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IgG4-related Disease: 2013 Update

Paul A. Monach, MD, PhD

Vasculitis Center and Section of Rheumatology, Boston University School of Medicine, 72 East Concord Street, E-533, Boston, MA 02118, Phone: 617-414-2503, Fax: 617-414-2510, pmonach@bu.edu

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Opinion statement

Having diagnosed a patient as having IgG4-related disease, I would have a low threshold for recommending immune-suppressive treatment, and would make that recommendation for any patient with vascular involvement. My initial approach would be prednisone at 40–60 mg/day with a plan to reduce the dose every two weeks, e.g., 40, 30, 20, 15, 10, 7.5, 5, and 2.5 mg for 2 weeks each. In the event of relapse, I would double the current prednisone dose, slow the taper, and add azathioprine, anticipating using that drug for one year if the patient were to remain in remission. In the event of subsequent relapse, I would stop azathioprine and use rituximab. In a patient with large artery involvement, I would consult a vascular surgeon soon after diagnosis, anticipating a need for surgical repair.

Introduction

Over the past decade, researchers from multiple specialties have discovered that a group of rare fibro-inflammatory diseases of diverse organ systems share pathologic features, including a striking prominence of plasma cells secreting the immunoglobulin subtype IgG4¹. A recent consensus conference produced a recommendation to use the term “IgG4-related disease” to encompass these entities, and to add “IgG4-related” to terms denoting inflammation in individual organ systems^{1*}. Those organ systems are numerous and include the pancreas, orbit (including lacrimal gland, extraocular muscles, and/or other soft tissues producing an orbital pseudotumor), salivary glands, meninges, pituitary, thyroid, lymph nodes, lungs (parenchyma or pleura), kidney (tubulointerstitial nephritis), biliary tree, gall bladder, liver, breast, prostate, skin, peripheral nerve, and—of greatest importance to cardiovascular physicians and surgeons—pericardium^{2–4}, mediastinum², retroperitoneum^{5,6}, aorta^{5–8*}, and large arteries⁹. It is likely that involvement of additional organ systems by IgG4-related disease will be confirmed.

Many patients have only one organ system involved (at least on clinical grounds), but the majority have two or more organs involved, although involvement of numerous organ systems is uncommon^{10,11}. Many patients with pancreatitis also have sclerosing cholangitis (70%) and/or sialadenitis (40%), but less than 20% of patients presenting with sialadenitis also have pancreatitis^{11,12}. Involvement of additional organs can occur over time¹³. Since the disease was defined recently, the overall prevalence of this disease and involvement of specific organs is uncertain. Most of the literature consists of small case series in individual organ systems, and the largest series of IgG4-related disease across multiple organ systems described 114 cases¹⁰. Two recent surveys estimated that 10,000 patients in Japan had IgG4-related disease in 2009^{14,15}, for a prevalence of about 1 in 20,000 people. It is not

known whether the disease is most common in Japan, or simply that it was first recognized by Japanese investigators^{16, 17}. More than 60% of patients are men, and the majority are over age 50^{13, 14}.

Pancreatitis and sialadenitis (inflammation of salivary glands) are probably the two most common manifestations, but the likelihood of IgG4-related disease also varies depending on the prevalence of other conditions that can compromise organ function or cause tumor-like masses. For example, IgG4-related thyroid disease (Reidel's thyroiditis in the older literature), sialadenitis (Mikulicz's syndrome if also associated with dacryoadenitis = inflammation of the lacrimal gland, Kuttner's tumor if limited to the submandibular gland), and pericarditis are presumed to be far less common than other causes of hypothyroidism, sialadenitis, and chronic pericarditis. For less-common clinical presentations such as chronic pancreatitis or sclerosing cholangitis, IgG4-related disease probably accounts for 2–10% of cases^{13, 18}, and percentages in that range might also be predicted for pseudotumors in various locations.

