Use of Filgrastim (r-metHuG-CSF) in Human Immunodeficiency Virus Infection

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1 Introduction

In 2008, an estimated 33.4 million individuals worldwide were infected with the human immunodeficiency virus (HIV) [1]. Only a few years ago, infection with HIV almost invariably culminated in the development of the acquired immunodeficiency syndrome (AIDS), characterized by severe depletion of $CD4^+$ lymphocytes leading to derangements predominantly affecting cell-mediated immunity, but affecting humoral immunity as well [2]. In the later stages of AIDS, neutropenia and neutrophil functional deficits were common sequelae of HIV infection, other opportunistic infections, or HIV- or opportunistic infection-related treatment [3]. The care of the HIV-infected patient was palliative in nature, and the possibility that use of filgrastim (rHuG-CSF) might extend survival in late-stage AIDS patients with severe neutropenia or severe opportunistic infections, or might be a treatment for HIV infection itself, was explored [4]. Subsequently, however, the development of protease inhibitors and the widespread adoption of their use in multidrug regimens of highly active antiretroviral therapy (HAART) revolutionized the care of HIV-infected patients, and the number of patients dying from HIV decreased dramatically [5]. Patients with HIV can, with current regimens, achieve prolonged survival with preservation of immunologic function, although patients infected with HIV have shortened lifespans compared with uninfected people [6] secondary to

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comorbid conditions and increased rates of cardiovascular [7] and oncologic death [8]. However, despite the widespread availability of HAART in the developed world, patients still present with late-stage AIDS and its attendant complications, including neutropenia, because of late diagnosis of HIV [9] or progression of HIV infection due to nonadherence to HAART [10]. Furthermore, patients with HIV face an increased risk of malignancy and the subsequent need to be treated with cytotoxic chemotherapy [11]. Accordingly, filgrastim has continued to play a role in the management of selected patients with HIV.

2 Epidemiology of Neutropenia in HIV-Infected Individuals

From the earliest days of the AIDS pandemic, neutropenia was identified as a consequence of HIV infection. In 1987, an absolute neutrophil count (ANC) of $<2.0 \times 10^9$/L was reported in 4 of 20 patients with clinically diagnosed AIDS and 15 of 59 with persistent generalized lymphadenopathy [12]. As this report predates the development of antibody testing for HIV, it was not possible to determine whether patients with persistent generalized lymphadenopathy were truly HIV-infected or not. No patient had an ANC $<1.0 \times 10^9$/L in this report, although the same author had noted an ANC of 0.4×10^9/L in one patient in a case series of homosexual men with neutropenia in 1985 [13].

Neutropenia is primarily a consequence of late-stage AIDS, with the mean $CD4^+$ lymphocyte count during the first episode of neutropenia in one large study being 85 cells/mm^3. However, 14% of patients with a neutropenic episode in this study were observed to have a $CD4^+$ lymphocyte count >200 cells/mm^3, and one patient's $CD4^+$ lymphocyte count at the time of neutropenia was 858 cells/mm^3 [14]. It is worth noting that several case reports have associated neutropenia with acute HIV infection [15–18]. Since most instances of acute HIV infection are unrecognized [19], the true incidence of neutropenia associated with acute HIV infection remains unknown.

The epidemiology of neutropenia was examined in the Women's Interagency HIV Study, a prospective cohort study of 2,059 HIV-infected women enrolled in 1994 and 1995. In this cohort, 1,729 women had a documented ANC measured. It was observed that 7% of women were neutropenic at enrollment, which reflected the prevalence of neutropenia in the pre-HAART era, and that 31% of the study cohort experienced at least one episode of neutropenia (defined as a measured ANC $<1.0 \times 10^9$/L) during the study. Low $CD4^+$ lymphocyte count and high viral load, suggestive of progression of disease, were associated with the development of neutropenia [20].

Neutropenia is often multifactorial in AIDS patients, with HIV itself, myelosuppressive drugs, opportunistic infections, and malignancy most frequently identified as the etiology. Although zidovudine is the most common antiretroviral associated with neutropenia, other nucleoside reverse transcriptase inhibitors have been implicated in drug-induced neutropenia as well [21]. Indinavir-induced neutropenia has been reported [22], as has neutropenia exacerbated by efavirenz [23].

