REVIEW ARTICLE

B cell targeted therapy for immunoglobulin G4-related disease

Motohisa Yamamoto

Department of Rheumatology and Allergy, IMSUT Hospital, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

ABSTRACT
Glucocorticoids are the first-line drug for the remission induction therapy of immunoglobulin (Ig) G4-related disease. Achieving drug-free remission using glucocorticoids alone is difficult, however, and many patients require maintenance therapy with glucocorticoids and immunosuppressants. Studies have recently found that the number of peripheral memory B cells and plasmablasts is increased in IgG4-related disease and have indicated the efficacy of rituximab, which, in remission induction therapy, rapidly reduces serum IgG4 levels and has the tapering effect of glucocorticoids. Rituximab has been shown to reduce the risk of relapse more than oral immunosuppressants such as azathioprine. However, maintaining drug-free remission is difficult with a single course of rituximab alone, and many cases require maintenance therapy with rituximab. This article outlines the potential of B-cell targeted therapy, focusing on the efficacy, and safety of rituximab for IgG4-related disease.

ARTICLE HISTORY
Received 11 January 2021
Accepted 31 January 2021

KEYWORDS
B cell; BTK inhibitor; IgG4-related disease; rituximab

1. Introduction
Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a chronic inflammatory condition that presents with elevated serum IgG4 levels and a prominent infiltration of IgG4-positive plasma cells with characteristic fibrosis in the swollen affected organs. IgG4-RD is a systemic disorder that affects lacrimal and salivary glands, pancreas, bile ducts, kidneys, lungs, and the retroperitoneal cavity [1]. Over the past 20 years, the concept of this disease was developed in Japan [2], with the diagnostic criteria established in 2011 [3] and the criteria revised in 2020 [4]. Although the treatment guidelines for autoimmune pancreatitis [5] and IgG4-related sclerosing cholangitis [6] have been published, no definite treatment guidelines have yet been established for IgG4-RD as a whole.

At the International Symposium on IgG4-RD held in 2015, the participants agreed that glucocorticoids are the first-line induction therapy for IgG4-RD [7]. According to the data collected by the end of 2019 in the SMART registry (Sapporo Medical University and related institutes database for investigation and best treatment for IgG4-RD) [8], which we constructed, the treatment performance rate for the 307 patients with IgG4-RD was 74.3%. Of these patients, 85.0% were undergoing maintenance therapy with glucocorticoids alone, and only 4.4% were in drug-free remission. During the same year, 1.8% of the patients experienced a relapse, and 10.8% were taking immunosuppressants, including biologic agents. A review of 62 articles on treatments, which included nearly 3000 cases, found that of the nearly 2000 cases for which details of the initial treatment were available, glucocorticoids were prescribed to induce remission in 74%, with a high remission rate of 97% with glucocorticoids alone but with a relapse rate of 33%. Of these, 64% were relapses after the discontinuation of the glucocorticoid [9]. In 2018, the results of a single-center, 215-patient study comparing glucocorticoid monotherapy and combined immunosuppressants in the induction were presented. The therapeutic goal was to maintain disease activity below 50% at 6 months and to maintain prednisolone at a dosage of 10 mg/day or less. The percentage of patients who did not achieve the goals was 20.8% in the single-agent steroid group and 7.2% in the immunosuppressive combination group [10].

Regarding the importance of maintenance therapy, Masamune at al. randomly divided 49 patients with autoimmune pancreatitis into two groups: those who withdrew the glucocorticoid at 24 weeks after induction therapy and those who continued maintenance therapy for approximately 3 years. The authors analyzed the relapse-free rate during the course of the study and found it to be very high in the group that discontinued the maintenance therapy. The relapse-free rate was 85.0% in the discontinuation group, while it was 40.9% in the continuation group [10].
therapy for a short period (60.9%) but significantly lower in the group that continued the maintenance therapy for a long period (23.8%) [11]. In a previously reported analysis of maintenance therapy in more than 1000 patients, immunosuppressants employed during the therapy were superior to glucocorticoids alone in preventing relapses (odds ratio 3.36; 1.44, 7.83). However, there were no differences in the adverse events (odds ratio 0.96; 0.08, 12.09) [12], which suggests that achieving drug-free remission is very difficult with glucocorticoids alone and that maintenance therapy with glucocorticoids alone might involve a certain risk of relapse. In cases with a risk of relapse, such as male patients, young patients [13], history of allergy, multi-organ involvements [14], higher levels of serum IgG4 [15], peripheral counts of eosinophils [14,16] and patients with repeated relapses, the use of immunosuppressants may be considered during the course of treatment.

