CHAPTER 32

OFF-LABEL USES OF THE RITUXIMAB IN DERMATOLOGY

Tamer İrfan Kaya, MD

Antibody-based therapeutic approaches have had a significant impact on the treatment of dermatological diseases. Of the new biological therapies, rituximab (RTX), a chimeric mouse/human monoclonal antibody of the immunoglobulin G1 (IgG1) kappa isotype directed against the CD20 surface antigen of B cells. FDA approved RTX for the treatment of B-cell non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), and refractory rheumatoid arthritis (RA).[1] In addition it has been used successfully off-label in some refractory B-cell-mediated autoimmune diseases and inflammatory conditions such as SLE, Sjögren's syndrome and some autoimmune dermatological diseases. As CD20 is expressed by all B-cells, RTX produces a profound and sustained depletion of B lymphocytes, which covers the spectrum from pre-B cells to mature B cells without affecting stem cells or plasma cells. Once bound, RTX induces B-cell depletion through several mechanisms, such as complement-mediated cytolysis, antibody-dependent cell-mediated cytotoxicity, inhibition of signaling apoptosis induction, and direct inhibition of cell growth. B-cells can act as antigen-presenting cells, secrete pro-inflammatory cytokines (including tumour necrosis factor-α (TNF-α)), produce rheumatoid factor (RF) and other autoantibodies, and activate T cells.[2-4] Particularly, the secondary effects of RTX on T cells thought to be important and studies have noted decreased co-stimulatory molecules on CD4+ T cells, decreased numbers of memory T cells, and increased numbers of regulatory T cells.[5,6]

Dosage and Pharmacokinetics

The lymphoma protocol is 375mg/m^2 weekly, given on four consecutive weeks. The standart dosage range of RTX in autoimmune diseases is two 1000 mg IV infusions separated by two weeks; each infusion is preceded by 100 mg IV methylprednisolone, an antihistamine and an analgesic (paracetamol 1 g) to help prevent unwanted unfusion related symptoms. The infusion lasts about 4 hours. When a second cycle is needed, it is given about 6 months after the first cycle, if there is still residual disease activity or if a relapse of symptoms occurs.[1,3,7] The first FDA approved lymphoma protocol was used in early studies in dermatological diseases. Since, dermatological diseases are mostly autoimmune, the protocol used in treating RA was preferred more frequently in dermatology in recent years.[8]

The mean terminal elimination half-life of RTX is 20 days, similar to native IgG. Because of variation in the amount of patients' available CD20 (especially in the oncologic setting), RTX's half-life can vary among individuals. In addition, levels of serum RTX increase with repeated doses, as less and less antigen becomes available due to depletion. Contribution of body surface area to the variability in drug clearance was only 19.7%. This findings shows that in autoimmune diseases, drug administration is independent of body surface area, and 2-weekly 1 g infusions are more reasonable.[1,9,10]

RTX therapy generally leads to a rapid and marked depletion of circulating B-cells within 2–3 weeks of initial treatment in the majority of patients. Depletion of B cells is sustained on average for 6 months. B cell recovery began at about 6 months after completion of therapy, until median B cell levels often return to normal levels after about 12 months. Overall immunoglobulin levels do not decline dramatically, due to the surviving of the immunoglobulin producing plasma cells that do not bear surface CD20.[1,11]

Pre Treatment Assesment

Electrocardiogram, blood cell counts, serum protein electrophoresis, immunoglobulin levels (IgG, IgA, IgM), hepatitis B and C serologies, chest X-ray are the first line invastigations. Phenotype determination of circulating lymphocytes (B-cell and T-cell counts) and HIV serology are also recommended. Severe heart failure or severe uncontrolled cardiovascular disease, and severe, chronic, and/or recurrent infections (bacterial, viral) are the main contraindications to RTX.[12]

RTX safety

As with the other biologic agents utilized, RTX use carries potential risks and detailed medical history and laboratory screening should be performed before starting biologic therapies. Clinicians should be aware of the safety profiles associated with RTX and they

lung disease.[52] These data shows that RTX may be a promising drug to control the progression of skin and lung involvement in SSc.

