**Commentary: Rituximab in scleritis**

Over the last few years, there has been an increasing number of reports on the scleritis refractory to standardized therapy. Scleritis can be associated with an underlying systemic disease in up to 50% of patients, with the most common being rheumatoid arthritis (RA) and granulomatosis with polyangiitis (GPA).[1] Management of treatment-resistant scleritis and/or associated systemic disease remains a major challenge. Biological agents have emerged out as a useful alternative in such a scenario. In this current issue of the journal, Murthy et al.[2] highlighted the role of rituximab in managing a case of necrotizing scleritis in a patient with GPA.

Rituximab is a chimeric monoclonal immunoglobulin G (IgG) antibody against CD-20, a B cell surface antigen. It has been used successfully in treating various autoimmune
Table 1: Review of literature on the use of Rituximab in scleritis

| Author                     | Dose of RTX/Interval | Aetiology                                                                 | Relapse (N) |
|----------------------------|----------------------|---------------------------------------------------------------------------|-------------|
| Joshi[5]                   | 1 gm/2 week          | GPA                                                                       | 12          |
| Cao[4]                     | Variable*            | GPA (6) Idiopathic (4) RA (4) Other (1)                                   | 3           |
| Suhler[6]                  | 500 mg/1 gm, 2 week  | Idiopathic (5) RA (4) Systemic Vasculitis (1) GPA (1) Cogan Syndrome (1) | 7           |
| You et al[13]             | Variable*            | GPA                                                                       | 2           |
| Ahmed[8]                   | Variable*            | GPA                                                                       | 1           |
| Recillas-Gispert[14]       | 1 gm/2 week          | GPA                                                                       | 3           |
| Taylor[15]                 | 1 gm/2 week          | GPA                                                                       | 0           |
| Pérez-JacoisteAsín[16]     | 375 mg/m², 4 weekly dose | GPA                                                                       | NA          |
| Chauhan[7]                 | 1 gm/2 week          | RA                                                                        | 0           |
| Hardy et al[17]            | 1 gm/2 week          | RA                                                                        | 0           |
| Kurz[19]                   | 1 gm/2 week          | Idiopathic (1) RA (1)                                                    | 2           |
| Bogdanic-Werner[19]        | 375 mg/m², 4 weekly dose | Idiopathic                                                               | 0           |
| Fujita[20]                 | 375 mg/m², 4 weekly dose | GPA                                                                       | 0           |
| Xu[21]                     | 1 gm/2 week          | Autoimmune hypophysitis                                                  | 0           |
| Kasi[8]                    | NA                   | Necrotizing Scleritis with Idiopathic Orbital Inflammation               | 0           |
| Caso[22]                   | 1 gm/2 week          | IgG4-related disease                                                    | 0           |
| Fidelix[23]                | 1 gm/2 week          | SINS                                                                      | 0           |
| Onal[9]                    | 1 gm/2 week          | GPA                                                                       | 0           |
| Ahmadi-Simab[9]            | 375 mg/m², 4 weekly dose | Primary Sjogren’s syndrome.                                               | 0           |
| Cheung[24]                 | 1 gm/2 week          | GPA                                                                       | 0           |
| Morarija[25]               | 1 gm/2 week          | GPA                                                                       | 0           |
| Iaccheri[26]               | 1 gm/2 week          | RA                                                                        | 1           |

Interval interval between the doses; GPA Granulomatosis with polyangitis (Wegener's granulomatosis); RA Rheumatoid arthritis; SINS Surgically induced necrotizing scleritis; Relapse Number of patients showing relapse of scleral inflammation after treatment with Rituximab. *Variable doses: These studies used the following doses - rheumatology protocol: 2 doses of 1 gm (2 weeks apart) every 3-6 months; Institute protocol: 375 mg/m² body surface area×8 consecutive weeks, and monthly infusions thereafter and oncology protocol: 375 mg/m² body surface area×4 consecutive weeks.

diseases, including RA, systemic lupus erythematosus, and GPA. The drug has shown promising results in the treatment of various ocular inflammatory disorders and intraocular lymphoma in recent years. Rituximab has been shown to be efficacious for the management of scleritis by various case reports, a few small case series, and a randomized trial [Table 1].

