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Prevention and Control of Infections in Patients with Severe Congenital Neutropenia; A Follow up Study.

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Abstract

Severe Congenital Neutropenia is one of primary immunodeficiency disorders that characterized by severe neutropenia and is associated with severe systemic bacterial infections from early infancy. Granulocyte Colony Stimulating Factor (GCSF) is clinically used as a treatment for congenital and acquired neutropenia. The aim of this study was evaluation of GCSF (PD- Grastim) in treatment of these patients. Patients with severe congenital neutropenia referred to Immunology, Asthma and Allergy Research Institute between Jan 2007 and Dec 2010 enrolled the study. Other causes of neutropenia were excluded by serial CBC and bone marrow studies, medical and drug histories and immunological tests. Patients were visited and examined monthly to evaluate their CBC and ANC (Absolute Neutrophil Count), GCSF side effects and dosage adjustment. Cytogenetic studies were being done for all the patients for early detection of progression to AML/MDS. From twenty two patients who enrolled this study, 16 patients regularly evaluated. They were ten males and six females, range in age from 2 to 18 years old. Two patients failed to continue our follow up unfortunately and four patients died due to disease complications. Patients were followed for 24 to 48 months. In a period of 12-24 months before treatment, the mean of hospitalization frequency was 3.1 times and duration was 10 days; while during receiving treatment, they decreased to 0.2 times and 3 days, respectively ($p < 0.01$). Also significant increase in mean ANC was observed during follow up (315/ μ l before treatment versus 1749/ μ l after 12 month regular treatment). Bone pain was the most common side effect. There have been no evidences of developing AML/MDS up to present time. Treatment with GCSF significantly reduced the duration and the frequency of hospitalization. Because of plausible progression to AML/MDS, regular follow-up of patients should be continued.

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Prevention and Control of Infections in Patients with Severe Congenital Neutropenia; A Follow up Study

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ABSTRACT

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There have been no evidences of developing AML/MDS up to present time. Treatment with GCSF significantly reduced the duration and the frequency of hospitalization. Because of plausible progression to AML/MDS, regular follow-up of patients should be continued.

Keywords: GCSF; Immunodeficiency; Neutropenia; Severe Congenital Neutropenia

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INTRODUCTION

Severe congenital neutropenia (SCN) includes a variety of hematologic disorders characterized by severe neutropenia, with absolute neutrophil count (ANC) less than $0.5 \times 10^9/\text{lit}$, and is associated with severe systemic bacterial infections from early infancy. In these patients myelopoiesis is arrested at the promyelocyte/myelocyte stage of maturation.¹

There are two major subtypes of congenital neutropenia: 60% of patients show an autosomal dominant type that caused by neutrophil elastase mutation and 30% of them show autosomal recessive type and mutation in HAX1 are the main mutations in this type.^{2,3}

Granulocyte colony-stimulating factor (G-CSF) is the main cytokine in controlling neutrophil production which is clinically used as a therapy for congenital and acquired neutropenia. It increases the number of circulating neutrophils and improves their function invitro. It has various effects on granulocytes cells: not only stimulates growth and differentiation of myeloid precursors, but also reinforces mature neutrophils' functions.⁴

More than 90% of neutropenic patients respond to G-CSF by increasing ANC above $1 \times 10^9/\text{lit}$. They significantly benefit from G-CSF including improving their life quality, social function, socio-economic state, decreasing in frequency and severity of infections, fever, antibiotic usage, hospitalization, oral ulcers and increasing survival. Treatment with G-CSF strongly decreases the risk of sepsis in patients with severe congenital neutropenia.^{5,6}

According to previous studies, G-CSF's side effects include: splenomegaly, thrombocytopenia, osteopenia and osteoporosis, bone pain, vasculitis, skin rashes, and malignant change to AML/MDS. In other sporadic studies, hypersplenism, glomerulonephritis, myalgia, erythema, dyspnea, hypotension, sweating and flushing were reported as well.^{7,8}

The most important side effect are the progression to AML/MDS, while it is not still clear whether G-CSF causes this transformation or because of the natural tendency of congenital neutropenia disease to progress to AML/MDS, the prolonged survival of patients due to G-CSF treatment, provides enough contingency to develop this malignancy.⁹⁻¹¹

As treatment of AML/MDS by chemotherapy or BMT is associated with a high mortality (70%), the

watchful follow up of patients with SCN is necessary for early detection of cytogenetic changes leading to this malignancy. The more important point is that hematopoietic stem cell transplantation (HSCT) outcome -which remains the final treatment for these people - is poor after this transformation, while performing HSCT before evidence of progression to malignancy may result in treatment of many patients.¹²

