Scientific Research Publishing

Case Reports in Clinical Medicine, 2022, 11, 448-456
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

Rituximab for the Treatment of Multiple Sclerosis: A Retrospective Observational Cohort in Morocco

Siham Bouchal[1,2*], Nabila Lahmadi[1], Sara Zejli[1], Naima Chtaou[1,2], Youssef Hafidi[3], Faouzi Belahsen[1,2]

[1]Department of Neurology, Hassan II University Teaching Hospital, Fez, Morocco
[2]Laboratory of Epidemiology, Clinical Research, and Health Community, Faculty of Medicine and Pharmacy, Sidi Mohammed Ben Abdellah University, Fez, Morocco
[3]Department of Pharmacology, Hassan II University Teaching Hospital, Fez, Morocco
Email: *bouchalsiham@gmail.com

How to cite this paper: Bouchal, S., Lahmadi, N., Zejli, S., Chtaou, N., Hafidi, Y. and Belahsen, F. (2022) Rituximab for the Treatment of Multiple Sclerosis: A Retrospective Observational Cohort in Morocco. *Case Reports in Clinical Medicine*, **11**, 448-456.
https://doi.org/10.4236/crcm.2022.1110062

Received: August 15, 2022
Accepted: October 16, 2022
Published: October 19, 2022

Abstract

Background: RITUXIMAB (RTX) is a chimeric anti-CD20 monoclonal antibody that has initially demonstrated efficacy in patients with B-cell lymphoma. Then, over time, it has demonstrated its efficacy in systemic inflammatory diseases and recently in neurological diseases such as multiple sclerosis (MS). Here we describe our experience with rituximab from one MS center from MOROCCO. **Objectives:** To investigate the safety and efficacy of Rituximab in MS in a Moroccan population. **Methods:** A retrospective uncontrolled observational single-center study from January 2017 to July 2020, was including all off-label Rituximab-treated patients with MS with at least 6 months of follow-up. Outcome data were collected and evaluated relapse rate, EDSS score, and adverse events (AEs) from the medical charts. Adverse events grade according to the Common Terminology Criteria for Adverse Events. **Results:** A total of 63 MS patients were treated with RTX, 47 patients were included, while 12 cases had just initiated treatment and 4 cases were lost to follow-up. The mean age of the patients was 39 ± 12 years with a female predominance (F/M: 1.6). All forms of MS were included, 83% of whom had relapsing-remitting MS. The duration of disease progression was 8 ± 5 years. Median EDSS before RTX initiation was 5.5 (0 - 7). 51% of patients were treated with RTX as second-line therapy after failure of other disease-modifying therapies, whereas 34% received it as first-line therapy. The annualized relapse rates decreased from 0.8 to 0.2 after RTX treatment. The Median EDSS remained unchanged at 71%. Radiological stability was noted in 83.7%, while 13.5% had a single new T2 lesion. Infusion-related AEs occurred during

27.6% of infusions and most were mild. Simple infection grades ≤ 2 were noted in 19%. Abortion occurred in only one patient. **Conclusion:** Our study confirms the usability of rituximab treatment for MS in the MOROCCO healthcare environment.

Keywords

B-Lymphocyte, CD20, Multiple Sclerosis, Rituximab, Moroccan Population

1. Introduction

MS is a chronic inflammatory demyelination disease of the central nervous system. It was first described in 1868 by Jean-Martin Charcot, and since then several forms of the disease have been identified. MS is the commonest non-traumatic disabling disease to affect young adults, especially women. In 2020, an estimated 2.8 million people were affected by MS worldwide [1].

The etiology and pathogenesis of MS remain unclear, and the most likely theory is that genetic susceptibility at birth and exposure to environmental factors during one's life trigger an immune reaction directed against CNS autoantigens [2] [3]. MS has historically been considered an autoimmune disease mediated by $CD4^+$ T cells with an imbalance between helper-1 CNS-reactive effector T cells, Th17, and regulatory T cells [2] [3]. However, an important paradigmatic shift in the immunology of MS has occurred in the past decade. It is now clear the important role of B cells in the pathogenesis of MS [2] [4]. The presence and persistence of oligoclonal bands in the CSF in 90% of patients with MS is also an indirect marker of the involvement of B cells in this theory. The efficacy of anti-CD20 treatments through depletion of B cells has also drawn the attention of researchers to the involvement of B cells in the pathogenesis of MS.