Although estimates are imprecise, IgG4-related disease seems to account for a relatively large fraction (10–50%) of patients with non-infectious inflammatory aortitis or retroperitoneal fibrosis^{5–8, 19, 20}. Estimates have been higher for abdominal than thoracic aneurysms, but the studies are too small and too few in number to draw firm conclusions^{8, 19, 20}. An isolated inflammatory thoracic aortic aneurysm presents in the same manner as a non-inflammatory aneurysm, either with catastrophic rupture, aortic valve insufficiency, or without symptoms (discovered incidentally on imaging). The inflammatory nature of the aneurysm is often a surprising finding noted on pathologic examination. In contrast, patients with retroperitoneal fibrosis and inflammatory abdominal aortic aneurysm (IAAA) present with back pain in 80% of cases, and sometimes with abdominal pain or symptoms of ureteral obstruction²¹. IAAA appears to have a lower risk of rupture (5%) than atherosclerotic AAA, but that possibility still needs to be considered (REF). Even before the discovery that retroperitoneal fibrosis and IAAA can be part of the spectrum of IgG4-related disease, it was proposed that they are part of a continuum of disease that might be summarized as periaortitis²¹. Although periaortitis is indeed a prominent feature in IgG4-related disease affecting the aorta, true aortitis affecting the media is also seen^{1, 8} and is presumably responsible for the development of aneurysms. In the recent consensus conference on nomenclature, the term “IgG4-related aortitis/periaortitis” was advocated¹.

A few cases of IgG4-related disease affecting arteries smaller than the aorta have been published, and affected arteries have been more often dilated than stenotic^{2, 9, 22–25}. Arteries involved have included the superior (n=3) and inferior (n=1) mesenteric arteries as well as more peripheral branches of these arteries (n=1)^{2, 22}, the splenic artery (n=1)²², and the coronary arteries (n=3)^{2, 23, 24}.

In addition, at least two cases of coronary periarteritis associated with periaortitis were reported before the definition of IgG4-related disease, in patients who also had severe atherosclerosis^{26, 27}. Whether the coronary arteries are at particular risk, or whether this site is simply of particular danger and interest, is unclear. Some cases of IgG4-related pulmonary disease have been described as including vascular inflammation^{28, 29}, but others have regarded pulmonary disease as parenchymal^{30, 31}. In addition to an enrichment for IgG4-positive plasma cells, the pathology of IgG4-related disease shows remarkable similarity in different organ systems. At the same consensus conference at which nomenclature was proposed, standardized pathological criteria were developed, and these criteria emphasize the morphological appearance more than the number of IgG4-positive plasma cells or the ratio of IgG4-positive to total IgG-positive cells³². The three key morphologic features are a dense lymphoplasmacytic infiltrate, a storiform pattern of fibrosis (“matted and irregularly

whorled”¹³), and obliterative phlebitis^{13,32}. Since application of rigorous criteria can be expected to reduce sensitivity, the authors emphasized that their guidelines “do not supplant careful clinicopathologic correlation and sound clinical judgment.”³² Most patients with IgG4-related disease have elevated serum IgG4, but as many as 40% do not¹³, so normal circulating IgG4 does not rule out the disease. Similarly, many other diseases feature elevated IgG4¹³, and only 29 of 158 patients (18%) with elevated IgG4 in a hospital-wide laboratory medicine survey were thought to have IgG4-related disease³³. Thus, biopsy remains important in most cases, but unfortunately, the organs involved in IgG4-related disease are often those that surgeons are not eager to biopsy, such as the pancreas, bile duct, or periaortic tissue. It is likely that there will be a rapid transition from IgG4-related disease being under-diagnosed to being overdiagnosed based on elevated serum IgG4.

IgG4-related disease is suspected to be autoimmune in origin, but investigations in this area are in their infancy, and convincing data are lacking. The best evidence for antigen-specific immunity in pathogenesis is an association of IgG4-related autoimmune pancreatitis with the class II HLA alleles DRB1*0405 and DQB1*0401³⁴.

TREATMENT

Pharmacologic treatment

There are no controlled trials of treatment for IgG4-related disease, so the evidence behind treatment recommendations is based on case series and expert opinion. Since spontaneous improvement occurs in about 70% of patients with autoimmune pancreatitis (AIP), at least among those with milder disease³⁵, case series need to be interpreted with caution. That being said, the anecdotal evidence that glucocorticoids (prednisone and similar drugs) are effective is quite strong, and it is remarkable that a disease with such a strong fibrotic component usually shows objective evidence of improvement within 1 month of starting prednisone treatment^{35,36}. Outcome measures are in an early stage of development³⁷ and have not yet been validated, but in critically interpreting the anecdotal data, it is notable that IgG4-related disease in most organ systems is amenable to objective measurement of tumorous lesions or, in the cases of pancreatitis or sclerosing cholangitis, using biomarkers of organ function. Permanent organ damage preceding treatment may still place limits on reversibility with medical treatment, for example with aortic aneurysms, and it is in that setting that evaluation of medical treatment is most challenging, and that need for surveillance with possibility of surgical approaches should be anticipated.