The abnormal cytogenetic transformations reported to be concomitant with high risk of progression to this malignancies include: CSF₃R (G-CSF receptor) mutation, ELA2 mutation, activation of ras oncogen, 7 chromosome monosomy and 21 chromosome changes.¹³

PATIENTS AND METHODS

Patients with severe congenital neutropenia referred to Immunology, Asthma and Allergy Institute for four years (2007 to 2010) enrolled and followed in this study. Demographic data, familial history, history of infectious disease and frequency and duration of infection and hospitalization were registered. CBC and bone marrow studies were done and diagnosis was confirmed by cytogenetic study. Patients examined by subspecialist of pediatric immunology and allergy. Patients were eligible for enrollment if they met the following criteria: A confirmed diagnosis of severe chronic neutropenia based on documented absolute neutrophil counts of less than $0.5 \times 10^9/\text{L}$ on at least three occasions in the three months prior to enrollment.¹⁴ For patients with presumed cyclic neutropenia, documentation of at least two neutrophil cycles for 3 to 6 months was preferred that showed ANC less than $0.5 \times 10^9/\text{L}$ with 21 days intervals.¹⁵ Independent of hematological parameters, including patients with the following diagnosis were included: Shwachman-Diamond syndrome, Glycogen storage disease type Ib (GSD1b), Barth syndrome. All of them showed histories of recurrent infections. Other causes of neutropenia were excluded by serial CBC and bone marrow studies, medical and drug history and immunological tests.

The GCSF (PD-Grastim; Pooyesh Darou, Iran) was given to patients free of charge and patients were visited and examined by hematologists and immunologists at least monthly to evaluate their CBC and ANC, for response to GCSF in case of increase in ANC (more than $1 \times 10^9/\text{L}$) and decrease in frequency,

Prevention and Control of Infections

duration of infections and hospitalization¹ and monitoring all patients to indicate complications of G-CSF such as splenomegaly, headache, bone pain, fever, fatigue, skin rash, injection site reaction, eosinophilia and thrombocytopenia then dosage adjustment were made. Cytogenetic studies were being done for all the patients for early detection of progression to AML/MDS.

The study protocol was approved by ethical committee and research board of Immunology, Asthma and Allergy Institute. An informed consent was also obtained from the patients, their parents or closed relatives before the entrance to the study as well.

RESULTS

During the study period 22 patients were referred to Immunology, Asthma and Allergy Research Institute that definite diagnosis of severe congenital neutropenia was done for them and then enrolled in this study. Four patients died due to disease complication, and two patients failed to continue our follow up and were excluded from the study thus 16 patients regularly evaluated for 24 to 48 months.

All patients were registered in Iranian Primary Immunodeficiency Disease Registry (IPIDR).

The patients were 12 males and 4 females with age ranging from 2 to 18 years old.

The majority of patients (83.3%) were progenies of consanguineous marriages, while there was not any history of immunodeficiency disease in their families.

For all cases bone marrow aspiration and biopsy were performed. Maturation arrest in myelocyte and pro-myelocyte stages were reported in 12 patients.

Gene distributions in these patients consisted: mutation in *Ela2* in one patient, *HAX1* in eight patients, and *G6PC3* in one patient. Also one patient had WHIM syndrome and five patients showed no mutation in *HAX 1*, *Ela2* and *G6PC3*. Results suggest no correlation between genetic subtype and ANC response. Also mutation in *G-CSFR* was noticed in one patient (P5). This patient compared to other patients responded to higher dose of G-CSF.

Patients treated with G-CSF (PD-Grastim). The drug dosage adjustment was based on their weights, symptoms severity, and response to drug treatment, drug side effects and regular absolute neutrophil counts (ANC). G-CSF prescribed 2-5 µg/kg three times per week (mean dose: 5.1 µg/kg three times per week.)

Patients were followed for 24-48 months. (Nine patients for 48 months, four patients for 36 months and three patients for 24 months.) In this period two patients experienced major infections (otitis media and eyelid abscess) and were treated out patiently, and two patients experienced hospitalization during the treatment course because of pneumonia.