Noteworthy also are case reports of patients receiving chemotherapy concomitantly with antiretroviral regimens containing ritonavir, a potent inhibitor of the CYP450 system, and subsequently developing neutropenia due to increased concentrations of chemotherapeutic agents [24–26]. Other prophylactic agents including dapsone [27], antifungals, and beta-lactam antibiotics [28] have also been reported to cause neutropenia. Disseminated infections with bone marrow involvement caused by fungal (e.g., endemic mycoses, cryptococcosis) [29], mycobacterial (e.g., tuberculosis or *Mycobacterium avium* complex), protozoal (e.g., leishmaniasis), or viral (e.g., cytomegaloviral) pathogens have been identified as contributors to HIV-associated neutropenia [30]. Finally, infiltration of bone marrow with lymphoma is not infrequently a cause of HIV-associated neutropenia [31], and this possibility should be considered before ascribing neutropenia to medications alone.

The proportion of neutropenic episodes attributable to each of the above causes depends on the patient population. In one Italian study including 81 neutropenic patients in the pre-HAART era, most of whom were intravenous drug users, neutropenia was attributed to HIV itself in 18.5% of the patients, to infiltration of bone marrow with lymphoma or infection in 24.6% of patients, and drugs in 56.7%. Of patients with drug-induced neutropenia, zidovudine was a contributor to 48.2% of cases, chemotherapy to 21.3% of cases, trimethoprim-sulfamethoxazole to 18.7%, amphotericin B to 17.5%, ganciclovir to 13.6%, pyrimethamine to 11.1%, and dapsone to 6.4% of cases [32]. In a different study, zidovudine therapy was a contributing factor to neutropenia in 51% of patients, trimethoprim–sulphamethoxazole treatment in 45% of patients, ganciclovir therapy in 18% of patients, and cytotoxic chemotherapy in 11.3% of patients; neutropenia was attributed to lymphoma in 6.5% of cases and HIV infection itself in 1.6% of patients [31].

The epidemiology of neutropenia in HIV patients has drastically changed with the advent of HAART. HAART prevents progression of HIV, and was found to prevent the development of neutropenia in the Women's Interagency HIV study cohort [20]. Furthermore, HAART itself is an effective long-term treatment for HIV-associated neutropenia [33, 34]. In addition, the decreased dose of zidovudine employed as part of HAART regimens may be less likely to cause neutropenia than the higher dose used in the pre-HAART era. One study where patients were routinely converted from stavudine to zidovudine after 6 months of HAART therapy reported that only 7.7% of patients developed an ANC $<0.75 \times 10^9$/L [33], and a similar conversion study of 78 HIV-infected children reported that only 6% developed an ANC $<1.0 \times 10^9$/L. In the latter study, no individual's ANC decreased to $<0.75 \times 10^9$/L [34].

3 Impaired Neutrophil Function in HIV Infection

In addition to neutropenia, there are functional defects of neutrophils, as well as monocytes and macrophages, in HIV infection and other lentivirus infections. These defects are not unique to HIV infection, and a number of viral infections

have been associated with impaired neutrophil function [35]. A wide range of functional defects exist, including defects in chemotaxis, phagocytosis, the respiratory (oxidative) burst, and microbicidal capacity [36–41]. Neutrophils isolated from HIV-infected patients have a profound defect in chemotaxis in response to interleukin (IL)-8 and bacterial chemoattractant peptides, such as f-met-leu-phe (fMLP), and the degree of impairment correlates with the degree of $CD4^+$ T-cell depletion. Other physiologic functions related to recruitment to sites of infection, rolling, adhesion, and emigration are also affected, as shown in a feline leukemia virus (FIV) infection model. Evidence that this may be due to a maturation defect is decreased granularity of neutrophils from the blood and bone marrow of FIV-infected animals. The results of different studies of neutrophil function in HIV infection are at times conflicting and can be explained by different assays, different conditions, and differences in the patient populations studied. The most important clinical variable is the stage of HIV disease as evidenced by absolute $CD4^+$ T-cell count.

