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Association of serum IgG4 and disease outcomes in patients with inflammatory bowel disease

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Abstract

Background The etiology of inflammatory bowel disease (IBD) is multifactorial and thought to be influenced by inappropriate activation of the gut mucosal immune system. As the only immunoglobulin G (IgG) subclass unable to activate the classical complement cascade, the role of IgG4 in IBD pathophysiology as an immunomodulator is controversial. This study aimed to determine the association of low, normal and high IgG4 levels with the outcomes of IBD patients.

Methods This was a retrospective study of a multisite tertiary care center database evaluating patients with IBD who had an IgG4 level drawn between 2014 and 2021. Subjects were divided into low, normal, and high IgG4 level groups for evaluation of demographic and clinical indicators of IBD activity and severity.

Results Of 284 patients with IBD, 22 had low (7.7%), 16 high (5.6%), and 246 (86.6%) normal IgG4 levels. There was no difference in IBD subtype, mean age, age at IBD diagnosis, or smoking between the 3 groups. There was no difference in number of hospitalizations (P=0.20), C-reactive protein levels, need for intestinal resection (P=0.85), or presence of primary sclerosing cholangitis (P=0.15), pancreatitis (P=0.70), or perianal disease (P=0.68) between the groups. Significantly more patients in the low IgG4 group had previous exposure to vedolizumab compared to the other groups and more patients in the low IgG4 group received vedolizumab (P=0.04), azathioprine (P=0.04) and prednisone (P=0.03) during the 5-year follow up.

Conclusion In this study, a low serum IgG4 level was associated with higher rates of vedolizumab, azathioprine, and steroid use.

Keywords IgG4, inflammatory bowel disease, disease severity, disease outcomes

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Introduction

Immunoglobulin G (IgG) is the main serologic component of the humoral immune response [1]. There are multiple subclasses of IgG, including IgG1, IgG2, IgG3 and IgG4, numbered in the order of their discovery. IgG4 is produced at a much lower concentration than the other IgG subclasses, comprising only 5% of total serum IgG [2]. Functionally, IgG4 is the only IgG subclass that is unable to activate the classical complement pathway via the C1q protein complex [3,4]. Although the specific function of IgG4 is not known, it probably serves an immunomodulatory function. Its bivalency prevents immune complex formation and cross-linking that signal for endocytosis of transmembrane antigens. It has also been shown to serve an immunoprotective role by competitive binding of antigens that trigger a traditional allergic immune response [5].

The IgG4 subclass has been linked to chronic relapsing and remitting inflammatory diseases in different organs of the body. In the pancreas, an increase in IgG4-secreting plasma cells infiltrating diseased tissue results in the formation of mass lesions with high serum IgG4 levels [3,6]. Characteristic

Conflict of Interest: None

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pathology on biopsy, or radiographic evidence of intra-organ mass formation in patients with a high clinical suspicion, are considered entry criteria for the diagnosis of IgG4-related disease (IgG4-RD) [7,8]. Although IgG4 positive plasma cell infiltration is pathognomonic, the serum concentration of IgG4 may be organ specific and is not required for the diagnosis of an IgG4-RD. The variance of IgG4 serum concentration within IgG4-RD is still under investigation [7]. The most common target organs for IgG4-mediated autoimmune disease are the central and peripheral nervous systems, including the neuromuscular synapse, mucosa and skin, lungs, kidneys, vasculature, salivary glands, and the pancreato-biliary system [5,8]. Given the subclinical nature and the difficulty of early detection without biopsy or radiologic evidence, IgG4-RD often results in an insidious proinflammatory state that can predispose patients to other autoimmune conditions [8]. Specifically, IgG4-RD has been linked to autoimmune pancreatitis and primary sclerosing cholangitis (PSC), which are extraintestinal manifestations of inflammatory bowel disease (IBD) [9].

