

Rituximab Therapy Leads to Rapid Decline of Serum IgG4 Levels and Prompt Clinical Improvement in IgG4-Related Systemic Disease

Arezou Khosroshahi, Donald B. Bloch, Vikram Deshpande, and John H. Stone

Objective. Patients with IgG4-related systemic disease (IgG4-RSD) frequently show an incomplete response to treatment with glucocorticoids and traditional disease-modifying antirheumatic drugs (DMARDs). B lymphocyte depletion is a therapeutic strategy known to be effective for pemphigus vulgaris, an autoimmune condition mediated by IgG4 autoantibodies. This study was performed to assess the clinical and serologic responses to B lymphocyte depletion therapy with rituximab in patients with IgG4-RSD.

Methods. Four patients with IgG4-RSD were treated with 2 intravenous doses (1 gram each) of rituximab. Clinical improvement was assessed by monitoring the tapering/discontinuation of prednisone and DMARDs, and by measuring the serum concentrations of B lymphocytes, immunoglobulins, and IgG subclasses before and after therapy.

Results. Clinical features of IgG4-RSD in these 4 patients included autoimmune pancreatitis, sclerosing cholangitis, lymphoplasmacytic aortitis, salivary gland involvement, orbital pseudotumor, and lacrimal gland enlargement. The 3 patients with elevated serum IgG and IgG4 levels at baseline had a mean IgG concentration of 2,003 mg/dl (normal range 600–1,500 mg/dl) and a mean IgG4 concentration of 2,160 mg/dl (normal range 8–140 mg/dl). Among these patients, the serum IgG4 concentrations declined by a mean of 65% within 2 months of rituximab administration. All 4 patients demonstrated striking clinical improvement within 1 month of the initiation of rituximab therapy, and taper-

ing or discontinuation of their treatment with prednisone and DMARDs was achieved in all 4 patients. A decrease in IgG concentration was observed for the IgG4 subclass only.

Conclusion. Treatment with rituximab led to prompt clinical and serologic improvement in these patients with refractory IgG4-RSD, and is a viable treatment option for this condition. The decline in serum IgG4 concentrations was substantially steeper than that of the autoantibody concentrations in immune-mediated conditions in which rituximab is effective, such as in rheumatoid arthritis. In addition, the reduction in IgG-subclass levels appeared to be specific for IgG4. The swift improvement of IgG4-RSD suggests that rituximab achieves its effects in IgG4-RSD by depleting the pool of B lymphocytes that replenish short-lived IgG4-secreting plasma cells.

Recognition of disease processes that are associated with elevated serum concentrations or tissue deposition of IgG4 has grown substantially (1–3). Some conditions associated with elevated serum IgG4 concentrations share striking histopathologic similarities across a wide range of organ systems (4). These shared features have led to the concept of IgG4-related systemic disease (IgG4-RSD) (3,5). The rapidly expanding list of organs associated with this condition includes the pancreas, biliary tree, salivary glands, periorbital tissues and ocular adnexa, kidneys, lungs, lymph nodes, meninges, aorta, breast, colon, prostate, and thyroid gland (6–8). The different organs affected by IgG4-RSD can be involved simultaneously, but organ system involvement is often observed to be metachronous, thereby making the full recognition of this disorder challenging (9). Serum assays to determine the concentration of IgG4 have indicated that IgG4 levels are elevated in the majority, but not all, of the patients with this condition. The sine qua

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non of this disease is the presence of tissue-infiltrating plasma cells that bear IgG4 (10).

The optimal treatment approach for IgG4-RSD has not been established. Data on treatment are derived primarily from previous experience with patients with autoimmune pancreatitis. Several reports have emphasized that serum IgG4 concentrations decline in most patients after treatment with glucocorticoids, but they still remain above normal levels (11,12). In some patients, the disease remains refractory to glucocorticoid tapering (13). Autoimmune pancreatitis appears to relapse in up to one-third of patients treated with a maintenance dose of glucocorticoids and in more than half of those in whom a maintenance glucocorticoid regimen is not used (14). Reports of the experience with disease-modifying antirheumatic drugs (DMARDs) as steroid-sparing agents are limited in both number and detail.

