

The relation between the level of interleukin-23 with duration and severity of ulcerative colitis

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ABSTRACT

Aim: In this study, we determined the relationship between the serum level of IL-23 and the severity of ulcerative colitis (UC) among our population.

Background: A recent major breakthrough for describing the pathogenesis of intestinal tissue injury in inflammatory bowel disease (IBD) is the pathway related to interleukin-23 (IL-23).

Patients and methods: We performed a prospective case-control study on a total of 85 new patients with ulcerative colitis, recruited from a general referral hospital. Forty ethnically matched healthy controls were also enrolled among hospital staffs and analyzed. Serum IL-23 level was quantified using an electrochemiluminescence immunoassay (ECLIA) method with an immunoassay analyzer.

Results: The mean serum IL-23 level in the group with ulcerative colitis was significantly higher than the healthy individuals (347.5 ± 130.8 pg/ml versus 233.5 ± 86.3 pg/ml; $p < 0.001$). There was a positive correlation between the serum level of IL-23 and disease duration ($r = 0.27$, $p = 0.04$). Also, a direct relationship was found between the serum level of IL-23 and the severity of disease (mean IL-23 in mild UC = 296.2 ± 51.2 pg/ml; in moderate UC = 356.1 ± 142.9 pg/ml; and in severe UC = 399.3 ± 163.8 pg/ml, $p = 0.04$).

Conclusion: Serum level of IL-23 is directly correlated with the duration and severity of ulcerative colitis.

Keywords: IL-23, Severity of disease, Ulcerative colitis.

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Introduction

Epidemiological studies suggested that genetic susceptibility related to the inflammatory processes have been identified as a major contributing factor to inflammatory bowel diseases (IBD). Molecular data from total genome scans and from candidate gene studies have led to

the identification of genetic determinants of susceptibility and disease phenotype of these diseases (1, 2). The primary goal of genetic research is to identify genetic variants within specific genes which could modify inflammatory processes and thus increase disease susceptibility (3).

A recent major breakthrough for describing the pathogenesis of intestinal tissue injury in inflammatory bowel disease is the interleukin-23/interleukin-17 pathway (4). This inflammatory

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pathway is induced by interleukin-23, a heterodimeric cytokine that shares the p40 subunit with interleukin-12, but couples it with the p19 instead of the p35 subunit. Interleukin-23 can drive a population of T lymphocytes that produce interleukin-17, interleukin-6 and TNF- α . These cells are involved in tissue damage in many diverse pathologic conditions (5, 6).

Studies with IL-23 deficient mice showed that IL-23 is essential for the manifestation of intestinal inflammation and a dominant role for IL-23 in central nervous system and joint autoimmune inflammation (7, 8) has been described. These findings point to IL-23, as the necessary mediator for organ specific autoimmune diseases development. Yen and colleagues (9) reported that the activation of tissue-homing memory T cells by IL-23 is responsible for IBD. Therefore, genetic researches on the role IL-23 in IBD has provided knowledge about the complexity and heterogeneity of the disease and started to correlate the interactions between genetic and risk factors in IBD; however, the complex genetic background that allows the development of IBD through the activation of IL-23 is not fully understood.

In this study, we tried to determine the association of the interleukin-23 serum level with duration and severity of disease in patients with ulcerative colitis.

Patients and Methods

We performed a prospective case-control study on a total of 85 Iranian new patients with ulcerative colitis, recruited from a general referral hospital between October 2008 and January 2011. Forty ethnically matched healthy controls were also enrolled among hospital staffs and analyzed. Ulcerative colitis patients were diagnosed by standard clinical, radiological, endoscopic and histological criteria (10). All the subjects included in the study signed an informed consent and the

study was approved by the Ethics Committee of the referral hospital.

At the first admission time, the patients were given self-administered questionnaires about their demographics and medical history. Venous blood samples were drawn at a patient's first visit from an antecubital vein into a chilled ethylenediaminetetraacetic acid Vacutainer test tube after 30 minutes of supine rest. Samples were placed immediately on ice, and plasma separation was performed at -4°C. Plasma samples were frozen at -80°C until assay. Serum IL-23 level was also quantified using an electrochemiluminescence immunoassay (ECLIA) method (ELIZA kit, Bender-med, Ostrich) with an immunoassay analyzer.

Disease severity was measured using a modified version of the Mayo Scoring System for assessment of UC activity that categorized the severity based on frequency of bowel movements, amount of blood in bowel movements, and physician assessment of disease severity as: low severity (modified Mayo Score 0-2), moderate severity (modified Mayo Score 3-5), high severity (modified Mayo Score 6-9) (11).

Statistical Methods: Continuous data were shown as mean and standard deviation (SD) and categorical variables were presented as percentages. Patients' characteristics were compared by means of the t-test or ANOVA test for continuous variables and the chi-square test or the Fisher's exact test for categorical variables. The spearman r was calculated to measure the association of IL-23 serum level and other continuous parameters. Multivariable logistic regression analyses were used to assess the differences in IL-23 serum level between the diseased and control subjects in addition to a series of other potential risk factors. Analysis was carried out using SPSS (version 16.0, SPSS Inc., Chicago, IL, USA). All *p*-values were two-sided, with statistical significance defined by $p \leq 0.05$.

