Medical Journal of the
Islamic Republic of Iran

Volume 15
Number 1
Spring 1380
May 2001

ULCERATIVE COLITIS AND HLA CLASS II PHENOTYPING IN IRAN

H. FOROOTAN, B. NIKBIN,* GH. ANANI SARAB, AND F. KHOSRAVI***

*From the Departments of Internal Medicine and *Immunogenetics, School of Medicine, Tehran University of Medical Sciences, Tehran, and the **Department of Immunology, School of Medicine, Birjand University of Medical Sciences, Birjand, I.R. Iran.*

ABSTRACT

Ulcerative colitis (UC) is a nonspecific acute and chronic inflammatory bowel disease that diffusely involves the colonic mucosa. The etiology of UC has not yet been elucidated fully. However, many studies have found that immunologic disorders may play a role in the pathogenesis of UC. In addition, due to an increased frequency of UC in families, especially an increased monozygotic compared with dizygotic twin concordance, many implicate genetic factors in the development and regulation of the immune responses, such as the HLA class II genes, as candidates for conferring the genetic susceptibility. We studied the distribution of HLA-DR and DQ antigens and duration of sickness in 42 Iranian patients suffering from UC using the standard microlymphocytotoxicity technique. The phenotypic frequencies of HLA-DR2 were present in 24 of 84 controls and 18 of 42 patients (p= 0.24, corrected p, not significant). The present study reveals no association between HLA class II antigens and UC, suggesting that the HLA-DR2 is not a predominant susceptibility gene for UC in the population studied.

MJIRI, Vol. 15, No. 1, 7-9, 2001.

Keywords: Ulcerative colitis; HLA phenotyping.

INTRODUCTION

Ulcerative colitis (UC) is an inflammatory bowel disease of unknown etiology principally affecting the mucosa of the rectum and colon. It is a chronic disease exhibiting remissions and exacerbations. A role for genetic factors in the pathogenesis of UC is shown by studies showing ethnic and familial aggregation, and an increased monozygotic compared with dizygotic twin concordance.[1-3]

There is a 10 to 15 percent frequency of ulcerative colitis among first-degree relatives of patients with the disorder.[4]

Considering the central role of the immune system in mediating the tissue damage in UC, genes that participate in the development and regulation of the immune response, such as the HLA class II genes, are candidates for conferring genetic susceptibility.[5-8] This study was carried out to clarify the frequency deviation of HLA-DR and DQ antigens in patients with ulcerative colitis as compared with controls.

Correspondence: H. Forootan Pishbijari, Associate Professor of Gastroenterology, Tehran University of Medical Sciences, GI Endoscopy Section, Imam Khomeini Hospital, Keshavarz Blvd., Tehran, Iran.

PATIENTS AND METHODS

Patient population

The study consisted of 42 patients (19 males and 23 females) with UC, who were outpatients and inpatients of Imam Khomeini Hospital. The age range was 7-80 years. On the basis of past and present history, physical examination, intestinal x-ray studies, colonoscopy and histologic findings, the diagnosis of UC was established. The control group were recruited from 84 healthy unrelated Iranian organ donors. None of the control group

Table I. Phenotype frequency (PF) of HLA antigens in patients wiht ulcerative colitis and controls.

HLA antigen	UC (N= 42)		Controls (N= 84)	
	Cases (N)	PF (%)	Cases (N)	PF (%)
DR1	4	9.52	9	10.71
DR2	17	40.47	24	28.57
DR3	8	19.04	11	13.09
DR4	9	21.42	23	27.38
DR6	3	7.14	5	5.95
DR7	7	16.66	12	14.28
DR11	22	52.38	38	45.23
DR12	0	0	0	0
DR52	40	95.2	67	79.76
DR53	23	54.76	43	51.19
DQ1	29	69.04	54	64.28
DQ2	8	19.04	18	21.42
DQ3	21	50	34	40.47
DQ7	3	7.1	2	2.38

Table II. The phenotype frequency of HLA-DR2 in relation to the various clinical patterns in patients with ulcerative colitis.

UC N= 42	Male N= 19	Female N= 23	Proctitis N= 3	Left colon colitis N= 12	Rectosigmoiditis N= 24	Pancolitis N= 3
Frequency of DR2 (%)	57.84	26.08	33.33	25	41.6	100

had a disease with known genetic predisposition.

HLA typing

Well defined antisera from different sources (Behring and Biotest) as well as some local antisera were used for detection of 19 HLA class II antigens (DR and DQ), using the standard microlymphocytotoxicity test.

Statistical analysis

Results for the UC study group were compared with results for controls using the χ^2 test or, in case of small numbers, Fisher's exact test was employed. The corrected p values were expressed after correction for the number of antigens tested in each locus.

RESULTS

The distribution of phenotype frequencies of loci of DR and DQ alleles in control individuals and patients with UC are shown in Table I. The antigen of high frequency in patients with UC was DR2. However, this increase was not statistically significant (40.5% vs 28.6% in controls, $p>0.5$). HLA DR2 frequency in patients with UC was assessed in relation to the various clinical patterns, such as sex and extent of involvement (Table II). In UC no overall association was present with the HLA class II antigens.

