The Efficacy of Intravenous Immunoglobulin in Guillain-Barré Syndrome: The Experience of a Tertiary Medical Center

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ABSTRACT:

Background: Guillain-Barré syndrome (GBS) is an autoimmune disease of the peripheral nervous system with a typical presentation of acute paralysis and hyporeflexia. Intravenous immunoglobulin (IVIG) and plasma exchange (PLEX) are treatments that have proven to expedite recuperation and recovery of motor function.

Objectives: To describe our experience at one tertiary medical center treating GBS with IVIG and to compare the efficacy of IVIG as the sole treatment versus combined therapy of IVIG and plasma exchange.

Methods: We reviewed the records of all patients diagnosed with GBS and treated with IVIG at the Sheba Medical Center from 2007 to 2015 and collected data on patient demographics, disease onset and presentation, and treatments delivered. The motor disability grading scale (MDGS) was used to evaluate the motor function of each patient through the various stages of the disease and following therapy.

Results: MDGS improvement from admission until discharge was statistically significant ($P < 0.001$), as was the regainment of motor functions at 3 and 12 months follow-up compared to the status during the nadir of the disease. The effectiveness of second-line treatment with IVIG following PLEX failure and vice versa was not statistically significant ($P > 0.15$).

Conclusions: The majority of patients included in this study experienced a significant and rapid improvement of GBS following treatment with IVIG. Combined therapy of PLEX and IVIG was not proven to be effective in patients who encountered a failure of the first-line treatment.

IMAJ 2018; 20: 754–760

KEY WORDS: autoimmunity, Guillain-Barré syndrome (GBS), intravenous immunoglobulin (IVIG), motor disability grading scale (MDGS), plasma exchange (PLEX)

Guillain-Barré syndrome (GBS) was first described by Jean-Baptiste Landry, a French physician and medical researcher, in 1859. In 1916, the French neurologists Georges Guillain, Jean Alexandre Barré, and André Strohl diagnosed two World War I soldiers with a syndrome presenting with acute onset paralysis and hyporeflexia with spontaneous recovery. In addition, they reported an abnormal cerebrospinal fluid analysis with elevated levels of protein but a normal white blood cell count. Elevated cerebrospinal fluid (CSF) protein levels without pleocytosis is referred to as albuminocytologic dissociation and found in up to 66% of patients diagnosed with GBS [1]. GBS is a heterogeneous condition with several distinct variants and is the eponym under which the acute, immune-mediated polyneuropathies are classified. The most common of these variants is acute inflammatory demyelinating polyradiculoneuropathy (AIDP) that most often presents as an acute, monophasic, progressive paralysis accompanied by decreased or absent deep tendon reflexes [2]. The most common form of the axonal GBS subtypes is acute motor axonal neuropathy (AMAN), a form with selectiveness for motor nerves and axonal damage as shown in the electrophysiologic studies. Acute motor and sensory axonal neuropathy (ASMAN) is a more severe form of AMAN as it involves both sensory and motor nerve fibers. The axonal variants of GBS are associated with a disease of greater severity, rapid progression, and a more extended recovery period compared with the demyelinative variants. Incomplete recovery and permanent disability are also more frequent when prominent axonal features are present [3]. An additional noteworthy variant of GBS, known as Miller–Fisher syndrome (MFS), is characterized by a typical presentation of ophthalmoplegia, ataxia, and areflexia. MFS patients will often develop extremity weakness of varying degrees, irrefutably making it a variant of GBS rather than an independent entity [4]. The pathogenesis of GBS is proposed to be that of an immune response elicited by an antecedent event, namely an infection, via the mechanism of molecular mimicry [5]. The pathogen most frequently mentioned as a precipitant of GBS is *Campylobacter jejuni*, a gram-negative bacteria and a widespread cause of gastroenteritis [6].