2. Significance of B cell regulation in IgG4-related disease

When selecting immunosuppressants, clinicians need to choose those that are appropriate for regulating the diseases. In recent years, 4 types of acquired immune cells have attracted attention for IgG4-RD (Figure 1), the first of which are type 2 helper T (Th2) cells. IgG4-RD is often associated with allergic disorders [17], and it has been reported that the expression of the messenger ribonucleic acid (mRNA) of Th2 cytokines such as interleukin (IL)-4 and IL-13 is upregulated in organs involved in IgG4-RD [18]. Zen reported increased infiltration of GATA3+Th2 lymphocytes in the involved organs [19]. On the other hand, Maehara et al. performed a quantitative analysis of immune cells in affected organs and reported that CD4+GATA3+Th2 cells did not significantly proliferate, which suggests that Th2 cells themselves might not play a major role in this disease [20]. The role of Th2 cells in the pathogenesis has remained controversial.

Follicular helper T (Tfh) cells mainly produce IL-4 and IL-21 and play a role in the formation of germinal centers, the maturation and activation of B cells, and the regulation of differentiation into antibody-producing cells. In the subset analysis of Tfh cells in peripheral blood, the levels of activated Tfh1 and Tfh2 cells are increased [21]. In particular, a study indicated that Tfh2 cells produce cytokines (IL-4, IL-10, and IL-21) that are involved in the class switch to IgG4 [22] and might be directly involved in the pathogenesis of IgG4-RD.

Mattoo et al. reported the presence of granzyme-positive CD4+ cytotoxic T lymphocyte (CTL) infiltration in the organs affected by IgG4-RD and that these CD4+ CTLs secrete profibrotic cytokines such as IL-13 and TGF-β.
as transforming growth factor (TGF)-β, IL-1β, and interferon gamma, which might be involved in the fibrosis of this disease [23]. We found increased levels of peripheral helper T cells in the peripheral blood of patients with IgG4-RD, a subset that was also found to possess cytotoxic granules such as granzyme A [24].

Memory B cells and plasmablasts are found in increased numbers in the peripheral blood before the treatment of IgG4-RD. In particular, CD19+CD20−CD27hiCD38hi plasmablasts oligoclonally proliferate in cases with high disease activity or relapse, and these cells have been shown to produce IgG4 [25]. Shiokawa reported the possibility of the pathogenic antibodies, as serum IgG from patients with autoimmune pancreatitis can be administered to mice to induce inflammation in their pancreas [26]. Under such circumstances, autoantibodies in IgG4-RD have recently been attracting attention, and autoantibodies against prohibitin [27], annexin A11 [28], galectin-3 [29], and laminin 511E8 [30] have been reported. On the other hand, spleen tyrosine kinase expression on CD19+B cells, which is one of the activation indicators of B cells, did not change before and after induction therapy with glucocorticoids [31]. B cells therefore also play a major role in the pathogenesis of this disease, which might explain the limitations of glucocorticoid-only therapy and the potential of B cells as a new therapeutic target.

