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RESEARCH ARTICLE

The safety and efficacy of intravenous immunoglobulin in autoimmune encephalitis

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Abstract

Objective: Although intravenous immunoglobulin (IVIG) is the first-line immunotherapy in autoimmune encephalitis, all supporting evidence comes from retrospective case series. Here, we performed a prospective clinical trial of IVIG for functional recovery in autoimmune encephalitis. **Methods**: This single-arm, open-label study assessed the efficacy and safety of 10% intravenous IVIG treatment in newly diagnosed patients with possible autoimmune encephalitis. Patients received IVIG (0.4 g/kg/day) for 5 days. Rescue immunotherapy was permitted when the patient deteriorated before day 8 or showed no improvement at day 8. The primary outcome was the change in the modified Rankin Scale (mRS) score at day 8 and 29. The secondary outcomes were the mRS score improvement and the score changes and improvements on four other clinical scales. **Results**: Overall, 23 patients received IVIG (intension-to-treat, ITT), and 18 patients completed the study according to the protocol (per-protocol, PP). mRS improved significantly at days 8 and 29 compared to baseline in both the ITT and PP populations. Other secondary outcomes also improved significantly at day 8, 15, and 29 versus baseline. In the PP population, 6/18 patients achieved favorable outcomes with IVIG alone (mRS = 0~2 at day 8), and 12/18 patients received rescue immunotherapy. Five adverse events were reported in relation to IVIG, all of which were mild. **Interpretation**: IVIG improved neurological functional outcomes, and the improvement was evident by day 8. Adverse effects were tolerable. These data provide the prospective evidence regarding the efficacy of IVIG in improving the functional outcomes of autoimmune encephalitis.

Introduction

Autoimmune encephalitis is emerging as a major immune-mediated neurological disease, mainly presenting with memory loss, seizures, psychosis, and altered mentality.[1,2] The major pathogenesis includes multiple mechanisms, such as autoantibody-mediated synaptic dysfunction, neuronal loss, or cell/cytokine-mediated neural inflammation.[1] In the last decade, various immunotherapies have been implemented to improve the neurological outcomes of the disease, including corticosteroids, immunoglobulin, plasma exchange, rituximab, cyclophosphamide, and tocilizumab.[3–6] However, the evidence of the efficacy of immunotherapies on functional recovery was from retrospective case series, and no immunotherapy drug has received regulatory approval for the treatment of autoimmune encephalitis.

Intravenous immunoglobulin (IVIG) is a mixture of human immunoglobulin and is currently used as the first-line immunotherapy in autoimmune encephalitis.[7] However, only one prospective study investigated the efficacy of IVIG in terms of reducing seizure frequency in leucine-rich, glioma-inactivated 1 (LGI1), and contactin-associated protein-like 2 (CASPR2) encephalitis.[8] All other evidence is retrospective case series that have shown that IVIG improves modified Rankin Scale (mRS) scores and seizure frequency in seropositive autoimmune encephalitis, such as anti-N-methyl D-aspartate receptor (NMDAR) encephalitis and LGI1 encephalitis.[3,4,6,9,10]

Accordingly, there has been an unmet need for a prospective trial of IVIG for both clinical and regulatory reasons, and the trial should investigate how fast and effective IVIG can improve the overall neurological outcome in autoimmune encephalitis and whether the efficacy of IVIG is evident in all possible autoimmune encephalitis cases, including not only seropositive, but also seronegative cases.[11]

For this reason, we conducted this single-arm, open-label clinical trial to investigate the efficacy and safety of IVIG in terms of neurological outcomes in autoimmune encephalitis. We analyzed how fast IVIG improves neurological scales and collected adverse effect data to provide prospective evidence of IVIG use in autoimmune encephalitis. The product used in this study is 10% IVIG, which has a higher concentration than conventional 5% IVIG and thus uses a smaller total volume and reduced infusion time.[12-14]

Subjects and Methods

Study design and participants

This single-arm, open-label, single-center study assessed the efficacy and safety of 10% IVIG in autoimmune encephalitis from December 2019 to June 2020. Eligibility criteria included an age of 12 years or more and newly diagnosed possible autoimmune encephalitis according to the consensus criteria[11]: (1) subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms; (2) at least one of the following: new focal central nervous system (CNS) findings, seizure not explained by a previously known seizure disorder, cerebrospinal fluid (CSF) pleocytosis (white blood cell count $\geq 5/mm^3$), and MRI features suggestive of encephalitis; and (3) reasonable exclusion of alternative causes. Autoantibodies causing autoimmune encephalitis were screened with conventional antibody assay kits for synaptic antibodies (Euroimmune Ag, Lübeck, Germany) and flow cytometric assay for anti-myelin oligodendrocyte glycoprotein (MOG) antibody.[6,15]

Exclusion criteria included subjects (1) who had received immunoglobulin therapy within 10 weeks prior to the screening, (2) who had a history of hypersensitivity or shock to ingredient of immunoglobulin, (3) who had been diagnosed with IgA deficiency, (4) who had renal disorder (creatinine clearance <10 mL/min) or required dialysis, (5) who had been diagnosed with hemolytic anemia or anemia from blood loss, (6) who had been diagnosed with immunological incompetence or immunodeficiency, (7) who were at high risk for thrombus or embolism (history of thrombus/embolism or cerebrovascular/cardiovascular disorder within 3 months prior to screening), (8) who had impaired cardiac function (congestive heart failure > New York Heart Association (NYHA) functional class II: unstable coronary artery disease or myocardial infarction within 3 months prior to screening), (9) who could not stop their previously administered steroid regimens according to the investigator's discretion, (10) who were pregnant or breastfeeding, or (11) who were considered by the investigator to be ineligible for the study.

This study was approved by the Institutional Review Board of Seoul National University Hospital, South Korea (IRB no. H-1908-066-1054; ClinicalTrials.gov no. NCT04175522). The trial was conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice,[16] and the provisions of the Declaration of Helsinki.[17] All participants or their legal representatives provided written informed consent.

Trial procedures and outcomes

Patients received intravenous infusion of 10% immunoglobulin 0.4 g/kg/day for 5 days (IV-Globulin SN™, GC Pharma; from day 1 to day 5). Infusion started at a speed of 0.01~0.02 mL/kg/min for the first 30 minutes and increased up to 0.06 mL/kg/min if no abnormalities are observed. Patients were evaluated for neurological outcomes and safety assessments every day up to day 8 and then at days 15 and 29 by the treating physician (Fig. 1).

Rescue immunotherapies were allowed (1) if patients showed neurological deterioration from the initiation of IVIG to day 7 as defined by aggravation of the mRS score by more than 1 point or of the CGI-I score by 6 or more, or (2) if patients had no improvement in their mRS score compared to the baseline or their CGI-I score was 3 or more from day 8. Otherwise, concomitant immunotherapies were not permitted until day 29.