B lymphocyte depletion with rituximab is now utilized as a treatment approach in a growing number of conditions associated with autoimmunity. In many cases, the initial rationale for rituximab treatment is to blunt the effects of disease-associated autoantibodies. However, the precise mechanisms through which rituximab achieves its effects appear more complex than simply via the elimination of autoantibodies (2,15). Indeed, strong indications of the clinical efficacy of rituximab have been reported in many diseases, despite the persistence of disease-associated autoantibodies (16).

We hypothesized that B lymphocyte depletion might be effective in patients with IgG4-RSD that is refractory to treatment with glucocorticoids and DMARDs, because rituximab has been observed to be an effective therapy for pemphigus vulgaris, another disorder in which IgG4 plays an important role (2). Herein we report our experience with 4 patients treated with rituximab in whom conventional treatment approaches had failed. The patients' responses to this intervention provide important information on how B lymphocytes achieve their effects in this condition, and raise important questions about the pathophysiology of IgG4-RSD.

PATIENTS AND METHODS

Diagnosis of IgG4-RSD. Our patients were diagnosed as having IgG4-RSD based on the following criteria: 1) histopathologic features consisting of a lymphoplasmacytic infiltrate, obliterative phlebitis, fibrosis, and sclerosis within the involved organs (7–17), and 2) either an IgG4+:IgG+ plasma cell ratio of >50% within the parenchyma of affected organs or >10 IgG4-bearing plasma cells per high-power field (3). All 4

of our patients had a history of elevated serum IgG4 concentrations. In addition, all 4 patients had displayed an incomplete response to glucocorticoids and DMARDs and had demonstrated refractoriness to glucocorticoid tapering.

IgG4 plasma cell quantitation and serum assay. We quantified the degree of plasma cell infiltration and IgG4 staining within biopsy specimens using the following methods. Immunohistochemical studies were performed on formalin-fixed, paraffin-embedded tissue sections using antibodies to IgG4 (1:200 dilution; Zymed) and IgG (1:3,000 dilution; Dako). For each case, the number of plasma cells staining for IgG4 was assessed in 3 nonoverlapping high-power fields (400 $\times$ magnification). The 3 fields with the highest degree of IgG4 reactivity were selected for quantitation. The number of IgG4+ plasma cells was then divided by the total number of IgG-bearing plasma cells in these fields.

The serum concentrations of IgG4 were measured by nephelometry (Mayo Medical Laboratories).

Rituximab regimen. Patients received 2 doses of rituximab (1 gram each), administered intravenously 2 weeks apart, except for that in patient 3, whose interval between the 2 doses was 1 month apart. Patients received methylprednisolone (100 mg) with each rituximab infusion, to prevent infusion reactions.

RESULTS

Case series. The baseline clinical histories of the 4 patients are summarized in Table 1. The mean interval between symptom onset and the diagnosis of IgG4-RSD was 6.5 years (range 3–9 years). Descriptions of the clinical courses of the patients before and after rituximab treatment are provided below. All patients achieved B lymphocyte depletion after the administration of rituximab.

Clinical course. Patient 1. Patient 1 is a 70-year-old man who had undergone replacement of his bicuspid aortic valve and dilated ascending aorta (9). Preoperative assessment showed extensive mediastinal and hilar lymphadenopathy. A lymph node resected at surgery showed follicular hyperplasia. Histopathologic examination of the aorta revealed chronic sclerosing aortitis. One year later, the patient developed painless swelling in both submandibular glands, a symptom consistent with sialadenitis.

