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Submission date: 07-Mar-2021 11:39PM (UTC-0800)
Submission ID: 1527226926
File name: ivities_of_Systemic_Lupus_Erythematosus_in_Javanese_Patients.pdf (484.07K)
Word count: 4756
Character count: 25001

Vol. 7 April 2015
Print ISSN 2244-1557 • Online ISSN 2244-1565
International Peer Reviewed Journal
DOI: http://dx.doi.org/10.7718/iamure.ijscl.v7i1.633
Journal Metrics: H index = 2 from Publish or Perish
This Journal is produced by IAMURE Multidisciplinary Research,
an ISO 9001:2008 certified by the AJA Registrars Inc.

Single Nucleotide Polymorphisms Promoter Gen Il-10 as Predictor Disease Activities of Systemic Lupus Erythematosus in Javanese Patients

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Gunning Fog Index: 10.42 Originality: 100% Grammar Check: 90%
Flesch Reading Ease: 54.93 Plagiarism: 0%

ABSTRACT

Systemic Lupus Erythematosus is a complex disease, signifying that genetic and environmental factors are involved in diseases development. Although the role of genetic factor in many populations had been studied, the genetic factor associated with diseases activity has not been identified yet. This study was performed to determine polymorphisms in the IL-10 gene promoter with diseases activity SLE in Javanese population. This study was performed to analyze the genotype IL-10 gene proximal promoter in SLE patients using a pair of specific primer of the IL-10 gene proximal promoter and sequenced by Applied Biosystem Method. This study enrolled 47 SLE patients (ACR criteria) in active diseases. Disease activity was evaluated using SLAM. The level of IL–10 was measured by ELISA kit. There were three locus SNP at -294 A/G, -296 A/T and -301 A/G of

IL- 10 gene proximal promoter, with three variant combination: -294G/-296A/-301G, -294G/-296T/-301G and -294A/-296A/- 301A. The serum level of IL-10 among three groups was significantly different. The patients with variant -294G/-296A/-301G had a significantly higher score of disease activity (severe diseases) compared with the other groups of patients. The combination -294A/-296A/-301A was similar to the sequence IL-10 gene proximal promoter from GenBank NCBI. It is concluded that Interleukin-10 proximal promoter SNP as predictor diseases activity of Systemic Lupus Erythematosus.

KEYWORDS

Science, disease activity, Systemic Lupus Erythematous, observational study, Autoantibodies, SNP, IL-10 descriptive-evaluative design, Indonesia

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is chronic systemic rheumatic diseases. SLE is a fatal autoimmune disease characterized by B cell polyclonation and excessive production of autoantibodies against all the cell material (Lahita, 2004; Tutuncu & Kalunian, 2007).

Clinical manifestations vary very widely from mild to severe, known as the 'disease of 1000 face'. Early detection of disease activity is very important because it can determine the prognosis. SLE disease activity is associated with prognosis and mortality (Lahita, 2004; Rahman & Isenberg, 2008). It is not yet known to the pathogenesis of severe SLE disease activity in certain populations (Urowitz & Gladman, 2000; Fernandez et al., 2007).

Mortality of patients with SLE is five times higher than the normal population. Death in the early phase of the disease is caused by the disease activity. Survival rate in the last five years showed an improvement, for the ten-year survival rate is currently close to 90%, while the 15-year survival rate reached 80%. Progress is due to a more aggressive approach to therapy and advance use of immunosuppressants to suppress disease activity, however, not all populations can reach the survival rate number (Urowitz & Gladman, 2000; Urowitz, Gladman, Abu-Shakra, & Farewell, 1997).