The primary outcome of this study was changes from baseline in mRS scores at day 8 and 29. Secondary outcomes were changes from baseline and improvement in mRS at day 15, and 29 other than primary outcomes, and the changes from baseline and improvements on four clinical scales, including the Clinical Assessment Scale in Autoimmune Encephalitis (CASE),[18] Glasgow Coma Scale (GCS), Clinical Global Impression–Severity scale (CGI-S), and Clinical Global Impression–Improvement scale (CGI-I),[19] at days 8, 15, and 29. Improvement on these scales was defined as a score change of 1 point or more in the favorable direction. Favorable mRS was defined by a mRS score of 0~2, and a favorable CASE score was defined by a total CASE score of 0~3.

Safety assessments included adverse events, vital signs, and clinical laboratory tests. The treating physician and

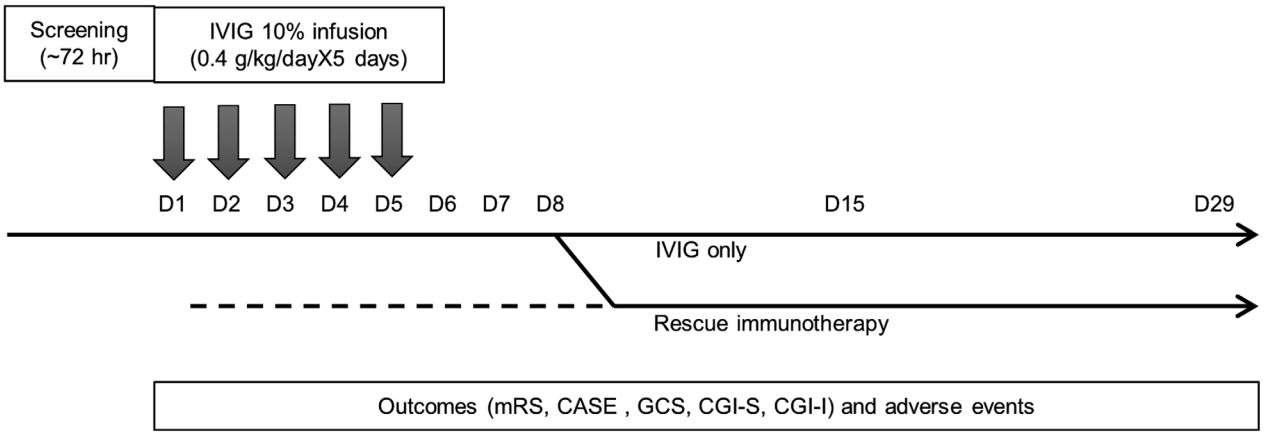

Figure 1. Trial design. After screening for up to 72 hours, eligible patients received 10% IVIG infusion for 5 days (0.4 g/kg/day). Outcomes and adverse events were monitored until day 29 after the initiation of IVIG (day 1~8, day 15, and day 29). Rescue immunotherapy was permitted if the patient deteriorated (mRS change +1 or CGI-I > =6) before day 8 or was not improved (no improvement in mRS or CGI-I > =3) when evaluated at day 8.

investigators assessed the relationship between adverse events and IVIG and classified them into predefined categories [related (definitely, probably, possibly, unlikely, unassessable/unclassifiable), and not related].

Statistical analysis

Because the current study is an exploratory study to provide a proof-of-concept, the sample size (n = 24) was determined considering the feasible number of patients who are recruitable in a single institution and the number needed to allocate approximately triple patients for each of the six mRS scores (0~5, excluding death) at the endpoint, taking into account a 25% withdrawal rate. In the outcome analysis, a normal distribution was determined by the Shapiro–Wilk test. For continuous variables, the paired *t*-test or the Wilcoxon signed-rank test was used for related data, and Student's *t*-test or the Mann–Whitney *U* test was used for independent data. For categorical variables, McNemar's test was used for related data, and Fisher's exact test [$np < 5$ or $n(1-p) < 5$]/Pearson's chi-squared test [$np \geq 5$ and $n(1-p) \geq 5$] were used for independent data. A *P*-value of <0.05 (two-tailed) was considered statistically significant. Statistical analyses were performed using IBM SPSS statistical software version 25.0 (IBM Inc., Armonk, NY, USA) and SAS V.9.2 (SAS Institute, Cary, NC, USA).

Role of the funding source

The funder of the study was involved in study design, data collection, data analysis, data interpretation, and writing of all related reports and publications.

Results

Study flow and patient characteristics.

A total of 24 patients were screened, and 23 patients met the inclusion and exclusion criteria (Fig. 2). These 23 patients received IVIG treatment (intention-to-treat, ITT population). Among them, three patients discontinued their participation: one by physician decision (to treat newly diagnosed cancer), one by patient decision, and one by death because of a comorbid disease not related to IVIG. Another two patients had protocol deviation. Finally, a total of 18 patients were treated according to the study protocol (per-protocol, PP). In this PP population, 6/18 patients were treated only with IVIG without any other rescue immunotherapy (PP-IVIG), and the other 12/18 patients had rescue immunotherapies (PP-rescue). Before the enrollment, 5/18 of the PP population and 6/23 of the ITT population received methylprednisolone (1,000 mg/kg intravenously, for 3~5 days) but stopped it without any clinical improvement.

The baseline characteristics are described in Table 1. Memory dysfunction and psychiatric symptoms were the main presentations, along with seizures, language problems, and gait instability. The median duration from symptom onset to enrollment was 2.9 ± 4.5 (ITT population) or 1.8 ± 1.7 weeks (PP population). Most of the patients were seronegative, and two LGI1 and one MOG-associated encephalitis were enrolled in the study. In the subtype classification according to the published criteria,[11] there were three definite seropositive AE, six definite limbic encephalitis, two acute demyelinating

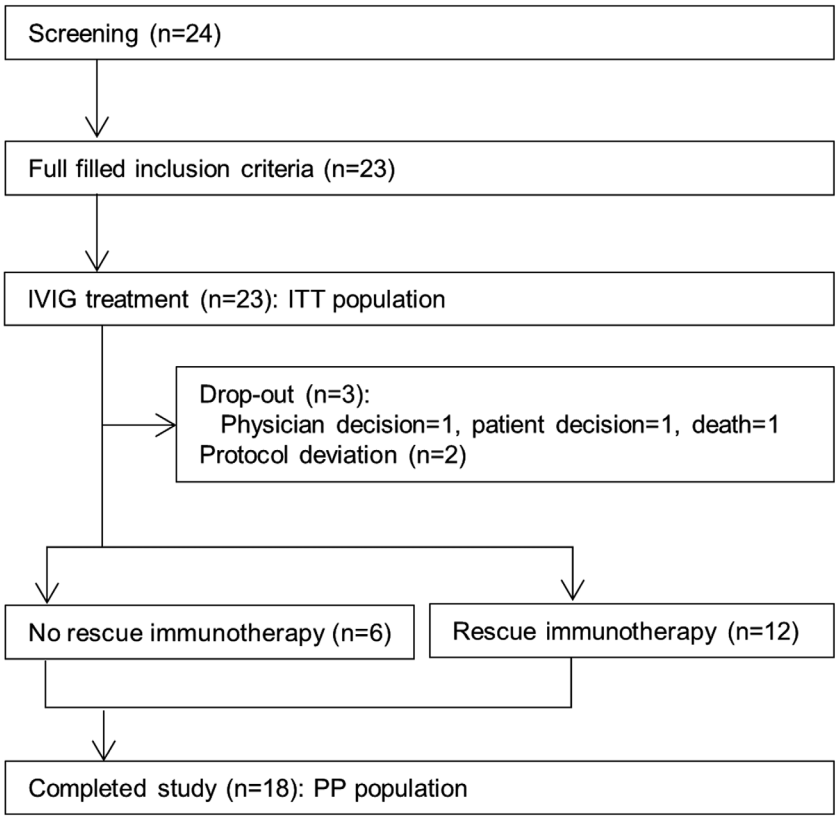

Figure 2. Study flow.