The respiratory burst is a very important part of the microbial killing by neutrophils, generating superoxide and other bactericidal reactive oxygen species. Our group previously examined the neutrophil respiratory burst by chemiluminescence in a cohort of 78 patients with HIV infection at different stages of disease [42]. Patients with HIV infection had altered oxidative metabolism in response to opsonin receptor-dependent stimulation with zymosan opsonized with purified human complement (C3bi) or immune globulin (IgG). Patients with early HIV infection with $CD4^+$ lymphocyte counts >500 cells/mm^3 exhibited increased neutrophil chemiluminescence in response to opsonized zymosan compared with controls, while patients with advanced disease with low $CD4^+$ lymphocyte counts showed significantly decreased chemiluminescence. Absolute $CD4^+$ lymphocyte count was the only patient variable significantly correlated with opsonin-dependent neutrophil chemiluminscence activity according to multiple regression analysis. Despite a good correlation between ANC and $CD4^+$ lymphocyte count ($R = 0.24$; $p = 0.04$), ANC was not an independent predictor of impaired neutrophil chemiluminescence by multiple regression analysis.

4 Pathogenesis of Neutropenia and Neutrophil Dysfunction

The pathophysiology of neutropenia and neutrophil dysfunction in HIV infection unrelated to drug therapy or secondary complications has been better elucidated in the past few years. A subset of neutropenic HIV-infected patients may have autoimmune neutropenia; however, this probably accounts for a small proportion of cases of neutropenia [13, 43]. A study of neutropenic children with HIV infection showed that while many children had circulating antineutrophil antibodies, the presence of these antibodies did not correlate with the ANC [44].

The various immune abnormalities observed in HIV infection occur in the setting of immune systemic activation. There has been considerable interest in

immune system activation occurring as a result of T-cell depletion in gut-associated lymphoid tissue (GALT) with loss of mucosal barrier function, which results in translocation of lipopolysaccharide (LPS) and other bacterial products that activate the immune system [45]. A number of investigators have shown that neutrophils are activated in vivo throughout the course of HIV infection, even in the absence of any clinical signs of secondary infectious complications [46]. Early in the course of HIV infection in vivo, activation or priming may actually result in enhanced function. This in vivo activation continues throughout the course of HIV infection, but eventually the functional capacity of the neutrophil begins to decrease significantly. It should also be noted that immune system activation has been proposed as a mechanism for impaired neutrophil function in patients with chronic hepatitis B infection [47].

Our studies of neutrophil chemiluminescence suggest that immune system activation may contribute to neutrophil dysfunction [42]. Maximum opsonin receptor expression (MOR) is achieved by exposing neutrophil to quantities of proinflammatory mediators (primers: fMLP, complement fragment C5a, and platelet-activating factor) to induce a maximal number of CD11b (C3bi receptor) and CD35 (C3b receptor or complement receptor 1) on the neutrophil surface. Priming may also enhance oxidative responses to a second stimulus by increasing the affinity of opsonin receptors for their particular ligand or enhancing intracellular signaling. Our experiments showed increases in the ratio of the chemiluminescence unprimed neutrophil at circulating opsonin receptor expression (COR) to chemiluminescence with MOR, i.e., an increased COR/MOR ratio. By whatever mechanism, neutrophils from HIV-infected patients behave as if they have been primed or activated by proinflammatory mediators in vivo. Opsonin receptor-independent NADPH-oxidase and myeloperoxidase activities, basal and stimulated, were significantly increased for HIV-infected patients, especially those with advanced disease with $CD4^+$ lymphocyte count <200 cells/mm^3. The increase in enzyme activities of NADPH-oxidase and myeloperoxidase may also be the result of in vivo activation. The decrease in myeloperoxidase activity for patients with very advanced HIV infection with $CD4^+$ lymphocyte count <100 cells/mm^3, although significantly higher than values seen in control subjects without HIV infection, may be due to degranulation resulting from in vivo activation. This chronic in vivo activation may lead to metabolic exhaustion or "burnout," and contributes to impaired neutrophil oxidative responses in HIV-infected patients at advanced stages of disease.

