Intravenous immunoglobulin for acute attacks in neuromyelitis optica spectrum disorders (NMOSD)

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Background

Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory autoimmune syndrome of the central nervous system with devastating clinical outcomes. During acute attacks of neuromyelitis optica spectrum disorder (NMOSD), intravenous immunoglobulin (IVIG) maybe useful building on experience treating autoimmune disorders.

Methods

We performed a retrospective, two-center study. All data were collected from March 2014 to March 2019 in neurology department of Beijing Tiantan Hospital and Tianjin Medical University General Hospital. All NMO/NMOSD patients were re-diagnosed according to the 2015 International Consensus criteria for NMOSD based on their hospital medical records including clinical presentation, lab test and MRI. Patients with questionable or AQP4-antibodies negatives were further judged by two independent neurologists. This study includes three types of treatments: HD-S, IVIG and HDS + IVIG. HD-S plus IVIG treatment is defined as treatment course that overlapping administration of HD-S and IVIG at the doses and time period specified for each of the foregoing treatment courses. Kurtzke's Expanded Disability Status Scale (EDSS) was used to assess neurological deficits. Treatment outcomes were calculated as the proportion of clinical score improvement: (onset−late) / (onset−baseline), to provide the advantage of a comparability. Baseline EDSS scores is the score in the remission state after the last episode. The primary outcomes were the good remission (GR), moderate remission (MR) and poor remission (PR), which were assigned respectively for 66%–100%, 33%-65% and 0%–32% improvement of initial EDSS scores. SPSS Statistics version 22 (IBM, Armonk, NY), and GraphPad Prism version 7.0 (GraphPad Software, La Jolla, CA) were used to analyze and create graphs. . P values of < 0.05 were considered significant.

Results

After excluding 125 patients (135 attacks) failed to meet the study's criteria or lack of the primary outcome, a total of 198 patients with 243 attacks were included in our analysis (Fig. 1). The female to male ratio was 5.9:1, and the mean age of attack onset was 38 ± 14.6 years. The median disease duration was 2.6±4.0 years. The average annualized relapse rate (ARR) was 0.88±0.06. About 70% of patients were positive for anti-AQP4 antibodies. The median baseline EDSS score was 1.0 (range, 0-7.0), median EDSS at onset was 5 (range, 2-9). The mean time of the last assessment was 8 weeks after onset (range 6-10). During 243 treatment courses, 153 attacks (63%) were treated with HD-S, 14 attacks (6%) with IVIG, and for 69 (28%) HD-S combined with IVIG was used. Due to the difficulty of PLEX implementation in China, only 7 (3%) attacks were treated with PLEX and excluded for further analysis. Among these treatment groups, the EDSS at onset (6.5 (4.5, 7.0)) was significantly higher in the recipients of HD-S + IVIG treatment than in the HD-S group (p = 0.001). Other baseline characteristics of the attacks included onset age, disease duration, relapse time, time since previous attack, baseline EDSS, time from onset to start of therapy, time of last assessment and various remission immunotherapies showing insignificant differences between different treatments.

