The aim of the present study was to evaluate the efficacy and safety of rituximab in central nervous system demyelinating disorders in the Indian context. **Methods:** We conducted a retrospective analysis of patients with MS, NMOSD, and myelin oligodendrocyte glycoprotein antibody disease (MOGAD) who were treated with rituximab at a single tertiary care centre in Mumbai. **Results:** The study enrolled 102 patients (61 MS, 37 NMOSD and 4 MOGAD) from June 2008 to January 2020. Following rituximab therapy, 96.7% of MS, 67% of NMOSD, and 50% of MOGAD patients were free of relapses. The mean annualized relapse rate reduced from 2.17 to 0 for patients with relapsing remitting MS (RRMS), from 0.8 to 0 for secondary progressive MS (SPMS), from 2.5 to 0.14 for NMOSD, and from 3.43 to 1.04 for MOGAD. The median expanded disability status scale improved significantly in RRMS patients, worsened non-significantly in the SPMS group, and remained unchanged in NMOSD and MOGAD patients. On follow-up magnetic resonance imaging, there was a significant reduction in the number of MS patients developing new contrast enhancing lesions or new T2 lesions. Adverse events (infusion reactions or severe infections) occurred in 12 patients. **Conclusion:** Rituximab is effective and safe in Indian patients with MS and NMOSD.

**Keywords:** Multiple sclerosis, myelin oligodendrocyte glycoprotein, neuromyelitis optica, neuromyelitis optica spectrum disorder, rituximab

**INTRODUCTION**

Multiple sclerosis (MS), a disease involving chronic immune dysregulation of the central nervous system (CNS), has traditionally been linked with T cell-mediated autoimmunity.[1] However, the success of B cell-depleting agents targeted against the CD 20 antigen has underscored the crucial role played by B cells in MS immunopathogenesis.[1,2]

Rituximab, a chimeric monoclonal anti-CD 20 antibody directed against B cell function,[1] was the first of these agents to demonstrate efficacy in MS patients.[3] It has been widely used in the treatment of B cell lymphoma, rheumatoid arthritis (RA), microscopic polyangiitis, and systemic lupus erythematosus (SLE).[4] It has also been used off-label to treat various immunological disorders like neuromyelitis optica spectrum disorders (NMOSD), autoimmune encephalitis, myasthenia gravis, and autoinimmune neuropathies, and myopathies.[4,5] The efficacy of rituximab in relapsing remitting MS (RRMS) and primary progressive MS (PPMS) was demonstrated in two major randomised controlled trials (RCTs).[6,7]

Ocrelizumab, a humanised version of rituximab, has recently been approved by the FDA for adult patients with relapsing MS and PPMS.[1,2] Rituximab has been used widely in MS patients over the last 8 years as an off-label therapy.[4,8] Beneficial effects with regard to slowing of disease progression and reduction of relapses have been reported. Importantly, a large observational study of MS patients from Sweden has shown no major adverse events with its prolonged administration.[8]

After rituximab’s efficacy in NMOSD was first reported by Cree et al.,[9] many subsequent studies from various countries have confirmed its safety and efficacy in reducing relapses and disability in this disorder.[10-15] The data on its use in patients with myelin oligodendrocyte glycoprotein antibody disease (MOGAD) is sparse.[16-20]

In this paper, we present our experience on the use of rituximab in MS, NMOSD, and MOGAD patients from a single tertiary care centre in Mumbai.

