ROLE OF CTLA-4 GENE AND REGULATORY T CELL AS RISK FACTOR RELAPSE IN GRAVES DISEASE

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OBJECTIVES

Graves' disease (GD) management in Indonesia are generally preceded by administration of antithyroid drugs. Antithyroid drug delivery requires along time to achieve remission, even more than 50 percent of patients who had remission can recur after antithyroid medication is stopped. The purpose of this study was to determine the role of CTLA-4 gene and regulatory T cells against recurrence in GD patients.

METHODS

The study was conducted using a case-control in 144 patients GD, comparing patients who relapse and non-recurrence. Definition of relapse if the patient is declared remission after antithyroid treatment for at least 18 months, but relapsed after 6 months of antithyroid medication is stopped. Examination of CTLA-4 gene polymorphism in nucleotide 49 codon 17 of exon 1 by the method of PCR RFLP, number of regulatory T cells was checked by flowcytometri and level of thyroid receptor antibody (TRAb) in serum was measured by ELISA method

Table 1 Risk of Recurrence Subject Research based on gene CTLA-4 exon 1

CTLA-4 ekson 1	Relapse	No relapse	p*	OR	IK95%
Genotype GG	38 (52.8)	12 (16.7)	0.016	7.312	1.439-37.164
Genotype GA	22 (30.5)	32 (44.4)	0.642	1.432	0.321-6.492
Genotype AA	12 (16.7)	28 (38.9)			

•Chi Square

Table 2 Risk of Recurrence Subject Research based on Immune Response

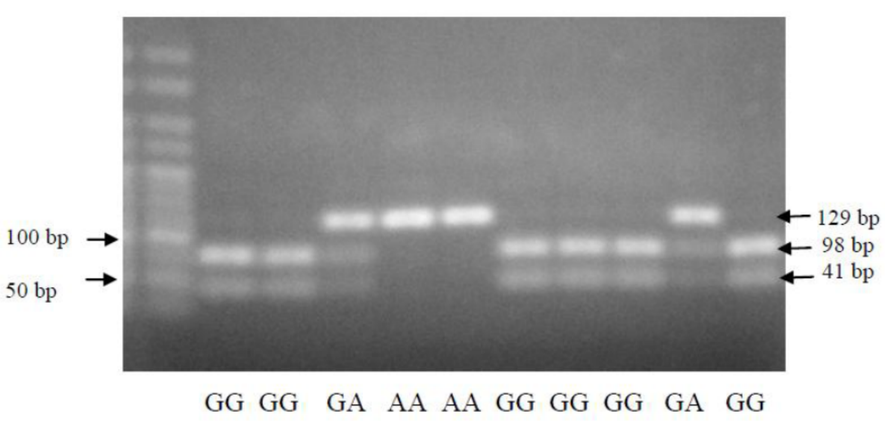
	Relapse	No relapse	p*
Regulatory T cell	4.43 (0.89-11.3)	9.25 (2.61-24.36)	0.001
TRAb (unit/l)	9.65 (6.30-25.95)	4.36 (0.33-11.4)	0.002

*Mann Whitney

Tabel 3Association of Gene CTLA-4 exon 1 with Regulatory T Cell and TRAb

	Regulatory T Cell	TRAb (unit/l)
Genotype GG	5,07 (0,89-15,94)	8,27 (1,50-25,95)
Genotype GA	8,71 (1,74-24,36)	5,42 (0,34-16,94)
Genotype AA	9,63 (0,89-22,31)	5,39 (0,30-16,46)
p	0,035	0,069

•Kruskal Wallis



Picture 1: PCR RFLP Gene CTLA-4 nucleotide 49 codon 17 of exon 1

RESULTS

The results of this study indicate that patients with GD were when first diagnosed with the disease aged less than 30 years (p 0.036) and had relatives also suffer from the disease have a higher risk of relapse (p 0.008). Patients with degree 2 of ophtalmopathy (p 0.011), enlargement of the thyroid gland exceeded the lateral edge of the sternocleidomastoideus muscle (p 0.044) and remission periods of less than 2 years after the drug is stopped (p 0.029), are also more at risk for relapse.
GD subjects with GG genotype CTLA-4 gene nucleotide 49 codon 17 of exon 1 has a risk relapse 7.3 times higher than the AA genotype, and GA genotype CTLA-4 gene nucleotide 49 codon 17 of exon 1 has a risk relapse 1.4 times higher than the AA genotype. Number of Treg cells GD patients who relapse lower than patients who did not relapse (p 0.001), and levels TRAb serum higher than patients who did not relapse (p 0.002). GD patients with GG genotype has had lower regulatory T cells (p 0.035) and higher TRAb than GA and AA genotype (p 0.069).

CONCLUSIONS

GD patients with GG genotype CTLA-4 gene exon 1 and low number of regulatory T cells have higher risk of relapse. The risk of relapse in patients with GD can be determined prior to administration of antithyroid therapy based on clinical factors, genetics and immunology.

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