In vivo activation is not the only process that contributes to neutrophil dysfunction in HIV infection. Neutrophils isolated from patients with advanced HIV disease undergo accelerated apoptosis or programmed cell death. We studied apoptosis of neutrophils isolated from ten individuals with advanced HIV infection and seven control subjects [48]. Ex vivo apoptosis was examined morphologically by fluorescent microscopy after dual staining with acridine orange and ethidium bromide, fluorescent stains that intercalate DNA. Acridine orange stains the nucleus bright green and allows visualization of the nuclear chromatin pattern, while ethidium bromide identifies nonviable cells by staining the nucleus orange. Little apoptosis was evident immediately after isolation, but over time, apoptosis was observed and

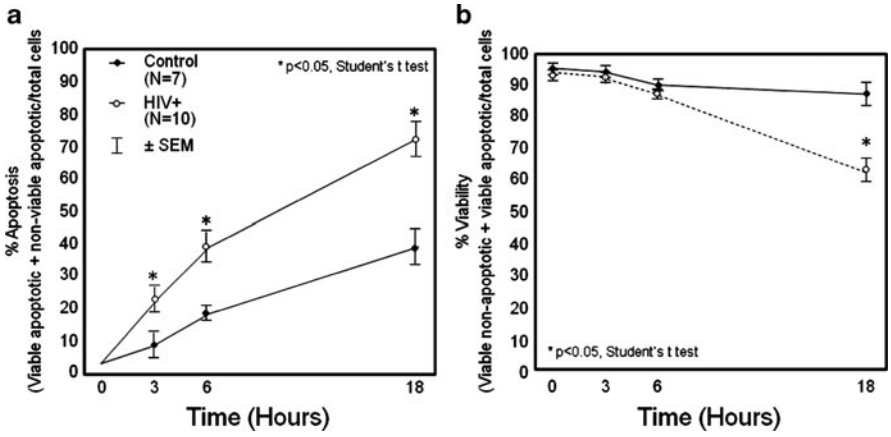

Fig. 1 Neutrophil apoptosis and viability in patients with AIDS compared with normal controls

the proportion of apoptotic cells was significantly higher for the patients with advanced HIV infection at 3, 6, and 18 h (Fig. 1). Apoptotic cells eventually die, and at 18 h there was a significant decrease in viability for the HIV patient's neutrophils due to an increased number of nonviable, apoptotic cells. As neutrophils become apoptotic, they become functionally impaired, and the accelerated apoptosis of neutrophils may in part explain the impairment of neutrophil function seen in this patient population, as well as neutropenia. A number of possible mechanisms for accelerated apoptosis exist, including increased levels of proinflammatory mediators that may accelerate the process. Other mechanisms may also be involved, including direct effects of viral proteins. HIV protease can directly induce apoptosis of a variety of leukocyte populations [49]. Alternatively, growth factor deficiency could result in accelerated apoptosis.

Granulocyte precursors can be infected by HIV, and this may affect normal proliferation and development of neutrophils, but mature cells are not targets and express very little, if any, HIV [50]. Infection of bone marrow stromal cells may affect the microenvironment for myelopoiesis. Both HIV and cytomegalovirus (CMV) can infect bone marrow stromal cells and impair production of endogenous colony-stimulating factors such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) [51, 52]. Altered cytokine secretion may result in abnormal neutrophil maturation. G-CSF is a key growth factor important in maintaining the normal number of circulating neutrophils. Although several growth factors can stimulate myelopoiesis, studies of G-CSF-deficient knock-out mice indicate G-CSF is a cytokine necessary to maintain normal neutrophil counts [53]. Evidence is accumulating that HIV infection results in a state of endogenous G-CSF deficiency [54, 55]. Patients with HIV have lower serum levels of endogenous G-CSF for a given degree of neutropenia compared with patients with neutropenia from other etiologies, such as aplastic anemia and cancer chemotherapy. The low levels of G-CSF may not only impair myelopoiesis and

affect neutrophil maturation, but also reduce the circulating half-life of neutrophils. The principle way growth factors cause clonal expansion of different bone marrow precursors is by inhibiting apoptosis of these cells [56]. Our data show that accelerated neutrophil apoptosis in HIV infection is reversible in vitro and ex vivo in patients receiving filgrastim [48, 57].

Why should a decrease in growth factor(s) required for neutrophil maturation occur in a disease characterized by abnormal cell-mediated immunity? The source of G-CSF, directly or indirectly, is activated T-cells, monocytes, and macrophages, all targets for HIV infection. Depletion or dysfunction of these cells as a result of HIV infection may result in decreased production of G-CSF that is required to support normal granulopoiesis and/or neutrophilic responses to infection. We previously reported that peripheral blood mononuclear cells (PBMC) isolated from patients with AIDS produce significantly less G-CSF in response to a challenge with LPS [54]. Local G-CSF production by bone marrow stromal cells is likely to be very important in granulopoiesis, and there is a decreased G-CSF response by bone marrow stromal cells from patients with HIV infection ex vivo in response to IL-1 and LPS [51].