3. Treatment experience and open-label study of rituximab for immunoglobulin G4-related disease

Reports on rituximab therapy for IgG4-RD have been accumulating in recent years. Rituximab is a chimeric anti-CD20 monoclonal antibody that acts by eliminating B cells (including autoreactive B cells), thereby ameliorating the conditions involving autoantibodies and immune complexes and subsequently inducing naïve B-cell reconstitution (regulation of humoral immunity). Another possible mechanism is the regulation of B-T-cell interaction by preferentially removing memory B cells that highly express co-stimulatory molecules such as CD40 and CD80 (regulation of cellular immunity). In Japan, rituximab is currently indicated for treating granulomatosis with polyangiitis, microscopic polyangiitis, refractory nephrotic syndrome, chronic idiopathic thrombocytopenic purpura, and acquired thrombotic thrombocytopenic purpura, which present with high disease activity or difficulty in remission with conventional therapies (as of January 2021).

The efficacy of rituximab for IgG4-RD was first reported in 2008. Topazian et al. reported that the use of rituximab for autoimmune pancreatitis with sclerosing cholangitis that flared up after the use of glucocorticoids and immunosuppressants resulted in improvement of bile duct stenosis and the removal of a bile duct stent [32]. Subsequently, Khosroshahi et al. reported their experience with the treatment in 10 patients [33]. In patients refractory to glucocorticoid therapy, 1 g of rituximab was administered twice a day at 15 day-intervals, and the patients were evaluated using the IgG4-RD responder index [34]. All of the patients, except for one with Riedel’s thyroiditis, showed clinical improvement, and decreased serum IgG4 levels after taking rituximab. All patients were able to discontinue glucocorticoids and other immunosuppressants. Four of the patients experienced a relapse or increased serum IgG4 levels and were retreated with rituximab 6 months later [33]. A subsequent prospective open-label study of rituximab was conducted in 30 glucocorticoid-refractory patients (22 with prior glucocorticoid use), using the treatment protocol as described above. Twenty-six of the patients were treated with rituximab alone and were assessed using the IgG4-RD responder index and the examining physician’s general assessment. The treatment was judged effective at 6 months in 23 patients (77%), with 14 patients (47%) in complete remission at 12 months. Rituximab was shown to be effective even in the absence of glucocorticoids [35].

4. Efficacy and safety of rituximab for immunoglobulin G4-related disease

Recently, 105 articles on rituximab therapy for autoimmune disorders were reviewed, showing its efficacy in IgG4-RD. Fifty-two patients enrolled in 5 non-randomized trials and other studies were observed for up to 4 years. Induction therapy with rituximab rapidly reduced serum IgG4 levels compared with serum IgG levels and might induce glucocorticoid tapering and even glucocorticoid withdrawal in certain cases [36]. Rituximab can eliminate B cells before they differentiate into plasma cells, but the drug cannot eliminate plasma cells that do not express CD20. Rituximab therefore likely does not immediately inhibit antibody-producing plasma cells. In general, immunoglobulins are produced by long-lived plasma cells, whereas IgG4 is produced by CD20-positive short-lived plasma cells under the influence of IL-4 and IL-21 [37]. Serum IgG4 levels are therefore considered to decrease earlier after rituximab administration. In a study comparing the efficacy of immunosuppressants (azathioprine and methotrexate) and rituximab...
as induction therapy for patients with relapsing autoimmune pancreatitis, rituximab was found to be more effective [38].

Numerous patients have been found to require maintenance therapy even after successful induction therapy with rituximab. Omar et al. showed that the risk of relapse tended to be lower with rituximab maintenance therapy than with only rituximab induction therapy after remission [12]. Forty-three patients with autoimmune pancreatitis and IgG4-related sclerosing cholangitis were divided into two groups: those who took rituximab only at the time of the induction therapy and those who continued maintenance therapy with rituximab after remission. The maintenance group had a significantly lower relapse rate of 11%; however, infection complications (pneumonia, sepsis due to urinary infection, *Clostridium difficile* colitis, dental abscess, sinusitis, and diverticulitis) were more frequent (20.7%) in the rituximab maintenance group [39]. We have also experienced good results with rituximab induction therapy in patients with repeated relapses. Initially, the clinical symptoms (Figure 2) and serum IgG4 levels improved rapidly in all patients. The use of glucocorticoids was therefore tapered, and rituximab was administered after each relapse (Figure 2); however, the interval between the rituximab administrations gradually became shorter. The patients eventually presented secondary failure [40], which raises the issue of the administration method for the long-term use of rituximab. At this point, there is no report of attenuated efficacy due to the appearance of anti-chimeric antibody (HACA) in patients treated with rituximab for IgG4-RD, but this phenomenon has been confirmed in rituximab treatment for pediatric systemic lupus erythematosus [41] and Sjögren’s syndrome [42]. HACA may be a possible cause of secondary failure in this disease as well. Optimization of the maintenance therapy with rituximab is therefore essential.

