Journal of Neuroimmunology 330 (2019) 81–86

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Reduced dosage rituximab in the treatment of anti-*N*-methyl-D-aspartate receptor encephalitis: An observation study in Chinese patients

Bo Deng[a,1], Hai Yu[a,1], Xiaoni Liu[b], Xue Yu[a], Xiang Zhang[a,b], Xiang Li[a], Wenbo Yang[a], Siqi Dong[a], Yue Qiu[a], Xiangjun Chen[a,b,*]

[a] Department of Neurology, Huashan Hospital, Fudan University, 12 Wulumuqi Zhong Road, Shanghai 200040, China
[b] Institute of Neurology, Fudan University, 12 Wulumuqi Zhong Road, Shanghai 200040, China

ARTICLE INFO

Keywords:
Anti-*N*-methyl-D-aspartate receptor encephalitis
Rituximab
Dosage regimen
B cell
Treatment

ABSTRACT

The aim of this study was to observe the treatment effect and investigate the possible mechanism of reduced dosage (600 mg) rituximab treatment on anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. The median modified Rankin Scale of ten enrolled patients decreased from 4 (range 2–4) before rituximab infusion to 0 (range 0–2) after a mean follow-up time of 24.3 ± 8.7 months. One patient relapsed 9 months after treatment. No severe adverse event was observed. The proportion of total B cells in lymphocytes was depleted from 13.4 ± 6.7% to 0.6 ± 0.8% one day after treatment. B cells started to regeneration at 3 months and reached 9.4 ± 3.7% at 12 months after treatment. At this time point, proportion of regulatory B cells (Breg) in reconstituted B cells was significantly higher than that before treatment (15.3 ± 12.1% vs. 0.5 ± 0.6%, $p = 0.006$), while proportion of memory B cells (Bmem) was significantly lower than baseline level (8.0 ± 4.5% vs. 30.2 ± 12.6%, $p < 0.001$). Our results supported that reduced dosage rituximab was effective and safe in treating anti-NMDAR encephalitis. B cell depletion and rebalance of Breg and Bmem might be involved in the treatment mechanism of this therapy.

1. Introduction

Autoimmune encephalitis is a newly recognized autoimmune disease of the central nervous system (Graus et al., 2016). Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is the most common type of autoimmune encephalitis (Titulaer et al., 2013). This disease is characterized by autoantibodies against NMDAR (Dalmau et al., 2008). Patients with anti-NMDAR encephalitis usually present with psychiatric symptoms, seizures, cognitive disorders, movement disorder, decreased consciousness and even life-threatening symptoms such as autonomic dysfunction and central hypoventilation (Graus et al., 2016; Titulaer et al., 2013). Currently, first-line immunotherapies for anti-NMDAR encephalitis are steroids, intravenous immunoglobulin and plasma exchange; second-line immunotherapies include rituximab, cyclophosphamide and others (Graus et al., 2016; Titulaer et al., 2013). These immunotherapies were effective in most cases (Titulaer et al., 2013). However, two problems regarding the treatment of this disease exist: treatment failure of first-line immunotherapies and relapse. Previous study reported 47% patients had poor response to first-line treatment and 25% patients needed second-line treatment (Titulaer et al., 2013). Relapse rate of anti-NMDAR encephalitis was about 12%, and patients without tumor were more likely to relapse (Titulaer et al., 2013).

A series of studies have demonstrated that autoantibodies against NMDAR were pathogenic (Hughes et al., 2010; Planaguma et al., 2015; Kreye et al., 2016). Pathological studies showed patients' brain parenchyma had B cell infiltration (Martinez-Hernandez et al., 2011). B cell-related cytokines and chemokines were also increased in patients' cerebrospinal fluid (CSF) (Leypoldt et al., 2015; Deng et al., 2017). All the above mentioned evidence supported that B cells played important roles in the pathogenesis of this disease. Thus, B cell depletion therapy was proposed as a rationale strategy to treat this disorder (Graus et al., 2016).

Rituximab is a mouse and human chimeric anti-CD20 monoclonal antibody that could specifically deplete $CD20^+$ B cells. Recently, several studies explored treatment effect of rituximab on anti-NMDAR encephalitis (Titulaer et al., 2013; Dale et al., 2014; Lee et al., 2016;

Abbreviations: NMDAR, *N*-methyl-D-aspartate receptor; CSF, Cerebrospinal fluid; CNS, Central nervous system; AEs, Adverse events; mRS, Modified Rankin Scale; CTCAE, Common Terminology Criteria for Adverse Events; Bmem, Memory B cells; Breg, Regulatory B cells

* Corresponding author at: Department of Neurology, Huashan Hospital, Fudan University, 12 Wulumuqi Zhong Road, Shanghai 200040, China.
E-mail address: xiangjchen@fudan.edu.cn (X. Chen).