More is known about how $CD4^+$ T-helper cells recruit and activate a wide variety of cell types, including macrophages, mast cells, neutrophils, eosinophils, and basophils, in addition to adaptive immune effector cells. Several different types of $CD4^+$ T-cells have been described that differentiate from naïve $CD4^+$ T-cells [55]. In addition to Th1 and Th2 cells, we now recognize regulatory T-cells (Treg) [58]. These cells not only are involved in immunosuppression, but also can differentiate into effector T-cells. More has also been discovered about the interactions between phagocytic cells and T-cells. The Th17 pathway has been characterized [59]. Th17 cells have been classified as a new lineage, distinct from Th1, Th2, and Treg cells. T17 cells develop as a result of a unique set of cytokines secreted by effector cells of the innate immune system (e.g., neutrophils) and additive effects of IL-1β and tumor-necrosis factor (TNF)-α. Transforming growth factor (TGF)-β and IL-6 are crucial factors in the generation of Th17 cells from naive T-cells. The functional capacity of Th17 cells depends on the additional cytokines IL-23 and IL-1.

Th17 cells are characterized by production of the proinflammatory cytokines IL-17A, IL-17F, IL-22, and IL-26. The activity of IL-17A and IL-17F is defined by induction of increased production of a number of proinflammatory mediators, including IL-1, IL-6, CXC chemokines, TNF-α, G-CSF, and GM-CSF by epithelial and endothelial cells, macrophages, and other stromal cells. IL-17A also promotes stem-cell factor (SCF)- and G-CSF-mediated granulopoiesis [60]. It has been controversial as to whether or not neutrophils directly respond to IL-17A or IL-17F, but the downstream production of cytokines induced by IL-17A and IL-17F leads to granulopoiesis, neutrophil recruitment, and neutrophil activation. Substantial evidence exists of cross-talk between neutrophils and Th17 $CD4^+$ T-cells [61]. Purified human neutrophils produce chemokines that attract Th1 and Th17 cells, while Th17 cells produce CXCL8, a potent chemoattractant for neutrophils.

Th17 cells are important in host defense against infections caused by both intracellular pathogens, such as listeriosis, salmonellosis, cryptococcosis, leishmaniasis, and

tularemia, and a variety of extracellular bacterial and fungal pathogens. The role of Th17 cells in specific infections is not completely understood and, in some infections such as invasive aspergillosis, the data are conflicting. It appears, however, that Th17 cells are very important for mucosal host defense against oral candidiasis, mainly through the recruitment of neutrophils, and may also be important in disseminated disease [62]. Th17 cells are also involved in the response to *Staphylococcus aureus* infection [63].

Th17 cells express CD4, so it is not surprising that dysfunction and depletion of Th17 cells occur in HIV infection. Th17 cells are efficiently infected by HIV-1 in vitro [64], which may help explain the broad range of bacterial and fungal pathogens, particularly extracellular pathogens, that infect patients with HIV. CD4+IL-17+ populations are greatly reduced in antiretroviral-naive HIV-infected patients compared to HIV-negative controls, but this subset is greatly increased after the initiation of HAART, while IFN-α T-cells (Th1) are unchanged [65]. Depletion of Th17 cells in the gut has been associated with decreased microbial barrier function of the gut and persistent immune activation due to gut translocation [66]. Other studies have even shown a decrease in TH17 cells and the Th17:Th1 ratio with preferential depletion of Th17 cells from GALT within weeks of simian immunodeficiency virus (SIV) infection in macaques [67].

The cross-talk between Th17 cells and neutrophils and other phagocytic cells of the innate immune system may explain previous observations that rHuG-CSF may be of potential benefit for immune reconstitution in HIV infection. Previously, our group was part of a study that demonstrated that rHuG-CSF can restore IL-2 production in the blood of HIV-infected individuals [68]. At that time, it was unknown how rHuG-CSF affected T-cell function or production of a lymphocyte growth factor. In retrospect, neutrophil activation may lead to IL-6 release, subsequent Th17 differentiation, and IL-17 production. An inverse relationship exists between Treg and Th17 cells, so an increase in Th17-inducing cytokines may lead to a decrease in Tregs that mediate immunosuppression. Furthermore, T-cells are not only the source but also the target of IL-17. IL-17 can modulate Th1 cell polarization both in vitro and in vivo by directly acting on $CD4^+$ T-cells [69]. Overall, however, the effects of rHuG-CSF on $CD4^+$ lymphocyte counts have been variable [70, 71].