**METHODS**

We conducted a retrospective analysis of patients with CNS demyelinating disorders who presented to a single tertiary care neurology clinic in Mumbai from June 2008 to January 2020.
Patients with MS, NMOSD, and MOGAD who were treated with rituximab injection were included in the study. The diagnosis of MS and NMOSD was based on the 2010 revised McDonald criteria [21] and the modified Wingerchuk criteria [22], respectively. MOGAD was diagnosed on the basis of clinical features, imaging findings and a positive MOG antibody test (cell-based assay) [10]. All patients who received rituximab for at least 1 year prior to study initiation were included. Exclusion criteria were rituximab treatment duration of less than 1 year, other co-existing autoimmune illness like Sjogren syndrome or SLE, and lack of regular follow-up after therapy. Data was collected from the IMED database of MS Base registry (single centre) and from hospital admission records. It included demographic details, clinical information of the number, site, severity and timing of attacks prior to and after rituximab treatment; previous therapies, reasons for switching to rituximab, details of rituximab treatment and its side effects. The points taken into consideration for initiating or switching to rituximab therapy were severe attack at onset, frequent attacks despite first-line and/or second-line drugs, early progression into secondary progressive phase, PPMS subtype, imaging features [multiple contrast enhancing lesions (CEls), occurrence of new CELs despite first-line and/or second-line drugs], and rapid decline in the expanded disability status scale (EDSS) despite therapy.

The protocol at our centre was as follows: Rituximab was administered as a slow intravenous infusion of two doses of 1000 mg each, at an interval of 2 weeks. The patients were premedicated with intravenous hydrocortisone, pheniramine, and oral acetaminophen. This cycle was repeated every 6 months. A relapse was defined as an objective worsening or the appearance of a new neurological symptom, lasting at least 24 hours. Acute relapses were treated with high-dose intravenous methylprednisolone. If severe disability persisted, plasma exchange or intravenous immunoglobulin (IVIg) was given.

Follow up clinical examinations were performed every 6 months. The magnetic resonance imaging (MRI) scans were repeated every 6 to 12 months, or earlier, if a new attack occurred. The outcome variables were annualized relapse rate (ARR) and disease progression using the EDSS. They were assessed either at the conclusion of rituximab therapy (in those who discontinued it) or at the last follow-up. Disability progression was defined as an increase from baseline of at least 1.5 EDSS points if baseline EDSS score was 0, 1.0 point if it was between 0.5 and 5.0, and 0.5 point if EDSS ≥5.5. Also considered were the number of CELs and T2 lesions on MRI scans prior to and after therapy. Data of adverse events occurring over the study duration were also obtained.

The main efficacy outcomes were (a) proportion of patients free from relapses, (b) change in ARR pre- and post- therapy, (c) change in EDSS pre- and post- therapy, and (d) proportion of patients free from new CELs and/or new T2 lesions on MRI.

Safety was assessed on the basis of the number of patients with drug infusion reactions (minor and major), severe infections, autoimmune disorders and malignancies. Minor infections were not included as they tended to get missed in retrospective records. Deaths, if any, were noted.

**Statistical analysis**

Normally distributed variables were presented as mean (standard deviation, SD) and parametric variables as median (range). The Mann-Whitney U test was used to compare mean ARR and median EDSS prior to and after therapy between various subgroups of patients. Chi-square test was used to analyse the proportion of patients free of new CELs and T2 lesions on follow-up imaging while on rituximab therapy. Wilcoxin signed-rank test was used to compare the median EDSS in various disease subgroups with regard to treatment naïve patients or previously treated patients who received first-line and/or second-line drugs.

**Results**

We screened 1540 records over a period of 11.5 years (June 2008 to Jan 2020). These included patients with various CNS demyelinating disorders, including MS, NMOSD, MOGAD, acute disseminated encephalomyelitis, recurrent or solitary tumefactive demyelination and mimics. A total of 1442 patients with MS, NMOSD, and MOGAD were identified (MS - 1286 patients, NMOSD - 138 patients, and MOGAD - 18 patients). Of the 110 patients who received injection rituximab, 102 patients (73 females, 29 males; F: M = 2.52:1) fulfilling the inclusion criteria were enrolled in the study [Figure 1]. Four patients with rituximab therapy duration of less than 1 year and 4 patients who were lost to follow up were excluded.

