The fourth newsletter produced by the Severe Chronic Neutropenia International Registry (SCNIR) continues to provide information to physicians who have patients enrolled in the Registry. This issue focuses on recent Registry activity, summaries of presentations at the American Society of Hematology meeting, and answers some questions often asked by physicians treating patients with severe chronic neutropenia (SCN).

Report on Registry Activity

The Registry continues to experience positive growth. As of March 25, 1997, the Registry had 445 actively enrolled patients in 10 countries. Enrollment by country is listed below. We continue to actively recruit patients and welcome all eligible patients for registration. Please contact any Advisory Board member or either Data Coordinating Center for more information.

<table>
<thead>
<tr>
<th>Country</th>
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<td>United States</td>
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Total Enrollment 445

* through March 25, 1997
SCNIR Initiates Protocol Changes

The SCNIR protocol was officially amended in 1996 to include autoimmune neutropenic patients and revise the bone marrow and cytogenetic evaluation requirements. These protocol changes are now effective and are summarized as follows:

1) SCN patients with autoimmune neutropenia are now eligible for Registry enrollment if they meet all other inclusion criteria.

2) Revision of registration bone marrow requirements:

To register patients not treated with a cytokine:

- Congenital and idiopathic neutropenia patients are required to submit documentation of a bone marrow evaluation for diagnostic purposes; cyclic neutropenia patients are not required to have a bone marrow evaluation.

To register patients receiving or about to initiate cytokine treatment:

- Congenital, idiopathic and cyclic neutropenia patients are required to have a bone marrow and cytogenetic evaluation within twelve months prior to SCNIR registration.

SCN at ASH '96

This newsletter will focus on recent advancements in the understanding of severe chronic neutropenia and its therapy. At the American Society for Hematology meeting in Orlando, Florida, Dec 6–10, 1996 there were several papers of interest.

The SCNIR Advisory Board presented three abstracts regarding information arising from the Registry. Additional papers were presented by board members and their collaborators regarding their own independent research, which will also be summarized here.

Dr. Mel Freedman, chair of the Safety Review subcommittee of the SCNIR advisory board, presented a current paper entitled “MDS/AML in patients with severe chronic neutropenia (SCN) receiving G-CSF”. This is an adverse outcome of SCN which has previously been reported both by the registry and others. The data presented indicated that this outcome has been exclusively seen (to date) in patients with congenital neutropenia as opposed to cyclic or idiopathic patients. No relationship between dose or duration of G-CSF therapy is apparent. Abnormalities in G-CSF-Receptor proteins have been found to develop in some patients, along with acquisition of a ras oncogene mutation and development of acquired monosomy 7 in marrow stem cells. These abnormalities have not been found to be present at onset of G-CSF therapy, meaning that they are not related to the etiology of the neutropenia. However, their development during therapy raises questions as to whether these patients, who are thought to have a pre-disposition to leukemia based on their underlying disorder, are now living long enough due to supportive care to develop leukemia, or whether the G-CSF is accelerating this conversion.
The outcomes of the patients who have developed MDS/AML while on G-CSF therapy were also reviewed. The only survivors are those who have had bone marrow transplants. Even in the transplanted group, there has been a high mortality (75%), at least partially related to advanced disease at the time of transplant. It is with this in mind that the Registry continues to strongly urge physicians to obtain yearly bone marrow examinations on patients with congenital neutropenia for routine morphology, as well as cytogenetics. For those patients who acquire a clonal cytogenetic abnormality, strong consideration should be given to bone marrow transplantation in an early stage.

Keeping in mind the above association of G-CSF receptor mutations in a group of patients who developed MDS/AML, two other papers presented in poster format are of note.

The first is an abstract entitled “G-CSF receptor point mutations in severe congenital neutropenia occur spontaneously and do not abrogate the in vivo response to G-CSF”. This poster was presented by N. Tidow and colleagues from Hannover Medical School, and described four patients out of 31 studied with SCN, who displayed a point mutation in the cytoplasmic region of the G-CSF receptor gene. By analyzing material obtained at different points in time, this group demonstrated that the mutations were acquired. Analysis of family members provided further evidence that the receptor mutations are not inherited. Two of the patients with the mutation developed AML. Despite the mutation, there was no change in response to G-CSF and no alterations in median ANCs were observed.

