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**Rituximab in neuromyelitis optica: A review of literature**

Wong E *et al.* Rituximab in neuromyelitis optica

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**Abstract**

Neuromyelitis optica spectrum disorders, or Neuromyelitis optica (NMO), is an autoimmune disease of the central nervous system that must be distinguished from multiple sclerosis. Therapeutic approaches to relapse prevention in NMO include immunosupressants and monoclonal antibodies. Rituximab, an antibody that targets CD20 antigen expressed on the surface of pre-B, mature B-lymphocytes and a small subset of T-lymphocytes, has been the most widely used monoclonal for the treatment of NMO. In this review, we aim to summarize global experience with Rituximab in NMO. We identified 13 observational studies that involved a total of 209 NMO patients treated with Rituximab. Majority of Rituximab-treated patients evidenced stabilization or improvements in their disability scores compared to pre-treatment period and 66% of patients remained relapse-free during treatment period. Monitoring Rituximab treatment response with CD19+ or CD27+ cell counts appears to improve treatment outcomes. We offer clinical pointers on Rituximab use for NMO based on the literature and authors’ experience, and pose questions that would need to be addressed in future studies.

**Key words:** Neuromyelitis optica; Rituximab; Longitudinally extensive transverse myelitis; Optic neuritis; CD19+; CD27+

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**Core tip:** Relapsing Neuromyelitis optica (NMO) is an autoimmune disorder of the central nervous system that often results in severe disability and death if untreated. Rituximab, an anti-CD20 monoclonal antibody, appears to be a promising treatment option for NMO. In this review, we summarize the results of 13 observational studies that assessed efficacy of Rituximab in Neuromyelitis Optica. On average, 66% of patients remained relapse-free during treatment period and in the majority of patients disability scores have stabilized or improved. Monitoring response to Rituximab with CD19+ and CD 27+ cell counts appears to improve outcomes.

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**INTRODUCTION**

Neuromyelitis optica spectrum disorders, hereafter referred to as “Neuromyelitis optica (NMO)”, is an autoimmune disease of the central nervous system (CNS)[1]. Diagnostic criteria for NMO have undergone several revisions in recent years, but core clinical syndromes - longitudinally extensive transverse myelitis (LETM) and optic neuritis (ON), have been retained. The most recent iteration of the diagnostic criteria for NMO is based on International Panel for NMO Diagnosis consensus paper[2]. In AQP4-IgG seropositive patients, diagnosis can be made after a single NMO-compatible relapse. AQP4-IgG seronegative NMOSD criteria include evidence of dissemination in space as well as at least one well-recognized syndrome of NMO, such as optic neuritis, longitudinally extensive myelitis or intractable vomiting/hiccups[2].

NMO has been reported worldwide with prevalence ranging from 0.52-4.4/100000[3]. In Western counties, NMO is rare relative to multiple sclerosis (MS) - ratio of 1:50-100[4-6], but in the developing counties, NMO may constitute up to 40% of all CNS autoimmune diseases[7]. Prognosis and treatment in NMO and MS are different. Five-year mortality of untreated relapsing NMO was 68% - a much higher rate than in MS - and half of the surviving patients had permanent monoplegia or paraplegia[8]. Disease modifying therapies for relapsing MS, such as Interferon and the remarkably effective Natalizumab, fail to prevent, and may even precipitate, relapses of NMO[9,10]. Current strategies for relapse prevention in NMO include immunosuppressants and monoclonal antibodies[11,12], but efficacy of these approaches has not been tested in randomized clinical trials. One of the most promising agents in NMO is Rituximab (RTX), a monoclonal antibody that targets CD20 antigen expressed on the surface of pre-B, mature B-lymphocytes (but not normal plasma cells)[13] and a small subset of T-lymphocytes[14].Our review aims to summarize global experience with RTX for the treatment of NMO and offer clinical pointers based on the literature and authors’ experience.

