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Therapy Options forGuillain-Barré Syndrome: A Review

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ABSTRACT:
Guillain–Barré syndrome (GBS) is an immune mediated polyradiculoneuropathy mostly characterized by acute flaccid paralysis with or without sensory/autonomic nerve dysfunction. Diagnosis is supported by cerebrospinal fluid albumino-cytological dissociation and electrophysiological signs of neuropathy. Up to 1.8 cases of Guillain-Benedict syndrome (GBS) occur per 100,000 people each year. Major subtypes include acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and acute motor-sensory axonal neuropathy (AMSAN), and acute motor axonal neuropathy (AMAN). The most common manifestation is limb weakness and pain is very commonly experienced by around 90%, and is often severe. Facial palsy is the most common type of cranial nerve involvement followed by ophthalmoplegia, tongue weakness, and bulbar weakness. Blood pressure and heart rate changes are the most common manifestations of dysautonomia. Intravenous immunoglobulin (IVIg) and plasma exchange (PE) with supportive care are the mainstays of treatment. PE became the first accepted therapy for GBS and was considered as "gold standard" due to its status as an evidence-based efficacious immunotherapy. IVIg has been used since 1988 for the treatment of GBS and other autoimmune inflammatory diseases. IVIg is obtained from pools of plasma from thousands of healthy donors thus enriching the preparation with important functions of humoral immunity; it comprises a range of antibodies directed to pathogens and foreign antigens as well as to self-antigens, essential for the effect in immune-mediated disorders.The zipper method, corticosteroids, complement targeted therapy, eculizumab, rEV567, nafamostatmesilate, microcept, interferon, bisphosphonates, cyclophosphamide, and other therapies are among the other treatments for GBS.In this article, the major treatments for GBS are outlined.

KEYWORDS: GuillainBarré syndrome, GBS, Plasma exchange, Intavenous immunoglobulin, Immunotherapy

I. INTRODUCTION

Guillain–Barré syndrome (GBS) is an immune mediated polyradiculoneuropathy mostly characterized by acute flaccid paralysis with or without sensory/autonomic nerve dysfunction typically preceded by infectious diseases and can affect all age groups. (1, 2) The classic presentation of the syndrome doesn't typically pose a diagnostic challenge, but atypical variants are missed when not considered. To support diagnosis, polyradiculoneuropathy can be detected on nerve conduction studies, and cerebrospinal fluid analysis can show albuminocytological dissociation, although both tests can be normal in the early stages. (3) Diagnosis is supported by cerebrospinal fluid (CSF) albumino-cytological dissociation and electrophysiological signs of neuropathy. (4, 5)It has an approximate annual incidence of 1.1 to 1.8 cases per 100 000 people worldwide. (6) Compared to North America and Europe, population-based studies in Bangladesh, the incidence was 1.5–2.5 cases per 100000 person-years in adults, and 3.25 in children. In East Asia, lower incidences of Guillain-Barré syndrome with 0.67 cases per 100,000 person-years in China and 0.44 in Japan. Single-centre studies in the Middle East report similar incidences to western countries, whereas in Latin America, the reported background incidences were highest in Chile (2·12 cases per 100000 person-years) and lowest in Brazil (0.40).There is a 20% increase in incidence for every 10-year increase in age, and unlike other autoimmune diseases, the risk of Guillain-Barré syndrome is higher in men than in women.(3) GBS patients are classified according to their electrophysiological profiles and major subtypes include acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor-sensory axonal neuropathy (AMSAN), and acute