**Patients with MS**

**Baseline characteristics:** There were 61 MS patients (41 females, 20 males; F:M = 2:1) who received rituximab. They were further sub-classified into those with RRMS, secondary progressive MS (SPMS), PPMS, and progressive relapsing MS (PRMS) [Table 1]. The baseline demographics, ARR, EDSS, and radiological features are presented in Tables 2 and 3, and Figure 2. There were 21 patients (34.4%) who were treatment naïve.
Of the remainder, 33 patients were switched from first-line drugs (interferons, glatiramer acetate, dimethyl fumarate, and teriflunomide) and 7 from second-line drugs (natalizumab and mitoxantrone). Table 2 gives the reasons for switching to rituximab in these patients. The average duration of treatment with first-line drugs was 2.18 years (range: 2 months to 8.1 years) and with second-line drugs, it was 3 years (range: 2 months to 7.1 years), prior to starting rituximab.

The mean age at initiation of rituximab therapy was 35.15 (± 11.7) years and the mean disease duration at the start of therapy was 6.53 (± 5.6) years. The mean duration of therapy was 2.36 years (range: 1 to 11.4 years). Thirty patients had a treatment duration of more than 2 years. The mean follow-up was 2.89 (± 2.28) years, with the longest follow-up being 11.4 years. The median number of cycles of rituximab infusion was 3 (range: 2–16).

**Efficacy data:** The proportion of MS patients free of relapses was 96.7% (59/61) over a mean follow-up of 2.89 years. None of the 20 RRMS and 4 PRMS patients suffered a relapse while on rituximab therapy. Only 2 of the 32 SPMS patients suffered a total of 5 relapses: patient 1 at 6 months and patient 2 at 4 months and subsequently 3 relapses over 18 months.

The mean ARR improved from 2.17 at baseline to 0 for RRMS, from 0.8 to 0.1 for SPMS, and from 0.56 to 0 for PRMS [see Figure 2]. The ARR improvement in the RRMS subgroup was statistically significant both in the treatment-naïve group (p = 0.0017) and in the group previously on first-line drugs (p < 0.0001).

The median EDSS also significantly improved by 2.5 points in the RRMS group (p = 0.012), but worsened by 1 point

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**Table 1: Multiple sclerosis (MS) subtypes in 61 patients**

| RRMS | SPMS | PPMS | PRMS | Total |
|------|------|------|------|-------|
| Male | 6    | 11   | 2    | 1     | 20    |
| Female | 14  | 21   | 3    | 3     | 41    |
| Total | 20   | 32   | 5    | 4     | 61    |

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**Table 2: Demographics and therapy details including rituximab (RTX) therapy of study patients**