Glucocorticoids (prednisone or prednisolone)

The best data related to glucocorticoids in IgG4-related disease are related to AIP with or without cholangitis, but recall that IgG4-related disease is only the first of two types of AIP. Although 74% (77/104) of untreated patients with AIP went into remission spontaneously in one large observational study, 98% (451/459) of patients treated with prednisolone achieved remission, and the latter group presumably had more severe disease³⁵. Time to remission was shorter in the treated group. Patients who were kept on low doses of prednisolone for “maintenance” therapy had lower rates of relapse (23%, 63/273) than patients who were tapered off prednisolone (34%, 35/104) or never received prednisolone but had gone into remission spontaneously (44%, 32/77). On the basis of this and smaller studies with consistent findings^{38,39}, consensus guidelines were developed in Japan for treatment of AIP⁴⁰: prednisolone 0.6 mg/kg/day initially for 2–4 weeks, then reduction by 5 mg every 1–2 weeks (if the patient does well) until a dose of 2.5–5 mg is reached (2–3 months), with a recommendation to consider continuing that maintenance dose for 6–36 months.

A somewhat different regimen has been developed at the Mayo Clinic, based on experience treating patients with cholangitis^{41,42}: prednisone 40 mg/day for 4 weeks, then reduction by

5 mg weekly until off completely (thus 11 weeks total). Relapses occurred in 53% (16/29) of patients treated this way⁴¹. Thus, although there is a hint that low-dose prednisone/prednisolone may reduce the risk of relapse, the data are not conclusive, but what is clear is that many patients remaining on glucocorticoids suffer relapses, and many who are tapered off steroids remain relapse-free.

The only randomized trial that might be considered to support the effectiveness of glucocorticoids in IgG4-related disease compared prednisone to tamoxifen for maintaining remission in retroperitoneal fibrosis, but it is unknown how many patients in that study had IgG4-related disease⁴³. Initial remission was induced in 90% of patients (36/40) using prednisone at 1 mg/kg for one month, a response rate compatible with the preceding anecdotal literature in a disease in which spontaneous remission, in contrast to autoimmune pancreatitis, has not been prominently reported²¹. Anecdotally, glucocorticoids are also highly effective for treating aortitis, sialadenitis, and orbital pseudotumor^{6, 44, 45}. Relapse after successful treatment is common in retroperitoneal fibrosis²¹, but data specifically on cases due to IgG4-related disease are limited.

The side effects of glucocorticoids are numerous and well-known. Those of greatest concern to physicians include diabetes, hypertension, osteoporosis, and risk of infection. Additional side effects that are often of greater concern to patients include disruption of sleep, effects on mood and concentration, weight gain, cushingoid appearance, easy bruising and poor wound healing, and muscle weakness. Whether these risks and side effects are considered to be major or minor contraindications to treatment depends on the patient. Glucocorticoids have few if any clinically relevant interactions with other drugs. Prednisone is the standard oral glucocorticoid used in the U.S. and is inexpensive. It must be converted to its active metabolite, prednisolone, in the liver; cases in which patients apparently cannot activate prednisone to prednisolone occur but are thought to be rare, and it is arguably only in those cases in which an active and more expensive drug, methylprednisolone, should be used. Methylprednisolone, which is also the most common IV glucocorticoid used in the U.S., is 25% more potent than prednisone, so that 4 mg methylprednisolone is equivalent to 5 mg prednisone. Prednisolone, which is also an active drug with equal potency to prednisone, is the most common oral glucocorticoid in many European and Asian countries.

Oral immune-suppressive drugs

Because of the numerous side effects of glucocorticoids, particularly when they are continued long-term even at low doses, alternative immune-suppressive treatments have been sought. In patients who do not respond to prednisone, or do not tolerate it, or suffer relapses requiring repeated courses of high doses, other drugs have been used empirically as “steroid-sparing” agents. Azathioprine (2–2.5 mg/kg/day) and mycophenolate (750 mg twice/day) have been associated with maintenance of steroid-free remission in very small numbers of cases⁴¹, but since these drugs appear to be beneficial in a wide range of chronic autoimmune inflammatory disease, their use in the setting of relapsing IgG4-related disease in any organ system seems quite reasonable³⁶. Methotrexate, another widely used drug in rheumatology, has not been advocated in IgG4-related disease, probably because the main report on steroid-sparing agents was in sclerosing cholangitis⁴¹, and hepatic fibrosis is a major concern with long-term use of methotrexate. Anecdotally, methotrexate and azathioprine have been advocated as steroid-sparing agents in retroperitoneal fibrosis, without reference to IgG4-related disease²¹.