[1] Bo Deng and Hai Yu contributed equally to this work.

https://doi.org/10.1016/j.jneuroim.2019.02.008
Received 16 November 2018; Received in revised form 17 February 2019; Accepted 17 February 2019

Wang et al., 2017). However, dosage of rituximab adopted in those studies were varied. Most studies referred to the dosage used in large B cell lymphoma (Gastaldi et al., 2016). This high dosage could cause some adverse events (AEs), such as infection and lymphopenia (Titulaer et al., 2013; Dale et al., 2014; Lee et al., 2016). We asked whether reduced dosage rituximab was safe and efficient in treating this disorder. If so, what was the possible mechanism of treatment?

The aim of this study was to observe efficacy and safety of reduced dosage rituximab on anti-NMDAR encephalitis and to investigate the change of patients' peripheral B cell subsets before and after treatment, thus providing possible treatment mechanism of reduced dosage rituximab in this disorder.

2. Methods

2.1. Patients

Ten patients with anti-NMDAR encephalitis who were admitted to Huashan Hospital, Fudan University during January 2015 to December 2016 were included in this retrospective study. Anti-NMDAR autoantibodies in serum and CSF from patients were tested with commercially available cell-based assay kit (Euroimmun, Lubeck, Germany). All these patients meet current diagnostic criteria of anti-NMDAR encephalitis (Graus et al., 2016). Demographic, clinical and laboratory examination data of these patients were collected. Ten age-matched healthy subjects were taken as controls. This study was approved by the Institutional Review Board of Huashan Hospital, Fudan University. All the enrolled participants or their surrogates signed informed consent prior to enrollment in the study.

2.2. Rituximab treatment

All patients had received at least one cycle of first-line immunotherapy before rituximab treatment. One cycle of immunotherapy was defined as a 5 day-course of 500–1000 mg i.v. methylprednisolone, or 2 g/kg intravenous immunoglobulin, or 4 or more sessions of plasma exchange according to previous research (Lee et al., 2016). Patients who received rituximab treatment should meet at least one of the following conditions: first-line treatment failure or relapse. According to previous study (Titulaer et al., 2013), initial first-line treatment failure was defined as no sustained improvement within 4 weeks after initiation of immunotherapy or tumor removal, and if the modified Rankin Scale (mRS) sustained higher than 3. Relapse was defined as new onset or worsening of encephalitis symptoms occurring after at least 2 months of improvement or stabilization (Titulaer et al., 2013).

Before rituximab treatment, all patients underwent latent infection screen. Two doses of rituximab (100 mg and 500 mg) were given in 2 consecutive days. This reduced dosage was based on the experience in treating neuromyelitis optica spectrum disorders in our institute (Quan et al., 2015). Dexamethasone and promethazine were used before rituximab to ameliorate infusion-related AEs. Repeated treatment with 500 mg rituximab was given when patient experienced relapse or serum autoantibody became positive again or titer increased.

2.3. Patients' follow-up, safety and outcome evaluation

All patients' mRS at initiation of rituximab treatment and the worst status were recorded. Patients were followed at regular intervals within one year after rituximab treatment (one day, 3 months, 6 months and 12 months). We evaluated patients' symptoms and mRS at each follow-up time point. Peripheral blood flow cytometry and serum autoantibody detection were assessed at the same time. After one year, patients' clinical status were recorded by telephone interview. Favorable outcome was defined as mRS $\leq$ 2 at last follow-up according to previous study (Titulaer et al., 2013). We used the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (National Institutes of Health, 2010. Accessed 1 January 2015) to record AEs.

2.4. Flow cytometry study

Peripheral blood samples from patients were obtained before rituximab treatment (baseline), and one day, 3 months, 6 months and 12 months after treatment. Blood from ten healthy individuals served as control. Expression of the B cell surface markers were detected by flow cytometry. Briefly, fresh blood samples were mixed and incubated with the following monoclonal antibodies: anti-CD19 (Molecular Probes, Frederick, MD, USA) and anti-CD27, anti-CD24, anti-CD38, anti-CD45 (all from Biolegend, San Diego, CA, USA) for 20 min. After erythrocytes were lysed, samples were centrifuged at 100*g* for 10 min. The supernatant was removed and cells were resuspended in 300 μl PBS. Then, samples were analyzed using Cytoflex (Beckman Coulter, Suzhou, China) or Epics XL (Beckman Coulter, Miami, FL, USA). Data were analyzed with Flowjo version 10 (ThreeStar, San Carlos, CA, USA). SSA, SSC and CD45 were used to discriminate lymphocytes. Proportion of $CD19^+$ B cells in lymphocytes, $CD19^+CD27^+$ memory B cells (Bmem) and $CD19^+CD24^{high}CD38^{high}$ regulatory B cells (Breg) in lymphocytes and total B cells were calculated. Proper isotypes were used as controls.

