

Biological Drugs in Guillain-Barré Syndrome: An Update

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Abstract: Background: Guillain-Barré Syndrome (GBS) is currently considered the most common global cause of acute flaccid paralysis. Currently, standard therapy for Guillain-Barré Syndrome includes intravenous immunoglobulin or plasma exchange. Despite medical advances regarding these treatments, many treated patients do not reach full recovery. Therefore several biological agents have attracted the attentions from researchers during the last decades, and various studies have investigated their role in Guillain-Barré Syndrome.

Objective: The present study aims to address emerging biological approaches to GBS while considering their efficiency and safety in treating the disease.

Materials and Methods: An extensive electronic literature search was conducted by two researchers from April 2016 to July 2016. Original articles, clinical trials, systematic reviews (with or without meta-analysis) and case reports were selected. Titles and abstracts of papers were screened by reviewers to determine whether they met the eligibility criteria, and full texts of the selected articles were retrieved.

Results: Herein authors focused on the literature data concerning emerging biological therapeutic agents, namely anti-C5 monoclonal antibody (Eculizumab), anti-C1q monoclonal antibody, anti-T cell monoclonal antibody, anti-CD2 monoclonal antibody, anti L-selectin monoclonal antibody, anti-CD20 monoclonal antibody (Rituximab), anti-CD52 monoclonal antibody (Alemtuzumab) and cytokine targets. By far, none of these agents have been approved for the treatment of GBS by FDA.

Conclusion: Literature findings represented in current review herald promising results for using these biological targets. Current review represents a summary of what is already in regards and what progress is required to improve the immunotherapeutic approach of treating GBS via future studies.

Keywords: Guillain-barré syndrome, immunotherapy, biological, drug, therapy, treatment, monoclonal antibody.

1. INTRODUCTION

Guillain-Barré Syndrome (GBS) is a term used to describe acute autoimmune peripheral neuropathy with specific characteristic of ascending symmetrical flaccid paralysis of limbs accompanied with hyporeflexia or areflexia. Many consider GBS as a post-infectious inflammatory disorder, since it is commonly preceded by a viral or bacterial infection [1-4]. Due to near eradication of Poliomyelitis, GBS is now considered the most common universal cause of acute flaccid paralysis [5]. It predominantly commences with a progressive bilateral weakness in muscles of lower limbs, which rapidly ascends and spreads to the muscles of upper

body, upper limbs and face. This motor dysfunction is frequently associated with a loss or attenuation of deep tendon reflexes throughout body [6]. In severe cases of GBS, patients require mechanical ventilation as a result of respiratory failure [3]. Main GBS variants comprise acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and Miller-Fisher syndrome (MFS) [7].

Since the introduction of GBS in 1859, its pathogenesis has received tremendous amount of attention. Initially, it was believed that pathogenesis of GBS is mostly dependent on T-cell mediated immune system. EAN (Experimental allergic neuritis) which is an animal model of GBS contributed largely to this idea as well. EAN could be induced by either immunization with proteins of PNS myelin (e.g. P0, P2, and PMP22) or transfer of sensitized T cells to animals. It was greatly considered as an equivalent model of AIDP variant of GBS. Since EAN prevailed the preclinical studies of GBS

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for more than two decades, it contributed to several studies evaluating the T cell mechanism in elicitation of inflammatory response observed in GBS, and potential therapeutic targets in its pathogenesis. However, EAN has been extensively criticized for its inability to introduce specific antigenic targets for T cell auto reactivity in GBS and other peripheral neuropathies. In addition, EAN is inadequate in describing other variants of GBS spectrum other than AIDP, namely AMAN [8, 9].

The role of both Th-1 and Th-2 immune response in pathogenesis of GBS has been previously suggested. Th-1 (pro-inflammatory) cytokines including IFN- γ , IL-1 β , TNF, IL-6 have been found to rise in progressive (acute) phase of GBS and EAN, while increase in TH-2 (anti-inflammatory) cytokines such as TGF- β and IL-4 is accompanied with recovery phase of the disease. In other words, it seems that the imbalance between Th-1 and Th-2 responses (which could be illustrated by an increase in IFN- γ /IL-4 ratio) greatly contributes to the pathogenesis of GBS [10-12]. Th-1 responses are believed to provoke the disease by activating and recruiting macrophages to the site of peripheral nerves, which subsequently leads to nerve damage induced by either direct effect of macrophages or *in situ* release of toxic and inflammatory materials. The final events of Th-1 pathway eventuate injuries to myelin (demyelination), axons and Schwann cells [13, 14]. Th-2 response on the other hand seems to function as a suppressor and regulator of Th-1 pathway, and therefore may have a resolution effect observed in recovery phase of both GBS and EAN [15-17]. Recently, the role of Th-17 cells and their characteristic cytokine product (*i.e.*, IL-17) in pathogenesis of GBS has been mentioned [14, 18]. Evidence by far suggests that AIDP (demyelinating GBS) is often associated with cellular infiltrations rather than antibody mediation or complement fixation pathways. In another recognized mechanism involved in GBS known as molecular mimicry, antibodies produced as a response to virulent antigens cross-react and bind to self-antigens located on peripheral nerves [2]. These antibodies activate the complement cascade through binding gangliosides in Ranvier nodes and terminal axons. This event will lead to the deposition of antibodies and immune complexes in the nodal area and recruiting macrophages, which finally eventuates in a complete conduct block [19, 20]. It is believed that both AMAN and MFS variants share this complement-dependent pathogenesis [21].