Dermatomyositis

Dermatomyositis (DM) is an inflammatory myopathy characterized by proximal muscle weakness and associated cutaneous findings, such as the heliotrope eruption, Gottron papules, midfacial erythema. Treatment of the DM is quite problematic because of its complex etiopathogenesis and its many different clinical pictures, the intensity of clinical symptoms and other relevant clinical aspects, including age, comorbidity and the putative risk/benefit ratio of the available treatment choices.[53]

Levine reported a study of 7 adult patients with long-standing DM refractory to currently available immunosuppressive agents received 4-weekly 375 mg/m2 RTX. He observed that all 6 evaluable patients exhibited major clinical improvement, with muscle strength (dynamometry) increasing over baseline by 36-113%, with peak results seen 12 weeks after completion of RTX infusions. All patients also showed muscle enzyme improvement. Four patients experienced a return of symptoms that coincided with the return of B cells before the 52-week end point. He report significant improvement in the cutaneous manifestations of DM, such as less "rash" and partial resolution of alopecia. In 3 patients with impaired baseline pulmonary disease, he demonstrated an improvement in their forced vital capacity after RTX therapy.[54] Dinh et al. report positive responses with RTX in 3 female patients with recalcitrant DM documented by clinical improvement and increasing independence from concomitant medications. In their patients, the heliotrope changes and violaceous poikiloderma seemed to be the cutaneous manifestations that responded best to RTX therapy.[55] Chung et al. used RTX in 8 patients, which received 2-weekly 1 g RTX infusions. Muscle deficit was reduced by at least 50% only in 3 patients (Manual Muscle Test) at 24 weeks, which was the criterion set as partial remission. Three other patients also improved their muscle strength. The limited efficacy was likely due to muscle atrophy of chronic disease or long-term steroid use. They did not observe any serious infectious complications, however one of their patients died of metastatic cancer 9 months after his last infusion.[56] In a retrospective review of 4 pediatric patients ages 10-17 years with juvenile DM who were treated with RTX, 3 of 4 patients showed sustained (at least 12 months) clinical improvement after 4-weekly 375 mg/m2 RTX and 1 patient had worsening of her disease following RTX. In 2 children, relapses were controlled with a second course of RTX.[57] In a retrospective study of nine patients with severe Juvenile DM treated with RTX. Complete response of skin and muscle involvement in three of six evaluable patients were noted, RTX was found to be ineffective for calcinosis in six patients (58). In a retrospective review of 19 patients (13 polymyositis and 5 DM) analysed, a 81 years old male who were unable to swallow and resistant to the other treatment options was died from aspiration pneumonia 3 weeks after the first RTX infusion. They observed response in 9 of 13 polymyositis patients, interestingly, all five DM patients responded and none required re-treatment. They observed maximum RTX effects on myositis about 30 weeks after the first infusion.[59] In a recent large, double-blind, RTX study, 200 refractory polymyositis (PM) and DM patients randomized to receive RTX immediately or after 8 weeks. All patients were intolerant or had inadequate response to glucocorticoids and on average had failed more than three additional immunosuppressive agents. Although no significant difference detected in the 2 treatment arms, 83% of the patients in both arms reached the primary endpoint of improvement. Therefore, the authors concluded that RTX had an effect on these diseases. A total of 26 serious adverse events reported, most commonly infectious, with only one patient withdrawing because of an adverse event.[60] Aggarwal et al. analysed these patients and reported that the presence of antisynthetase and anti-Mi-2 autoantibodies, juvenile DM subset, and lower disease damage strongly predict clinical improvement in patients with refractory myositis who were treated with RTX.[61]

RTX may represent a safe and effective therapeutic option for some autoimmune dermatologic disorders. However, controlled, randomised trials are needed to clearly define indications and protocols.

