CASE REPORT

Effects of Autologous Bone Marrow Derived Stem Cell Transplant and Exercise Training Program on Rheumatoid Arthritis

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ABSTRACT

A 65 year old female patient suffering from Rheumatoid Arthritis reported with multiple joint pains, malaise, fatigue, difficulty in breathing, difficulty in opening Jaw, difficulty in holding objects and menopausal symptoms. She had been taking multiple medications including Indomethacin, Aspirin, Prednisolone, Methotrexate etc. Treatment at Al-Sayed Hospital Rawalpindi included autologous bone marrow derived stem cell transplantation and exercise training program. Specific exercises were given four weeks before and eight weeks after stem cell transplant at our center. After one year of treatment, the patient had improvement in all of her signs and symptoms, which enabled her to discontinue several medications. There was marked improvement in her joint pain, range of motion, muscle power, grip function, functional activities and Activities of Daily Living (ADLs).

Key Words: *Bone Marrow Derived Stem Cells, Exercise Training, Rheumatoid Arthritis.*

Introduction

"Rheumatoid Arthritis is a chronic progressive inflammatory disease of the joints resulting in painful deformities and immobility, especially in the small joints". It decreases red blood cell count and causes inflammation around lungs and heart. It also presents with fever and low energy.[1] Middle age women are affected 2.5 times more than men. The diagnosis is made mostly on the basis of a patient's signs and symptoms.[2,3]

The main objective of the treatment is to reduce pain and inflammation, and improve a person's overall daily activities. This may be assisted by ensuring proper balance between rest and exercise, by using splints and assistive devices. The progression of the disease may be delayed by the use of a class of medicines known as disease-modifying anti-rheumatic drugs (DMARDs). In certain cases surgery to repair, replace, or fuse joints is opted for and proves useful.[4]Alternative medicine and related treatments are not yet supported by evidence. Before the year 1999 biological treatments were not available for public use. It was only then that these pioneering endeavors saw their first introduction, thus dramatically changing the lives of Rheumatoid Arthritis patients with highly selective immunotherapy.[5] In a vast majority of patients, who were given Anti-Tumor Necrosis Factor (TNF) therapy, significant improvement was noted clinically with minimal adverse effects right after the treatment. Of late, the first anti- Inter Leukin1 (IL-1) therapy has been approved for use clinically as an IL-1 receptor antagonist (anakinra).[6]

Bone Marrow derived Stem cell transplant is a promising treatment choice for patients suffering from RA. It is suggested that hematopoietic stem cell transplantation (HSCT) is a useful therapy for severe RA on the basis of animal models and case reports of patients undergoing the procedure for other indications.

Case Report

A Sixty Five year old female came to us with the history of multiple joint pains since she was 19 years old and was diagnosed with Rheumatoid Arthritis 01 year later. She had taken multiple medicines including Indomethacin, Aspirin, Prednisone, Methotrexate, and Gold. She was complaining of severe pain, decreased range of motion (ROM) decreased mostly in lower limbs, muscle tightness, deformities, functional limitations, unable to change posture from lying to sitting and sitting to standing, muscle wasting, pulmonary problems, difficulty in opening jaw, difficulty in holding objects. Muscle

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Power is given in Table I.

Lab investigations showed: Hemoglobin: 11.1 g/dl, ESR: 84, RA Factor and Anti-CCP (cyclic citrullinated peptide) antibodies: Positive, HbA1C: 9.2.

Exercise training program included active and passive range of motion, stretching of tight musculoskeletal structures, isometrics, deep breathing exercises, cycle ergometry for upper and lower limbs to improve endurance and aerobics was given at our hospital for four weeks before and eight weeks after stem cell transplant. This session was given twice a day with twenty to thirty repetitions of each activity. Patient was then transitioned to home exercise management and followed up at three, six and twelve months after the procedure.

Stem Cell Extraction and Transplant Procedure: Patient was given Injection Filgrastim (Granulocyte colony stimulating factor analog) 10 µg per kg body weight subcutaneously without methyl prednisolone or cyclophosphamide and baseline CBC with HPC (hematopoietic progenitor cells) was performed. Two days later CBC with HPC was repeated and patient's Bone marrow stem cells were harvested by apheresis. A total of 100cc of Autologous Bone Marrow Stem Cells were harvested. CBC with HPC was repeated at the end of apheresis to confirm the total number of hematopoietic stem cells. Harvested Stem cells were then injected into her Knee, Shoulder, Metacarpophalyngeal and Inter-phalyngeal joints bilaterally in the procedure room under aseptic technique. Afterwards stem cells were transfused to the patient intravenously.

