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ORIGINAL ARTICLE

# Clinical outcome of autologous peripheral blood stem cell transplantation in opticospinal and conventional forms of secondary progressive multiple sclerosis in a Chinese population

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**Abstract** To evaluate clinical outcomes of autologous peripheral blood stem cell transplantation (APBCST) between opticospinal multiple sclerosis (OSMS) and conventional multiple sclerosis (CMS) during disease progressive stage in a Chinese population. Thirty-six secondary progressive MS patients, among whom 21 were with OSMS and 15 with CMS, underwent APBSCT and were followed up for an average of 48.92 months (range, 10–91 months). Peripheral blood stem cells were obtained by leukapheresis after mobilization with granulocyte colony-stimulating factor. Modified BEAM conditioning regimen (Tiniposide, melphalan, carmustin, and cytosine arabinoside) were administered. Outcomes were evaluated using the expanded disability status scale (EDSS). No maintenance treatment was administered if there was no disease progression. No treatment-related mortality occurred. Among the 36 patients, one OSMS patient dropped during the follow-up. Among the 22 relapse-free patients, 20 were with continuous neurological improvement without any relapse events, and two remained in neurologically stable states. Among the 13 relapse patients, seven had experienced of neurological relapse, but with no progression during the follow-up period; and six experienced neurological deterioration after transplantation and needed further immunosuppressant treatment. The confirmed relapse-free survival rate was 62.9% and progression-free survival rate was 83.3% after 91 months according to Kaplan and Meier survival curves. Eleven of the 20 OSMS patients (55%) and two of the 15 CMS patients (13.3%) stayed in disease active group ($P$=0.014). For the 20 OSMS patients, the overall EDSS score decreased significantly after transplantation ($P$=0.016), while visual functions had no significant improvement ($P$=0.716). Progressive OSMS has a higher relapse rate than CMS following APBSCT.

**Keywords** Autologous peripheral blood stem cell transplantation · Clinical outcome · Opticospinal multiple sclerosis · Chinese

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## Introduction

Multiple sclerosis (MS) is primarily an inflammatory disorder of the brain and spinal cord in which focal lymphocytic infiltration leads to damage of myelin and axon. Multiple involved sites results in various and non-disease-specific clinical manifestations, and brain and spinal cord magnetic resonance imaging (MRI) is helpful in the diagnosis. The cause of MS involves environmental

exposure and genetic susceptibility, and an autoimmune mechanism targeting central nervous system (CNS) myelin seems play an important role in the pathogenesis [1, 2].

In eastern Asians, the selective and severe involvement of the optic nerves and spinal cord is characteristic [3, 4]. This form is termed opticospinal MS (OSMS) and has similar features to the relapsing form of neuromyelitis optica (NMO) seen in Western populations, which is characterized by demyelination and necrosis of white and grey matter of the spinal cord, acute axonal injury, antibody deposition, and perivascular complement activation [5]. Whether OSMS in Asia is the same entity as NMO or overlaps NMO is being debated [6, 7]. OSMS has usually a high preponderance in females and a relapsing–remitting course, which accumulates severe disability resulting in disease progression [8]. Researchers have reported an NMO-IgG positivity rate of about 60% in a selected series of Japanese patients with OSMS [9–11]. The other form of MS is the conventional form (CMS) that shares similar clinical features with western type of MS [12]. Concerning the treatment options for OSMS/NMO, corticosteroids should be commenced as the first-line treatment early after attacks onset. When therapies with corticosteroids do not improve symptoms or prevent disease progression, rescue therapies with therapeutic plasma exchange or combining azathioprine should be considered [13, 14]. In addition, OSMS patients tend to experience disease relapses more frequently with the resultant more severe neurological deficit than CMS ones.

When both forms of diseases undergo progression, they continue to cause disabilities and tend to be unresponsive to the above therapies. In the last decade, autologous peripheral blood stem cell transplantation (APBSCT) has been introduced as a safe strategy to treat severe MS, with the possible mechanism of eradicating self-reactive immune cells by intensive immunosuppression, followed by full immune reconstitution of the engraftment of the autologous stem cells [15, 16]. In the current study, we aim to evaluate the clinical outcomes of APBSCT for the patients with OSMS and CMS in the disease progression stage in a Chinese population.