REFERENCES

1. Leonardi C, Heffernan MP, Gill JG. Rituximab and future biological therapies. In: Wolverton SE Ed. Comprehensive Dermatologic Drug Therapy. Elsevier Saunders, 3rd Ed, Edinburgh, 2013:333-41.
2. Smith MR. Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance. Oncogene 2003;22:7359–68.
3. Martín Mola E, Hernández B, García-Arias M, et. al. Consensus on the Use of Rituximab in Rheumatoid Arthritis. A document with evidence-based recommendations. Reumatol Clin 2011; 7: 30-44.
4. Reff ME, Carner K, Chambers KS, et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood 1994; 83: 435-45.
5. Iwata S, Saito K, Tokunaga M, et al. Phenotypic Changes of Lymphocytes in Patients with Systemic Lupus Erythematosus Who Are in Longterm Remission After B Cell Depletion Therapy with Rituximab. J Rheumatol 2011; 38: 633–41.
6. Vallerskog T, Gunnarsson I, Widhe M, et al. Treatment with rituximab affects both the cellular and the humoral arm of the immune system in patients with SLE. Clin Immunol 2007; 122: 62–74.

7. España A, Ornilla E, Panizo C. Rituximab in dermatology. Actas Dermosifiliogr 2013;104:380-92.
8. Ahmed AR, Shetty S. A comprehensive analysis of treatment outcomes in patients with pemphigus vulgaris treated with rituximab. Autoimmun Rev 2015; 14: 323-331.
9. Carr DR, Heffernan MP. Innovative Uses of Rituximab in Dermatology. Dermatol Clin 2010;28: 547–57.
10. Ng CM, Bruno R, Combs D, Davies B. Population pharmacokinetics of rituximab (anti-CD20 monoclonal antibody) in rheumatoid arthritis patients during a phase II clinical trial. J Clin Pharmacol 2005; 45: 792–801.
11. Plosker GL, Figgitt DR. Rituximab: a review of its use in non- Hodgkin's lymphoma and chronic lymphocytic leukaemia. Drugs 2003;63:803 43.
12. Mariette X, Pham T, Sibilia J. Management of patients on rituximab in daily practice. http://www.cri-net.com.
13. Allegra A Oteri G, Alonci A, et al. Association of osteonecrosis of the jaws and POEMS syndrome in a patient assuming rituximab. J Craniomaxillofac Surg 2014; 42: 279-82.
14. Buch MH1, Smolen JS, Betteridge N et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 2011; 70: 909-20.
15. El Tal AK, Posner MR, Spigelman Z, Ahmed AR. Rituximab: a monoclonal antibody to CD20 used in the treatment of pemphigus vulgaris. J Am Acad Dermatol 2006; 55: 449-59.
16. Kelesidis T, Daikos G, Boumpas D, Tsiodras S. Does rituximab increase the incidence of infectious complications? A narrative review. Int J Infect Dis 2011;15:e2-16.
17. Furst DE. The risk of infections with biologic therapies for rheumatoid arthritis. Semin Arthritis Rheum 2010; 39: 327-46.
18. Keystone E, Fleischmann R, Emery P, et al. Safety and efficacy of additional courses of rituximab in patients with active rheumatoid arthritis: an open-label extension analysis. Arthritis Rheum 2007; 56: 3896–908.
19. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra therapies for rheumatoid arthritis: meta-analyses of randomized placebo-controlled trials. Ann Rheum Dis 2009; 68: 25–32.
20. Fleischmann RM. Safety of biologic therapy in rheumatoid arthritis and other autoimmune diseases: focus on rituximab. Semin Arthritis Rheum 2009; 38: 265-80.
21. van Vollenhoven RF, Emery P, Bingham CO III et al. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. Ann Rheum Dis 2013; 72: 1496-502.
22. Gurcan HM, Keskin DB, Stern JN, et al. A review of the current use of rituximab in autoimmune diseases. Int Immunopharmacol 2009; 9: 10–25.