**RATIONALE FOR B-CELL DEPLETING THERAPY IN NEUROMYELITIS OPTICA**

Landmark pathologic study by Lucchinetti *et al*[15] concluded that “the pronounced Ig reactivity co-localizing with complement activation at sites of vessel damage… may be due to a specific antibody targeted to a vascular antigen”[15]. This prediction was borne out two years later when Lennon *et al*[16] discovered an exquisitely NMO-specific autoantibody directed against Aquaporin-4 (AQP-4), a water channel found in astrocytic end-feet[16]. Current conceptualization of NMO pathogenesis postulates that anti-AQP4 auto-antibody binds to AQP-4[17] and initiates complement-mediated astrocyte injury and inflammatory reaction that secondarily affects oligodendrocytes and leads to demyelination and neuronal loss[18]. This hypothesis successfully explains many features of NMO, but does not account for the diversity of observed pathologic findings[19], nor for disease pathogenesis in anti-AQP4- Ab seronegative NMO patients, who comprise approximately 30% of NMO cases in the United States[5].

In view of the central role of humoral autoimmunity to NMO pathogenesis, it is not surprising that B-cell lineage depletion would be proposed as a rational therapeutic strategy. Indeed, shortly after discovery of anti-AQP-4 Ab, Cree *et al*[20] reported an open label study of RTX in NMO that demonstrated high efficacy of the drug in all but one of their patients[20]. A number of reports on RTX efficacy in NMO from different parts of the globe have since appeared since. This review included all English-language studies that involved 5 or more RTX-treated NMO patients and recorded either relapse rate/number before and after treatment with RTX, or expanded disability status scale (EDSS) scores before and after treatment with RTX, or both outcome measures. We searched PubMed search for “Neuromyelitis Optica” and “Rituximab” and cross-checked references. We identified 25 articles and finally 13 articles were included in this study, which met our inclusion criteria. Two articles were excluded for multiple treatments used; four were excluded for other diseases included; four were excluded for having less than 5 patients; and another two articles were excluded for not documenting treatment effect. Two unpublished case series of RTX-treated NMO that were presented at recent international neurologic conferences were also included in this review; additional data was obtained from the authors[21,22].

**EFFICACY OF RTX IN NMO**

Thirteen studies met our inclusion criteria. The total number of treated patients was 209, of whom an overwhelming majority was women (approximately 90%). Table 1 summarizes demographic and clinical data from the 13 studies. Four out of the thirteen studies reported median annualized relapse rate (ARR) before and after RTX[20,23-25]. Median ARR prior to treatment ranged from 1.7-2.6 and it decreased to 0-0.4 during the treatment period, which was usually 1-2 years. Two studies reported change in mean ARR[26,27], which decreased from 1.2-2.4 pre-treatment to 0-0.3 after treatment was started. The remaining seven studies specified total number of relapses before and after RTX as detailed in Table 1[21-22,28-32]. In 11 out of 13 studies, 48%-75% of patients were relapse-free during treatment period. There were two exceptions: in the study by Lindsey *et al*[32] only 3 out of 9 patients (33%) were relapse-free[32]; this study was critiqued for possible under-dosing of RTX[33]. In the study of Yang *et al*[27] none of the 5 patients experienced any further relapses while on RTX.

In all but one study, some patients “failed to respond” to treatment. Javed *et al*[22] characterized nearly 33% of their NMO patients as “non-responders” based on the fact that RTX failed to delay further relapses, which occurred within 2.5 mo post treatment[22] (Table 1). Phenomenon of disease rebound in the immediate post-induction period was documented by Perumal *et al*[34] in 6 out of their 17 patients; however most patients with post-induction relapses evidenced disease stabilization with further RTX dosing and so need not be necessarily classified as “true non-responders”. Perumal *et al*[35] hypothesized that cytokine release and increases in BAFF and AQP4 levels that immediately follow RTX infusion[35] may precipitate a post-infusion relapse in highly active NMO patients.

Continual disease activity can occur in RTX-treated NMO patients with complete depletion of B-cells continued[29,30,32,36]. Risk factors that would predict non-responsiveness to RTX are presently unknown. It was suggested that RTX non-responders may require not only B-lymphocyte elimination with RTX, but an additional, “broad-spectrum immunosuppressant” to achieve disease suppression[31]. This strategy has been successfully adopted in the treatment of Rheumatoid Arthritis, where RTX is combined with Methotrexate or Cyclophosphamide to achieve disease remission[13]. We discuss potential mechanisms that may explain lack of response to RTX in “Variability in responses to RTX treatment” section below.