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motor axonal neuropathy (AMAN). The demyelinating and axonal forms vary in their relative prevalence across different geographical areas. Localized form of GBS includes Miller Fisher Syndrome (MFS). (5,6) No definitive causative factors for GBS have been identified, but a number of preceding events are described as triggers for the disease. Amongst the triggering factors, infection antecedence was complained by 2/3rd of patients. Antecedent infection or vaccine administration are known to precipitate the onset of GBS.(7) The most commonly reported causative pathogen is C. jejuni, which is found in around 33% of adult patients in western countries, rising to nearly 50% in Asian countries. A range of infections has been associated with GBS, including Hepatitis E, cytomegalovirus,Haemophilusinfluenzae, Epstein-Barr virus and Mycoplasma pneumoniae. There is asuspected association of GBS with arboviruses, including chikungunya and the flaviviruses like Zika, dengue and Japanese Encephalitis (JE).GBS may be a post-infectious disorder, and there's 2 to 4 weeks interim period from the event of infection to onset of GBS. It is now well known that the pathogenesis of GBS is mediated by cross-reaction of anti-microbial antibodies with gangliosides on the peripheral nerves. (6) The COVID-19 pandemic has also seen emerging reports of Guillain-Barré syndrome and Miller Fisher syndrome in association with SARS-CoV-2 infection.(3) Numerous case reports have been published which insinuate a possible association between SARS-CoV-2 infection and Guillain-Barre syndrome (GBS). Recently, an epidemiological and cohort study in the UK concluded that GBS wasn't related to COVID-19 (8). Therefore, it's still too early to rule out the association between SARS-CoV-2 infection and GBS. (9)The most common manifestation is limb weakness, in proximal more than distal.In about half the cases the illness is preceded by sensory symptoms. Altogether about 80% have sensory symptoms. Pain is very commonly experienced by around 90%, and is often severe. Facial palsy is the most common type of cranial nerve involvement (in 53%), followed by ophthalmoplegia, tongue weakness, and bulbar weakness. Autonomic dysfunction is seen in about two thirds of the cases, presenting as either increased or decreased activity of the sympathetic or parasympathetic nervous system.Blood pressure and heart rate changes are the most common manifestations of dysautonomia. (10) Intravenous immunoglobulin (IVIg) and plasma exchange (PE) with supportive care are the mainstays of treatment. (4)

II. TREATMENT

1. IMMUNOTHERAPIES

Several randomized controlled trials (RCTs) have acknowledged the effectiveness of Plasma Exchange (PE) and intravenous immunoglobulin (IVIg) as GBS immunotherapies. Early usage of PE or IVIg, preceding irreversible axonal damage, is equally efficacious to the other in improving neurological outcomes. (11)

a) PLASMA EXCHANGE (PE)

PE became the first accepted therapy for GBS and was considered as “gold standard” due to its status as an evidence-based efficacious immunotherapy. (11) PE consists of the removal of complement components, immune complexes, cytokines circulating antibodies and other immune mediators, by using centrifugation or membrane filtration techniques. Volume is replaced by infusion of fresh frozen plasma or albumin. (12)

Mechanism of action:

The mechanism of action of PE is not clearly known; however, it may nonspecifically remove immune complexes, circulating autoantibodies, cytokines, complement factors and other proinflammatoryhumoral mediators that contribute to GBS immunopathogenesis.(13, 14)

Efficacy:

Immune complex deposits are found on the surface of axons in GBS. When they are removed from the intravascular space,it causes a shift from the extravascular space through an injured nerve-blood barrier which explains the efficacy of PE and why repeated sessions are needed.(15)Based on clinical scrutinization, PE may help decrease the extent of axonal injury or demyelination with acceleration of clinical recovery compared with supportive care alone.(11)

The Quality Standards Subcommittee of the American Academy of Neurology (AAN) thereafter issued evidence-based guidelines for physician practice as follows: PE is advantageous for non-ambulatory GBS patients within 4 weeks of symptoms onset (Level A, Class II evidence) and for ambulatory patients, PE is recommended within 2 weeks of onset (Level B, limited Class II evidence).The therapeutic response may be better within 2 weeks of disease onset, especially in non-ambulatory patients. (16, 17)

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Regimen:

The treatment typically consists of five exchanges, one plasma volume each time (about 50 mL/kg body weight), administered over 1-2 weeks. (16, 18)

Two plasma exchange sessions can hasten recovery in patients with mild Guillain-Barré syndrome when compared with supportive care based on some evidence. (3)