encephalomyelitis, and 12 antibody-negative but probable autoimmune encephalitis (ANPRA) among the ITT population (Table 1). Two patients had tumors including breast cancer and renal cell carcinoma, fulfilling the criteria for probable paraneoplastic neurologic syndrome (PNS-Care score = 7).[20] The PP population included five patients who received steroid prior to IVIG [mean interval between the last day of steroid and the first day of IVIG treatment = 2.4 days (range = 1~3)]. In the ITT population, additional one patient took oral steroid during the IVIG treatment (protocol deviation).

In the PP population with rescue immunotherapy (n = 12), the time to rescue immunotherapy from the first IVIG treatment was 8.1 ± 1.7 days. Rescue immunotherapy included steroid (n = 2), rituximab (n = 5), steroid followed by rituximab (n = 3), tocilizumab (n = 1), and rituximab followed by tocilizumab (n = 1). One patient received the rescue immunotherapy because of the clinical deterioration, and the other 11 patients received it because of no improvement. In the ITT population, mRS was measured in 23 (baseline), 22 (day 8), and 21 patients (days 15 and 29). Other outcome scores (CASE score, GCS, CGI-I, and CGI-S) were measured in 23 (baseline), 22 (day 8), 21 (day 15), and 20 patients (day 29) in the population. In the PP population, all 18 patients were evaluated for all the outcome scales until day 29.

Efficacy

The primary outcomes defined by the changes in the mean mRS score from baseline showed significant improvement at all time points on days 8 and 29 (Table 2, Fig. 3A,B, $P < 0.01$). As the secondary outcome, the mRS improvement (improvement of 1 or more) was 50% at day 8 in both the ITT and PP populations and 85.7% (ITT) and 88.9% (PP) at day 29. The portion of favorable mRS (0~2) was also better at days 8, 15, and 29 compared to the baseline. In particular, at day 8 in the PP population, 10/18 (55.6%) patients reached favorable mRS scores (Fig. 3B). In more detail, while all 6/6 (100%) PP-IVIG patients showed favorable mRS at day 8 (Fig. 3C), 4/12 (33.3%) PP-rescue patients had favorable mRS at day 8 and were further treated with rescue immunotherapy (Fig. 3D).

The CASE score means and the favorable CASE score (0~3) outcomes showed improvements at all time points on days 8, 15, and 29 compared to the baseline (Table 2).

Table 1. Patient characteristics and demographics of the ITT (intention-to-treat) and PP (per-protocol) populations.

	ITT population (n = 23)	PP population (n = 18)
Age (mean ± SD)	48.8 ± 17.4	48.8 ± 17.0
Male – n (%)	12 (52.2)	9 (50)
Presenting symptoms - n (%)		
Seizure	10 (43.5)	7 (38.9)
Memory dysfunction	23 (100)	18 (100)
Psychiatric symptoms	19 (82.6)	14 (77.8)
Impaired consciousness	6 (26.1)	4 (22.2)
Language problem	21 (91.3)	16 (88.9)
Dyskinesia/Dystonia	4 (17.4)	2 (11.1)
Gait instability and ataxia	14 (60.9)	11 (61.1)
Brainstem dysfunction	3 (13.0)	3 (16.7)
Weakness	6 (26.1)	5 (27.8)
Increased CSF leukocyte (>5 cells/μL) - n (%)	12 (52.2)	11 (61.1)
Increased CSF protein level (> 40 mg/dL) - n (%)	16 (69.6)	14 (77.8)
Abnormality in brain MRI (%) - n (%)	18 (78.3)	14 (77.8)
Unilateral medial temporal involvement - n (%)	2 (8.7)	3 (16.7)
Bilateral medial temporal involvement - n (%)	8 (34.8)	6 (33.3)
Median duration from symptom onset to enrollment (weeks)	2.9 ± 4.5	1.8 ± 1.7
Autoantibody - n (%)		
Seronegative	20 (87.0)	16 (88.9)
LGI1 Antibody	2 (8.7)	1 (5.6)
MOG Antibody	1 (4.3)	1 (5.6)
Tumor association - n (%)	2 (8.7)	1 (5.6)
AE subtypes		
Definite seropositive AE - n (%)	3 (13.0)	2 (11.1)
Definite limbic encephalitis - n (%)	6 (26.1)	5 (27.8)
ADEM – n (%)	2 (8.7)	2 (11.1)
ANPRA – n (%)	12 (52.2)	9 (50)
Combined medications		
Use of antiepileptic drugs - n (%)	16 (69.6)	12 (66.7)
Use of antipsychotics - n (%)	13 (56.5)	11 (61.1)
Rescue immunotherapy - n (%)	15 (65.2)	12 (66.7)
Time to rescue immunotherapy from the first IVIG (days, mean ± SD)	8.1 ± 2.6	8.1 ± 1.7

ADEM, acute demyelinating encephalomyelitis; ANPRA, antibody-negative but probable autoimmune encephalitis.

On day 8, 16/18 (88.9%) patients in the PP population showed CASE improvement (improvement of 1 or more) by IVIG treatment. At day 29, 17/20 (85%) patients in the ITT and 15/18 (83.3%) in the PP population reached the favorable CASE score. The plotting of individual CASE scores depicts the trends of early improvements by IVIG treatment (Fig. 4A).

GCS scores showed significant improvement during the study, when analyzed by the mean difference compared to the baseline (Table 2). When the individual scores were plotted, the improvement occurred before day 8 (Fig. 4B).

CGI-S and CGI-I scores also improved significantly at days 8, 15, and 29 when analyzed by the mean difference compared to the baseline (Table 2). The two scores showed early improvement during the first week of treatment (Fig. 5). Thus, at day 8, 17/22 (77.3%) patients in the ITT population and 14/18 (77.8%) in the PP population had improvement in the CGI-I score (Table 2).