| RRMS | SPMS | PPMS | PRMS | NMOSD |
|------|------|------|------|-------|
| Baseline characteristics |
| Total number | 20 | 32 | 5 | 4 | 37 |
| Female, n (%) | 14 (70) | 21 (65.6) | 3 (60) | 3 (75) | 31 (83.7) |
| Age at onset (n) |
| <20 years | 5 | 6 | 1 | 0 | 6 |
| 20-39 years | 14 | 20 | 4 | 3 | 18 |
| 40-59 years | 1 | 6 | 0 | 1 | 10 |
| >60 years | 0 | 0 | 0 | 0 | 3 |
| Treatments received: |
| Treatment-naïve, n (%) | 8 (40) | 9 (28.1) | 2 (40) | 2 (50) | 25 (67.5) |
| No. of DMTs prior to RTX, median (range) | 1 (0-3) | 1 (0-2) | 1 (1) | 1 (1) | 1 (0-2) |
| Last DMT before RTX |
| First-line drugs, n (%) |
| Interferon | 9 (45) | 16 (50) | 2 (40) | 2 (50) | 0 (0) |
| Glatiramer acetate | 1 (5) | 1 (3.1) | 0 (0) | 0 (0) | 0 (0) |
| Dimethyl fumarate Teriflunomide | 3 (15) | 6 (18.7) | 0 (0) | 1 (25) | 0 (0) |
| Second-line drugs, n (%) | 1 (5) | 3 (9.3) | 20 (0) | 0 (0) | 0 (0) |
| Natalizumab | 0 (0) | 1 (3.1) | 0 (0) | 1 (25) | 0 (0) |
| Mitoxantrone | 0 (0) | 5 (15.7) | 0 (0) | 0 (0) | 1 (2.7) |
| Others (azathioprine, mycophenolate mofetil) | | | | | AZA-10 (27) MMF-5 (13.5) |
| Reason for changing to RTX, n (%) |
| Disease activity | 17/20 (85) | 28/32 (87.5) | 4/5 (80) | 4/4 (100) | 15/37 (40.5) |
| JC virus positivity | 0/20 (0) | 0/32 (0) | 1/5 (5) | 0/4 (0) | 0/37 (0) |
| No. of RTX infusion cycles, median (range) | 3 (2-16) | 3 (2-12) | 2 (2-3) | 4 (2-6) | 5 (2-18) |
in the SPMS group ($p = 0.34$), and worsened by 1.5 points each in the PRMS and PPMS groups. This worsening was not statistically significant. Despite this EDSS deterioration in SPMS patients as a group, it is interesting to note that in 25.8% of them, the EDSS remained the same, and in 29%, the EDSS scores improved by 0.5 to 3 points after 1 year of rituximab treatment. The median EDSS improved significantly in treatment naïve MS patients ($p = 0.0153$), as compared to those who had received first- or second-line drugs while on rituximab therapy [Table 4].

The MRI scan of the brain and spinal cord was performed at baseline, prior to rituximab infusion in all patients. A follow-up MRI scan was performed in 45 patients (73.8%) at a mean interval of 8 months after initiation of therapy. Of the 61 MS patients, 24 (12 RRMS, 11 SPMS, 1 PRMS) had a total of 95 CELs at baseline. On follow-up imaging, only 3 (1 RRMS and 2 SPMS) patients developed a total of 5 new CELs. Thus, 93.3% of patients had no new CELs ($p = 0.0001$) on rituximab therapy. New T2 lesions were seen in 19/45 patients. The rest showed stable plaque burden on T2/FLAIR images. This meant that the latter group (57.8%) of MS patients were free of new T2 lesions ($p < 0.0001$). In the PPMS patient group, 2 of 5 patients developed new T2 lesions, while none showed new CELs. None of the PRMS patients developed new CELs while on rituximab. Subsequent MRI scans in the following years also did not show any new CELs or increase in lesion load in any MS patient.

**Drug retention rate:** The drug retention rate was 72.1% (44 of 61 patients) over a mean duration of 2.89 years (range: 1 to 11.4 years). Seventeen patients discontinued treatment due to: disease progression (11 patients), infection (1 patient), cost of therapy (2 patients), and stable disease with a shift to first-line disease modifying therapy (DMT) (3 patients). The disease progression in the 11 patients occurred at a mean duration of 2.5 ($\pm$ 0.9) years.

### Table 3: Clinical and radiological details of study patients pre- and post-rituximab (RTX) therapy

| Parameters at RTX start: | RRMS ($n=20$) | SPMS ($n=32$) | PPMS ($n=5$) | PRMS ($n=4$) | NMOSD ($n=37$) |
|--------------------------|--------------|---------------|--------------|--------------|----------------|
| a) Mean age (y)          | 28.6±8.1     | 38.7±11.6     | 30±8         | 31.7±9.3     | 40.8±14.9      |
| b) Disease duration [y, mean] | 3.2±3.6     | 8.8±7.6       | 6±3          | 11.8±8.8     | 5.32±4.32      |
| c) EDSS, median (range)  | 2.5 (0-6)    | 4.5 (2-7)     | 4.5 (4-6)    | 4 (4-6.5)    | 2 (1-6.5)      |
| d) ARR, Mean (± SD)      | 2.17±2.8     | 0.8±1         | 0            | 0.56±0.35    | 2.5±3.65       |
| e) CELs at baseline, n (%) | 12 (60)      | 11 (34.3)     | 0 (0)        | 1 (25)       | 17 (40.5)      |