In a period of 12-24 months before our treatment commenced, the mean of hospitalization frequency and duration were 3.1 times and 10 days; while during receiving treatment (in a similar time period) these decreased to 0.2 times and 3 days, respectively ($P<0.01$). There was a significant increase in ANC mean (315/µl before treatment versus 1749/ µl after 12 months regular treatment and monthly follow up. Subsequently patients followed for 2-4 years with visiting every 2-3 months. The majority of the patients (10/16) showed at least one drug side effect. Bone pain was the most common side effect and was detected in 6 patients. Other side effects were fever (5/16), splenomegaly (2/16), thrombocytopenia (3/16), headache (1/16), and tiredness (1/16). There had been no evidence for developing AML/MDS up to present time. Two out of 4 patients experienced Considerable bone pain, suspended treatment because of pain severity. One of them was a 15 years old boy (P4) whose bone pain commenced after one year of treatment which discouraged him to continue drug injection. Another was a 5 years old boy (P7) with acute bone pain localized in lumbar spine, which resulted in drug injection discontinuation and further evaluation was conducted. We consulted hematologist and orthopedist to rule out malignancy. Bone scan and bone marrow biopsy were done and malignancy was ruled out finally. Patient's bone pain improved gradually after a month of PD- Grastim cessation. Nevertheless non acceptable ANC rates, because of patient disobedience, G-CSF was not prescribed again and patient was followed up regularly for his health status. Another noticeable patient was a 18 year old (P12) male with necrotic wounds on his auricles which was diagnosed as vasculitis. These wounds were worsening when G-CSF dosage was more than 2mg/kg three times per week and led to discontinue drug treatment by patient. Intermittent low dose G-CSF (less than 2 µg/kg three times per week) prediscrbed. Nevertheless ANC rate was less than acceptable or therapeutically rate. Although patient showed no infection.

Table 1. Clinical and laboratory findings of SCN patients

Patient	Sex/Age	ANC*	Bacterial infection	Bone marrow maturation arrest	Response to G-CSF	G-CSF side effect	G-CSF dosage	ANC after treatment CMCC	Gene mutation
1	M/9yrs	470	Pneumonia, otitis, oral ulcers gingivitis	Arrest	+	Splenomegaly	5µg/kg	1187	HAX1
2	F/14yrs	140	Pneumonia, otitis, gingivitis	Arrest	+	Trombocytopenia	5µg/kg	1938	HAX1
3	M/3yrs	125	Recurrent fever,	Arrest	+	No	3µg/kg	3118	HAX1
4	M/15yrs	199	Oral ulcers, otitis	Normal	+	Bonepain, fever Headache	3µg/kg	1134	Unknown
5	M/11yrs	300	Skin abscess, oral &anal ulcers, urinary tract infection	Arrest	+	Splenomegaly, Bone pain	2µg/kg	1541	ELA2
6	M/9yrs	432	Pneumonia, lung abscess	Arrest	+	No	4µg/kg	1082	HAX1
7	M/5yrs	82	Septicemia, neck& head abscess	Arrest	+	Bone pain	12µg/kg	1220	Unknown
8	M/14yrs	330	Oral ulcers, gingivitis, lung abscess	Arrest	+	No	2µg/kg	1230	HAX1
9	F/14yrs	509	Oral ulcers, gingivitis	Normal	+	Bone pain	2µg/kg	2635	HAX1
10	F/18yrs	752		Arrest	+	Bone pain, trombocytopenia	4µg/kg	1302	WHIM
11	M/3yrs	28	Pneumonia	Arrest	+	No	2µg/kg	1457	G6PC3**
12	M/18yrs	20	Pneumonia, otitis, skin abscess, gingivitis	Arrest	+	Trombocytopenia	2µg/kg	1250	Unknown
13	M/12yrs	750	Recurrent aphtous, recurrent respiratory infection	Arrest	+	No	2µg/kg	2240	HAX1
14	M/7yrs	70	Recurrent fever, recurrent respiratory infection, diarrhea	Arrest	+	No	2µg/kg	1700	HAX1
15	M/13yrs	640	Osteomyelitis, recurrent otitis media, submental abscess	Normal	+	Bone pain	2µg/kg	3300	Unknown
16	F/12yrs	190	Recurrent aphtuous	Normal	+	No	3µg/kg	3190	Unknown

* ANC=Absolute Neutrophil Count

**This case was reported in reference ²³

DISCUSSION

Severe congenital neutropenia is a rare primary immunodeficiency disorder, including heterogeneous types of diseases with increased susceptibility to bacterial and fungal infections.¹⁶ Many studies

conducted to find a suitable treatment, such as using corticosteroid, splenectomy, immunoglobulin and immunosuppressive drugs but they were found to be ineffective or unsuitable for long term usage because of their side effects. For many years close observation, follow up and antibiotic prescriptions were the basis of

treatment.^{17,18} In 1990-2000 several studies demonstrated benefits of G-CSF for congenital neutropenia treatment. G-CSF (Granulocyte Colony Stimulating Factor) is a colony stimulating factor that stimulates the production, proliferation, differentiation, and function of neutrophils which by using in treatment of neutropenia reduced life-threatening infections, increased longevity and improved quality of life.³