Expanded Disability Severity Score (EDSS) scores before and after RTX were reported in 9 out of 13 studies. In 7 of the 9 studies, EDSS at last follow-up was lower than prior to RTX initiation. Exceptions were the studies by Lindsey *et al*[32] and Pellkofer *et al*[30], in which EDSS at last follow-up increased by 0.8 and 0.5, respectively, compared to pre-treatment EDSS[30,32].

**ADVERSE EVENTS**

Two studies recorded fatal outcomes in RTX-treated NMO patients. In the study of Jacob *et al*[23], one patient died from a brainstem NMO relapse and another succumbed to suspected septicemia[23]. Pellkofer *et al*[30] reported one death due to presumed cardiovascular failure that occurred 3 d after a rituximab infusion[30].

Adverse events were not systematically documented across the studies, so estimates of their prevalence are not possible. A number of infections have been observed – mostly, herpetic rashes and tuberculosis reactivation. RTX treatment carries a small risk of progressive multifocal leukoencephalopathy (PML) - 1 case per 25000 individuals in one large cohort of patients with rheumatoid arthritis[37]. No cases of PML in RTX-treated NMO patients has been reported to date, though there was a single case report of PML in NMO patients treated with azathioprine[38]. Overall, adverse events profile of RTX in NMO appears to be consistent with known safety profile of the drug[13]. Infusion reaction to RTX are very common, but can usually be mitigated by pre-treatment with intravenous steroids and anti-histamine and slow titration of RTX.

**DOSING OF RTX AND BIOMARKERS OF TREATMENT RESPONSE**

The majority of studies used one of two “induction protocols”: 375 mg/m2 IV once a week for four consecutive weeks (“protocol A” in Table 1), or 1000 mg IV infused two weeks apart (“protocol B”). Timing of subsequent doses either followed a fixed schedule – with typical time to the next infusion cycle of 6-9 mo –or was based on monitoring parameters. The most commonly used test for monitoring B-cell suppression was CD19+ count assessed by flow cytometry. Since RTX interferes with the direct analysis of CD20 cell surface antigen *via* flow cytometry due to its mechanism of action, CD19+ antigen, which is largely co-expressed with CD20, is used as a surrogate marker to assess extent of B-cell depletion[26]. However, CD19+ count may also overestimate degree of B-cell depletion[39]. RTX typically depletes CD 19+ counts to undetectable levels (< 10 cells per uL) within 2-4 wk of infusion[13].

Table 2 summarizes the use of biomarkers to monitor treatment response to RTX in NMO. Several studies showed that CD19+ B cell population greater than 1% of lymphocyte total is a risk factor of a relapse. Farber *et al*[22] measured CD19 counts post-relapse and during periods of stability, and noted higher B cell counts in the immediate post-relapse period[22]. Yang *et al*[27] suppressed CD19+ count to less than 1% in all their patients and were able to achieved complete eradication of relapses, despite lower doses of RTX used[27]. Pellkofer *et al*[30] used monthly, highly sensitive flow cytometry measurements to demonstrate that complete B-cell suppression led to sustained clinical stabilization in most patients. Bomprezzi *et al*[31] showed that B-cells become undetectable within 2 wk of the first dose of RTX, but rise to 2%-12% at the time of a relapse[31].The early rise in CD19+ cells correlated with radiologically proven relapses, and 5 out of 7 patients experienced a relapse when CD19+ B cell population exceeded the 1% threshold [31]. In summary, preponderance of evidence favors suppressing CD19+ B cell to ≤ 1% of the total lymphocyte count in NMO patients for maximal efficacy.

Efficacy of “low dose” RTX on CD19 counts was assessed in two studies. Yang *et al*[27] used RTX 100 mg infusion once a week for 3 consecutive weeks, which was followed by the next RTX 100 mg dose when CD19+ cells were > 1% and the memory CD19+ CD27+ B cells were > 0.05%. In this regimen, CD19+ cells started to increase in 4 of the 5 patients approximately 140 d after the initial RTX infusion, necessitating a re-infusion[27]. In the Greenberg *et al*[40] study, RTX 100 mg dose resulted in early re-population of B cells compared to the 1000 mg dose[40]. The median number of days for CD19 population to reach threshold of 2% was 133 d in the 100-mg per dose arm *vs* 259 d in the 1000-mg per dose arm[40].

