Hubungan antara Reseptor Glukokortikoid dengan Ekspresi IB dan GILZ serta Faktor yang Memengaruhi Respons Terapi Kortikosteroid pada Pasien COVID-19 Derajat Sedang-Berat = Relationship between Glucocorticoid Receptors and IKB and GILZ Expression and Factors Influencing Response to Corticosteroid Therapy in Moderate-Severe COVID-19 Patients

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Abstrak

Terapi kortikosteroid pada pasien COVID-19 dimediasi oleh efek supresifnya terhadap regulasi respons inflamasi. Namun, hasilnya seringkali tidak dapat diprediksi. Penelitian ini bertujuan untuk mengeksplorasi prediktor respons kortikosteroid pada pasien COVID-19 derajat sedang-berat. Penelitian ini dibagi dalam 2 tahap, tahap pertama merupakan studi kohort retrospektif yang melibatkan 244 pasien dan tahap kedua merupakan studi cross-sectional terhadap 34 pasien yang spesimen biologisnya tersimpan di RS pada awal dan hari kelima terapi kortikosteroid. Penelitian dilakukan pada bulan Oktober 2021 hingga Oktober 2022 di RSUP dr. M.Djamil, Laboratorium Pusat Diagnostik dan Riset Penyakit Infeksi FK UNAND, dan Laboratorium Kesehatan Daerah Provinsi Jawa Barat. Peneliti menganalisis berbagai variabel klinis (usia, derajat ARDS, riwayat penggunaan steroid, adanya diabetes, hipertensi, gangguan fungsi ginjal) dan laboratorium (rasio neutrofil-limfosit, kadar feritin dan D-dimer) dengan respons terhadap terapi kortikosteroid pada tahap pertama. Pada tahap kedua dilakukan penelusuran peran reseptor glukokortikoid (GR) berupa tingkat ekspresi, variasi isoform, dan mutasi ekson dengan respons klinis terhadap kortikosteroid. Ekspresi GR, isoform, dan mutasi dianalisis dengan RNA-sekuensing leukosit. Selain itu, hubungan ekspresi GR dan ekspresi IB dan glucocorticoid-induced leucine zipper protein (GILZ) sebagai jalur steroid juga dievaluasi. Pasien diklasifikasikan menjadi kelompok responsif dan tidak responsif berdasarkan perbaikan status klinis dan kebutuhan oksigen. Pada analisis multivariat terlihat bahwa kadar feritin dapat memprediksi respons terhadap terapi kortikosteroid (OR 2,95 [95% CI 1,336,53]). Kelompok responsif memiliki ekspresi GR, IB dan GILZ lebih tinggi pada awal dan hari kelima pemberian kortikosteroid dibandingkan pasien tidak responsif. Varian atau mutasi isoform GR tidak berkorelasi dengan respons klinis. Berdasarkan temuan tersebut disarankan bahwa kadar feritin dapat memprediksi respons steroid pada pasien COVID-19, namun perlu ditelusuri prediktor independen lainnya. Ekspresi GR, IB dan GILZ kemungkinan berkaitan dengan respons terapi terhadap kortikosteroid pada pasien COVID-19.
.....The effect of corticosteroid therapy in COVID-19 patients is mediated by its suppressive effect on the regulations of inflammatory response. However, its clinical outcome is often unpredictable. This study aimed to explore the predictors of corticosteroid response in Moderate-Severe COVID-19 patients. This research was conducted in 2 stages, the first stage was a retrospective cohort study involving 244 moderate-severe COVID-19 patients and the second stage was a cross-sectional study of 34 COVID-19 patients whose biological specimens were stored in the hospital at the baseline and fifth days of corticosteroid therapy. The research was conducted from October 2021 to October 2022 at Dr. M.Djamil General Hospital, Laboratory of Diagnostic and Research Center for Infectious Diseases Faculty of Medicine, Universitas Andalas, and Regional Health Laboratory of West Java Province. In the first stage, a multivariate analysis was conducted

between various clinical (age, degree of ARDS, history of steroid use, presence of diabetes, hypertension, impaired renal function) and laboratory variables (neutrophil-lymphocyte ratio, ferritin and D-dimer levels) with response to corticosteroid therapy. In the second stage, we attempted to explore the role of the glucocorticoid receptor (GR), such as the expression, the variation of GR isoform, and the mutations of GR exon with clinical response to corticosteroids. GR expression, isoform, and mutation were determined by RNA sequencing from white blood cells. In addition, the relationship between GR expression and the expression of IB and glucocorticoid-induced leucine zipper protein (GILZ) as steroid pathways was also evaluated. Based on the improvement of clinical and oxygen status, patients were classified into responder and non-responder groups. Our findings indicate that ferritin levels can predict response to corticosteroid therapy (OR 2.95 [95% CI 1.336.53]). The responder group had higher GR, IB dan GILZ expression at baseline and after five days of corticosteroid treatment than non-responsder group. The GR isoform variant or mutation did not correlate with clinical response. Based on this finding, we suggest that ferritin levels in covid-19 patients could predict steroid response. This study also shows that the expression of GR, IB and GILZ may be related to the therapeutic response to corticosteroids in COVID-19 patients.