| Parameters post RTX therapy: | RRMS ($n=20$) | SPMS ($n=32$) | PPMS ($n=5$) | PRMS ($n=4$) | NMOSD ($n=37$) |
|-------------------------------|--------------|---------------|--------------|--------------|----------------|
| a) Follow-up time since RTX start, y, median (range) | 2.1 (1-8.6) | 2.14 (1-11.5) | 1.2 (1-3) | 3.03 (1-7.9) | 4.84 (1-10.7) |
| b) EDSS, median (range)       | 0 (0-6) (p=0.012) | 5.5 (0-7) (p=0.34) | 6 (4.5-6) | 5.5 (2-7) (p=0.103) | 2 (0-6.5) (p=0.103) |
| c) ARR Mean (± SD)            | 0 (p<0.0001) | 0.1±0.45 (p=0.0001) | 0 | 0 (p=0.24) | 0.14±0.32 (p=0.0001) |
| d) CELs after RTX, n (%)      | 1 (4.5) | 2 (6) | 0 (0) | 0 (0) | 0 (0) |

### Table 4: EDSS in treatment naïve versus previously treated MS and NMOSD patients

| Treatment Naïve | RRMS ($n=17$) | SPMS ($n=28$) | PRMS ($n=4$) | NMOSD ($n=25$) |
|-----------------|--------------|---------------|--------------|----------------|
| All patients with MS (including RRMS, SPMS, PPMS, PRMS) ($n=41$) * | 4 | 2.5 |
| Patients with RRMS ($n=8$) | 3 | 0 |
| Patients with SPMS ($n=9$) | 4.5 | 5.5 |
| Patients with PRMS ($n=4$) | 3 | 4 |

### Pre-Rituximab

| Median EDSS | Post-rituximab |
|-------------|----------------|
| 4 | 2.5 |
| 3 | 0 |
| 4.5 | 5.5 |
| 3 | 4 |

### Previously treated

| Median EDSS | Post-rituximab |
|-------------|----------------|
| 4 | 5 |
| 1 | 1 |
| 4.5 | 4.5 |
| 3 | 2 |

* $P=0.015$ (significant), † $P=0.024$ (Significant)
Patients with neuromyelitis optica (NMOSD)

Baseline characteristics: There were 37 patients with NMOSD who received rituximab (31 females, 6 males; F: M = 5.2:1). Thirteen of these patients had been reported earlier by our group (Jade et al.)[23] The baseline demographics, ARR, EDSS, and radiological features are presented in Tables 2 and 3, and Figure 2. Five patients presented with spinal cord and optic nerve involvement; while isolated myelitis occurred in 16 patients (13 with longitudinally extensive transverse myelitis and 3 with recurrent myelitis). Of the 11 patients with isolated optic neuritis, 10 had unilateral optic nerve involvement (single attack in 7, recurrent attacks in 3) and 1 had bilateral optic neuritis. In addition, 4 patients presented with an acute area postrema syndrome, while the remaining patient had an acute brainstem disturbance.

Twenty-five patients (67.5%) were treatment naïve, while the remainder were on long-term immunosuppressive drugs like prednisolone, azathioprine, or mycophenolate mofetil. The mean age at commencement of rituximab therapy was 40.8 (±14.9) years, while the mean disease duration prior to rituximab was 5.32 (±4.36) years.

The mean duration of rituximab therapy was 4.84 years (range: 1 to 10.7 years). Thirty-two patients (86.5%) were on it for more than 2 years, with 19 of them (51.3%) having a duration greater than 5 years. The median number of cycles of rituximab infusions was 5 (range: 2–18).