In the subgroup analysis in the PP population comparing those treated only with IVIG (PP-IVIG, n = 6) and those with rescue immunotherapies (PP-rescue, n = 12), some baseline characteristics were severe in PP-rescue group evidenced by CGS and CGI-S (Table 3). The PP-IVIG group had better outcomes at day 8 than the PP-rescue group in terms of mRS mean, favorable mRS, CASE mean, favorable CASE, GCS mean, CGI-S mean, and CGI-I mean (Table 4). At days 15 and 29, both the PP-IVIG and PP-rescue groups continued to improve, but the outcome differences between the groups diminished.

Adverse events

A total of 36 adverse events were reported (Table 5). Among them, 31 events were not related with IVIG. In the other five, there were two adverse events definitely related (two events of shivering during infusion), one probably related (chest discomfort during infusion), one possibly related (chest discomfort during infusion), and one unlikely related (diplopia between the infusion) to the IVIG treatment: all these events were transient and mild. Among the 31 events not related to IVIG, one patient developed acquired hemophilia as a manifestation of systemic autoimmune syndrome and died because of intracerebral hemorrhage by the bleeding tendency. One patient developed symptoms of deep vein thrombosis (DVT) before the start of IVIG and was diagnosed as DVT during the use of IVIG (not related to IVIG). Otherwise, all the other unrelated adverse events were not severe. In blood laboratory tests, no clinically significant finding was observed in relation to IVIG treatment at days 8, 15, and 29.

DISCUSSION

In this study, 10% IVIG improved the neurological outcomes (mRS, CASE, GCS, CGI-I, and CGI-S) at days 8, 15, and 29 in the autoimmune encephalitis. In particular, the efficacy of IVIG was significant early at day 8, and

Table 2. Outcomes of mRS, CASE scores, GCS, CGI-S, and CGI-I.

	ITT population		PP population	
	Values	*P*-value	Values	*P*-value
mRS				
Baseline - Mean ± SD (n)	3.48 ± 0.90 (23)	–	3.44 ± 0.92 (18)	–
Favorable mRS at baseline - n (%)	1 (4.3)	–	1 (5.6)	–
Day 8 - Mean ± SD (n)	2.82 ± 1.14 (22)	0.001	2.78 ± 1.22 (18)	0.004
Favorable mRS at day 8 - n (%)	11 (50)	0.002	10 (55.6)	0.004
mRS improvement at day 8 - n (%)	11 (50)	–	9 (50.0)	–
Day 15 - Mean ± SD (n)	2.33 ± 1.02 (21)	<0.0001	2.28 ± 1.02 (18)	<0.0001
Favorable mRS at day 15 - n (%)	15 (71.4)	0.0001	13 (72.2)	0.0005
mRS improvement at day 15 - n (%)	17 (81.0)	–	15 (83.3)	–
Day 29 - Mean ± SD (n)	1.90 ± 1.45 (21)	<0.0001	1.78 ± 1.11 (18)	<0.0001
Favorable mRS at day 29 - n (%)	17 (81.0)	<0.0001	15 (83.3)	0.0001
mRS improvement at day 29 - n (%)	18 (85.7)	–	16 (88.9)	–
CASE score				
Baseline - Mean ± SD (n)	8.39 ± 4.45 (23)	–	7.94 ± 4.68 (18)	–
Favorable CASE at baseline - n (%)	2 (8.7)	–	2 (11.1)	–
Day 8 - Mean ± SD (n)	5.32 ± 3.50 (22)	<0.0001	5.06 ± 3.76 (18)	<0.0001
Favorable CASE at day 8 - n (%)	9 (40.9)	0.016	9 (50.0)	0.016
CASE improvement at day 8 - n (%)	20 (90.9)	–	16 (88.9)	–
Day 15 - Mean ± SD (n)	3.71 ± 3.62 (21)	<0.0001	3.67 ± 3.82 (18)	<0.0001
Favorable CASE at day 15 - n (%)	14 (66.7)	0.0005	12 (66.7)	0.0005
CASE improvement at day 15 - n (%)	21 (100)	–	18 (100)	–
Day 29 - Mean ± SD (n)	2.15 ± 3.23 (20)	<0.0001	2.33 ± 3.36 (18)	<0.0001
Favorable CASE at day 29 - n (%)	17 (85.0)	0.0001	15 (83.3)	0.0001
CASE improvement at day 29 - n (%)	20 (100)	–	18 (100)	–
GCS				
Baseline - Mean ± SD (n)	13.22 ± 2.24 (23)	–	13.22 ± 2.26 (18)	–
Day 8 - Mean ± SD (n)	14.23 ± 1.54 (22)	0.002	14.06 ± 1.66 (18)	0.016
GCS improvement at day 8 - n (%)	10 (62.5)	–	7 (53.9)	–
Day 15 - Mean ± SD (n)	14.38 ± 1.60 (21)	0.002	14.39 ± 1.69 (18)	0.001
GCS improvement at day 15 - n (%)	12 (80.0)	–	11 (84.6)	–
Day 29 - Mean ± SD (n)	14.50 ± 1.61 (20)	0.001	14.44 ± 1.69 (18)	0.001
GCS improvement day 29 - n (%)	12 (85.7)	–	11 (84.6)	–
CGI-S				
Baseline - Mean ± SD (n)	4.70 ± 0.82 (23)	–	4.61 ± 0.85 (18)	–
Day 8 - Mean ± SD (n)	4.00 ± 1.02 (22)	0.0002	4.00 ± 1.08 (18)	0.002
CGI-S improvement at day 8 - n (%)	13 (59.1)	–	10 (55.6)	–
Day 15 - Mean ± SD (n)	3.52 ± 0.93 (21)	<0.0001	3.50 ± 0.92 (18)	<0.0001
CGI-S improvement at day 15 - n (%)	18 (85.7)	–	16 (88.9)	–
Day 29 - Mean ± SD (n)	2.95 ± 1.15 (20)	<0.0001	3.00 ± 1.19 (18)	<0.0001
CGI-S improvement at day 29 - n (%)	18 (90)	–	16 (88.9)	–
CGI-I				
Day 8 - Mean ± SD (n)	2.91 ± 0.75 (22)	<0.0001	2.94 ± 0.73 (18)	0.0001
CGI-I improvement at day 8 - n (%)	17 (77.3)	–	14 (77.8)	–
Day 15 - Mean ± SD (n)	2.38 ± 0.86 (21)	<0.0001	2.39 ± 0.78 (18)	<0.0001
CGI-I improvement at day 15 - n (%)	18 (85.7)	–	16 (88.9)	–
Day 29 - Mean ± SD (n)	2.00 ± 0.86 (20)	<0.0001	2.11 ± 0.83 (18)	<0.0001
CGI-I improvement at day 29 - n (%)	18 (90)	–	16 (88.9)	–

P values were calculated by using paired *t*-test, Wilcoxon signed-rank test, or McNemar's test compared to the baseline values. Favorable scores were defined by mRS = 0~2 or CASE = 0~3. Score improvement was defined by a score change of 1 point or more in the favorable direction. Score improvement in GCS was analyzed only in patients with impaired total GCS score. CASE, Clinical Assessment Scale in Autoimmune Encephalitis; CGI-I, Clinical Global Impression–Improvement scale; CGI-S, Clinical Global Impression–Severity scale; GCS, Glasgow Coma Scale; and mRS, modified Rankin Scale.

