Association of Serum IgG4 and Disease Outcomes in Patients with Inflammatory Bowel Disease

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INTRODUCTION

Etiology of IBD is multifactorial and is thought to be influenced by inappropriate activation of the gut mucosal immune system.

IgG subclass 4 (IgG4) cannot activate the classical complement cascade.

The role of IgG4 in IBD pathophysiology as an immunomodulator is controversial.

This study aims to characterize the association of low, normal, and high IgG4 levels on the outcomes of patients with IBD.

METHODS

Retrospective chart review of a multisite tertiary care center database evaluating all patients with IBD who had an IgG4 level drawn between 2014 and 2021.

Subjects were divided into low, normal, and high IgG4 level groups.

Demographic and clinical data stratifying IBD activity and severity was collected by manual chart review.

The SPSS program was used for data analysis. P-value of 0.05 was set to indicate statistical significance.

RESULTS

284 patients with IBD had an IgG4 level checked; 22 had a low IgG4 level (7.7%), 16 had a high IgG4 level (5.6%) and 246 (86.6%) had a normal IgG4 level.

No difference in IBD subtype (CD vs. UC), mean age, age at diagnosis with IBD, or smoking between the 3 groups or either group compared to other separately.

No difference in number of hospitalizations, CRP levels, need for intestinal resection, or presence of PSC, pancreatitis, or perianal disease 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, azathioprine, and prednisone during the 5-year follow up after IgG4 level was checked.

TABLE 1. Association of clinical characteristics & 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	p-values: Low vs. High IgG4	p-values: 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 of 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	1.00
	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	1.00	0.78
Stoma		6 (27.3)	39 (15.9)	4 (25.0)	0.23	0.23	1.00	0.31
Stricture		0 (0.0)	15 (6.1)	1 (6.3)	0.71	0.62	0.42	1.00
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)				
Joint		1 (4.5)	7 (2.8)	0 (0.0)	0.69	0.50	1.00	1.00
Ocular		0 (0.0)	6 (2.4)	0 (0.0)	1.00	1.00	–	1.00
Oral		2 (9.1)	4 (1.6)	0 (0.0)	0.11	0.08	0.50	1.00
Dermatologic		1 (4.5)	12 (4.9)	1 (6.3)	0.83	1.00	1.00	0.57
Total Extraintestinal Manifestations	None	20 (90.9)	222 (90.2)	15 (93.8)	1.00	1.00	1.00	1.00
	One or more	2 (9.1)	24 (9.8)	1 (6.3)				
CRP before IgG4 lab draw (mg/L)	≤6.675	3 (13.6)	50 (20.3)	2 (12.5)	0.71	0.58	1.00	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	1.00
	>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	1.00	0.28
	>7.70	18 (81.8)	163 (66.3)	13 (81.3)				

TABLE 2. Association of medications before, at time of, and after IgG4 level check

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	p-values: Low vs. High IgG4	p-values: Normal vs. High IgG4
Vedolizumab use before IgG4 Level	7 (31.8)	29 (11.8)	2 (12.5)	**0.04**	**0.02**	0.25	1.00
Vedolizumab use at time of IgG4 Level	4 (18.2)	24 (9.8)	2 (12.5)	0.35	0.27	1.00	0.67
Vedolizumab use after IgG4 level	8 (36.4)	40 (16.3)	3 (18.8)	0.07	**0.04**	0.30	0.73
Hydrocortisone Aerosol Foam at time of IgG4 Level	1 (4.5)	0 (0.0)	1 (6.3)	**0.02**	0.08	1.00	0.06
Prednisone PO use after IgG4 Level	7 (31.8)	31 (12.7)	4 (25.0)	**0.03**	**0.02**	0.73	0.24
Azathioprine use after IgG4 Level	5 (22.7)	19 (7.8)	1 (6.3)	0.07	**0.04**	0.37	1.00

There was no statistically significant difference in temporal use between groups of the following medications not included in the table: mesalamine suppository, mesalamine retention enema, hydrocortisone suppository & enema, sulfasalazine, olsalazine, balsalazide, infliximab, adalimumab, certolizumab pegol, cyclosporine, thioprine, azathioprine, 6-mercaptopurine, ustekinumab, natalizumab, vedolizumab, methotrexate, tofacitinib, and no medication use were

DISCUSSION

- Hypothesis: decreased serum IgG4 levels may correspond with higher prevalence of markers of IBD severity.
- When evaluating markers of disease severity including stricture formation, perianal disease, history of intestinal resection, need for a stoma, and presence of PSC or pancreatitis, there was no statistically significant difference between low, normal, and high levels of IgG4.
- Variable reference ranges for IgG4 subclass concentration between studies may lead to discrepancies. A less stringent IgG4 reference may lead to differences between groups not found in this study.
- 51% concurrence of IBD with PSC may be suggestive of IgG4 ordering bias. IgG4 levels had historically been ordered for evaluation of PSC rather than IBD at this institution.
- First study to observe relationship between previous Vedolizumab administration and low IgG4 subclass concentration.

CONCLUSIONS

- **A low serum IgG4 level is associated with increased rates of vedolizumab, azathioprine, and steroid use.**
- **Study limitations include potential bias in ordering IgG4 levels which in our practice is reserved for patients not responding to therapy.**