

Case Report

Plasmapheresis versus intravenous immunoglobulins administration in the treatment of Guillain Barre' syndrome. Risks and benefits of early treatment – Update data from literature and case report

Assoc. Prof. Mihaela Lungu^{1*} and Assist. Prof. Violeta Sapira²

Abstract

¹Head of Neurological Department, Emergency Clinical Hospital Galati, Romania; Faculty of Medicine and Pharmacy, "Dunarea de Jos" University of Galati, Romania

²Neurological Department, Emergency Clinical Hospital Galati, Romania; Faculty of Medicine and Pharmacy, "Dunarea de Jos" University of Galati, Romania

*Corresponding Author's E-mail: mihaelalungu17@yahoo.com
micalungu@gmail.com
Phone: +40724365046

Guillain Barré syndrome is an acute demyelinating polyneuropathy with an allegedly immune mediated mechanism. The therapeutic options for this condition include intravenous administration of immunoglobulins or plasmapheresis, both of which prove to be safe and effective. To improve prognosis, the neurologist may be tempted to apply one of the two therapies in the early stages of the disease which, according to some authors, may increase the risk of relapse. We report a case of a patient with Guillain Barré syndrome, hospitalized in our clinic, where plasmapheresis treatment was initiated on the 7th day after the onset of the disease. Favorable progression after 6 sessions of plasmapheresis complicated after 4 days from the last procedure with a relapse, requiring resumption of treatment. That is why we chose 6 doses of intravenous immunoglobulins that improved the symptoms, but unfortunately 3 days after the last dose a new episode of worsening motor deficit reappeared. Plasmapheresis was restarted with 4 cures which improved the symptomatology. The numerous relapses have created a discomfort for both the patient and the attending physician and have involved increased treatment costs. We can interpret these relapses either by setting to early a–treatment or by having a very active and persistent immune process.

Keyword: Guillain Barré syndrome, plasmapheresis, immunoglobulins, relapse

INTRODUCTION

Guillain Barré syndrome, a demyelinating disorder with an allegedly immunomodulatory mechanism can take the form of a fulminant ascending-shaped polyneuropathy – landry form, involving cranial nerves and causing respiratory failure with the risk of death.

Prognostic factors with a role in the evolution of the disease are the severity of muscle weakness, the early relapse, diarrhea that precedes the polyneuropathy onset, advanced age, fulminant evolution.

Severe residual disability or deaths are quoted in trials ranking from 9 to 17% despite the risk reduction by 6% gained through plasmapheresis.

In an effort to improve prognosis the neurologist may be tempted to apply one of the two therapeutic options – plasmapheresis or intravenous immunoglobulins – in early stages of the disease, which may, according to some authors, increase the risk of relapse.

CASE REPORT

In the following we present the case of a 33-year-old patient hospitalized for Guillain Barré syndrome – Landry form, on the 7th day after the onset of an asymmetric flapped tetraparesis with a predominantly straight-forward motor deficit associated with peripheral facial diparesis and which started with paresthesia in the lower limbs and had an ascending course. Paresthesia was followed by the installation of motor deficiency and an abolition of osteo-tendinous reflexes, later associated with dysphagia and dysphonia.

From the pathological history, we retained a respiratory viral infection that occurred 30 days before.

From the laboratory tests we have obtained the following results:

The examination of the cerebrospinal fluid showed cytological albumin dissociation, 10 elements/ mm³ with normal levels of chloride and glucose in the cerebral spinal fluid, with no germs identifiable in cultures.

Chest X-ray has highlighted the interstitial pattern.

The cervical region computed tomography excluded a cervical medullary compression. Tests for borreliosis and HIV were negative, no hepatitis viruses were detected, the blood ionogram was within acceptable limits, as were the tumor markers for the digestive tract and prostate. White blood cells were increased in number – $9,35 \times 10^3$. Fibrinogen was highly modified with elevated levels up to 1447mg/dl, then reduced to 628mg/dl. Anti-GM1 antibodies could not be determined.

Nerve conduction velocity-electromyography NCV-EMG testing showed blocked nerve conduction and delayed F waves and prolonged distal latencies.

