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Mesenchymal Stem Cell Secretome Improves Bone Quality in Autoimmune Rheumatic Patients (AIIRD): A Case Report

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ABSTRAK

Autoimmune Inflammatory Rheumatic Disease (AIIRD) is a group of different disorders, which have similar clinical, laboratory and immunological manifestations. In East Asia, the top 3 diseases included in AIIRD are Systemic Lupus Erythematosus, Rheumatoid Arthritis, and Sjogren's Syndrome. Glucocorticoids are still one of the therapeutic modalities for AIIIRD with their antiinflammatory and immunosuppressive effects. However, glucocorticoids have some side effects. One side effect of concern is decreased bone density. The condition of glucocorticoid induced osteoporosis (GIOP) is reported with increasing prevalence. The main effect of the use of glucocorticoids on bones is the presence of impaired bone formation regardless of the role of inflammation. Secretome stem cells contain bioactives that exhibit diverse physiological functions such as immunomodulation, anti-inflammatory, angiogenesis, anti-apoptotic and anti-oxidation. Secretome can modulate cell differentiation by promoting osteogenesis and inhibiting adipogenesis. In this case report, it showed improvements in markers of bone damage, inflamation, and vitamin D levels after stem cell secretome administration in AIIRD patients with long-term corticosteroid use.

Keywords: AIIRD, Autoimmune, Steroid, GIOP, Secretome;

INTRODUCTION

Autoimmune Inflammatory Rheumatic Disease (AIIRD) is a set of different disorders that have clinical symptoms, laboratory tests, and immune tests. The main pathobiological outcome of AAIRD is an antigen-induced and self-reactive excessive immune response. AIIRDs are classified into three groups based on the absence of a proinflammation response. The first is autoinflammation (such as ankylosing spondylarthritis), autoimmune (such as systemic lupus erythematosus (SLE), Sjogren's Syndrome, or those with overlapping characteristics (such as rheumatoid arthritis). Auto-reactive immunocytes as well as proinflammatory cytokines infiltrate the affected organ, no matter the type of disease. With its anti-inflammatory and immunosuppressive effects, glucocorticoids are still one of the treatment options for AIIRD (Kim et al, 2020; Chen et al, 2022). However, prolonged use of glucocorticoids will reduce bone formation rate, the number of osteoblasts, and the activity of osteocytes. The use of glucocorticoids over a long period of time can increase osteoclast activity and decrease osteoblast activity, leading to osteoporosis. In addition, glucocorticoids increase RANK-ligand expression and decrease osteoprotegerin expression in stromal and osteoblastic cells (Briot *and* Roux, 2015). Secretome stem cells contain bioactive that exhibit diverse physiological functions such as immunomodulation, anti-inflammatory, angiogenesis, anti-apoptotic and anti-oxidation. Secretome can modulate cell differentiation by promoting osteogenesis and inhibiting adipogenesis. Secretome treatment also increases the expression of osteogenesis markers such as RUNX2 and OCN and suppresses adipogenesis regulators such as PPAR-c2 and leptin. The following describes several cases of stem cell Secretome administration in AIIRD patients with glucocorticoid therapy toward the overview of osteocalcin, CTX and Vitamin D (Singh, et al, 2016).

CASE ILLUSTRATION

Case 1. The 26-year-old female patient was diagnosed with SLE since 1.5 years ago. The existing complaints were patients sometimes still feel pain in the wrist and right elbow joints, hair loss and also, fatigue. At that time, the patient's Mex-SLEDAI examination exhibited moderate activity. The patient was in methylprednisolone 8 mg therapy, cumulative dose of methylprednisolone 3526.6 mg and standard drugs namely MMF 500mg 2 times a day and HCQ 200mg once a day. The results of laboratory tests obtained CRP levels of 0.03 IU / L, Calcium 1.12 mmol / L, CTX 0.54 ng / L, Osteocalcin 15.86 ng / mL and vitamin D 9.6 ng / L. The patient received injections of Stem Cell Secretome sourced from Umbilical Cord with the Hypoxia method as much as 1.5cc intramuscularly for 6 times with an interval of 1 week. During administration at week 4 and after administration at week 8 the patient was re-examined for the levels of CRP, Potassium, CTX, Osteocalcin and Vitamin D. After the Secretome injection, the complaint of joint pain symptom was much reduced, hair loss still occurred and fatigue was reduced. Mex Sledai measurements showed mild activity (5). The examination results obtained an increase in OCN and vitamin D, as well as a decrease in CTX, LED, and CRP. (See Figure 1-3).