Clinical efficacy data: Of the 37 NMOSD patients, 25 (67.6%) were free of relapses over a mean period of 4.84 years. The mean ARR improved significantly from a baseline mean of 2.5 to 0.14 on rituximab therapy (p < 0.0001). The median EDSS remained unchanged at 2 during the study period [please see Table 3 and Figure 2]. Despite this unchanged median EDSS in the NMOSD patients as a group, 16 (43.2%) of them were free of disability at 1 year of treatment or later. The EDSS worsened by 0.5 to 2 points in 12 patients, and remained unchanged in the remainder. In the NMOSD subgroup, those who were switched to rituximab from prior treatment, showed significant improvement in median EDSS (p = 0.0024), compared to drug naïve patients [Table 4].

Drug retention rate: The drug retention rate in NMOSD patients was 78.3% (29/37 patients) over a mean duration of 4.84 years, the longest follow-up being 10.4 years. Of the 8 patients who discontinued the drug, 5 stopped treatment due to stable disease, while the remaining 3 discontinued therapy due to cost considerations.

Patients with MOGAD

Baseline characteristics: Four patients (1 female, 3 males) with MOGAD received rituximab. Acute myelitis followed by relapsing optic neuritis occurred in 2 of them, while recurrent optic neuritis was the presentation in 1 patient and recurrent optic neuritis followed by myelitis was seen in the remaining patient. The mean age and disease duration at the initiation of rituximab therapy were 35.5 years and 9.4 years respectively. The mean duration of therapy was 1.6 years. The median number of rituximab infusion cycles was 3 (range: 2–4).

Clinical efficacy data: Two out of 4 patients had no relapses after rituximab therapy over a mean duration of 1.6 years. The remaining 2 patients experienced 9 relapses between them (8 with optic neuritis and 1 with meningoencephalitis). These relapses occurred despite being on an additional immunosuppressant drug- azathioprine in 1 patient and mycophenolate mofetil in the other. One patient required plasma exchange during a severe relapse while on rituximab therapy. The mean ARR improved from 3.43 to 1.04. The median EDSS remained unchanged at 2 during the study period.

Drug retention rate: All 4 patients continued to be on rituximab therapy.

Adverse reactions

Of the 102 patients enrolled in the study, 12 had an adverse event after rituximab therapy. Table 5 lists the details of the adverse reactions. There were drug infusion reactions in 8, infections in 2, allergic rhinosinusitis in 1 and pancytopenia with mucositis in 1 patient. No patient developed an autoimmune disorder or malignancy. Progressive multifocal leukoencephalopathy (PML) was not seen, despite JC virus positivity in 1 MS patient. No deaths were recorded during the study duration.

Discussion

The purpose of the present study was to evaluate the efficacy and safety of rituximab in CNS demyelinating disorders in the Indian context. Rituximab has been efficacious and used widely in patients with MS and NMOSD. A large retrospective study

| Table 5: Adverse reactions (n=12)                          | Number of patients |
|-----------------------------------------------------------|--------------------|
| Adverse reaction                                          |                    |
| Drug Infusion Reactions                                   | 8                  |
| Minor (at first infusion)                                 | 7 (2 MS, 5 NMOSD)  |
| Major*                                                    | 1 (NMOSD; cardiotoxicity with ST-T changes) |
| Infections (Herpes zoster)                                | 2 (1 NMOSD and 1 MOGAD) |
| Oral mucositis with pancytopenia †                        | 1 (MS)             |
| Allergic rhinosinusitis †                                  | 1 (NMOSD)          |

*: Occurred at second infusion, necessitated its discontinuation. Subsequent cycles were uneventful. †: Occurred after 4 months of the second infusion cycle. ‡: Occurred after 4 infusion cycles, did not require discontinuation of drug.
of 882 patients across 3 MS centres in Sweden.[8] underlined the robust efficacy of rituximab. The authors reported lower relapse rates in RRMS patients on rituximab therapy than in those who were on first- or second-line DMT.[9] In the Indian context, Mathew et al.[24] reported their rituximab experience in 80 MS patients across 3 centres in South India. In their group of 58 RRMS patients, they found a significant improvement in ARR (p < 0.05), with 97% of them having no relapses during a 1 year follow-up period after rituximab therapy. The present study yielded similar results. In our cohort of all MS patients, 96.7% of them were relapse free at a mean follow up duration of 2.89 years. Not a single RRMS or PRMS patient suffered a relapse during the entire study period. A significant reduction of ARR in the RRMS and SPMS subgroups was observed.