2.5. Statistical analysis

Data were presented as the mean ± SD for normal distribution data and median (ranges) for non-normal distribution data. Statistical analysis was performed with SPSS version 21 (IBM, Chicago, IL, USA) and GraphPad Prism version 6 (GraphPad Software, San Diego, CA, USA). Comparisons of normal distribution data were performed using Student's *t*-test or Student's paired *t*-test. The Wilcoxon test was used to compare non-normal distribution data. $P < 0.05$ was considered as statistically significant different.

3. Results

3.1. Patient characteristics

A total of ten patients (7 males, 3 females) were included in this study. The mean age was 24.3 ± 8.7 years. No patient had a tumor. The median mRS was 5 (range 4–5) at the worst disease status. Seven patients needed intensive care unit admission. Patients had received 3.5 (range 2–7) cycles of first-line immunotherapies before rituximab treatment. The mean interval from onset to first-line immunotherapy was 17.9 ± 12.4 days. Five patients received rituximab after first-line treatment failure. The other 5 patients received rituximab because of relapse, and their median relapse time was 1 (range 1–3). Patients' demographic, clinical and paraclinical profiles were summarized in Table 1.

3.2. Treatment efficacy

The mean disease duration at infusion of rituximab was 59.6 ± 31.5 days. Patients' median mRS was 4 (range 2–4) at the time of rituximab infusion. The mean follow-up time after rituximab treatment was 24.3 ± 8.7 months. No patient receive other second-line immunotherapies before and after rituximab treatment. Overall, all patients had good outcome, the median mRS at last follow-up was 0 (range 0–2). Eight patients achieved complete recovery (mRS = 0). Patients' mRS at different disease status were shown in Fig. 1. Eight patients only received one cycle of rituximab. One patient received the second cycle of rituximab because of relapse at 9 months. Interestingly, her serum autoantibody also became positive when she experienced relapse. After an additional rituximab infusion, her serum autoantibody became negative one year later, and symptoms improved gradually but still had memory impairment at the last follow-up time (mRS = 2). Another one patient's serum autoantibody became positive without

Table 1
Demographics and clinical characteristics of patients treated with reduced dosage rituximab.

Patient no.	Sex /onset age, y	No. of relapse	mRS at worst/ RTX infusion	ICU admission	Abnormal brain MRI	CSF cell, /μL	CSF protein, mg/L	Disease duration before first-line treatment, d	Accumulated preceding immunotherapies	Disease duration before RTX, d	Follow up time post RTX, m	Repeated RTX infusion	Adverse event	Outcome mRS
1	M/18	0	5/4	Yes	No	8	375	17	Steroids + IVIG*3	64	34.2	No	Infusion related Class I	0
2	M/33	0	5/4	Yes	No	2	545	27	Steroids + IVIG*2	69	31.4	No	None	0
3	M/17	0	5/4	Yes	No	16	303	42	Steroids + IVIG*2	88	27.2	No	None	0
4	F/17	0	5/4	Yes	Yes	106	577	5	Steroids + IVIG + PE	74	13.7	No	None	0
5	M/14	0	5/2	Yes	No	1	436	11	Steroids + IVIG + PE	122	30.4	No	None	0
6	M/14	1	4/3	No	No	6	332	22	Steroids*2	37	13.0	No	None	0
7	F/29	1	5/4	Yes	No	3	260	31	Steroids*2 + IVIG*3 + PE	63	30.7	Yes[a]	None	2
8	F/20	1	4/4	Yes	No	1	388	11	Steroids + IVIG*3	19	21.9	Yes[b]	None	0
9	M/43	2	4/4	No	No	390	1470	4	Steroids*3 + IVIG*3 + PE	31	29.4	No	None	1
10	M/23	3	4/3	No	Yes	22	194	9	Steroids*2 + IVIG*2	29	11.2	No	None	0

CSF: cerebrospinal fluid, d: day, F: female, ICU: intensive care unit, IVIG: intravenous immunoglobulin, m: month, M: male, MRI: magnetic resonance imaging, mRS: modified Rankin Scale, No.: number, PE: plasma exchange, RTX: rituximab, y: year.

[a] Patient received repeated RTX infusion because of relapse.

[b] Patient received repeated RTX infusion because serum autoantibody became positive again.