## Patients and methods

### Patients

From September 2001, a total of 36 Chinese patients with secondary progressive MS, diagnosed at the Department of Neurology, Xuan Wu Hospital according to the criteria of McDonald et al. [2], were included in this study. Among whom, 21 were diagnosed as OSMS, and 15 as CMS. There were 19 females in the OSMS group and eight females in the CMS group. The average age of the patients was 35.00 (20–51) years, the average disease duration (interval between diagnosis and transplantation) was 72.39 months (7–336), and the average scores of expanded disability status scale (EDSS) were 6.58 (4.5–9.0) prior to transplantation. The average follow-up time was 48.92 months (10–91). Spinal cord lesions longer than three vertebral segment lengths in MRI were considered to be longitudinally extensive spinal cord lesions (LESCL), which was observed in 63.89% patients. There were no significant differences between the OSMS and CMS groups in age, disease duration, follow-up time and EDSS score ($P>0.05$), except gender ($P=0.019$) and LESCL ($P=0.012$) (Table 1). The study has been approved by the Ethics Committee of Xuan Wu Hospital, Beijing, China. All patients provided written informed consent.

### Diagnosis

The MS patients were clinically classified into OSMS and CMS subtypes [17]. Briefly, patients who had a relapsing–remitting course and both optic nerve and spinal cord involvement without any clinical evidence of disease in either the cerebrum or the cerebellum were considered to have OSMS. Patients with minor brainstem signs, such as transient double vision and nystagmus, in addition to opticospinal involvement were included in this subtype. Patients with multiple involvement of the CNS, including the cerebrum and cerebellum, were considered to have CMS. When there was neurological deterioration at the relapse or remission stages, the patients were considered as progressive MS.

**Table 1** Clinical characteristics of the 36 Chinese patients before transplantation

| Characteristics | Total | OSMS | CMS | *P* value |
|---|---|---|---|---|
| No. of patients | 36 | 21 | 15 | – |
| Gender(F/M) | 27/9 | 19/2 | 8/7 | 0.019* |
| Age(years) | 35.00±8.48 | 34.52±9.11 | 35.67±7.75 | 0.696 |
| Disease duration (months) | 72.39±66.44 | 81.29±75.47 | 59.93±51.12 | 0.349 |
| Follow-up (months) | 48.92±25.36 | 50.43±24.47 | 46.80±27.27 | 0.678 |
| EDSS score | 6.58±1.22 | 6.45±1.34 | 6.77±1.05 | 0.455 |
| LESCL | 23 | 17 | 6 | 0.012* |
| Evaluble for outcome | 35 | 20 | 15 | – |

*OSMS* opticospinal multiple sclerosis, *CMS* conditional multiple sclerosis, *EDSS* expanded disability status scale, *LESCL* longitudinally extensive spinal cord lesions

*$P<0.05$

### Transplantation

The inclusion and exclusion criteria of the patients for APBSCT was made according to the guideline of European Group for Blood and Marrow Transplantation [15]. Mobilization regimen was subcutaneous granulocyte colony-stimulating factor (Filgrastim, Amgen, USA) at 5 μg/kg daily for 4 to 6 days. Peripheral blood stem cells were obtained by leukapheresis after mobilization. The graft were manipulated by positive selection of $CD34^+$ cells in 28 patients (16 in the OSMS group and 12 in the CMS group) with anti-CD34 antibody using the CliniMACS device (Miltenyi Biotech, Bergisch Gladbach, Germany), and the purity of $CD34^+$ cells were determined by flow cytometry, as described [18]. The reason why CD34+ cells were not purified for the other eight patients was that we had not the device until November 2002 and some patients denied because of the expense. All transplantations were performed in reverse isolation rooms equipped with high-efficiency particle air filtration systems. Modified BEAM regimen, Tiniposide (600 mg/$m^2$), melphalan (140 mg/$m^2$), carmustin (300 mg/$m^2$), and cytosine arabinoside (800 mg/$m^2$), were administered as the conditioning regimen [19]. Twenty-four hours later, the graft was transfused intravenously. No maintenance treatment was given after transplantation if no disease activity was observed.

### Assessment of bone marrow engraftment

Neutrophil engraftment was defined as an absolute neutrophil count being greater than $0.5\times10^9$/L in the first three consecutive days. Platelet engraftment was defined as a platelet count being greater than $20\times10^9$/L or $50\times10^9$/L without platelet transfusions on the first day.