Our patients had all the risk factors for relapse after rituximab induction therapy: elevated serum IgG4 and IgE levels and increased counts of peripheral eosinophils [43]. Although these factors might indicate high IgG4-RD activity, they might not be the only reasons for the incidence of refractoriness to rituximab. In systemic lupus erythematosus, rituximab therapy for glucocorticoid-resistant patients resulted in the disappearance of CD19<sup>+</sup>IgD<sup>+</sup>CD27<sup>−</sup> naïve B cells, CD19<sup>+</sup>IgD<sup>−</sup>CD27<sup>+</sup> class-switched memory B cells, and CD19<sup>+</sup>IgD<sup>−</sup>CD27<sup>−</sup> memory B cells from peripheral blood within 4 weeks. After that period, naïve B cells recover in approximately 3-9 months and are maintained for 2-6 years. In patients with systemic lupus erythematosus in remission for a extended period, memory B cells and plasmablasts remain absent for 6 months to 6 years. Rituximab inhibits the activation and differentiation of T cells, which are normally mediated by memory B cells via co-stimulatory molecules (increase in CD4<sup>+</sup> naïve T cells and decrease in CD40L<sup>+</sup>CD4<sup>+</sup> T cells and ICOS<sup>+</sup>CD4<sup>+</sup> T cells), thereby regulating the disease [44]. It has been reported, however, that some patients with systemic lupus erythematosus relapsed after remission with rituximab with no changes in the B-cell lineage but with abnormalities in the T-cell lineage, such as increased CD4<sup>+</sup>CD45RO<sup>+</sup> memory T cells and increased ICOS and CD69 expression in CD4<sup>+</sup>T cells [45]. The same phenomenon might occur in IgG4-RD. In the case of our patients who presented a second failure to rituximab, tissue re-biopsy was performed to rule out transformation to malignant lymphoma. With this in mind, the patient was switched to abatacept, which regulates T cells [46]. The patient has so far safely remained in remission with abatacept maintenance therapy for approximately 6 years.

Evidence for the use of rituximab in IgG4-RD is therefore accumulating. Recently, the efficacy of
rituximab biosimilar CT-P10 (Truxima™) has also been confirmed in both naïve patients and patients switched from the originator [47]. At this time, however, there have been no randomized controlled trials for this disease. In addition, rituximab therapy has been associated with the risk of generalized herpes zoster infection [48], reactivation of hepatitis B virus [49], and development of progressive multifocal leukoencephalopathy [50]. In particular, since the frequency of herpes zoster is higher in the elderly [51], in whom IgG4-RD predominate in the Japanese population. It is desirable to limit the use of rituximab in both induction and maintenance therapy for IgG4-RD, to younger patients and others who are at less risk of complications. To verify that, randomized controlled trials for rituximab in IgG4-RD need be conducted as soon as possible to properly evaluate its efficacy and safety.

5. Other B-cell targeted therapies

The clinical trial of obexelimab (XmAb5871) and anti-CD19 antibodies with high affinity for FcγRIIb has been completed in the United States. Phase III trials have also been started for inebilizumab, a humanized anti-CD19 monoclonal antibody. In addition, belimumab, an anti-B-cell activating factor belonging to the tumor necrosis factor family, has been shown to be useful in treating IgG4-RD [52]. A study on belimumab has been started in China to evaluate its efficacy with glucocorticoids. Clinical trials have also began or are scheduled to start for B-cell-targeted agents such as zanubrutinib and rilzabrutinib, which are oral, molecular-targeted Bruton’s tyrosine kinase inhibitors (as of January 2021) (Table 1).

