DISERTASI

HUBUNGAN POLIMORFISME RS2228145 GEN *INTERLEUKIN 6 RECEPTOR* DENGAN PENYAKIT JANTUNG KORONER MELALUI *SOLUBLE INTERLEUKIN 6 RECEPTOR, SOLUBLE GLYCOPROTEIN 130, INTERCELLULAR ADHESION MOLECULE 1* DAN *C-REACTIVE PROTEIN*

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ABSTRAK

HUBUNGAN POLIMORFISME RS2228145 GEN *INTERLEUKIN 6 RECEPTOR* DENGAN PENYAKIT JANTUNG KORONER MELALUI *SOLUBLE INTERLEUKIN 6 RECEPTOR, SOLUBLE GLYCOPROTEIN 130, INTERCELLULAR ADHESION MOLECULE 1* DAN *C-REACTIVE PROTEIN*

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Suatu polimorfisme gen reseptor IL-6 (IL-6R), yaitu SNP rs2228145, diduga berhubungan dengan PJK melalui mekanisme inflamasi lewat jalur aktivasi interleukin 6 (IL-6). Terdapat dua jalur aktivasi IL-6 yaitu jalur klasik, dimana IL-6 berikatan dengan IL-6R dan menghasilkan respon inflamasi melalui produksi c-reactive protein (CRP), dan jalur trans-sinyal dimana IL-6 berikatan dengan reseptor IL-6 yang terlarut (sIL-6R), dengan salah satu produknya yaitu intercellular adhesion molecule 1 (ICAM-1). Inhibitor jalur trans-sinyal, yaitu glycoprotein 130 yang terlarut (sgp130), dapat mengikat kompleks IL-6/sIL-6R sehingga aktivasi trans-sinyal terhenti. Tujuan penelitian ini untuk membuktikan adanya hubungan antara SNP rs2228145 gen IL-6R dengan PJK melalui sIL-6R, sgp130, ICAM-1 dan CRP.

Penelitian ini merupakan penelitian analitikal dengan desain studi kasus-kontrol. Populasi penelitian adalah penderita PJK Eka Hospital Pekanbaru yang telah menjalani pemeriksaan angiografi koroner dan didapatkan stenosis $\geq$ 70% pada minimal satu pembuluh koroner. Kontrol adalah subjek sehat yang sedang menjalani pemeriksaan kesehatan di Eka Hospital Pekanbaru, tanpa keluhan nyeri dada dan riwayat keluarga PJK, dengan EKG normal. Diambil masing-masing 30 sampel kelompok PJK dan kontrol, sesuai kriteria inklusi dan eksklusi. Kemudian diambil sampel darah untuk pemeriksaan SNP rs2228145 dengan metode PCR dan kadar sIL-6R, sgp130, ICAM-1 dan CRP dengan metode ELISA.

Karakteristik pasien tidak berbeda bermakna, kecuali hipertensi 53,3% pada kelompok PJK berbanding 6,7% pada kelompok kontrol ($p < 0,05$) dan diabetes melitus 30,0% pada kelompok PJK berbanding 6,7% pada kelompok kontrol ($p < 0,05$). Penelitian ini menunjukkan bahwa SNP rs2228145 juga dijumpai di Indonesia. Penelitian ini juga mendapatkan satu SNP lain gen IL-6R, yaitu rs4845374. Kelompok PJK 56,7% terdapat mutasi rs2228145, pada kelompok kontrol 53,3% ($p > 0,05$). sIL-6R dan ICAM-1 menunjukkan hubungan dengan PJK, yaitu pada sIL-6R $\geq$ persentil 50 persentase PJK lebih tinggi dibandingkan sIL-6R < persentil 50 (70% berbanding 30%, $p < 0,05$), dan pada ICAM-1 < persentil 50 persentase PJK lebih tinggi dari ICAM-1 $\geq$ persentil 50 (66,7% berbanding 3,3%, $p < 0,05$). Tidak terdapat hubungan antara SNP rs2228145 dengan sIL-6R, sgp130, ICAM-1, maupun CRP. Tetapi ada kecenderungan kadar ICAM-1 lebih tinggi pada subjek yang tidak ada mutasi rs2228145 (1850,31$\pm$1827,41 pg/ml berbanding 1570,71$\pm$1205,91 pg/ml), dan kecenderungan kadar CRP lebih tinggi pada subjek yang tidak ada mutasi rs2228145 (2480,45$\pm$3071,97 ng/ml berbanding 1649,55$\pm$1622,79 ng/ml). Dalam analisis multivariat tidak didapati adanya hubungan antara SNP rs2228145 dengan PJK melalui sIL-6R, sgp130, ICAM-1, dan CRP.