All of these drugs increase the risk of infection, probably to a similar degree although it has been argued that the risk is low with methotrexate⁴⁶; in any case, all are thought to be less immune-suppressive than moderate or high doses of prednisone. All of them can cause gastrointestinal discomfort and constitutional symptoms, and concern has been raised about

increased risk of lymphoma. Methotrexate and mycophenolate are teratogens and are absolutely contraindicated during pregnancy; azathioprine, in contrast, has an acceptable safety record during pregnancy based on series of patients with lupus or organ transplants. Azathioprine, methotrexate, and mycophenolate can cause marrow suppression, usually manifested by isolated leukopenia, which is seen more frequently with azathioprine; it is often advised to perform a genetic or metabolic test to screen patients for deficiency in thiopurine methyltransferase (TPMT), since patients lacking this enzyme cannot metabolize azathioprine efficiently and are at high risk of hematologic toxicity. Azathioprine has an important drug interaction with allopurinol, which blocks another enzyme important in the metabolism of azathioprine (xanthine oxidase) and thus can generate dangerously elevated drug levels. Other important side effects of azathioprine include, but are not limited to, hepatitis and pancreatitis. Methotrexate has an important interaction with alcohol in synergistically or additively increasing the risk of hepatic fibrosis and cirrhosis, and patients are advised to drink little or no alcohol. Other important side effects of methotrexate include oral ulcers and, rarely but importantly, a pulmonary hypersensitivity reaction that can be life-threatening. Many of the side effects of methotrexate can be reduced or prevented with the use of daily folic acid (1–2 mg/day) or weekly folinic acid (at least 5 mg the day after methotrexate). Mycophenolate has particularly prominent gastrointestinal side effects and has occasionally been associated with colonic bleeding. Azathioprine and methotrexate are inexpensive; mycophenolate is more expensive.

Rituximab

Rituximab is a monoclonal antibody that eliminates B cells by binding the cell-surface marker CD20. Since plasma cells do not express CD20, rituximab does not deplete them, and since plasma cells are thought to be the main producers of IgG antibodies, it was somewhat surprising that rituximab was found to be effective in treating diseases mediated by IgG antibodies, and that titers of the pathogenic antibodies fall after treatment, either modestly or dramatically. It has subsequently been found that there are long-lived and short-lived plasma cells, that short-lived plasma cells must be continually regenerated by differentiation of CD20+ B cells, and that short-lived plasma cells are often major producers of antibodies in autoimmune diseases. Thus, it was plausible to consider rituximab as a potential treatment for IgG4-related disease, even though the pathology of the disease is so closely linked to IgG4-secreting plasma cells.

The first case of a patient with steroid-refractory IgG4-related disease (AIP and cholangitis) who responded well to rituximab was reported in 2008⁴⁷. More recently, a series of 10 patients, 5 of whom had required chronic treatment with prednisone for years, was treated with rituximab, two 1000 mg IV treatments two weeks apart⁴⁸. Improvement was seen in 90% (9/10) patients within a month, and all 10 patients were able to discontinue prednisone and other immune-suppressive drugs. Two patients suffered relapses about 6 months after rituximab treatment, but responded to re-treatment with rituximab either with or without a short course of prednisone. Thus, in contrast to oral immune-suppressive drugs, there is anecdotal evidence that rituximab can act as a remission-inducing agent rather than merely as a remission-maintenance agent.

Among the 6 patients with elevated serum IgG4 at the time of rituximab treatment, IgG4 levels dropped at least 40% within 2 months, and levels of other IgG subclasses did not drop significantly⁴⁸. The prospect of serum IgG4 as a biomarker of disease activity and/or risk of relapse is appealing but requires further study.

