HUBUNGAN INTERLEUKIN-1 (IL-1) DAN IL-1 RECEPTOR ANTAGONIST (IL-1Ra) DENGAN KERADANGAN PADA ARTRITIS PIRAI AKUT

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RINGKASAN

Keradangan pada artritis pirai akut (APA) adalah akibat penumpukan kristal urat pada sendi sehingga menyebabkan aktivasi sel radang, terutama makrofag dan neutrofil untuk mengeluarkan berbagai mediator kimiawi, antara lain interleukin-1 (IL-1) dan t*umor necosis factor*-α (TNF-α).

Peran IL-1 dalam proses keradangan secara umum bersifat tidak spesifik. Kelompok IL-1 (*IL-1 gen family*) terdiri dari 3 jenis yaitu IL-1α, IL-1β dan IL-1 receptor antagonist (IL-1Ra). IL-1α dan IL-1β bersifat agonis menimbulkan reaksi radang atau disebut sitokin proinflamasi. IL-1Ra bersifat menghambat efek biologis IL-1 atau disebut sitokin antiinflamasi.

Keseimbangan IL-1 sebagai sitokin proinflamasi dan IL-Ra sebagai sitokin antiinflamasi adalah penting dalam proses keradangan pada berbagai organ. Kekurangan sitokin antiinflamasi diduga akan menyebabkan proses keradangan akan berlanjut menjadi kronis.

Tujuan penelitian ini adalah untuk menentukan adanya perubahan IL-1 dan IL-1Ra , rasio IL-1/IL-1Ra dan hubungan IL-1 dan IL-Ra dengan aktivitas keradangan dalam perjalanan penyakit pada APA.

Untuk mencapai tujuan tersebut maka dilakukan studi *case-kontrol* dan dilanjutkan dengan *follow up study*. Kelompok kasus adalah penderita APA laki berdasarkan kriteria diagnosis menurut *American Collegge of Rheumatology Subcommittee on Diagnostic and Therapeutic Criteria* (1977). Kelompok kontrol adalah hiperurisemia asimptomatis laki, dengan melakukan padanan usia dengan kelompok kasus. Dengan rumus studi kasus kontrol berpadanan maka didapatkan masing-masing kasus dan kontrol adalah 14 orang.

Pada penelitian ini dilakukan analisis masing-masing 15 orang laki pada kasus dan 15 orang laki pada kontrol. Penelitian dilakukan pada awal pemeriksaan dan diikuti selama 7 hari dengan pemberian obat kolkhisin dan indometain pada kasus APA. Dilakukan pemeriksaan dan dihubungkan IL-1 dan IL-1Ra dengan variabel keradangan komplemen (C3), leukosit, laju endap darah (LED), *C-rective protein* (CRP) dan temperatur pada prauji dan pascauji.

Hasil penelitian menunjukkan pada kasus APA dan kontrol tidak menunjukkan perbedaan bermakna dalam usia, pendidikan, agama, pekerjaan, *relative body weight*, riwayat keluarga pirai, gejala batu ginjal, kebiasaan minum alkohol, makan lawar, kadar kreatinin serum, kecuali kadar asam urat darah.

Pada APA prauji terjadi peningkatan dan berbeda bermakna dengan kontrol pada semua variabel keradangan komplemen C3 ($p = 0,002$), leukosit ($p = 0,003$), LED ($p = 0,001$), CRP ($p = 0,003$) dan temperatur ($p = 0,000$). Pada pascauji terjadi penurunan variabel komplemen dan LED menjadi normal, sedangkan variabel leukosit ($p = 0,002$) , CRP ($p = 0,011$) dan temperatur ($p = 0,021$) masih tetap tinggi atau berbeda dengan kontrol pascauji. Jadi dari data ini menyatakan bahwa pada pascauji proses keradangan tetap berlanjut.

Pada APA prauji terjadi peningkatan kadar IL-1 (p = 0,0001) dan IL-1Ra (p = 0,000) dan berbeda bermakna dengan kontrol. Pada APA pascauji terjadi penurunan IL-1 bermakna (p = 0,0038) dengan APA prauji, namun masih tetap tinggi dan berbeda bermakna (p=0,010) dengan kontrol pascauji. Penurunan IL-1Ra bermakna (p=0,009) dengan APA prauji tetapi tidak bermakna (p=0,073) dengan kontrol pascauji. Jadi pada prauji terjadi peningkatan IL-1 dan IL-1Ra, pada pascauji sitokin proinflamasi IL-1 masih tetap tinggi, sedangkan sitokin antiinflamasi IL-1Ra telah menjadi normal.

Peningkatan rasio IL-1/IL-1Ra menyatakan adanya peningkatan sitokin keradangan IL-1 dan mencerminkan proses keradangan sedang terjadi. Pada penelitian ini, rasio IL-1/IL-1Ra pada APA prauji adalah 0,097, lebih tinggi dan berbeda bermakna (p=0,0264) dibandingkan dengan kontrol prauji. Pada APA pascauji, rasio IL-1/IL-1Ra tetap tinggi atau tidak berbeda bermakna dibandingkan dengan APA prauji (p = 0,43).