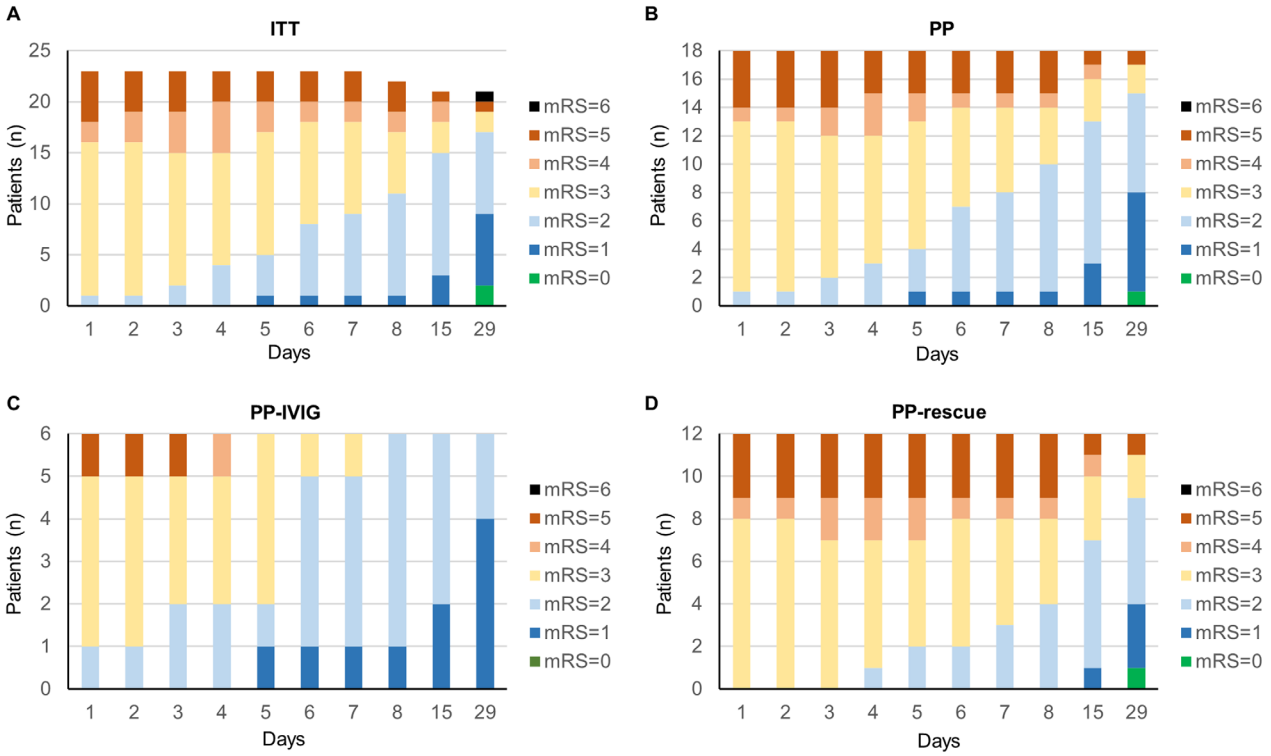

Figure 3. Changes in mRS scores. Early and continuing improvement in mRS was notable in both the ITT (A) and PP populations (B). In the PP population, those treated only with IVIG (PP-IVIG) had early improvement in mRS up to day 8 (C), and those treated with rescue immunotherapy (IVIG-rescue) had poorer early response but showed continuing improvement at days 15 and 29 (D). mRS, modified Rankin Scale.

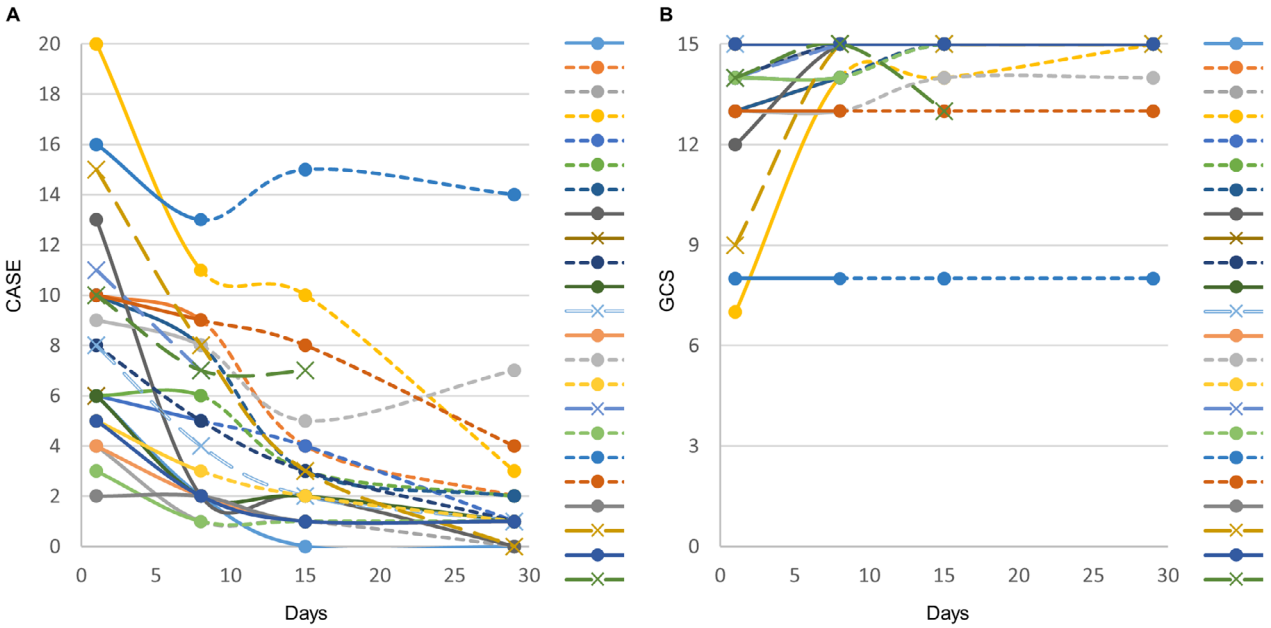

Figure 4. Individual recovery of CASE and GCS scores. When the individual changes were plotted, CASE scores showed early improvement before day 8 (A). GCS plotting also showed early improvement in the scores before day 8 (B). Solid lines depict the IVIG-only period, and dotted lines depict the period after rescue immunotherapies. Dashed lines with X marks indicate the ITT subjects who dropped out from the PP population. CASE, Clinical Assessment Scale in Autoimmune Encephalitis, and GCS, Glasgow Coma Scale.