Kim *et al*[26] proposed that CD27+ memory B cells may be a more relevant biomarker of pathogenic B-cells depletion in NMO than CD19+ B cells[26]. Memory B cells can elicit larger and faster responses to antigen than naive B cells, and so may be more relevant to disease pathogenesis. Re-emergence of CD27+ memory B cells above the therapeutic target (< 0.05% of PBMCs) may occur even when CD19+ B cells levels were < 0.5% of PBMCs. Perhaps, presence of memory cells in patients with ostensible absence of CD19+ cells can be explained by a recent study in which loss of CD19 surface antigen from healthy donor B cells exposed to rituximab *in vitro* was not necessarily associated with B cell death[39]. In the study of Kim *et al*[26], no relapses were observed in 29 out of 30 patients in whom CD27+ memory B-cell fraction was below the therapeutic target[26]. This important finding is corroborated by the small series of Yang *et al*[27], cited above. More studies are needed to determine if CD27+ should replace CD19+ as the biomarker of choice in monitoring response to RTX in NMO.

Pellkofer *et al*[30] studied utility of AQP4-Ab, total B-cell counts and B-cell fostering cytokines, such as BAFF (B-cell activating factor) or APRIL (a proliferation-inducing ligand) as biomarkers in NMO. They found that disease activity correlated with B-cell depletion, but not with AQP4-Ab or APRIL levels[31]. Relationship between CD19 counts and Anti-AQP4 titers was analyzed by Jarius *et al*[17], who concluded that administration of RTX was followed by a “prompt and marked decline” in AQP-4 Ab, though the auto-antibody remained detectable in nearly all patients[17].

**VARIABILITY IN RESPONSES TO RTX TREATMENT**

The mechanisms responsible for variability in RTX treatment responses are unclear. An early, post-infusion relapse may be related to incomplete elimination of pathologic B cells as well as transient increase in B-cell activating factor, anti-AQP4 Ab titers and other cytokines following infusion[34]. Greenberg *et al*[40] reported an NMO patient who was “resistant” to RTX: after an initial fall of CD19 cell count to 0, patient continued to experienced clinical relapses and marked early return of B cells at 91 d after RTX, which could not be suppressed by further doses of RTX. This appears to be an exceptional case, as most “true” non-responders in the Greenberg *et al*[40] study – 6 out of 8 - had CD19 count below 2% at the time of relapse[40]. Kim *et al*[26] also noted that 13 out of 20 relapses (65%) occurred even when CD19 B-cell fraction was less than 0.5% PBMCs[26]. Lindsey *et al*[32] ask whether in patients with continued relapses despite complete B-cell suppression, pathogenic T-cell may play a relatively more prominent role in pathogenesis[32]. It is also possible RTX does not completely eliminate pathogenic clones in the periphery or that CD19+ count overestimates the degree of peripheral B-cell depletion[39]. Furthermore, peripherally administered monoclonal antibodies have limited penetration across the blood brain barrier – typically CSF concentration is < 0.1% of serum antibody concentration[41]. Although CSF Rituximab concentration may be considerably higher if blood-brain barrier is perturbed[42], its concentration may be insufficient for elimination of B-cells from CSF.

**CONCLUSION AND QUESTIONS FOR FUTURE STUDIES**

Thirteen observational studies from across the world (Table 1) have documented stabilization or improvement in disability scores in a majority of NMO patients upon initiation of RTX. Pooling data across the studies shows that 66% of patients were relapse-free throughout the treatment period (typically 1-2 years). It is possible that with a more rigorous monitoring of response with CD19+ or CD27+ biomarkers and improved strategies to avoid relapses in the post-induction period even more impressive results could be achieved. Although the studies in our review have been uncontrolled and mostly retrospective and so subject to various biases (*e.g*., ascertainment bias, selection bias, publication bias), they are consistent in demonstrating robust treatment response. Considering the natural history of untreated NMO[8], it would seem highly unlikely that the observed reduction of relapses and improved disability scores in RTX-treated patients is accounted for solely by artifacts of data collection or “regression to the mean” phenomenon. The accumulated weight of evidence, in authors’ opinion, casts serious doubt with regard to possibility of genuine clinical equipoise in NMO at the present time.