In a study carried out by The Severe Chronic Neutropenia International Registry, (SCNIR) in the United States from 1994 to 2000 on over 800 patients with SCN, 90% of them, treated with Filgrastim (G-CSF).⁶ Results of four years study by Donadieu J. and colleagues in France in 1997 on 19 patients with SCN treated with Lenograstim human-identical glycosylated (rHuG-CSF) showed significant reduction in infections and hospitalization for infection compared with their previous study.¹⁹

In our study, treatment with G-CSF also showed significant increase in the ANC and a significant reduction in the frequency and duration of hospitalization due to infection, resulting in improvement of quality of life.

Plausible G-CSF side effects have been studied in several surveys. According to SCNIR study, important complications of G-CSF include bone pain, splenomegaly, thrombocytopenia, osteoporosis and increased risk of progression to AML/ MDS.⁶ Also in other studies hypersplenism, glomerulonephritis, fatigue, edema and proteinuria were reported as G-CSF side effects.^{20,21} In our study fever was the most common side effects that was found in 47% of patients. Severity of side effects resulted in discontinuation of G-CSF in two patients, and dosage reduction to 2 µg/kg three times per week in another one. Increased risk of progression to AML/MDS is the most important side effect of patients with SCN receiving G-CSF. It is still unclear whether the inherent tendency of SCN leads to progression to AML/MDS or G-CSF causes this tendency. However, before the introduction of hematopoietic growth factors to treat this disease, conversion to AML/ MDS had been reported clearly in patients with SCN.⁹⁻¹¹

In SCNIR study, 35 out of 387 patients receiving G-CSF developed AML or MDS while no predictable relationship with dosage or duration of treatment was seen. Follow up of these patients showed a cumulative risk of 13% after 8 years of G-CSF treatment. Among these patients, 29% receiving G-CSF for 10 years died,

and the cause of death was AML/MDS in 21%, and sepsis in 8% of them.⁶

Some studies implicated a significant relationship between G-CSF dosage and risk of AML/MDS occurrence; recommending the lowest possible dosage prescription to achieve and maintain an acceptable absolute neutrophil count. Also the type of congenital neutropenia, disease severity and age at the time of diagnosis were suggested to be other risk factors.⁵

In this study, there are no evidences of disease progression to AML/MDS that can be due to low sample size, inadequate follow-up period (four years) and receiving minimum dose of PD-grastim by patients (average 5.1 µg/kg three times per week). Also, it should be noted that most of our patients showed HAX1 mutations, so the risk factor of genetic effect for progression AML could be considered as some studies suggested that ELA2 mutations is a risk factor for AML/MDS progression.^{23,24}

Development of MDS/AML is a process of cellular genetic abnormalities, so screening for mutations and cytogenic changes in these patients is necessary to refer the patients for hematopoietic stem cell transplantation (HSCT) as soon as possible. In particular treatment of AML/MDS with chemotherapy and bone marrow transplantation in chronic neutropenic patients is associated with high mortality.¹² Regarding to this, we observed and evaluated all patients for evidences of progression to AML/MDS; and no cellular and cytogenic changes were found up to present time.

In conclusion; regarding treatment with G-CSF, this therapy significantly reduced the duration and the frequency of hospitalization. It can be used for severe congenital neutropenia. However because of plausible progression to AML/MDS, regular follow-up of patients should be adhered to.

REFERENCES

1. Welte K, Zeidler C. Severe congenital neutropenia. *Hematol Oncol Clin North Am* 2009; 23(2):307-20.
2. Klein C, Welte K. Genetic Insights into Congenital Neutropenia. *Clin Rev Allerg Immunol* 2010; 38(1):68-7.
3. Ward AC, Dale DC. Genetic and molecular diagnosis of severe congenital neutropenia. *Curr Opin Hematol* 2009; 16(1):9-13.
4. Liongue C, Wright C, Russell AP, Ward AC. Granulocyte colony-stimulating factor receptor: Stimulating