The second related paper was presented by T. Bernard and colleagues from London, UK and was entitled, “Mutations of the granulocyte colony-stimulating factor receptor in Kostmann’s syndrome may be transient and may not herald leukemic transformation”. These investigators studied the G-CSF receptor in 11 patients with Kostmann’s Syndrome. They found an abnormality in the receptor in two of the patients. Both patients have remained well, with neither morphological or cytogenetic evidence to suggest (pre)leukaemic progression. In one of the patients, the mutation first appeared 2.5 years after commencing G-CSF and disappeared 3 years later, within 6 months of stopping treatment. These investigators postulate that the mutations in the receptor are not involved in the pathogenesis of the severe neutropenia and arise by random mutation. In a polyclonal marrow, such mutations will only be present in a small proportion of cells and may disappear by either clonal succession or removal of selective pressure. In an already clonal marrow, the mutation may appear more prominent, but this does not necessarily imply involvement in the leukaemogenesis. These studies combined may point towards a predisposition for patients with congenital neutropenia to develop clonal abnormalities, but do not provide evidence for a causal role of G-CSF.

Three more clinically oriented papers were also presented in poster format.

Dr. George Kannourakis presented data derived from the SCNIR in collaboration with Dr. J. Kurtzberg regarding the subset of patients with Glycogen Storage Disease 1b. In a paper entitled “Report on patients with glycogen storage disease 1b with severe chronic
neutropenia (SCN) treated with Filgrastim™, the experience of treating 17 patients with this disorder was described. The mean dose of G-CSF required for stabilization of ANC for these patients was 3.9 mcg/kg/day with a range of 0.5–9.6 mcg/kg/day. All patients had an increase in the ANC, a reduction in the number of infections and improvement in the management of their metabolic status. Splenomegaly developed or progressed while on G-CSF in all of the patients, requiring dose reduction in 4 of the patients, although one patient went on to splenectomy due to persistent hypersplenism. No cytogenetic abnormalities have been reported to date in this group of patients.

Another paper reported on behalf of the SCNIR was a “Report on patients with severe chronic neutropenia (SCN) refractory to G-CSF”10 presented by Dr. Connie Zeidler. This outlined the course of 8 patients in the data base of 476 patients who received doses of G-CSF between 100 and 240 mcg/kg/day. Out of the 8 patients, 4 were refractory to even these high doses. Two of these four patients remain neutropenic, although they have shown an increase in monocyte count to >1000/ul, which may afford some protection and justify the high dosage of G-CSF, despite lack of a neutrophil response. A third patient is well, following allogenic BMT from an HLA-identical sibling, and a fourth died of a severe pneumonitis at 11 years of age. This report indicates that only a small number of patients are refractory to G-CSF, but that BMT may be a suitable alternative to G-CSF therapy, due to the ongoing risk of severe infections in truly refractory patients.

Finally, Dr. Sally Kinsey and colleagues from the UK presented a paper entitled “Bone mineralisation in chronic neutropenia and its relationship to treatment with G-CSF”11. These investigators assessed bone mineralisation in 9 children with chronic neutropenia, of whom 7 were on G-CSF. The children had chronic neutropenias of various etiologies, with 2 being classified as congenital, 2 having Shwachman-Diamond Syndrome, 3 with cyclical neutropenia and 2 who had idiopathic neutropenia. Bone mineral content (BMC) was assessed by single photon absorptiometry and bone turnover was assessed by plasma osteocalcin, bone alkaline phosphatase, and urinary deoxypyridinoline. Eight of the children had a normal adjusted BMC score, although the lowest scores were seen in the 2 patients with congenital neutropenia. Markers of bone turnover were normal in all of the children, except for one child with previously diagnosed osteoporosis and vertebral fracture, who was being treated with anti-resorptive agents. Although somewhat reassuring regarding the degree of abnormality in bone mineralisation in these patients, this study points out that the subset of children with SCN on a congenital basis may be at particular risk of osteopenia or osteoporosis, and merit regular monitoring with bone densitometry.
References


1. When should Bone Marrow Transplantation (BMT) be considered for patients with Severe Chronic Neutropenia?

Reports of bone marrow transplantation for severe chronic neutropenia predate the cytokine era. At that time, bone marrow transplant was reserved for patients who were severely symptomatic with their neutropenia.

Presently, we would consider BMT to be indicated in the following situations:

a. Refractoriness to high-dose G-CSF: This can be defined as an ANC of <200 x 10⁹/L despite one month of high dose G-CSF therapy (in the range of 100 mcg/kg/day)

b. A cytogenetic clonal change, e.g., monosomy 7 or other poor prognostic cytogenetic changes, or the development of MDS/AML.

2. Is G-CSF likely to be required as a life-long therapy for my patient with SCN?

Severe chronic neutropenia is an end-result of varying pathophysiologic processes. The duration of therapy will depend on the etiology of the neutropenia.

Patients with congenital neutropenia are likely to require therapy on a life-long basis. Congenital neutropenias include patients clinically characterized as Kostmann’s syndrome; Schwachman-Diamond syndrome; other forms of congenital neutropenia, type unspecified; and glycogen storage disease type Ib. These patients have neutropenia recognized from birth or shortly thereafter, generally accompanied by frequent and severe problems with infections because neutrophil production is severely impaired. The bone marrow shows “maturation arrest” of neutrophil production at an early stage.