The treatment for GBS consists of supportive care when required (e.g., pain control, intensive care unit monitoring, or

mechanical ventilation) and is combined with a disease-modifying therapy such as plasma exchange (PLEX) or intravenous immunoglobulin (IVIG) [7]. Both treatments hasten recovery and are believed to have equivalent beneficial effects. A combined regimen of PLEX followed by IVIG showed no significant advantage compared to either modality alone. IVIG is derived from the plasma of a minimum of 1000 donors and is purified to separate the desired IgG and discard any of the pathogens or prions that may be present. The exact mechanism of action of IVIG remains unclear. It has been shown, however, that the anti-inflammatory and immunomodulatory effects of IVIG are likely due to coalescence of several mechanisms, with a varying degree of dominance for different diseases [8-10]. IVIG is now used to treat a multiplicity of autoimmune diseases as well as a replacement therapy for patients afflicted with various immunodeficiency disorders [11-13]. Side effects are commonly classified into immediate or delayed reactions. Immediate reactions occur during the infusion or within the first 6 hours and may include non-IgE mediated anaphylaxis, headaches, and fever. Delayed complications ensue in the hours to days subsequent to treatment and may include aseptic meningitis, thromboembolic events (e.g., myocardial infarction), and acute kidney injury. Many of the known side effects correlate with the dose and rate of infusion, and thus can be ameliorated by reducing them.

Patients with a history of severe post-treatment headaches may benefit from prophylactic glucocorticoids. Nonetheless, IVIG is regarded as a treatment with a high safety profile [14]. While life-threatening adverse effects are possible, most reactions experienced by patients are typically mild and transient, have no lasting sequel, and consist mainly of flu-like symptoms (e.g., headaches, nausea, malaise) [15]. In addition, IVIG is not associated with an increased risk of infection, a distinctive property compared to other therapy options for patients with autoimmune diseases [16]. GBS is a well-accepted indication for IVIG products therapy [17]. Although its actions are not fully elucidated, the marked advantages of IVIG translate to a reality in which it is considered as a possible treatment modality for a steadily growing list of illnesses [18-20].

In this current study, we present the clinical experience gained at an academic medical center in Guillain-Barré syndrome treatment. We describe prevalent clinical presentation, evaluate possible indicators for a severe disease, and assess the efficacy of treating these patients with intravenous immunoglobulin or combined treatment of IVIG and plasma exchange therapy.

PATIENTS AND METHODS

STUDY POPULATION

The study was comprised of all patients who were diagnosed with GBS and were treated with at least one course of IVIG from June 2007 to December 2015 at the Sheba Medical Center. All patients chose to be treated at our medical center and were not recruited by the medical center. All patients were hospitalized. Some were later transferred to rehabilitation, while others were discharged with or without follow-up treatment.

METHODS

This retrospective study was conducted at the Sheba Medical Center (Tel Hashomer), an academic, tertiary medical center. Table 1 details the scoring system of the motor disability grading scale (MDGS) used to assess clinical outcome and reaction to treatment. Each patient was evaluated according to the MDGS during the time of hospital admission, at the nadir of the disease; at discharge; and at 3, 6, and 12 months follow-up, as appropriate. We manually reviewed each medical record and collected data on patient demographics, diagnosis, clinical evaluations, treatments, and outcomes. Data were collected regarding the number of days needed to achieve an improvement of at least 1 grade in the scale. Patients failing to attain

Table 1. Clinical evaluation of the patients

Motor disability grading scale	
0	No signs or symptoms
1	Minor signs or symptoms
2	Able to walk 5 meters without assistance
3	Able to walk 5 meters with assistance
4	Chair bound or bedridden
5	Requires respiratory support
6	Dead

Brighton diagnostic criteria for Guillain-Barré syndrome		
Level 1 diagnostic certainty	Level 2 diagnostic certainty	Level 3 diagnostic certainty
Bilateral and flaccid weakness of limbs	Parameters 1–4 of level 1	Parameters 1–4 of level 1
AND Decreased/absent deep tendon reflexes in weak limbs	**AND** Normal CSF WBC count elevated/normal protein levels **OR** electrophysiologic findings consistent with GBS if CSF not collected or results not available	
AND Monophasic illness pattern and interval between onset, nadir of 12 hours to 28 days, and subsequent clinical plateau		
AND Absence of alternative diagnosis explaining weakness		
AND Cytoalbuminologic dissociation (i.e., elevated CSF protein level with a normal CSF WBC count)		
AND Electrophysiologic findings consistent with GBS		

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CSF = cerebrospinal fluid, GBS = Guillain-Barré syndrome, WBC = white blood cell

improvement within 14 days following initiation of therapy were considered non-responders. Diagnosis of GBS was made in concordance with the Brighton diagnostic criteria [Table 1].