Two years after his aortic surgery, he presented with painless jaundice. Computed tomography (CT) evaluation of the abdomen showed a hypodense lesion in the liver, intrahepatic ductal dilatation, and thickening of the abdominal aortic wall. A liver biopsy revealed a lymphoplasmacytic infiltrate with positive staining for IgG4 (37 IgG4+ plasma cells per high-power field; IgG4+:IgG+ plasma cell ratio 0.92). The serum IgG concentration was 4,160 mg/dl (normal range 600–1,500 mg/dl), of which 86% was of the IgG4 subclass (total

Table 1. Characteristics of the 4 patients with IgG4-related systemic disease (IgG4-RSD)

Patient/age/sex	IgG4-RSD manifestations	Treatment before rituximab (duration)	Serum IgG4, mg/dl*	
			Before rituximab	After rituximab
1/70/M	Lymphoplasmacytic aortitis, submandibular gland enlargement, autoimmune pancreatitis, sclerosing cholangitis, lymphadenopathy	Prednisone (3 years), azathioprine 100 mg/day (2 months), mycophenolate mofetil 1,000 mg twice daily (18 months), 6-mercaptopurine (1 month)	3,580	889 (6 months after)
2/53/M	Orbital soft tissue infiltration and lacrimal gland enlargement, sialadenitis of the parotid and submandibular glands	Prednisone (4 years), methotrexate 15–20 mg/week (4 years)	1,560	104 (8 months after first course; 2 months after second course)
3/65/M	Lymphoplasmacytic aortitis, mediastinal lymphadenopathy	Prednisone (1 year)	1,340	305 (6 months after)
4/54/F	Orbital pseudotumor, sialadenitis of the parotid glands	Prednisone (18 months), methotrexate 17.5 mg/week (1 year)	67	58 (4 months after)

* Normal range 8–140 mg/dl.

IgG4 concentration 3,580 mg/dl, normal range 8–140 mg/dl). The patient was diagnosed as having IgG4-RSD, with involvement of the liver, pancreas, aorta, submandibular glands, and lymph nodes. His serum IgG4 con-

centration decreased substantially, but did not normalize, following the institution of prednisone (60 mg/day) (Figure 1A).