Case 2. The 43-year-old female patient was diagnosed with SLE 2 years ago. The existing symptoms were joint pain, redness on the face, and fatigue. At that time, the patient's Mex-SLEDAI examination showed moderate activity. The patient was in methylprednisolone 4 mg therapy, cumulative dose of methylprednisolone 2975 mg and standard drugs namely MPA 360mg 2 times daily and HCQ 200mg once daily. The results of laboratory tests obtained CRP levels of 1.1 IU / L, Calcium 0.77 mmol / L, CTX 0.29 ng / L, Osteocalcin 16.05 ng / mL and vitamin D 29.50 ng / L. The patient received injections of Stem Cell Secretome sourced from Umbilical Cord with Hypoxia method as much as 1.5cc intramuscularly for 6 times with an interval of 1 week. During administration at week 4 and after administration at week 8 the patient was re-examined for the levels of CRP, Calcium, CTX, Osteocalcin, and Vitamin D. The patient did not feel fatigue, no joint pain, there was still a little redness on the face. The measurement results of Mex SLEDAI showed mild activity (1). The examination results found an increase in Osteocalcin, and a decrease in Vitamin D, CTX, LED and CRP (See Figure 1-3).

Case 3. The 40-year-old female patient was diagnosed with RA 2.5 years ago. The DAS 28 examination showed moderate activity. The patient complained of joint pain in the little and ring fingers of both hands. The patient was in methylprednisolone therapy 4 mg, cumulative dose of methylprednisolone 32440 mg, and standard drug Leflunomide 2 times daily. The results of laboratory tests obtained CRP levels of 0.21 mmol / L, Calcium 1 mg / dL, CTX 0.28 ng / mL, Osteocalcin 4.4 ng / L and vitamin D 3 ng / L. The patient received injections of Stem Cell Secretome sourced from Umbilical Cord with Hypoxia method as much as 1.5cc intramuscularly for 6 times with an interval of 1 week. During administration at week 4 and after administration at week 8 the patient was re-examined for the levels of CRP, Calcium, CTX, Osteocalcin, and Vitamin D. After the Secretome injections the joint pain complaint was reduced, there was no joint swelling in the little fingers and ring fingers of both hands The examination results found an increase in Osteocalcin and vitamin D, and a decrease in CTX, LED and CRP (See Figure 1-3)

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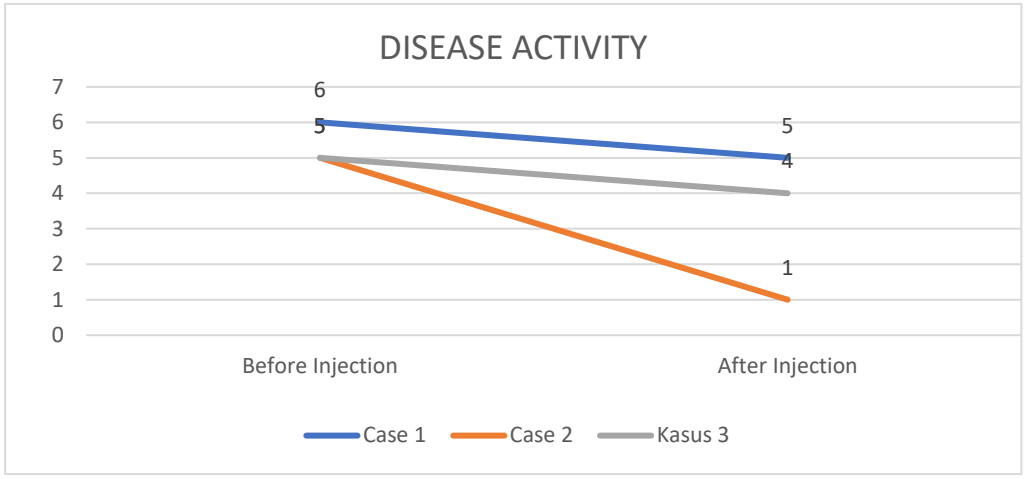