After confirming the diagnosis on the 10th day after the onset the plasmapheresis was the therapeutic choice.

The progression was favorable after 6 sessions of plasmapheresis performed at the rhythm of one session every 2 days.

Unfortunately, 4 days after the last sessions the paresthesia in the limbs relapsed and the motor deficit worsened with MRC-0/5 (Medical Research Council Scale) from 4/5. Swallowing and phonation disorders have been associated. The patient was transferred to the Intensive Care Unit where oral-tracheal intubation was imposed.

The worsening of the general condition of the patient determined us to review the therapeutic plan, so we administered intravenous immunoglobulins IVIg, at the dose of 0,4g/kg/day for 6 days. Following the new therapeutic approach, the general condition improved, the patient resumed swallowing, dysphonia disappeared and tetraparetic motor deficit improved, with MRC-4/5.

On the third day since the last IVIg administration a new relapse came up with tetraplegic motor deficit, swallowing and respiratory disorders occurred which, again, required the transfer into the Intensive Care Unit

and oro-tracheal intubation with the need for repeated trachea-bronchial aspiration.

In contrast to this new clinical status following immunoglobulin therapy, plasmapheresis was reinitiated – 16U iso- group, iso- Rh plasma, with plasmatic volume changed to 3.5l at a flow rate of 30-140ml/min, with a plasma blood ratio: 10-18%, in a rhythm of one session every two days. Four sessions of plasmapheresis were performed after which the general condition of the patient improved. Gradually, motor deficiency regressed to MRC-4/5, the patient resumed swallowing, facial diparesis gradually improved and osteo-tendinous reflexes in the upper limbs reoccurred.

We continued with the neurotrophic, neuro-recovering treatment with favorable evolution. The patient was discharged after 58 days of hospitalization and 65 days from the onset.

Subsequently the patient followed sustained rehabilitation treatment with overall clinical improvement. Currently he has no motor deficit and resumed his work as a driver.

DISCUSSIONS

The efficiency and safety of plasmapheresis-PE or intravenous immunoglobulins- IVIg treatment has been established by numerous literature studies.

These studies did not notice significant differences in PE versus IVIg treatment.

PE was introduced as a possible treatment in 1978 and offered a significant benefit, so it became the gold standard since 1986.

IVIg was introduced for Guillain Barré syndrome- GBS in 1988 and in 1992, the first randomized trial comparing IVIg and PE showed similar effects from each treatment (Richard et al., 2007).

An important prognostic factor for the outcome in the patients with Guillain Barré syndrome is the severity of muscle weakness.

The patients with fluctuations showed a trend to have fluctuations after a protracted disease course (Visser et al., 1999).

Negative previous prognosis factors were diarrhea, older age, disease severity and rapid disease onset (van der Meché et al., 1992). Death or severe residual disability in the trials ranged between 9-17%, despite a 6% risk reduction with PE.

The treatment related to clinical fluctuations seems to be due to a prolonged immune attack and there are no indications that the fluctuations are related to treatment modality.

In order to improve the patient's clinical condition as soon as possible, the neurologist is tempted to initiate early therapy, from the stage in which the patient still has autonomy of walking (Visser et al., 1998).

However, early recurrences and fluctuations in the

therapeutic response occurred in 8-10% of the treated patients (Osterman et al., 1988; Kleyweg et al., 1991).

Patients with GBS treated in the early stages of the disease have an increased risk of relapse (Ropper et al., 1988).

The nature of the treatment fluctuation is the same for both types of therapy PE and IVIg. The different pathophysiological mechanisms are involved in GBS and they seem to play an important role in therapeutic results. Therapeutic fluctuations can occur in 2 situations:

1. Relapses induced by early treatment: when the pathophysiological process is underway, treatment can only temporarily stop the progression of the disease. The worsening of muscle weakness occurs shortly after stopping the therapy, suggesting that fluctuations could be prevented by prolonged treatment (Visser et al., 1999).

2. In the second situation, post treatment relapse may occur when there is an ongoing immune activation, resulting in a more protracted clinical course (Visser et al., 1988). The fluctuations occurred more often in those who after start of treatment showed a more protracted disease process.

The time of onset of worsening is usually more than 10 days after the start of therapy (The French Coop Group, 1999).