Important questions remain with regard to place of RTX in the treatment algorithm of NMO. A recent retrospective review concluded that RTX had the lowest failure rate compared to the commonly used oral immunosuppressants[5]. Based on this data, and overall efficacy of RTX in the published studies, RTX should be strongly considered in any NMO patient who continues to relapse on oral immunosuppressants[13]. The question of whether RTX should replace prior treatment or be combined with it remains unresolved. Combination therapies, in wide use for rheumatologic diseases, have not received sufficient attention in neuro-immunology and will need to be studied in the future. An acute treatment often used for NMO is plasma exchange (PLEX)[43]. Efficacy and safety of PLEX in other refractory systemic autoimmune disease have been shown in several studies[44,45] and its role as maintenance therapy of NMO is currently being test[46].

Should RTX be the agent of choice for all previously untreated patients with NMO? The authors would consider RTX as a first-line therapy in a patient with aggressive disease course as well as in the older NMO patients, who tend to have worse outcomes[47]. It is less clear whether risk-to-benefit ratio calculation would favor RTX in milder and earlier cases, *e.g.*, in an AQP4-Ab seropositive patient after single relapse.

What would be the optimal timing for initiating RTX? If, as suggested by some studies[22,32,34], RTX could exacerbate NMO in the immediate post-infusion period, it would probably be safer to initiate RTX after a period of stability rather than during an acute exacerbation. This question requires further study as the data is conflicting. When switching a patient to RTX, a prudent recommendation is to avoid discontinuing prior therapy prematurely, as delay in starting RTX could put the patient at risk of relapse[24]. In our practice, we routinely continue treatment with oral immunosuppressant for at least one month after RTX is started. With regard to timing of repeat RTX cycles, the literature supports use of CD19+ and, possibly, CD27+ cell count, to monitor treatment response (Table 2). One goal of treatment should be to keep these counts below threshold levels.

Important questions remain regarding long term safety and efficacy of RTX, and duration of therapy. There is little data with regard to long-term safety of RTX in NMO, but the long-term safety record of RTX in rheumatoid arthritis is reassuring[48]. Would it be safe, from NMO standpoint, to discontinue treatment with RTX after a (prolonged) period of stability? A recent study documented that a period of several years of no disease activity after RTX is discontinued is possible in some patients, though 2 out of 4 patients in that series experienced relapses after years of quiescence[49]. Considering the potentially devastating consequences of an NMO relapse, routine discontinuation of RTX – “watchful waiting” - is probably not advisable.

It is hoped that randomized clinical trials, several of which are under way now (*e.g.*, [50]) as well as multi-center collaborative observational studies based on NMO registries, such as online NMOBase registry (www.msbase.org), could provide data on long-term safety and efficacy of RTX in NMO and help resolve the unanswered questions raised in our review. Quality of observational studies in NMO could be improved by adherence to accepted guidelines[51], especially with respect to reporting outcomes (relapse rates and disability scores).