### Evaluation of disease status

The disability status of the patients was scored according to the EDSS of Kurtzke. Severe optic neuritis was defined as grade 5 on Kurtzke's Visual Functional Scale [20]. Evaluation was performed prior to hematopoietic cell mobilization (baseline), 6 and 12 months after transplantation, and then every year. On each point of the follow-up, the EDSS was scored by one of the authors (Dong HQ, neurologist), and brain and spinal cord MRI was evaluated independently by two of the authors (Liu YO, radiologist, and Dong HQ), respectively.

Clinical outcomes of APBSCT are reported based on the last follow-up of each patient. According to the evaluation criteria of the European Group for Blood and Marrow Transplantation [16], we modified it and the outcomes were classified into four groups: (a) neurological improvement was defined as a decrease in the EDSS score of at least 0.5 points if the score at baseline was >5 and by ≥1 EDSS points if EDSS score at baseline was ≤5, and the neurological function improved constantly after transplantation with no any disease relapse event; (b) neurological stabilization was defined as a decrease of <0.5 EDSS points if EDSS score at baseline was >5 and by <1 EDSS points if EDSS score at baseline was ≤5 after transplantation with no disease relapse or progression; (c) relapse without progression was defined as neurological improvement had been achieved after transplantation and relapse occurred during the follow-up, while the smallest interval time between two relapse events prolonged more than 6 months compared with pre-transplantation and the EDSS score at relapse decreased ≥0 points compared with the baseline; and (d) relapse with progression was defined as a increase of ≥1 EDSS points if EDSS score at baseline was≤5 and by 0.5 EDSS points if EDSS score at baseline was >5 at any relapse event during the follow-up. A relapse was defined as an acute deterioration in neurological function that lasted for more than 24 h without intercurrent illness or another cause for neurological impairment and with objective changes on neurological examination.

The progression-free survival after APBSCT was therefore defined as the probability to be alive without neurological deterioration, compared with the baseline. These included neurological improvement, stabilization and relapse without progression. The time of the first increase of EDSS after transplantation compared with the baseline was taken as the time of disease progression. The relapse-free survival after APBSCT was defined as the probability to be alive without relapse after APBSCT. These included neurological improvement and stabilization. The time of the first increase of EDSS after transplantation compared with the last follow-up prior to the occurrence of relapse was taken as the time of disease relapse.

### Statistical analysis

Student's *t* test was used to compare groups with respect to age and EDSS score at transplantation and disease duration. Paired *t* test was used to compare the EDSS scores and visual function between pre- and post-transplantation in OSMS patients. Multiple logistic regression was performed used to assess possible factors contributing to disease relapse including age at transplantation, disease duration, EDSS score at transplantation and diagnosis group (OSMS or CMS). Survival analysis was performed to assess progressive-free survival and relapse-free survival, using Kaplan and Meier survival function. In all tests, statistical significance was set at $P<0.05$. Analysis was performed using the statistics software package SPSS 13.0.

## Results

### Stem cell collections and engraftment

The leukapheresis products from 36 patients had a median of $3.19\times10^8$ nucleated cells/kg (range, 1.8–$6.8\times10^8$/kg). After the CliniMACS procedure, the median yield of CD34+ selected cells from 28 patients of 36 patients was $2.71\times10^6$/kg (range, 0.89–$5.76\times10^6$/kg). The CD3+ T cells were depleted after CliniMACS separation at a median of $4.15\times10_{log}$ times (range, 3.8–$5.9\times10_{log}$).

Median recovery time of an absolute neutrophil >$0.5\times10^9$/L and platelet >$50\times10^9$/L was 13 days (range, 9–17 days) and 17 days (range, 12–21 days) after transplantation, respectively. No transplant related mortality occurred and the most common transplant toxicity were conditioning-related diarrhea (69.4%), neutropenic fever (52.78%), mild hepatic function damage (16.67%), tachycardia (13.89%), and transient deterioration of neurological function (13.87%).

### Neurological assessment following APBSCT

Among the 36 patients, one OSMS patient dropped during the follow-up. Twenty patients got continuous neurological improvement without any relapse events (defined as improvement) and their mean EDSS scores decreased from 6.54±1.21 at transplantation to 3.56±2.65 at last follow-up point ($P<0.0001$); two patients remained stable after transplantation and there was no neurological improvement after transplantation during the period of follow-up, although no disease relapse occurred (defined as neurological stabilization); seven patients had got neurological improvement, as well as with disease relapses after transplantation during follow-up (defined as relapse without progression); and six patients suffered relapse and neurological deterioration after transplantation (defined as relapse with progression) (Table 2). For the seven relapse patients with neurological improvement, the shortest interval time between relapse events prolonged and EDSS scores decreased at relapse compared with pre-transplantation. Thus, when the events appeared, low-dose steroid could relieve the symptoms. For the six relapse patients with neurological deterioration, the disease condition remained unchanged after transplantation and needed further immunosuppressant treatment. The confirmed relapse-free survival rate was 62.9% and progression-free survival rate was 83.3% at the 91st month according to Kaplan and Meier survival curves (Fig. 1).