Although IBD is an immunologically driven disease, the definitive role of IgG4 in IBD and its association with IgG4-RD remain unclear. IgG4 positive plasma cell infiltration on colonic biopsies was found to be elevated in patients with IBD compared to those without, suggesting that IgG4-RD may be involved in the pathophysiology of IBD [9]. The relationship between severe IBD and IgG4-RD remains controversial, and there is no agreement on the significance of serum IgG4 concentration in severe IBD. In a previously published study of 1193 patients, those with more markers of IBD severity, such as intestinal resection, more frequent hospital admissions and outpatient clinic visits, and IBD-related surgical procedures were noted to have a serum IgG4 subclass deficiency [10]. Additionally, there was a notable increase in concomitant autoimmune conditions associated with IBD, such as PSC, among these patients [10]. An IgG subclass deficiency of IgG1, IgG2, or IgG3 typically results in recurrent infection. However, since IgG4 is unable to activate complement, there is no clear increase in recurrent infections in patients with IgG4 subclass deficiency [11].

The ultimate role of serum IgG4 as a potential immunomodulator in IBD remains unclear. The aim of this study was to evaluate the relationship between various levels of serum IgG4 concentration and IBD severity. We hypothesized that patients with a low IgG4 would experience greater severity of their IBD in the form of more hospitalizations, higher C-reactive protein (CRP) levels, greater need for intestinal resection, greater need for immunosuppressive medications, and a higher incidence of concomitant PSC, pancreatitis or perianal disease.

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Patients and methods

This was a retrospective study of a multisite tertiary care center database. All patients with IBD who had a serum IgG4 level checked between January 1, 2014, and December 15, 2021, were included in the study. Subjects were divided into low, normal and high IgG4 level groups, based on the first serum IgG4 level recorded in the system. Serum IgG4 within 2.4-121.0 mg/dL was considered the range for the "normal" IgG4 serum level, based on results from Mayo Clinic Laboratories. Any individual with a serum IgG4 level under 2.4 mg/dL was included in the "low" group, while serum IgG4 levels above 121.0 mg/dL were included in the "high" IgG4 group. Subjects were categorized by IBD type: ulcerative colitis and Crohn's disease.

Demographic and clinical data stratifying IBD activity and severity were collected. Demographic information included age at serum IgG4 level draw, age at diagnosis of IBD, and smoking status. CRP levels were divided into 3 groups: all prior to 1 week before serum IgG4 level draw; within 1 week before or after IgG4 level draw; and all after 1 week following IgG4 serum level draw. Number of hospitalizations, history of intestinal resection and concomitant conditions, such as PSC, pancreatitis, or perianal disease, were recorded for each patient. All pharmacologic agents for the treatment of IBD that were used before, during, and after IgG4 serum level collection were recorded.

The institutional review board of Mayo Clinic reviewed and approved this study.

Statistical analysis

The Statistical Package for Social Sciences (SPSS, version 25) was used for data cleaning, management and analysis. Categorical variables were summarized using number and percentage, and continuous variables were summarized by mean and standard deviation. Analysis was completed using the chi-square or Fisher's exact test for categorical variables, and ANOVA or Kruskal-Wallis test for continuous variables. A P-value <0.05 was considered statistically significant.

Results

A total of 284 patients with IBD and IgG4 level were included in the study. Of those patients, 22 (7.7%) had a low, 16 (5.6%) had a high, and 246 (86.6%) had a normal IgG4 level. The mean age at diagnosis of IBD was 34.2±16.7 years, while the mean age at IgG4 serum level draw was 44.9±17.6 years old. There

was no statistical difference between IBD subtypes (P=0.58), age at IBD diagnosis (P=0.47), or mean age at IgG4 serum level draw (P=0.60) among the IgG4 serum level groups. There was no statistical difference in rates of smoking between IgG4 groups (P=0.60). Table 1 displays the patient demographics and patient outcomes in terms of their measured IgG4 level.

As seen in Table 1, the number of hospitalizations (P=0.20), CRP levels preceding IgG4 level draw (P=0.71), CRP level at time of IgG4 draw (P=0.64), and CRP level after IgG4 level draw (P=0.18) did not differ in relation to IgG4 levels. Regarding indicators of greater disease severity, there was no difference between the IgG4 groups in terms of development of intestinal strictures (P=0.71), perianal disease (P=0.68), need for a stoma (P=0.23), or history of intestinal resection (P=0.85). There was no difference in the presence of concomitant pancreatitis (P=0.70) or PSC (P=0.15) between the groups. Extraintestinal manifestations of IBD were similar between the IgG4 groups, with no significant difference in joint (P=0.69), ocular (P>0.99), oral (P=0.11), or dermatologic involvement (P=0.83).