The disease activity in MS is also determined by the appearance of CELs and increase in plaque burden on MRI scans.[8] The Swedish study found that the proportion of patients with CELs dropped from 26.2% to 4.6% on rituximab therapy, with new CELs occurring only during the initial 6 months after the start of therapy.[8] In the South Indian cohort (Mathew et al.),[24] CELs were seen in 20% of RRMS patients and in 10% of PPMS patients at baseline. After 1 year of treatment, no new enhancing lesions were observed in both groups. The number of MS patients free of new CELs was also significantly lower in the present study. Most of the newly detected CELs appeared early (within 4 months) after rituximab initiation. The present study also found a significant decrease in the number of MS patients with new T2 lesions. The OLYMPUS trial had also reported a lower T2 plaque burden in rituximab treated PPMS patients. Benefits were more likely to occur in young patients with CELs on imaging.[7] None of the 5 PPMS patients in the present study had CELs at baseline or on therapy. New T2 lesions occurred in 2 of them.

Disease progression with disability is measured by change in the EDSS score. In the South Indian study (Mathew et al.),[24] the EDSS score improved by 0.5–2.0 in 68 (85%) patients (58 RRMS, 6 PPMS, 4 SPMS). It was unchanged in 10 (12.5%) patients (9 SPMS and 1 PPMS), and worsened in 2 patients (both SPMS). In the present study, the median EDSS score also improved significantly in the RRMS subgroup. Although there was a non-significant worsening of the median EDSS in the SPMS, PPMS, and PRMS groups as a whole, 54.8% of SPMS patients showed either improved or unchanged EDSS scores after rituximab therapy. Those who improved were younger and received rituximab early in their disease course.

With regard to NMOSD, a recent meta-analysis of 26 studies comprising 577 patients concluded that therapy with rituximab caused a significant reduction in mean ARR (−1.56 reduction from baseline). A relapse free state was observed in 62.9% of these patients.[15] The present study of 37 NMOSD patients (inclusive of 13 patients reported earlier by Jade et al.[23]) also found that rituximab resulted in a significant reduction in the mean ARR.

In the meta-analysis of NMOSD patients mentioned earlier, the mean EDSS score reduced (−1.16 reduction from baseline) after rituximab therapy.[16] Although the median EDSS remained unchanged in our NMOSD patients as a group, 16 (43.2%) of them were free of disability during the study period. In those whose EDSS worsened or remained unchanged, the initial severity and frequency of attacks and delay in initiating treatment may have contributed to the relatively poor clinical outcome.

As MOGAD is still an evolving entity, information on rituximab use in these patients is also limited. In a cohort of 59 MOGAD patients from a multicentre study (Ramanathan et al.),[19] only 6 patients were treated with rituximab as a long-term maintenance therapy. Treatment response occurred in 5 of the 6 patients, with 2 of them becoming completely relapse free after a single infusion cycle. From Western India, 4 out of 31 MOGAD patients were shifted to rituximab therapy in view of severe disease.[25] The mean ARR reduced from 1.08 to 0.43 on rituximab with no further relapses on follow up.[25] In the present study, 4 MOGAD patients received rituximab as a second or third-line agent. As mentioned earlier, 2 of them were free of relapses over a period of 2.5 years after initiation of therapy. The remaining 2 patients continued to have relapses despite receiving rituximab combined with azathioprine or mycophenolate mofetil. A relatively small number of MOGAD patients had received rituximab in all of these studies. Even with these small numbers, rituximab appeared promising as a therapeutic option. Well-designed large trials of this drug in MOGAD are needed to confirm its efficacy in this group.