Intravenous immunoglobulins (IVIg) and plasma exchange (PE) are used for treating nearly all cases of GBS. Overall, both PE and IVIg significantly hasten recovery compared to supportive treatment alone [22]. IVIg is generally tolerated well and has mild side effects which are mostly related to infusion rate (including headaches, nausea, vomiting, chills and fever, back pain and fatigue) [23]. However, it could be accompanied with serious side effects including thrombotic events, anaphylaxis, and renal impairment [24]. In PE treatment, plasma volume is exchanged with albumin. Adverse effects of PE include allergic reactions, hypotension and hypocalcemia which might result in discontinuation of treatment in some cases [25]. Despite medical advances regarding IVIg and PE, their mechanism of action is mostly unclear and it seems that

they mediate through unspecific pathways and their details are not fully recognized. Many patients treated with either one or a combination of these therapies do not reach full recovery, and disability rate among treated individuals is highly frequent. On the other hand, as it was mentioned, both IVIg and PE have their own complications [26]. Due to mentioned limitations, more efficacious approaches beyond IVIg and PE are required. Therefore, a better understanding of the pathoimmunology of the disease is leading to innovation of emerging new drugs.

Further advances in molecular understanding of the disease immunopathology have resulted in the identification of novel therapeutic targets. Emergence of biological treatments in medicine has contributed to this fact as well. Biological agents are protein class drugs that mediate their effects through modulating the immune system by targeting specific cells or chemicals; therefore their role in ameliorating several immune-mediated inflammatory or malignant disorders have been addressed [27-30]. During last decades, the role of several biological agents in GBS has attracted the attention from researchers, and various studies have investigated their capacity of modulation in affecting GBS patients or its animal models.

The efficiency of many chemical drugs (such as Mycophenolate or Tripterygium) has been addressed in prior studies. Therefore, the present study aims to address a comprehensive update of biological approaches to GBS (in human and animal models) which have contributed significantly to advancing knowledge of its pathogenesis and development of efficacious models for treatment of GBS.

2. MATERIALS AND METHODS

Original articles (both in human and animal models of GBS), clinical trials, systematic reviews (with or without meta-analysis) and case reports on treatments of GBS were selected. Among these, studies that represented evidence of using at least one biological approach (whether accompanied with other standardized therapies or not) were included; while studies that assessed the efficacy of traditional therapeutic interventions in GBS (IVIg and PE) were excluded. Given the lack of an electronic database that contains all publications of all medical journals, it was necessary to combine multiple databases for a comprehensive literature search. For this reason, an extensive electronic literature search was conducted by two independent researchers during a period from April 2016 to July 2016 in MEDLINE *via* PubMed interface, SCOPUS, Google Scholar, clinicaltrial.gov database and the Cochrane Library for all articles published from inception to July 2016. The findings were compared and combined with each other when necessary. Database-specific search strings were developed and included search terms describing biological treatments (population/exposure/intervention) and GBS (study design/description of cases). A combination of medical subject headings and keywords (including “biological treatments/therapies”, “immunotherapy”, “monoclonal antibody”, “Guillain barre syndrome”, *etc.*) was used. Titles and abstracts of identified papers were screened by reviewers to determine whether they met the eligibility criteria of interest to develop current review. Subsequently, full texts of the

remaining articles were independently retrieved by mentioned reviewers for eligibility. All studies were searched through their references as well to check for possible relevant articles.

3. APPROACHES TO COMPLEMENT PATHWAY AND ANTIBODIES

3.1. Cobra Venom Factor, Soluble Complement Receptor and APT070 (Mirocept)

First study on therapeutic effects of anti-complement agents was conducted in 1987. EAN-induced Lewis rats were treated with Cobra venom factor (CVF) which was believed to deplete C3 component of complement system, and therefore interfere with cascade. Rats treated with CVF developed neurological signs with a delayed onset, and in general experienced a milder disease. Sections of lumbosacral roots also demonstrated no demyelination, in contrast with untreated rats which showed infiltrations and axonal demyelination. Therefore it was suggested that complement system may be involved in pathogenesis of GBS in humans, and it could be investigated as a target of treatment [31]. In 1995, Jung *et al.* investigated the effect of soluble complement receptor type 1 (sCR1) in EAN-induced Lewis rats. sCR1 binds to complement components C3b and C4b, and therefore inhibits both classical and alternative pathways of complement cascade. Rats treated with sCR1 demonstrated protective effects of complement inhibition and had better electrodiagnostic nerve results. This study suggested a therapeutic effect of sCR1 in the treatment of GBS [32]. Another study conducted by Halstead in 2005 evaluated the role of complement inhibitor APT070 (Mirocept) in *in-vivo* and *in-vitro* MFS animal models. APT070 is a derivation of CR1 (complement receptor type 1) which similar to sCR1 in previous study, has complement inhibiting activity. Both *in-vivo* and *in-vitro* studies used immunohistological assays to investigate complement deposition in presynaptic Schwann cells (pSC) and axon motor terminals in neuromuscular junctions (NMJ). It was demonstrated that APT070 has C5 convertase and C3 convertase regulatory functions, and could protect nerve terminals from the effects of anti-ganglioside antibodies by inhibiting deposition of MAC formations. Therefore, APT070 (Mirocept) was suggested as a therapeutic option for treating GBS [33].

3.2. Anti-C5 Monoclonal Antibody (Eculizumab)

Eculizumab is a humanized monoclonal antibody, which binds to C5 component of complement system with high affinity and prevents it from being cleaved to C5a and C5b by C5 convertase; thereby it blocks the cascade at level of C5 and inhibits the formation of C5b-9 complex or MAC pores. Inhibition of complement cascade at the level of C5 is beneficial since it blocks terminal components of complement system whilst preserving the activity of proximal products such as C3b, which at a low level are essential for immunoprotective functions (including pathogen opsonization and elimination of immune complexes) [34]. Eculizumab first received FDA approval in the treatment of Paroxysmal nocturnal hematuria (PNH) in March 2007 [35], although its efficacy had been primarily assessed in Systemic lupus erythematosus and Rheumatoid arthritis [36, 37]. PNH is a