Regarding medication use, significantly more patients in the low IgG4 group had previous exposure to vedolizumab compared to the other groups (P=0.04), as displayed in Table 2. A larger number of patients in the low IgG4 group received vedolizumab (P=0.04), azathioprine (P=0.04), and prednisone (P=0.03) 1 week or more after the IgG4 level was checked, as shown in Tables 3 and 4.

Discussion

In this retrospective cohort study of patients with IBD from a multisite tertiary care institution we investigated the association between IgG4 serum levels and multiple markers of IBD severity and its extraintestinal manifestations. We hypothesized that low serum IgG4 levels would be associated with markers of IBD severity. Our results, however, did not show an association with intestinal stricture formation, perianal disease, history of intestinal resection, need for a stoma, or the presence of PSC or pancreatitis. Among the patients with IBD who were included in this study, only 7.7% were categorized to have "low" IgG4 levels, probably because of the very low laboratory value cutoffs that are used for "low" IgG4 at our institution. This contrasts with a previous study that described up to 20% of patients meeting the criteria for "low" IgG4 levels [5]. In this latter study, however, the authors used a reference range of 9-89 mg/dL to identify low IgG4 patients, potentially leading to the higher percentage and to the difference in results [5]. It has been previously suggested that an IgG4 subclass deficiency should be defined by a reference range of 5.2-125 mg/dL [11]. This demonstrates the need for more consistent reference ranges for IgG4 serum levels in future studies.

It has been shown previously that up to 70-75% of patients with PSC may develop IBD within their lifetime [12,13]. In our study, the high IgG4 subgroup was associated with almost twice the rate of concurrent PSC when compared to the low IgG4 subgroup. Approximately 8% of patients with IBD will go on to develop radiologically significant evidence of PSC [14]. This rate is far below our observed rate of 51% concurrence of IBD and PSC within the study cohort. This discrepancy may be related to the higher-acuity patient demographic frequently attracted to our multisite tertiary care facility. In addition, an IgG4 serum level ordering bias was likely among our patient sample, as IgG4 was often ordered for evaluation of PSC rather than the concurrent IBD. This in turn may have led to selection bias and inclusion of more patients with concomitant PSC and IBD in our study population.

There are no clear guidelines as to when to check an IgG4 serum level among patients with IBD and how this will change patient management. In our practice, we typically consider IgG4 evaluation if the patient displays a refractory or complicated disease course.

Our observation that those with low serum IgG4 levels were more likely to have had prior treatment with vedolizumab could be explained by that drug's mechanism of action. Vedolizumab is a monoclonal antibody that functions as an inhibitor to the $\alpha_4\beta_7$ integrin, which is instrumental in homing leukocytes specifically to the gastrointestinal tract. Vedolizumab thereby inhibits lymphocyte trafficking to gastrointestinal inflammatory targets. Vedolizumab's blocking of the $\alpha_4\beta_7$ integrin to MAdCAM-1 on the endovascular surface prevents T memory cells from extravasation to the gastrointestinal submucosa [15]. The suppression of T memory cell extravasation in the gastrointestinal submucosa may lead to decreased gastrointestinal IgG4+ plasma cell production and therefore lower IgG4 serum concentrations. However, this observation was first made within our study and requires further evaluation.

Our study had several strengths, including the multisite nature of our IBD patient cohort, representing a geographically diverse patient population treated at large tertiary care centers located in the US southeast, midwest, and southwest. We evaluated multiple surrogate markers of disease severity and extraintestinal manifestations related to IBD. Given the retrospective nature of this study, we were able to identify potential bias within the existing ordering paradigm of IgG4 subclass levels. Our study was limited by its 5-year duration. Given a relatively strict definition of low IgG4 subclass levels compared to other studies, due to our laboratory cutoffs, we had lower numbers of participants in the high and low IgG4 groups, which also limited our ability to perform multivariate analyses. A longer-duration study might have resulted in more significant data beyond the trends we have identified and discussed. Finally, our sample was overwhelmingly Caucasian, and these results may not apply to other racial groups. A limitation of the study is that not all patients with IBD undergo IgG4 testing, which contributes to a selection bias.