23. Slimani S, Lukas C, Combe B, Morel J. Rituximab in rheumatoid arthritis and the risk of malignancies: report from a French cohort. Joint Bone Spine 2011; 78: 484-7.
24. Bhandari PR, Pai VV. Novel applications of Rituximab in dermatological disorders. Indian Dermatol Online J 2014; 5: 250-9.
25. Sehgal VN, Pandhi D, Khurana A. Biologics in dermatology: an integrated review. Indian J Dermatol 2014; 59: 425-41.
26. Leshem YA, Hodak E, David M, et al. Successful treatment of pemphigus with biweekly 1-g infusions of rituximab: a retrospective study of 47 patients. J Am Acad Dermatol 2013; 68: 404-11.
27. Schmidt E, Goebeler M, Zillikens D. Rituximab in severe pemphigus. Ann N Y Acad Sci 2009; 1173: 683-91.
28. Ahmed AR, Spigelman Z, Cavacini LA, et al. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. N Engl J Med 2006; 355: 1772–9.
29. Joly P, Mouquet H, Roujeau JC, et al. A single cycle of rituximab for the treatment of severe pemphigus. N Engl J Med 2007;357:545–52.
30. Currimbhoy S1, Zhu V, Dominguez AR, Pandya AG. Rituximab in the treatment of 38 patients with Pemphigus with long-term follow-up. J Eur Acad Dermatol Venereol. 2015;19. doi: 10.1111/jdv.13103.
31. Cianchini G, Lupi F, Masini C, et al. Therapy with rituximab for autoimmune pemphigus: results from a single-center observational study on 42 cases with long-term follow-up. J Am Acad Dermatol. 2012; 67: 617-22.
32. Horvath B, Huizinga J, Pas HH, et al. Low dose rituximab is effective in pemphigus. Br J Dermatol 2012;166:405-12.
33. Heelan K, Al-Mohammedi F, Smith MJ, et al. Durable remission of pemphigus with a fixed-dose rituximab protocol. JAMA Dermatol 2014;150:703-8.
34. Vinay K, Kanwar AJ, Mittal A, et al. Intralesional Rituximab in the Treatment of Refractory Oral Pemphigus Vulgaris. JAMA Dermatol. 2014; 23. doi: 10.1001/jamadermatol.2014.3674.
35. Ingen-Housz-Oro S, Valeyrie-Allanore L, Cosnes A, et al. First-line treatment of pemphigus vulgaris with a combination of rituximab and high-potency topical corticosteroids. JAMA Dermatol 2015;151:200-3.
36. Vinay K, Kanwar AJ, Sawatkar GU, et al. Successful use of rituximab in the treatment of childhood and juvenile pemphigus. J Am Acad Dermatol 2014; 71: 669-75.
37. Daniel BS, Murrell DF, Joly P. Rituximab and its use in autoimmune bullous disorders. Dermatol Clin 2011; 29: 571-5.
38. Lourari S, Herve C, Doffoel-Hantz V, et al. Bullous and mucous membrane pemphigoid show a mixed response to rituximab: experience in seven patients. J Eur Acad Dermatol Venereol 2011; 25: 1238-40.
39. Shetty S, Ahmed AR. Treatment of bullous pemphigoid with rituximab: critical analysis of the current literature. J Drugs Dermatol 2013; 12: 672-7.
40. Le Roux-Villet C, Prost-Squarcioni C, Alexandre M, et al. Rituximab for patients with refractory mucous membrane pemphigoid. Arch Dermatol 2011;147:843–9.
41. Shetty S, Ahmed AR. Critical analysis of the use of rituximab in mucous membrane pemphigoid: a review of the literature. J Am Acad Dermatol 2013; 68: 499-506
42. Lafyatis R, Kissin E, York M et al. B cell depletion with rituximab in patients with diffuse cutaneous systemic sclerosis. Arthritis Rheum 2009; 60: 578-83.
43. Moazedi-Fuerst FC, Kielhauser SM, Brickmann K, et al. Rituximab for systemic sclerosis: arrest of pulmonary

disease progression in five cases. Results of a lower dosage and shorter interval regimen. Scand J Rheumatol. 2014; 43: 257-8.