Although its efficacy, safety profile, and treatment regimen in MS are not well codified, RTX is a frequently used off-label anti-CD20 for the treatment of MS in several countries [5] [6] [7]. This work aims to evaluate the efficacy and safety of the use of RTX on a Moroccan population with MS.

2. Methods

Objectives of the study:

- Evaluate the clinical and radiological efficacy of RTX in Moroccan patients with MS.
- Evaluate the tolerance of RTX at the time of infusion and the Adverse events (AEs) recorded since the initiation of RTX. The grades of AEs are according to the Common Terminology Criteria for Adverse Events.

Study protocol:

Monocentric retrospective cohort within the neurology department of hospital university HASSAN II FES, from January 01, 2017, to July 31, 2020, including

47 patients followed for MS and treated with RTX with at least a 6-month follow-up.

- Inclusion criteria:

Patients with a diagnosis of MS according to the McDonalds 2010 and 2017 criteria and treated with RTX with at least 6 months of follow-up.

- Exclusion criteria:
  - RTX start date is recent: less than 6 months follow-up.
  - Patient lost to follow-up.
- To assess clinical effectiveness, annualized relapse rates and Expanded Disability Status Scale (EDSS) scores before and after rituximab initiation were collected from medical records.
- The baseline MRI was defined as the most recent MRI before the RTX initiation. We recorded the presence and number of new lesions in follow-up MRI
- The Adverse events (AEs) recorded since the initiation of RTX was collected from medical records.
- The therapeutic regimen used in our center.
  - Initial 2 doses: 1000 mg intravenous infusions once; repeat dose 2 weeks later.
  - Subsequent doses: 500 mg IV every 6 to 12 months.
  - Premedication: 1 g of paracetamol and L'hydroxyzine (at a dose of 50 mg) orally 30 to 60 minutes before each infusion then direct intravenous injection of methylprednisolone (120 mg) 30 min before starting the rituximab infusion.

Statistical analysis

Statistical analysis was performed using SPSS software. Descriptive results were presented in the form of numbers and percentages for qualitative variables. Quantitative variables were presented in the form of an average accompanied by their standard deviation in the case of normal distribution, otherwise by the median with its extremes. The statistical significance threshold was set at 0.05.

3. Results

75 patients followed in the Neurology department for the demyelinating disease of the CNS, were treated by RTX (n = 63 MS and n = 12 Neuromyelitis Optica).

Among the 63 MS, we excluded 12 MS patients who had just started RTX and 4 who had been lost to sight (Figure 1).

Of 47 patients with MS, the average age was 39 ± 12 years, with a female predominance of 61.7% (n = 29) with a sex ratio F/M of 1.6.

The average duration of disease progression of MS was 8 ± 5 years. The most common progressive form was RRMS in 83% (n = 39). The median EDSS before RTX initiation was 5.5 (0 to 7). The annualized relapse rate (ARR) in the 24 months before RTX initiation is 0.8. The socio-demographic and clinical characteristics of the patient are summarized in Table 1.

Reasons for rituximab initiation among MS patients are described in Table 2. The reasons mainly were lack of efficacy with previous treatment in 24 patients

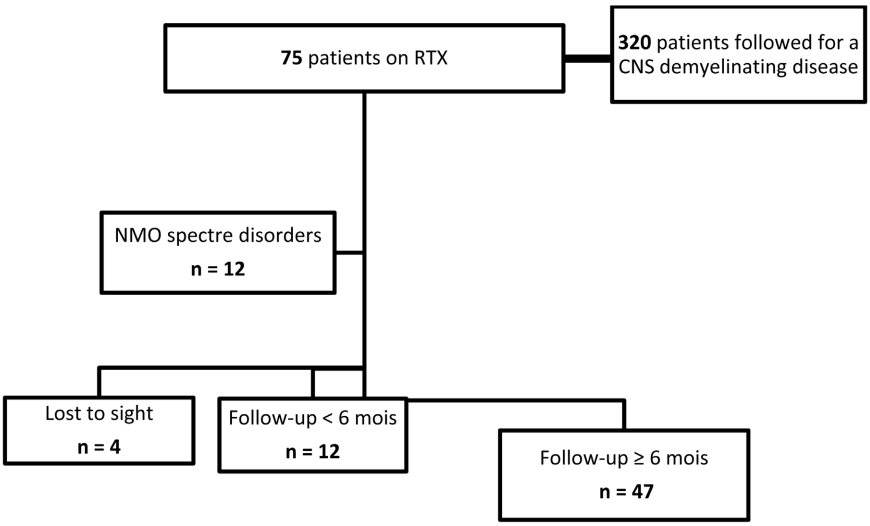

Figure 1. Patient inclusion.

