The role of cytotoxic t-lymphocyte-associated protein 4 (ctla-4) gene, thyroid stimulating hormone receptor (tshr) gene and regulatory t-cells as risk factors for relapse in patients with graves disease

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Abstrak

Background: graves disease (GD) is the most common condition of thyrotoxicosis. The management of GD is initiated with the administration of antithyroid drugs; however, it requires a long time to achieve remission. In reality more than 50% of patients who had remission may be at risk for relapse after the drug is stopped. This study aimed to evaluate the role of clinical factors such as smoking habit, degree of ophtalmopathy, degree of thyroid enlargement; genetic factors such as CTLA 4 gene on nucleotide 49 at codon 17 of exon 1, CTLA 4 gene of promotor -318, TSHR gene polymorphism rs2268458 of intron 1; and immunological factors such as regulatory T cells (Treg) and thyroid receptor antibody (TRAb); that affecting the relapse of patients with Graves disease in Indonesia. Methods: this was a case control study, that compared 72 subjects who had relapse and 72 subjects without relapse at 12 months after cessation of antithyroid treatment, who met the inclusion criteria. Genetic polymorphism examination was performed using PCR-RFLP. The number of regulatory T cells was counted using flow cytometry analysis and ELISA was used to measure TRAb. The logistic regression was used since the dependent variables were categorical variables.
Results: the analysis of this study demonstrated that there was a correlation between relapse of disease and family factors (p=0.008), age at diagnosis (p=0.021), 2nd degree of Graves ophthalmopathy (p=0.001), enlarged thyroid gland, which exceeded the lateral edge of the sternocleidomastoid muscles (p=0.040), duration of remission period (p=0.029), GG genotype of CTLA 4 gene on the nucleotide 49 at codon 17 of exon 1 (p=0.016), CC genotype of TSHR gene on the rs2268458 of intron 1 (p=0.003), the number of regulatory T cells (p=0.001) and TRAb levels (p=0.002).
Conclusion: genetic polymorphisms of CTLA 4 gene on the nucleotide 49 at codon 17 of exon 1, TSHR gene SNP rs2268458 of intron 1, number of regulatory T cells and TRAb levels play a role as risk factors for relapse in patients with Graves disease.
.....Latar belakang: penyakit Grave atau Graves disease (GD) merupakan kondisi yang umum dijumpai pada tirotoksikosis. Tatalaksana GD diawali dengan pemberian obat antitiroid, meskipun pasien memerlukan waktu lama untuk mencapai kesembuhan atau remisi. Pada kenyataannya, lebih dari 50% pasien yang mengalami remisi masih berisiko mengalami kekambuhan (relaps) setelah obat dihentikan. Penelitian ini bertujuan untuk menilai peran faktor klinis seperti kebiasaan merokok, derajat oftalmopati, derajat pembesaran tiroid, faktor genetik misalnya gen CTLA-4 pada nukleotida 49 di kodon 17 pada ekson 1, gen CTLA-4 pada promotor 318, polimorfisme gen TSHR rs2268458 pada intron 1 dan faktor imunologi sperti sel-sel T regulator (Treg) dan antibodi reseptor tiroid (TRAb) yang memengaruhi terjadinya relaps pada pasien dengan penyakit Grave di Indonesia.
Metode: penelitian ini merupakan studi kasus kontrol yang membandingkan 72 subjek dengan relaps dan 72 subjek tanpa relaps pada 12 bulan setelah penghentian pengobatan antitiroid, yang memenuhi kriteria inklusi. Pemeriksaan polimorfisme genetik dilakukan menggunakan PCR-RFLP. Jumlah sel T regulator

dihitung menggunakan analisis sitometri alir (flow cytometry) dan pemeriksaan ELISA untuk mengukur TRAb. Regresi logistik dilakukan karena variabel dependen adalah variabel kategorik.
Hasil: terdapat korelasi antara kekambuhan penyakit dan faktor keluarga (p=0,008), usia saat diagnosis ditegakkan (p=0,021), oftalmopati Graves derajat dua (p=0,001), pembesaran kelenjar tiroid yang melebihi batas lateral otot sternokleidomastoideus (p=0,040), lamanya masa remisi (p=0,029), genotipe GG dari gen CTLA-4 pada nukleotida 49 di kodon 17 dari ekson 1 (p=0,016), genotipe CC dari gen TSHR pada rs2268458 dari intron 1 (p=0,003), jumlah sel T regulator (p=0,001) dan kadar TRAb (p=0,002).
Kesimpulan: polimorfisme genetik gen CTLA-4 pada nukleotida 49 di kodon 17 pada ekson 1, gen TSHR SNP rs2268458 pada intron 1, jumlah sel T regulator dan kadar TRAb berperan sebagai faktor risiko terjadinya relaps pada pasien penyakit Graves.