Advantages:

A significantly higher improvement was seen with PE-treated over supportive care alone, without a significant increase in adverse events according to evaluation of numerous cochrane systematic reviews. (14) PE reduces the likelihood and duration of mechanical ventilation, reduces the time required to walk with assistance and increases the likelihood of fully recovering muscle strength after one year. (14, 19, 20)

Adverse effects:

PE is associated with significant adverse effects which include hemodynamic instability, dilutional coagulopathy, fever, hypotension, hypocalcemia, acute myocardial infarction, septicemia, hematoma, thrombosis, pneumonia, complications from central venous access and allergic reactions. (21)

Contraindications:

Hemostatic disorders, unstable cardiovascular status, active infection, and pregnancy are considered relative contraindications to PE. (22)

Limitations:

Lack of widespread access to plasma exchange, need for close monitoring and its serious adverse effect profile have restricted the general use of PE for GBS. Additionally, prolonged hospitalization and its related monetary burden have led to PE being a relative restricted immunotherapy for GBS. (23, 24)

b) IVIg

IVIg has been used since 1988 for the treatment of GBS and other autoimmune inflammatory diseases. Preparations of IVIg consist of IgG molecules with a distribution of subclasses that corresponds to the one observed in human serum, including IgM, IgG and IgA. IVIg is obtained from pools of plasma from thousands of healthy donors thus enriching the preparation with important functions of humoral immunity; it comprises a range of antibodies directed to pathogens and foreign antigens as well as to self-antigens, essential for the effect in immune-mediated disorders (25, 26)

Mechanism of action:

No single mechanism has been deemed to play a vital role. Important mechanisms include modulation of proinflammatory cytokines, neutralization of activated complement, and signaling through Fc receptors on Fcγexpressing cells, including phagocytes and B cells. (15, 27)

Regimen:

A dose of 0.4g/kg IVIg per day for five days was established to be effective, with a total of 2 g/kg. Administering the total dose over 2 days is equally efficacious when compared to 5 days. (27)

Efficacy:

A 2012 Cochrane systematic review compared IVIg with PE and it was found that IVIg showed similar efficacy with lower rates of adverse events and was more likely to be completed than treatment with PE due to the facilities of administration and no need of special equipment. (28)IVIg and PE treatments have similar basic activities of daily living (ADL) functional outcomes. (29)

Advantages:

IVIg is often the preferred option for GBS because of its efficacy, the more favorable side-effect profile and the higher availability. It is preferred over PE specially in patients with hemodynamic risk because of volume shifts and in young children because of the facility of application.(30) IVIg is favorable in pregnancy.(31, 32)

Adverse effects:

IVIg administration associated adverse events are usually minor and rare, occurring in less than 10% of GBS patients. The most significant adverse reactions of IVIg reported in GBS clinical trials include myocardial infarction, renal failure and vomiting. (16, 33, 34).Headache, aseptic meningitis, cerebral vascular contraction syndrome, thromboembolism, and stroke are neurological complications that were rarely reported.(35)

Limitations:

Caution should be exercised in GBS patients with coronary artery disease, congestive heart failure, recent deep vein thrombosis, pre existing kidney disease, and IVIg should be

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avoided in patients with selective IgA deficiency due to the risk of anaphylaxis. Slowing the rate of infusion, administering intravenous fluids following transfusion, using low osmolality brands, and screening for IgA deficiency should help reduce the risk of adverse events. (31, 32) Comparison between IVIg and PE is shown in table-1.

