ABSTRAK

MEKANISME IMUNOREGULASI DAN REGENERASI KERUSAKAN EPITEL ALVEOLAR SETELAH PEMBERIAN *BONE MARROW DERIVED MESENCHYMAL STEM CELL* PADA *ACUTE RESPIRATORY DISTRESS SYNDROME* AKIBAT VIRUS *HIGHLY PATHOGENIC AVIAN INFLUENZA* H5N1

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Latar belakang: Virus *highly pathogenic avian influenza* (HPAI) H5N1 merupakan salah satu penyebab tingginya insiden *Acute respiratory distress syndrome* (ARDS). Penelitian tentang pemberian BM-MSCpada ARDS akibat infeksi virus pernapasan akut belum banyak dilaporkan dan menunjukan hasil yang bertentangan. Tujuan penelitian ini adalah mengetahui potensi BM-MSC pada ARDS akibat paparan *virus* HPAI H5N1 dan menjelaskan mekanismenya.

Metode: Sebanyak 86 ekor mencit BALB/c digunakan pada penelitian ini. Hewan coba dibagi menjadi empat kelompok yaitukontrol sehat, kontrol sakit, kelompok sakit dengan terapi pelarut dan kelompok sakit dengan terapi BM-MSC. Model Kerusakan paru akutdibuat dengan cara instilasi virus HPAI A/turkey/East Java/Av154/2013 (H5N1). Kuantitas BM-MSC yang digunakan pada penelitian ini adalah $5{,}5 \times 10^5$ dengan *booster* sebanyak dua kali. Pemeriksaan ekspresi *β-catenin*, PGE2, NFκβ, IL-1β, RAGE, Sftpc, Aqp5+, dihitung dengan pengecatan *immunohistochemistry*. Luas kerusakan paru dihitung dengan pengecatan *Haematoxyllin eosin.* Titer virus dihitung dengan uji Haemaglutination. Pemeriksaan analisis gas darah untuk mengetahui rasio PaO2/FiO2.

Hasil: Pemberian BM-MSC meningkatkan ekspresi *β-catenin*, ekspresi PGE2, ekspresi Sftpc, ekspresi Aqp5+, rasio PaO2/FiO2 dan menurunkan ekspresi NFκβ, ekspresi IL-1β, ekspresi RAGE, ekspresi TNFα, skor HE. Pemberian BM-MSC tidak terbukti menurunkan titer virus.Analisis jalur membuktikan adanyahubungan antaraPGE2, β-catenin, NFκβ dan TNF-α

Kesimpulan: Penelitian ini membuktikanmekanisme imunoregulasi lebih dominan untukmenghambat terjadinya kerusakan fungsi paru lebih lanjut, melalui jalur PGE2, β catenin, NFkβ dan TNFα. Pemberian BM-MSC tidak dapat menjelaskan perbaikan kerusakan paru akut melalui mekanisme regenerasi

Kata Kunci: Aqp5+, ARDS, *β-catenin*, BM-MSC, IL-1β, NFκβ, PaO2/FiO2, PGE2, RAGE, Sftpc, Titer Virus.

ABSTRACT

MECHANISMS OF IMMUNOREGULATION AND REGENERATION OF ALVEOLAR EPITHELIAL DAMAGE AFTER ADMINISTRATION OF BONE MARROW DERIVED MESENCHYMAL STEM CELL INACUTE RESPIRATORY DISTRESS SYNDROME INDUCED BY HIGHLY PATHOGENIC AVIAN INFLUENZA H5N1VIRUS

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Background: Highly pathogenic avian influenza (HPAI) H5N1 virus is one of the causative agentswith a high incident rate in *Acute respiratory distress syndrome* (ARDS). Studies on therapeutic administration of bone marrow-derived mesenchymal stem cells (BM-MSCs) in ARDS caused by the viral infection have been limited and shown conflicting results.
Objective: The aim of this study was to investgate for therapeutic potential of BM-MSCs administration in ARDS caused by a HPAI H5N1 virus, and to explain its mechanism.
Methods: There were 86BALB/c mice used in this study. The animals model were divided into four groups; healthy control, ARDS control, ARDS group with PBS therapy and ARDS group with BM-MSC therapy.The model of acute lung injury was made by instillation of HPAI A/turkey/East Java/Av154/2013 (H5N1) virus, with dosage of 1 x 10^{-3} intranasally. The BM-MSC quantity applied in thisstudy was 5,5 × $10^{5}$with*booster*applied twice.The expression of *β-catenin,* PGE2, NFκβ, IL-1β, RAGE, Sftpc and Aqp5+ were measured byImmunohistochemistrystaining. Lung injury was scored by haematoxyllin-eosin staining. Viral titer was calculated by Haemaglutination (HA) examination. Blood gas examination was done to know the PaO2/FiO2 ratio.
Results: This study had proven that the administration of BM-MSC in acute lung injury induced by HPAI H5N1 increased the expression of *β-catenin,* PGE2, Sftpc, Aqp5+andthe level of PaO2/FiO2, while decreased the expression of NFκβ, IL-1β, RAGE, TNFα, and HE score. Path analysis proves that there is a correlation between PGE2, β-catenin, NFκβ and TNF-α
Conclusions: The administration of BM-MSCs had a tendency to inhibit acute lung injury caused by the HPAI H5N1 virus. Mechanism immunregulation is more dominant to inhibit further damage of pulmonary function, through the PGE2, β catenin, NFkβ and TNFα pathway.

Keywords: Aqp5+, ARDS, *β-catenin,* BM-MSC, IL-1β, NFκβ, PaO2/FiO2, PGE2, RAGE, Sftpc, Viral titer.