In conclusion, our study showed that a low serum IgG4 level is associated with higher rates of vedolizumab, azathioprine and steroid use. Study limitations include potential bias in the ordering of IgG4 levels, which in our practice is typically reserved for patients who do not respond to therapy and those with concomitant PSC.

Table 1 Association of demographic data, comorbid conditions, and patient outcomes with IgG4 levels

Variables	Low IgG4 N=22 7.7%	Normal IgG4 N=246 86.6%	High IgG4 N=16 5.6%	P-value	P-values		
					Low vs. Normal IgG4	Low vs. High IgG4	Normal vs. High IgG4
Age (years)							
Mean±SD	48.0±15.5	44.9±17.6	44.9±19.7	0.60	0.31	0.63	0.97
≤30	4 (18.2%)	60 (24.4%)	5 (31.3%)	0.88	0.82	0.91	0.68
31-40	3 (13.6%)	51 (20.7%)	1 (6.3%)				
41-50	5 (22.7%)	43 (17.5%)	3 (18.8%)				
51-60	4 (18.2%)	38 (15.4%)	3 (18.8%)				
>61	6 (27.3%)	54 (22.0%)	4 (25.0%)				
Age at IBD diagnosis (years)							
Mean±SD	37.4±15.9	34.2±16.7	32.8±15.7	0.47	0.26	0.33	0.66
≤30	8 (36.4%)	120 (48.8%)	9 (56.3%)	0.20	0.32	0.09	0.21
31-40	7 (31.8%)	46 (18.7%)	1 (6.3%)				
41-50	1 (4.5%)	28 (11.4%)	4 (25.0%)				
51-60	4 (18.2%)	24 (9.8%)	2 (12.5%)				
>61	2 (9.1%)	28 (11.4%)	0 (0.0%)				
Number of hospitalizations							
None or only once	8 (36.4%)	135 (54.9%)	7 (43.8%)	0.20	0.12	0.74	0.44
More than once	14 (63.6%)	111 (45.1%)	9 (56.3%)				
Smoking							
Never	17 (77.3%)	181 (74.8%)	13 (81.3%)	0.60	0.26	0.68	>0.99
Past	3 (13.6%)	52 (21.5%)	3 (18.8%)				
Current	2 (9.1%)	9 (3.7%)	0 (0.0%)				
PSC	8 (36.4%)	128 (52.2%)	11 (68.8%)	0.15	0.18	0.10	0.30
Pancreatitis	2 (9.1%)	37 (15.1%)	3 (18.8%)	0.70	0.75	0.63	0.72
Perianal disease	2 (9.1%)	19 (7.8%)	0 (0.0%)	0.68	0.69	0.50	0.62
Intestinal resection	8 (36.4%)	78 (31.8%)	6 (37.5%)	0.85	0.81	>0.99	0.78
Stoma	6 (27.3%)	39 (15.9%)	4 (25.0%)	0.23	0.23	>0.99	0.31
Intestinal stricture	0 (0.0%)	15 (6.1%)	1 (6.3%)	0.71	0.62	0.42	>0.99
IBD Type							
Crohn's disease	9 (40.9%)	89 (36.2%)	4 (25.0%)	0.58	0.82	0.49	0.43
Ulcerative colitis	13 (59.1%)	157 (63.8%)	12 (75.0%)				
Total extraintestinal manifestations							
None	20 (90.9%)	222 (90.2%)	15 (93.8%)	>0.99	>0.99	>0.99	>0.99
One or more	2 (9.1%)	24 (9.8%)	1 (6.3%)				
Joint	1 (4.5%)	7 (2.8%)	0 (0.0%)	0.69	0.50	>0.99	>0.99
Ocular	0 (0.0%)	6 (2.4%)	0 (0.0%)	>0.99	>0.99	–	>0.99
Oral	2 (9.1%)	4 (1.6%)	0 (0.0%)	0.11	0.08	0.50	>0.99
Dermatologic	1 (4.5%)	12 (4.9%)	1 (6.3%)	0.83	>0.99	>0.99	0.57
CRP before IgG4 lab draw (mg/L)							
≤6.675	3 (13.6%)	50 (20.3%)	2 (12.5%)	0.71	0.58	>0.99	0.75
>6.675	19 (86.4%)	196 (79.7%)	14 (87.5%)				
CRP at the time of IgG4 lab draw (mg/L)							
≤6.05	6 (27.3%)	49 (19.9%)	3 (18.8%)	0.64	0.41	0.71	>0.99
>6.05	16 (72.7%)	197 (80.1%)	13 (81.3%)				
CRP after IgG4 lab draw (mg/L)							
≤7.70	4 (18.2%)	83 (33.7%)	3 (18.8%)	0.18	0.16	>0.99	0.28
>7.70	18 (81.8%)	163 (66.3%)	13 (81.3%)				