- granulopoiesis and much more. *Int J Biochem Cell Biol* 2009; 41(12):2372-5.
5. Leung TF, Li CK, Kwok KL, Chik KW, Shing MM, Yuen PM. Severe chronic neutropenia in Chinese children in Hong Kong *J Paediatr Child Health* 2001; 37(2):137-41.
 6. Dale DC, Cottle TE, Fier CJ, Bolyard AA, Bonilla MA, Boxer LA, et al. Severe Chronic Neutropenia: Treatment and Follow-Up of Patients in the Severe Chronic Neutropenia International Registry. *Am J Hematol* 2003; 72(2):82-93.
 7. James RM, SE Kinsey. The investigation and management of chronic neutropenia in children. *Arch Dis Child* 2006; 91(10):852-8.
 8. Cottle TE, Fier CJ, Donadieu J, Kinsey SE. Risk and benefit of treatment of severe chronic neutropenia with granulocyte colony-stimulating factor. *Semin hematol* 2002; 39(2):134-40.
 9. Niemeyer CM, Kratz CP. Is granulocyte colony-stimulating factor therapy a risk factor for myelodysplasia/leukemia in patients with congenital neutropenia? *Haematologica* 2005; 90(1):2-3.
 10. Ancliff PJ, Gale RE, Liesner R, Hann I, Linch DC. Long-term follow-up of granulocyte colony-stimulating factor receptor mutations in patients with severe congenital neutropenia: implications for leukaemogenesis and therapy. *Br J Haematol* 2003; 120(4):685-90.
 11. Zeidler C, Germeshausen M, Klein C, Welte K. Clinical implications of ELA2-, HAX1-, and G-CSF-receptor(CSF3R) mutations in severe congenital neutropenia. *Br J Haematol* 2009; 144(4):459-67.
 12. Zeidler C, Welte K, Barak Y, Barriga F, Bolyard AA, Boxer L, et al. Stem cell transplantation in patients with severe congenital neutropenia without evidence of leukemic transformation. *Blood* 2000; 95(4):1195-8.
 13. Badolato R, Fontana S, Notarangelo LD, Savoldi G. Congenital neutropenia: advances in diagnosis and treatment. *Curr Opin Allergy Clin Immunol* 2004; 4(6):513-21.
 14. Rezaei N, Moin M, Pourpak Z, Ramyar A, Izadyar M, Chavoshzadeh Z. The Clinical, Immunohematological, and Molecular Study of Iranian Patients with Severe Congenital Neutropenia. *J Clin Immunol* 2007; 27(5):525-33.
 15. Rezaei N, Farhoudi A, Pourpak Z, Aghamohammadi A, Ramyar A, Moin M, et al. Clinical and Laboratory Findings in Iranian Children with Cyclic Neutropenia. *Iran J Allergy Asthma Immunol* 2004; 3(1):37-40.
 16. Boztug K, Welte K, Zeidler C, Klein C. Congenital Neutropenia Syndromes. *Immunol Allergy Clin North Am* 2008; 28(2):259-75.
 17. Beaupain B, Leblanc T, Reman O, Hermine O, Vannier JP, Suarez F, et al. Is Pegfilgrastim Safe and Effective in Congenital Neutropenia? An Analysis of the French Severe Chronic Neutropenia Registry. *Pediatr Blood Cancer* 2009; 53(6):1068-73.
 18. Shannon K. Reconsidering how we treat severe congenital neutropenia. *Blood* 2006; 107(12):4575-6.
 19. Donadieu J, Boutard P, Bernatowska E, Tchernia G, Couillaud G, Philippe N, et al. A European phase II study of recombinant human granulocyte colony-stimulating factor (lenograstim) in the treatment of severe chronic neutropenia in children. Lenograstim Study Group. *Eur J Pediatr* 1997; 156(9):693-700.
 20. Calderwood S, Kilpatrick L, Douglas SD, Freddman M, Smith-Whitely K, et al. Recombinant human granulocyte colony-stimulating factor therapy for patients with neutropenia and/or neutrophil dysfunction secondary to glycogen storage disease type 1b. *Blood* 2001; 97(2):376-82.
 21. Sotomatsu M, Kanazawa T, Ogawa C, Watanabe T, Morikawa A. Complication of rapidly progressive glomerulonephritis in severe congenital neutropenia treated with long-term granulocyte colony-stimulating factor (filgrastim). *Br J Haematol* 2000; 110(1):234-5.
 22. Alizadeh Z, Fazlollahi M, Eshghi P, Hamidieh A, Ghadami M, Pourpak Z. Two cases of syndromic neutropenia with a report of novel mutation in G6PC3. *Iran J Allergy Asthma Immunol* 2011; 10(3):227-30.
 23. Dale DC. Recent progress in understanding the congenital neutropenia. *Curr Opin Hematol* 2010; 17(1):1-2.
 24. Rosenberg PS, Alter BP, Link DC, Stein S, Rodger E, Bolyard AA, et al. Neutrophil elastase mutations and risk of leukemia in severe congenital neutropenia. *Br J Haematol* 2008; 140(2):210-3.