

SEVERE NEUTROPENIA INTERNATIONAL REGISTRY PROTOCOL

Introduction

The Severe Chronic Neutropenia International Registry (the Registry, SCNIR) is an organization dedicated to improving understanding and treatment for diseases causing severe chronic neutropenia, i.e. conditions with blood neutrophil levels less than $0.5 \times 10^9/L$ for months or years. These diseases include various forms of congenital neutropenia, cyclic neutropenia and idiopathic neutropenia. The Registry was initiated under sponsorship from Amgen, Thousand Oaks, CA, in 1994 to monitor the clinical course and long-term treatment of patients with severe chronic neutropenia (SCN) after controlled clinical trials demonstrated the effectiveness of granulocyte colony-stimulating factor (G-CSF) for the treatment of these conditions. In July of 2000, the Amgen Foundation became the principal sponsor of the Registry, with additional support from private and governmental sources. The Registry is based in the School of Medicine, University of Washington, Seattle, WA, USA, with principal data coordinating centers in Seattle, WA, USA and Hannover, Germany.

Objectives

The original objectives were to document the clinical course of severe chronic neutropenia and develop a database on the safety and efficacy of long-term treatment with G-CSF and other therapies. Additional goals were to establish a physician network to increase the understanding of SCN.

Over the last nine years, the Registry has successfully developed its database on efficacy and safety of treatment of SCN, and its resources have been extremely valuable for defining the genetic, molecular and cellular basis for cyclic and congenital neutropenia. The current objectives of the Registry are:

1. Document the clinical course of SCN patients and their responses to therapy.
2. Determine the incidence and outcome of various clinical events associated with SCN and its treatment including: a. osteoporosis; b. vasculitis; c. glomerulonephritis; d. splenomegaly/hepatomegaly; e. cytogenetic abnormalities; f. myelodysplastic syndrome; g. leukemia.
3. Evaluate the outcome for pregnancies in SCN patients, including patients receiving various therapies for their neutropenia.
4. Evaluate the effectiveness of hematopoietic transplantation as a treatment for SCN.
5. Serve as a comprehensive information resource for the education of physicians, patients and families interested in SCN.

As of May 2003, there are approximately 1300 patients enrolled in the Registry, including patients in the French Severe Chronic Neutropenia Registry. The goal of the Registry is to include information on 2400 patients by December 31, 2008. Continued enrollment is important to increase the diversity of enrollees, particularly patients with uncommon inherited conditions associated with SCN. In addition, continued enrollment is important for studies on etiology and pathogenesis of SCN and the evolution of some patients to leukemia.

Patient Eligibility

Inclusion criteria – Patients are eligible for enrollment if they meet the following criteria:

1. A confirmed diagnosis of severe chronic neutropenia based on documented absolute neutrophil counts of less than $0.5 \times 10^9/L$ on at least three occasions in the three months prior to enrollment.
2. For patients with presumed cyclic neutropenia, documentation of at least two neutrophil cycles is preferred. Documentation should include the nadirs with neutrophil counts of less than 200 followed by a clear increase in the counts generally to at least 500 to 1000 followed by a second nadir, usually expected to occur at about three weeks after the first nadir, i.e., cycling with a three week periodicity. Documentation with at least six weeks of counts and two expected nadirs is preferred. Cases not showing clear oscillations will be categorized as congenital (if neutropenia or neutropenic complications appear to have occurred from birth) or idiopathic (if all symptoms in evidence points to an acquired disorder occurring after the first year of life).
3. Bone marrow aspiration consistent with the diagnosis of congenital, cyclic or idiopathic neutropenia. In all of these conditions, it is expected that the marrow aspirate evaluation at the time of neutropenia will show a deficiency of mature neutrophils. An exception is myelokathexis, a condition with large accumulations of neutrophils with pycnotic nuclei in the marrow. Bone marrow aspirates may show some dyspoiesis of the neutrophil lineage, but abnormalities of erythropoiesis or platelet formation are, in general, inconsistent with the diagnosis of SCN.
4. Normal cytogenetic evaluation. The only exception being cases of well documented severe congenital neutropenia with preferably previously documented normal cytogenetic evaluation will now be enrolled in the Registry at the time of evolution to leukemia.
5. History of recurrent infections (i.e. severe mouth ulcers, gingivitis and sinusitis).
6. Age greater than three months.
7. Independent of hematological parameters, patients with the following diagnoses may be included: Shwachman-Diamond syndrome (SDS), glycogen storage disease type Ib (GSD1b), Barth syndrome.
8. Patients with moderately severe chronic neutropenia (i.e., ANC less than $1.0 \times 10^9/L$) and recurrent severe infections (i.e., deep tissue infections of subcutaneous areas, lungs, liver, etc.).
9. Immune neutropenia with positive anti-neutrophil antibodies meeting criteria in 1, 3, 5 and 6.
10. All SCN patients previously enrolled in Amgen-sponsored SCN studies.