Data from Dr. Soetomo Hospital in Surabaya, indicate that 30% of 153 patients have severe disease activity with clinical manifestations. Majority are lupus nephritis, hematological and cerebral lupus (Yuliasih, 2006). SLE mortality

rate from Dr. Soetomo Hospital rate is 0.025% of the population (Rus & Hochberg, 2007) which higher than the world's mortality rate

Over the last decade, many researchers thought that cytokines have an important role causing severe disease activity such as IL-10, IL-6 and IFN gene (Mocellin, Panelli, Wang, Nagorsen, & Marincola, 2003; Mocellin, Rossi, & Pilati, 2006; Chun et al., 2007). There is impaired balance of pro-inflammatory cytokines and anti-inflammatory cytokines in SLE and a change at a specific cytokine expression. Interleukin-10 is thought to contribute to SLE disease activity, especially in the Asian population (Nath, Harley, & Lee, 2005). Interleukin-10 is associated to SLE disease activity through changes in IL-10 expression because of the micro-environment around the cell (Sharif et al., 2004).

Llorente and Richard-Patin (2003) found that level of IL-10 in patients with active SLE is 40 times higher than the normal population. Some researchers reported that elevated levels of IL-10 because of IL-10 gene promoter polymorphisms or Single Nucleotide Polymorphism (SNP) in (Lazarus et al., 1997; Mongan et al., 1997; Mehrian et al., 1998; Mok et al., 1998; Rood et al., 1999; D'Alfonso, Rampi, Bocchio, Colombo, Scorza-Smeraldi, & Momigliano-Richiardi, 2000; Gibson et al., 2001; Peng, Ku, Shu, & Lung, 2008; Schotte et al., 2004; Chong et al., 2004; Khoa & Sugiama, 2005; Sung et al., 2006; Yilmaz, Yentür, & Saruhan-Direskeneli, 2005). Single Nucleotide Polymorphism (SNP) in the promoter region of IL-10 gene at positions -1082 G / A, -819 C / T, -592 A / C, significantly elevate levels of IL-10 polymorphism in position, especially at-1082A / G. These three SNPs are in the form haplotypes GCC, ACC and ATA.

IL-10 as immunoregulator has two functions: as immunosuppressor and immunomodulatory (Mocellin et al., 2003). IL-10 as an immunomodulator is a very powerful cytokine to stimulate B cells differentiation, proliferation and antibody synthesis. Increased B cell proliferation and antibody synthesis are associated with SLE disease activity.

Based on studies reported above, the SNP in the promoter IL-10 genes was associated with SLE disease activity, therefore it was expected that we found the gene associated in SLE disease activity at Dr. Soetomo Hospital, thus lower the mortality rate. In this study, we aimed to analyze whether the SNP promoter gen IL-10 is associated with SLE disease activity in Dr. Soetomo Hospital.

OBJECTIVE OF THE STUDY

The study aimed to determine polymorphisms in the IL-10 gene promoter with diseases activity SLE in Javanese population.

MATERIALS AND METHOD

The design of this study was observational with cross-sectional method. The population in this study was SLE in-patients or out-patients who met the criteria of the American College of Rheumatology (ACR) 1997 in Dr. Soetomo Hospital Surabaya during the period January 2009 until December 2009. Based on data from a population of SLE patients who were treated in the period January 2009 to December 2009 in Dr. Soetomo Hospital, there were 70 SLE patients, and 47 patients were enrolled.

The sampling technique used was random or simple random sampling in populations that have been determined. The technique was being used because the study population is homogeneous (Lwanga & Lemeshow, 1991). Disease activity of each sample was measured by SLAM score.

Analyzed the promoter of IL-10 genotyping and DNA sequencing

PCR step for DNA extraction was done using blood nucleospin (Macherey-Nagel) and performed by PCR with primers IL-10 gene promoter at -1082 base as much as 20bp which is front primer 5'CAAGACAACACTACTAAGGC'3 and back primer 5'ATTGGCCTTAGAGTTTCTTTTAG'3.