### Multiple logistic regression of risk factors for disease relapse

Among the clinical parameters (age, disease duration, EDSS score at transplantation and diagnosis of OSMS or CMS) examined, only diagnosis of OSMS was significantly related to disease relapse rate (OR=10.830, $P=0.012$).

### Comparisons of disease relapse and diagnosis

Eleven out of 20 OSMS patients relapsed, and among them, six experienced disease progression and five had relapse without progression after APBSCT. Out of 15 patients with CMS, two patients relapsed without progressive (Fig. 2).

### Comparison of recovery of the EDSS score and visual function post-transplantation in OSMS patients

The overall pre- and post-transplantation EDSS score and visual function were evaluated in 20 OSMS patients. After transplantation, the overall EDSS score decreased from 6.37±1.33 to 5.73±1.63 ($P=0.016$), while visual functions had no significant improvement ($P=0.716$, Fig. 3).

## Discussion

APBSCT has been proposed as a therapeutic option for patients with severe refractory autoimmune diseases. The intense immunosuppression can be a treatment that in some severe autoimmune diseases can halt, at least for a period of time of a few years, the progression of the disease. The clinical outcomes should be associated with the eradication of the self-reactive immune cells and the restoration of the immune system that is tolerant to self-antigens. However, it is unclear whether the same clinical outcome can be achieved for OSMS and CMS forms of progressive MS following APBSCT. Our results showed that the active events are more, and more severe in OSMS than CMS patients following APBSCT.

It raises the question of whether the modified BEAM conditioning regimen could not destroy the auto-activity

**Table 2** Clinical outcomes of the evaluable patients after transplantation (*n*, %)

| Outcome | Total (*n*=35) | OSMS (*n*=20) | CMS (*n*=15) |
|---|---|---|---|
| Neurological improvement | 20 (57.14%) | 7 (35.00%) | 13 (86.67%) |
| Neurological stabilization | 2 (5.71%) | 2 (10.00%) | 0 (0.00%) |
| Relapse without progression | 7 (20.00%) | 5 (25.00%) | 2 (13.33%) |
| Relapse with progression | 6 (17.14%) | 6 (30.00%) | 0 (0.00%) |

*OSMS* opticospinal multiple sclerosis, *CMS* conditional multiple sclerosis

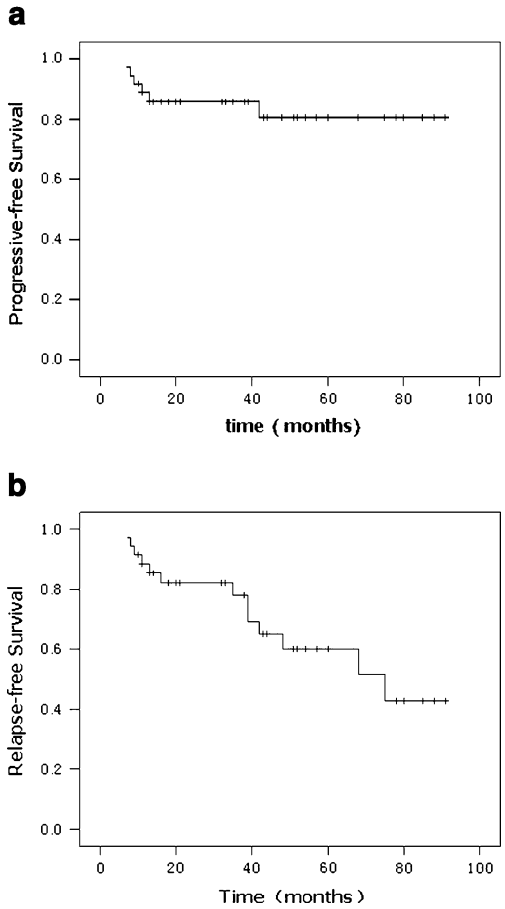


**Fig. 1** The post-transplantation survival curves of the 35 patients. **a** Progression-free survival; **b** Relapse-free survival

immune cells in those patients, or whether the OSMS patients are not appropriate candidates for APBSCT due to the different immunological mechanisms. In contrast to CMS, OSMS/NMO attacks are predominantly mediated by B cells and antibody response, instead of by T cells, and therefore, humoral immunity, including complement activation, plays an important role in their pathogenesis [5, 21].