STUDY DATA SOURCES

The information technology (IT) department produced all of the data from the hospital computerized system. First, a computerized search was conducted for patients who were prescribed one of the following drugs: BERIGLOBIN P, GAMIMUNE - N IMMUNE GLOBULIN, GAMMAGARD, GAMMAPLEX, GAMUNEX, IG GAMMA, IMMUNOGLOBULINE HUMAN, INTRATECT, KIOVIG, OMRIGAM, SANDOGLOBULIN or VIGAM. We identified 34 patients with international classification of diseases (ICD-9-CM) code 357.0 "Acute infective polyneuritis." Three patients were excluded from the study due to alternative diagnoses made during hospitalization (e.g., myositis, transverse myelitis, and spinal muscular atrophy). The study was approved by the institutional ethics committee at our medical center, confirmation number 2368-15-SMC.

STATISTICAL ANALYSIS

Continuous variables were analyzed into descriptive statistics. Mean and median ± standard deviation were used to describe quantitative variables of the study population. Number and percentage (%) were used for qualitative variables. Student's t-test and Fisher's exact test were used for comparisons in groups. $P < 0.05$ was considered to be significant.

RESULTS

STUDY POPULATION CHARACTERISTICS

During the study period, 31 patients received IVIG as a treatment for GBS at the Sheba Medical Center, as shown in Table 2. The age at diagnosis ranged from 2 to 76 years with an average age of 26 ± 24 years. Although many autoimmune diseases are more common in females, we found no noteworthy difference in prevalence by gender, with females constituting 61% of the study population. Unsurprisingly, Israel was the country of birth for all but five of the patients. Three patients had a positive history of an autoimmune or an autoinflammatory disease. One patient had a history of GBS, with the first episode occurring 14 years prior the second one [Table 3].

DISEASE ONSET AND PROGRESSION

In the majority of cases (52%), an antecedent event was confirmed either by a story of infection before the appearance of symptoms or through evidence obtained by the laboratory. Among these patients, 38% had a story of gastroenteritis, 31% of a respiratory infection, and 19% of fever, and 12% had positive anti-CMV IgM. As depicted in Table 3, weakness of the lower extremities was the most common presenting symptom (38%) and was present at hospital admission in 87% of the cases.

Properties of dysautonomia (e.g., urinary incontinence, excessive blood pressure values, and tachyarrhythmias) were evident in 23% of patients; 75% of patients in this cohort were admitted to the hospital within 7 days of disease onset and 25% of them required respiratory support. The mean MDGS score in this group was 3.9 compared to 3 in patients admitted more than 7 days after symptoms appearance. Cerebrospinal fluid (CSF) analysis revealed a typical GBS finding – an acellular rise in total protein – in 50% of patients [Table 3]. Routine blood work showed 45% of patients with hyponatremia, which is a possible manifestation of dysautonomia. Patients with hyponatremia did not present with significantly more aggressive disease conditions compared to non-hyponatremic patients ($P > 0.1$). Nerve conduction studies were performed in 27 of the cases; 67% showed a predominance of demyelinating features and 33% presented axonal injury dominance.

TREATMENT OF GUILLAIN-BARRÉ SYNDROME

Supportive care was given to 65% of the patients [Table 3]; 19% in total required mechanical ventilation ascribable to respiratory failure. All patients were treated with 2 gr/kg IVIG over 3–5 days; 26% were treated with plasma exchange (PLEX) in addition to IVIG, 75% of those patients received PLEX therapy as the first modality of treatment and with IVIG was subsequently added due to a lack of an adequate response. The remaining 25% were treated with IVIG first. In both cases, the addition of PLEX did not improve clinical outcome in a manner that is significant ($P > 0.15$).