Cyclic neutropenia is a syndrome where typically patients have 21-day oscillations of blood neutrophil counts, the levels usually fluctuating between the lower limit of normal and zero. During the periods of severe neutropenia, the patients are prone to severe infections, but between
these periods they are relatively well. Those patients with cyclic neutropenia who warrant therapy are likely to require it on a life-long basis, although the tendency in some families for amelioration of symptoms with increased age might warrant a trial of withdrawal in well patients.

Patients with idiopathic neutropenia are a much more heterogeneous group. Idiopathic neutropenia includes both childhood and adult patients without evidence for a neoplastic or immunological or other cause for neutropenia. The clinical problems of patients with idiopathic neutropenia tend to vary considerably, but in general, the patients with the more severe neutropenia have the greater frequency of fevers and infections. Idiopathic patients may warrant a trial of withdrawal of G-CSF if their ANCs are not fluctuating on therapy, and if they are clinically well.

Finally, there is a small group of children with autoimmune neutropenia who may have infections significant enough to require G-CSF therapy, but whose condition is expected to be self-resolving. When it is used, periodic trials of weaning to assess if a natural remission of the disease has occurred is advised. This may take the form of either one of the following two methods:

1) Decrease the number of doses per week, and if the ANC remains elevated, then decrease the actual dose given.

2) Decrease the actual dose given, and if the ANC remains elevated, then decrease the number of doses per week.

This should be undertaken in conjunction with re-educating the family regarding the possibility that the patient may become neutropenic, and the steps that should be taken if a fever develops.

3. What are the indications to start G-CSF therapy for severe chronic neutropenia?

Patients with SCN, defined as an ANC < 0.5 x 10^9/L on at least three occasions over a period of three months and if they have had a history of recurrent or significant infections, may be candidates for G-CSF if they have had exclusion of an underlying myelodysplastic syndrome as the basis for their neutropenia.
SCNIR Advisory Board Members

Dr. Mary Ann Bonilla  
St. Barnabas Medical Center  
101 Old Short Hills Road  
Suite 400-A  
West Orange, NJ 07052  
Tel: (201) 325-6700  
Fax: (201) 243-6253

Dr. Laurence A. Boxer  
University of Michigan Women’s Hospital  
Room L 2110  
1500 E. Medical Center Drive  
Ann Arbor, MI 48109-0238  
Tel: (313) 764-7126  
Fax: (313) 938-8520

Dr. Patricia Catalano  
Amgen  
3200 Walnut Street  
Boulder, CO 80301  
Tel: (303) 541-1421  
Fax: (303) 938-8246

Dr. Bonnie Cham  
Manitoba Cancer Treatment and Research Foundation  
100 Olivia Street  
Winnipeg, Manitoba Canada R3E 1V9  
Tel: (204) 787-2188, ext. 4147  
Fax: (204) 783-6875

Dr. Melvin Freedman  
Hospital for Sick Children  
555 University Avenue  
Toronto, Ontario Canada M5G 1X8  
Tel: (416) 813-6152  
Fax: (416) 813-5327

Dr. George Kannourakis  
Cancer Research Centre  
University of Ballarat  
St. John of God Hospital  
1002 Mair Street  
Ballarat, Victoria, Australia  
Tel: 61-53-33-4811  
Fax: 61-53-33-4813

Dr. Sally Kinsey  
Consultant Paediatric Haematologist  
Children’s Day Hospital  
St. James’s University Hospital  
Beckett Street  
Leeds LS9 7TF, UK  
Tel: 44 113 283 7014  
Fax: 44 113 247 0248

Professor Pier Giorgio Mori  
IV Divisione Pediatria  
Ematologia ed Oncologia  
Istituto Giannina Gaslini  
16148 Genova Quarto  
Genova, Italy  
Tel: 00 39 10 5636556  
Fax: 00 39 10 3776590

Professor Karl Welte  
Kinderklinik  
Medizinische Hochschule  
Konstanty Gutschow Str 8  
30623 Hannover, Germany  
Tel: 00 49 511 532 9020  
Fax: 00 49 511 532 9120

Contacts

Audrey Anna Bolyard, RN, BS  
Clinical Manager  
Tammy Cottle  
Data Manager  
University of Washington  
SCNIR Puget Sound Plaza  
1325 4th Ave. Suite 620  
Seattle WA 98101-2509  
Phone: 1-800-726-4463 or 206-543-9749  
Fax: 206-543-3668

Thomas Weiberlenn, MD  
Clinical Manager  
Kristine Crusius  
Data Manager  
Cornelia Zeldier, MD  
Medical Consultant  
SCNIR  
The Medical Park  
Feodor-Lynen-Str.27  
30625 Hannover, Germany  
Phone: 011-49-511-546-0918  
Fax: 011-49-511-546-0919