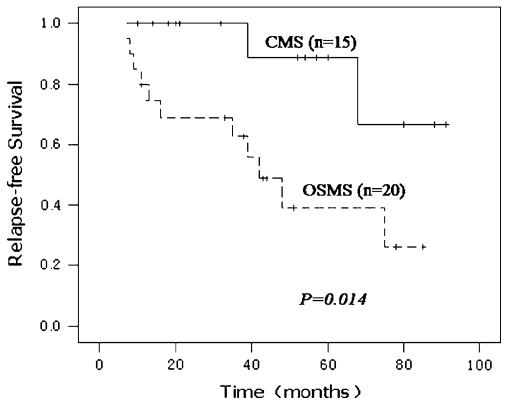


**Fig. 2** Relapse-free survival of the OSMS and CMS groups following APBSCT

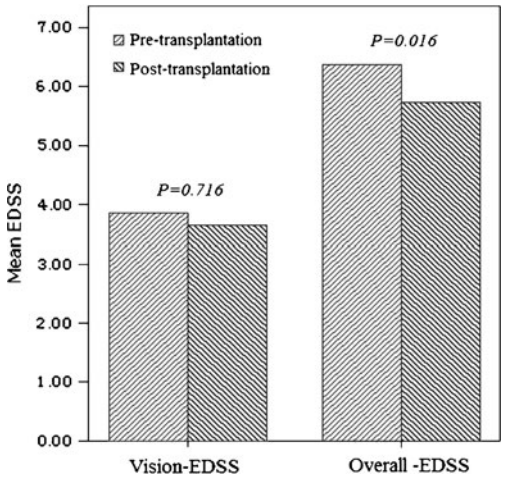


**Fig. 3** Recovery of visual functions and overall EDSS scores in 20 OSMS patients after transplantation

T cells may also play a role in the initiation and perpetuation of OSMS/NMO, but aquaporin epitopes recognized by T cells have not as yet been mapped [22]. Since APBSCT mainly eradicates the autoreactive T cells with high-dose chemotherapy, it may be less efficient for B-cell mediated autoimmune conditions. The pathology of active lesions of MNO also differs from that seen in CMS because their prominent perivascular distribution of immune complexes corresponds to the normal expression of aquaporin 4 in the endfeet of astrocytes [23]. These differences may be related to the different clinical outcomes between OSMS and CMS following APBSCT.

Among the 20 OSMS patients, even though overall EDSS score decreased following APBCST, there were minimal changes in vision function score during follow-up. A possible mechanism may be related to humoral autoimmune background or secondarily to tissue breakdown that may prolong the resolution of tissue edema, thereby contributing to further tissue destruction in NMO and OSMS patients [9]. Optic nerves are especially vulnerable to the detrimental effects of tissue edema in the optic canal, where space is tight and increased tissue pressure easily reduced blood supply. Prolongation of vasogenic edema at sites where the surrounding space is tight or vascular supply is poor may cause poor recovery of tissue damage in patients of OSMS.

Racial differences in immune responses may also play a role. Prior pathological studies showed considerable variability in the degree of inflammatory cell infiltration in Asian OSMS patients, with some showing marked perivascular inflammatory cell cuffing or heavy infiltration of T cells and neutrophils in the parenchyma of the spinal cord lesions, while others showing scant inflammatory cell infiltrates [24]. In pathological studies of Western NMO cases, eosinophil infiltration has frequently been observed

in lesion sites [5]. Such pathological differences may be related to the heterogeneity of an effectors arm in OSMS or NMO. Our results call for further investigations to clarify the role of APBSCT in clinical outcomes of OSMS and CMS. Also, it is suggested that other treatment specially targeting B cells, e.g., monoclonal antibody to CD20 (Rituximab), may be more effective to OSMS/NMO patients than APBSCT, which has been reported recently with hopeful results [25, 26].