Exclusion Criteria

1. Neutropenia known to be drug induced.
2. Primary myelodysplasia
3. Primary leukemia
4. Aplastic anemia
5. Known HIV disease
6. Systemic autoimmune diseases such as rheumatoid arthritis or systemic lupus, erythematosus
7. Chemotherapy-induced neutropenia (within the last 5 years)

Diagnostic Evaluation and Enrollment Procedures

Enrollment will occur through referrals to expert hematologists who are members of the Severe Chronic Neutropenia International Registry (SCNIR) or, in Europe, through members of the SCNIR Liaison Physician Group, all of whom are specialists in the diagnosis and treatment of severe chronic neutropenia.

Enrollment Procedures

For patient enrollment, the patient's physician usually contacts the Registry office or one of the physicians on the Registry Advisory Board or in Europe, the appropriate member of the Liaison Physician Group in their home country. When patients contact the Registry, they are asked to provide their physician's name and contact information. The registration is conducted through the physician's office. To enroll a patient requires completing a set of patient registration forms (enrollment forms are attached). A consent form is also sent with the registration forms and must be completed for the patient to become enrolled in the Registry.

The registration form requires: the name, telephone / fax numbers and address of the referring physician, the signed consent (or documentation of signed consent), the name, demographic information, diagnoses for the patient, information on the significant clinical history of infections and other medical problems (i.e. splenomegaly, hepatomegaly), information on growth and development, information on the treatment history for the patient, including growth factor cytokine treatment, information on bone marrow and cytogenetic evaluations and bone density assessment, and records of the patient's blood counts and other hematological tests. A clinical summary of the patient's problems with neutropenia may also be included. In addition, information is requested regarding neutropenia, leukemia, other blood disorders for immediate family members and relatives and whether the individuals listed are living or deceased.

Enrollment forms are reviewed by the expert physician associated with the Registry. If further information is needed the information will be requested from the enrolling physician. After enrollment, the enrolling physician is notified and receives an annual follow-up form requesting information regarding the health status of the patient (follow-up form attached). Physicians are encouraged to communicate about serious health events occurring between annual follow-ups and may consult with experts from the Registry about diagnosis and treatment options. This may involve requests for additional clinical information regarding patients with a specific cause for their neutropenia, i.e., glycogen storage disease, Barth syndrome, or a complication of their disease, such as glomerulonephritis, vasculitis, osteoporosis, myelodysplasia or leukemia. Further information may also be requested for patients undergoing hematopoietic transplantation. Patients enrolled in the Registry may be invited to participate in other protocols for the study of patients with neutropenia. The diagnosis assigned at the time of enrollment is the responsibility of the SCNIR expert physician associated with the Registry, rather than the enrolling physician. IRB approval at participating sites may also be required.

Bone Marrow Slides

With each new registration, the Registry requests at least one bone marrow slide preferentially from the diagnostic bone marrow aspirate or any other bone marrow sample prior to the onset of any G-CSF therapy. These slides are utilized to confirm the diagnosis of SCN.