Rituximab increases the risk of infection, probably to a greater extent than the oral immune-suppressive drugs discussed above and in the same range as other “biologics” that are widely used in rheumatology, although it is difficult to draw firm conclusions on this

topic ⁴⁹. There appears to be a specifically increased risk of a fatal viral infection of the brain known as progressive multifocal leukoencephalopathy (PML), but this infection is quite rare, and the great majority of cases have been observed in patients with multiple sclerosis (in which the adhesion-molecule-blocking antibody natalizumab increases the risk to at least 1/1000) or lupus ⁵⁰. There is a substantial risk of infusion reaction during the first treatment, so rituximab should only be administered by persons experienced with its use, and it is routine to pre-medicate with IV glucocorticoids (e.g., 100 mg methylprednisolone), diphenhydramine (25 mg), and acetaminophen (650 mg) in order to reduce that risk. A delayed and transient neutropenia, of unclear cause, has been observed in some patients ⁴⁹. Rituximab, like monoclonal antibodies in general, is not expected to have drug interactions but is known to cross the placenta and so is considered to be contraindicated in pregnancy ⁴⁹. Rituximab is very expensive, at least \$10,000 per course of treatment.

Emerging therapies

Therapies that specifically target plasma cells might be attractive for treating IgG4-related disease, but their safety would need to be carefully considered, and it is important to note that standards for acceptable toxicity, with regard to infection or other side effects, are understandably more stringent in rheumatology than in oncology, where experience with plasma-cell-targeting therapies will be gained first. One case of a patient with IgG4-related disease successfully treated with bortezomib (a proteasome inhibitor that is toxic to plasma cells) has been reported ⁵¹, but since the patient also received cyclophosphamide and dexamethasone, this report is difficult to interpret.

Differentiation of B cells to produce IgG4 is promoted by cytokines produced by Th2 CD4+ T cells, so blockade of interleukin-4, interleukin-13 or other Th2 cytokines might be useful in treating IgG4- related disease. Patients with IgG4-related disease frequently have prominent features of allergic disease, which supports the likelihood of excessive Th2-weighted responses ¹³. Moderate infiltration with eosinophils is seen in many lesions in IgG4-related disease, so blockade of interleukin-5, as has been reported to be effective in hypereosinophilic syndromes and Churg-Strauss syndrome ^{52, 53}, might also have prospects in IgG4-related disease.

Interventional procedures

Stenting of bile ducts is commonly used in IgG4-related disease, and ability to remove biliary stents is used as a marker of successful medical treatment. Similarly, ureteral stents are often needed in retroperitoneal fibrosis, although the literature does not refer to the IgG4-related subset. In contrast, the use of endovascular procedures in vascular IgG4-related disease appears to be limited. Periaortitis is rarely if ever capable of compressing the aorta, and involvement of the aorta itself produces dilation rather than stenosis. The few cases of involvement of smaller arteries have mostly involved aneurysms as well. Nevertheless, there is no reason to think that stenting is contraindicated in a patient with a critically stenotic lesion in whom medical therapy will take time to work and in whom bypass surgery is a less attractive option.

It is not clear whether the interventional experience with Takayasu's arteritis, in which the vessel wall is the site of chronic inflammation and stenoses are the usual result, has relevance to IgG4- related vascular disease. In the U.S., rates of restenosis after angioplasty (usually without stenting) in Takayasu's have been greater than 60% ⁵⁴, but investigators in India report much greater success ^{55, 56}. Some experts advocate use of prednisone and/or other immune-suppressive drugs following interventions in patients with Takayasu's, and there is one observational study supporting that recommendation ⁵⁷, but the topic remains controversial.

Radiation therapy has been used successfully in idiopathic orbital pseudotumor^{58–60} without reference to association with IgG4. However, since radiation therapy for malignancy is regarded as one of the etiologies of retroperitoneal fibrosis, it is doubtful that this approach will be a prominent component of therapy for IgG4-related disease in general.

Surgery

Large aneurysms of the aorta and large arteries are presumed to be hemodynamically unstable, and medical therapy is unlikely to reduce vessel dilation, so surgery is expected to continue to play an important role in managing the consequences of prior damage in IgG4-related vascular disease. Indications for surgical or endovascular repair are based on the degree of vessel dilation and are presumed to be the same as for atherosclerotic disease and other causes. Observational studies have suggested that endovascular repair may result in better outcomes than open repair of inflammatory abdominal aortic aneurysms^{61, 62}. The literature on surgical repair of inflammatory thoracic aortic aneurysms is quite limited⁶³. Undoubtedly, surgeons would prefer to operate on tissue in which inflammation has been reversed with medication, but the inflammatory origin of aortic aneurysms is frequently only discovered by pathological examination of the tissue^{8*}. There is clearly a need for additional data regarding outcomes of patients with vascular lesions due to IgG4-related disease.

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• Of importance

•• Of great importance

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