GPA is an antineutrophil cytoplasmic antibody (ANCA)-associated small-vessel, necrotizing granulomatous vasculitis. Ophthalmic involvement in GPA can occur up to 45% of the patients and can be presenting manifestation of the systemic disease in 16% of the patients. Ophthalmic involvement in GPA includes episcleritis, scleritis, peripheral ulcerative keratitis, uveitis, retinal vasculitis, and orbital inflammation. Scleritis is considered as one of the most common ocular presentations of GPA, and GPA remains the second most common cause of scleritis after RA.[4] Rituximab was reported to be as efficacious and even superior to cyclophosphamide in the management of ocular GPA.[5,6] The response to the treatment with rituximab may show variable responses, especially in cases with granulomatous manifestations of ANCA-associated vasculitis (such as orbital inflammation) and may take relatively longer time to remission in some cases of scleritis.[4] Scleral inflammation in GPA is thought to be mediated by ANCA produced by B cells. Depletion of B lymphocytes by rituximab thus helps in the management of scleritis. However, not only ANCA-associated scleritis, rituximab has been found to be efficacious in the management of scleritis secondary to RA and various other autoimmune disorders also.[6-9]

Recurrence of scleral inflammation was reported with rituximab, especially in studies with a longer follow-up period.[5,6,10] The majority of such cases responded to the re-treatment with the same drug.[5,10] Rituximab appeared to be superior in terms of safety and efficacy when compared to cyclophosphamide.[10] Stilling-Vinther and Pedersen[11] reported a case of posterior scleritis in a 81-year-old man with multiple comorbidities who developed Pneumocystis jirovecii pneumonia following treatment with rituximab and died. There are reports of cystoid macular edema following successful treatment of scleritis with rituximab therapy.[12] Secondary infection was reported in 16% of the patients in a retrospective study, with 8% requiring hospitalization.[5]

Rituximab may be considered as the second-line agents for noninfectious scleritis refractory to conventional immunosuppressive therapy. Further prospective controlled long-term studies may help us to confirm and expand our insight on the use of the drug in patients with scleritis.

Parthopratim Dutta Majumder
Department of Uvea, Medical and Vision Research Foundations, Sankara Nethralaya, Chennai, Tamil Nadu, India
References