chronic hemolytic anemia disorder, with potentially life-threatening characterizations including venous thrombosis and bone marrow failure. Pathology of the disease includes an acquired somatic mutation in hematopoietic stem cells that results in deficiency of specific surface proteins, namely CD55 and CD59. These proteins involve in regulation and inhibition of complement system; therefore in their deficiency, RBCs are greatly predisposed to complement-mediated cell lysis by the formation of MAC complexes [38]. Eculizumab (Soliris; Alexion Pharmaceuticals, Inc., Cheshire, CT, US) consists of IgG2 and IgG4 heavy chains constant regions and human kappa light chain constant regions, which are unable to bind Fc-receptors and activate complement cascade. Its variable regions are comprised of both human and murine sequences that have high affinity for human C5. Eculizumab binds to C5 in PNH patients and prevents blood cells from hemolysis [34]. Its safety and efficacy in 600–900 mg weekly intravenous administration were evaluated and confirmed appropriate in PNH clinical trials [39]. A more recent phase II study on Myasthenia gravis patients also showed safety of the drug [40].

In 2008, Halstead *et al.* investigated the role of Eculizumab in a model of mice which was identical to MFS. Both *in-vivo* and *in-vitro* results supported the protective effects of Eculizumab in preventing complement damage by Immunohistochemical assays and electrophysiological evaluations. The levels of C3 and MAC deposition were evaluated in phrenic nerve and diaphragm muscle of mice injected intraperitoneally with anti-GQ1 antibodies and normal human sera (as a source of complement). Similar to previous study by author (Halstead 2005), deposition of complement products in presynaptic Schwann cells and motor axonal terminals was significantly prevented. Compared to control groups treated with control monoclonal antibody, mice injected with eculizumab were completely protected from developing neurological symptoms including respiratory paralysis and muscle weakness associated with anti-ganglioside antibody. Therefore, authors indicated the need for clinical trials with Eculizumab in MFS and other variants of neuropathies [41].

The first administration of Eculizumab in GBS was reported as a case report in 2014. Patient was a 13-year-old boy with severe GBS that was unresponsive to IVIg treatment (started on day 3 from onset of disease). His condition continued to deteriorate and led to mechanical ventilation and subsequent tracheostomy due to respiratory failure. A single dose of Eculizumab was administered (time unspecified), and thereafter the patient commenced recovery phase which took 8 weeks. No clinical trial was conducted on Eculizumab in GBS patients at the time [42]. Currently, two phase II randomized blinded placebo-controlled clinical trials are going on; one commenced in 2014 in Scotland (ICA-GBS or Inhibition of Complement Activation (Eculizumab) in Guillain-Barre Syndrome Study) [43] and the other one started in 2015 in Japan (JET-GBS or Japanese Eculizumab Trial for GBS) [44].

3.3. rEV576

In 2008, Halstead *et al.* investigated the role of another complement-inhibiting agent known as rEV576 in a mice

model of MFS. This material is obtained from a tick's (*Ornithodoros moubata*) saliva protein, which defends tick against host's complement system by inhibiting both classic and alternative pathways. Like Eculizumab, rEV576 binds to C5 and prevents it from being cleaved by C5 convertase into C5a. Like prior studies conducted by Halstead *et al.*, mentioned study also represented a significant decrease in functional and electrophysiological indicators of NMJ damage after treatment with rEV576, namely presynaptic Schwann cell injury and axonal conduction. Therefore, it was suggested as a therapeutic option in need of clinical trial studies; although up to date no clinical trial has been conducted in this regard [45].

3.4. Nafamostat Mesilate (NM)

Another 2008 study by Phongsisay *et al.* investigated the effect of Nafamostat mesilate (NM: 6-amidino-2-naphthyl-p-guanidino-benzoate dimethanesulfonate, which is a synthetic serine protease inhibitor with complement-inhibition functions) in a rabbit model identical to AMAN associated with anti-GM1 antibody. Intravenous administration of NM was demonstrated to be correlated with the inhibition of C3 products deposition. As a result, MAC formation was not detected in group treated with NM, and Na channels of Ranvier nodes and nerve terminals were protected from deleterious effects of injected anti-ganglioside antibodies. Mechanism of action for NM is believed to be correlated with inhibiting initial complement components C1r and C1s. This event results in significant decrease of C3 deposition. Previous Japanese studies have also suggested that NM inhibits C3/C5 convertase in both classical and alternative pathways. Therefore it shuts down the whole complement cascade including C1s, C1r, C3a, C3b, C5a, C5b and C5b-9; a fact that is contrary to previous anti-complement agents like Eculizumab and rEV576.

Similar to Eculizumab and in contrast with previous complement inhibitors (including Mirococept, CVF, sCR I and rEV576), NM has been used in clinical treatment of complement-mediated situations such as DIC (Disseminated intravenous coagulation), acute pancreatitis and during plasmapheresis. Japanese GBS patients treated with plasmapheresis (40 mg/h for 5 h) often receive NM instead of heparin at a 300 ng/mL concentration. According to the study (Phongsisay *et al.*) no adverse effect has ever been reported in human administrations. Therefore, authors called for randomized controlled trials of NM in treatment of GBS [46-48]. No clinical trials seem to have been conducted on this specific complement-inhibitor component in GBS; while its effect on different situations has been investigated.

3.5. Anti-GD3 Idiotypic Monoclonal Antibody (BEC2)

In 2010, Usuki *et al.* proposed the application of anti-idiotypic monoclonal antibodies instead of IVIg in the treatment of GBS. Due to adverse effects related to IVIg and the fact that its mechanism of function bears elimination of both pathologic and non-pathologic immunoglobulins, Usuki *et al.* suggested using specific anti-idiotypic monoclonal antibodies that target pathogen immunoglobulins specifically. In this study, an antibody-induced animal model of GBS was

generated using LPS of *C.jejuni*. Due to molecular mimicry between LPS and nerve gangliosides, this event resulted in producing anti-ganglioside antibodies named as anti-GD3 autoantibodies. It was shown that anti-GD3 was associated with clinical symptoms and pathological changes in nerve sections of subject animals. Thereafter, induced animals were treated with designed anti-idiotypic antibody (BEC2), which was associated with significant amelioration in demyelination and clinical course. ELISA assays also confirmed the potency of BEC2 in inhibiting anti-GD3 antibodies competitively. Usuki *et al.* declared BEC2 an effective and feasible monoclonal antibody against pathogenic anti-ganglioside antibodies induced in this particular animal model, which could be considered as a prototype in future novel therapies for treating GBS [49]. In spite of this, no reports of further studies could be found in this regard.

