

# Prediction of flare-ups in IgG4-related disease

A new disease concept and call for further elucidation

Tadashi Nakamura<sup>1,2</sup> and Kiyoshi Migita<sup>3,4</sup>

<sup>1</sup>Section of Clinical Rheumatology, Kumamoto Shinto General Hospital, <sup>2</sup>Department of Rheumatology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, <sup>3</sup>Department of Rheumatology, Nagasaki Medical Center, Omura and <sup>4</sup>Department of Molecular Immunology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.

Correspondence to: Tadashi Nakamura, Section of Clinical Rheumatology, Kumamoto Shinto General Hospital, 1-17-27 Shinyashiki, Chuo-ku, Kumamoto 862-8655, Japan.  
E-mail: [nakamura@k-shinto.or.jp](mailto:nakamura@k-shinto.or.jp)

Relatively recently, IgG4-related disease (IgG4-RD) was proposed to be an independent chronic inflammatory disorder [1]. It has been thought to be a subtype of SS, but recent studies have suggested that Mikulicz's disease is an IgG4-RD and is distinguishable from SS [2, 3]. Characteristic features of IgG4-RD include elevated serum IgG4 levels and inflammation of various organs. The primary histopathological characteristics of the swollen organs consist of extensive infiltration of IgG4-bearing plasma cells, retroperitoneal fibrosis and obliterative phlebitis [4]. Although the aetiology and pathogenesis of this disorder are still uncertain, inflammation and the consequent fibrosis occur because of excessive production of cytokines by type 2 T helper (Th2) cells and regulatory T cells [5]. IgG4-RD can comprise various organ manifestations, including dacryoadenitis, sialadenitis, autoimmune pancreatitis, kidney dysfunction, retroperitoneal fibrosis and lung disorders. IgG4-RD has been linked to an increased incidence of some malignancies [2]. Early intervention with glucocorticoids can improve the disease, however, patients often relapse when doses of steroids are tapered [6].

In this issue of Rheumatology, Yamamoto et al. [7] identified a total of 79 patients with IgG4-RD, known as Mikulicz's disease, who were diagnosed between April 1997 and

October 2013 and were followed up for more than 2 years after the initial induction treatment. They analysed various clinical factors using the Cox proportional hazards model, performed uni- and multivariate analyses of each clinical factor and identified predictors of relapse. For the multivariate analysis, they used the backward elimination method and extracted factors having high predictive power. Their results showed that the existence of organ involvement was a strong risk factor for relapse. They divided the patients into groups with and without organ lesions at diagnosis and performed uni- and multivariate analyses for each group.

Yamamoto et al.'s [7] retrospective statistical study assessed the identification of relapse predictors in IgG4-RD at the first visit and initial treatment. They identified these predictive factors as male sex and younger age at disease onset in patients without organ involvement at diagnosis of IgG4-RD and as low levels of serum IgG4 in patients with organ dysfunction at diagnosis. Furthermore, complication with autoimmune pancreatitis and low steroid dose at initial treatment tended to be associated with recurrence. They thus concluded that male sex and younger age at onset in patients without organ damage at diagnosis predicted relapse of IgG4-RD [7]. In addition, careful follow-up was important for patients with recognized risk factors for relapse. These findings will provide useful information for clinicians in developing a treatment plan.

Although applying data obtained from the statistical analysis to daily clinical practice would be preferable, predictions based on such resultant factors may not in fact correlate with clinical medicine as practised. For example, one of the predictive factors was low levels of serum IgG4 in patients with organ dysfunction at diagnosis, despite the article's finding that organ lesions were related to elevated levels of serum IgG4 at diagnosis [7]. However, IgG4-RD itself involves elevated serum levels of IgG4 [7]. From a pathological point of view, interpreting the levels of serum IgG4 as the authors stated is rather difficult, suggesting the clinicopathological heterogeneity of IgG4-RD. In addition, the definition of organ involvement in IgG4-RD seems unclear. IgG4-RD has unique clinical, serological, radiological and pathological features associated with multiorgan involvement, but how do we estimate the degree of involvement of lacrimal and salivary glands, autoimmune pancreatitis, kidney and lung disease, retroperitoneal fibrosis and so on? It should be kept in mind that from the multivariate analysis of a total of 79 patients with IgG4-related dacryoadenitis/sialadenitis, other organ involvement was identified as a risk factor for relapse.

IgG4-RD is a disorder based on Th2 inflammation [2]. The authors interpreted male sex and younger age at onset at diagnosis as being predictors of relapse in IgG4-RD [7].