5 Risk of Infections in HIV-Induced Neutropenia

Initial reports in the pre-HAART era suggested that the risk of infection in patients with HIV-associated neutropenia was less than the risk of infection in patients with neutropenia due to chemotherapy or hematologic malignancy, a fact attributed to, among other factors, the lack of mucosal injury in neutropenia not due to cytotoxic chemotherapy and the relatively mild nature of HIV-associated neutropenia compared to neutropenia associated with hematologic malignancy or cytotoxic chemotherapy. Farber et al., in one of the first studies to examine the risk of infection,

retrospectively examined the records of 30 HIV-infected patients with ANC $<1.0 \times 10^9$/L and $CD4^+$ lymphocyte count <200 cells/mm^3, comparing infection rates during neutropenic periods and non-neutropenic periods and comparing infection rates in these patients with 37 patients with hematologic malignancies as controls. In that study, no difference was found between infection rates in HIV patients during neutropenic periods compared with non-neutropenic periods [72]. Piliero et al., in reviewing blood culture data from 38 HIV-infected patients with ANC $<0.5 \times 10^9$/L and 1,071 non-neutropenic HIV patients, found that the presence of a central venous catheter, but not neutropenia, was a risk factor for positive blood cultures in a multiple logistic regression model [73].

A number of subsequent studies, however, have suggested that HIV-associated neutropenia is associated with an increased risk of infection. Shaunik and Bartlett, in an era when zidovudine monotherapy dosed at 1,200 mg/day was the standard of care for HIV treatment (compared with the dose of 600 mg/day used in current HAART regimens), found in a study of 30 patients that an ANC $<0.5 \times 10^9$/L was associated with an incidence of bacterial infection that was 600% higher than the incidence observed when ANC was $>1.0 \times 10^9$/L [74]. Keizer et al. performed a case–control study comparing 29 HIV-infected patients followed from 1991 to 1993 with two consecutive measured ANC $<1.0 \times 10^9$/L with 29 HIV-infected controls without history of neutropenia matched for age, sex, $CD4^+$ lymphocyte count, and month of entry into the clinic. An incidence of 12.6 episodes of bacteremia per 100 patient-months was observed in the patients with a history of neutropenia compared with an incidence of 0.87 episodes of bacteremia per 100 patient-months observed in the controls, a statistically significant difference ($p = 0.0027$). In a multiple logistic regression model, neutropenia (OR = 22.7) and the presence of a central venous catheter (OR = 8.5) were independent predictors of the development of bacteremia [75]. Hambleton et al. compared the outcomes of HIV-infected inpatients who developed neutropenia after treatment with cytotoxic chemotherapy and those who developed neutropenia for other reasons from 1987 to 1990. In their cohort, few patients received filgrastim, and most patients were white men who had sex with men. They found no statistically significant difference in the rates of bacteremia or mortality between the two groups in both bivariate analysis and in multiple logistic regression models [70]. At the same center, but examining a different time period (1992–1993), Jacobsen et al. examined the rates of hospitalization for HIV-infected outpatients stratified by ANC, using ICD-9 codes to evaluate for the presence of infection. A total of 2047 outpatients were analyzed for this study. A progressive and statistically significant increase in the risk of hospitalization was noted as the nadir ANC decreased. The number of days hospitalized per 10,000 days of risk increased from 61 for patients whose ANC was always $>0.5 \times 10^9$/L during the study period to 487 for patients with ANC nadir $<0.3 \times 10^9$/L [71].