3.6. Anti-C1q Monoclonal Antibody (M1)

A recent 2016 study investigated the role of a novel monoclonal antibody (mAb) against C1q in an *in-vivo* mice model of AMAN and MFS [50]. A similar antibody was used in a prior study in a mice model of Neuromyelitis Optica (NMO), which demonstrated effectivity in decreasing demyelination [51]. Similar to NM study and in contrast with other complement studies, McGonigal *et al.* study evaluated the influencing effect of inhibiting proximal components of cascade in mice. Target component was C1q and it was inhibited by anti-C1q antibody known as M1. As a result of treatment, C1q circulation was reduced in both AMAN and MFS treated models. In addition, complement deposition, nerve injuries and other immune cells recruitment were decreased in animals treated with M1. Moreover, their respiratory functions were improved. This study suggested a beneficial effect of inhibiting C1q compared to inhibition of cascade at a more downstream level with Eculizumab. In C5 inhibition all three pathways would be inhibited and therefore there would be a higher risk for infections. On the other hand, with inhibition of C5 convertase, C3a and C5a (chemotaxis agents) are free to recruit macrophages and mononuclear cells to the site of injury. M1 inhibition of C1q is not accompanied with producing these products; therefore in antibody/complement mediated pathogenesis of AMAN and MFS, treatment with anti-C1q could prevent and treat the pathology without generating chemotaxis products. In addition, other complement pathways are free to maintain complement system's functionality and prevention of infections [50, 52]. This is the first report of anti-C1q monoclonal antibody (M1) in an animal model of GBS, and therefore further future preclinical and clinical studies are required to determine its effectivity.

4. APPROACHES TO CELLULAR AND HUMORAL IMMUNE SYSTEM

4.1. OK3 (Anti-T Cell Monoclonal Antibody)

After investigating the therapeutic effect of anti-T cell monoclonal antibodies in animal studies [53], Feasby *et al.* evaluated the effect of a murine anti-T cell monoclonal antibody (OK-3) directing against human T cells in a pilot study with 3 GBS patients. OK-3 had previously proved

effectivity in treatment of acute transplant rejections; therefore according to the probability of T cell mediation pathogenesis, it was assumed that it might be beneficial in GBS treatment as well. In spite of this, OK-3 proved to be inefficient in ameliorating the symptoms. Treatment with OK-3 resulted in immediate drop in T cell lymphocytes and sustained lymphopenia. Furthermore, it was associated with significant complications in one patient, namely aseptic meningitis and reactivation of genital herpes lesions [54]. Therefore this approach failed to attract further attentions.

4.2. OX34 (Anti-CD2 Monoclonal Antibody)

In 1996, Jung *et al.* investigated the role of anti-CD2 monoclonal antibody in a model of Lewis rats EAN. Anti-CD2 monoclonal antibodies had previously suggested effectivity in treating animal models of autoimmunity (including diabetes and transplant rejection). Jung *et al.* demonstrated that administration of OX34 prior to inducing EAN in rat models prevented clinical signs of EAN significantly. Furthermore, OX34 represented therapeutic effects when administered after initiation of EAN clinical signs. This study claimed that mechanism of action of OX34 in ameliorating EAN was mediated *via* its inhibitory effect on migration of T cells through blood-nerve-barrier. Since no T cell depletion, anergy or inhibition of T cell activation was not observed, the study recommended anti-CD2 monoclonal antibodies as a possible candidate immunotherapy for GBS [55]. However, no further evidence of investigation regarding anti-CD2 monoclonal antibodies and GBS was found in the literature.

4.3. HRL3 (Anti L-selectin Monoclonal Antibody)

The role of anti L-selectin monoclonal antibody was assessed in 1997 by Archelos *et al.* L-selectin is an adhesion molecule located on leukocytes. One of the crucial steps of cellular infiltration into the tissues involves transmigration of leukocytes from endothelium into the interstitial tissue surrounding them. L-selectin facilitates this function by binding different ligands including CD-34, GlyCAM and MAdCAM (located on endothelial venules), and assists the leukocytes in initial steps of transendothelial migration [56]. Prior studies had suggested the contributory effect of blocking L-selectin in different inflammatory conditions [57]. Archelos *et al.* also investigated the role of HRL3 (hamster anti L-selectin monoclonal antibody) in a model of Lewis rat EAN. This study showed that severity of the disease was significantly reduced in HRL3-treated rats compared to controls. Moreover, histopathological assays were associated with lesser demyelination in treated animals. These effects were observed both in the group injected with HRL3 *in onset of induction of EAN*, and subjects that were treated *after* beginning of the disease. Therefore, it was concluded that L-selectin inhibitory analogues could be beneficial in treatment of GBS [56]. No further studies were found in this regard.

4.4. Rituximab (Anti-CD20 Monoclonal Antibody)

Rituximab is a monoclonal antibody that targets CD20+ B cells, and results in B cell depletion via complement-dependent cytotoxicity (CDC), antibody-dependent cell

cytotoxicity (ADCC) involving NK cells and phagocytosis by macrophages and neutrophils. CD20 is expressed on surface of B cells from pre-B cell stage to mature B cells, and it is also expressed by most B cell neoplasms. Rituximab was the first FDA-approved antibody used in cancer therapy (in 1997), initially administered for treating Non-Hodgkin Lymphoma (NHL) [58, 59]. Rituximab is also suggested to have beneficial effects in treatment of steroid-refractory chronic GVHD (Graft Versus Host Disease) [60, 61].