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**Table 1 Case series of Rituximab in Neuromyelitis optica**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  Year | Ref. | Country; Type of study | No. of patients (Total = 209) | Mean age at RTX; % Female | % Anti-AQP4 Ab seropositive | RTX Protocol / treatment duration | ARR before RTX  | ARR after RTX | % Relapse-free | EDSS (median) before --> after RTX |
| 2005 | Cree *et al*[20] | United States; Retrospective | 8 | 37a; 88%  | n/a | A- treatment B- retreatment |  2.6 (median) | 0 (median) | 75% (6/8 pts at 12 mo f/u) | 7.5--> 5.5  |
| 2008 | Jacob *et al*[23]  | United States/England; Retrospective | 25 | 43a; 88%  | 70% | A or B; median interval between cycles-8 mo 19 mo follow up | 1.7 (median)  | 0 (median)  | 72% (17/25 at 12 mo estimated) | 7--> 5 2 patients deceased |
| 2011 | Bomprezzi *et al*[31] | United States; Retrospective | 18 | 46 (+/-12); 83%  | 67% | B | 15 pts-RTX tx and 7 had relapses. 42% (5/12) showed “positive treatment effects”, the other 7 continued to relapse despite RTX therapy  |  | 53% (8/15) | Severe disability from NMO’ - 10 patients |
| 2011 | Bedi *et al*[24] | United States; Retrospective | 23 | 46a; 91%  | 72% | A or B; 32.5 mo | 1.87 (median) | 0 (median)  | 74 % (17/23 pts) | 7--> 5.5 |
| 2011 | Pellkofer *et al*[30] | Germany; Prospective | 10 | 47a; 90%  | 100% | B; number of cycles of RTX 1-5 | Ever before RTX: 1.3 mo, 12 m before RTX: 2.4 mo, 24 m before RTX: 1.72mo, With RTX: 0.93mo |  | 50% (5/10 at 12 mo estimated) | 6--> 6.5a 1 patient deceased |
| 2011 | Javed *et al*[22] | United States; Retrospective | 15 | 34; N/A | N/A | B; patients were given RTX 1g x1 usually 6-9 mo after the initial dose | 2/10 had 2 relapses in 6 mo post RX. 5 non-responders had mean of 1.45 (median 1) relapses in mean 12.2 (median 10) mo |  | 67% (RTX delayed further relapses for 9 mo or more)  | N/A |
| 2012 | Gredler *et al*[28] | Austria; Retrospective | 6 | 38; 83% | 66% | 375 mg/m2; no of infusions 3-16 (mean = 6.67), interval between infusions 3.3-11 mo | 2.5 (mean)a | 0.4 (mean)a | 67% (4/6) | 5.25--> 2.25a |
| 2012 | Ip *et al*[25] | China; Prospective | 7 | 52; 85% | 66% | A or B: Mean # trx courses: 2.85. median 2. | Mean ARR = 2.4 median ARR = 2a 5 became relapse free. 2 had 50% reduction over median 24 mo |  | 71 % (5/7) | 8--> 7 |
| 2012 | Lindsey *et al*[32] | United States; Retrospective | 9 | N/A; 89% | 60% | A or B: Mean duration: 74.2 mo | 3 pts with early relapses in first month after RTX, 4 pts (including 1 pt with early relapse) with later relapses |  | 33% (3/9) | 3.5--> 4.3a |
| 2013 | Kim *et al*[26] | South Korea; Retrospective | 30 | 38.4 (± 10.5); 90% | 77% seropositive | A or B; mean 61 mo (range 49-82 mo), median 60 mo |  2.4 (mean) | 0.3 (mean) | 70% (21/30 at 2 yr f/u) | 4--> 3 |
| 2013 | Yang *et al*[27] | China; Prospective | 5 | 42a; N/A | 80% | 100 mg (50-59 mg/m2) RTX IV 1 dose/wk for 3 cons wk; mean duration: 12.2 mo | 1.16a (mean) | 0a (mean) | 100% | 4.5--> 4 |
| 2014 | Mealy *et al*[29] | United States; Retrospective | 30 | 45a; 83% | 50% | B; median of 20 mo (range 5-83 mo) | Total pretreatment ARR- 2.89 | Total post-treatment ARR- 0.33 | 67% (20/30) | N/A |
| 2014 | Farber *et al*[21] | United States; Retrospective | 23 | 38; 100% | 74% | Mean of 22 mo (range 2-96 mo) |  |  Median ARR was 0.24; mean was 1.02 (SD 1.36) | 48% (11/23)  | N/A |

aEstimated based on results table or manuscript when possible. A or B (in RTX protocol column): There were two treatment protocols used- Protocol A with 4 doses RTX 375 mg/m2 IV weekly for 4 weeks; Protocol B with 2 doses of RTX 1000mg IV 2 wk apart. NMO: Neuromyelitis optica; ARR: Annual relapse rate; EDSS: Expanded disability status scale; RTX: Rituximab; AQP4: Ab – aquaporin 4 antibody; N/A: Not available.