IgG4, immunoglobulin G4; PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; CRP, C-reactive protein

Table 2 Association of medications taken before IgG4 lab draw with IgG4 levels

Variables	Low IgG4 N=22 7.7%	Normal IgG4 N=246 86.6%	High IgG4 N=16 5.6%	P-value	P-values		
					Low vs. Normal IgG4	Low vs. High IgG4	Normal vs. High IgG4
Mesalamine suppository	1 (4.5%)	13 (5.3%)	0 (0.0%)	>0.99	>0.99	>0.99	>0.99
Mesalamine enema	0 (0.0%)	6 (2.4%)	2 (12.5%)	0.11	>0.99	0.17	0.08
Oral sulfasalazine	2 (9.1%)	10 (4.1%)	0 (0.0%)	0.35	0.26	0.50	>0.99
Oral mesalamine	7 (31.8%)	96 (39.2%)	8 (50.0%)	0.57	0.65	0.32	0.44
Oral prednisone	8 (36.4%)	60 (24.5%)	6 (37.5%)	0.29	0.31	>0.99	0.25
Infliximab	6 (27.3%)	53 (21.6%)	1 (6.3%)	0.29	0.59	0.20	0.21
Adalimumab	3 (13.6%)	36 (14.7%)	3 (18.8%)	0.87	>0.99	0.68	0.72
Ustekinumab	1 (4.5%)	11 (4.5%)	0 (0.0%)	>0.99	>0.99	>0.99	>0.99
Vedolizumab	7 (31.8%)	29 (11.8%)	2 (12.5%)	0.04	0.02	0.25	>0.99
Azathioprine	3 (13.6%)	39 (15.9%)	2 (12.5%)	>0.99	>0.99	>0.99	>0.99
6-Mercaptopurine	0 (0.0%)	2 (0.8%)	0 (0.0%)	>0.99	>0.99	–	>0.99
Methotrexate	2 (9.1%)	13 (5.3%)	2 (12.5%)	0.24	0.36	>0.99	0.23
Tofacitinib	0 (0.0%)	1 (0.4%)	0 (0.0%)	>0.99	>0.99	–	>0.99
No medications	0 (0.0%)	16 (6.5%)	0 (0.0%)	0.42	0.38	–	0.61

IgG4, immunoglobulin G4

Table 3 Association of medications present during IgG4 lab draw with IgG4 levels

Variables	Low IgG4 N=22 7.7%	Normal IgG4 N=246 86.6%	High IgG4 N=16 5.6%	P-value	P-values		
					Low vs. Normal IgG4	Low vs. High IgG4	Normal vs. High IgG4
Mesalamine suppository	1 (4.5%)	3 (1.2%)	0 (0.0%)	0.44	0.29	>0.99	>0.99
Mesalamine enema	0 (0.0%)	5 (2.0%)	0 (0.0%)	>0.99	>0.99	–	>0.99
Oral sulfasalazine	0 (0.0%)	7 (2.9%)	0 (0.0%)	>0.99	>0.99	–	>0.99
Oral mesalamine	5 (22.7%)	56 (22.9%)	3 (18.8%)	>0.99	>0.99	>0.99	>0.99
Oral prednisone	6 (27.3%)	39 (15.9%)	2 (12.5%)	0.35	0.23	0.43	>0.99
Infliximab	2 (9.1%)	20 (8.2%)	3 (18.8%)	0.28	0.70	0.63	0.16
Adalimumab	3 (13.6%)	19 (7.8%)	3 (18.8%)	0.12	0.41	0.68	0.14
Ustekinumab	0 (0.0%)	11 (4.5%)	0 (0.0%)	0.80	0.61	–	>0.99
Vedolizumab	4 (18.2%)	24 (9.8%)	2 (12.5%)	0.35	0.27	>0.99	0.67
Azathioprine	1 (4.5%)	18 (7.3%)	0 (0.0%)	0.86	>0.99	>0.99	0.61
6-Mercaptopurine	0 (0.0%)	1 (0.4%)	0 (0.0%)	>0.99	>0.99	–	>0.99
Methotrexate	0 (0.0%)	3 (1.2%)	0 (0.0%)	>0.99	>0.99	–	>0.99
Tofacitinib	0 (0.0%)	0 (0.0%)	0 (0.0%)	–	–	–	–
No Medications	2 (9.1%)	25 (10.2%)	1 (6.3%)	>0.99	>0.99	>0.99	>0.99
Anti-TNF + immunomodulator	0 (0.0%)	3 (1.2%)	0 (0.0%)	>0.99	>0.99	–	>0.99
Ustekinumab + immunomodulator	0 (0.0%)	0 (0.0%)	0 (0.0%)	–	–	–	–
Vedolizumab + immunomodulator	1 (4.5%)	4 (1.6%)	0 (0.0%)	0.52	0.35	>0.99	>0.99
Any biologic + immunomodulator	1 (4.5%)	7 (2.9%)	0 (0.0%)	0.69	0.50	>0.99	>0.99