DISCUSSION

The present study reveals no association between HLA class II antigens and UC. An association of HLA-DR2 with Japanese UC has been shown in several studies. However, studies of HLA class II association with UC in other populations have conflicting results.[9-18] With the exception of the small samples size and/or lack of ethnic matching in patient and control populations in some of the studies that contribute to the conflicting results, ethnic differences between the populations studied probably account for these discrepancies (Table III).

In white non-Jewish of the European population, DRE1*1501 is the only common allele of DR2, and

Table III. Relative frequency (%) of DR2 alleles in different ethnic groups (Source reference 4).

	Jews (Israel)	North European Non-Jews	Japanese
DRB1*1501	27.7	96.0	39.5
DRE1*1502	55.5	1.0	57.0
DRB1*1601/2	16.8	3.0	3.5

DRE1*1502 accounts for less than 5% of alleles. By contrast, DRE1*1502 which is responsible for the HLA-DR2 association in patients with UC is the most common allele representing DR2 in Japanese and Jewish populations.[13-14] Further molecular studies are recommended to confirm the mentioned hypothesis.

Another possible explanation for the conflicting results described is heterogeneity within UC. The HLA-DR2 alleles may influence genetic susceptibility to other forms of UC, and genetic susceptibility may not be a factor in some forms of UC.[15-18]

Additional studies examining candidate susceptibility genes for UC that are located in and near the HLA class II region are warranted. Additionally, considering some clinical and subclinical parameters such as circulating antineutrophil cytoplasmic antibodies (ANCA) can divide UC to more homogeneous subgroups.

The nature of the genetic susceptibility is only partly understood, although concordance studies in monozygotic twins suggest a greater genetic influence for Crohn's disease than for ulcerative colitis.

REFERENCES

1. Van Heel DA, Jewell DP: Genetics of inflammatory bowel disease-an update. Acta Gastroenterol Belg Apr-Jun; 64(2): 160, 2001.
2. Satsangi J: Genetics of inflammatory bowel disease: from bench to bedside? Asta Odontol Scand Jun; 59(3): 187-92, 2001.
3. Yang H: Inflammatory Bowel Disease: From Bench to Bedside. Baltimore, MD: Williams & Wilkins, pp. 32-64, 1994.
4. Robert E, et al: Weekly Clinicopathological Exercises. NEJM 340 (3): 215-221, 1999.
5. Ahmad T, Satsangi J, McGovern D, Bunce M, Jewell DP: The genetics of inflammatory bowel disease. Aliment Pharmacol Ther 15(6): 731-48, 2001.
6. Dela Concha EG, Fernandez-Arquero M, Lopez-Nava G, Martin E, Allcock RJ, Conejero L, Paredes JG, Diaz-Rubio M: Susceptibility to severe ulcerative colitis is associated with polymorphism in the central MHC gene IKBL. Gastroenterology Dec; 119(6): 1491-5, 2000.
7. Elson CO: The immunology of inflammatory bowel disease. In: Kirsner JB, Shorter RG, (eds.), Inflammatory Bowel Disease, 3rd ed. Philadelphia: Lea & Febiger, pp. 97-164, 1988.
8. Duerr RH, Neigut DA: Molecularly defined HLA-DR2 alleles in ulcerative colitis and an antineutrophil cytoplasmic antibody-positive subgroup. Gastroenterology 108: 423-7, 1995.
9. Sugimura K, Ota M, Matsuzawa J, Katsuyama Y, Ishizuka K, Mochizuki T, Mizuki N, Seki SS, Honma T, Inoko H, Asakura H: A close relationship of triplet repeat polymorphism in MHC class I chain related gene A(MICA) to the disease susceptibility and behavior in ulcerative colitis. Tissue Antigens 57(1): 9-14, 2001.
10. Satsangi J, Welsh RI: Contribution of genes of the major histocompatibility complex to susceptibility and disease phenotype in inflammatory bowel disease. Lancet 347: 1212-17, 1996.
11. Toyoda H, Wang SJ, Ying H: Distinct associations of HLA class II genes with inflammatory bowel disease. Gastroenterology 104: 741-748, 1993.
12. Froutan H, Nikbin B, Habibabadi M: HLA typing of ulcerative colitis in Iran. Acta Medica Iranica 34: 52-54, 1996.
13. Asakura H, Tsuchiya M, Also S, et al: Association of the human lymphocyte-DR2 antigen with Japanese ulcerative colitis. Gastroenterology 82: 413-18, 1982.
14. Sugimura K, Asakura H, Mizuki N, et al: Analysis of genes within the HLA region affecting susceptibility to ulcerative colitis. Human Immunology 36: 112-18, 1993.
15. Futami S, Aoyaama N, Honsako R, et al: HLA-DRB1 1502 allele, subtype of DR15, is associated with susceptibility to ulcerative colitis and its progression. Digestive Disease and Sciences 40: 814-18, 1995.
16. Lashner BA: Genetic heterogeneity in ulcerative colitis. Am J Gastroenterol 89: 1927-8, 1994.
17. Kobayashi K: Inflammatory bowel disease and immunology. Intern Med 32: 909-10, 1993.
18. Smolen JS, Gangl A, Polterauer P, et al: HLA antigens in inflammatory bowel disease. Gastroenterology 82: 34-38, 1982.