The evaluation of GBS patients through electrophysiological studies 15 days after the onset of the disease did not show differences in response to treatment either by PE or IVIg (Hadden et al., 1998).

Specialty literature studies recommend plasma-pheresis for non-ambulant adult patients who seek treatment within 4 weeks of the onset of neuropathic symptoms. PE should also be considered for ambulant patients examined within 2 weeks of the onset of neuropathic symptoms.

Although, PE was more frequently associated with severe adverse effects, requiring cessation of therapy, including a bleeding diathesis. PE is feasible only in major referral centers, requiring the appropriate equipment and trained personal.

Plasma-exchange –PE on the 10th day of the onset is useful in removing autoantibodies, immune complexes and serum cytotoxic constituents. Studies show that PE decreases recovery time by slightly increased risk of relapse (Andary et al., 2018).

PE hastens recovery from GBS and improves its long-term outcome in severely affected adult patients.

IVIg is recommended for non-ambulant adult patients within 2 or possibly 4 weeks of the onset of neuropathic symptoms (Hughes et al., 2003). IVIg is also preferred for hemodynamically unstable patients or for those who are unable to move.

Patients not responsive to an initial dose of immunoglobulins may benefit from a second dose, but this is not a standard therapeutic indication.

IVIg treatment is easier to apply and potentially safer than PE, which gives it an extra-argument in choosing it in GBS therapy.

Immunoglobulin doses recommended in various studies range from 0.4g/kg/day for 5 days to 1g/kg/day for 2 days with comparative dosing and duration of treatment (Korinthenberg et al., 2005; Raphael et al., 2001).

By using Erasmus GBS Prognosis Scale- EGOS it is possible to select GBS patient with a poor prognosis. These patients potentially may benefit from a second IVIg dose. A standard dose is not sufficiently effective in many GBS patients (van Doom et al., 2010).

The effects of PE and IVIg are equivalent. Sequential treatment with PE followed by IVIg is not recommended (Hughes et al., 2003).

The efficiency of IVIg versus PE has been shown to be similar in well-controlled clinical trials.

Combination treatment of PE-IVIg did not improve the prognosis, neither did it shorten the duration of disease progression. However, some clinicians prefer PE first and if this does not provide patient improvement, then they use IVIg.

But, if IVIg is given first, then the plasma exchange will be removing the IVIg which was just given days earlier (Andary et al., 2018; Richard et al., 2007).

In Cochrane Database, there are also studies which show that PE followed by IVIg is not recommended for patients with GBS, because it did not confer significant extra-benefit (Cochrane Data Base Syst, 2010).

There are numerous studies that compare IVIg treatment to PE, comparing both their doses and duration (van der Meché et al., 1992; Nomura et al., 2000).

In adult patients, the effect of IVIg is equivalent. Because of its greater convenience and availability, IVIg is usually used.

If IVIg fails as a first-line drug, then PE should be applied (Shahar et al., 2006).

In present, Cochrane systematic reviews of PE and IVIg for GBS treatment are update regularly. There are not randomized controlled trials that allow one to decide on the best treatment plan.

Summing up the results from randomized trials, the conclusion is that both IVIg and PE have similar effects.

CONCLUSIONS

1. Analyzing the literature studies it can be deduced that our patient was treated relatively early, which probably increased the risk of relapse.

2. On the other hand, his general condition, rapid worsening of the motor deficit, the occurrence of swallowing disorders and respiratory failure phenomena are clinical elements that alert the clinician and cause him to institute treatment right away, as the timing of the therapy may be life threatening, causing even the death

of the patient.

3. The two relapse episodes with clinical worsening and downward change of MRC and EGOS have suggested an extremely active pathophysiological process, with serious rebound phenomena.

4. We preferred to use PE after the 3rd day since the last IVIg dose, considering that this interval was sufficient for IVIg to have shown its effect.

5. There are no randomized controlled trials that allow one to decide on the best plan.

6. The two treatment methods are costly and relapses and prolonged hospitalization have involved significant additional costs.

7. PE requires equipment and qualified personnel, IVIg being easier to administer but at a higher cost. From this point of view, PE is preferred.