Moore et al. performed a case–control study of patients followed from 1990 to 1994; 118 HIV-infected patients with a measured ANC $<1.0 \times 10^9$/L were matched with HIV-infected non-neutropenic controls on the basis of history of intravenous drug use, $CD4^+$ lymphocyte count, enrollment date in the clinic, and

duration of follow-up. A statistically significant association between neutropenia and the development of a bacterial infection was observed. In an adjusted analysis, the relative risk for developing a bacterial infection was 2.33 times higher in patients with an ANC $<1.0 \times 10^9$/L, and 7.92 times higher for patients with an ANC $<0.5 \times 10^9$/L, compared with patients with an ANC $>1.0 \times 10^9$/L; the incidence of bacterial infections was estimated as 3.5–4.5 per 100 patient-months of neutropenia [76].

Eng et al. performed a retrospective cohort study examining the records of patients who received HIV care from 1990 to 1992. Of 930 patients, 85 experienced at least one episode of neutropenia, and of 12 patients with "severe" neutropenia (ANC $<0.3 \times 10^9$/L), 3 experienced gram-negative bacteremia, compared with four episodes of gram-negative bacteremia in 61 patients with less severe neutropenia [77].

Subsequently, Caperna et al. performed a retrospective cohort study examining patients who had at least two ANC measurements between 1991 and 1995. As the degree of neutropenia worsened, increases in the observed incidence of bacteremia with *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* were noted in this cohort of 1,645 patients [78]. A subsequent nested case–control study from the same cohort during the same time interval concluded that, adjusting for $CD4^+$ lymphocyte count, clinical stage of HIV infection, and other confounders, a measured ANC $<0.5 \times 10^9$/L conferred an eightfold increased risk of bacteremia with one of the three aforementioned pathogens [79].

Tumbarello et al. retrospectively examined 9 years of patient records from a single center in Italy, comparing HIV-infected patients with bacteremia with both HIV nonbacteremic and HIV-uninfected bacteremic controls. In a multivariate analysis of HIV-infected patients, most of whom were intravenous drug users, low $CD4^+$ lymphocyte count, presence of a central venous catheter, and ANC $<1.0 \times 10^9$/L (OR 3.05; $p = 0.04$) were independent risk factors for the development of bacteremia [32].

Hermans et al., from a cohort of 1,870 HIV-infected patients seen at a Belgian HIV care center from 1982 to 1993, found 1,403 whose ANC had been measured at least once. From this sample, they identified 484 patients with episodes of neutropenia, defined in this study as a measured ANC $<1.0 \times 10^9$/L. A history of neutropenia was associated with bacteremia or bacterial pneumonia. Subsequently, 177 neutropenic patients from this cohort were compared with 177 non-neutropenic controls matched for initial $CD4^+$ lymphocyte count and duration of follow-up. Although, in unadjusted analysis, neutropenia was associated with increased odds of developing infection (OR 3.29), this association disappeared in a multiple logistic regression model which also included clinical stage of AIDS and hemoglobin concentration [80].

Meynard et al. performed a single-institution prospective study that enrolled 62 HIV-infected patients with a measured ANC $<1.0 \times 10^9$/L. In their study, a higher risk of infection was noted in neutropenic patients with malignancy compared with other neutropenic patients, and logistic regression modeling identified a history of neutropenia, the presence of a central venous catheter, and trough ANC as independent predictors of developing an infection [31].

Moore et al. retrospectively identified 328 HIV-infected individuals at their center in the United Kingdom with an ANC $<1.0 \times 10^9$/L from 1994 to 1995, excluding 78 patients receiving cytotoxic chemotherapy. Bacteremias were documented in 21% of patients and were observed more commonly in patients with brief, profound neutropenias, rather than in patients with milder but more prolonged neutropenic episodes, and the degree of neutropenia correlated with the risk of infection [14]. A subsequent prospective study at the same center enrolled 87 patients in 1996 and 1997. No patients were receiving chemotherapy. Upon enrollment in the study, blood was sampled weekly to measure the duration of neutropenia. Filgrastim was only given for documented infection. The median duration of neutropenia was 13 days. Twelve subjects (17%) were diagnosed with neutropenia-associated infection, in whom six were found to have infection serious enough to warrant filgrastim therapy, and four required hospital admission. All serious infections occurred in patients with ANC $<0.5 \times 10^9$/L. A further four patients received filgrastim due to prolonged neutropenia [81].

Most of the studies on the risk of infection in neutropenia were conducted in the pre-HAART era. Relatively fewer studies have attempted to assess the link between neutropenia and infection after the widespread implementation of HAART. In the Women's Interagency HIV study, which began in the pre-HAART era but extended through the development of HAART, it was observed that, independent of $CD4^+$ lymphocyte count and viral load, which were strong predictors of mortality, the presence or absence of neutropenia was not predictive of mortality [20].