Fig. 1. Patients' mRS at the worst disease status, rituximab infusion and the last follow-up time.
The mRS score of 0–2 was regarded as good outcome. The dotted line represented the change of patient number whose mRS score was 0–2 at these three time points.mRS: modified Rankin Scale, RTX: rituximab.

relapse at 12 months and received an additional rituximab treatment. She had no relapse and serum autoantibody became negative since the second time of rituximab infusion.

3.3. Treatment safety

No severe AE was observed during the infusion and the subsequent follow-up time. Only one patient had mild infusion reaction (symptoms of sweating and sneezing) during the first day of rituximab infusion (Class I), which remitted spontaneously after a slower infusion rate (Table 1).

3.4. Change of B cell subsets in patients with anti-NMDAR encephalitis

We compared subsets of B cell between patients with anti-NMDAR encephalitis and healthy subjects. The result showed that both proportion of Breg in lymphocytes and total B cells were greatly reduced in patients compared to controls (0.1 ± 0.1% vs. 0.8 ± 0.5%, $p = 0.001$; 0.5 ± 0.6% vs. 7.1 ± 3.4%, $p < 0.001$; Fig. 2). Proportion of Bmem in lymphocytes and total B cells were higher in patients compared to controls, but did not reach statistical difference (data not shown).

3.5. Change of B cell subsets after reduced dosage rituximab treatment

The proportion of total B cells in lymphocytes decreased sharply from 13.4 ± 6.7% to 0.6 ± 0.8% one day after rituximab infusion ($p < 0.001$). This number reached to the lowest level at 3 months after treatment, which was 0.1 ± 0.1%. Thereafter, B cells started to reconstitute. The mean proportion of total B cells in lymphocytes was 3.4 ± 3.0% at 6 months. This number reached to 9.4 ± 3.7% after 12 months in patients without relapse, which did not showed significant difference with baseline level ($p = 0.243$). Proportion of B cells before and after rituximab treatment were shown in Fig. 3. Here, we described the period within 3 months after treatment as “depletion stage”, while the period after 3 months as “reconstitution stage”.

In reconstitution stage, patients' proportion of Breg in total B cells increased to 29.8 ± 18.5% at 6 months, which was significantly higher than its level before treatment ($p = 0.001$; Fig. 4). In contrast, proportion of Bmem in the reconstituted B cells reduced to 14.0 ± 18.9%, which was significantly lower than baseline level ($p = 0.017$; Fig. 4). One year after treatment, mean proportion of Breg was higher than baseline level (15.3 ± 12.1% vs. 0.5 ± 0.6%, $p = 0.006$; Fig. 4). The percentage of Bmem was still lower than baseline level (8.0 ± 4.5% vs.