Outcome Measurements

Patient showed marked improvement in muscle power one year after the stem cell transplant. A comparison of muscle power before starting the treatment at our center and one year after stem cell transplant is given in Table I.

Patient's pain was reduced from severe to pain free. Range of motion (ROM) significantly increased. Range of motion (ROM) was measured by Goniometry. Grip function was measured by the "Sollerman test". The results of Sollerman test are given in Table II.

Modified HSS (Hospital for Special Surgery) Score for both knees were measured that improved from 57 to 90 for her left knee and 57 to 87 for her right knee.

Table I: Muscle Power Before and One Year after Bone Marrow Derived Stem Cell Transplant

Region	Right Side		Left Side	
	Before Rx	1yr After Rx	Before Rx	1yr After Rx
Shoulder Girdle	-2/5	-4/5	3/5	4/5
Elbow (Flexor/Extensor)	2/5	4/5	-2/5	4/5
Wrist (Flexor/Extensor)	-2/5	4/5	2/5	4/5
Finger (Flexor/Extensor)	-2/5	+3/5	2/5	4/5
Hip Girdle	-2/5	+3/5	2/5	+3/5
Knee (Flexor/Extensor)	+2/5	+4/5	2/5	+4/5
Ankle(DorsiFlexor/Plantar flexor)	-3/5	+4/5	-3/5	+4/5

Table II. "Sollerman Test" Result. Performance is Graded from 4 (best) to 0 (worst). Grade 04 is Used for Correct Grip and Performance of the Activity within 20 Seconds. Grip Strength was Measured in Newton's by Means of an Electronic Hand Dynamometer

Type of Grip	Right Side		Left Side	
	Before Rx	1yr After Rx	Before Rx	1yr After Rx
Pulp pinch	1	3	0	3
Lateral pinch	1	3	0	3
Tripod pinch	1	2	1	2
Five finger pinch	2	3	1	3
Diagonal volar grip	2	4	1	3
Transverse volar grip	2	4	2	3
Spherical volar grip	2	4	2	4
Extension grip	1	3	1	2

Discussion

Bone marrow contains hematopoietic and non-hematopoietic (mesenchymal) stem cells, the latter being with immunoregulator properties. It is suggested that adult Mesenchymal Stem Cells (MSC) are useful as cellular therapy in several inflammatory diseases, including RA.[7] As MSC may transfer to sites of injury in vivo, it is suggested that inflamed joints are targeted by cells which might have a therapeutic effect on arthritis through MSC-mediated immunosuppression.[8] Leeds group presented a study in 1997 in which G-CSF was used at a dose of 5µg/kg/day to mobilize stem cells in five patients. In peripheral blood CD34+ count was checked to establish good efficacy. Patients remained stable after the treatment but we observed that administering methylprednisolone (median 80mg,

range 40–120mg) intramuscular or intra-articular diminished any pro-inflammatory effects of filgrastim. A phase I placebo controlled 1110 study was conducted in Australia to investigate the efficacy of G-CSF in patients suffering from active form of RA for the use of stem cell collection.[9] In Paris, four patients had their stem cells mobilized with cyclophosphamide 4g/m2 followed by G-CSF 5µg/kg/day. Probably, in three of the patients CD34+ cell yields were higher with G-CSF along with cyclophosphamide than with G-CSF alone. Arthritis and extra-articular manifestations improved markedly in these patients. To some extent the disease activity persisted in three patients, although it never went back to the same level even two years after the procedure.[10] In this case, the patient presented with inflammatory arthritis of almost forty five years' duration. She described the pain in her hands, wrists, elbows, shoulders and knees as frequently unbearable. She had significant muscle wasting, decreased muscle power, deformities, and weak grip strength. One year after autologous bone marrow stem cell transplant, the patient felt significant decrease in all subjective symptoms and discontinued her medications. ESR had normalized, indicative of clinical reduction of arthritis. She also felt improvement in ADLs. In our study Autologous Bone marrow derived Stem cells combined with exercises showed that it is a safe and effective treatment option for the patient suffering from Rheumatoid Arthritis and warrants a larger scale Phase I / II clinical study.

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