Table 1. Socio-demographic and clinical characteristics of the patient.

Socio-demographic and clinical characteristics	
average age	39 ± 12 years
Female	61.7% (n = 29)
The duration of disease (mean)	8 ± 5 years
RRMS	83% (n = 39)
EDSS median at baseline	5.5
The annualized relapse rate (ARR)	0.8

Table 2. Reasons for rituximab initiation.

Reasons for Rituximab initiation	MS n (%)
Lack of efficacy with previous treatment	24 (51.10%)
Treatment naïve with active disease	16 (34 %)
Side effects from previous treatment	5 (10.60%)
Planning for pregnancy	1 (2.10%)
poor compliance with previous treatment	1 (2.10%)

(51%), and active disease in 16 patients (34%). RTX was proposed in 5 patients (10.6%) for intolerance to previous treatment (3 had an intolerance to cyclophosphamide and 2 to azathioprine).

The mean duration of RTX treatment was 21.8 ± 14.3 months. The ARR decreased from 0.8 to 0.2 after RTX initiation. 83% (n = 37) were relapse-free, in 5 patients (10.6%) had a single relapse, and 6.4% (n = 3) had 2 relapses.

During the observation time, the median EDSS remained unchanged at 70.2% (n = 33), and there was an improvement at 21.4% (n = 11). Progression was

noted in 6.4% (n = 3), of which 2 developed a secondarily progressive form and one refused to take her treatment during the COVID-19 pandemic.

The mean time for the baseline MRI was 4 ± 2 months. The average time for the control MRI was 16 ± 3 months. 78.7% (n = 37) had at least one control MRI, of which 83.7% (n = 30) had a stable MRI with no new lesions. 13.5% (n = 5) had a single new T2 lesion, and 5.4% (n = 2) had 2 new T2 lesions. Contrast enhancing lesions were absent in all patients who had an MRI with an injected T1 sequence (n = 25).

The side effects observed during the infusion were reported at 27.6% (n = 13). All these SEs were classified as grades 1 and 2 and no serious incident of hypersensitivity was recorded. For this side effect, the flow rate of the infusion was reduced and we did not stop completely the treatment.

Infections were observed in 19% (n = 9): All these infections were upper respiratory infections or lower urinary tract infections classified as grade 1 or grade 2.

Abortion was at 10 weeks of amenorrhea in one patient whose pregnancy occurred at 20 weeks from the last RTX infusion.

No cancerous or autoimmune complications have been reported so far.

4. Discussion

RTX is a chimeric anti-CD20 monoclonal antibody that was developed in the 1990s as a treatment for B-cell non-Hodgkin lymphomas [2]. Over time, this indication has been extended to other autoimmune diseases such as rheumatoid arthritis and Gougerot-Sjogren syndrome [2] [5]. Several recent studies have also suggested the effectiveness of RTX in some peripheral and central inflammatory neurological diseases, in particular MS [4] [5] [6] [7].

RTX binding to the CD20 causes depletion of CD20-expressing B-cells and T-cells. A depletion of autoreactive B cells will interfere with cell-mediated antigen presentation and impair T cell activation, antibody production, and cytokine secretion [2]. RTX works through three main mechanisms: induction of apoptosis, complement-dependent cytotoxicity, and antibody-dependent cellular cytotoxicity [2] [4] [5] [6].

CD20 is a very specific marker of B cells from the pre-B stage and on mature B cells, but it is not expressed on hematopoietic stem cells, or on the earliest precursors of the B line, or on plasma cells, thus making it possible to explain the transient nature of the depletion of B cells and the normal level of immunoglobulins in treated patients, which explains its acceptable safety profile [4].

It has been described that a subset of T cells also express CD20 and therefore their depletion may contribute to the therapeutic effect of RTX [2] [5].

A randomized, double-blind, phase II controlled study of RTX against placebo, over 48 weeks, including 104 patients with RRMS (HERMES study), proved its clinical and radiological efficacy with an acceptable safety profile [6]. The randomized phase III trial (OLYMPUS) of RTX, involving 439 patients with

primary progressive MS was negative, but the analysis of the subgroups showed a significant slowing of the progression of the disability in young patients (age < 51 years) with gadolinium-enhancing lesions on MRI [7].