With regard to the relationship between Th1/Th2 cytokine balance and sex hormones, oestrogen promotes the Th1 response, whereas progesterone stimulates Th2-related inflammation. Although the authors stated that symptoms worsened when a woman with IgG4-RD became pregnant [7], we often find that symptoms in patients with rheumatic diseases tend to be ameliorated during the late phase of pregnancy because of up-regulated production of steroids by the placenta. Therefore the situation is too complex to state definitely that male sex and younger age at onset are predictive factors of relapse in patients with IgG4-RD. Among patients with organ involvement at the first visit who relapsed during the follow-up period, the prevalence of positive RF was extremely high compared with other groups [7], which suggests a close relationship between IgG4-RD and rheumatic diseases. Also, increased knowledge about the aetiology and pathology of these disorders may explain the similarities between IgG4-RD and various rheumatic diseases and may allow the development of novel treatments of these disorders [8].

Increasing clinical awareness of IgG4-RD may lead to consultation with rheumatologists regarding the various organ dysfunctions involved and the abnormal immune responses observed, which resemble those associated with rheumatic diseases. IgG4-RD manifests features of a systemic disease, relapses do not always take the same form as the clinical disease and disease relapses are common [6]. Additional studies are required to compare different strategies to prevent and treat IgG4-RD and maintain disease remission. An algorithm to guide treatment decisions for patients with IgG4-RD exists [2]; however, no regimen for the disease includes the use of immunosuppressants. Glucocorticoid treatment can achieve short-term clinical remission, but about 20-30% of patients relapse after steroid doses are reduced [9, 10]. Long-term glucocorticoid exposure is associated with substantial morbidity. Improved understanding of disease pathogenesis may allow for more targeted immunotherapy. With the advent of biologic therapies, interest in targeted treatment with specific inflammatory mediators, such as cytokines, in patients with IgG4-RD has increased. Early intervention is required for improved outcomes in patients with IgG4-RD. Further efforts are needed to develop an understanding of IgG4-RD and resolve the problems shown in Table 1.

### **Acknowledgements**

T.N. and K.M. are supported in part by a Grant-in-aid for scientific research from the Japanese Ministry of Health, Labour, and Welfare.

Disclosure statement: The authors have declared no conflicts of interest.

## References

- 1 Takahashi H, Yamamoto M, Suzuki C et al. The birthday of a new syndrome: IgG4-related diseases constitute a clinical entity. *Autoimmun Rev* 2010;9:5914.
- 2 Yamamoto M, Takahashi H, Shinomura Y. Mechanisms and assessment of IgG4-related disease: lessons for the rheumatologist. *Nat Rev Rheumatol* 2013;10:14859.
- 3 Umehara H, Okazaki K, Masaki Y et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 2012;22:2130.
- 4 Kuruma S, Kamisawa T, Tabata T et al. Clinical characteristics of patients with autoimmune pancreatitis with or without Mikulicz's disease and Mikulicz's disease alone. *Gut Liver* 2013;7:969.
- 5 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;64:25463.
- 6 Yamamoto M, Takahashi H, Ishigami K et al. Relapse patterns in IgG4-related disease. *Ann Rheum Dis* 2012;71: 1755.
- 7 Yamamoto M, Nojima M, Takahashi H et al. Identification of relapse predictors in IgG4-related disease using multivariate analysis of clinical data at the first visit and initial treatment. *Rheumatology* 2015;54:459.
- 8 Himi T, Takano K, Yamamoto M, Naishiro Y, Takahashi H. A novel concept of Mikulicz's disease as IgG4-related disease. *Auris Nasus Larynx* 2012;39:917.
- 9 Khosroshahi A, Stone JH. Treatment approaches to IgG4- related systemic disease. *Curr Opin Rheumatol* 2011;23: 6771.
- 10 Shimizu Y, Yamamoto M, Naishiro Y et al. Necessity of early intervention of IgG4-related disease-delayed treatment induces fibrosis progression. *Rheumatology* 2013; 52:6798

**TABLE 1** Problems in IgG4-RD to be solved

---

Determine the mechanism of serum IgG4 elevation in Th2-associated inflammation of IgG4-RD.

Clarify the autoimmune pathogenic processes in IgG4-RD. Develop tools to analyse quality and quantity in organ failures.

Establish screening procedures for underlying malignancies.

Elucidate disease susceptibility in different races and districts.

Determine a worldwide consensus for diagnostic criteria. Provide a therapeutic steroid regimen to prevent relapses. Pursue novel therapeutic interventions.

---

IgG4-RD: IgG4-related disease.