In this patient, the IgG4-related cholangitis was

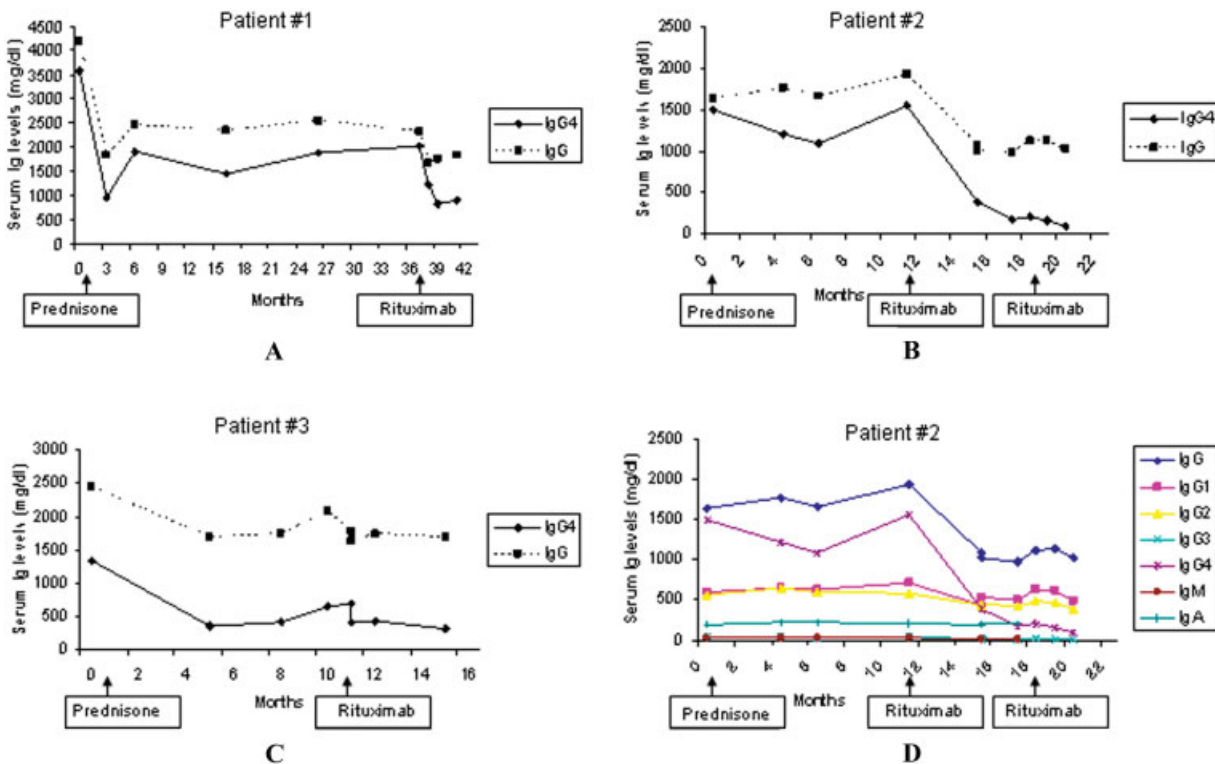


Figure 1. Serum immunoglobulin concentrations in patients with IgG4-related systemic disease (IgG4-RSD) treated with prednisone followed by rituximab. A–C, IgG and IgG4 concentrations from the time of diagnosis of IgG4-RSD in patients 1, 2, and 3. D, Concentrations of IgG, IgA, and IgM and all IgG subclasses (IgG1, IgG2, IgG3, and IgG4) in patient 2, showing no significant decline in any IgG subclass except for IgG4.

Table 2. Results of liver function tests and serum assays for IgG4 and IgG in patient 1 according to treatment course*

Treatment	AST, units/liter	ALT, units/liter	Alk. phos., units/liter	Total bilirubin, mg/dl	IgG4, mg/dl	IgG, mg/dl
No therapy, presentation 2006	53	88	498	13.3	3,580	4,160
Prednisone 60 mg/day	48	44	127	0.5	949	1,830
Prednisone 10 mg/day	66	85	328	0.6	1,910	2,460
Mycophenolate mofetil plus prednisone	61	61	304	2.2	1,890	2,550
Before rituximab	211	216	492	1.2	>2,000	2,310
1 month after rituximab	39	53	155	0.5	1,220	1,670
2 months after rituximab	33	45	128	0.6	823	1,740
6 months after rituximab, off prednisone	30	40	123	0.5	889	1,830

* Normal ranges are as follows: for aspartate aminotransferase (AST), 10–55 units/liter; for alanine aminotransferase (ALT), 10–44 units/liter; for alkaline phosphatase (Alk. phos.), 45–115 units/liter; for total bilirubin, 0–1 mg/dl; for IgG4, 8–140 mg/dl; and for IgG, 600–1,500 mg/dl.

refractory to glucocorticoid tapering, and his condition remained active despite treatment with prednisone at a dose of 20 mg/day and azathioprine at 100 mg/day. Biochemical evidence of active inflammation within the liver and biliary tree persisted following the replacement of azathioprine with mycophenolate mofetil at 1,000 mg twice daily; the patient did not tolerate treatment with 6-mercaptopurine (Table 2). He therefore underwent treatment with rituximab. Within 7 weeks of completing the rituximab course, the patient's serum IgG4 concentration declined from its peak of 2,020 mg/dl right before rituximab administration to 823 mg/dl at 7 weeks after rituximab administration (a 60% decline) (Figure 1A). The levels of liver enzymes declined promptly (Table 2) and continued to decline to normal levels within 6 months after administration of the rituximab infusions.

In this patient, treatment with prednisone was tapered and then completely discontinued 6 months after the initiation of rituximab therapy. His serum IgG4 concentration 6 months after rituximab therapy was 889 mg/dl, which was ~2,700 mg/dl lower than the concentration at baseline (pretreatment).