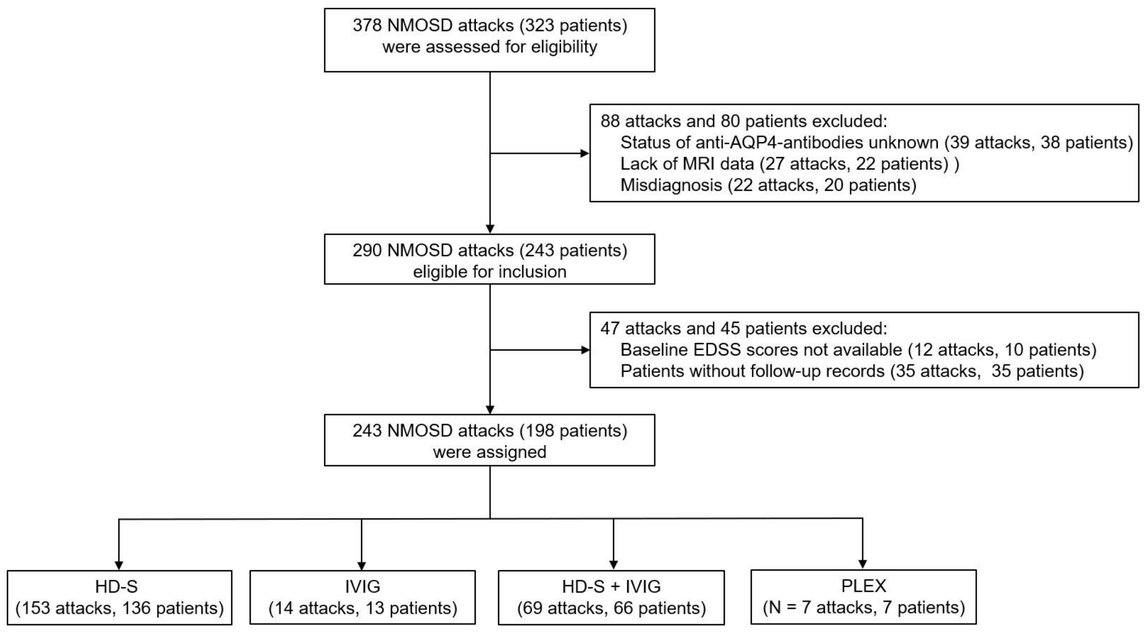
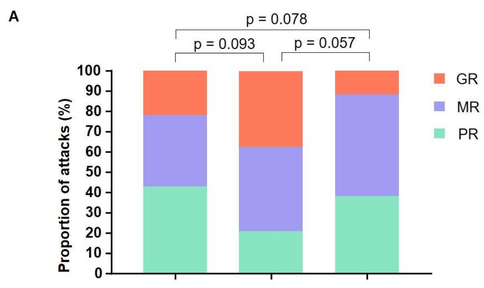
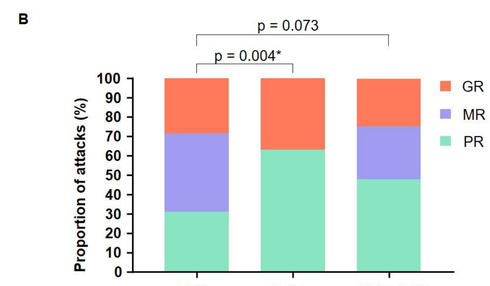
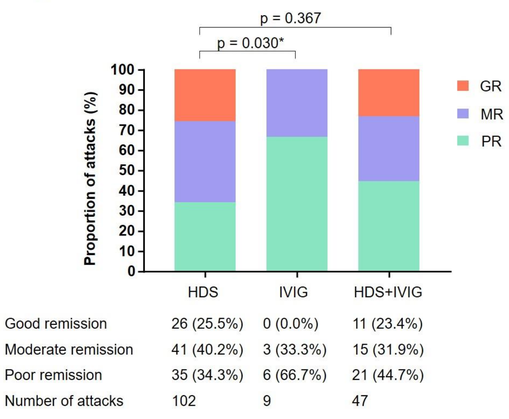


Figure 1. Study profile. *HD-S = high-dose intravenous steroids; IVIG = intravenous immunoglobulin; PLEX = plasma exchange.*

Among 243 attacks, attacks of isolated MY (n = 123, 50.6%) were more frequent than isolated ON (n = 24, 9.9%) and simultaneous MY and ON (n = 34, 14.0%). In another 62 attacks (25.5%) with other presentations. Regardless of the treatment course, the remission rates were insignificantly higher for isolated ON than for isolated MY (p = 0.093) and MY combined with ON (p = 0.057, Fig. 2A). Apart from PLEX, 5% ON attacks received IVIG, 72% ON attacks received HD-S and 23% used HD-S combined with IVIG therapy. The medium Visual Functional System (VFS) score was 4.0 (3.0, 5.0) at onset and was 2.0 (1.0, 4.0) at the last evaluation. Due to the limited number of patients in the IVIG group, further analysis couldn't be performed. In myelitis, 8% attacks used IVIG, 68% attacks used HD-S and 24% attacks were on HD-S plus IVIG therapy. There was no significant difference in the treatment distribution between these two groups with different clinical symptoms (p = 0.667).