OVERALL OUTCOMES

The hospitalization period spanned 7–495 days, mean 78 ± 110 days. Having failed to achieve an adequate clinical improvement in 14 days or less since treatment onset, 29% of patients were regarded as IVIG non-responders. Among the responders, the number of days required to achieve clinical improvement was 8 ± 3.46. In the non-responder group, three patients showed no such improvement on discharge. Of the nine patients who exhibited an insufficient response to IVIG therapy, five had an axonal variant of GBS, and three cases warranted respiratory support. Statistical significance was established ($P < 0.001$) regarding the clinical improvement of patients from admission to discharge. Sixteen patients continued for 3 months of follow up; 25% had recovered entirely and 12% showed no improvement (subjective or objective). We observed a significant motor function improvement after 3 months follow-up compared to the peak of disease duration. A similar result was noted after 12 months follow up ($P < 0.001$).

ADVERSE EFFECTS

Of the 26% of patients who experienced adverse IVIG effects, cessation of treatment was necessary in only one patient, due

Table 2. Relevant data for each individual patient diagnosed with Guillain-Barré syndrome and treated with intravenous immunoglobulin at the Sheba Medical Center between June 2007 and December 2015

#	Gender	Age at diagnosis, years	GBS variant	Presenting symptom	MDGS at nadir	Respiratory support	Treated with PLEX	MDGS at discharge	Responded to IVIG
1	Female	8	AIDP	Pain	4	No	No	2	Yes
2	Male	10.5	AMAN	LEW	4	No	No	3	No
3	Female	14	AIDP	SENS	4	No	Yes	2	Yes
4	Male	2.9	N/P	GEN	4	No	No	3	Yes
5	Female	8.5	MFS	Diplopia	2	No	No	1	Yes
6	Female	26	AIDP	SENS	5	Yes	No	2	No
7	Female	2	AIDP	Pain	2	No	No	1	Yes
8	Female	3.5	AIDP	Gait	4	No	No	3	Yes
9	Male	3	AIDP	Pain	4	No	Yes	3	Yes
10	Female	4	MFS	Pain	3	No	No	2	Yes
11	Female	4	N/P	Pain	4	No	No	3	Yes
12	Female	4	AIDP	Pain	4	No	No	1	Yes
13	Female	8	AIDP	LEW	2	No	No	2	No
14	Male	8.5	AIDP	LEW	2	No	No	1	Yes
15	Male	9	AIDP	Pain	3	No	No	2	Yes
16	Female	13	AIDP	LEW	4	No	Yes	4	No
17	male	15	AMAN	LEW	4	No	No	3	No
18	female	16	N/P	LEW	3	No	No	2	Yes
19	Male	17	AMAN	LEW	4	No	Yes	2	No
20	Male	23	ASMAN	LEW	3	No	No	3	No
21	Female	28	ASMAN	SENS	2	No	Yes	1	Yes
22	Female	35	AIDP	SENS	5	Yes	Yes	2	Yes
23	Female	41	AIDP	UEW	5	Yes	Yes	4	No
24	Female	47	N/P	UEW	4	No	No	3	Yes
25	Male	48	AMAN	SENS	4	No	No	2	Yes
26	Male	64	AMAN	LEW	5	Yes	Yes	3	No
27	Male	64	AIDP	LEW	5	Yes	No	3	Yes
28	Female	65	AMAN	LEW	4	No	No	3	Yes
29	Female	65	AIDP	SENS	3	No	No	2	Yes
30	Female	76	AMAN	SENS	4	No	No	2	Yes
31	Male	76	AIDP	LEW	5	Yes	No	3	Yes

AIDP = acute inflammatory demyelinating polyradiculoneuropathy, AMAN = acute motor axonal neuropathy, ASMAN = acute motor and sensory axonal neuropathy, GBS = Guillain-Barré syndrome, GEN = general deterioration, IVIG = intravenous immunoglobulin, LEW = lower extremity weakness, MDGS = motor disability grading scale, MFS = Miller–Fisher syndrome, N/P = not performed (electrophysiologic study), PLEX = plasma exchange, SENS = sensory deprivation/paresthesia, UEW = upper extremity weakness

to non-ischemic chest pain. The most common side effect reported by patients was headache (75%), which prompted prophylactic preparation with glucocorticoids in one case. Additional side effects encountered by patients are listed in Table 3. Only 25% of the patients who reported adverse effects from IVIG did so during the first course of the treatment. As mentioned, four patients received an additional course of IVIG at 3 months follow-up. All had an increase in MDGS status, two had side effects (e.g., hypotension, fever, rash). None required treatment to be discontinued.