8. We initially chose PE because we benefited from this treatment approach and the patient's severe general condition forced hospitalization in the Intensive Care Unit where PE is also performed.

9. After the first relapse we chose to administer IVIg, which could be administered in the Neurology Department, but the second relapse resumed the transfer to Intensive Therapy where we had to perform orotracheal intubation on the patient.

10. Considering the risk of death and recurrence we believe that GBS treatment should take place, regardless of the clinical condition at the onset, only with the patient hospitalized in a department of Neurology, but with the possibility of being immediately transferred to the Intensive Care Unit, none the less, the patient should be hospitalized during the whole period of the treatment and should not be ambulatory treated, as some authors from other studies suggest.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

Financial disclosure: None.

Grant information

This article did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Informed consent

The patient's informal approval has been obtained and recorded in the chart.

Author contributions

All the authors have equal contributions in this presentation.

ACKNOWLEDGEMENTS

For providing language help and for proof reading the article.

REFERENCES

- Andary MT, Milton JK et al. (2018). Guillian Barré Syndrome. Treatment and Management. Approach considerations, <http://emedicine.medscape.com/article/315632-treatment#d13>. May, 04
- Hadden RO, Comblath DR, Hughes RA, Zielasek J, Hartung HP, Toyka KV, Swan AV (1998). Electrophysiological classification of Guillian Barré syndrome: clinical associations and outcome, <http://reference.medscape.com/medline/abstract/9818934?prt=true,1>
- Huges RA, Wijdicks EF, Barohn R, Benson E, Comblath DR, Hahn AF, Meythaler JM, Miller RG, Sladky JT, Stevens JC. Practice parameter: immunotherapy for Guillian Barré syndrome, <http://reference.medscape.com/medline/abstract/14504313?prt=true,1>
- Kleyweg RP, van der Meché FGA (1991). Treatment related fluctuations in Guillian Barré syndrome after high-dose immunoglobulins or plasma-exchange. *J Neurol Neurosurg Psychiatry*.14:1103-9
- Korintenberg R, Schessl J, Kirschner J, Montning JS (2005). Intravenous immunoglobulin in the treatment of childhood Guillian Barré syndrome. *Pediatrics*, 116:8-14
- Nomura T, Hamaguchi K, Hatton T, Satou T, Mannen T et al. (2000). A randomized controlled trial comparing intravenous immunoglobulin and plasmapheresis in Guillian Barré syndrome. *Neurol Therapeutics* 18:69-81
- Osterman PO, Fagius J, Safwenberg J et al. (1988). Early relapse of acute inflammatory polyradiculoneuropathy after successful treatment with plasma exchange. *Acta Neurol Scand*. 77: 273-7
- Raphaël JC, Chevret S, Hughes RA, Annane D (2002). Plasma exchange for Guillian Barré syndrome. *Cochrane Database Syst Rev*, CD001798
- Richard ACH, Swan AV, Raphaël JC, Annane D, van Koningsveld R, van Doorn P. *Brain* (2007).130(9):2245-2257.
- Ropper AE, Albert JW, Addison R (1988). Limited relapse in Guillian Barré syndrome after plasma exchange. *Arch Neurol*, 77: 273-7
- Shahar E (2006). Current therapeutic options in severe Guillian Barré syndrome. *Clin Neuropharmacol.*; 29(1):45-51
- The French Cooperative Group on plasma exchange in Guillian Barré syndrome (1997). Appropriate number of plasma exchanges in Guillian Barré syndrome. *Ann Neurol* 41: 298-306
- van der Meché FGA, Schmitz PIM (1992). Guillian Barré Dutch, Study Group. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain Barré syndrome. *New England J Med* 326:1123-9
- Visser LH, Schmitz PL, Meulstee J, van Doorn PA, van der Meché FG (1999). Prognostic factors of Guillain Barré syndrome after intravenous immunoglobulin or plasma exchange. Dutch Guillain Barré Study Group. *Neurology*, Aug 11. 53(3): 598-604
- Visser LH, van der Meché FG, Meulstee J, van Doorn PA and The Dutch Guillain Barré study group (1998). *J. Neurol Neurosurg Psychiatry*, 64: 242-244