Treatment: Rituximab

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Introduction

A steroid-responsive cholangiopathy associated with thyroiditis, sialoadenitis, and hypergammaglobulinemia was first described in 1963 [1] and again in 1979 [2], and the discovery by Japanese investigators of serum IgG4 as a biomarker of autoimmune pancreatitis [3] has led to increased recognition of both pancreatic and biliary IgG4-related disease (IgG4-RD). Hepatobiliary involvement by IgG4-RD is currently termed IgG4-associated sclerosing cholangitis (IgG4-SC) and in the past has been called IgG4-associated cholangitis (IAC) or IgG4-related cholangitis (IRC). IgG4-SC may involve the intrahepatic and/or extrahepatic bile ducts and may mimic the biliary strictures of chronic pancreatitis, hilar cholangiocarcinoma, or intrahepatic sclerosing cholangitis. Diagnosis of IgG4-SC may be particularly difficult if the biliary tree is the sole anatomical area affected. The classification and diagnostic approach to IgG4-SC are discussed in other chapters.

Although most cases of IgG4-SC are steroid responsive, some patients are unable to discontinue steroid therapy or relapse after steroids are withdrawn, and occasional patients do not respond adequately to steroid treatment [4]. This has led several investigators worldwide to explore alternative treatment strategies. In this chapter, we will focus on the role of rituximab (RTX) in the treatment of IgG4-SC.

Definition of Treatment Response

Successful treatment of IgG4-SC may not result in radiologic normalization of the biliary tree, and residual ductal strictures may be due to fibrosis that persists after the inflammatory process has resolved. Definition of treatment outcomes is important to guide judicious treatment decisions and for comparing effectiveness of different treatment modalities. We use the following terms and definitions for treatment response in IgG4-SC:

(a) Complete remission: Resolution of symptoms and imaging or laboratory findings of active IgG4-RD (clinical, radiographic, and biochemical), without an ongoing need for medical therapy (Fig. 18.1)
(b) Partial remission: Improvement without resolution of inflammatory changes, without an ongoing need for medical therapy
(c) Incomplete remission: Improvement without resolution of inflammatory changes and with ongoing need for medical therapy to maintain response

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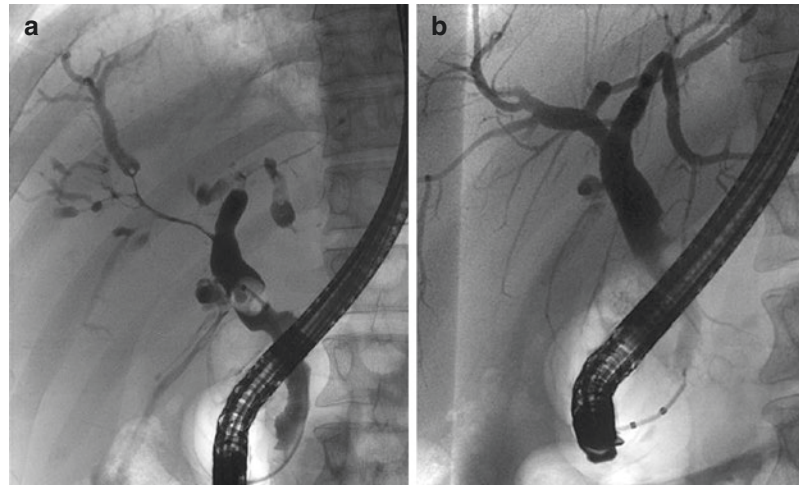

Fig. 18.1 Endoscopic cholangiogram before (**a**) and after (**b**) treatment for IgG4-SC in a patient who achieved complete remission

(d) Relapse: Development of symptoms, radiologic findings, and/or biochemical abnormalities consistent with a new or worsening inflammatory process after previous successful medical therapy, requiring retreatment
(e) Recrudescence: Development of symptoms, radiologic findings, and/or biochemical abnormalities consistent with a new or worsening inflammatory process during steroid taper and requiring an increase in the dose of steroids or additional treatments

Rituximab (RTX)

RTX is a chimeric mouse-human monoclonal antibody that binds specifically to the CD20 antigen, a transmembrane receptor located on the cell surface of pre-B and mature B lymphocytes, and induces apoptosis. RTX was initially approved by the US Food and Drug Administration in 1997 to treat resistant B-cell non-Hodgkin lymphomas. Subsequently it was approved for use in rheumatoid arthritis and has been used off-label in other autoimmune and inflammatory conditions including systemic lupus erythematosus, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, and pemphigus vulgaris. RTX was also shown to be effective in treating orbital pseudolymphoma [5], a manifestation of IgG4-RD, and pemphigus vulgaris, which is characterized by the presence of IgG4 antibodies. Primarily because of its efficacy in treatment of hematologic malignancies, RTX is on the World Health Organization's List of Essential Medicines.