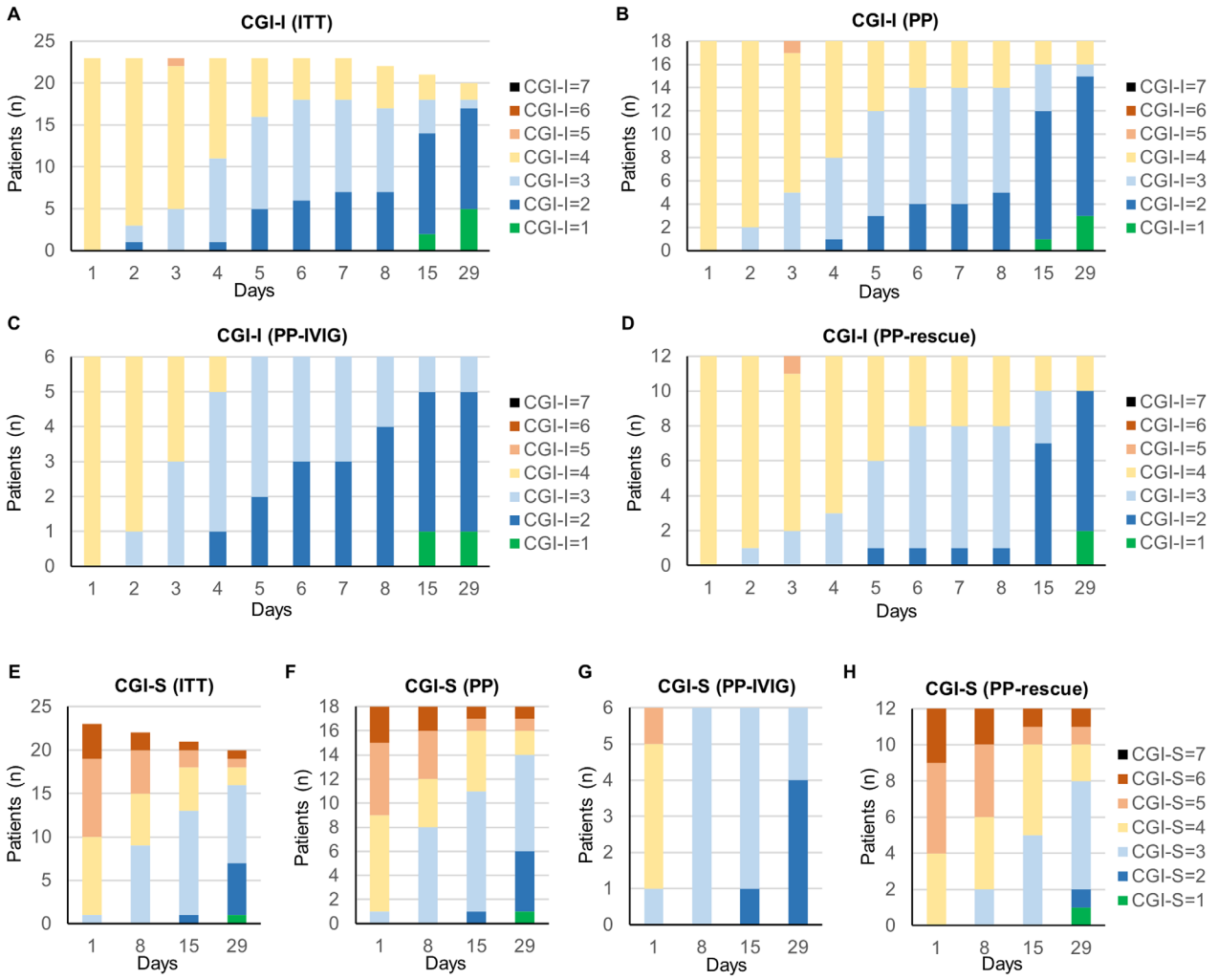

Figure 5. Changes in CGI-I and CGI-S scores. Patients showed continuing improvement in CGI-I during the study period in both the ITT (A) and PP populations (B). In the PP population, those treated only with IVIG (PP-IVIG) had major improvement in CGI-I before day 8 (C), and those treated with rescue immunotherapy (PP-rescue) showed slower response curve of CGI-I up to day 29 (D). In CGI-S outcomes, both the ITT (E) and PP (F) populations showed improvement patterns. Early improvement was prominent in PP-IVIG (G), and slow improvement was noted in PP rescue (H). CGI-S, Clinical Global Impression–Severity scale, and CGI-I, Clinical Global Impression–Improvement scale.

one-third (6/18) of the PP patients reached a favorable outcome without rescue immunotherapy. In the evaluation of safety, IVIG was generally well tolerated since the majority of adverse events were mild in severity.

Our open-label evidence suggests that IVIG is safe and effective in autoimmune encephalitis. IVIG has been used with level A evidence in some autoimmune neurological conditions, such as Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and myasthenia gravis.[21,22] In autoimmune encephalitis, however, only retrospective case series have suggested the possible efficacy of IVIG for neurological recovery, and other multiple immunotherapies used in the disease also have retrospective evidence so far, such as steroids, rituximab, cyclophosphamide, and tocilizumab.[3–10] Accumulating retrospective evidence has even made it somewhat unethical to conduct a placebo-controlled trial in the disease. While one previous randomized study in LGI1/CASPR2 encephalitis showed that IVIG decreases seizure frequency,[8] it is unknown whether this efficacy can be explicated to the functional outcome of whole autoimmune encephalitis, especially in seronegative patients. Our current study used the proposed operational criteria of autoimmune

Table 3. Patient characteristics comparing those treated only with IVIG (PP-IVIG) and those treated with rescue immunotherapy (PP-rescue) in the PP population.

	PP-IVIG (n = 6)	PP-rescue (n = 12)	*P*-value
Age (mean ± SD)	44.2 ± 19.6	51.1 ± 16.0	0.569
Male - n (%)	3 (50)	6 (50)	1.000
Presenting symptoms - n (%)			
Seizure	2 (33.3)	5 (41.7)	1.000
Memory dysfunction	6 (100)	12 (100)	-
Psychiatric symptoms	3 (50)	11 (91.7)	0.083
Impaired consciousness	0 (0)	4 (33.3)	0.245
Language problem	5 (83.3)	11 (91.7)	1.000
Dyskinesia/Dystonia	0 (0)	2 (16.7)	0.529
Gait instability and ataxia	2 (33.3)	9 (75.0)	0.141
Brainstem dysfunction	1 (16.7)	2 (16.7)	1.000
Weakness	1 (16.7)	4 (33.3)	0.615
Increased CSF leukocyte (>5 cells/μL) - n (%)	3 (50)	8 (66.7)	0.627
Increased CSF protein level (> 40 mg/dL) - n (%)	4 (66.7)	10 (83.3)	0.569
Abnormality in brain MRI (%) - n (%)	5 (83.3)	9 (75)	1.000
Medial temporal involvement in brain MRI (%) - n (%)	3 (60)	6 (66.7)	1.000
Median duration from symptom onset to enrollment (weeks)	1.63 ± 0.99	1.89 ± 1.92	0.345
Autoantibody - n (%)	0 (0)	2 (16.7)	1.000
Tumor association - n (%)	1 (16.7)	0 (0)	0.146
AE subtypes			0.457
Definite seropositive AE - n (%)	0 (0)	2 (16.7)	
Definite limbic encephalitis - n (%)	2 (33.3)	3 (25)	
ADEM - n (%)	0 (0)	2 (16.7)	
ANPRA - n (%)	4 (66.7)	5 (41.7)	
Combined medications			
Use of antiepileptic drugs - n (%)	3 (50)	9 (75)	0.344
Use of antipsychotics - n (%)	3 (50)	8 (66.7)	0.627

