

Effects of granulocyte colony-stimulating factor therapy for osteogenesis imperfecta: a case report

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A- Conception and study design; B - Collection of data; C - Data analysis; D - Writing the paper; E- Review article; F - Approval of the final version of the article; G - Other (please specify)

ABSTRACT

Introduction: Osteogenesis imperfecta (OI) is a genetic disorder of increased bone fragility and low bone mass. OI type IV.

Materials and methods: We examined the safety and effectiveness of a low dose of analog granulocyte colony-stimulating factor (G-CSF) in a 15-year-old girl OI type IV. G-CSF 5 µg/kg was given subcutaneously, for 5 days/month for 3, 6 and 12 months. Laboratory tests, including blood, biochemical tests were performed, in addition to clinical examination.

Results: Clinical examination revealed an increase of muscle strength in the upper and lower limbs between base line and day 6 and 12 months. We found no serious adverse events. Leukocyte levels remained below 38,000/µL. Low dose G-CSF was safe and well tolerated by the patient.

Conclusions: A significant increase in muscle strength in this patient may indicate beneficial effects of G-CSF factor in this disorder. These results are inspiring and warrant further studies.

Keywords: Osteogenesis imperfecta; granulocyte colony-stimulating factor; muscle strength

DOI: 10.5604/01.3001.0010.1885

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Received: 12.02.2017

Accepted: 18.05.2017

Progress in Health Sciences

Vol. 7(1) 2017 pp 205-208

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INTRODUCTION

Osteogenesis imperfecta (OI) is a genetic disorder signified by increased bone fragility and low bone mass. The incidence of this disease is somewhere from one in 10,000 to one in 60,000 [1]. Severity varies widely, ranging from intrauterine fractures and perinatal lethality to very mild forms without fractures. Typical extraskelatal manifestations can be associated variably with the disorder. These include blue sclera, dentinogenesis imperfecta, hyperlaxity of ligaments and skin, hearing impairment, and presence of wormian bones on skull radiographs. Based on the pattern of inheritance, age at presentation, radiologic features, and natural history, Sillence et al. [2] described four types of OI, which provide the clinical framework for diagnosis. Normal height or mild short stature, blue sclera, and no dentinogenesis imperfecta are presented in type I of OI. Type II is lethal in the perinatal period. OI type III is the most severe form in children surviving the neonatal period. These patients are of very short stature and have limb and spine deformities secondary to multiple fractures, which can lead to respiratory difficulties. Patients with mild to moderate bone deformities and variable short stature are classified as OI type IV [3,4]. This last group includes all individuals who are not clearly part of the first three types. These disorders have been named OI type V, VI, and VII [5].

Granulocyte colony-stimulating factor (G-CSF) is a glycoprotein. This cytokine promotes survival, proliferation, and differentiation of cells in the neutrophil lineage [6]. Currently, G-CSF is used to treat neutropenia, stimulating the bone marrow to increase production of neutrophils during chemotherapy and bone marrow transplantation.

Skeletal muscle has resident stem cells, called satellite cells, which are responsible for generating new muscle under both physiological and pathophysiological conditions. Satellite cells are located beneath the basal lamina that surround each myofiber and act as myogenic precursors for repair following muscle injury with stem cell-like characteristics [7]. Several studies have identified various growth factors and cytokines regulating skeletal muscle and nerve development and regeneration [8].

Many growth factors, such as insulin-like growth factor 1, hepatocyte growth factor, epidermal growth factor, transforming growth factors, and platelet-derived growth factors, as well as cytokines, have been identified as causing proliferation of satellite cells, with subsequent transformation into myotubes and muscle fibers, to regulate myoblast proliferation and differentiation, and to muscle regeneration or repair [9]. Furthermore, both G-CSF and stem cells can induce the production of the earlier-mentioned factors. It

was also demonstrated that G-CSF promoted the restoration of damaged spinal cord tissue and the recovery of neural function in experimental spinal cord injury in both mice and rats [10].

Recent studies have indicated that G-CSF can potentially be used for the treatment of spinal cord injuries and neurodegenerative diseases [11, 12]. Scientific articles indicating the use of G-CSF for children with OI have not yet been found.

Physiotherapy and orthopaedic surgery are the mainstays of treatment for patients with OI [5, 13, 14]. Therapeutic efforts aim to get the most out of mobility and other functional capabilities. Physical activity programs are encouraged – as far as is possible with the raised risk of fracture – to prevent contractures and immobility-induced bone loss [15]. Children who are ready to stand but are under 5 years old are often considered for hip, knee, ankle, and foot orthoses. Orthoses are used to protect the legs during the early phases of mobilization [5,16]. The bisphosphonates clodronate, pamidronate, and olpadronate have all been administered to children with OI [18]. Studies using cyclical pamidronate infusions suggest that the bisphosphonate group of drugs may be a clinically effective therapy for affected infants and children [17]. G-CSF has been used for a patient with OI to increase muscle, allowing her independent locomotion.