Figure 1. Disease Activity Before Injection and After 6x Injections

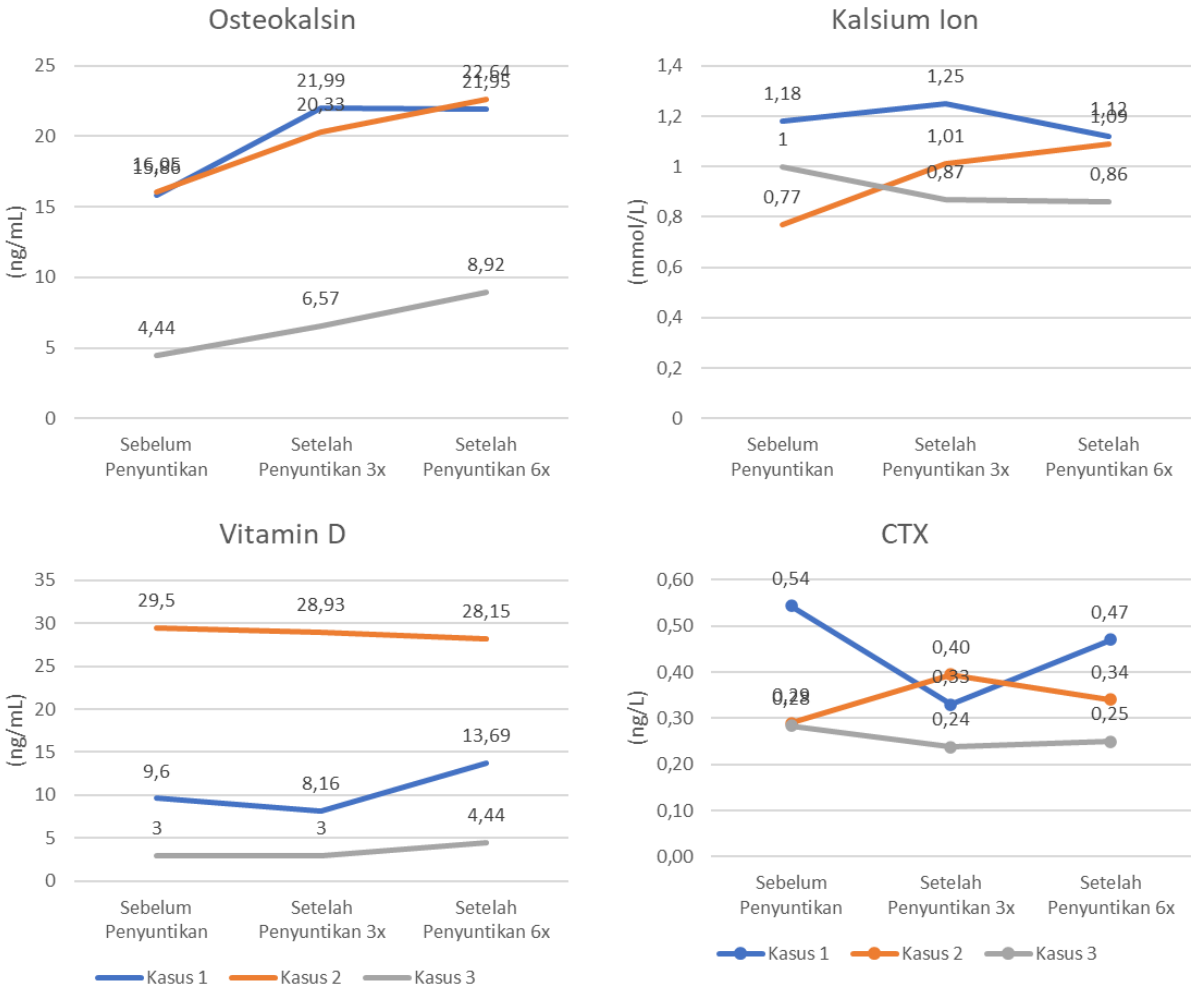

Figure 2. Examination Results of Osteocalcin, Calcium Ions, Vitamin D, and Mex SLEDAI