IgG4, immunoglobulin G4

Table 4 Association of medications taken after IgG4 lab draw with IgG4 levels

Variables	Low IgG4 N=22 7.7%	Normal IgG4 N=246 86.6%	High IgG4 N=16 5.6%	P-value	P-values		
					Low vs. Normal IgG4	Low vs. High IgG4	Normal vs. High IgG4
Mesalamine suppository	2 (9.1%)	7 (2.9%)	0 (0.0%)	0.23	0.16	0.50	>0.99
Mesalamine enema	0 (0.0%)	4 (1.6%)	0 (0.0%)	>0.99	>0.99	–	>0.99
Oral sulfasalazine	0 (0.0%)	5 (2.0%)	0 (0.0%)	>0.99	>0.99	–	>0.99
Oral mesalamine	3 (13.6%)	65 (26.5%)	2 (12.5%)	0.23	0.21	>0.99	0.37
Oral prednisone	7 (31.8%)	31 (12.7%)	4 (25.0%)	0.03	0.02	0.73	0.24
Infliximab	2 (9.1%)	35 (14.3%)	1 (6.3%)	0.80	0.75	>0.99	0.71
Adalimumab	2 (9.1%)	15 (6.1%)	0 (0.0%)	0.63	0.64	0.50	0.61
Ustekinumab	1 (4.5%)	30 (12.2%)	1 (6.3%)	0.64	0.49	>0.99	0.70
Vedolizumab	8 (36.4%)	40 (16.3%)	3 (18.8%)	0.07	0.04	0.30	0.73
Azathioprine	5 (22.7%)	19 (7.8%)	1 (6.3%)	0.07	0.04	0.37	>0.99
6-Mercaptopurine	0 (0.0%)	2 (0.8%)	0 (0.0%)	>0.99	>0.99	–	>0.99
Methotrexate	0 (0.0%)	7 (2.9%)	0 (0.0%)	>0.99	>0.99	–	>0.99
Tofacitinib	0 (0.0%)	1 (0.4%)	0 (0.0%)	>0.99	>0.99	–	>0.99
No Medications	2 (9.1%)	21 (8.6%)	1 (6.3%)	>0.99	>0.99	>0.99	>0.99

IgG4, immunoglobulin G4

Summary Box

What is already known:

- Of the 4 subclasses of immunoglobulin G (IgG), IgG4 is the only subclass that is unable to activate the classical complement pathway and probably serves an immunomodulatory function
- The definitive role of IgG4 in inflammatory bowel disease (IBD) remains unclear; recent data revealed that low serum IgG4 was associated with more surrogate markers of IBD severity
- A notably greater incidence of IBD-associated autoimmune conditions, such as PSC, is found in patients with low serum IgG4

What the new findings are:

- Low serum IgG4 level was associated with higher rates of vedolizumab, azathioprine, and steroid use
- Not all patients with IBD undergo IgG4 testing
- IgG4 serum concentration was ordered on average 10 years after the initial IBD diagnosis

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