	IVIg	**PE**
Mechanism	Modulation of proinflammatory cytokines, neutralization of activated complement, and signaling through Fc receptors on Fcγ expressing cells, including phagocytes and B cells. (12)	Nonspecifically removes immune complexes,circulating autoantibodies, cytokines, complement factors and other proinflammatoryhumoral mediators that contribute to GBS immunopathogenesis.(11)
Efficacy	Diminishes pathogenic antibodies, machine independent and easy delivery, and effective especially in pediatric cases. (67)	Removes pathogenic antibodies without frozen plasma; hastens recovery; shortens MV and hospitalization; and effective in treating AMAN (67)
Advantages	IVIg is often the preferred option for GBS because of its efficacy, the more favorable side-effect profile and the higher availability. It is preferred over PE specially in patients with hemodynamic risk because of volume shifts and in young children because of the facility of application.(12) IVIg is favorable in pregnancy.(11)	A notably higher improvement was seen with PE-treated over supportive care alone, without a significant increase in adverse events (12)PE has proven to reduce the likelihood and duration of mechanical ventilation, reduce the time required to walk with assistance and increase the likelihood of fully recovering muscle strength after one year.(11)
Disadvantages	IVIg should be used with caution in GBS patients with coronary artery disease, congestive heart failure, recent deep vein thrombosis, pre existing kidney disease, and should be avoided in patients with selective IgA deficiency due to the risk of anaphylaxis.(11)	Limited access, need for close monitoring and its serious adverse effect profile have restricted the general use of PE for GBS. Additionally, prolonged hospitalization and its related monetary burden have led to PE being a relative restricted immunotherapy for GBS.(11)
Regimen	A dose of 0.4g/kg IVIg per day for five days was established to be effective, with a total of 2 g/kg.(12)	The treatment typically consists of five exchanges, one plasma volume each time (about 50 mL/kg body weight), administered over 1-2 weeks. (11)
Adverse effects	The most significant adverse reactions of IVIg reported in GBS clinical trials include myocardial infarction, renal failure and vomiting .(11).Headache,	PE is associated with significant adverse effects which include hemodynamic instability, coagulopathy, fever, hypotension,

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	aseptic meningitis, cerebral vascular contraction syndrome, thromboembolism, and stroke are neurological complications that were rarely reported.(14)	hypocalcemia, acute myocardial infarction, septicemia, hematoma, thrombosis, pneumonia, complications from central venous access and allergic reactions.(11,12)

Table-1: Comparison between IVIg and PE

2. ZIPPER METHOD

The zipper method as an innovative treatment approach reduces mortality, fastens weaning from mechanical ventilation, and shortens hospital stay, with excellent outcome in severe Guillain-Barre syndrome patients, who require intensive care. This technique stands as a promising immunomodulation strategy in numerous cases. In this method, succeeding the diagnosis of Guillain-Barre´syndrome, plasma exchange was started immediately. In the first session of plasma exchange, a one and a half volume of patients' plasma was removed by using 5% albumin as a replacement solution. At the end of the plasma exchange session, the intravenous immunoglobulin infusion rate was set at 0.4 g/kg straightaway. After 24 hours had passed since the conclusion of the intravenous immunoglobulin infusion, a second plasma exchange session with one volume change was used. Intravenous immunoglobulin infusions were administered after each plasma exchange session. Five times were completed in this intravenous immunoglobulin cycle for Plasma Exchange. This method may be promising, but it needs further clinical studies to prove its efficacy. (36)

3. NEUROMUSCULAR ELECTRICAL STIMULATION IN EARLY REHABILITATION OF GUILLAIN-BARRÉ SYNDROME:

Previous studies in critical illness neuropathy and chronic conditions with associated muscle wasting have suggested that neuromuscular electrical stimulation (NMES) can prevent weakness or atrophy. (37, 38) Severely weak muscles can be inexcitable due to distal conduction failure and NMES may not result in muscle contraction. In those cases, direct muscle fiber stimulation (MFS) can be used instead. (39) Our hypothesis is that electrical stimulation can reduce muscle atrophy in the early severe phase of GBS, until patients have recovered to a level at which they can undergo conventional physiotherapy. We, therefore, initiated a pilot study to evaluate the feasibility, safety, and effect on muscle atrophy of NMES and MFS in the acute and subacute phases of GBS. However, MFS and NMES were found to be safe and feasible as adjunct therapy supplementing standard supportive therapy and rehabilitation in the acute and subacute phases of GBS. To further explore the potential benefits of electrical muscle and neuromuscular stimulation in GBS, we recommend that future studies include stimulation of several muscle groups bilaterally, a fixed study period, and an untreated control group. (40)