The therapeutic role of Rituximab has been investigated and reported in several chronic neuropathies, including neuropathies associated with monoclonal gammopathies and polyneuropathy associated with antibodies against myelin-associated glycoprotein (anti-MAG) [62-64]. In spite of research literature regarding chronic neuropathies, effectivity of Rituximab in treating GBS has never been attended as an extensive investigation.

In 2008, Ostronoff *et al.* reported a case of GBS following hematopoietic stem cell transplantation (HSCT) who was treated with Rituximab. The patient was a 58-year-old male with a history of MDS who had developed AML after two years of monitoring, and had undergone T cell depleted HSCT (TCD-HSCT) as treatment. 69 days after transplant, he developed neurological clinical signs and electrophysiological characteristics of AMAN variant of GBS. As a result, he was treated with two courses of IVIg which were both ineffective. At day 40 since onset of the disease (GBS), PCR detected EBV viremia. After this, patient was started on Rituximab 375 mg/m² once a week for four consecutive weeks, which not only resulted in amelioration of clinical signs of GBS but also in EBV viremia subsidence. It was concluded that in this case, GBS was most likely a presentation of post-transplant GVHD. Since the patient expressed an AMAN subtype of GBS which is associated with production of anti-ganglioside antibodies, Rituximab was effective in diminishing pathogenic B cells and recovery. Therefore, this case report suggested that it would be beneficial if the role and effectivity of Rituximab in amelioration of antibody-dependent subtypes of GBS (AMAN) would be further investigated [65].

Although Rituximab could be beneficial in various autoimmune conditions, there are case reports that suggest administering Rituximab itself could cause GBS in patients [66-68]. Possibly, this is the reason why Rituximab has not been further evaluated as a therapeutic agent for GBS.

4.5. Alemtuzumab (Anti-CD52 Monoclonal Antibody)

Alemtuzumab is a humanized monoclonal antibody targeting CD52, which results in prolonged depletion of B cells and T cells. It is mostly used in treating relapsed or refractory chronic lymphocytic leukemia (CLL) [69]. Alemtuzumab has experienced controversy in treatment of immune neuropathies. This is due to the fact that Alemtuzumab can both ameliorate and induce autoimmune disorders. For instance, it has been suggested that Alemtuzumab could be beneficial in diminishing relapse rate and disability of MS [70]; while on the other hand its use could induce other autoimmune disorders. A 2011 cohort study estimated cumulative risk for developing autoimmune

disorders following treatment of MS with Alemtuzumab to be 22% [71]. As a matter of fact, there are evidence suggesting that Alemtuzumab might possibly be associated with triggering GBS itself (similar to Rituximab) [72, 73].

Nevertheless, a 2014 case report by Tzachanis *et al.* suggested improvement of GBS after receiving Alemtuzumab. The patient was a 79-year-old male with history of CLL diagnosed nearly 10 years ago. About 6 months prior to onset of GBS, he had undergone treatment with Rituximab and Bendamustine, and he currently presented signs and symptoms consistent with rapidly progressive GBS associated with high-titers of anti-GQ1b antibody. He received various treatments starting with corticosteroids, to 4 courses of IVIg and at the end plasma-exchange, which were all ineffective.

GBS in this case could be considered as a result of underlying CLL (which could be associated with autoimmunity), the treatment he had received for it (Rituximab and Bendamustine) or infection triggers. Therefore, in order to cover both CLL and GBS treatments and also to avoid Rituximab, it was decided to start GBS treatment with Alemtuzumab.

Thereafter, patient was started on escalating doses of subcutaneous Alemtuzumab to the goal dose of 30 mg three times a week, which was associated with significant improvement in symptoms. It was suggested by authors that observed recovery could be both due to eliminating effect of Alemtuzumab on anti-GQ1b autoantibodies, or as a result of controlling the underlying malignancy (CLL) [74]. In spite of this, no further study has investigated the effect of Alemtuzumab in GBS patients.

5. APPROACHES TO CYTOKINE MODULATION

5.1. IFNs ($\alpha/\beta/\gamma$)

The role of IFN- γ in pathogenesis of EAN and the effect of an *in-vivo* monoclonal antibody to neutralize it was first investigated in 1990 by Hartung *et al.*, which demonstrated the deterioration of peripheral nerve injury induced in rat EAN with administration of IFN- γ . Furthermore, injecting anti-IFN- γ monoclonal antibody was associated with ameliorating effects [75]. In 1996, Vriesendorp *et al.* investigated the effect of administering oral IFN type I (α/β) in an EAN model of Lewis rats. Prior to this study, both parenteral and oral administration of IFN type I was reported to be associated with reduced relapses in Multiple Sclerosis (MS) and its animal model Experimental allergic encephalomyelitis (EAE). Therefore, Vriesendorp *et al.* conducted their study with the purpose of assessing the effect of IFN in treating EAN. Their findings were suggestive of effectivity of IFN in ameliorating the clinical and histological severity of the disease in treated subjects compared to controls. Treated rats demonstrated lower levels of demyelination in their biopsies, although the total amount of inflammation was not altered. It was suggested that a possible mechanism for IFN type I (α/β) effectivity was mediated through reducing IFN- γ production, since its levels were reported to be decreased. Therefore, IFN type I (α/β) was suggested as a possible therapeutic candidate [76].

In 1998, Creange *et al.* reported a case of 47-year-old GBS male patient who showed recovery when treated with IFN- β . Patient had initially undergone four courses of plasma-exchange during days 1 to 8, which were associated with inconsiderable recovery. Thereafter, a course of 6 mIU subcutaneous IFN- β 1a (Rebif) on alternate days was started. Clinical course of the disease was significantly improved after receiving IFN- β , and the disability score experienced rapid recovery. Although this study admits to the possible synergistic ameliorating effects of plasma-exchange and IFN- β , the most rapid improvement of clinical course was observed immediately after commencing IFN- β . Therefore, this case report suggested IFN- β to have potential therapeutic effects in treating GBS [77].