6. Conclusion

In this article, we reviewed the evidence on the efficacy and safety of rituximab and other agents for IgG4-RD. B-cell-targeted therapies for this disease are undergoing continuous development. In particular, Bruton’s tyrosine kinase inhibitors are employed to control the disease through a novel mechanism of action. We look forward to examining their long-term efficacy and safety, their use in short-term induction therapy and in preventing relapses, and their potential for curing IgG4-RD.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Motohisa Yamamoto  http://orcid.org/0000-0003-2742-2484

References

[1] Yamamoto M, Takahashi H, Shinomura Y. Mechanisms and assessment of IgG4-related disease: lessons for the rheumatologist. Nat Rev Rheumatol. 2014;10(3):148–159.
[2] Umehara H, Okazaki K, Masaki Y, et al. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. Mod Rheumatol. 2012;22(1):1–14.
[3] Umehara H, Okazaki K, Masaki Y, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD). 2011. Mod Rheumatol. 2012; 22(1):21–30.
[4] Umehara H, Okazaki K, Kaw S, et al. The 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD. Mod Rheumatol. 2020. DOI:10.1080/14397595.2020.1859710
[5] Kamisawa T, Okazaki K, Kawa S, et al. Amendment of the Japanese consensus guidelines for autoimmune pancreatitis, 2013 III. Treatment and prognosis of autoimmune pancreatitis. J Gastroenterol. 2014;49(6):961–970.
[6] Kamisawa T, Nakazawa T, Tazuma S, et al. Clinical practice guidelines for IgG4-related sclerosing cholangitis. J Hepatobiliary Pancreat Sci. 2019;26(1):9–42.
[7] Khosroshahi A, Wallace ZS, Crowe JL, et al. International consensus guidance statement on the management and treatment of IgG4-related disease. Arthritis Rheumatol. 2015;67(7):1688–1699.
[8] Yamamoto M, Yajima H, Takahashi H, et al. Everyday clinical practice in IgG4-related dacryoadenitis and/or sialadenitis: results from the SMART database. Mod Rheumatol. 2015;25(2):199–204.
[9] Brito-Zerón P, Kostov B, Bosch X, et al. Therapeutic approach to IgG4-related disease: a systematic review. Medicine. 2016;95(26):e4002.
[10] Wang L, Zhang P, Wang M, et al. Failure of remission induction by glucocorticoids alone or in

| Drugs               | Therapeutic target | Mechanism of action | Development phase |
|---------------------|--------------------|---------------------|-------------------|
| Rituximab (XmAb5871) | CD20               |                     | Phase 3           |
| Inebilizumab        | CD19               |                     | Phase 3           |
| Zanubrutinib        | BTK inhibitor      |                     | Phase 2           |
| Rilzabrutinib       | BTK inhibitor      |                     | Phase 2           |
| Abatacept           | CD80/86            |                     | Phase 2           |
| Dupilumab           | IL-4R             |                     | –                 |