4. CORTICOSTEROIDS

Other corticosteroids and prednisolone has been showing efficacy in the treatment of various autoimmune diseases such as myasthenia gravis, chronic inflammatory demyelinating polyneuropathy and rheumatoid arthritis; due to the autoimmune characteristics of corticosteroids, its use has been studied in GBS (41) One study evaluates high-dose steroid therapy showed apparent positive results (42) and the other study showed slight increase in the benefits with prednisolone over IVIg (43), further studies have proved that high doses of corticosteroids may exert immunosuppressive effects on macrophages, inhibiting their beneficial effect on injury site (44). The latest 2016 Cochrane systematic review showed no significant difference in disability grade between the corticosteroid and non-corticosteroid treated patients. When corticosteroids were administered orally, the corticosteroid group showed significantly less improvement. (45) When disease progresses beyond eight weeks in adults or four weeks in children, or when relapses occur later than eight weeks after the onset, this leads to a diagnosis of CIDP, where corticosteroids shows to be effective in 70-80% of all age group patients.(5) Despite the conventional efficacy of corticosteroids in immune-mediated disorders and in the EAN animal model of GBS, it has been clearly established to have no efficacy in GBS. (45)

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5. POTENTIAL IMMUNOTHERAPIES

Four different potential immunotherapies as treatments for GBS have been published. These include

- 123 interferon β-1a (a cellular immunomodulatory drug used in multiple sclerosis) compared to placebo in 19 patients
- CSF filtration in 1737 patients compared to PE,
- 124-126 brain-derived neurotrophic factor (a growth factor which gives protection against degeneration or cause regeneration in motor axons) in 10 patients comparison to placebo127
- Chinese herbal medicine, TripterygiumWilfordiipolyglycoside (an extract with anti-inflammatory, antiproliferative and immunosuppressive properties) compared to IV corticosteroids in 43 patients.

In a trial differentiating the Chinese herbal medicine **tripterygiumpolyglycoside** with high-pitched dose corticosteroids, the foremost outcome for this review was unavailable but those getting tripterygiumpolyglycoside possibly had further improvement in disability grade after eight weeks (Zhang 2000). The finding, if factual, could have been due to a advantageous effect of tripterygiumpolyglycoside or a detrimental effect of corticosteroids.

The muromonab-CD3 monoclonal antibody against T cells was used in 3 people with serious GBS but the results were discouraging. None of these studies was great enough to confirm or disprove clinically remarkable benefit or harm of any of these interventions.(46)

6. Complement Targeted Therapy

In the pathophysiology of GBS complement plays an important role by antibodymediated complement-dependent mechanisms that cause nerve injury, mainly on axonal variants of the disease. (47, 48)Research on newly discovered drugs that could modulate complement activation and the development of the MAC have driven greater focus. (48)

a) Eculizumab (anti C-5 monoclonal antibody)

Humanized monoclonal antibody eculizumab can particularly stick to complement C5 to block its splitting and strongly inhibit membrane attack complex formation. Eculizumab can constructively avert respiratory paralysis and fatal motor neuropathy functionally and morphologically in anti-ganglioside GQ1b antibody–mediated neuropathy in a murine model. (1) Two randomized, placebo-controlled phase 2 trials have assessed the safety and efficacy of eculizumab.Activation in GBS study, patients randomly received IVIg with eculizumab or placebo. The small number of patients ruled out conclusions on efficacy, but eculizumab was considered safe and well tolerated. The Japanese Eculizumab Trial for GBS used the same study protocol, and randomized 23 patients to IVIg with eculizumab, and 12 patients to IVIg with placebo. In this trial a larger number of patients in the eculizumab group were able to run at 24 weeks(74%)in comparison to placebo group (18%)These studies implicate that eculizumab seems safe and well tolerated, and might potentially improve outcome in GBS as add-on treatment to IVIg, but larger trials are required. (49) Brain abscess and anaphylaxis happened as significant adverse effects in the eculizumab group and the causation could not be eliminated. (1)