Patient 2. Patient 2 is a 53-year-old man with a history of asthma who developed left eye swelling 8 years before presentation. He had marked enlargement of the extraocular muscles, swelling of the left fifth cranial nerve, and abnormal soft tissue extending from his left orbit through the left greater palatine foramen into the pterygomaxillary cistern. He was diagnosed as having an idiopathic orbital pseudotumor following a biopsy of the periorbital region. Treatment with prednisone (60 mg/day) improved his periorbital swelling, but lowering of



Figure 2. Decrease in parotid gland swelling 2 months after (B) versus before (A) rituximab therapy in a patient with IgG4-related systemic disease (patient 2). Color figure can be viewed in the online issue, which is available at <http://www.arthritisrheum.org>.

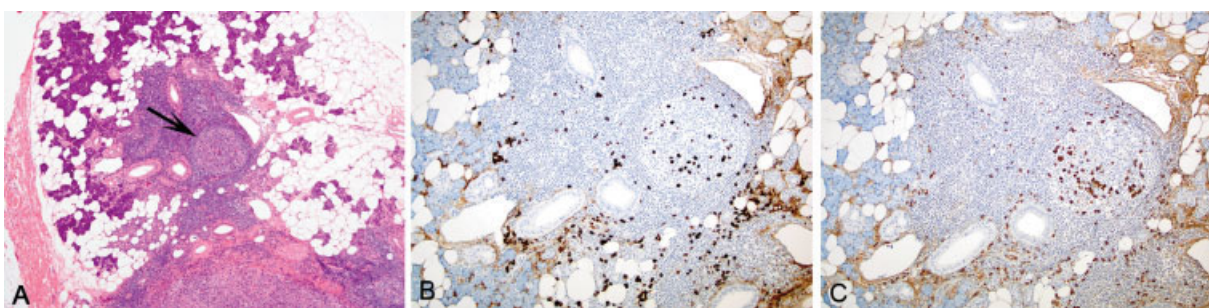


Figure 3. Histopathology (A) and immunohistochemical analyses (B and C) of the parotid gland of patient 2, showing chronic sialadenitis of the parotid gland with a germinal center (arrow) surrounded by a lymphoplasmacytic infiltrate (stained with hematoxylin and eosin) (A), as well as numerous IgG4+ cells, including some within the germinal center (stained with IgG4 immunoperoxidase) (B), and IgG+ plasma cells (stained with IgG immunoperoxidase) (C). The ratio of IgG4+ to IgG+ cells is >0.9 . (Original magnification $\times 100$.)

the daily prednisone dose resulted in recurrent, bilateral periorbital disease and parotid enlargement (Figure 2A). A biopsy of his parotid gland revealed chronic sialadenitis (Figure 3A). Six years before presentation, mediastinal lymphadenopathy was detected on a chest radiograph, and a large lymph node was noted in the left axilla. Biopsy of the axillary node revealed lymphoid hyperplasia without evidence of malignancy.

Four years before presentation, weekly injections of methotrexate (15–20 mg/week) were added to the patient's prednisone regimen (at that time, 20 mg/day). Attempts to taper the dose of prednisone were accompanied by worsening periorbital and parotid gland disease and the development of recurrent sinusitis. Serum IgG-subclass concentrations were measured because of concern about a possible immunodeficiency. The serum IgG4 concentration was 1,560 mg/dl (normal range 8–140 mg/dl). Reevaluation of the parotid gland biopsy findings revealed a lymphoplasmacytic infiltrate with intense IgG4 staining (120 IgG4+ plasma cells per high-power field; IgG4+:IgG+ plasma cell ratio >0.9) (Figures 3B and C).

This patient tolerated treatment with methotrexate poorly, experiencing nausea after treatment, and developed hypertension, hyperglycemia, and obesity while receiving prednisone. For these reasons, treatment with rituximab was initiated. During rituximab treatment, the patient's serum IgG4 concentrations declined, as shown in Figure 1B. Within 1 month of completing the rituximab regimen, the ocular and salivary gland swelling had improved dramatically (Figure 2B). CT imaging confirmed substantial decreases in the size of the left extraocular muscles, the left lacrimal gland, and the left parotid soft tissue lesion. Six months after receiving the rituximab infusions, the patient's serum IgG4 concentration had declined from 1,560 mg/dl at

baseline to 178 mg/dl. Among all of the IgG subtypes, only the IgG4 concentration decreased, accounting entirely for the decline in total serum IgG concentrations (Figure 1D).