44. Daoussis D, Liossis S-NC, Tsamandas AC et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. Rheumatology 2010;49: 271-80.

45. Daoussis D, Liossis S-NC, Tsamandas AC et al. Effect of long-term treatment with rituximab on pulmonary function and skin fibrosis in patients with diffuse systemic sclerosis. Clin Exp Rheumatol 2012;30 (2 Suppl 71):S17-22.

46. Smith V, Van Praet JT, Vandooren B et al. Rituximab in diffuse cutaneous systemic sclerosis: an open-label clinical and histopathological study. Ann Rheum Dis 2010; 69: 193-7.

47. Smith V, Piette Y, van Praet JT et al. Two-year results of an open pilot study of a 2-treatment course with rituximab in patients with early systemic sclerosis with diffuse skin involvement. J Rheumatol 2013; 40: 52-7.

48. Bosello S, De Santis M, Lama G et al. B cell depletion in diffuse progressive systemic sclerosis: safety, skin score modification and IL-6 modulation in an up to thirty-six months follow-up open-label trial. Arthritis Res Ther 2010; 12:R54.

49. Meier FM, Frommer KW, Dinser R, et al. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis 2012;71: 1355–60.

50. Iudici M, Moroncini G, Cipriani P, et al. Where are we going in the management of interstitial lung disease in patients with systemic sclerosis? Autoimmun Rev 2015 Feb 21. pii: S1568-9972(15)00035-X. doi: 10.1016/j.autrev.2015.02.002. [Epub ahead of print].

51. Jordan S, Distler JHW, Maurer B et al. Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group. Ann Rheum Dis 2014 Jan 17. doi: 10.1136/annrheumdis-2013-204522.

52. Keir GJ, Maher TM, Ming D, et al. Rituximab in severe, treatment-refractory interstitial lung disease. Respirology 2014;19:353–9.

53. Iorizzo LJ 3rd, Jorizzo JL. The treatment and prognosis of dermatomyositis: an updated review. J Am Acad Dermatol 2008;59:99-112.

54. Levine TD. Rituximab in the treatment of dermatomyositis: an open-label pilot study. Arthritis Rheum 2005;52:601-7.

55. Dinh HV, McCormack C, Hall S, Prince HM. Rituximab for the treatment of the skin manifestations of dermatomyositis: a report of 3 cases. J Am Acad Dermatol 2007;56:148-53.

56. Chung L, Genovese MC, Fiorentino DF. A pilot trial of rituximab in the treatment of patients with dermatomyositis. Arch Dermatol 2007;143:763-7.

57. Cooper MA, Willingham DL, Brown DE, et al. Rituximab for the treatment of juvenile dermatomyositis. Arthritis Rheum 2007;56;3107–11.

58. Bader-Meunier B, Decaluwe H, Barnerias C, et al. Safety and efficacy of rituximab in severe juvenile dermatomyositis: results from 9 patients from the French Autoimmunity and Rituximab registry. J Rheumatol 2011; 38: 1436–40.

59. Unger L, Kampf S, Lüthke K, Aringer M. Rituximab therapy in patients with refractory dermatomyositis or polymyositis: differential effects in a real-life population. Rheumatology (Oxford) 2014; 53: 1630-8.

60. Oddis CV, Reed AM, Aggarwal R et al. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. Arthritis Rheum 2013; 65: 314-24.

61. Aggarwal R1, Bandos A, Reed AM, et al. Predictors of clinical improvement in rituximab-treated refractory adult and juvenile dermatomyositis and adult polymyositis. Arthritis Rheumatol 2014; 66: 740-9.