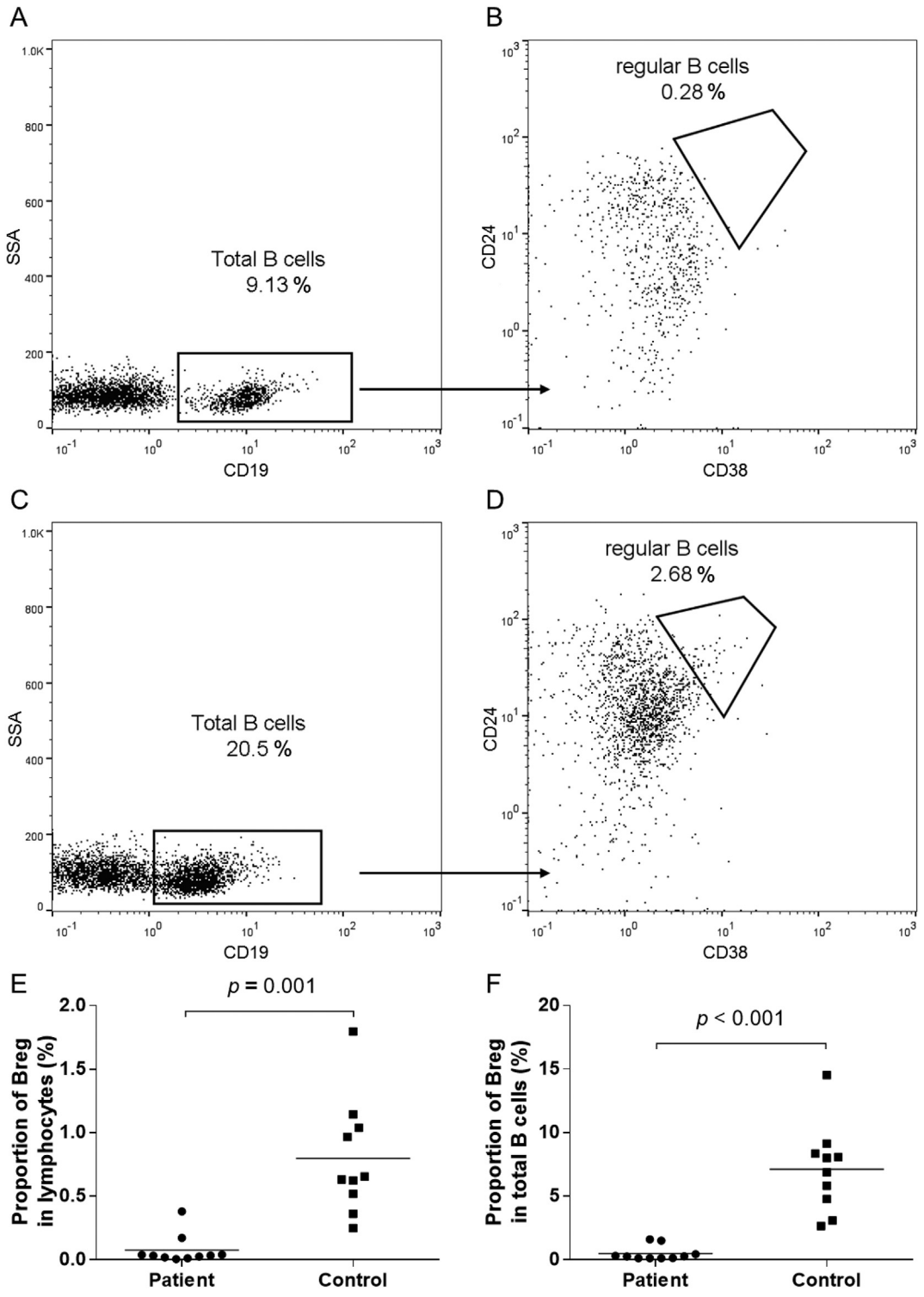

Fig. 2. Regulatory B cells in patients with anti-NMDAR encephalitis and healthy subjects. Representative data of patients' and controls' total B cells (denoted in rectangular gate) and regulatory B cells (denoted in polygon gate) were shown in A, C and B, D respectively. Patients' mean proportions of regulatory B cell subsets in lymphocytes and total B cells were both significantly reduced than that of controls (E and F).Breg: regulatory B cells.

30.2 ± 12.6%, $p < 0.001$; Fig. 4).

4. Discussion

In this study, we observed that reduced dosage rituximab was safe and effective in treating patients with anti-NMDAR encephalitis who had poor response to first-line immunotherapies or experienced relapse. In addition, we investigated the possible treatment mechanism of this dosage regimen. Our results demonstrated that reduced dosage rituximab could sustain B cells at low level within 3 months after infusion. Thereafter, Breg had a fast reconstitution, while proportion of Bmem was reduced in regenerated B cells.

Recently, several studies have observed the treatment effect of rituximab in patients with anti-NMDAR encephalitis (Dale et al., 2014;

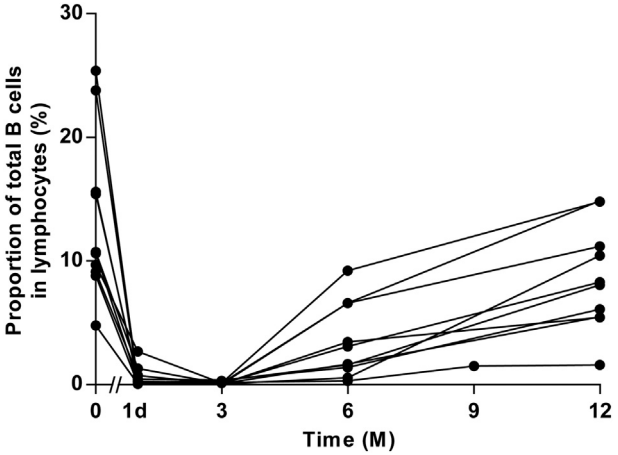

Fig. 3. Proportion of total B cells in lymphocytes before and after reduced dosage rituximab treatment. Rituximab rapidly depleted B cells one day after treatment and this effect could sustain 3 months (depletion stage). Thereafter, B cells gradually regenerated (reconstitution stage).d: day, M: month.

Lee et al., 2016; Wang et al., 2017). One study found that 32 in 39 pediatric patients had treatment benefit from rituximab (Dale et al., 2014). The other two studies, which included 27 and 10 patients respectively, found that rituximab was effective in patients with poor response to first-line immunotherapy (Lee et al., 2016; Wang et al., 2017). In our study, patients who had poor response to early first-line immunotherapies or experienced relapse were included, indicating that those patients had less possibility of spontaneous remission. The result showed all 10 patients had improved neurological status and 9 had no relapse after rituximab treatment. Therefore, our results and previous studies supported rituximab was effect in treating anti-NMDAR encephalitis.