In a review of the literature of 38 studies concerning the off-label use of RTX in RRMS, RTX appears to be effective in comparison to the placebo, IFNs, and glatiramer acetate [8] [9] [10]. A prospective phase III study (RIFUND-MS: NCT02746744) compares RTX to dimethyl fumarate in RRMS in Sweden, and the results are not yet been published of RTX.

Real-world data Off-label use of RTX in the treatment of MS is widespread throughout the world for its efficacy, its safety profile, and its easy administration [1] [2] [9]-[15], but protocols remain heterogeneous and uncodified.

We report our experience regarding the use of off-label RTX in Moroccan patients with MS with a mean treatment duration of 21.8 months. RTX has been used mainly as second-line therapy in patients with RRMS or in the case of first-line active forms. We observed a significant reduction in the ARR and the number of new lesions in the follow-up MRI after rituximab initiation.

The demographic data of our series are similar to the literature data concerning the population with MS. The diagnostic delay and the particular severity of MS in Moroccan patients may explain the high baseline EDSS in our series [16].

AEs during infusion are of variable severity, sometimes requiring treatment in an intensive care unit (18). Their incidence varies from 25% to 85% of cases [17]. This risk is more frequent when RTX is used in hematological malignancies than in autoimmune diseases [18] [19] [20].

Premedication, in particular glucocorticoid infusion, increases tolerance to first courses and reduces the risk of occurrence of serious AEs [2] [19] [20].

In our series, with compliance with premedication, no serious AEs during infusion were reported.

Data on the safety of RTX are reassuring based on the long-standing use of RTX in many diseases other than with low risks of serious opportunistic infections or malignancy [18] [19] [20].

The risk of serious infectious complications under RTX is explained by several hypotheses such as B cell depletion, hypogammaglobulinemia, and neutropenia [18] [19] [20] [21] [22].

It is important to note that the risk of infectious complications is also related to the indication of RTX, comorbidities, age, and association with other immunosuppressants. To minimize this risk, screen for hepatitis B and pulmonary tuberculosis, offer pneumococcal vaccination, and monitor white blood cells count and immunoglobulin levels before RTX infusion [21] [22].

A few rare cases of PML under RTX have been reported in other indications other than MS and it seems that the risk of PML is not related to the number of cures or the length of exposure to RTX [22] [23] [24] [25].

In our practice, hepatitis B serology as well as screening for pulmonary tuberculosis and serum protein electrophoresis is routinely done before initiating RTX. Pneumococcal vaccination should be done routinely but not necessarily

before initiation.

Data on the safety of RTX are reassuring based on the long-standing use of RTX in many diseases other than with low risks of serious opportunistic infections or malignancy [18] [19].

The risk of malignancy on RTX appears similar to that of the general population [18]. Our study has some limitations. First, the number of included patients is small. Second, our study was a retrospective longitudinal study.

5. Conclusions

Despite some methodological limitations, our work, like many series, confirms the efficacy and tolerance profile in MS and the easy administration of the treatment. From an economic point of view, it seems accessible compared to other long-term treatments.

So RTX represents an attractive therapeutic alternative, especially with resource-limited settings in developing countries like MOROCCO.

Conflicts of Interest

The authors declare that they have no competing interests.

Ethical Approval

The local ethic committee approved this study.

References

[1] Walton, C., King, R., Rechtman, L., Kaye, W., Leray, E., Marrie, R.A., Robertson, N., La Rocca, N., Uitdehaag, B., van der Mei, I., Wallin, M., Helme, A., Angood Napier, C., Rijke, N. and Baneke, P. (2020) Rising Prevalence of Multiple Sclerosis Worldwide: Insights from the Atlas of MS, Third Edition. *Multiple Sclerosis*, **26**, 1816-1821. https://doi.org/10.1177/1352458520970841

[2] Chisari, C.G., Sgarlata, E., Arena, S., Toscano, S., Luca, M. and Patti, F. (2022) Rituximab for the Treatment of Multiple Sclerosis: A Review. *Journal of Neurology*, **269**, 159-183. https://doi.org/10.1007/s00415-020-10362-z

[3] Arneth, B.M. (2019) Impact of B Cells to the Pathophysiology of Multiple Sclerosis. *Journal of Neuroinflammation*, **16**, Article No. 128. https://doi.org/10.1186/s12974-019-1517-1

