

Early Therapeutic Intervention for IgG4-related Dacryoadenitis and Sialadenitis: The Balance Between Risk of Observation Only and Therapeutic Adverse Effects

To the Editor:

Immunoglobulin G4-related disease (IgG4-RD) is a systemic, chronic, and fibroinflammatory disorder^{1,2}. Some problems remain to be resolved in IgG4-RD. We consider here the indication of therapeutic intervention for IgG4-RD. The correct time to initiate treatment remains unclear. Prescription of glucocorticoids is recommended for patients with clinical symptoms such as abdominal pain and obstructive jaundice, or other organ involvement in autoimmune pancreatitis³. One of the reasons is that such lesions show spontaneous improvement, although the frequency is low. We have previously reported steroid treatment for patients having IgG4-related sialadenitis more than 2 years, but that failed to improve salivary gland function⁴. We concluded that delayed therapeutic intervention in those cases had progressed to irreversible fibrosis in the involved organs. We have mainly treated IgG4-related dacryoadenitis and sialadenitis (IgG4-DS) in our department.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All study-related recruitment and procedures were approved by the Sapporo Medical University Hospital Institutional Review Board (282-205). Participants provided written informed consent for inclusion in this study.

We currently initiate glucocorticoid treatment (0.8 mg/kg/day of prednisolone) as soon as possible for patients with IgG4-DS with other organ involvement (OOI; systemic type) as an absolute therapeutic indication. On the other hand, IgG4-DS patients without OOI (focal type) can be followed up either without treatment or prescribed low-dose prednisolone (0.6 mg/kg/day)⁵. We recently encountered several patients with expansion of lesions to other organs (transition from focal type to systemic type). We aimed to clarify the relationship between therapeutic intervention and outcome. The subjects comprised 202 IgG4-DS cases. We performed systemic evaluation with 18F-fluorodeoxyglucose positron emission tomography and enhanced computed tomography (CT) at the initial visit, and

divided the subjects into the following groups: nontreated or followup-only group (49 cases), treatment intervention group (146 cases), and patients who discontinued therapy with clinical remission (7 cases). We followed up with enhanced CT once a year. We defined clinical remission as having no organ involvement, and we analyzed the progression rate in the nontreated group and the relapse rates in the treatment intervention group in 2017. Each group profile included the following: the nontreated group had 19 males and 30 females (aged 65.92 ± SD 11.31 yrs at the last visit), the treatment intervention group had 79 males and 67 females (65.24 ± 11.98 yrs), and the discontinued therapy group had 1 male and 6 females (74.14 ± 10.21 yrs). There was no significant difference among these 3 groups. Mean followup periods in each group were 2.67 ± 2.46 years, 5.83 ± 4.08 years, and 7.76 ± 4.66 years, respectively. Mean followup was significantly shorter in the nontreated patient group than for the treatment intervention group ($p < 0.001$). There was no case presented with spontaneous remission without treatment.

Our result showed that the progression rate in the nontreated group was very high at 10.20%. On the other hand, the relapse rate in the therapeutic intervention group was only 2.74%. Further, no relapse was seen in the group that discontinued steroids. In other words, 10.2% of untreated IgG4-DS patients will transition from focal type to systemic type disease within 2.7 years. A significant difference was seen between the progression rate in the nontreated group and the recurrence rate in the treated group ($p = 0.031$; Figure 1). In the entire observation period, mean rates of progression and relapse in each group were 3.82% per year, 1.72% per year, and 0.00% per year, respectively. The progression rate in the followup-only group was more than double the relapse rate in the treated group.