The main drawback of rituximab is humoral immune suppression and the subsequent risk of infection (Damato et al., 2016). It should be noted that many anti-NMDAR encephalitis patients needed admission of intensive care unit and had already received immunosuppressive therapies. The probability of infection increased when rituximab was added. The protocol of 375 mg/m^2 weekly for 4 weeks was widely used in previous studies. However, infection AEs were the main concerned problem of this large dosage regimen (Jacob et al., 2008; Dale et al., 2014; Gastaldi et al., 2016). We used reduced dosage rituximab to reduce the risk of AEs, which was the most important difference between our study and previous studies. Indeed, no long term infection AEs was observed in our study. Meanwhile, reduced dosage means less medical expense. Therefore, we proposed this dosage regimen could be adopted in Chinese patients.

How to monitor the treatment effects of rituximab and when treatment should be repeated are controversial. Some studies used proportion of total B cells over 1% or Bmem over 0.5% in lymphocytes as indication of repeated infusion (Kim et al., 2013; Wang et al., 2017). Regular rituximab infusion every 6 months regardless of B cells

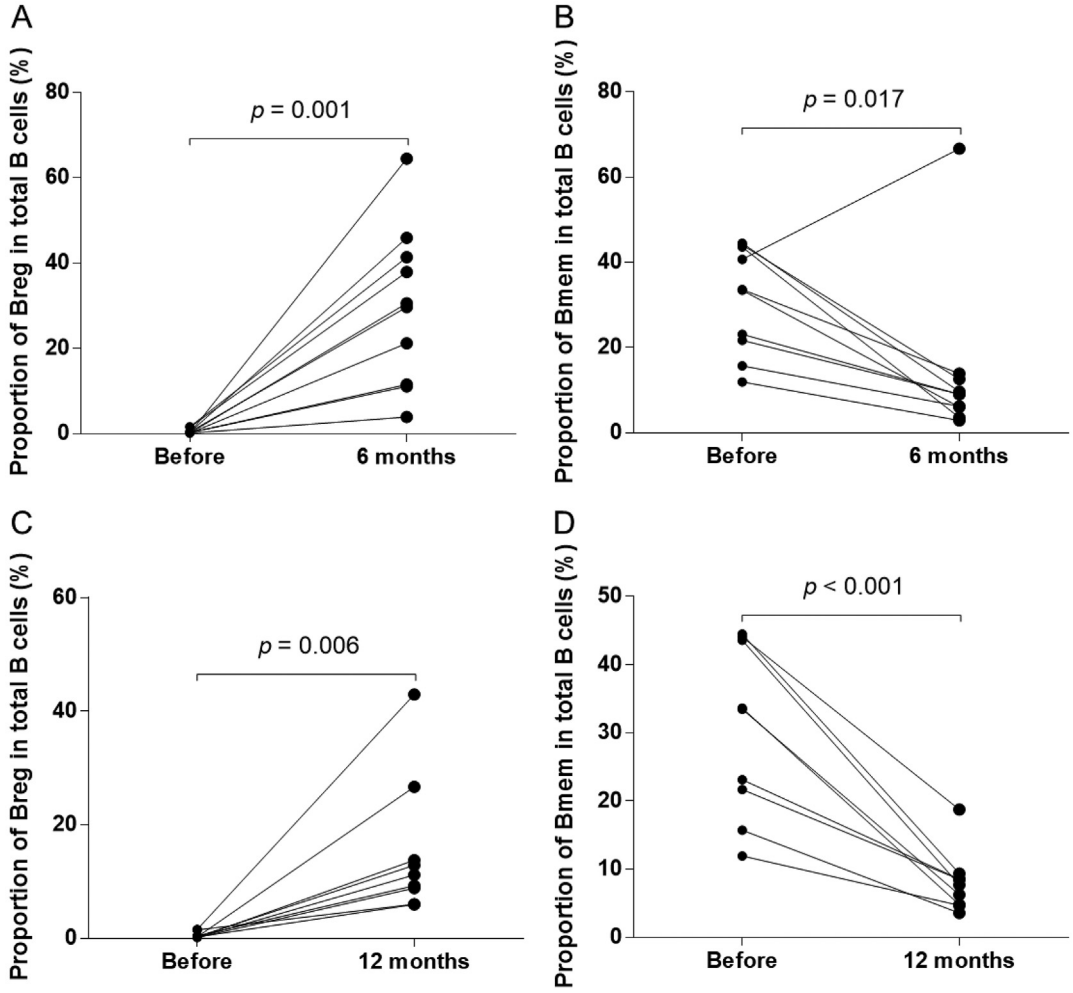

Fig. 4. Reconstitution of B cell subsets after reduced dosage rituximab treatment. In 6 and 12 months post treatment, the regenerated B cells had increased proportion of regulatory B cells (A, C) while decreased proportion of memory B cells (B, D).Breg: regulatory B cells, Bmem: memory B cells.

regeneration was also suggested (Radaelli et al., 2016). However, we found proportion of total B cells over 1% or Bmem over 0.5% in lymphocytes was an over strict indication of additional rituximab treatment in anti-NMDAR encephalitis. In fact, most patients in our study could maintain free of relapse even over one year of follow-up. Therefore, monitor of B cells regeneration might be helpful, but a more appropriate threshold of proportion of B cells which indicate additional treatment still need further studies.