Pada penelitian ini didapatkan hubungan antara sitokin IL-1 dan IL-1Ra dengan semua variabel keradangan pada prauji (r = 0,47; p = 0,008) dan pascauji (r = 0,46 ; p = 0,011). Jadi pada APA terdapat korelasi sitokin IL-1 dan IL-1Ra dengan semua variabel keradangan.

Keseimbangan antara sitokin proinflamasi IL-1 dan sitokin antiinflamasi IL-1Ra adalah penting dalam perjalanan proses keradangan akut. Pada penelitian ini, pada APA pascauji kadar IL-1 sebagai sitokin proinflamasi, rasio IL-1/IL-1Ra dan variabel keradangan (leukosit, CRP dan temperatur) masih tetap tinggi, yang menunjukkan proses keradangan tetap berlanjut. Keadaan ini terjadi kemungkinan

karena agen penyebab yaitu asam urat pada APA pascauji masih tetap tinggi dan berbeda bermakna dengan kontrol pascauji (p=0,003).

Kesimpulan penelitian ini, sitokin IL-1, IL-1Ra dan rasio IL-1/IL-1Ra meningkat pada keradangan akut dari APA. Setelah pengobatan sitokin proinflamasi IL-1 dan rasio IL-1/IL-1Ra masih tetap tinggi serta sesuai dengan variabel keradangan leukosit, CRP dan temperatur. Sitokin IL-1 dan Il-1Ra mempunyai hubungan dengan semua variabel keradangan. Keadaan ini mencerminkan proses keradangan tetap berlanjut.

Pada masa mendatang peran sitokin IL-1 dan IL-1Ra menjadi penting pada patogenesis APA, dan mungkin juga pada penyakit reumatik karena keradangan lainnya, sehingga IL-1Ra yang berperan sebagai antiinflamasi akan menjadi andalan utama dalam pengobatan APA.

THE CORRELATION OF INTERLEUKIN-1 (IL-1) AND INTERLEUKIN-1 RECEPTOR ANTAGONIST (IL-1RA) WITH INFLAMMATION IN ACUTE GOUTY ARTHRITIS

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SUMMARY

Inflammation in Acute Gouty Arthritis (AGA) is due to deposition of urate crystal, which activates the inflammatory cells, especially macrophages and neutrophils and induces a plethora of inflammatory mediators such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α).

The effect of IL-1 on the inflammatory process is nonspecific. There are three members of the IL-1 gene family : IL-1α, IL-1β and IL-1 receptor antagonist (IL-1Ra). IL-1α and IL-1β have an agonist effect and are a potent inflammatory cytokine. The IL-1Ra appears to competitively inhibit the biologic effect of IL-1, hence called antiinflammatory cytokine.

The balance between IL-1 as a proinflammatory cytokine and IL-1Ra as an anti-inflammatory cytokine is important in preventing the progression of inflammatory processes in certain organs. An insufficient in the amount of anti-inflammatory cytokine leads to the progression of chronic inflammation.

The objectives of this study were to observe the change of IL-1 and IL-1Ra and the ratios of IL-1/IL-1Ra in the progression of AGA , and to determine the correlation between cytokine of IL-1 and IL-1Ra with the activity of inflammation. For that purpose, a case control and follow up study was carried out. The case group consisted of male patients of AGA, who were diagnosed by

the Criteria of American College of Rheumatology Subcommittee on Diagnostic and Therapeutic Criteria (1977). The control group were male asymptomatic hyperuricaemic individuals, who were matched in age with the case group. Based on matched case-control formula, the sample size was 14 persons for each group.

In this study the number of samples was 15 male patients of AGA and 15 males of the control group. The study was done on the day of first examination , and followed for 7 days during treatment with colchicine and a non steroid anti-inflammatory drug on the case group. The IL-1 and IL-1Ra were assessed and their correlation was determined with the variable of inflammation activity such as complement (C3), leukocyte count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and temperature, in pre-study and post-study periods.

The result showed that in both groups no significant differences were found in age, education, religion, occupation, relative body weight, familial history of gout, nephrolithiasis symptom, alcohol consumption, *lawar* food consumption and serum creatinine level, except the uric acid level.

All inflammation variables in pre-study of AGA increased and were significantly different from the control group; complement C3 ($p = 0.002$), leukocyte count ($p = 0.003$), ESR ($p = 0.001$), CRP ($p = 0.003$), and temperature ($p = 0.000$). In the post-study, the variable of complement and ESR decreased to normal level, but the variable of leukocyte ($p = 0.002$), CRP ($p = 0.011$) and temperature ($p = 0.021$) were still high and were significantly different from those in the post-study control. This data suggest that the inflammation process was still taking place in the post-study period.