[4] Disanto, G., Morahan, J.M., Barnett, M.H., Giovannoni, G. and Ramagopalan, S.V. (2012) The Evidence for a Role of B Cells in Multiple Sclerosis. *Neurology*, **78**, 823-832. https://doi.org/10.1212/WNL.0b013e318249f6f0

[5] Palanichamy, A., Jahn, S., Nickles, D., Derstine, M., Abounasr, A., Hauser, S.L., Baranzini, S.E., Leppert, D. and von Büdingen, H.C. (2014) Rituximab Efficiently Depletes Increased CD20-Expressing T Cells in Multiple Sclerosis Patients. *The Journal of Immunology*, **193**, 580-586. https://doi.org/10.4049/jimmunol.1400118

[6] Hauser, S.L., Waubant, E., Arnold, D.L., *et al.* (2008) B-Cell Depletion with Rituximab in Relapsing-Remitting Multiple Sclerosis. *The New England Journal of Medicine*, **358**, 676-688. https://doi.org/10.1056/NEJMoa0706383

[7] Hawker, K., O'Connor, P., Freedman, M.S., Calabresi, P.A., Antel, J., Simon, J., Hauser, S., Waubant, E., Vollmer, T., Panitch, H., Zhang, J., Chin, P., Smith, C.H.

and OLYMPUS Trial Group (2009) Rituximab in Patients with Primary Progressive Multiple Sclerosis: Results of a Randomized Double-Blind Placebo-Controlled Multicenter Trial. *Annals of Neurology*, **66**, 460-471. https://doi.org/10.1002/ana.21867

[8] Naismith, R.T., Piccio, L., Lyons, J.A., Lauber, J., Tutlam, N.T., Parks, B.J., Trinkaus, K., Song, S.K. and Cross, A.H. (2010) Rituximab Add-On Therapy for Breakthrough Relapsing Multiple Sclerosis: A 52-Week Phase II Trial. *Neurology*, **74**, 1860-1867. https://doi.org/10.1212/WNL.0b013e3181e24373

[9] Salzer, J., Svenningsson, R., Alping, P., Novakova, L., Björck, A., Fink, K., Islam-Jakobsson, P., Malmeström, C., Axelsson, M., Vågberg, M., Sundström, P., Lycke, J., Piehl, F. and Svenningsson, A. (2016) Rituximab in Multiple Sclerosis: A Retrospective Observational Study on Safety and Efficacy. *Neurology*, **87**, 2074-2081. https://doi.org/10.1212/WNL.0000000000003331

[10] Siddiqui, M.K., Singh, B., Attri, S., Veraart, C., Harty, G. and Wong, S.L. (2020) Use of Rituximab in Adults with Relapsing-Remitting Multiple Sclerosis: A Systematic Literature Review. *Current Medical Research and Opinion*, **36**, 809-826. https://doi.org/10.1080/03007995.2020.1739009

[11] Yamout, B.I., El-Ayoubi, N.K., Nicolas, J., El Kouzi, Y., Khoury, S.J. and Zeineddine, M.M. (2018) Safety and Efficacy of Rituximab in Multiple Sclerosis: A Retrospective Observational Study. *Journal of Immunology Research*, **2018**, Article ID: 9084759. https://doi.org/10.1155/2018/9084759

[12] Airas, L., Nylund, M., Mannonen, I., Matilainen, M., Sucksdorff, M. and Rissanen, E. (2020) Rituximab in the Treatment of Multiple Sclerosis in the Hospital District of Southwest Finland. *Multiple Sclerosis and Related Disorders*, **40**, Article ID: 101980. https://doi.org/10.1016/j.msard.2020.101980

[13] Mathew, T., John, S.K., Kamath, V., Murgod, U., Thomas, K., Baptist, A.A., Therambil, M., Shaji, A., Nadig, R., Badachi, S., Souza, D.D., Shivde, S., Avati, A., Sarma, G.R.K., Sharath Kumar, G.G., Deepalam, S. and Parry, G.J. (2020) Efficacy and Safety of Rituximab in Multiple Sclerosis: Experience from a Developing Country. *Multiple Sclerosis and Related Disorders*, **43**, Article ID: 102210. https://doi.org/10.1016/j.msard.2020.102210

[14] Leonidou, E., Pantzaris, M., Kleopa, K.A., Loizidou, M.A., Kyriakides, T. and Christou, Y.P. (2019) A Retrospective Observational Study of Rituximab Treatment in Multiple Sclerosis Patients in Cyprus. *Postgraduate Medicine*, **131**, 486-489. https://doi.org/10.1080/00325481.2019.1649975

