatment after 15 -25 days from symptoms onset.

Inclusion criteria were age older than 16 years, disease duration shorter than 25 days and written informed consent was obtained from all patients before randomization. The study was approved by the ethics committee of Colentina Clinical Hospital. The diagnosis of Guillain-Barré Syndrome was based on patient history, physical examination, and the results of neurodiagnostic testing including cerebrospinal fluid, nerve conduction studies and magnetic resonance imaging.

Electro-diagnostic testing was performed to support the clinical impression that the acute motor paralysis is caused by a peripheral neuropathy. Nerve conduction studies (NCS) of GBS patients often also demonstrated features of demyelination, such as temporal dispersion, significantly slow conduction velocities, and prolonged distal and F-wave latencies. Only 12 patients had nerve conduction velocities in the demyelinating range in at least one nerve and only 9 of them demonstrated conduction block in at least one nerve. On the other hand, temporal dispersion was seen in at least one nerve in more than 70%, and significantly prolonged distal compound muscle action potential (CMAP) latencies were seen in at least one nerve of approximately two thirds of patients studied. Needle examination demonstrated the finding of reduced motor unit action potential recruitment in clinically weak muscle. In 20 patients NCS were normal at first. We repeated the electro-diagnostic tests after 3 weeks of admission. In this study we included patients who were diagnosed with GBS at first and became chronic after that.

Magnetic resonance imaging (MRI) of the spine or brain was performed to rule out the differential diagnoses, such as myelopathy or infiltrative or compressive causes of polyradiculoneuropathy. Moreover, MRI can support the diagnosis of GBS by revealing enhancement of involved nerve roots or cranial nerves. We chose to treat promptly our patients after randomization on the basis of the clinical suspicion and if the diagnosis, later, proved to be incorrect, then the patient was removed from the study.

Exclusion criteria were pregnancy, severe underlying disease (cancer, blood dyscrasia, insulin dependent diabetes mellitus, severe liver or kidney disease, or human immunodeficiency virus infection), atypical GBS, spontaneous motor improvement before randomization, residual motor

dysfunction due to an earlier disease, and contraindications for IV Ig (known allergic reaction to blood products and selective Ig A deficiency).

Initial presentations were limb weakness 100%, limb numbness 91.3%, pain 69.5%, and facial and pharyngeal weakness 17.3%. Neurological examination showed mild to severe muscle weakness, hyporeflexia or areflexia, mild and moderate sensory involvement, vibration and joint position sense in the toes and fingers were usually reduced (Table I).

Table I
Clinical Features in 69 Patients with Guillan- Barré Syndrome

Variable	No. of Patients*
Males/females	42/27
Age range, y	28-62
Weakness	69(100%)
Limb numbness	63 (91.30%)
Pain	48 (69.56%)
Facial weakness	12 (17.39%)
Elevated CSF protein level	51 (73.91%)
Severity at admission	
Mild	14 (20.28%)
Moderate	34 (49.27%)
Severe	18 (26.08%)
No. ultimately intubated	0 (0%)

Table II
Guillain- Barré syndrome disability scale (Hughes)

0. Healthy
1. Minor symptoms or signs of neuropathy but capable of manual work/capable of running
2. Able to walk without support of a stick(5m across an open space) but incapable of manual work/running
3. Able to walk with a stick, appliance or support (5m across an open space)
4. Confined to bed or chair bound
5. Requiring assisted ventilation (for any part of the day or night)
6. Death

Study Design

Treatment with immunoglobulin was started as soon as possible after randomization. During the five subsequent days, 400mg/kg body weight of immune globulin (Flebogamma® 50mg/mL, Instituto Grifols S.A. Spain) was administered per day, as a 12 hours infusion, every 4 weeks for up to 20

weeks. In some patients the primary response to treatment may be followed by a secondary deterioration, but which responded to treatment after another cure of IV Ig. The option of repeating the same treatment was included in the protocol if after a partial recovery or stabilization there was registered a secondary deterioration or no improvement after the first cure.

The functional ability of the patient during the course of the disease was scored with a 7 point scale, the GBS disability scale (Table II). Patients were examined at randomization, then every day for the first 5 days, every week, and monthly thereafter until discharge. Each examination included a complete neurological assessment with evaluations of cranial nerve function, trunk and respiratory muscle involvement, sensory loss, reflexes, and the GBS disability grade. Relapse was defined as deterioration in at least 2 functional score items at 2 consecutive examinations. A final neurological examination was scheduled after 6 months.

For patients with such severe disease that they could not walk independently (GBS disability grade 3 or more), we considered that the primary outcome measure was the time needed to regain the ability to walk without assistance. For patients who could still walk without aid (GBS disability grade 2 or less), we used time to the onset of motor recovery as outcome, defined by improvement of 1 or more points in adjusted GB disability scale.

To monitor side effects of IV Ig treatment, daily examinations of vital signs and blood pressure and weekly examinations of blood counts and creatinine levels were performed for 3 weeks after IV Ig treatment. Bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyl transferase (γ -GT), and alkaline phosphatase (AP) were assayed in the plasma using routine laboratory methods at randomization and after 3 weeks of treatment. Liver dysfunction was defined as a ratio between measured values and the upper limit of the normal range greater than 1.5 for ALT and γ -GT.

Results and Discussion

For a period of 19 months (January 2010 to July 2011), 69 patients were included in the study and fulfill the diagnostic criteria for GBS. No patients were excluded or left the hospital before the data were obtained. Of the 69 patients classified as having GBS, 42 were male and 27 were female. Their ages ranged from 28 to 62 years, with a peak at 45 years. At inclusion in the study, 44 patients were able to walk without aid and 25 were not and we had no patients on ventilator. Liver dysfunction was found in 14 (20.29%) patients at randomization (15% in group A and 27.58% in group B) and in 21 patients (30.43%) on day 15 (22.5% and 41.38%). Between day 0

and day 15, liver function tests worsened in 11 patients (four in group A and seven in group B) and improved in four. After 6 months, all study patients had normal liver function tests.