In the treatment intervention group, the dose of prednisolone at the relapse was 4.50 ± 2.89 mg/day. On the other hand, the maintenance doses in the patients without relapse were 5.82 ± 3.29 mg/day. There was no significant difference between the treatment intervention group with and without the relapse ($p = 0.39$). The patients treated with a combination of the immunosuppressants did not present with recurrence. The severe adverse effects in 2017 were observed infections (2.7%), bone fractures (2.1%), osteonecrosis (1.4%), steroid-induced psychosis (1.4%), diabetes mellitus

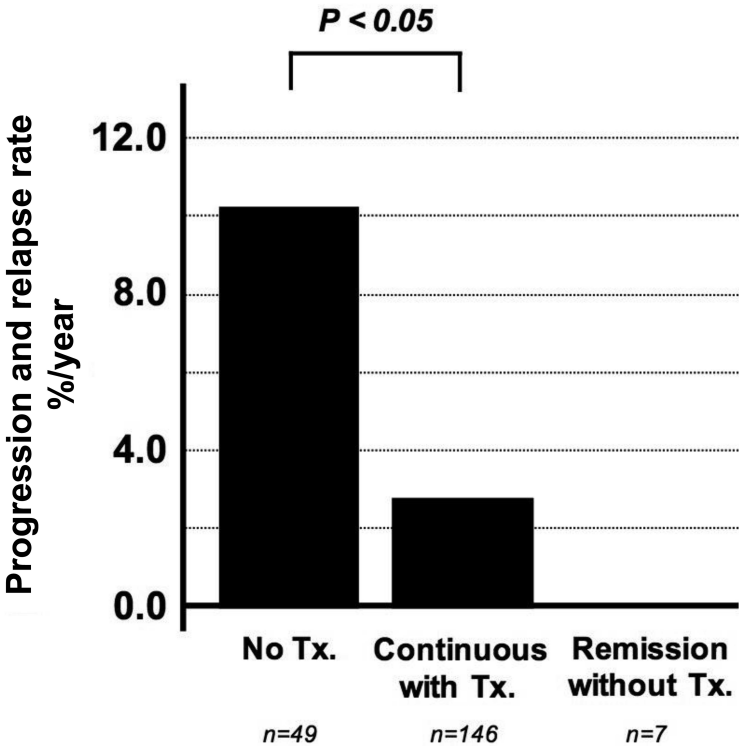



Figure 1. Comparisons of progression and relapse rates in patients with IgG4-related disease, with and without glucocorticoid treatment. The ratio of progression in patients without any treatment was 10.2%, compared to a relapse rate of 2.7% in treated patients in 2017 ($p < 0.05$). IgG4: immunoglobulin G4; Tx: treatment.

(0.7%), and glaucoma (0.7%). Lung cancer was observed in a patient (14.3%) belonging to the discontinued therapy group.

Our results show that the progression rate is very high in nontreated patients despite the shorter observation period, as compared to other groups. The results also offer important data regarding the natural course of IgG4-RD. We have treated the patients with IgG4-DS with glucocorticoid only upon the patients' request. However, according to these results, it is more difficult to consider whether we should prescribe steroids to IgG4-DS patients without OOI. Early therapeutic intervention for IgG4-RD may be important not only for organ protection but also for suppressing lesion expansion. At the same time, we know the difficulty of treating middle-aged and elderly patients because of the adverse effects associated with glucocorticoids⁶.

We have reported this result with the aim of taking steps toward better clinical practice for IgG4-RD.

MOTOHISA YAMAMOTO , MD, PhD, Department of Rheumatology and Clinical Immunology, Sapporo Medical University School of Medicine; KEN-ICHI TAKANO, MD, PhD, Department of Otolaryngology, Sapporo Medical University School of Medicine; HIROKI TAKAHASHI, MD, PhD, Department of Rheumatology and Clinical Immunology, Sapporo Medical University School of Medicine, Sapporo, Japan. This work was supported by the Research on Measures for Intractable Diseases Project matching fund subsidy from the Ministry of Health, Labor, and Welfare, Japan, and the Japan Agency for Medical Research and Development. Address correspondence to Dr. M. Yamamoto, Department of Rheumatology and Clinical Immunology, Sapporo Medical University School of Medicine, South 1 West 16, Chuo-ku, Sapporo, Hokkaido 0608543, Japan. E-mail: mocha@cocoa.plala.or.jp

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