DNA amplification is done using GeneAmp PCR System 2400 machine (PERKIN ELMER). PCR reaction mixture (10 µl) was containing buffer. To make one sample required 3.6 µl H_2O, 5 µl PCR mix; 0.2 µl forward primer; 0.2 µl primer reverse and 1 µl of DNA from 10 samples of DNA.

Shake the sample with fingers carefully, spin down, then put in a PCR machine set at regular intervals as follows: denaturation carried out at 94°C for one minute, followed by 40 cycles of PCR consisting of denaturation 94°C for 30 second, aneling at 59°C for 30 seconds, then synthesis 72° C for one minute.

The reaction was terminated with a final synthesis at 72° C for seven minutes, followed by a drop in temperature to 4 ° C to stop the reaction. The PCR results electrophoresed in 1.5% agarose gel in 1 X TAE buffer solution (Tris EDTA pH 8.0) at 70 volts for 90 minutes. After PCR detected DNA about 200bp, then sequencing done according to protocols Applied Biosystem sequencing.

Examination of IL-10 Elisa

Cytokine IL-10 examination was done by ELISA-Sandwich. Reagents used are human IL-10 ELISA-made by Bender MedSystems. This assay used enzyme sandwich immunoassay techniques. Monoclonal antibody specific to IL-10 was placed into a microplate. Standard, samples and conjugate added using a pipette into the well, IL-10 was sandwiched by mobilized antibody and enzyme-linked polyclonal antibody specific to IL-10. The result of IL-10 optical density examination was read in ELISA reader then the result was converted to pg / ml according to the instructions in the kit.

Statistical Analysis

The statistical test was performed. Patient characteristic, the frequency of ACR criteria, the frequency of SNPs were analyzed using descriptive statistics. SNPs and SNP combinations relationship with level of IL-10 and SLAM score was done using ANOVA test (SPSS software version 17 for Windows XP; SPSS, Chicago, IL).

To find a relationship between levels of IL-10, antibody increase and complement decrease, LISREL pathway analysis (version 8:50 for Windows 2000 & NT) was done. Paired T-test was done to see the difference in the secretion of TNF-α exposure in PBMC before and after the exposure.

RESULTS AND DISCUSSION

PCR results were sequenced with the software ClustalX2 and obtained 170 bp. Multiple alignments with complete region of IL-10 gene promoter from NCBI along 1381bp were done to sequencing result. Clustal multiple sequence alignments result in the studied samples obtained at position 270 - 442bp (Fig.1). Three Single Nucleotide Polymorphism (SNP) in this study was found SNPs at positions -294 A / G, -296 A / T and -301 A / G. Table 1 shows the most frequent allele was found at the position -294 * G, -296 * A and -301 * G.

IL-10 levels were measured by ELISA KIT. In Table 2, it was found that level of IL-10 in each haplotypes group was different. In the group of SLE patients with -294G/-296A/-301G haplotype (GAG) showed significant ($p = 0.000$) higher levels of IL-10 than mean value (338.16 pg / ml) and only found in severe disease activity group compared with the another group of SLE patients with Brown-Forsythe test statistic method.

Haplotype 294A/-296A/-301A is a combination of unchanged nucleotides

(same as IL-10 gene promoter from Gen Bank NCBI). It can be concluded that all haplotype has significantly increase level of IL-10, but from the frequency, it was more significant to haplotype (GAG) -294G/-296A/-301G, whereas haplotype 294A/-296A/-301A (AAA) was in accordance to the sequence of IL-10 gene promoter.