**Table 2 Monitoring parameters in Neuromyelitis optica patients treated with Rituximab**

|  |  |
| --- | --- |
| Ref. | Monitoring parameter/Comments |
| Cree *et al*[20] | CD19 levels- when detectable, patients were re-treated. CD 19 followed bimonthly. 2 protocols-planned infusions every 6 mo or 12 mo |
| Jacob *et al*[23] | CD19 not routinely monitored. Some RTX given when B-cell counts detectable either 6 or 12 mo in intervals or when CD19+ became detectable |
| Bomprezzi *et al*[31] | Flow cytometry used to test circulating B cells. Suggest clinical relapses occurring while on RTX therapy correlate with reconstitution of circulating B cells. Correlated that even early rise in CD20+ cells correlated with radiologically proven relapses. B cells had re-sent between 2 and 12% at time of new attack. Total of 7 patients relapsed after RTX-5 had acute event when B cell counts just returned to greater than 1%, whereas 2 patients continued to relapse despite B cells being undetectable. Detected significant variability in timing of reconstitution of normal values, which implies that scheduling of doses of RTX can be adjusted accordingly. |
| Bedi *et al*[24] | CD19 cell counts planned every 2-3 mo, but not collected systematically for report.  |
| Pellkofer *et al*[30] | Measured lymphocyte subsets by flow cytometry; B cell depletion defined as counts below 0.01 × 109 /L. B cells became undetectable in 9 out of 10 patients within 14 d after 1st dose. Time of B-cell repopulation varied. After 3 patients experienced a relapse shortly after reappearance of B cells, RTX given at fixed interval every 6 to 9 mo, which this led to improved outcomes |
| Javed *et al*[22] | “Non-responders” were defined as clinical attack < 6 mo post rituximab treatment, when B cell count was still undetectable |
| Gredler *et al*[28] | Flow cytometry used; B cells quantified using following combinations of monoclonal antibodies: CD3/19/45, 19/27/45, 19/38/45. Two patients out of 6 had relapses while B-cells were absent |
| Lindsey *et al*[32] | 4 patients had relapses after more than 1 mo when peripheral B cell count “very low”. Case 1: CD19 increased to 250 cells/µL had sensory relapse, no further symptoms for 18 mo. Case 2. Had relapses with CD19 count of 0. Case 3, 4, 6 no further relapses. Case 5: CD19 1 cells/µL at 10 mo, 12 cells/µL at 13 mo and subsequent relapses. Case 7--continued to have relapses with 1 cell/µL at 7 mo, 4 cells/µL at 12 mo. Case 8. CD19 count 3 cells/µL, with continued relapses. Case 9: continued relapses with CD19 1 cells/µL |
| Kim *et al*[26] | Blood samples obtained every 6 wk in 1st year, every 8 wk in second year. Therapeutic target for CD 27+ memory B cell depletion was less than 0.05% of PBMCs. Patients received additional infusion of 375 mg/m2 if frequency of re-emerging memory CD27+ B cells in PBMCs exceeded 0.1% by flow cytometry. CD 19 B cells counts measure- less than 0.01 × 109 /L or less than 0.5% of PBMCs (considered B cell depletion in prior studies. 60%-65% relapses occurred when CD19 were depleted. Authors argue CD27+ more informative biomarker than CD19 |
| Yang *et al*[27] | Goal of CD19+ B cells to less than or equal to 1%, as well as CD19 CD27 B cells to less than or equal to 0.05% of PBMCs. All with no relapses despite low doses of RTX (100 mg single infusion and follow up infusion at mean of 35 wk) |
| Mealy *et al*[29] | CD19 cell counts tested monthly, repeated dosing scheduled on detection of CD19 greater than 1% of total lymphocyte population or at regular 6 mo intervals |
| Farber *et al*[21] | Total of 23 relapses, of which 70% occurred when B cells < 1% of lymphocytes. 7 relapses (30%) occurred when B cells greater or equal to 1% of lymphocytes. CD19 > 1% was associated with higher rate of relapses |

RTX: Rituximab.