Table 1. Drugs currently under development for immunoglobulin G4-related diseases (as of January 2021).
combination with immunosuppressive agents in IgG4-related disease: a prospective study of 215 patients. Arthritis Res Ther. 2018;20(1):65.
[11] Masamune A, Nishimori I, Kikuta K, et al. Randomised controlled trial of long-term maintenance corticosteroid therapy in patients with autoimmune pancreatitis. Gut. 2017;66(3):487–494.
[12] Omar D, Chen Y, Cong Y, et al. Glucocorticoids and steroid sparing medications monotherapies or in combination for IgG4-RD: a systematic review and network meta-analysis. Rheumatology. 2020; 59(4):718–726.
[13] Yamamoto M, Nojima M, Takahashi H, et al. Proposal for a Th2 immune pancreatitis. Gut. 2017;66(3):487–494.
[14] Peng Y, Li JQ, Zhang PP, et al. Clinical outcomes and predictive relapse factors of IgG4-related disease following treatment: a long-term cohort study. J Intern Med. 2019;286(5):542–552.
[15] Sasaki T, Akiyama M, Kaneko Y, et al. Risk factors of relapse following glucocorticoid tapering in IgG4-related disease. Clin Exp Rheumatol. 2018; 112(3):186–189.
[16] Mizushima I, Tsuge S, Fujisawa Y, et al. Different factors underlie recurrent and de novo organ involvement in immunoglobulin G4-related disease. Rheumatology. 2020;59(3):513–518.
[17] Masaki Y, Dong L, Kurose K, et al. Involvement of CCL1-CCR8 interaction in IgG4-related disease. Clin Exp Rheumatol. 2009; 27(8):1310–1315.
[18] Tanaka A, Moriyama M, Nakashima H, et al. Th2 and regulatory immune reactions contribute to IgG4 production and the initiation of Mikulicz disease. Arthritis Rheum. 2012;64(1):254–263.
[19] Zen Y, Liberal R, Nakanuma Y, et al. Possible involvement of CCL1-CCR8 interaction in lymphocytic recruitment in IgG4-related sclerosing cholangitis. J Hepatol. 2013;59(5):1059–1064.
[20] Maehara T, Mattoo H, Ohta M, et al. Lesional CD4+ IFN-γ+ cytotoxic T lymphocytes in IgG4-related dacyroadenitis and sialoadenitis. Ann Rheum Dis. 2017;76(2):377–385.
[21] Akiyama M, Suzuki K, Yamaoka K, et al. Number of circulating follicular helper 2 T cells correlates with IgG4 and interleukin-4 levels and plasmablast numbers in IgG4-related disease. Arthritis Rheumatol. 2015;67(9):2476–2481.
[22] Morita R, Schmitt N, Bentebibel S, et al. Human blood CXCR5(-)CD4+ T cells are counterparts of T follicular cells and contain specific subsets that differentially support antibody secretion. Immunity. 2011;34(1):108–121.
[23] Mattoo H, Mahajan VS, Maehara T, et al. Clonal expansion of CD4(+) cytotoxic T lymphocytes in patients with IgG4-related disease. J Allergy Clin Immunol. 2016;138(3):825–838.
[24] Kamekura R, Yamamoto M, Takano K, et al. Circulating PD-1+ CXCR5-CD4+ T cells underly-ing the immunological mechanisms of IgG4-related disease. Rheumatol Adv Pract. 2018;2(2): rky043.
[25] Mattoo H, Mahajan VS, Della-Torre E, et al. De novo oligoclonal expansions of circulating plasmablasts in active and relapsing IgG4-related disease. J Allergy Clin Immunol. 2014;134(3): 679–687.
[26] Shioikawa M, Kodama Y, Kuriyama K, et al. Pathogenicity of IgG in patients with IgG4-related disease. Gut. 2016;65(8):1322–1332.
[27] Du H, Shi J, Chen P, et al. Prohibitin is involved in patients with IgG4 Related Disease. PLoS One. 2015;10(5):e0125331.
[28] Hubers LM, Vos H, Schuurman AR, et al. Annexin A11 is targeted by IgG4 and IgG1 autoantibodies in IgG4-related disease. Gut. 2018;67(4): 728–735.
[29] Perugino CA, AlSalem SB, Mattoo H, et al. Identification of galectin-3 as an autoantigen in patients with IgG4-related disease. J Allergy Clin Immunol. 2019;143(2):736–745.e6.
[30] Shioikawa M, Kodama Y, Sekiguchi K, et al. Laminin 511 is a target antigen in autoimmune pancreatitis. Sci Transl Med. 2018;10(453): eaau9997.
[31] Iwata S, Saito K, Hirata S, et al. Phenotypic changes of lymphocyte in a patient with IgG4-related disease after corticosteroid therapy. Ann Rheum Dis. 2012;71(12):2058–2059.
[32] Topazian M, Witzig TE, Smyrk TC, et al. Rituximab therapy for refractory biliary strictures in immunoglobulin G4-associated cholangitis. Clin Gastroenterol Hepatol. 2008;6(3):364–366.
[33] Khosroshahi A, Carruthers MN, Deshpande V, et al. Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients. Medicine. 2012;91(1):57–66.
[34] Carruthers MN, Stone JH, Deshpande V, et al. Development of an IgG4-RD responder index. Int J Rheumatol. 2012;2012:259408.
[35] Carruthers MN, Topazian MD, Khosroshahi A, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. Ann Rheum Dis. 2015; 74(6):1171–1177.
[36] Kaegi C, Wuest B, Schreiner J, et al. Systematic review of safety and efficacy of rituximab in treating immune-mediated disorders. Front Immunol. 2019;10:1990.
[37] Unger PA, Lighaam LC, Vermeulen E, et al. Divergent chemokine receptor expression and the consequence for human IgG4 B cell responses. Eur J Immunol. 2020;50(8):1113–1125.
[38] Soliman H, Vuillermie MP, Maire F, et al. Risk factors and treatment of relapse in autoimmune pancreatitis: rituximab is safe and effective. United European Gastroenterol J. 2019;7(8):1073–1083.
[39] Majumder S, Mohapatra S, Lennon RJ, et al. Rituximab maintenance therapy reduces rate of relapse of pancreaticobiliary immunoglobulin G4-related disease. Clin Gastroenterol Hepatol. 2018; 16(12):1947–1953.
[40] Yamamoto M, Awakawa T, Takahashi H. Is rituxi-mab effective for IgG4-related disease in the long term? Experience of cases treated with rituximab for 4 years. Ann Rheum Dis. 2015;74(8):e46–e46.
[41] Marks SD, Tullus K. Targeted B-cell depletion therapy in childhood-onset systemic lupus erythe-matosus: progress to date. Paediatr Drugs. 2007; 9(6):371–378.
Isaksen K, Jonsson R, Omdal R. Anti-CD20 treatment in primary Sjögren’s syndrome. Scand J Immunol. 2008;68(6):554–564.