Table 1. Frequency of the alleles and haplotypes of the IL-10 promoter in SLE patients

Allele	SLE Patients	
	n=47	Frequencies (%)
Allele		
-294 A	10	21.3
-294 G	37	78.7
-296 A	37	78.7
-296 T	10	21.3
-301 A	10	21.3
-301 G	37	78.7
Haplotype		
GAG	27	57.4
GTG	10	21.3
AAA	10	21.3

Table 2. Association between alleles and haplotypes of the IL-10 promoter with the serum level of IL-10 in Javanese SLE patients

	n (%)	IL-10		*p*
		Mean ± SD (Mild)	Mean ± SD (Severe)	
Allele				
-294 AàA	10 (21.3)	14.62 ± 3.42	-	0.000
-294 AàG	37 (78.7)	83.22 ± 5.41	338.16 ± 8.58	
-296 AàA	37 (78.7)	14.20 ± 3.42	338.16 ± 8.58	0.002
-296 AàT	10 (21.3)	83.22 ± 5.41	-	
-301 AàA	10 (21.3)	14.62 ± 3.42	-	0.000
-301 AàG	37 (78.7)	83.22 ± 5.41	338.16 ± 8.58	

Haplotype				
GAG	27 (57.4)	-	338.16 ± 8.58	0.000
GTG	10 (21.3)	83.22 ± 5.41	-	
AAA	10 (21.3)	14.62 ± 3.42	-	

In Table 3, below is an overview of from clinical data and SLE autoantibody in Javanese patients. In the table shows photosensitivity, oral ulcers and arthritis have a higher frequency in SLE patients. From Table 3, only malar rash that is significant to GAG haplotype ($p < 0.05$ using Chi-Square Test).

Table 3. Clinical features of Javanese SLE patients.

Clinical Features	Haplotype (-294/-296/-301)			*P*
	GAG n=27 (%)	GTG n=10 (%)	AAA n=10 (%)	
Malar Rash	8(29.63)	3(30)	8(80)	0.016
Discoid Rash	5(18.52)	5(50)	1(10)	0.070
Photosensitivity	16(59.26)	7(70)	9(90)	NS
Oral Ulcer	19(70.37)	10(100)	8(80)	NS
Arthritis	25(92.59)	9(90)	10(100)	NS
Serositis	4(14.81)	1(10)	0(0)	NS
Renal Disorder	13(48.15)	3(30)	1(10)	0.090
Neurologic Disorder	22(81.48)	9(90)	9(90)	NS
Hematologic Disorder	17(62.96)	6(60)	4(40)	NS
Antibodies				
ANA	14(51.85)	8	5	NS
dsDNA	11(40.74)	8	1	NS

Path analysis was used to determine the effect of multicollinearity among variables, the total effect, the direct and indirect effects of one variable to another variable. The analysis results of the test track showed significant T-values obtained between IL-10 and ANA (showed a red color). T-values between ANA and ds DNA was found significant.

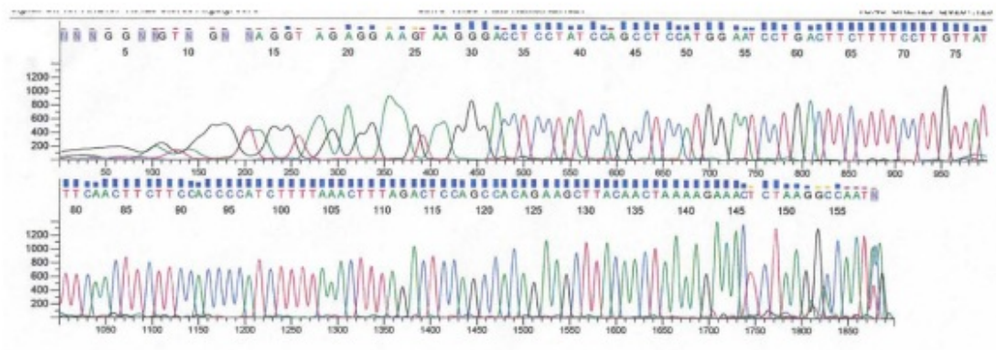
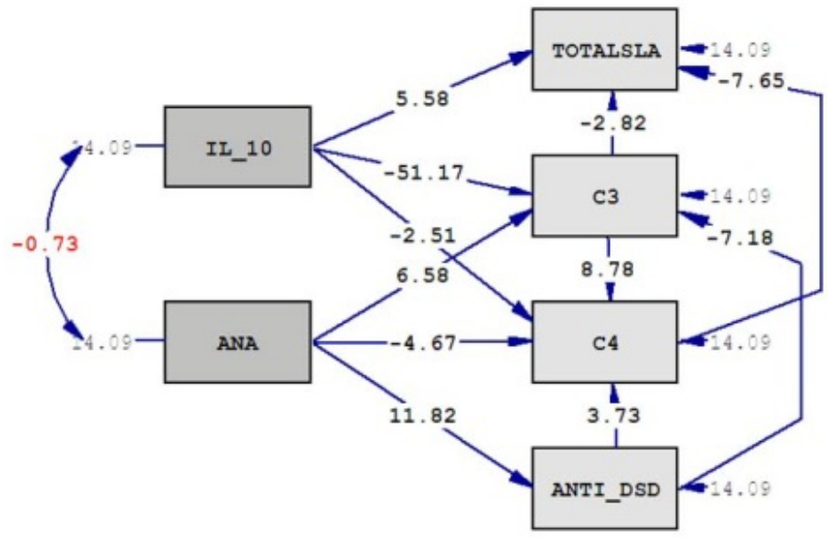