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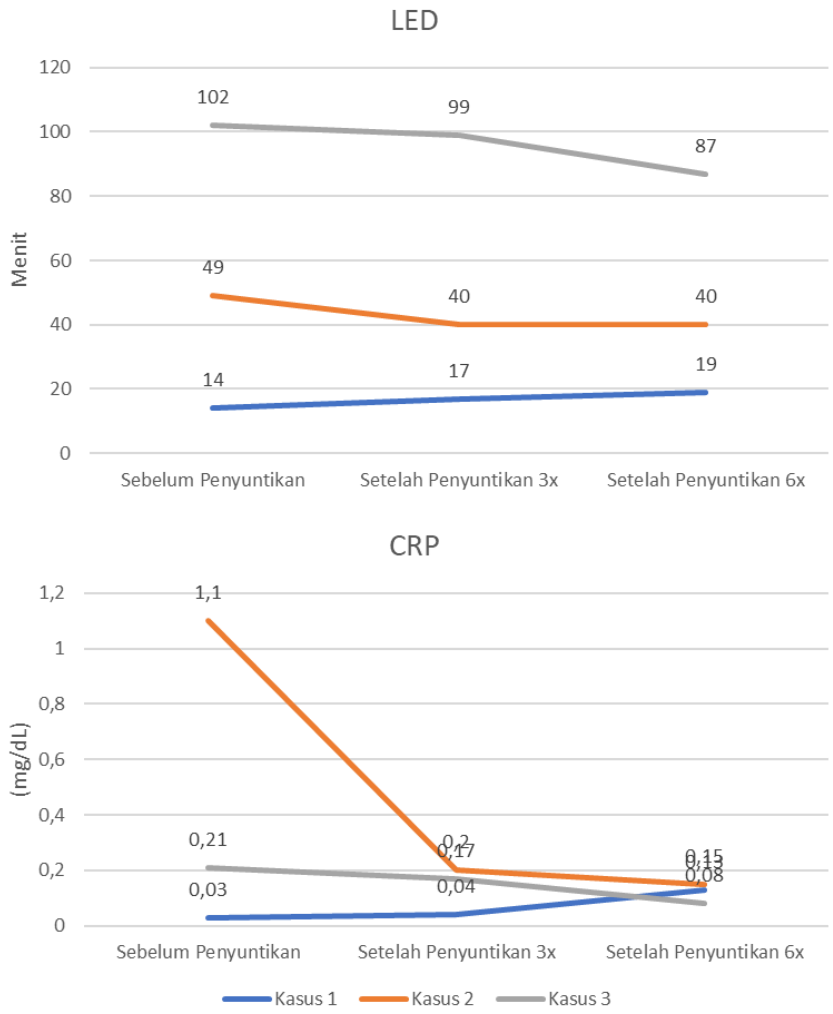

Figure 3. LED and CRP Examination Results

DISCUSSION

Glucocorticoid is still one of the therapeutic modalities for AIIRD with its anti-inflammatory and immunosuppressive effects. Glucocorticoid-induced osteoporosis (GIOP) is one of secondary osteoporosis. GIOP is the leading cause of osteoporosis before age of 50 and the leading iatrogenic cause of the disease. Exposure to glucocorticoids can increase the risk of fracture and bone loss. Glucocorticoid-induced osteoporosis is characterized by decreased bone formation, with an additional early but temporary increase in bone resorption. Glucocorticoids at high concentration dramatically decrease the rate of bone formation, the number of osteoblasts, and the number and activity of osteocytes (Chotiyarnwong and McCloskey, 2020, Compsto j, 2018).

In this case, the administration of mesenchymal stem cell Secretome to patients with AIIRD who have received glucocorticoid therapy provides changes in bone quality parameters. Administration of mesenchymal stem cell Secretome can increase vitamin D levels in patients with Type 1 Diabetes Mellitus (Dantas et al, 2022). Vitamin D is a vitamin that contributes to bone formation. The active form of Vitamin D, Calcidiol (D-25 OH) has an effect in increasing the absorption of calcium in the intestines. Calcium is one of the minerals useful in the formation of bone matrix (Hua C, et al, 2017; Firestein and Mcinnes, 2017).
In other variables (Calcium, Osteocalcin, and CTX) given the Secretome, changes were obtained in the examination results of Calcium, Osteocalcin, and CTX. In a study by Jiang et al, administration of mesenchymal stem cell Secretome post-menopausal osteoporosis

model (performed ovariectomy) show an increase in osteocalcin after the Secretome administration. The study by Jiang et al also reveals that giving mesenchymal stem cell Secretome can increase serum calcium levels. (Jiang et al, 2021, Kuo and Chen, 2019)). MSC Secretome has an effect in regenerative therapy as the newest alternative or even superior to MSC whole cell therapy. Notably, a recent preclinical study has exhibited that Secretome have been successfully applied in preventing bone loss of calvaria, femoral, and periodontal bones (Shang F, et al,. 2021; ocario,et al, 2010, Singh, et al, 2016). Secretome can modulate cell differentiation by promoting osteogenesis and inhibiting adipogenesis. Secretome treatment also increases the expression of osteogenesis markers such as RUNX2 and OCN and suppresses adipogenesis regulators such as PPAR-c2 and leptin. Collectively, Secretome can promote osteogenesis rather than adipogenesis of old BMSCs in the absence of genetic manipulation (Liang M, et al,. 2019).

CONCLUSION

Based on the above case, the administration of stem cell Secretome in AIIRD patients with long-term corticosteroid use, can reduce bone damage markers, improve vitamin D levels, is expected to prevent GIOP.

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