P values were calculated by using Student's *t*-test for continuous variables and Fisher's exact test [$np < 5$ or $n(1-p) < 5$]/Pearson's chi-squared test [$np \geq 5$ and $n(1-p) \geq 5$] for categorical variables. ADEM, acute demyelinating encephalomyelitis; ANPRA, antibody-negative but probable autoimmune encephalitis.

encephalitis,[11] thus including many seronegative autoimmune encephalitis patients, and showed functional improvement on various neurological scales.

IVIG has multifactorial action, such as the induction of antibody degradation by saturation of the neonatal Fc receptor, blockade of the Fcγ receptor on immune cells, upregulation of the inhibitory Fcγ receptor IIB, downregulation of immune cell activation and

Table 4. Comparison of mRS, CASE score, GCS, CGI-S, and CGI-I between PP-IVIG and PP rescue.

	PP-IVIG (n = 6) Values	PP-rescue (n = 12) Values	*P* value
mRS			
Baseline - Mean ± SD (n)	3.17 ± 0.98	3.58 ± 0.90	0.366
Favorable mRS at baseline - n (%)	1 (16.7)	0 (0)	0.333
Day 8 - Mean ± SD (n)	1.83 ± 0.41	3.25 ± 1.22	0.010
Favorable mRS at day 8 - n (%)	6 (100)	4 (33.3)	0.013
mRS improvement at day 8 - n (%)	5 (83.3)	4 (33.3)	0.131
Day 15 - Mean ± SD (n)	1.67 ± 0.52	2.58 ± 1.08	0.061
Favorable mRS at day 15 - n (%)	6 (100)	7 (58.3)	0.114
mRS improvement at day 15 - n (%)	5 (83.3)	10 (83.3)	1.000
Day 29 - Mean ± SD (n)	1.33 ± 0.52	2.00 ± 1.28	0.198
Favorable mRS at day 29 - n (%)	6 (100)	9 (75.0)	0.515
mRS improvement at day 29 - n (%)	5 (83.3)	11 (91.7)	1.000
CASE score			
Baseline - Mean ± SD (n)	6.00 ± 3.74	8.92 ± 4.94	0.223
Favorable CASE at baseline - n (%)	1 (16.7)	1 (8.3)	1.000
Day 8 - Mean ± SD (n)	2.00 ± 0.00	6.58 ± 3.78	0.019
Favorable CASE at day 8 - n (%)	6 (100)	3 (25.0)	0.009
CASE improvement at day 8 - n (%)	5 (83.3)	11 (91.7)	1.000
Day 15 - Mean ± SD (n)	1.17 ± 0.75	4.92 ± 4.14	0.006
Favorable CASE at day 15 - n (%)	6 (100)	6 (50)	0.054
CASE improvement at day 15 - n (%)	6 (100)	12 (100)	-
Day 29 - Mean ± SD (n)	0.67 ± 0.52	3.17 ± 3.88	0.029
Favorable CASE at day 29 - n (%)	6 (100)	9 (75)	0.515
CASE improvement at day 29 - n (%)	6 (100)	12 (100)	-
GCS			
Baseline - Mean ± SD (n)	14.33 ± 1.21	12.67 ± 2.50	0.048
Day 8 - Mean ± SD (n)	15.00 ± 0.00	13.58 ± 1.88	0.007
GCS improvement at day 8 - n (%)	2 (100)	5 (45.5)	0.462
Day 15 - Mean ± SD (n)	15.00 ± 0.00	14.08 ± 2.02	0.245
GCS improvement at day 15 - n (%)	2 (100)	9 (81.8)	1.000
Day 29 - Mean ± SD (n)	15.00 ± 0.00	14.17 ± 2.04	0.441
GCS improvement day 29 - n (%)	2 (100)	9 (81.8)	1.000
CGI-S			
Baseline - Mean ± SD (n)	4.00 ± 0.62	4.92 ± 0.79	0.038
Day 8 - Mean ± SD (n)	3.00 ± 0.00	4.50 ± 1.00	0.002

(*Continued*)

Table 4 Continued.

	PP-IVIG (n = 6) Values	PP-rescue (n = 12) Values	*P* value
CGI-S improvement at day 8 - n (%)	5 (83.3)	5 (41.7)	0.152
Day 15 - Mean ± SD (n)	2.83 ± 0.41	3.83 ± 0.94	0.022
CGI-S improvement at day 15 - n (%)	5 (83.3)	11 (91.7)	1.000
Day 29 - Mean ± SD (n)	2.33 ± 0.52	3.33 ± 1.30	0.046
CGI-S improvement at day 29 - n (%)	5 (83.3)	11 (91.7)	1.000
CGI-I			
Day 8 - Mean ± SD (n)	2.33 ± 0.52	3.25 ± 0.62	0.012
CGI-I improvement at day 8 - n (%)	6 (100)	8 (66.7)	0.245
Day 15 - Mean ± SD (n)	2.00 ± 0.63	2.58 ± 0.79	0.208
CGI-I improvement at day 15 - n (%)	6 (100)	10 (83.3)	0.529
Day 29 - Mean ± SD (n)	2.00 ± 0.63	2.17 ± 0.94	0.769
CGI-I improvement at day 29 - n (%)	6 (100)	10 (83.3)	0.529

P values were calculated by using Student's *t*-test/Mann–Whitney *U* test for continuous variables, and Fisher's exact test [$np < 5$ or $n(1-p) < 5$]/Pearson's chi-squared test [$np \geq 5$ and $n(1-p) \geq 5$] for categorical variables. Score improvement was defined by a score change of 1 point or more in the favorable direction. Score improvement in GCS was analyzed only in patients with impaired total GCS score. CASE, Clinical Assessment Scale in Autoimmune Encephalitis; CGI-I, Clinical Global Impression–Improvement scale; CGI-S, Clinical Global Impression–Severity scale; GCS, Glasgow Coma Scale; and mRS, modified Rankin Scale.

cytokines, and interruption of complement activation.[23,24] Although seropositive autoimmune encephalitis can be definitely diagnosed by autoantibody tests and has a clearer mechanism of disease that can be targeted with antibody-modulating drugs such as IVIG, the majority of our study population was seronegative. This might be explained by enrollment bias because seropositive cases tend to be treated immediately with any immunotherapy when diagnosed rather than being enrolled in a clinical trial. Nevertheless, our study population could derive direct evidence that seronegative autoimmune encephalitis can be a good candidate for IVIG treatment that has a complex mechanism of action. IVIG is not immunosuppressive and has an advantage over other immunosuppressants particularly in the era of a pandemic, although its cost is a drawback.