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## References

1. Compston A, Coles A (2008) Multiple sclerosis. Lancet 372:1502–1517
2. McDonald WL, Compston A, Edan G et al (2001) Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. Ann Neurol 50:121–127
3. Kira J (2003) Multiple sclerosis in the Japanese population. Lancet Neurol 2:117–127
4. Wasay M, Khatri IA, Khealani B et al (2006) MS in Asian countries. Int MS J 13:58–65
5. Lucchinetti CF, Mandler RN, McGavern D et al (2002) A role for humoral mechanisms in the pathogenesis of Devic's nueromyelitis optica. Brain 125:1450–1461
6. Weinshenker BG, Wingerchuk DM, Nakashima I et al (2006) OSMS is NMO, but not MS: proven clinically and pathologically. Lancet Neurol 5:110–111
7. Kikuchi S, Fukazawa T (2005) "OSMS is NMO, but not MS": confirmed by NMO-IgG? Lancet Neurol 4:594–595
8. Wingerchuk DM, Pittock SJ, Lucchinetti CF et al (2007) A secondary progressive clinical course is uncommon in neuromyelitis optical. Neurology 68:603–605
9. Nakashima I, Fujihara K, Miyazawa I et al (2006) Clinical and MRI features of Japanese patients with multiple sclerosis positive for NMO-IgG. J Neurol Neurosurg Psychiatry 77:1073–1075
10. Matsuoka T, Matsushita T, Kawano Y et al (2007) Heterogeneity of aquaporin-4 autoimmunity and spinal cord lesions in multiple sclerosis in Japanese. Brain 130:1206–1223
11. Kira J (2008) Neuromyelitis optica and Asian phenotype of multiple sclerosis. Ann N Y Acad Sci 1142:58–71
12. Matsui M (2008) Classification of MS and treatment strategy. Nippon Rinsho 66:1112–1116
13. Keegan M, Pineda AA, McClelland RL, Darby CH et al (2002) Plasma exchange for severe attacks of CNS demyelination: predictors of response. Neurology 58:143–146
14. Wingerchuk DM, Weinshenker BG (2005) Neuromyelitis Optica. Curr Treat Options Neurol 7:173–182
15. Comi G, Kappos L, Clanet M et al (2000) Guidelines for autologous blood and marrow stem cell transplantation in multiple sclerosis: a consensus report written on behalf of the European group for blood and marrow transplantation and the European Charcot foundation. J Neurol 247:376–382
16. Saccardi R, Kozak T, Bocelli-Tyndall C et al (2006) Autologous stem cell transplantation for progressive multiple sclerosis: update of the European group for blood and marrow transplantation autoimmune disease working party database. Mutl Scler 12:814–823
17. Kira J, Kanai T, Nishimura Y et al (1996) Western versus Asian types of multiple sclerosis: immunogenetically and clinically distinct disorders. Ann Neurol 40:569–574
18. Beelen DW, Peceny R, Elmaagacli A et al (2000) Transplantation of highly purified HLA-identical sibling donor peripheral blood CD34+ cells without prophylactic post-transplant immunosuppression in adult patients with first chronic phase chronic myeloid leukemia: results of a phase II study. Bone Marrow Transplant 26:823–829
19. Fassas A, Anagnostopoulos A, Kazis A et al (2000) Autologous stem cell transplantation in progressive multiple sclerosis—an interim analysis of efficacy. J Clin Immunol 20:24–30
20. Kurtzke JF (1983) Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33:1444–1452
21. Graber D, Levy M, Kerr D et al (2008) Neuromyelitis optica pathogenesis and aquaporin 4. J Neuroinflammation 5:22–42
22. Nielsen S, Nagelhus EA, Amiry-Moghaddam M et al (1997) Specialized membrane domains for water transport in glial cells: high-resolution immunogold cytochemistry of aquaporin-4 in rat brain. J Neurosci 17:171–180
23. Roemer SF, Pa risi JE, Lennon VA et al (2007) Pattern-specific loss of aquaporin-4 immunoreactivity distinguishes neuromyelitis optica from multiple sclerosis. Brain 130:1194–1205
24. Ishizu T, Osoegawa M, Mei FJ et al (2005) Intrathecal activation of the IL-17/IL-8 axis in opticospinal multiple sclerosis. Brain 128:988–1002
25. Jacob A, Weinshenker BG, Violich I et al (2008) Treatment of neuromyelitis optica with Rituximab. Arch Neurol 65:1443–1448
26. Hawker K, O'Connor P, Freedman MS et al (2009) Rituximab in patients with primary progressive multiple sclerosis. Results of a randomized double-blind placebo-controlled multicenter trial. Ann Neurol 66:460–471