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Editorial

The Role of Immunoglobulin G4 in Patients With Rheumatoid Arthritis

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Humans have four subclasses of immunoglobulin G (IgG): namely IgG1, IgG2, IgG3, and IgG4. IgG4 is the least-represented IgG subclass and comprises only 5% of the total IgG [1]. However, serum concentration of IgG4 increases in IgG4-related diseases (IgG4-RD), IgG4 autoimmune diseases, and in some other diseases. Serum levels of IgG4 can also be elevated in up to 5% of the normal population [2]. IgG4-RD are characterized by elevated serum IgG4 levels, chronic fibroinflammatory conditions with lymphoplasmacytic infiltration, and tumefactive fibrosis [3]. IgG4 autoimmune diseases are characterized by the presence of antigen-specific auto-antibodies of the IgG4 subclass, and include muscle-specific kinase myasthenia gravis, pemphigus, thrombotic thrombocytopenic purpura, and chronic inflammatory demyelinating polyradiculoneuropathy [4]. Elevated serum IgG4 levels have also been reported in patients with primary sclerosing cholangitis, bronchiectasis, non-IgG4-related pancreatitis, vasculitis, chronic rhinosinusitis, and pancreatic or bile duct cancer [2]. Additionally, elevated serum levels of IgG4 were demonstrated in systemic autoimmune rheumatic diseases, such as antineutrophil cytoplasmic antibody-associated vasculitis, systemic lupus erythematosus, rheumatoid arthritis (RA), dermatomyositis, systemic sclerosis, and ankylosing spondylitis [5].

There have been reports that demonstrate the relationship between RA and serum levels of IgG4. Lin and Li [6] reported that serum IgG4 levels were significantly higher in people with RA than in healthy people, and that the concentration of serum IgG4 was unrelated to disease activity. Yu et al. [2] demonstrated that of 433 RA patients, 30.3% had elevated levels of serum IgG4. Yamamoto et al. [7] examined serum levels of IgG4 in 29 patients with RA and found that the frequency of elevated serum IgG4 levels in patients with RA was 17.2%. Chen et al. [8] reported that of 136 RA patients, 46% had elevated serum IgG4. They also suggested that elevated serum IgG4 levels may be associated with a specific clinical phenotype of RA, which is characterized by higher disease activity, higher level of autoantibodies, and poor response to methotrexate and leflunomide therapy [8]. In a past issue of *Journal of Rheumatic Diseases*, Kim et al. [9] demonstrated that 6.3% (6/96) of patients with RA had elevated serum levels of IgG4 and the levels correlated with RA disease activity. However, it is worth noting that the proportion of RA patients with increased IgG4 reported by Kim et al. [9] was lower than those in previous reports [2,6-8]. These discrepancies may be explained by differences in the selection of the patient populations for study.

IgG1 and IgG4 were found to be the predominant IgG subclasses against rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA) in RA patients [10,11]. Some reports suggest that the serum level of IgG4 ACPA may serve as a biomarker for monitoring the response of RA patients to therapy [12-14]. Engelmann et al. [12] showed that the levels of IgG4 ACPA decreased significantly after three months of therapy, specifically within the responder group, whereas IgG1 ACPA levels remained stable. Bos and colleagues [13] demonstrated a preferential decrease in IgG4 ACPA during treatment with tumor necrosis factor alpha blocking agents in patients with RA. It was reported that toclizumab reduced

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the levels of IgG4 ACPA, but had minimal effect on ACPA [14].

Accumulating data and a report by Kim et al. [9] suggest that IgG4 is involved in RA pathogenesis. However, the role of IgG4 in the pathology of RA remains unclear. It has been considered that the exuberant production of IgG4 in IgG4-RD is an epiphenomenon rather than a contributor to the pathologic player in disease development [15]. This was supported by the fact that IgG4 does not bind to complement and has a weak binding affinity for FcR. IgG4 also has anti-inflammatory activity by dynamic Fab arm exchange. Patients with IgG4 myeloma do not develop features of IgG4-RD [16]. However, some studies demonstrated that IgG4 is involved in disease development. Human IgG4 is an asymmetrical bispecific antibody with half-molecule exchange (Fab-arm exchange). Carbone et al. [14] suggested that bispecific antibodies may be more pathogenic because of crosslinking of different molecules. Other studies have shown that IgG4 is associated with the presence of natural bispecific antibodies against cyclic citrullinated peptide in RA [17]. Kawa [18] suggested that IgG4 might participate in the complement activation system via both the classical and the mannose-binding lectin pathways. Holland et al. [19] reported that IgG4-ANCA can activate neutrophils via constitutively expressed Fc γ RII α /IIIb.

The mechanism of IgG4 elevation in patients with RA is still unknown. It is suggested that certain cytokines such as, interleukin-10 (IL-10), IL-6, and IL-21 or follicular helper 2 T (Tfh2) cells, regulate synthesis of IgG4 [8,20]. It is known that IL-10 increases the production of IgG4 by promoting IL-4-induced IgG4 switching [21]. Carbone et al. [14] reported that tocilizumab therapy decreased serum concentration of IgG4 in seven of eight RA patients and IL-21 production in memory/ activated CD4 T cells [14].

Interestingly, serum levels of previously mentioned cytokines were reported to be higher in RA patients compared to healthy controls [22]. However, it is reported that the number of Tfh2 cells in the peripheral blood of RA patients is not different from that of healthy controls [23].

Further studies, with larger numbers of RA patients, are needed to identify the clinical characteristics of patients with elevated serum IgG4 levels. These characteristics should include response to treatment, relation to autoantibodies, and extent of radiologic progression. Additionally, identifying mechanisms that increase serum IgG4 production in RA patients will help to clarify the pathogenesis of RA.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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