Breg was a subset of B cells which had negative immune modulation effect by multiple pathways (Mauri and Blair, 2010), while Bmem was a well-known marker of inflammation (Kim et al., 2013). We found patients with anti-NMDAR encephalitis contained low proportion of Breg, indicating that the immune modulation of Breg was impaired in this disease. In addition, we discovered that low dosage rituximab had two kinds of effect on B cell population. Firstly, rituximab nearly eliminated all B cells and this effect remained as long as 3 months after infusion, which was the direct treatment effect. Secondly, in B cells reconstitution stage, Breg had a faster reconstitution than Bmem, which result in reestablishment of balance between Breg and Bmem. This effect might participate in the long term treatment efficacy. In summary, reduced dosage rituximab treatment not only ameliorated this disease by B cell depletion, but also had immunomodulation effect by induction of Breg. This mechanism was different from standard dosage treatment, whose primary goal was elimination of B cells.

We have to acknowledge the following limitations of this study. Firstly, we did not compared the treatment effect of first-line treatment add on rituximab with only first-line treatment. Therefore, residual benefits from first-line treatment or spontaneous recovery could not be completely ruled out. Secondly, the patient number was small and follow-up time was relatively short. Thirdly, we only investigated regeneration of two groups of B cells. Whether other B cell subsets participate in treatment effect and relapse in this disease deserve further studies.

Despite the above mentioned limitations, considering the rarity and lack of standard second-line treatment protocol for anti-NMDAR encephalitis, our study provided primary data about treatment effect and possible mechanism of reduced dosage rituximab in this disease. Most importantly, this dosage regimen showed good tolerability in patients. Our results encouraged further researches on long-term efficacy, safety and treatment mechanism of this therapy.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

None

Acknowledgements

We are grateful to all patients involved in the study.

References

Dale, R.C., Brilot, F., Duffy, L.V., Twilt, M., Waldman, A.T., Narula, S., Muscal, E., Deiva, K., Andersen, E., Eyre, M.R., Eleftheriou, D., Brogan, P.A., Kneen, R., Alper, G., Anlar, B., Wassmer, E., Heineman, K., Hemingway, C., Riney, C.J., Kornberg, A., Tardieu, M., Stocco, A., Banwell, B., Gorman, M.P., Benseler, S.M., Lim, M., 2014. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology. 83, 142–150.

Dalmau, J., Gleichman, A.J., Hughes, E.G., Rossi, J.E., Peng, X., Lai, M., Dessain, S.K., Rosenfeld, M.R., Balice-Gordon, R., Lynch, D.R., 2008. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 7, 1091–1098.

Damato, V., Evoli, A., Iorio, R., 2016. Efficacy and safety of rituximab therapy in neuromyelitis optica spectrum disorders: a systematic review and meta-analysis. JAMA. Neurol. 73, 1342–1348.

Deng, B., Liu, X.N., Li, X., Zhang, X., Quan, C., Chen, X.J., 2017. Raised cerebrospinal fluid BAFF and APRIL levels in anti-N-methyl-D-aspartate receptor encephalitis: correlation with clinical outcome. J. Neuroimmunol. 305, 84–91.

Gastaldi, M., Thouin, A., Vincent, A., 2016. Antibody-mediated autoimmune encephalopathies and immunotherapies. Neurother. 13, 147–162.

Graus, F., Titulaer, M.J., Balu, R., Benseler, S., Bien, C.G., Cellucci, T., Cortese, I., Dale, R.C., Gelfand, J.M., Geschwind, M., Glaser, C.A., Honnorat, J., Hoftberger, R., Iizuka, T., Irani, S.R., Lancaster, E., Leypoldt, F., Pruss, H., Rae-Grant, A., Reindl, M., Rosenfeld, M.R., Rostasy, K., Saiz, A., Venkatesan, A., Vincent, A., Wandinger, K.P., Waters, P., Dalmau, J., 2016. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 15, 391–404.