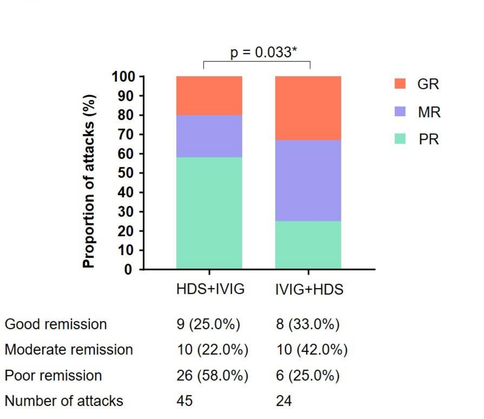


Fig. 2. Clinical outcomes by treatment courses.
A: The remission status of attack manifestations with MY (n = 123), ON (n = 24) and ON with MY (n = 34). ON = Optica neuritis; MY = myelitis. *p < 0.05. B: The remission status of all treated attacks (n = 236) among HD-S alone, IVIG alone and HD-S + IVIG treatments. HD-S = high-dose intravenous steroids; IVIG = intravenous immunoglobulin. *p < 0.05. C: The remission status of attacks (n = 158) with AQP4-IgG positive among HD-S alone, IVIG alone and HDS + IVIG treatments. HD-S = high-dose intravenous steroids; IVIG = intravenous immunoglobulin. *p < 0.05. D: The remission status of attacks treated by HDS + IVIG and IVIG + HDS. HD-S + IVIG = start high dose intravenous steroids before intravenous immunoglobulin. IVIG + HD-S = start intravenous immunoglobulin before high-dose intravenous steroids. *p < 0.05.

In patients with NMOSD,14 acute attacks were treated with IVIG alone. Of 14 attacks, 5 (35.7%) showed a moderate decrease of EDSS score (33%-65%), the other attacks poorly alleviated less than 33%. None of them manifested improvement of disability over 66%. The proportion of the better clinical remission rate in the IVIG alone group was obviously lower than that in the HD-S alone treatment group (p = 0.004), whereas it did not differ significantly between the HD-S-treated group and HD-S plus IVIG treated group (Fig. 2B). 158 of 236 attacks were positive for AQP4-IgG. Patients treated with IVIG alone presented lower clinical remission rates than those who received HD-S alone (p = 0.030), and there was no significant difference between the HD-S treatment group and the HD-S plus IVIG treatment group (Fig. 2C). In univariate analysis, IVIG alone treatment was less effective than HD-S alone therapy (p = 0.012). In multivariate modelling, better clinical outcome was associated with lower EDSS at onset (p < 0.0001), as well as the choice of first treatment courses. Compared with HD-S alone treatment, IVIG alone treatment demonstrated less likelihood of better clinical improvement (B = -1.90, OR = 0.15, R2 = 0.401, p = 0.006), while onset age (p = 0.133), last evaluation time (p = 0.600) and time from start of therapy (p = 0.311) demonstrated a less influence for multivariate modelling.

Of the 69 episodes of HD-S plus IVIG treatment, 45 cases started IVIG after poor response to HD-S treatment, and other 24 cases continued HD-S after the early initiation of IVIG treatment. Compared to patients who started IVIG after HD-S treatment, patients who added HD-S in early IVIG treatment were significantly more likely to regain the highest third strata of improvement (p = 0.033, Fig. 2D).
Our attacks were stratified by onset EDSS score (≤ 6.0 or ≥ 6.5). In univariate analysis of attacks with EDSS ≥ 6.5, IVIG combined with HD-S therapy was superior to HD-S alone treatment (p = 0.040). The better outcome was also significantly related with the lower onset EDSS (p = 0.005). After adjustment by multivariable ordinal logistic regression, the better clinical outcome was associated with lower onset EDSS scores (p = 0.003) and the first treatment's choice of attack. Adding HD-S to IVIG treatment yielded better clinical improvement than HD-S alone treatment (B = 1.77, OR = 5.85, R2 = 0.403, p = 0.007, Table 2). However, adding IVIG to HD-S wasn't superior to HD-S alone treatment (p = 0.989).

Conclusion and Limitations

These results did not support IVIG-alone therapy as a first-line option for acute NMOSD. However, adding HD-S to IVIG therapy was superior to HD-S alone for patients with high-onset EDSS.
Limitations*:* This is a retrospective study, all review data were extracted from medical records. Because PLEX was rarely used in our study, the possible superiority of PLEX + IVIG as a second line "rescue therapy" was not considered. And the small cohort sizes of the IVIG may influence the result.

Disclosure and Conflict of Interest

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Conflict of Interest: None.