b) rEV567

rEV567 is a recombinant protein obtained from the saliva of a soft tick. It binds C5 blocking its cleavage to C5a and C5b hindering both the classical and other possible pathways. (13, 48, 50, 51) The same effects on the complement cascade described for Eculizumab are seen with rEV576 (48, 50). In an in vitro model of MFS, rEV576 showed absolute inhibition of MAC formation preventing motor nerve terminals from immune-mediated neuropathy. (13, 48) There are no clinical trials in humans. (12)

c) Nafamostatmesilate

Nafamostat is a synthetic serine protease inhibitor. Voltage-gated sodium channels are there in a high density at nodes of Ranvier and are related with the production of muscle action potentials. Dysfunction of voltage-gated sodium channels by antigen-antibody interaction in the axonal membrane at nodes of Ranvier has been suggested as an chief pathophysiological mechanism in GBS causing reversible conduction failure (52). By its complement inhibitory effect, Nafamostat prevents voltage-gated sodium channels disruption and has proved helpful effects in Rabbit models of AMAN. (13, 48, 52)

d) Microcept (APT070)

The complement inhibitory charecteristics of Mirococept, C3/C5 convertase inhibition were evaluated in a model of MFS (13, 48, 53). In vitro

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and in vivo studies showed efficacy of Mirococept in hindering C3/C5 convertase with a greater effect over C5 convertase, hence preventing nerve injury and MAC formation. (53)

e) Human soluble complement receptor type 1

This protein inhibits the classical and other alternative pathways of complement activation by binding to C3b and C4b, through degeneration of these factors due to its activity as cofactor of the serum protease-I. (13) In EAN, sCR1 administration caused declination in severity and demyelination; one of the treated rats was entirely protected from the disease. However, the differences were not statistically significant. (54)

f) Interferon

Interferon-β (IFN-β) is a cellular immunomodulator that inhibits TNF-α production, regulates macrophage activity and antigen presentation. The immunomodulatory action of IFN-β is stated by the elevation in the production of TGF-β and anti-inflammatory functions of T cells. (55)TGF-β has shown to rise and regulate Schwann cell proliferation and differentiation helping to the self-limiting course of GBS. (55, 56) Due to the numerous anti-inflammatory characteristics of IFN-β, it has been put forward as a target for the GBS treatment. In EAN, IFN-β resulted in slow onset of clinical signs and repressed disease activity by reducing T and B cell responses and lessening the inflammatory cells. (57) Despite the fact that two case reports have shown constructive effects of IFN-β as an adjunct to IVIg or PE. (58) A randomized clinical trial showed no remarkable differences between placebo and IFN-β added to IVIg treatment for any efficacious outcome. (59)

g) Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is a neurotrophin with significant inferences for brain and peripheral nervous system myelination and development.One clinical trial evaluated the utilization of BDNF in GBS patients after its potential for reducing axonal degeneration was proved. (58) BDNF showed no statistically noteworthy difference with placebo in terms of effectiveness; BDNF seemed to be safe and well tolerated. Results of this study have to be cautiously interpreted because it has a compact sample size due to early stop of recruitment. (60)

h) Bisphosphonates

Bisphosphonates exact mechanism of action is unclear; still, studies for etidronate and clodronate suggest that these drugs act by building up the osteoclast apoptosis. By mediating osteoclast apoptosis, bisphosphonates activate macrophage apoptosis and some inhibit macrophage's nitric oxide (NO) production. (61, 62) Clodronate was evaluated in EAN showing a dose-dependent beneficial effect (62). No clinical trials have been registered yet. (12)