In 1999, Zou *et al.* investigated effects of subcutaneous recombinant rat IFN- β (rrIFN- β 300,000 U/rat/every other day) in a rat model of EAN. This study reported ameliorating effects of IFN- β , both when injected at the day of immunization (EAN induction) and when administered at the onset of the disease. Histopathological and immunohistochemistry assays of rats' Sciatic nerves demonstrated reduced infiltration of CD4+ T cells and macrophages in the nerve tissues in treated animals. Furthermore, expression of MHC-II and monocyte chemotactic protein-1 (MCP-1) production were significantly diminished in the evaluated nerve tissues. As one justifying mechanism, it seemed that IFN- β mediated its recuperating effects by suppressing both T and B cells responses *via* inhibiting migration of inflammatory cells and their homing into the nerve tissues. In addition to these findings, the study reported an increase in gene expression of TGF- β (anti-inflammatory) cytokine, while IFN- γ mRNA expressions were significantly reduced. Therefore, authors suggested both preventive and therapeutic effects for IFN- β [78].

Creange *et al.*, investigated the effect of administrative IFN- β in GBS *via* a clinical study in human patients. The aim of this study was focused on effect of IFN- β on transmigration of inflammatory cells in GBS patients, and it was conducted as an *in-vitro* study. Incubating lymphocytes of GBS patients with IFN- β was associated with their lower binding to adhesion molecules including VCAM and ICAM. Furthermore, lymphocyte transmigration capacities were observed to be reduced compared to control lymphocytes. Therefore, this study also suggested IFN- β as a possible beneficial candidate in GBS treatment [79].

Schellar *et al.* published a case report representing a GBS patient treated with both IVIg and IFN- β in 2001. Patient was a 51-year-old male, and received a course of IVIg (0.4 g/kg/day) during first week from onset of the disease which did not result in any improvement. In day 14, IFN- β (Rebif subcutaneous 6 mIU on alternate days) was started that resulted in no clinical response. Therefore on 21st day a second dose of IVIg (during 5 days) was added to IFN- β . This combination was associated with significant improvement in clinical course. In contrast with prior studies in which single administration of IFN- β demonstrated improvement, in this case recovery was associated with combined administration of both IVIg and IFN- β . Therefore, the authors suggested that observed amelioration could be attributed to synergistic

effects of IVIg and IFN- β ; but on the other hand they could not exclude the possibility that a longer period of treatment might be required when treating GBS with IFN- β monotherapy, which was not followed in this case [80].

In 2003, a pilot double-blind placebo controlled randomized controlled trial was conducted by Pritchard *et al.* to investigate the safety and effects of administration of IFN- β (Rebif) or placebo, combined with IVIg in a total of 19 GBS patients. 13 patients received IVIg plus IFN- β (22 μ g/week for 1 week, then 44 μ g until 24 weeks or improvement to disability grade 2); while 6 patients received IVIg plus a placebo drug (with the same order). The rate of adverse events was not significantly different between two groups, or attributable to either treatment. Interestingly, no significant disparity in recovery was observed between two groups. Furthermore, IFN- β -treated subjects were associated with an increase in serum TNF- α level, two weeks after starting the treatment. Therefore, findings of this study did not support the ameliorating effects suggested for IFN- β by previous studies [81]. There are no other reports of clinical trials investigating the effect of IFN- β in GBS patients.

5.2. TNF Receptor Type I (sTNFR I)

Bao *et al.* investigated the effects of exogenous soluble TNF receptor type I (sTNFR I) in a model of murine EAN in 2003. Due to key role of TNF- α in pathogenesis of GBS and EAN, it was proposed that blocking its effects would result in amelioration of the disease [82]. TNF- α mediates its functions via binding to its surface receptor (TNFR) in different cells, specifically CD4⁺ and CD8⁺ cells. Following this attachment, TNFRs are cleaved and persist in serum as a soluble form (sTNFR), functioning as an endogenous antagonist to TNF by competing with membranous TNFR in binding TNF and neutralizing it [83, 84]. The role of sTNFR I in ameliorating many inflammatory conditions was suggested by prior studies [85, 86]. Bao *et al.* study observed that both severity and duration of the disease course were significantly reduced in treated rats compared with controls. sTNFR I therapy was associated with a decrease in serum level of TNF- α , infiltration of cells into the peripheral nerves, and IFN- γ secretion. In other words sTNFR I functions via inhibition of T cell proliferation and activation, which are required for Th-1 immune injuries [82].

5.3. Linomide

In 1997, the effectivity of Linomide (quinoline-3-carboxamide) in a rat model of EAN was investigated by Bai *et al.* Prior to the mentioned study, the role of Linomide had been evaluated in different immunoinflammatory conditions including EAE (experimental autoimmune encephalomyelitis) [87] and EAMG (experimental autoimmune myasthenia gravis) [88]. Bai *et al.* reported that daily subcutaneous administration of Linomide in EAN-induced rats was associated with amelioration of clinical signs. In addition, when exposed to IFN- γ and LPS, expression of IL-1 β , TNF- α and IL-6 mRNA was suppressed in macrophages of treated rats. This study explained the observed Linomide function in reducing the pro-inflammatory cytokines by postulating that Linomide prevents macrophage activation, resulting in less

antigen-presentation and naive T cell activation (in lymph organs). Furthermore, the study suggested that Linomide affects antigen-presentation and injury in nerve regions as well; therefore lower damage by macrophage toxic products (such as NO) is observed [89]. Another study in 1998 by Karpati *et al.* resulted in similar findings. This study demonstrated that oral administration of Linomide (before the symptoms of EAN started) correlated with significant prevention of the disease. It was also reported that adhesion molecules expression (*e.g.* ICAM-1 and LFA-1) was lower in Linomide-treated rats compared to controls. Linomide was associated with an increase in apoptosis of lymphocytes in lymph organs as well [90]. Another study in 1999 also demonstrated that Linomide suppressed the severity of clinical course in EAN-induced rats, and was associated with lower pro-inflammatory cytokines such as TNF- α in treated animals. B cell responses (assessed by measuring the level of immunoglobulins) and T cell responses (evaluated by lymph node proliferation) were also decreased in Linomide-treated rats [91]. All three aforementioned studies consistently suggested that Linomide could be a therapeutic candidate in treating GBS, via its role in regulation of cytokines.