Figure 1. DNA sequencing



Chi-Square=38.30, df=3, P-value=0.00000, RMSEA=0.172

Figure 2. Path Analysis of several variables influence
SLE disease activity (t model)

Effect of IL-10 to disease activity was significant (T-values = 5.58) which mean that IL-10 directly affects the increase in SLAM score. Effect of IL-10 to C3 showed significant result (T-values = -51.17), which mean that any increase in the levels of IL-10 followed by decreased level of C3, as well as the influence of IL-10 to C4 (T-values = -2 , 51).

Effect of C3 (T-values = -2.82) and C4 (T-values = -7.65) significantly to the SLAM score, mean C3 and C4 direct influence of the SLAM score, any

decrease in C3 and C4 increased SLAM score. In the analysis of this pathway can be concluded that IL-10 directly affects the increase in SLAM score can also affect indirectly through increased SLAM score of C3 and C4.

Knowledge of a disease based on science-based research and clinical observations yield optimal knowledge in the handling of a disease. Recently gene based approach was developed as a theoretical basis for understanding the disease, both in terms of prognosis, diagnostics and therapeutics.

Very high level of IL-10 is found in very high active SLE. Increased level of IL-10 is associated with gene promoter SNP. SNP IL-10 gene promoter determines the difference in level of IL-10 between individual. Gene promoter is a transcriptional regulator of the DNA. Promoter consists of the core promoter, proximal promoter and distal promoter. The proximal promoter is a very important part to regulate transcription rate. The speed of transcription will be affected if the compositions of nucleotides in the proximal promoter region change (Mok & Lau, 2003).

Changes in nucleotide composition in this area will facilitate the attachment of transcription factor to DNA binding site in the promoter regulator region, which will enhance transcription (Mok & Lau, 2003).

In this study found SNP at three nucleotide position in the proximal promoter, which leads to changes in transcription rate. Three positions obtained in this study were SNP at position -294 A / G, -296 A / T and -301 A / G. This SNP forms three haplotype 1) -294G/-296A/-301G (GAG) which was found in SLE group with a high SLAM score and significantly increase levels of IL-10, and two was found in mild SLAM score 2) -294G/-296T/- 301G (GTG) and 3) -294A/-296A/-301A (AAA). Based on these results, SNP found could be categorized as a predictor because in severe SLE haplotypes 294G/-296A/-301G (GAG)was found and was not found in mild SLE.

In this study found the average levels of IL-10 215 pg / ml, while Gibson, et al., (2001) in Caucasian populations had average levels of IL-10 was: 543 pg / ml in active SLE and Mongan, et al., (1997) [16], reported average levels of IL-10: 66.25 + 16.34 pg / ml.