Penelitian ini menunjukkan SNP rs2228145 dijumpai pada lebih dari separuh kelompok pasien PJK, tetapi tidak terbukti ada hubungan antara SNP rs2228145 dengan PJK, maupun hubungan antara SNP rs2228145 dengan PJK melalui sIL-6R, sgp130, ICAM-1, dan CRP. Namun demikian penelitian ini menunjukkan terdapatnya hubungan antara sIL-6R dengan PJK. Hal ini membutuhkan penelitian lebih lanjut.

Kata Kunci : SNP rs2228145 gen IL-6R, sIL-6R, sgp130, ICAM-1, CRP, penyakit jantung koroner

ABSTRACT

RELATIONSHIP BETWEEN POLYMORPHISM RS2228145 OF INTERLEUKIN 6 RECEPTOR GENE WITH CORONARY HEART DISEASE THROUGH SOLUBLE INTERLEUKIN 6 RECEPTOR, SOLUBLE GLYCOPROTEIN 130, INTERCELLULAR ADHESION MOLECULE 1 AND C-REACTIVE PROTEIN

Jajang Sinardja

A polymorphism of the IL-6 receptor gene (IL-6R), SNP rs2228145, is thought to be associated with CHD through an inflammatory mechanism via the activation pathway of interleukin 6 (IL-6). There are two pathways, the classical pathway, where IL-6 binds to IL-6R and produces an inflammatory response through the production of c-reactive protein (CRP), and the trans-signaling pathway where IL-6 binds to the soluble IL-6 receptor (sIL-6R), and one of its product is intercellular adhesion molecule 1 (ICAM-1). Trans-signal pathway inhibitors, which is soluble glycoprotein 130 (sgp130), can bind to IL-6/sIL-6R complex to stop the trans-signal activation. The purpose of this study was to prove the relationship between the SNP rs2228145 of IL-6R gene with CHD through sIL-6R, sgp130, ICAM-1 and CRP.

This is an analytical study with case-control design. The study population was Eka Hospital Pekanbaru CHD patients who had undergone coronary angiography which showed stenosis $\geq$ 70% of at least one coronary vessel. Control group were healthy subjects who were undergoing health examination at Eka Hospital Pekanbaru, without chest pain and family history of CHD, and normal ECG. Each group contained of 30 samples, taken according to the inclusion and exclusion criterias. Blood samples were taken for SNP rs2228145 examination using PCR method and for sIL-6R, sgp130, ICAM-1 and CRP levels using the ELISA method.

The patient characteristics were not significantly different, except for hypertension which showed 53,3% in the CHD group vs 6,7% in the control group ($p < 0,05$) and diabetes mellitus which showed 30,0% in the CHD group vs 6.7% in the control group ($p < 0.05$). This study showed that SNP rs2228145 is also found in Indonesia. This study also showed another SNP of the IL-6R gene, which is rs4845374. In the CHD group, 56,7% had mutation of rs2228145, vs 53,3% in control group ($p > 0.05$). sIL-6R and ICAM-1 showed relationship with CHD, in which in sIL-6R $\geq$ percentile 50th the percentage of CHD was higher than sIL-6R < percentile 50th (70% vs 30%, $p < 0.05$), and in ICAM-1 < percentile 50th percentage of CHD was higher than ICAM-1 > percentile 50th (66.7% vs 3.3%, $p < 0.05$). There is no relationship between SNP rs2228145 with sIL-6R, sgp130, ICAM-1, or CRP. But there is a tendency for ICAM-1 levels to be higher in subjects with no mutation of rs2228145 (1850,31$\pm$1827,41 pg/ml vs 1570,71$\pm$1205.91 pg / ml), and the tendency for CRP levels to be higher in subjects with no mutation of rs2228145 (2480,45$\pm$3071,97 ng/ml vs 1649,55$\pm$1622,79 ng/ml). In multivariate analysis, there was no relationship between SNP rs2228145 with CHD through sIL-6R, sgp130, ICAM-1, and CRP.

This study showed that SNP rs2228145 of IL-6R gene was found in more than half of the CHD group, but failed to show relationship between SNP rs2228145 with CHD. This study also showed no relationship between SNP rs2228145 with CHD through sIL-6R, sgp130, ICAM-1 and CRP. However, there was a relationship between sIL-6R level with CHD. This results requires further study.

Keywords: SNP rs2228145 IL-6R gene, sIL-6R, sgp130, ICAM-1, CRP, coronary heart disease