5.4. Rolipram (Phosphodiesterase Type 4 Inhibitor)

In 2000, the effects of a phosphodiesterase type 4 inhibitor known as Rolipram in Lewis rat EAN was evaluated by Zou *et al.* Anti-inflammatory influences of Rolipram, (namely inhibition of *in-vivo* and *in-vitro* TNF- α production, down regulation of proliferation of peripheral blood mononuclear cells (MNC) and their cytokine generation) had been suggested in previous studies. Zou *et al.* reported reduced amount of macrophage and lymphocyte infiltration in histopathology of rats treated with Rolipram. Serum level of TNF- α and amount of IFN- γ secreting cells were also significantly decreased in Rolipram-treated rats compared to controls, and T cell proliferation was considerably diminished. Interestingly, clinical relapse was observed in subjects that discontinued Rolipram after 7 days treatment duration; while rats treated for 14 days did not experience similar phenomenon [92]. Another study at the same year, conducted by Abbas *et al.*, reported similar findings. Rolipram-treated cases revealed significantly lower numbers of IFN- γ /chemokine producing cells in histopathology assays of their sections of Sciatic nerve; while IL-4 (an anti-inflammatory cytokine) secreting cells were estimated markedly higher than controls [93]. The results of these two studies are generally in favor of suggesting Rolipram as possible therapeutic candidate, whose mechanism of function mediates through cytokine regulation and balance.

5.5. Anti-IL-18 Monoclonal Antibody

In 2002, Yu *et al.* evaluated the effect of neutralizing antibodies to IL-18 in a mice model of EAN. IL-18 was initially recognized as a molecule with function of inducing IFN- γ (it was named IFN- γ inducing factor (IGIF)), and seemed to have pro-inflammatory characteristics [94]. Data prior to the study of Yu *et al.*, had presented an upregulation of IL-18 in both EAN and GBS patients, suggesting a possible role in disease pathogenesis [95]. Therefore, Yu *et al.* study aimed to investigate both its effect in pathogenesis

of EAN, and therapeutic effect of anti-IL-18 monoclonal antibody in ameliorating the course of the disease in mice. Administration of anti-IL-18 monoclonal antibody was associated with improving pathophysiological and clinical signs of EAN. It seemed that after treating subjects with monoclonal antibody, infiltration of cells into the PNS compared to control animals was significantly reduced. Also, the imbalanced increased ratio of Th1/Th2 was reported to experience a shift towards Th2 cells and cytokines (with an increase in IL-4 expressing cells, and a decrease in IFN- γ and TNF secreting cells), which was suggested as a therapeutic effect [94]. No further study investigating anti-IL-18 monoclonal antibody in GBS was found.

5.6. Macrophage Migration Inhibitory Factor (MIF)

The role of another pro-inflammatory cytokine known as Macrophage migration inhibitory factor (MIF) in pathogenesis of GBS and its effect as a therapeutic target was investigated in 2005 by Nicoletti *et al.* [96]. MIF is a pleiotropic cytokine produced during several inflammatory

and autoimmune conditions and seems to have a crucial role in their pathogenesis. MIF is secreted by different immune cells including T cells and macrophages [97]. The exact mechanism through which MIF mediates its functions is not completely clear yet, but it has been shown that it could increase the generation of pro-inflammatory cytokines involved in GBS, namely IL-1, TNF- α and IFN- γ [96, 98]. A prior study showed that blocking MIF in an animal model of MS (EAE) was correlated with significant amelioration [99]. Therefore, Nicoletti *et al.* conducted a similar study using a mice model of EAN and two blocking patterns, one by an anti-MIF monoclonal antibody and the other by pharmacological inhibitor of MIF, named ISO-1 ((S,R)-3-(4-hydroxyphenyl)-4,5-dihydro-5-isoxasole acetic acid methyl ester). The study illuminated that both anti-MIF monoclonal antibody and ISO-1 were associated with milder course of the disease when administered in a therapeutic manner (on 12th day after induction of EAN), and were both well-tolerated by animal subjects. The study concluded that although both agents are possible to have beneficial effects

Table 1. Resume of the biological approaches used for treatment of GBS in animal studies.