i) Mycophenolatemofetil

Mycophenolatemofetil (MMF) is an anti-inflammatory and immunosuppressive drugused in diseases such as chronic inflammatory demyelinating polyneuropathy, autoimmune myopathies and various animal models of autoimmune diseases. MMF employ its action by the inhibition in the formation of T and B cells through the blockade of guanine nucleotide synthesis. A pilot study assessed the use of MMF added to methylprednisolone and IVIg in GBS patients; results showed no relevant difference between groups. It is presumed that the use of a lower dose for this study might be one of the reasons for not having sufficient clinical improvement. (12)

j) Cyclophosphamide

Cyclophosphamide (CY) is an antineoplastic and immunomodulatory agent used since 1958; it is a pro-drug. Although CY is disapproved for the GBS treatment, a case report published in 1976 depicted the use of CY in 15 patients with GBS. Results showed improvement in the rate of recovery, time to start of improvement and time to stop of progression. The immunosuppressive effect of CY was evaluated in EAN; when given as prophylaxis, it averted the development of EAN and decreased cytokine expression on nervous tissue. Reduction in EAN symptoms was noticed when CY was therapeutically administered. Continuous study is needed to clarify the exact mechanism of action of CY on EAN and in GBS patients. (12)

k) Rituximab

Rituximab is a monoclonal antibody. Apoptosis, complement-mediated cytotoxicity and antibody dependent cell-mediated cytotoxicity are the chief mechanisms of action of Rituximab. (59, 63, 64) The effects of rituximab in GBS patients has not been assessed in any clinical trial,however, in one case a patient who developed GBS after T-cell depleted hematopoietic stem cell transplantation for myelodysplastic syndrome showed better neurological symptoms after

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rituximab administration (65) The most common side effects of rituximab are headache fever and asthenia, (4) In the presence of increased levels of anti-neurofascin or other antibodies, treatment with rituximab can be helpful, although this is currently built on a few observations.(5) The status of all the treatment of Guillain–Barré syndrome (GBS) is given in table-2.

TREATMENT	**STATUS**
Plasma exchange	Serves as an alternative to IVIg in case of IVIg contraindications or allergy. (20)
IVIg	IVIg is often the preferred option for GBS because of its efficacy, the more favorable side-effect profile and the higher availability. (12)
Zipper method	This method may be promising, but it needs further clinical studies to prove its efficacy. (37)
Corticosteroids	It has been clearly established to be non-efficacious in GBS. (11)
NMES and MFS	They can serve as adjunct therapy in the acute and subacute phases of GBS. (41)
Tripterygiumwilfordiipolyglycoside	More trials needed to get conclusive evidence.
Muromonab CD-3 Monoclonal antibody	More trials needed to get conclusive evidence.
Eculizumab	It seems safe and well tolerated, and might potentially improve outcome in GBS as add-on treatment to IVIg, but larger trials are required.(18)
rEV567	No clinical trials conducted in humans.(12)
Nafamostatmesilate	Proved beneficial effects in Rabbit models of AMAN (12)
Interferon-β	Small RCT showed no remarkable therapeutic efficacy (12)
BDNF	Small RCT showed no significant therapeutic efficacy.(12)
Bisphosphonates	No clinical trials have been registered yet. (12)
Rituximab	No clinical trials have assessed the effects of rituximab.
Cyclophosphamide	More trials needed to get conclusive results.(4)
MMF	A small historical controlled clinical trial could not show the efficacy.(12)
ANX005	A phase 2 clinical trial is planned.
IdeS	Phase II study in combination with standard care IVIg is planned.

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SVPE	Efficacy has only been shown in few patients, large-scale studies are needed before this technique can be implemented in routine clinical practice(2)
Pleiotropic cytokine erythropoietin	Proven to be neuroprotective and pro regenerative in animal models of antibody and T-cell-mediated Guillain-Barré syndrome.(3)

Table-2: Treatment and status of Guillain–Barré syndrome (GBS)