DISCUSSION

The purpose of this study was to describe the clinical experiences of a tertiary medical center with regard to GBS and its treatments with either IVIG alone or combined with PLEX therapy. We describe the disease onset, progression, frequent signs and symptoms as exhibited by our patients, and the existence of a precursory event. Objective parameters as found in blood tests and nerve conduction studies, in conjunction with treatment efficacy and experienced adverse effects, were

Table 3. Baseline characteristics, disease, and treatment of patients diagnosed with Guillain-Barré syndrome and treated with intravenous immunoglobulin at the Sheba medical center from June 2007 to December 2015

Variable		Value	%
Age at diagnosis	Mean ± SD	26 ± 25 years	
Gender	Male	12	39
	Female	19	61
Patients with history of an autoimmune disease	Previous episode of GBS	1	3
	Sjögren's syndrome	1	3
	Diabetes mellitus type 1	1	3
	Familial Mediterranean fever	1	3
Prevalent signs and symptoms*	Decreased or absent reflexes	30	97
	Weakness of lower extremities	27	87
	Pain	21	68
	Paresthesia/sensory symptoms	11	35
Laboratory values on admission	Elevated CSF protein levels	19	63
	Normal CSF WBC count	25	83
Electrodiagnostic studies	Demyelination predominance	18	67
	Axonal predominance	9	33
Supportive treatment	Overall treated	20	65
	Respiratory support	6	19
Disease modifying treatment	Duration of hospitalization, mean ± SD	74 ± 110 days	
	Treated with plasma exchange	8	26
	IVIG non-responders	9	29
	Non-responders with an axonal variant of GBS	5	56
	Non-responders with a severe disease	7	78
Adverse effects	Number of patients who experienced side effects	8	26
	Headache	6	75
	Fever	4	50
	Other symptoms**	4	50
	Adverse effects took place the during first dose	2	25

*During the entire course of the disease

**Other symptoms (each reported once) included nausea, tachycardia, chest pain, and hypotension

CRP = C-reactive protein, CSF = cerebrospinal fluid, GBS = Guillain-Barré syndrome, IVIG = intravenous immunoglobulin, MDGS = motor disability grading scale, SD = standard deviation, WBC = white blood cell

noted as well. The MDGS and similar scales have been used in randomized controlled trials to achieve comparability of the motor function for each patient through the various stages of the disease and treatment and was therefore implemented in this study [17]. As noted, some cases of GBS can be traced to a triggering event, usually an infection [21]. Commonly named pathogens include *Campylobacter jejuni*, human immunodeficiency virus, cytomegalovirus, and Epstein–Barr virus. Noninfectious events have also been reported as having the potential of evoking the immune response that is at the base of the disease. Surgery, trauma, and bone marrow transplant have all been associated with GBS, as has *Neisseria meningitidis* and influenza vaccines [22]. In the current study, evidence of infection followed by GBS was identified by the laboratory or medical history in over 50% of cases; however, seasonal incidence was not noted.

Seventy-one percent of the patients diagnosed with GBS and treated with IVIG reached the endpoint – an improvement of at least one level in the MDGS – within 14 days of treatment onset.

Overall, 90% of patients managed to procure this endpoint on discharge or during follow-up examinations. As the defining features of the disease, it was not unexpected to learn that the most common symptoms were weakness of the lower limbs and decreased or absent deep tendon reflexes. Pain, a result of nerve root inflammation, was also a significant cause of discomfort for patients, and one of the most persistent symptoms reported by some patients for over 1 year following disease onset. An onset to admission interval of less than 7 days was shown to be a predictor of respiratory failure by Sharshar and co-workers in 2003 [23]. In this study, 77% of the patients were admitted to the hospital within 7 days of the presenting symptom and all six patients who warranted the use of mechanical ventilation were included in this group. Despite that fact, the increased risk of respiratory failure for patients hospitalized < 7 days since GBS onset did not reach statistical significance ($P > 0.25$).