The patient's B cells began to return 6 months after his initial course of rituximab, and his serum showed an elevation in the IgG4 concentration to 206 mg/dl. He was given a second course of rituximab using the same infusion protocol. Three weeks after the second rituximab course, the patient's serum IgG4 concentration had normalized, this being the first normalization of his IgG4 levels known to occur during his treatment course, to a concentration of 104 mg/dl (1,400 mg/dl lower than his pretreatment peak concentration). This patient has been able to completely discontinue prednisone treatment for the first time in several years.

Patient 3. Patient 3 is a 65-year-old man with a history of mediastinal lymphadenopathy and a lymph node biopsy that showed reactive follicular hyperplasia. He was found to have a focal aortic dissection in the ascending aorta (8). He underwent repair of the ascending aorta and hemiarch, as well as replacement of the aortic valve. Pathologic analysis of the aorta revealed the presence of lymphoplasmacytic aortitis. Immunohistochemical studies yielded positive staining for IgG4 (IgG4+:IgG+ plasma cell ratio 0.74). His serum IgG concentration was 1,863 mg/dl (normal range 600–1,500 mg/dl), and his serum IgG4 concentration was 1,340 mg/dl (normal range 8–140 mg/dl). Reexamination of the lymph node, which was removed 4 years earlier, revealed extensive infiltration by IgG4+ plasma cells, with more than 50% of plasma cells staining for IgG4.

The patient was treated with glucocorticoids in order to prevent recurrent aortitis. He began treatment with 40 mg/day prednisone, which was tapered to 30 mg/day after 1 month and 10 mg/day after 6 months. His

serum IgG4 concentration declined, initially to 347 mg/dl (normal range 8–140 mg/dl), but rose to 688 mg/dl after his daily prednisone dose was tapered to 10 mg/day (Figure 1C). He tolerated treatment with prednisone poorly, as indicated by a posttreatment 20-pound weight gain and development of hyperglycemia. He was therefore treated with rituximab as a potential glucocorticoid-sparing agent. Four weeks after treatment with rituximab, the serum IgG4 concentration had declined to 424 mg/dl. The patient's prednisone dose was tapered to 2.5 mg/day within 1 month of the rituximab infusions.

Six months after receiving his first rituximab dose, his serum IgG4 concentration continued to decline to its lowest level ever recorded, 305 mg/dl (more than 1,000 mg/dl lower than his pretreatment peak concentration). Currently, the patient has been able to achieve complete discontinuation of his prednisone treatment. A followup CT scan revealed a decrease in his mediastinal lymphadenopathy.

Patient 4. Patient 4 is a 54-year-old woman who developed swelling of her eyelids and sinus discharge 9 years before presentation. She underwent unsuccessful sinus surgeries for her symptoms, which were attributed to allergies. Five years before presentation, the patient underwent a biopsy of her enlarged periorbital soft tissue. The histologic findings were interpreted as indicative of reactive lymphoid hyperplasia. The eye swelling responded to a 1-month course of glucocorticoids. Three years before presentation, the patient's periorbital swelling worsened and she developed bilateral parotid gland enlargement. An orbital CT scan showed abnormal soft tissue widening at the pterygopalatine fossa bilaterally and enlargement of the lacrimal and parotid glands. Histopathologic examination of her retrobulbar tissue revealed a sclerosing inflammatory pseudotumor. More than 50% of the infiltrating plasma cells stained for IgG4. The serum IgG4 concentration was 401 mg/dl (normal range 8–140 mg/dl).