III. FUTURE PERSPECTIVE

There are many ongoing studies and trials for newer therapeutic options in the treatment of GBS. A phase 1b double-blind, placebo-controlled, single ascending dose study including 23 participants was conducted in Bangladesh to assess anti-C1q antibody **ANX005** in patients with Guillain-Barré Syndrome (GBS) which concluded thatthe classical complement inhibitor ANX005 was well tolerated and demonstrated robust target engagement, impact on biomarkers of neuronal damage, and preliminary evidence of efficacy. They have also planned a phase 2 trial. (66) **IdeS (imlifidase)** is an endopeptidase derived from Streptococcus pyogenes which has specificity for human IgG, and when infused intravenously results in rapid cleavage of IgG(17). In an AMAN rabbit model, IdeS reduced the frequency of axonal motor degeneration and improved recovery. (15) An open-label, single arm, multi-centre, phase II study of imlifidase in combination with standard care IVIg in patients with GBS is currently recruiting patients in European countries(ClinicalTrials.gov Identifier: NCT03943589). An open label,single arm study for **CK0801** (Cord blood-derived T-regulatory cells) with 18 participants is planned to be conducted to determine its safety and practicality in patients with GBS(ClinicalTrials.gov Identifier: NCT03773328). Treg cells in their natural state play an important role in maintaining immune homeostasis and limiting autoimmune responses by modulating both innate and adaptive immunity. The administration of Treg cells in human clinical trials has emerged as an alluring method to induce immune tolerance in patients based on literature reports of animal studies showing induction of immune tolerance by Treg cells in autoimmune diseases, graft-versus-host disease, and solid organ transplant rejection. Small volume plasma exchange (SVPE) has been demonstrated to be a safe and effective therapy for GBS in resource-constrained countries like India and Bangladesh. It is a novel, inexpensive ($500), straight forward procedure for selective removal of plasma. But before this procedure can be used in regular clinical practise, larger trials are needed because the effectiveness of SVPE has only been demonstrated in a small number of patients.(2) Another potential therapy that merits further study is **pleiotropic cytokine erythropoietin**, which has been found to be neuroprotective and pro regenerative in animal models of antibody and T-cell-mediated Guillain-Barré syndrome. (3)

IV. CONCLUSION

Due to its quick and unanticipated onset, Guillain-Barré Syndrome can be a severe condition. Additionally, recuperation may not always occur quickly. As was previously mentioned, patients typically experience significant weakening or paralysis a few days or weeks following the onset of symptoms. Patients have both physically challenging and emotionally trying times. For patients, adjusting to unexpected paralysis and needing assistance with daily tasks from others can be extremely challenging. Therefore, raising awareness of this condition among patients and medical professionals would certainly assist to improve the existing state of treatment. Immunotherapy undeniably helps GBS patients recover, and both PE and IVIg are equally beneficial. Because of its minimal side-effect profile and simplicity of administration, IVIg may be recommended. Due to financial limitations, however, small volume PE can be utilised with equivalent effectiveness. Equally crucial to lowering GBS morbidity and death is attentive anticipatory supportive care.

V. ACKNOWLEDGEMENT

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VI. ABBREVIATIONS

GBS: Guillain–Barré syndrome, **CSF**: Cerebrospinal Fluid, **AIDP**: acute inflammatory demyelinating polyradiculoneuropathy, **AMSAN**:

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acute motor-sensory axonal neuropathy, **AMAN**: acute motor axonal neuropathy, **MFS**: Miller Fisher Syndrome, **JE**: Japanese Encephalities, **RCTs**: Randomised Controlled Trials, **PE**: Plasma Exchange, **IVIg**: Intravenous Immunoglobulin, **AAN**: American Academy of Neurology, **NMES**: Neuromuscular Electrical Stimulation, **CIDP**: Chronic Inflammatory Demyelinating Polyneuropathy, **EAN**: Experimental Autoimmune Neuritis, **MAC**: Membrane Attack Complex, **sCR1**: Soluble Complement Receptor 1, **BDNF**: Brain- derived Neurotrophic Factor, **MMF**: MycophenolateMofetil, **CY**: Cyclophosphamide,**IdeS**: Imlifidase , **SVPE**: Small volume plasma exchange

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