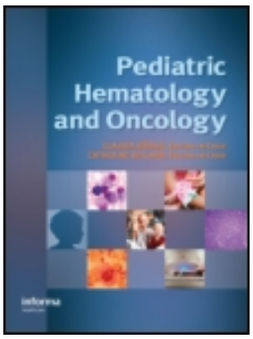

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**Letter to the Editor**

# OFF-LABEL USE OF GRANULOCYTE COLONY-STIMULATING FACTOR IN NONCONGENITAL NEUTROPENIA: Retrospective Data from the Italian Neutropenia Registry

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Whilethe use of G-CSF (granulocyte colony-stimulating factor) is based on solid evidence in severe congenital neutropenia, few data are available to sustain the off-label use of G-CSF in "acquired neutropenias" [1–4]. In this respect the experience of the Italian Neutropenia Registry (INR) may be contributory. Between December 2003 and December 2005, 30 patients affected by autoimmune neutropenia were registered. Diagnosis of autoimmune neutropenia was defined by detection of three consecutive values of neutrophils under $0.5 \times 10^9$/L (or $<1 \times 10^9$/L with severe infections) on

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at least 3 occasions within 6 months and detection of granulocyte-specific antibodies in serum (at least 1 test out of 4). Among these patients, those who needed treatment with G-CSF for at least 3 months for severe and/or recurrent infections unable to be cured only with antibiotic therapy at an age older than 6 months were selected for the analysis [5].

Quantitative changes (modification of infection rate [IR], defined as number of infection episodes during a given period of time) and qualitative modifications (type and site of the acute infections) before and after G-CSF supplementation were recorded (Table 1). A qualitative improvement of infections pattern was judged according to criteria derived by the current medical knowledge (e.g., skin and/or breast abscesses worse than upper respiratory tract infections, pneumonia and bronchitis worse than fever of unknown origin).

Ten patients affected by autoimmune neutropenia were treated with G-CSF at a median age of 2 years (0.5–12 years). Five out of 10 patients received 5 $\mu$g/kg/day on a continuative schedule, whereas in the remaining 5 the treatment was tailored to maintain neutrophils above $1 \times 10^9$/L or to lower the incidence of infections. The median duration of G-CSF therapy was 4.5 months (3–108 months).

The median absolute neutrophil count derived from all patients before G-CSF was $255 \times 10^9$/L and rose to $1484 \times 10^9$/L during G-CSF. In all patients but one (2), G-CSF treatment was effective since it caused either an quantitative or qualitative improvement of the infection pattern. An overall quantitative improvement was shown in 9 patients (1 and 3–10). This improvement was marginal in two patients (5 and 9) and relevant in another two (8 and 10) in whom previous infections were eradicated. Patient 1, whose IR declined throughout G-CSF treatment, was considered to have a worsened qualitative pattern of infections).

Six patients out of the 9 (4, 5, 7, 8, 9, 10) showed both a quantitative and qualitative improvement. In 7 patients, including the one whose IR apparently did not improve (2), G-CSF treatment had been stopped and no further administrations were necessary. Three subjects needed longer treatment because of the recurrence of infections.

No major acute clinical side effects were observed. Among the patients who received longest G-CSF supplementation, bone density was evaluated and subject 1 showed a reduced bone mineral density (osteopenia).

This retrospective study on a small group of patients with acquired severe neutropenia shows that G-CSF treatment, even for short courses, may reduce morbidity and improve quality of life, without important side effects. Further study is needed to confirm our data and to analyze the cost/efficacy.

**TABLE 1** Characteristics of the Cohort

| Case number | Sex | Age at diagnosis[a] (mo) | Age at start G-CSF (mo) | Dose of G-CSF ($\mu$g/kg) | G-CSF duration (mo) | Length of FUP (mo) | Continuous G-CSF | Median PMN before G-CSF | Median PMN during G-CSF | Number of infections/ months before G-CSF (IR) | Number of infections/ months during G-CSF (IR) | Infections before G-CSF | Infections during G-CSF |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 60 | 108 | 5/day | 108 | 126 | Yes | 204 | 1148 | 10/12 (0.83) | 24/108 (0.22) | Skin abscesses<br>RAS<br>Otitis | Skin furuncles<br>RAS<br>Periorbitarial cell<br>Bronchitis Purulent adenitis |
| 2 | F | 30 | 36 | 5/day | 3 | 19 | Yes | 198 | 420 | 13/10 (1.3) | 4/3 (1.33) | URTI<br>Skin furuncles<br>RAS | FUO<br>Skin furuncles<br>RAS |
| 3 | F | 14 | 14 | 5/day | 33 | 43 | Yes | 444 | 752 | 4/4 (0.83) | 15/33 (0.45) | Pneumonia<br>Bronchitis | FUO<br>Otitis |
| 4 | M | 3 | 6 | 5/5 days | 22 | 36 | Yes | 415 | 1820 | 3/6 (0.5) | 5/22 (0.22) | Skin abscesses | URTI |
| 5 | F | 36 | 60 | 7.5/day | 3 | 21 | Yes | 380 | 2840 | 5/12 (0.41) | 1/3 (0.33) | Gingivitis<br>URTI | URTI |
| 6 | F | 12 | 13 | 10 every other day | 3 | 11 | No | 250 | 520 | 2/2 (1.0) | 2/3 (0.66) | URTI<br>Impetigo | Vulvovaginitis<br>Vulvar furuncles |
| 7 | F | 30 | 18 | 5/d | 3 | 12 | No | 180 | 6360 | 4/3 (1.33) | 1/3 (0.33) | Otitis<br>Skin abscesses<br>Breast abscess | URTI |
| 8 | M | 144 | 144 | 7.every other day | 6 | 18 | Yes | 480 | 1876 | 5/6 (0.83) | 0/6 (0.00) | Gingivitis<br>Otitis<br>URTI | Eradication of the infections |
| 9 | M | 3 | 6 | 3.5 every other day | 7 | 18 | Yes | 260 | 2500 | 6/5 (1.2) | 6/7 (0.85) | FUO<br>Otitis<br>Bronchitis<br>Pneumonia | FUO<br>Bronchiolitis |
| 10 | M | 8 | 12 | 5 every other day | 3 | 11 | Yes | 210 | 720 | 2/2 (1.00) | 0/3 (0.00) | Anal abscess<br>Scrotum cellulitis and suppurative lymphadenitis | Eradication of the infections |

[a]Age at diagnosis the time of diagnosis is the first detection of indirect antibody test against neutrophils.

*Note*. IR, infectious rate defined as number of infections/number of months; RAS, recurrent aphthous stomatitis; URTI, upper respiratory tract infections; FUO, fever of unknown origin.

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