1. Okhravi N, Odufuwa B, McCluskey P, Lightman S. Scleritis. Surv Ophthalmol 2005;50:351-63.
2. Murthy SL, Shah S, Bagga B, Dudam R. Rituximab therapy combined with methotrexate for severe necrotizing scleritis in a case of granulomatosis with polyangiitis. Indian J Ophthalmol 2020;68:1981-3.
3. Ahmed A, Foster CS. Cyclophosphamide or rituximab treatment of scleritis and uveitis for patients with granulomatosis with polyangiitis. Ophthamologic Res 2019;61:44-50.
4. Oral S, Kazokoglu H, Koc A, Yavuz S. Rituximab for remission induction in a patient with relapsing necrotizing scleritis associated with limited Wegener's granulomatosis. Ocul Immunol Inflamm 2008;16:230-2.
5. Joshi L, Tanna A, McAdoo SP, Medjeral-Thomas N, Taylor SR, Sandhu G, et al. Long-term outcomes of rituximab therapy in ocular granulomatosis with polyangiitis: Impact on localized and non-localized disease. Ophthalmology 2015;122:1262-8.
6. Suhler EB, Lim LL, Beardsley RM, Giles TR, Pasadukha S, Lee ST, et al. Rituximab therapy for refractory scleritis: Results of a phase I/II dose-ranging, randomized, clinical trial. Ophthalmology 2014;121:1885-91.
7. Chauhan S, Kamal A, Thompson RN, Estrach C, Moots RJ. Rituximab for treatment of scleritis associated with rheumatoid arthritis. Br J Ophthalmol 2009;93:984-5.
8. Kasi SK, Kim HJ, Basham RF, Cunningham ET, Sy A, Lustig L, et al. Idiopathic orbital inflammation associated with necrotizing scleritis and temporal bone inflammation. Ophthal Plast Reconstr Surg 2016;32:e77-9.
9. Ahmad-Simak K, Lamprecht P, Nölle B, Ai M, Gross WL. Successful treatment of refractory anterior scleritis in primary Sjögren's syndrome with rituximab. Ann Rheum Dis 2005;64:1087-8.
10. Cao JH, Oray M, Cocho L, Foster CS. Rituximab in the treatment of refractory noninfectious scleritis. Am J Ophthalmol 2016;164:22-8.
11. Stilling-Vinther MK, Pedersen BS. Fatal pneumocystis jiroveci pneumonia following immunosuppressive therapy with rituximab and prednisolone for posterior scleritis. Acta Ophthalmol (Copenh) 2012;90:e154-5.
12. Bussone G, Kaswin G, de Menthon M, Delair E, Brézin A, Guillemin L. Macular oedema following rituximab infuion in two patients with Wegener's granulomatosis. Clin Exp Rheumatol 2010;28(1 Suppl 57):90-2.
13. You C, Ma L, Lasave AF, Foster CS. Rituximab induction and maintenance treatment in patients with scleritis and granulomatosis with polyangiitis (Wegener’s). Ocul Immunol Inflamm 2018;26:1166-73.
14. Recillas-Gispert C, Serna-Ojeda JC, Flores-Suárez LF. Rituximab in the treatment of refractory scleritis in patients with granulomatosis with polyangiitis (Wegener’s). Graefes Arch Clin Exp Ophthalmol 2015;253:2279-84.
15. Taylor SRJ, Salama AD, Joshi L, Pusey CD, Lightman SL. Rituximab is effective in the treatment of refractory ophthalmic Wegener’s granulomatosis. Arthritis Rheum 2009;60:1540-7.
16. Pérez-Jacobo-Asín MA, Charles P, Rothschild PR, Terrier B, Brézin A, Mouthon L, et al. Ocular involvement in granulomatosis with polyangiitis: A single-center cohort study on 63 patients. Autoimmun Rev 2019;18:493-500.
17. Hardy S, Hashemi K, Catanese M, Candil M, Zufferey P, Gabison E, et al. Necrotising scleritis and peripheral ulcerative keratitis associated with rheumatoid arthritis treated with rituximab. Klin Monatsbl Augenheilkd 2017;234:567-70.
18. Kurz PA, Suhler EB, Choi D, Rosenbaum JT. Rituximab for treatment of ocular inflammatory disease: A series of four cases. Br J Ophthalmol 2009;93:546-8.
19. Bogdanic-Werner K, Fernandez-Sanz G, Alejandre Alba N, Ferrer Soldevila P, Romero-Bueno FJ, Sanchez-Pernaute O. Rituximab therapy for refractory idiopathic scleritis. Ocul Immunol Inflamm 2013;21:329-32.
20. Fujita Y, Fukui S, Endo Y, Tsuji S, Takatani A, Shimizu T, et al. Peripheral ulcerative keratitis associated with granulomatosis with polyangiitis emerging despite cyclophosphamide, successfully treated with rituximab. Intern Med Tokyo Jpn 2018;57:1783-8.
21. Xu C, Ricciuti A, Caturegli P, Keene CD, Kargi AY. Autoimmune lymphocytic hyposis in association with autoimmune eye disease and sequential treatment with infliximab and rituximab. Pitsuitary 2015;18:441-7.
22. Caso F, Fiocco U, Costa L, Sfriso P, Punzi L, Doria A. Successful use of rituximab in a young patient with immunoglobulin G4-related disease and refractory scleritis. Joint Bone Spine 2014;81:190-9.
23. FidelixTS de A, Vieira LA, Trevisani VF. Management of necrotizing scleritis after pterygium surgery with rituximab. Arq Bras Ofthalmol 2016;79:339-41.
24. Cheung CM, Murray PJ, Savage COS. Successful treatment of Wegener’s granulomatosis associated scleritis with rituximab. Br J Ophthalmol 2005;89:1542.
25. Morarji J, Joshi L, Tomkins-Netzer O, Lightman S, Taylor SR. Combined infliximab and rituximab in necrotising scleritis. Case Rep Ophthalmol 2012;3:286-90.
26. Iaccheri B, Androudi S, Bocci EB, Gerli R, Cagini C, Fiore T. Rituximab treatment for persistent scleritis associated with rheumatoid arthritis. Ocul Immunol Inflamm 2010;18:223-5.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms."

Access this article online
Quick Response Code:

Cite this article as: Dutta Majumder P. Commentary: Rituximab in scleritis. Indian J Ophthalmol 2020;68:1983-5.