Wallace ZS, Mattoo H, Mahajan VS, et al. Predictors of disease relapse in IgG4-related disease following rituximab. Rheumatology. 2016;55(6):1000–1008.

Iwata S, Saito K, Tokunaga M, et al. Persistent memory B cell down-regulation after 6-year remission induced by rituximab therapy in patients with systemic lupus erythematosus. Lupus. 2013;22(5):538–540.

Iwata S, Saito K, Tokunaga M, et al. B cell or T cell-dominant recurrence after rituximab therapy in patients with SLE. Ann Rheum Dis. 2012;71(10):1749–1750.

Yamamoto M, Takahashi H, Takano K, et al. Efficacy of abatacept for IgG4-related disease over 8 months. Ann Rheum Dis. 2016;75(8):1576–1578.

Della-Torre E, Lanzillotta M, Campochiaro C, et al. Efficacy and safety of rituximab biosimilar (CT-P10) in IgG4-related disease: an observational prospective open-label cohort study. Eur J Intern Med. 2020;84:63–67.

Yun H, Xie F, Delzell E, et al. Risks of herpes zoster in patients with rheumatoid arthritis according to biologic disease-modifying therapy. Arthritis Care Res. 2015;67(5):731–736.

Loomba R, Liang TJ. Hepatitis B reactivation associated with immune suppressive and biological modifier therapies: current concepts, Management Strategies, and Future Directions. Gastroenterology. 2017;152(6):1297–1309.

Focos D, Tuccori M, Maggi F. Progressive multifocal leukoencephalopathy and anti-CD20 monoclonal antibodies: what do we know after 20 years of rituximab. Rev Med Virol. 2019;29(6):e2077.

Imafuku S, Dormal G, Goto Y, et al. Risk of herpes zoster in the Japanese population with immunocompromising and chronic disease conditions: results from a claims database cohort study, from 2005 to 2014. J Dermatol. 2020;47(3):236–244.

Yamamoto M, Aochi S, Suzuki C, et al. A case with good response to belimumab for lupus nephritis complicated by IgG4-related disease. Lupus. 2019;28(6):786–789.