The researchers SNP IL-10 gene promoter in SLE include Lazarus et al., (1997); Mongan et al. (1997); Rood et al. (1999); Schotte et al. (2004) in the Caucasian population, Mehrian et al. (1998) (American-Mexican); D'Alfonso et al. (2000) Italy; Gibson et al. (2001) Africa; Tyrrell-Price, Lydyard, & Isenberg (2001) Afro-Carribean and Caucasians; Mok and Lau (2003) Hong Kong; Chong et al. (2004) China; Khoa, Sugiyama, & Yokochi (2005) Vietnam; and

Sung et al. (2006) Korean. These researchers reported the position of the gene promoter SNP at position IL-10 -1082 G / A, -819 C / T, -592 A / C which were significant to elevate levels of IL-10.

SNP positions difference in this study may be caused to differences in the process of adaptation or evolution. In this study, the location of SNPs was similar to the theory, which was the mutated nucleotide (proximal promoter region) between 300bp from start site will increase the transcription.

IL-10 role in SLE disease activity caused by two mechanisms, the first mechanism is IL-10 increases proliferation, differentiation and increases the cell B synthesis of autoantibodies and the second mechanism is IL-10 as a pro-inflammatory cytokine. Both of these mechanisms lead to severe dysregulation of the immune system.

Cohen, Crawley, Kahan, Feldmann, and Foxwell (1997) as well as Mehrian et al. (1998) reported that IL-10 can enhance survival of B cells through the expression of bcl2 that extends survival of B cells. Increase proliferation and survival of B cells will increase the synthesis of these autoantibody and autoantibodies to form immune complexes in peripheral blood vessels. Ronnelid et al. (2003) reported that the accumulation of immune complexes due to defect of FcγRII. Circulating immune complexes in the peripheral can activate monocytes and macrophages to secrete cytokines IL-10 so that B cells are always in a state of hyperactivity. Autoantibody formed an immune complex. Immune complexes that are deposited in the tissue activate the complement so that the complement in active SLE decreased.

In this study, ANA and dsDNA antibodies were not significant with the increase of IL-10 so it can be predicted that major antibody which form immune complexes was not ANA and dsDNA, considering that there are a lot of antibodies involve in SLE, based on the pathway analysis of IL -10 significantly related to C3 and C4 decreased .

The results of IL-10 pathway analysis in this study significantly related to disease activity based on SLAM score. Increase levels of IL-10 indirectly affected the increase of SLAM score and IL-10 indirectly affected the score of SLAM through C3 and C4. It can be concluded that IL-10 indirectly related to disease activity through the indirect pathway of C3 and C4 due to the formation of immune complexes and through the mechanism of IL-10 as a pro-inflammatory substance because of disease activity associated with the existing level of inflammation in the body.

Rood et al. (1999) and Peng et al. (2008) reported IL-10 increases the risk of CNS lupus while CNS lupus associated with disease activity. Mok et al. (1998)

reported that IL-10 associated with the risk of lupus nephritis, also report from Chan et al. (2005). Clinical manifestations of lupus nephritis, CNS lupus and cardiac abnormalities are the predictor of poor prognosis. Report from Nossent et al., (2007) evaluated the cause of death in SLE in Europe 2000-2004 is due to active lupus. In this study an increase in IL-10 detected through the pathways analysis significantly affected disease activity based on SLAM score.

CONCLUSIONS

1. *Single Nucleotide Polymorphism (SNP)* in the promoter region of IL-10 gene at positions -294 A -> G, -296 A ->T, -301 A -> G on Javanese patients especially at Surabaya (Hospital Dr. Soetomo) was different from the Caucasian population, Italy, China, Hongkong, Vietnam, Korea, Africa, Mexico.
2. IL-10 SNPs promoter is significantly associated with disease activity, especially in -294G/-296A/-301G haplotypes in SLE Javanese patients.

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