The physiological effect of RTX can be monitored by flow cytometry of peripheral blood. After RTX administration, B lymphocytes (CD19- or CD20-positive cells) disappear from the peripheral circulation. Flow cytometry can be performed at intervals (for instance, 6 months after induction RTX therapy and then every 3 months thereafter) to guide decisions about maintenance infusions, if desired. Human antichimeric antibodies (HACA) directed against the murine fragments of RTX have been described and may be associated with lack of therapeutic response [6].

Rituximab is administered as a slow intravenous infusion. The optimum RTX regimen for treating IgG4-SC is unknown, and treatment regimens continue to evolve. Initially we used a lymphoma regimen that included induction with four weekly infusions of 375 mg/m^2 followed by a maintenance infusion of 375 mg/m^2 every 3 months for up to 2 years. Currently we typically prescribe two induction doses of 1000 mg spaced 2 weeks apart, with or without subsequent maintenance infusions of 1000 mg every 6 months or when B cells return in the peripheral blood. However, as the overall experience continues to grow, future studies are expected to further refine these regimens to optimize patient outcomes.

RTX in IgG4-SC

The overall experience with RTX for IgG4-SC is limited, and there are no randomized or placebo-controlled data available. A case of RTX therapy for IgG4-SC refractory to steroid therapy was reported in 2008 [4]. A case series of 12 patients with autoimmune pancreatitis, 7 with concomitant IgG4-SC, who were treated with RTX induction followed by maintenance dosing was reported in 2013 [7]. Of the seven patients with IgG4-SC, five had a complete remission, one had an incomplete remission (requiring low-dose steroid therapy), and one had a partial remission followed by worsening cholestasis and was found to have cholangiocarcinoma. The use of RTX was also described in a prospective open-label clinical trial of 30 patients with IgG4-RD, including 10 with IgG4-SC [8]. A treatment response was seen in 97% of patients in the trial, and all patients with IgG4-SC achieved a complete remission. In this cohort of patients, two induction doses of RTX were administered without maintenance therapy, and at 6 months postinduction, less than 80% of patients were steroid-free. In another retrospective study of 60 patients receiving RTX induction therapy for IgG4-RD, including five with biliary or hepatic IgG4-RD, almost half of patients had relapsed within 1 year [9]. We recently reviewed our institutional experience comparing RTX induction and maintenance therapy (n = 29) to induction therapy alone (n = 14) in pancreaticobiliary IgG4-RD, including 35 patients with IgG4-SC [10]. Overall, 86% patients in this study, the majority of whom had relapsing or recrudescent disease, were in steroid-free remission 6 months after initiating RTX. Relapses were more common in those treated with induction alone compared to those also receiving maintenance RTX (3-year event rate 45% vs. 11%). Maintenance therapy effectively prolonged remission, but the relapse rate after treatment discontinuation was not significantly different between the two groups. Although RTX was fairly well tolerated in this cohort, maintenance therapy was associated with an increased risk of bacterial infections, which occurred in 5 of 29 patients during maintenance therapy.

Adverse Effects of RTX

The adverse effects of RTX have been investigated in large series of patients receiving the drug for hematologic malignancies or other inflammatory diseases. In contrast to corticosteroids, the majority of patients receiving RTX experience no adverse effects of the drug. Certain adverse effects, such as tumor lysis syndrome and bowel perforation related to tumor lysis, are seen only in patients with malignancies. The main adverse effects of RTX in treatment of benign disorders are:

(a) Infusion reactions. Mild infusion reactions are commonly Grade 1 or 2 reactions (characterized by a rash, pruritus, flushing, urticarial, nausea/vomiting, throat or chest tightness, or asymptomatic bronchospasm) and are usually treated by stopping the infusion, administering intravenous antihistamines (H1 and H2 blockers), allowing findings to resolve, and then resuming the infusion at a slower rate [11]. Patients with Grade 3 or 4 infusion reactions (including symptomatic bronchospasm, dyspnea, hypoxia, wheezing, anaphylaxis, or hypotension) may have recurrent symptoms during same-day rechallenge and may benefit from further evaluation prior to rechallenge [11]. Severe, sometimes fatal, infusion reactions, including anaphylaxis, shock, acute respiratory distress syndrome, and myocardial infarction, have been reported in 0.04–0.07% of patients receiving rituximab. Severe mucocutaneous reactions, including Stevens-Johnson syndrome, have also been reported. Premedications (often including methylprednisolone 100 mg IV, oral acetaminophen, and diphenhydramine) are given prior to infusions to decrease the incidence of infusion reactions.