Drugs	Biological Approach	Type of Study	Subjects	Efficient /Non-efficient	Year and Author
Cobra venom factor (CVF)	Complement modulation	Original article	Lewis rats	Efficient	1987/Feasby [31]
Soluble complement receptor type I (sCR I)	Complement modulation	Original article	Lewis rats	Efficient	1995/Jung [32]
IFN type I (α & β)	Cytokine modulation	Original article	Lewis rats	Efficient	1996/Vriesendorp [76]
Anti-CD2 mAb (OX34)	T cell modulation	Original article	Lewis rats	Efficient	1996/Jung [55]
Linomide	Cytokine modulation	Original article	Lewis rats	Efficient	1997/Bai [89]
Anti L-selectin mAb (HRL3)	T cells and monocytes trans-endothelial migration modulation	Original article	Lewis rats	Efficient	1997/Archelos [56]
IFN β	Cytokine modulation	Original article	Lewis rats	Efficient	1999/Zou [78]
Rolipram	Cytokine modulation	Original article	Lewis rats	Efficient	2000/Abbas [93]
Anti-IL-18 mAb	Cytokine modulation	Original article	mice	Efficient	2002/Yu [94]
TNF receptor type I (TNFR I)	Cytokine modulation	Original article	mice	Efficient	2003/Bao [82]
APT070 (Mirococept)	Complement modulation	Original article	mice	Efficient	2005/Halstead [33]
Neutralizing anti-MIF mAb	Cytokine modulation	Original article	mice	Efficient	2005/Nicoletti [96]
rEV576	Complement modulation	Original article	mice	Efficient	2008/Halstead [45]
Eculizumab	Complement modulation	Original article	mice	Efficient	2008/Halstead [41]
Nafamostat mesilate (NM)	Complement modulation	Original article	rabbit	Efficient	2008/Phongsisay [46]
Anti-GD3 anti-idiotypic mAb (BEC2)	Autoantibody modulation	Original article	Lewis rats	Efficient	2010/Usuki [49]
Erythropoietin	Cytokine modulation	Original article	Lewis rats	Efficient	2011/Mausberg [100]
Erythropoietin	Cytokine modulation	Original article	Lewis rats	Efficient	2011/Zhang [101]
Anti-C1q monoclonal antibody (M1)	Complement modulation	Original article	mice	Efficient	2016/McGonigal [50]

Table 2. Resume of the biological approaches used for treatment of GBS in human studies.

Drugs	Biological Approach	Type of Study	Subjects	Efficient /Non-efficient	Year and Author
Anti-T cell monoclonal Ab (OK3)	T cell modulation	Original article	3 adult GBS patients	Non-efficient	1991/Feasby [54]
IFN β	Cytokine modulation	Case report	1 adult GBS patient	Efficient	1998/Creange [77]
IFN β	Cytokine modulation	Original article	26 GBS patients & 6 healthy controls	Efficient	2001/Creange [79]
IFN β + IVIg	Cytokine modulation	Case report	1 adult GBS patient	Efficient	2001/ Schaller [80]
IFN β + IVIg	Cytokine modulation	Randomized controlled clinical trial	13 GBS cases (IFN β +IVIg) & 6 GBS controls (Placebo+IVIg)	Non-efficient	2003/Pritchard [81]
Rituximab	B cell modulation	Case report	1 adult GBS patient	Efficient	2008/Ostronoff [65]
Eculizumab	Complement modulation	Case report	1 pediatric GBS patient	Efficient	2014/Ram [42]
Alemtuzumab	T and B cell modulation	Case report	1 adult GBS patient	Efficient	2014/Tzachanis [74]
Eculizumab	Complement modulation	Clinical trial	Unknown	Unfinished	2014 start/Glasgow [43]
Eculizumab	Complement modulation	Clinical trial	Unknown	Unfinished	2015 start/Kuwabara [44]

in GBS, targeting MIF with ISO-1 should be considered for treating GBS due to clinical limitations of monoclonal antibodies (like high cost) [96]. No further investigation was found in this regard.

5.7. Erythropoietin (EPO)

In 2011, the effects of Erythropoietin (EPO) in EAN were investigated as two distinct publications [100-101]. Prior to this, EPO was associated with diminished demyelination and improvement of clinical score in EAE which is considered as the animal model of MS [102]. This result led to proposal of possible neuroprotective effects of EPO in GBS animal model or EAN. In Histological analysis of rats, Mausberg *et al.* reported that number of T cells infiltrated in Sciatic nerve sections of EPO-treated cases was lower compared to control group. In addition EPO was associated with lower demyelination and even presence of remyelination in nerves; although the study noted that latter finding was insignificant. In spite of this, Frequency of axonal degeneration was markedly and significantly decreased in EPO-treated rats. These findings were consistent with improvement which was observed in clinical course of rats treated with EPO. Furthermore, treated subjects were associated with higher levels of TGF- β expression. TGF- β is an anti-inflammatory cytokine, which modulates the immune system via different mechanisms, including effecting T-Reg cells and interfering with innate immune system. In general, this study proposed that EPO mediates its effect in ameliorating peripheral neuritis indirectly *via* TGF- β [100]. Another study by Zhang *et al.* (conducted in the same year), addressed EPO from another point of view. This study investigated the association among EPO, neuron regeneration and anti-ganglioside antibodies in an antibody-mediated

animal model of GBS, which resembles AMAN [101]. As prior studies had also noted [103], Zhang *et al.* demonstrated that anti-ganglioside antibodies obtained from GBS patients' sera could significantly inhibit neuron regeneration in animal model. Furthermore, current study noted that this inhibition could be reversed by administration of EPO, resulting in neuron regeneration and outgrowth. As a justifying mechanism for mentioned outgrowth, EPO-EPO receptor (EPOR) binding eventuates in a cascade of intracellular signaling involving JAK2/STAT5, which at the end lead into expression of certain neurotropic genes [101]. Therefore as this study noted, EPO seems a favorable treatment candidate for GBS due to its wide clinical experience in treatment of different hematologic disorders [101, 104].

CONCLUSION

Treatment of GBS could present a challenge for patients and physicians. GBS is a disease with diverse outcomes and various severity in different cases. Although many of the patients reach full recovery with routine treatments (IVIg and PE), residual defects could be still detected in a high prevalence of the cases. In some cases in spite of receiving immunotherapy with traditional treatments, patients remain unable to walk unaided 6 months after the onset of the disease. Advancing molecular understanding of GBS patho-immunology accounts for extensive potential biological treatments. Evidence by far suggests various possible biological agents for modulating GBS pathogenesis. Literature findings represented in current review herald promising results for using these biological targets. In regards, Tables 1 and 2 summarize all the studies addressing biological approaches to treat GBS. Current review represents a summary of what is already investigated regarding immunotherapeutic

biological approaches to GBS, and what progress is required to improve these approaches *via* future studies. It is to be hoped that by further investigating biological drugs, GBS patients will experience better clinical outcomes and earlier function retrieval.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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