This single-arm study design raises some future questions. Even though the placebo control is not ethical, our data had to analyze the changes in functional outcomes compared to the baseline. While the symptoms of autoimmune encephalitis are rapidly progressive in general and the observed improvement in functional scales cannot be explained only by natural recovery, the confounding effect of natural recovery cannot be excluded. In addition, the upfront use of steroid before the trial enrollment in some of the patients might have accelerated the recovery during the trial. Steroid might be more effective than IVIG in the acute treatment of LGI1 encephalitis,[25] and is still one of the cost-effective treatments. Accordingly, future studies can investigate the optimal first-line treatment protocols by comparing some of them, or enroll patients with steroid-non responsiveness. In addition, because each antibody subtypes could have different disease courses and treatment responsiveness, further studies need to stratify the antibody subtypes and adjust the treatment protocols and the duration of outcome monitoring.

In addition, our study allowed rescue immunotherapy during the study period if the patients deteriorated before day 8 or had little improvement at day 8. Accordingly, the outcomes at days 15 and 29 might represent the mixed effects of both IVIG and rescue immunotherapy. Nevertheless, the significant improvement in mRS and CASE scores at day 8 confirms the early efficacy of IVIG in autoimmune encephalitis. Thus far, it has been unclear how long we should wait for the effect of first-line immunotherapy and to implement next-line immunotherapy.[7,26] Because all 6/18 good responders (PP-IVIG) had favorable outcomes before day 8 in our study, it would be considerable to decide the use of secondary immunotherapy early at day 8 after IVIG. Because two-thirds (12/18) of the PP population needed early rescue treatment, the long-term efficacy of IVIG monotherapy should be evaluated in further studies. In addition, as the PP-rescue group had more severe baseline characteristics in CGS and CGI-S compared to PP-IVIG, IVIG might be more useful as monotherapy in mild AE. Other limitations of the current study include non-blinded assessments, small patient number, non-homogenous cohort, and low number of seropositive cases. Because the majority of the enrolled patients were ANPRA without any antibody biomarker, there still remains diagnostic uncertainty in the population.

In conclusion, 10% IVIG infusion in possible autoimmune encephalitis improved various neurological outcomes from early day 8 to day 29 in this study. This prospective evidence supports the use of IVIG in autoimmune encephalitis diagnosed according to the operational criteria and provides the basis for next clinical trials in the disease.

Table 5. Adverse events, causality to IVIG, and outcomes.

Patient No	Adverse event	Severity	Causality to IVIG	Action	Treatment	Outcome
2	Chest discomfort	Mild	Possibly related	Temporarily discontinued	None	Recovered/Resolved
2	Diplopia	Mild	Unlikely related	Maintained infusion	None	Recovered/Resolved
2	Low calcium level	Mild	Not related	Not applicable	Medication	Recovered/Resolved
2	Low back pain	Mild	Not related	Not applicable	Medication	Recovering/Resolving
2	Thrombocytopenia	Mild	Not related	Not applicable	None	Recovered/Resolved
3	Low calcium level	Mild	Not related	Maintained infusion	Medication	Recovered/Resolved
3	Insomnia	Mild	Not related	Not applicable	Medication	Recovered/Resolved
4	Low platelets	Mild	Not related	Maintained infusion	None	Recovered/Resolved
4	Contact dermatitis	Mild	Not related	Not applicable	Medication	Recovering/Resolving
4	Deep vein thrombosis	Mild	Not related	Not applicable	Medication	Recovering/Resolving
5	Shivering	Mild	Definitely related	Temporarily discontinued	None	Recovered/Resolved
6	Shivering	Mild	Definitely related	Maintained infusion	None	Recovered/Resolved
7	Influenza	Mild	Not related	Maintained infusion	Medication	Recovered/Resolved
7	Fever	Mild	Not related	Not applicable	None	Recovered/Resolved
7	Hyperglycemia	Mild	Not related	Not applicable	None	Recovered/Resolved
8	Pericardial effusion	Mild	Not related	Maintained infusion	None	Not Recovered/Not Resolved
9	Chest discomfort	Mild	Probably related	Temporarily discontinued	None	Recovered/Resolved
9	Pelvic mass	Moderate	Not related	Not applicable	None	Recovering/Resolving
10	Postural orthostatic tachycardia syndrome	Mild	Not related	Maintained infusion	Medication	Recovering/Resolving
10	Skin Eruption	Mild	Not related	Maintained infusion	None	Recovered/Resolved
11	Headache	Mild	Not related	Maintained infusion	Medication	Recovered/Resolved
12	Headache	Mild	Not related	Maintained infusion	Medication	Recovered/Resolved
12	Chest pain	Mild	Not related	Maintained infusion	None	Recovered/Resolved
12	Insomnia	Mild	Not related	Not applicable	None	Recovered/Resolved
13	Vomiting	Mild	Not related	Maintained infusion	None	Recovered/Resolved
13	Nausea	Mild	Not related	Maintained infusion	Medication	Recovered/Resolved
14	Hypertension	Mild	Not related	Not applicable	Medication	Recovered/Resolved
15	Epistaxis	Mild	Not related	Maintained infusion	None	Recovered/Resolved
16	Constipation	Mild	Not related	Maintained infusion	Medication	Recovered/Resolved
16	Constipation	Mild	Not related	Not applicable	Medication	Recovered/Resolved
17	Constipation	Mild	Not related	Maintained infusion	Medication	Recovered/Resolved
19	depressive mood	Mild	Not related	Not applicable	Medication	Recovering/Resolving
20	Back pain	Mild	Not related	Maintained infusion	Medication	Recovered/Resolved
22	Post puncture headache	Mild	Not related	Maintained infusion	None	Recovered/Resolved
23	Intracerebral hemorrhage	Severe	Not related	Not applicable	Medication	Death
23	Finger inflammation	Mild	Not related	Not applicable	Medication	Not Recovered/Not Resolved

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Author Contributions

STL, HAC, KC, and SKL conceived and designed the study. STL, HSL, WJL, HAC, SHK, SYS, KC, and SKL collected the data. STL, HSL, WJL, HAC, SHK, KC, and SKL interpreted the data. STL, HAC, and SHK wrote or contributed to the writing of the manuscript. STL, HAC, SHK, and SYS have accessed and verified all the data in the study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of Interest

STL reports advisory roles for Roche/Genentech, UCB, Ono Pharmaceuticals, Biofire Diagnostics, and Advanced Neural Technologies. HAC and SHK are employees of GC Pharma. Other authors report no conflict of interests.

Data Availability Statement

GC Pharma is committed to sharing anonymized patient-level and study-level clinical trial data, upon requests

from qualified external researchers and subsequent approval by an independent review panel. Information about analytic methods, syntax, and output files of statistical analyses will be made available by the corresponding author upon reasonable request.

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