The patient began receiving prednisone (15 mg/day) for Mikulicz's disease, which improved her symptoms. After 9 months of prednisone, her serum IgG4 concentration had decreased to 95.4 mg/dl (normal range 8–140 mg/dl). Methotrexate was added as a glucocorticoid-sparing agent, and the dose was increased to 17.5 mg/week, but periorbital and parotid gland swelling increased whenever the prednisone dose was decreased to below 10 mg/day. The patient received more than 6 months of methotrexate therapy at a dose of 17.5 mg/week. She experienced side effects from the prednisone and methotrexate regimens, which included obesity, hypertension, hyperglycemia, alopecia, and serum transaminase elevation, and was therefore treated

with rituximab. Decreases in periorbital swelling and parotid gland firmness were detected within 2 weeks of her first rituximab infusion. She was able to discontinue both the methotrexate and the prednisone within 1 month of completing the rituximab infusions, without worsening of her symptoms. The patient has been able to remain off these medications, and her serum IgG4 concentration at 4 months after rituximab treatment is 58 mg/dl (normal range 8–140 mg/dl).

DISCUSSION

In this report, we describe 4 patients with diverse manifestations of IgG4-RSD who underwent B lymphocyte depletion therapy with rituximab. Their treatment responses suggest that B lymphocyte depletion is a viable therapeutic option for patients with refractory IgG4-RSD. The results in these patients also provide important information about the mechanism of the effectiveness of rituximab and raise important questions about the pathophysiology of IgG4-RSD.

Four major observations have framed the concept of IgG4-RSD. First, the entity of autoimmune pancreatitis was identified in the early to mid 1990s (18). Second, it was recognized that autoimmune pancreatitis is associated with elevations in the serum IgG4 concentration (17–19). Third, the similarity of histopathologic findings across a spectrum of organ systems infiltrated by IgG4-bearing plasma cells was established (20). Finally, the frequent co-occurrence of similar disease processes within at least 2 organs of the same patient was recognized (14). IgG4-RSD is capable of involving multiple organs in an insidious and potentially destructive manner (8,9,21). The fundamental nature of IgG4-RSD, and whether IgG4+ plasma cell infiltration is actually a primary phenomenon or, rather, a secondary phenomenon remain unclear.

Rituximab is a chimeric monoclonal antibody directed against the B lymphocyte-specific antigen CD20. The CD20 antigen is first expressed in the bone marrow on components of the B lymphocyte lineage at the pre-B lymphocyte stage (15). This antigen is lost following the maturation of fully developed B lymphocytes into plasma cells. Rituximab depletes all components of the B lymphocyte lineage from the pre-B lymphocyte stage through the mature B lymphocyte stage within 2–4 weeks of administration (22). Of note, the infiltrating cells in patients with IgG4-RSD are plasma cells, not B lymphocytes. Plasma cells do not normally express CD20 and are not affected directly by anti-CD20 strategies.

We hypothesize that rituximab achieves its effects

in IgG4-RSD by disrupting the normal differentiation of IgG4-bearing B lymphocytes into plasma cells. This hypothesis is supported by the observed rapid decrease in serum IgG4 concentrations relative to those of other IgG subclasses and total IgG, suggesting that IgG4-bearing plasma cells are inherently shorter-lived than plasma cells that express other IgG subclasses. Treatment with rituximab leads indirectly to the disappearance of IgG4-bearing plasma cells within 2 weeks; such plasma cells are not replaced because of the effects of rituximab on IgG4-bearing B lymphocytes. The dramatic shrinkage of the parotid glands in patient 2 (Figures 2A and B) and the rapid decline in the levels of liver enzymes in patient 1 (Table 2) are consistent with the effects achieved in other conditions by the removal of cells, leading to relief of a mechanical obstruction. It is likely that our patients' swift clinical improvement was mediated by a reduction in the plasma cell mass.

Our observation of a rapid decrease in the IgG4 concentrations contrasts significantly with the effects of rituximab in other diseases. In rheumatoid arthritis (RA), the impact of rituximab on immunoglobulin concentrations is far less pronounced. After treatment, titers of rheumatoid factor decrease by 30–60%, but this only begins 3–6 months after rituximab administration (23,24). The decline in anti-cyclic citrullinated peptide antibody titers is less marked. RA patients treated with rituximab demonstrate modest declines in serum IgG concentrations, but the overall concentrations remain normal. Serum IgM concentrations decline slowly, but continuously, with each subsequent course of rituximab (25). In patients with systemic lupus erythematosus, the effects of rituximab vary according to the specific autoantibody. Levels of antibodies to double-stranded DNA and C1q decrease as early as 2 months after rituximab administration (22). In contrast, autoantibodies directed against the Sm, RNP, Ro, and La antigens remain unchanged (23,26). To our knowledge, the effect of rituximab on the concentrations of IgG subclasses has not been reported in RA, lupus, or other diseases.