CASE REPORT

A 15-year-old girl diagnosed with congenital OI type IV was born from the fourth pregnancy and the fourth labour. Her family lineage was not stressed with genetic disease; her parents were healthy and unrelated. The patient experienced multiple breakages in a range of top and bottom limbs (last in 2012, fracture of distal section of right radius), which were treated in the Department of Paediatrics and Developmental Disorders with cyclic Pamidronian administration (11th-cycle in May 2013), multiply rehabilitated, and the Department of Pediatric Rehabilitation with the objective of motor improvement.

The patient walked independently until 8 years old, but stopped due to frequent bone fractures. On admission to our department, she was in a wheelchair moving and rarely stood at her walker. With subjective examination, she was diagnosed with phenotypical characteristics of congenital osteogenesis imperfecta: triangular face shape, dentonogenesis imperfecta, bulgy chest shape, shortened, arch-like curved bottom limbs, deformed left humerus, and characteristics of right hip-joint dislocation.

Manual muscle testing was 4/5 throughout the upper and lower extremities. Isometric force was measured with the hand dynamometer and Lovett test. The patient had decreased muscle

strength of the lower limbs (4 in Lovett test). The patient was able to stand using a walker and took a few steps with it. The six-minute walk test was possible after giving the patient the first series of G-CSF.

Before and after the last series of G-CSF, a bone densitometrical examination was performed. Laboratory investigations included full blood count, biochemistry, and urine. Blood was sampled before G-CSF administration and on day five of each treatment cycle. G-CSF (5 µg/kg/body/d) was subcutaneously administered for five consecutive days during the first, second, third, sixth, and twelfth month. Abdominal ultrasonography with a spleen assessment was performed before and after seven days of G-CSF administration.

The ethics committee of the Medical University of Białystok approved the study, and written informed consent was obtained from the patient and her parents.

RESULTS

The patient reported increased muscle strength in the lower limbs after twelve months of G-CSF treatment. We confirmed the increase in muscle force of the upper extremities. The patient had increased muscle strength of the upper (right hand 16 kg and left hand 16.6 kg, by dynamometer, and after 360 days, right hand 20.6 kg and left hand 19.6 kg) (Table 1).

There was observable strength growth of shins of both limbs (4.5/5). The six-minute walk test was performed in the second month of treatment (day 30 of treatment). The patient walked with the help of a walker noticeably more efficiently after 30 days of treatment, and her efficiency was significantly improved after six months and after twelve months. The patient was able to walk with a walker for 45 meters within the six-minute walk test; after three months, the patient walked for 60 meters; after 6 months, 70 meters; and after twelve months, 85 meters within the six minutes.

The patient did not report any side effects following G-CSF administration. White blood cell count increased at five days after G-CSF administration, climbing to 38,000. A slight increase of alkaline phosphatase serum was observed: before G-CSF treatment, 143U/L; after the second cycle, 221U/L; after the third cycle, 239U/L; after 6 months it increased from 124U/L to 220U/L; and after 12 months, from 100U/L to 179U/L. Other laboratory test results were within the normal range. In an abdominal ultrasonography, the spleen was normal during treatment. In densitometrical examination of bone mass of the lumbar spine indicated growth of skeletal bones with a rate of 7.1% per year (06-08-2013-29-08-2014).

DISCUSSION

We observed the beneficial effects of G-CSF in a patient with OI. After three months of treatment, there was a noticeable hand-strength gain, and the distance the patient walked in a six-minute walk was longer. Muscle strength and walk endurance remained static through the twelve months of treatment. Our findings are in partial agreement with previous reports. [10,11]. Sakuma et al. [10] administered G-CSF for 15 adult patients with worsening symptoms of compressive myelopathy in a clinical trial.

We confirmed the increase in muscle force of the upper and lower extremities in an objective assessment using a dynamometer and leg tensor. The patient was able to walk 420 meters within six minutes after three months, 450 meters after six months, and 480 meters after twelve months.

Possible explanations for these effects may relate to the ability of G-CSF to stimulate the bone marrow to produce stem cells and release them into the bloodstream. G-CSF also exerts anti-inflammatory, antiapoptotic effects, and stimulates neurogenesis. It enhances muscle proliferation of skeletal muscle injury in animals and promotes vessel formation [8, 10]. In our patient, G-CSF was administered for five consecutive days as in similar studies [11,12]. The results indicated improvements in muscle strength and motor functions after three months of therapy and, a 7.1% increase in skeletal bone mass per year was reported in the study of bone densitometry system. No serious adverse events were reported. In this report, the increase of white blood cells after G-CSF was similar to that of other clinical studies using G-CSF [11,12].

Our report has several limitations. The biggest limitation of this report was that this case report. The patient also received physical rehabilitation during the course of the study. To date, there have been no reports of G-CSF improving clinical status in a young adult OI. We are going to conduct a clinical trial for better assessment of the efficacy of G-CSF therapy in patients with osteogenesis imperfecta.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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