Many autoimmune conditions are characterized by a specific set of antibodies. However, with the exception of anti-GQ1b, which is typical of the Miller-Fisher variant, no specific antigens have been identified for GBS [24]. The only laboratory test that is considered indicative of GBS and supports the diagnosis is elevated cerebrospinal fluid protein parallel to a normal white blood cell count [Table 1], which was detected in 50% of our patients. Hyponatremia is more prevalent in GBS compared to non-GBS patients. Rumalla and co-authors [25] showed that it prolonged the length of hospitalization and affected patient outcome ($P < 0.0001$). However, our results do not indicate that patients with hyponatremia at hospital admission experience a more severe disease compared to patients presenting with normal serum sodium levels ($P > 0.1$). Furthermore, hospitalization duration was longer in the non-hyponatremic group with a median of 38 days compared to 18 days for patients with hyponatremia. The most common GBS variant we encountered was AIDP. Table 2 shows the diagnosed GBS subtype for each patient. Axonal variants are largely regarded as a more severe disease with a longer recovery period and higher rates of lingering disability compared to their demyelinative counterparts. No remarkable differences in the average MDGS values at the nadir and at the time of discharge were noted in the two groups. However, when we examined hospitalization duration and the number of days required to achieve clinical improvement, we found that these periods were twofold to threefold longer in patients with an axonal GBS. Furthermore, the proportion of patients experiencing a severe disease, defined as an MDGS score of 4–5 at the nadir, was higher in the axonal group (78%) in relation to the demyelinative subtype (64%), as illustrated in Figure 1.

A vital component of the treatment for GBS is supportive care when needed, which may include the use of blood pressure support, pain management, anticoagulation, or mechanical ventilation. Overall, 65% of the patients were managed with at least one of those treatments. Six cases required assisted ventila-
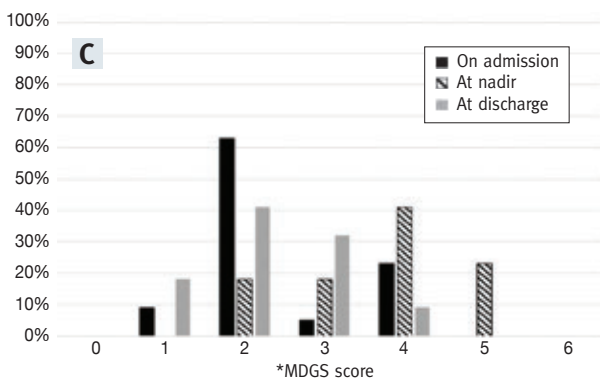
Figure 1. Motor disability grading scale scores during various stages of the disease **[A]** Motor disability grading scale scores of all study population, **[B]** Motor disability grading scale scores of patients with an axonal GBS variant, **[C]** Motor disability grading scale scores for patients with a demyelinative GBS variant
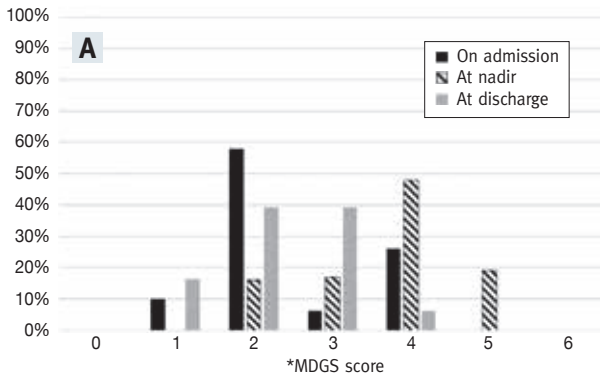
*MDGS scores of the study population in its entirety at admission to the hospital, at the nadir of the disease, and at discharge
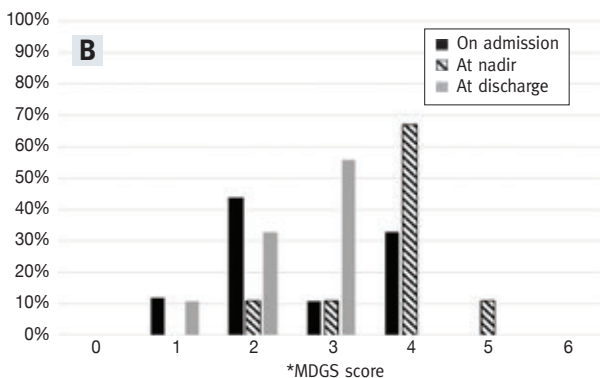
*MDGS scores of patients with an axonal GBS variant at admission to the hospital, at the nadir of the disease, and at discharge