Cytokine release syndrome may occur with rituximab infusions. This syndrome mimics sepsis and is characterized by fever, rigors, and hypotension. This adverse effect is uncommon, especially when premedications are administered.

(b) Infectious complications. Rituximab can cause reactivation of hepatitis B virus (HBV) infection, sometimes leading to fulminant hepatitis. Patients who are hepatitis B surface antigen (HBsAg) positive are at high risk. Patients who are HBsAg negative but have HBV core antibodies (HBcAb+) are also at risk of reactivation, even if HBV DNA is undetectable in their blood [12], and in such patients suppressive therapy with a nucleotide or nucleoside analog should be considered for the duration of rituximab therapy (i.e., until B cells return to the peripheral circulation). In addition, reactivation of tuberculosis (TB) may occur on rituximab therapy, and guidelines recommend screening patients for TB exposure (for instance, with a QuantiFERON test) prior to prescribing RTX.

Serious bacterial infections may occur at an increased rate in patients receiving RTX. In a registry analysis of patients with rheumatoid arthritis receiving RTX, predisposing factors for bacterial infections included age, comorbidities, and low initial serum immunoglobulin G levels [13]. Patients with baseline serum IgG levels of <6 g/L may be at a fivefold increased risk, and this should be taken into account when considering RTX therapy.

(c) Progressive multifocal leukoencephalopathy (PML). PML is a frequently fatal demyelinating infection of the central nervous system caused by reactivation of JC polyomavirus infection. Neurologic presentation is highly variable depending on the regions of the brain that are affected. PML has been associated with RTX therapy, however the absolute risk is small (estimated at 1 in 20,000 rheumatoid arthritis patients receiving RTX) [14]. Pretreatment screening for JC virus infection is not recommended as over half of the adult American population has serologic evidence of prior infection.

(d) Cytopenias and hypogammaglobulinemia. These may develop following RTX induction therapy, and low immunoglobulin levels may be associated with increased rates of bacterial infections. Neutropenia is uncommon, may occur up to 1 year after RTX therapy, and is probably not an absolute contraindication to repeat RTX treatment.

Predictors of Relapse After RTX Induction Therapy

In our experience, elevated pre-RTX alkaline phosphatase levels are associated with a higher risk of relapse. Compared to patients with AIP, those with IgG4-SC were three times more likely to relapse if their alkaline phosphatase normalized with induction RTX therapy and six times more likely to relapse if their alkaline phosphatase did not normalize with induction therapy [10]. These findings highlight the high risk of disease recurrence in patients with IgG4-SC, many of whom will need repeat courses of treatment or maintenance treatment to prevent progressive liver disease.

In studies of various manifestations of IgG4-RD treated with RTX, elevations in pretreatment serum IgG4, immunoglobulin E (IgE), and blood eosinophil concentrations independently predicted future relapses in IgG4-RD. [9] Data from our center suggest that younger age and a higher IgG4-RI (IgG4-Responder Index) [15] score after induction RTX therapy are also associated with a higher likelihood of relapse in pancreaticobiliary IgG4-RD. [10] Future studies aimed at identifying predictors of relapse after RTX induction therapy are needed to identify the optimum duration of RTX treatment and guide accurate selection of patients who would benefit the most from maintenance RTX therapy.

Which Patients Should Be Considered for RTX Therapy?

While steroids remain the mainstay of initial treatment for IgG4-RD, relapse is likely in those with proximal biliary strictures. We have seen relapsing IgG4-SC rapidly lead to decompensated biliary cirrhosis and death. Therefore we monitor patients for relapse after successful steroid therapy,

including periodic measurement of serum liver tests to detect recurrent cholestasis, and promptly advise additional therapy when relapse occurs. In our experience, traditional oral immunomodulators are not effective for prevention of relapse [7], and we no longer use these drugs routinely in our practice, favoring RTX therapy in patients with relapsing disease. In addition, we may consider RTX as an initial therapeutic option in patients with a history of or risk factors for steroid intolerance and in those who are not responding to steroid therapy or unable to successfully taper steroids. An algorithm for treatment of IgG4-SC incorporating RTX therapy is shown in Fig. 18.2. Prior to initiating RTX therapy, we measure serum IgG levels and screen patients for tuberculosis, HIV, hepatitis B, and hepatitis C.