The etiology of IgG4-RSD remains obscure. Infiltration by IgG4+ plasma cells and the histopathologic features of storiform fibrosis, eosinophilic infiltration, and obliterative phlebitis are consistent findings in IgG4-RSD, regardless of the organs affected (7,17). The cellular histopathology is also characterized by numerous T and B lymphocytes, some of which are organized into lymphoid aggregates. Germinal centers, packed with B lymphocytes, are prominent, particularly in the salivary and lacrimal glands. IgG4-bearing plasma cells are frequently seen within these germinal centers. Prominence of fibroblasts and tissue fibrosis are typical of

IgG4-RSD, which is often regarded as a sclerosing disease.

Two explanations for the elevated number of IgG4-bearing plasma cells in this disease appear plausible. First, the overproduction of IgG4-bearing plasma cells could be caused by a subset of dysregulated T cells that recruit IgG4-bearing B lymphocytes to the affected organs and thus drive their differentiation into secretory IgG4-bearing plasma cells. In support of this point, Treg cells have been reported to be present in large numbers within the tissue of patients with IgG4-related autoimmune pancreatocholangitis (27). These Treg cells are accompanied by excessive quantities of cytokines, e.g., interleukin-4 (IL-4), IL-5, IL-13, IL-10, and transforming growth factor β (TGF β), that fall within a Th2 profile (27). Both IL-4 and IL-10 play major roles in directing B lymphocytes to produce IgE and IgG4, respectively (28,29). Cytokines produced by these Treg cells could fuel the infiltration of secretory IgG4+ plasma cells into the different organs and explain the elevated serum concentrations of IgG4. The tissue fibrosis that is characteristic of IgG4-RSD corresponds to the presence of TGF β .

A second possibility is that the primary overproduction of IgG4 is an antigen-driven Th2 immune response, triggered by an infection, autoantigen, allergen, or some other environmental factor. In this scenario, the production of IgG4+ B lymphocytes and subsequent differentiation of these cells into plasma cells is the primary event; Treg cells are recruited secondarily to the affected tissues for the purpose of dampening the immune response. The frequent presence of eosinophils within involved tissues, reports of elevated serum IgE concentrations in patients with IgG4-RSD, and the elevations of serum IgG4 concentrations are consistent with both this theory and the first theory discussed above (30).

Caution is appropriate when interpreting these results. This report includes data on only 4 patients with IgG4-RSD, and the followup on these patients remains relatively short. The findings reported herein require confirmation and refinement in larger studies of prospectively collected cohorts of patients whose clinical features represent the broad spectrum of IgG4-RSD. It is possible that certain disease subsets with IgG4-RSD will respond better than others to B cell depletion strategies, and that duration of disease, the degree of tissue fibrosis, and other factors will also affect treatment response.

Thus, rituximab appears to be a viable treatment option for patients with IgG4-RSD that is refractory to conventional immunosuppressive therapy. The precise

mechanism of the effectiveness of rituximab is not known, but hypotheses concerning either dysregulated T cells or antigen-driven processes must be explored further. Detailed investigations of B lymphocyte depletion strategies in this condition are essential in order to determine the precise place of rituximab in the treatment algorithm. In addition, mechanistic studies that examine the specific effects of B lymphocyte depletion on different components of the immune system may yield new insights into the nature of IgG4-RSD.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Stone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Khosroshahi, Bloch, Deshpande, Stone.

Acquisition of data. Khosroshahi, Bloch, Deshpande, Stone.

Analysis and interpretation of data. Khosroshahi, Bloch, Deshpande, Stone.

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