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Elevated serum IgG4 defines a specific clinical phenotype of Rheumatoid arthritis

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Background: Rheumatoid arthritis (RA) is a heterogeneous autoimmune disease and subtyping of RA may help optimal therapeutic strategies and outcome prediction. There is no available satisfying classification method until now. Recently, much attention has been paid to IgG4 since the recognition of IgG4-related disease, a new emerging disease entity. Elevated serum IgG4 (sIgG4) was also reported in some RA patients. However, the clinical significance of elevated sIgG4 in RA remains elusive.

Objectives: To explore the correlation of sIgG4 with disease activity and therapeutic response in RA.

Methods: Consecutive 114 RA patients with active disease (DAS28 ≥2.6) were recruited and all patients were followed up at regular interval (1, 3, and 6 months). SIgG4 were detected by immunonephelometry at baseline and sIgG4≥1.35 g/L was considered as elevated.

Results:

1. Among 114 RA patients, 60% were female and median age was 57 years. The mean sIgG4 was 1.63±1.32g/L, with 48% had elevated sIgG4. The mean sIgG4/sIgG ratio was 10.5%±7.6%, with 55% had elevated sIgG4/sIgG ratio (≥8%), and 95% of patients with elevated sIgG4 accompanied by elevated sIgG4/sIgG ratio.

2. Patients with elevated sIgG4 had higher PtGA, PrGA, CRP and ESR than those with normal sIgG4 (all $P<0.05$). Spearman's rank order correlation test showed significant correlation of sIgG4 with CRP ($r=0.316$, $P=0.001$) and ESR ($r=0.351$, $P<0.001$).

3. Baseline level of RF and anti-CCP antibody were both higher in patients with elevated sIgG4 than those with normal sIgG4 (both $P<0.05$). Spearman's rank order correlation test showed significant correlation of sIgG4 with RF ($r=0.302$, $P=0.001$) and anti-CCP antibody ($r=0.225$, $P=0.017$).

4. Seventy-five patients fulfilled ≥6 months follow-up and 60% received MTX + leflumonmide (LEF) therapy with or without low-dose corticosteroid, 24% received MTX + TNF-α antagonist (≥ 3 months) and 16% received other DMARD(s) therapy. Among 45 patients with MTX + LEF therapy, 50% (9/18) of patients with elevated sIgG4 and 85% (23/27) of patients with normal sIgG4 reached remission or low disease activity (DAS28<3.2) at 6-month visit ($\chi 2=6.508$, $P=0.011$). Among 18 patients with MTX + TNF-α antagonist therapy, 70% (7/10) of patients with elevated sIgG4 and 88% (7/8) of patients with normal sIgG4 reached DAS28<3.2 at 6-month visit ($P>0.05$). After 6 months treatment, RF level of patients with elevated sIgG4 were significantly lower than those with normal sIgG4, and the declined ratio of RF of patients with elevated sIgG4 were significantly higher than those with normal sIgG4 (both $P<0.05$).

Conclusions: Obtained results showed that elevated sIgG4 in RA is common and disproportional to total IgG and RA with elevated sIgG4 may be a specific clinical phenotype with higher disease activity, higher level of autoantibodies, and poor response to MTX + LEF therapy.

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