At what time period after starting rituximab are patients with CNS demyelinating disorders likely to experience a relapse? Literature reviews suggest that most relapses occur after the first infusion with a mean interval of 4–6 months between therapy initiation and clinical relapse.[8,15,24,26,27] In the present study, too, those patients who relapsed (10 out of 16), did so within 6 months of the infusion. A possible explanation for this is that B cells tend to repopulate towards the end of the 6-month cycle. In NMOSD patients, the release of a B-cell activating factor may be an additional cause for relapses.[26]

Rituximab is generally reported to be safe and well-tolerated in patients with CNS demyelinating disorders likely to experience a relapse? Literature reviews suggest that most relapses occur after the first infusion with a mean interval of 4–6 months between therapy initiation and clinical relapse.[8,15,24,26,27] In the present study, too, those patients who relapsed (10 out of 16), did so within 6 months of the infusion. A possible explanation for this is that B cells tend to repopulate towards the end of the 6-month cycle. In NMOSD patients, the release of a B-cell activating factor may be an additional cause for relapses.[26]
mild to moderate infusion reactions were seen in 6 patients. Only 1 patient had a severe reaction. Similar to the above findings, the present study reported infusion related reactions in only 7.8% of all patients. No anaphylactic reaction was seen in any of our patients. In patients with malignancies, the reported cardiotoxic side effects of rituximab included cardiac arrhythmias, myocardial infarction, ventricular tachycardia, and possible Takotsubo cardiomyopathy. In the present study, reversible cardiotoxicity with ECG changes occurred in only 1 NMO patient. It did not recur on subsequent infusions. In order to minimize the risk of infusion reactions, it is important to follow an established protocol, especially with regard to the slow rate of infusion. Mathew et al. found fewer infusion reactions when they used a very slow infusion rate protocol lasting 9 to 10 hours for the first infusion and 6 hours for subsequent infusions.

The incidence of serious infections reported in RA patients receiving rituximab was 3.94/100 patient years. The most common was herpes zoster (9/1000 patient years). The dreaded PML occurred rarely (0.2–1/100,000 patient years). Hypogammaglobulinemia was the other notable side-effect (3.5% to 22.4%). Serious infections were noted in 4.5% patients in the OLYMPUS trial and 2.9% in the HERMES trial. In the cohort of 882 patients reported by Salzer et al., infections occurred in 76 patients and malignancies in 3. There were 4 deaths in their study. Mathew et al. however, did not find any serious infections, autoimmune disorders, or malignancies in their MS cohort over a period of 4 years. There was only one death of unclear cause in their patients. In the South Indian cohort (Netravathi et al.), out of the 14 NMO patients who received rituximab, only 1 developed pancytopenia and severe chest infection. The present study reported infections in only 2 patients in the NMOSD and MOGAD groups. One patient had allergic rhinosinusitis which improved with anti-allergic drugs. He did not discontinue rituximab therapy. The patient with MOGAD who developed herpes zoster was additionally on low dose oral steroids and azathioprine for 15 months before developing the infection. No cases of PML or deaths were reported in the present study. So far, no case of PML has been reported with rituximab therapy in CNS demyelinating disorders.

There were some limitations of this study. This was a retrospective study. The assessment of disability was based on the EDSS score without study of other measures like brain atrophy on the MRI scans. A longer follow-up of patients could have brought out more potential side effects of rituximab. The number of MOGAD patients was also too small to draw definite conclusions in this sub-group.

Conclusions
The present study supports the use of rituximab as an effective and safe therapeutic option for CNS demyelinating disorders in Indian patients. As cost constraints were an issue with some patients leading to “dropouts”, it would be worth trying lower doses of rituximab after the initial dosing in future prospective trials.

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Conflicts of interest
There are no conflicts of interest.

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