In this trial all participants were identified as responders. The time needed for regaining the ability to walk without assistance was shorter in group A than in group B. A trend towards a higher proportion of patients with one grade or more of disability improvement at 4 weeks was found in group A. The proportion of patients with recovery of full muscle strength at 6 months was also higher in group A (80% vs. 41.38%). To determine when IV Ig responders achieved maximal improvement during the 20 weeks treatment period, the time to reach maximal improvement on the GB disability scale was examined in patients from both groups A and B. As shown in figure 1 the number of patients reaching maximal improvement continued through month 6. After the first cure of treatment with immunoglobulin, during the first 4 weeks, 10 patients (14.49%) had complete remission (8 vs. 2 patients), 39 patients had partial remission – were able to walk independently- (28 vs 11 patients) and 20 patients still had severe disability –able to walk only with support – (4 vs. 16 patients). After 6 months 44 patients (63. 76%) registered complete remission (32 vs 12 patients), 18 patients were able to walk independently (8 vs. 10 patients) and 7 patients were able to walk only with help (0 vs. 7 patients).

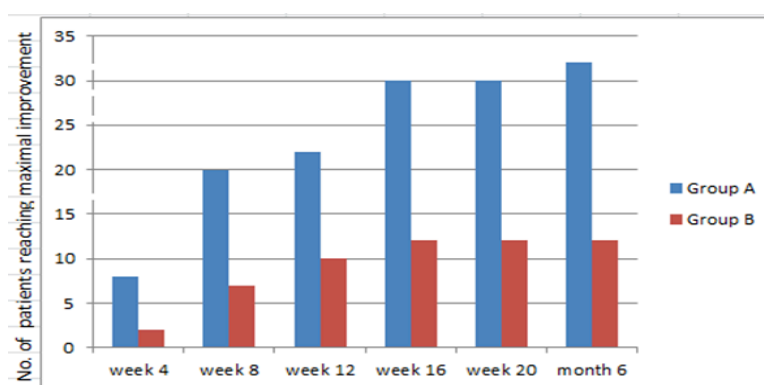


Figure 1

Responders who reached maximal improvement

Patients with complete remission more often had subacute onset, symmetrical symptoms and nerve conduction abnormalities predominant in the distal nerve terminals. In contrast, patients with insidious onset, asymmetrical symptoms, and electrophysiological evidence of

demyelination in the intermediate nerve segments were refractory to treatment or had relapsed during treatment.

When comparing changes in the GB disability scale over time (Figure 2), we found that patients in both groups A and B exhibited a statistically significant improvement compared with baseline. Patients in group A were more likely than those in group B to reach the main outcome measure of an improvement by one or more grades on the GBS disability scale.

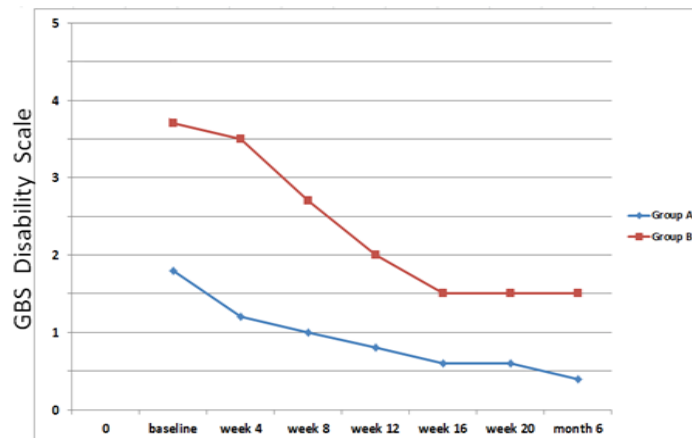


Figure 2

Mean change in GBS disability scale over time

The incidence and intensity of IV Ig related adverse effects were closely similar in the two groups. The most common adverse event was rash; fever defined as an at least 1 degree increase in body temperature during the IV Ig infusion (47, 5% in group A versus 34, 48% in group B); hypotension, defined as a decrease in systolic blood pressure of at least 40 mmHg occurred in six patients (10% in group A and 6. 89% in group B). One patient in each group complained of nausea. Other adverse events were headache and tachypnea. In no instance was the course of treatment interrupted. Seven relapses occurred in group B. There were only two relapses in group A.

Conclusions

The data reveal that more participants responded after the second courses of IV Ig treatment. These observations suggest that patients should be treated with at least two courses of IV Ig to determine whether they are responding to treatment.

Minor side-effects associated with IV Ig occur commonly, but serious adverse events such as stroke and renal failure were not present in

this study. Its main disadvantages are the costs and theoretical risk of transmission of infection by viruses, prions or other agents [4]. Independent adverse prognostic factors in each of the 2 groups were older age, disease severity and rapid disease onset. Intravenous immunoglobulin appears to be a safe and effective treatment for patients with Guillain-Barré Syndrome and because of its greater convenience and availability, IV Ig is the usual treatment of choice in many centers.

The GBS disability scale has the virtues of simplicity, face validity and reproducibility but it is non-linear and its large steps may be insufficiently sensitive to detect some clinically meaningful differences [8].

The results strongly suggest that early IV Ig treatment could ameliorate subsequent disease severity. Treatment with intravenous immunoglobulin (IV Ig) in the first two weeks from symptoms onset has proven its efficiency for shortening the recovery time in patients with Guillain-Barré syndrome.

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