[15] Granqvist, M., Boremalm, M., Poorghobad, A., *et al.* (2018) Comparative Effectiveness of Rituximab and Other Initial Treatment Choices for Multiple Sclerosis. *JAMA Neurology*, **75**, 320-327. https://doi.org/10.1001/jamaneurol.2017.4011

[16] Araqi-Houssaini, A., Lahlou, I., Benkadmir, Y., Elotmani, H., Hajjaj, I., Kissani, N., Chtaou, N., Zaam, A., Belahsen, M.F., Elmoutawakil, B., Rafai, M.A. and Slassi, I. (2014) Multiple Sclerosis Severity Score in a Cohort of Moroccan Patients. *Multiple Sclerosis*, **20**, 764-765. https://doi.org/10.1177/1352458513506504

[17] Kasi, P.M., Tawbi, H.A., Oddis, C.V. and Kulkarni, H.S. (2012) Clinical Review: Serious Adverse Events Associated with the Use of Rituximab—A Critical Care Perspective. *Critical Care*, **16**, Article No. 231. https://doi.org/10.1186/cc11304

[18] D'Arena, G., Simeon, V., Laurenti, L., Cimminiello, M., Innocenti, I., Gilio, M., Padula, A., Vigliotti, M.L., De Lorenzo, S., Loseto, G., Passarelli, A., Di Minno, M.N.D., Tucci, M., De Feo, V., D'Auria, F., Silvestris, F., Di Minno, G. and Musto, P. (2017) Adverse Drug Reactions after Intravenous Rituximab Infusion Are More Common in Hematologic Malignancies than in Autoimmune Disorders and Can Be

Predicted by the Combination of Few Clinical and Laboratory Parameters: Results from a Retrospective, Multicenter Study of 374 Patients. *Leukemia & Lymphoma*, **58**, 2633-2641. https://doi.org/10.1080/10428194.2017.1306648

[19] Shi, Y., Wu, Y., Ren, Y., Jiang, Y. and Chen, Y. (2019) Infection Risks of Rituximab versus Non-Rituximab Treatment for Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. *International Journal of Rheumatic Diseases*, **22**, 1361-1370. https://doi.org/10.1111/1756-185X.13596

[20] Emery, P., Fleischmann, R., Filipowicz-Sosnowska, A., Schechtman, J., Szczepanski, L., Kavanaugh, A., Racewicz, A.J., van Vollenhoven, R.F., Li, N.F., Agarwal, S., Hessey, E.W., Shaw, T.M. and DANCER Study Group (2006) The Efficacy and Safety of Rituximab in Patients with Active Rheumatoid Arthritis despite Methotrexate Treatment: Results of a Phase IIB Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Trial. *Arthritis & Rheumatology*, **54**, 1390-1400. https://doi.org/10.1002/art.21778

[21] Nixon, A., Ogden, L., Woywodt, A. and Dhaygude, A. (2017) Infectious Complications of Rituximab Therapy in Renal Disease. *Clinical Kidney Journal*, **10**, 455-460. https://doi.org/10.1093/ckj/sfx038

[22] Barmettler, S., Ong, M.S., Farmer, J.R., Choi, H. and Walter, J. (2018) Association of Immunoglobulin Levels, Infectious Risk, and Mortality with Rituximab and Hypogammaglobulinemia. *JAMA Network Open*, **1**, e184169. https://doi.org/10.1001/jamanetworkopen.2018.4169

[23] Berger, J.R., Malik, V., Lacey, S., Brunetta, P. and Lehane, P.B. (2018) Progressive Multifocal Leukoencephalopathy in Rituximab-Treated Rheumatic Diseases: A Rare Event. *Journal of NeuroVirology*, **24**, 323-331. https://doi.org/10.1007/s13365-018-0615-7

[24] Zaheer, F. and Berger, J.R. (2012) Treatment-Related Progressive Multifocal Leukoencephalopathy: Current Understanding and Future Steps. *Therapeutic Advances in Drug Safety*, **3**, 227-239. https://doi.org/10.1177/2042098612453849

[25] Berger, J.R. (2017) Classifying PML Risk with Disease Modifying Therapies. *Multiple Sclerosis and Related Disorders*, **12**, 59-63. https://doi.org/10.1016/j.msard.2017.01.006