Results

In the present study, 85 patients with ulcerative colitis (mean age 37.5 ± 16.1 years, 36.8% male) and 40 healthy individuals (mean age 36.8 ± 15.7 years, 40% male) were included. No significant differences were found between the groups in terms of gender ratio and age. There were also no significant differences between the two study groups with and without ulcerative colitis in the history of cigarette smoking (14.1% versus 15%) and opium addiction (5.9% versus 5%). Among the patients group, 14.1% had the family history of ulcerative colitis, while none of the healthy subjects had this family history. In all, 41.2% of ulcerative colitis patients suffered from extensive colitis and 47.1% showed extra intestinal manifestations. Regarding modified version of the Mayo Scoring System, mild, moderate and severe features were observed in 37.6%, 34.1%, and 28.2%, respectively.

The mean of serum IL-23 level in the group with ulcerative colitis was significantly higher than the healthy individuals (347.5 ± 130.7 pg/ml versus 233.5 ± 86.3 pg/ml, $p < 0.001$). There was a positive correlation between the serum level of IL-23 and disease duration (Pearson correlation coefficient = 0.27, $p = 0.04$).

Relationships between the level of this biomarker and other factors including cigarette smoking and opium use were not meaningful. However, patients with the family history of ulcerative colitis had significantly lower level of IL-23 than other ones (277.5 ± 75.5 pg/ml versus 358.7 ± 127.6 pg/ml, $p = 0.03$). Also, a direct relationship was found between the level of IL-23 and the severity of colitis (mean IL-23 in mild UC = 296.2 ± 51.2 pg/ml; in moderate UC = 356.1 ± 142.9 pg/ml; and in severe UC = 399.3 ± 163.8 pg/ml, $p = 0.04$).

Multivariable logistic regression analysis could confirm significant difference in serum IL-23 level

between the patients and healthy individuals with the presence of patients' demographics (Table 1).

Table 1. Multivariable regression analysis of the differences in serum IL-23 level between the patients with ulcerative colitis and healthy individuals

Variable	Beta	Standard Error	P-value
IL-23	114.8	32.03	0.001
Male gender	10.6	29.8	0.7
Advanced age	0.03	0.9	0.9

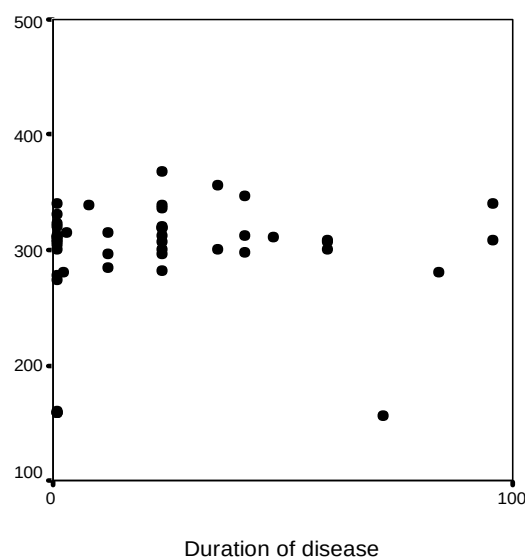


Figure 1. Correlation between serum IL-23 level (pg/ml) and disease duration (days)

Discussion

We found strong association of the marker IL-23 with duration and severity of disease in ulcerative colitis even with the presence of confounding factors such as age and gender. But, IL-23 was not involved in susceptibility to ulcerative colitis in some European population (11). The differences in other cases with ulcerative colitis may reflect genetic variation in the two populations at other ulcerative colitis risk loci (12). IL-23 gene variants have now been repeatedly implicated in a number of inflammatory diseases and perhaps suggest that these pathologies are mediated by the Th17

pathway. Despite many studies finding association of these diseases with the IL-23 region, few have reported functional evidence for the involvement of IL-23 variants. Data from immunologic studies suggest that IL-23 plays a significant role in the development of GI mucosal inflammation (13), and the critical role of the IL-23 pathway in IBD pathogenesis was confirmed by the association of several SNPs (single nucleotide polymorphism) throughout the IL23R gene with UC (14,15). Some studies demonstrated that the rare allele of a nonsynonymous polymorphism, Arg381Gln, confers a threefold increase in protection against UC (13). The importance of the IL-23R signaling pathway in UC is further underscored by the fact that variants within IL-23R, IL-12, and STAT3 have also been genetically associated with UC (16, 17). Based on our finding, variants related to the appearance of UC in our population should be studied in further studies.

Our findings strengthen the idea that IL-23 level measurement may be of value in the detection of disease severity in patients with significant UC. It might be subsequently postulated that IL-23 is predictive of outcome in these patients. Therefore, its assessing may be easier than other complex and expensive markers and protocols. Therefore, it is recommendable that the value of IL-23 can be defined as one of the variables or even as a new simple risk assessment tool for evaluating outcome of UC patients especially those with the evidences of life-threatening events. However, its prognostic ability needs to be approved by further studies with greater sample sizes and in various population subgroups.

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