Hughes, E.G., Peng, X., Gleichman, A.J., Lai, M., Zhou, L., Tsou, R., Parsons, T.D., Lynch, D.R., Dalmau, J., Balice-Gordon, R.J., 2010. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. J. Neurosci. 30, 5866–5875.

Jacob, A., Weinshenker, B.G., Violich, I., McLinskey, N., Krupp, L., Fox, R.J., Wingerchuk, D.M., Boggild, M., Constantinescu, C.S., Miller, A., De Angelis, T., Matiello, M., Cree, B.A.C., 2008. Treatment of neuromyelitis optica with rituximab retrospective analysis of 25 patients. Arch. Neurol. 65, 1443–1448.

Kim, S.H., Huh, S.Y., Lee, S.J., Joung, A., Kim, H.J., 2013. A 5-year follow-up of rituximab treatment in patients with neuromyelitis optica spectrum disorder. JAMA. Neurol. 70, 1110–1117.

Kreye, J., Wenke, N.K., Chayka, M., Leubner, J., Murugan, R., Maier, N., Jurek, B., Ly, L.T., Brandl, D., Rost, B.R., Stumpf, A., Schulz, P., Radbruch, H., Hauser, A.E., Pache, F., Meisel, A., Harms, L., Paul, F., Dirnagl, U., Garner, C., Schmitz, D., Wardemann, H., Pruss, H., 2016. Human cerebrospinal fluid monoclonal N-methyl-D-aspartate receptor autoantibodies are sufficient for encephalitis pathogenesis. Brain. 139, 2641–2652.

Lee, W.J., Lee, S.T., Byun, J.I., Sunwoo, J.S., Kim, T.J., Lim, J.A., Moon, J., Lee, H.S., Shin, Y.W., Lee, K.J., Kim, S., Jung, K.H., Jung, K.Y., Chu, K., Lee, S.K., 2016. Rituximab treatment for autoimmune limbic encephalitis in an institutional cohort. Neurology 86, 1683–1691.

Leypoldt, F., Hoftberger, R., Titulaer, M.J., Armangue, T., Gresa-Arribas, N., Jahn, H., Rostasy, K., Schlumberger, W., Meyer, T., Wandinger, K.-P., Rosenfeld, M.R., Graus, F., Dalmau, J., 2015. Investigations on CXCL13 in anti-N-methyl-D-aspartate receptor encephalitis: a potential biomarker of treatment response. JAMA. Neurol. 72, 180–186.

Martinez-Hernandez, E., Horvath, J., Shiloh-Malawsky, Y., Sangha, N., Martinez-Lage, M., Dalmau, J., 2011. Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis. Neurology. 77, 589–593.

Mauri, C., Blair, P.A., 2010. Regulatory B cells in autoimmunity: developments and controversies. Nat. Rev. Rheumatol. 6, 636–643.

National Institutes of Health, 2010. Common Terminology Criteria for Adverse Events Version. vol. 4. pp. 03. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Planaguma, J., Leypoldt, F., Mannara, F., Gutierrez-Cuesta, J., Martin-Garcia, E., Aguilar, E., Titulaer, M.J., Petit-Pedrol, M., Jain, A., Balice-Gordon, R., Lakadamyali, M., Graus, F., Maldonado, R., Dalmau, J., 2015. Human N-methyl-D-aspartate receptor antibodies alter memory and behaviour in mice. Brain. 138, 94–109.

Quan, C., Zhang, B.J., Lu, J., Zhao, C., Cai, T., Wang, B., Yu, H., Qiao, J., Lu, C., 2015. The immune balance between memory and regulatory B cells in NMO and the changes of the balance after methylprednisolone or rituximab therapy. J. Neuroimmunol. 282, 45–53.

Radaelli, M., Moiola, L., Sangalli, F., Esposito, F., Barcella, V., Ferre, L., Rodegher, M., Colombo, B., Fazio, R., Martinelli, V., Comi, G., 2016. Neuromyelitis optica spectrum disorders: long-term safety and efficacy of rituximab in Caucasian patients. Mult. Scler. J. 22, 511–519.

Titulaer, M.J., McCracken, L., Gabilondo, I., Armangue, T., Glaser, C., Iizuka, T., Honig, L.S., Benseler, S.M., Kawachi, I., Martinez-Hernandez, E., Aguilar, E., Gresa-Arribas, N., Ryan-Florance, N., Torrents, A., Saiz, A., Rosenfeld, M.R., Balice-Gordon, R., Graus, F., Dalmau, J., 2013. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 12, 157–165.

Wang, B.J., Wang, C.J., Zeng, Z.L., Yang, Y., Guo, S.G., 2017. Lower dosages of rituximab used successfully in the treatment of anti-NMDA receptor encephalitis without tumour. J. Neurol. Sci. 377, 127–132.