In the pre-study of AGA, the serum level of IL-1 (p = 0.0001) and IL-1Ra (p = 0.000) increased, and were significantly different from the control group. In the post-study, IL-1 decreased, and was significantly different (p = 0,0038) from the pre-study of AGA, but was still highly significantly different (p = 0,010) from the post-study control. The decline of IL-1Ra was significantly different (0.009) from the pre-study of AGA, but was not significantly different from the post-study control. The result of study, in pre-study IL-1 and IL-1Ra increased. In post-study, IL-1 was still high but IL-1Ra decreased to normal level.

The increased ratios of IL-1/IL-1Ra was due to an enhanced of IL-1 and showed that the process of inflammation was taking place. In This study, the ratios of IL-1/IL-1Ra was 0.097 in pre-study of AGA, that was higher and significantly different (p = 0.0264) from the pre-study control. In post-study of AGA , the ratios of IL-1/IL-1Ra decreased, but was still high or was not significantly different from the pre-study of AGA (p = 0.43).

In this study, it was found that cytokine of IL-1 and IL-1Ra had a correlation with all the inflammation variables in pre-study (r = 0.47; p = 0.008) and in post-study (r = 0.46; p = 0,010). The correlation between IL-1 and IL-1Ra and the activity of inflammation was shown.

The balance between pro-inflammatory cytokine and anti-inflammatory cytokine was important in the progression of acute inflammatory process. In this study, in post-study of AGA cytokine of IL-1, the ratios of IL-1/IL-1Ra and the inflammatory variables (leukocyte, CRP and temperature) were still high. This suggested that the inflammation process was prolonged. It may be due to the fact

that the level of uric acid as an agent of inflammation in post-study of AGA was still high and was significantly different from the control group ($p = 0.003$).

The conclusion of this study is, that cytokine of IL-1, IL-1Ra and the ratios of IL-1/IL-1Ra significantly increase in acute inflammation of AGA. The level of IL-1 as proinflammatory cytokine and the ratios of IL-1/IL-1Ra in post-study of AGA were still high and so were the inflammation variables of leukocyte, CRP and temperature. The cytokine of IL-1 and IL-1Ra have a correlation with all the variables of inflammation (complement, leukocyte, ESR, CRP and temperature). All above suggested that the inflammation process was prolonged.

In the future the role of IL-1 and IL-1Ra in the pathogenesis of AGA and probably in other inflammatory arthritis will be more important, therefore IL-1Ra as a potent anti-inflammatory will come very important in the treatment of AGA

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ABSTRACT

Inflammation in Acute Gouty Arthritis (AGA) due is to deposition of urate crystal, which activates the inflammatory cell and induces a plethora of inflammatory mediators such as IL-1. The IL-1 is a potent inflammatory cytokine. The IL-1Ra appears to competitively inhibit the biologic effect of IL-1, hence called an antiinflammatory cytokine. An insufficiency in the amount of anti-inflammatory cytokine leads to the progression of inflammation.

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In this study, the number of samples was 15 male patients of AGA and 15 males of control group. All inflammation variables in the pre-study of AGA increased and were significantly different from the control group : complement C3 ($p = 0.002$), leukocyte count ($p = 0.003$), ESR ($p = 0.001$), CRP ($p = 0.003$), and temperature ($p = 0.000$). In the post-study, the variable of complement and

ESR decreased to normal level, but the variable of leukocyte, CRP and temperature were still high and were significantly different from those in the post-study control. In the pre-study of AGA, the serum level of IL-1 ($p = 0.0001$) and IL-1Ra ($p = 0.000$) increased and were significantly different from the control group. In the post-study, IL-1 decreased and was significantly different ($p = 0,0038$) from the pre-study of AGA, but was still highly significantly different ($p = 0.010$) from the post-study control. The decline of IL-1Ra was significantly different (0.009) from the pre-study of AGA, but was not significantly different from the post-study control. The ratios of IL-1/IL-1Ra was 0.097 in pre-study of AGA, that was higher and significantly different from the pre-study control. In post-study of AGA, the ratios of IL-1/IL-1Ra was still high. The cytokine of IL-1 and IL-1Ra had a correlation with all the inflammation variables in the pre-study ($r = 0.47$; $p = 0.008$) and in the post-study ($r = 0.46$; $p = 0,011$).

The conclusion of this study is, that the cytokine of IL-1, IL-1Ra and the ratios of IL-1/IL-1Ra significantly increase in acute inflammation of AGA. The level of IL-1 as a proinflammatory cytokine and the ratios of IL-1/IL-1Ra in post-study of AGA were still high and so were the inflammation variable of leukocyte, CRP and temperature. The cytokine of IL-1 and IL-1Ra have a correlation with all the variables of inflammation. All above suggested that the inflammation process was prolonged. It may be due to the fact that the level of uric acid as an agent of inflammation was still high.

Key word : acute gouty arthritis, Interleukin-1 (IL-1), Interleukin-1 receptor antagonist (IL-1Ra)