Future Directions

Although available data support a role of RTX in managing patients with IgG4-SC, several key questions remain unanswered at this time. Most importantly, the optimum duration of RTX therapy needs to be better defined. It is also equally important to study long-term adverse effects of RTX, to explore alternative treatments that might more reliably induce a sustained clinical remission, and identify biomarkers that predict relapse and can be used to individualize therapy. Randomized clinical trials are needed to study the role of RTX as first-line therapy in IgG4-SC with the goal of sustained remission, improved patient outcomes, and cost-effectiveness.

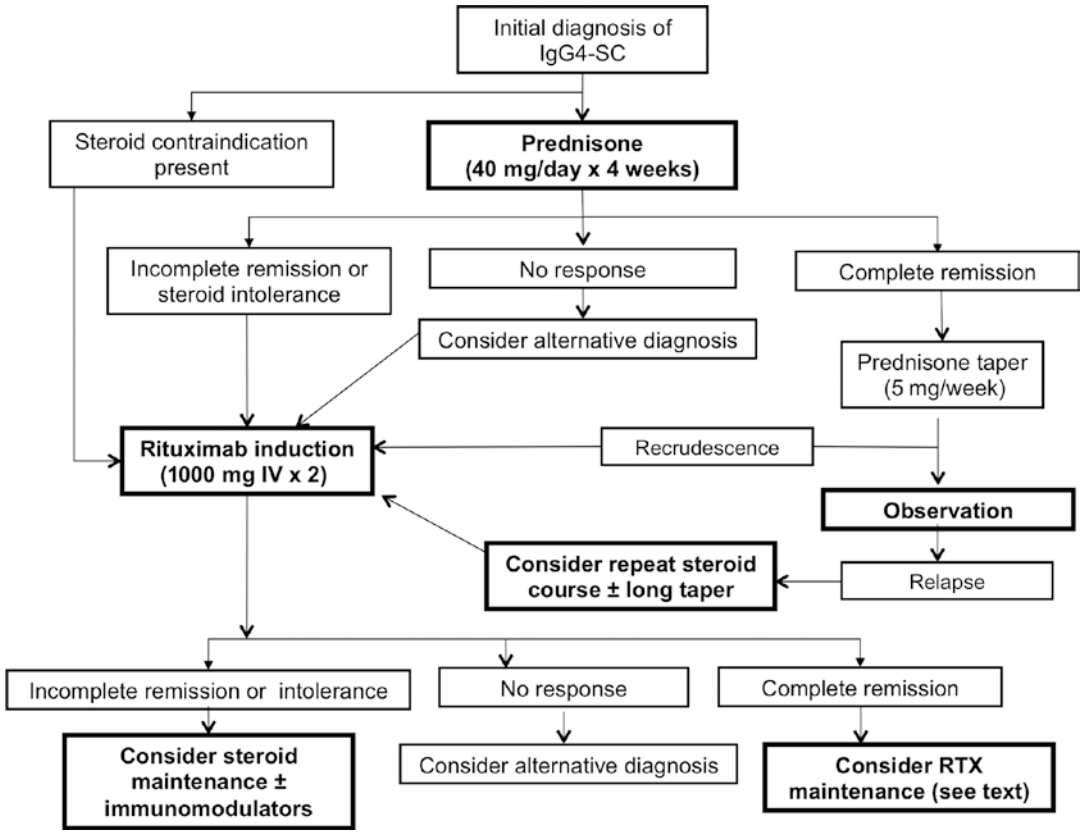

Fig. 18.2 Treatment algorithm for IgG4-SC incorporating rituximab therapy

Conclusion

The management of patients with IgG4-SC poses several challenges. Diagnosis may be difficult, response to steroid therapy may be suboptimal, and relapse is common. For patients with relapsing disease or contraindications to steroid use, RTX is the only agent currently available that will reliably induce remission. Maintenance therapy with RTX appears to effectively prolong remission and may be warranted, particularly in patients with persistent or recurrent serum alkaline phosphatase elevations. Patients receiving RTX should be screened and monitored for infections and should receive infusions in a therapeutic infusion center where infusion reactions can be properly assessed and treated.

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