*MDGS scores for patients with a demyelinative GBS variant at admission to the hospital, at the nadir of the disease, and at discharge

*Motor disability grading scale, as detailed in Table 1
GBS = Guillain-Barré syndrome, MDGS = motor disability grading scale

tion and only one had an axonal variant of GBS. Our results suggest that the axonal variants of GBS are not a predictor of respiratory failure. Based on the current literature, a response rate of at least 50% to IVIG was expected [17]. Of those treated, 71% attained the primary objective of motor function improvement within 14 days of the first IVIG dose, thus defining them as IVIG responders. A clinical improvement following IVIG administration was statistically significant ($P < 0.001$). Among non-responders, axonal variants ubiquity was not demonstrated. Similarly, age group was not a notable differentiator in individuals in this group, with six children under the age of 18 years and three adults. Patients experienced mostly mild side effects, consisting mainly of a headache and fever [Table 3], with no lasting damage to their health. Cessation of treatment was called for only once, due to chest pain (3%). Plasma exchange therapy was required in a total of 8 (26%) patients in addition to IVIG. Four of the patients who were treated with combined therapy improved in less than 14 days after the onset of the second modality. For all, PLEX was first-line of therapy. Despite that, administration of IVIG following PLEX failure did not prove to be effective ($P > 0.15$). The same is true for PLEX administration to IVIG non-responders ($P > 0.15$).

Our study has limitations. First, as it was a retrospective study, we were unable to control the outcome assessment and had to rely on the record keeping of the attending physician. In addition, this unique study is the first to describe the experience of an Israeli academic medical center studying GBS and IVIG and that addresses the controversial topic of combined treatment of IVIG with PLEX.

CONCLUSIONS

IVIG is effective in treating GBS ($P < 0.001$). However, for patients who did not achieve clinical improvement after receiving plasma exchange therapy, the benefit of IVIG is limited ($P > 0.15$). In addition, disease onset to admission interval of less than 7 days did not significantly increase the risk of respiratory failure ($P > 0.25$), and hyponatremia at admission was not a predictor of a severe disease, according to our results.

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Capsule

Tandem immunotherapy achieves synergy

Immune checkpoint-inhibitor therapies bolster the antitumor activity of CD8+ T lymphocytes. **Wang** et al. performed single-cell analysis of tumor-infiltrating lymphocytes in mouse cancer models in which inhibitory anti-PD-1 (programmed cell death protein 1) and stimulatory anti-GITR (glucocorticoid-induced tumor necrosis factor receptor-related protein) antibodies enhanced tumor control together. This combination immunotherapy led to a synergistic increase in tumor antigen-specific memory precursor effector T cells dependent on the CD226 costimulatory pathway. Biochemical studies in liposomes identified CD226 as an additional target of dephosphorylation mediated by the PD-1–SHP2 (Src homology region 2) complex. Thus, further clinical trials could usefully test the efficacy of combined anti-GITR and anti–PD-1 immunotherapy in human cancer.

Sci Immunol 2018; 3: eaat7061

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Capsule

The artificial intelligence clinician learns optimal treatment strategies for sepsis in intensive care

Sepsis is the third leading cause of death worldwide and the main cause of mortality in hospitals, but the best treatment strategy remains uncertain. In particular, evidence suggests that current practices in the administration of intravenous fluids and vasopressors are suboptimal and likely induce harm in a proportion of patients. To tackle this sequential decision-making problem, **Komorowski** and colleagues developed a reinforcement learning agent, the artificial intelligence (AI) clinician, which extracted implicit knowledge from patient data that exceeded, by many fold, the lifetime experience of human clinicians and learned optimal treatment by analyzing a myriad of (mostly suboptimal) treatment decisions. The authors demonstrated that the value of the AI clinician's selected treatment is on average reliably higher than human clinicians. In a large validation cohort independent of the training data, mortality was lowest in patients for whom clinicians' actual doses matched the AI decisions. This model provides individualized and clinically interpretable treatment decisions for sepsis that could improve patient outcomes.

Nature Med 2018; 24: 1716

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