Toure et al., in examining the incidence of neutropenia in a prospective cohort of 533 African patients over 6 years taking trimethoprim–sulfamethoxazole prophylaxis in a setting where HAART was available if indicated, found that 36% of patients had at least one measured ANC $<1.0 \times 10^9$/L during the study, that developing neutropenia was associated with low initial $CD4^+$ lymphocyte count, and that the adjusted hazard ratio of developing bacterial morbidity was 1.50 for patients with a history of neutropenia to that degree, but the overall likelihood of bacterial morbidity was low (36 patients overall) [82].

Most of the preceding discussion has focused on bacterial infections. In patients with hematologic malignancy or in patients undergoing stem cell transplantation, invasive aspergillosis is a feared complication of the prolonged neutropenia that these patients experience [83]. Case reports and case series have noted the occurrence of aspergillosis in patients with advanced HIV [84]; however, aspergillosis as a complication of neutropenia was an uncommon event in HIV-infected patients even before the advent of HAART [85]. Case series suggest that neutropenia or steroid use may predispose to invasive aspergillosis in HIV-infected patients [86, 87]. Mylonakis et al. reviewed 342 reported cases of aspergillosis in HIV-infected patients obtained by MEDLINE and AIDSLINE searches through 1997, and found that 93 patients were diagnosed with "definite" invasive aspergillosis, of whom 16 were reported to have an ANC $<0.5 \times 10^9$/L [88].

6 The Use of Filgrastim in Nonmalignant Conditions in HIV Infection

Since the beginning of the HIV epidemic, several dozen case reports, case series, and clinical trials have described the use of filgrastim and other formulations of rHuG-CSF in HIV-infected individuals without malignancy and have described outcomes (summarized in Table 1). Kimura et al. were the first to publish their experience, reporting on the use of rHuG-CSF in 14 Japanese patients, 11 of whom were neutropenic. The patient cohort primarily consisted of 12 patients with hemophilia, eight of whom demonstrated concurrent infection at the time of enrollment, and two of whom were experiencing fever of unknown origin. Patients were randomly assigned to receive 100 μg/m^2 or 200 μg/m^2 rHuG-CSF daily intravenously. The dose was subsequently titrated to maintain the ANC $>3.0 \times 10^9$/L. A dose-dependent increase in ANC was observed in patients not receiving zidovudine, and escalation of rHuG-CSF dosage prevented the development of neutropenia in patients receiving zidovudine [89].

Miles published the first reports specifically evaluating the benefit of filgrastim in neutropenic patients with HIV. In the first report, 13 patients were selected to receive filgrastim, which was initially dosed at 3 μg/kg daily with subsequent dose escalation until ANC $>6.0 \times 10^9$/L. Once an adequate dose was established, it was maintained for 2 weeks; rHuEPO was subsequently given. Of the 13 patients selected, 1 died and 1 was removed from the study for noncompliance. In the other 11 patients, filgrastim therapy alone was associated with an increase in BFU-E (burst forming unit-erythron) levels, as well as a statistically significant mean hemoglobin increase of 1.04 g/dL [90]. Patients were then given zidovudine, dosed at either 1,000 or 1,500 mg/day. In the full analysis based on 22 recruited patients, 20 of whom were included in the final analysis, growth factors ensured that no patient needed to discontinue zidovudine therapy secondary to neutropenia, although eight patients developed transfusion dependence necessitating cessation of therapy [91].

Bratt et al. were among the first to describe long-term outcomes from rHuG-CSF therapy, noting in their series of 17 patients that appropriate white blood cell counts could be maintained for up to 7 months in patients with initial counts $<1.0 \times 10^9$/L [92]. Several small case series and small pilot studies were published in the ensuing years, but a pair of studies notable due to their size are the retrospective cohort studies reported by Grutzmeier and colleagues in 1996, reflecting treatment experience in the pre-HAART era. In one cohort of gay men with CD4$^+$ lymphocyte counts <50 cells/mm^3 in Sweden, treatment with rHuG-CSF was initiated upon measuring a white blood cell count $<1.0 \times 10^9$/L or ANC $<0.5 \times 10^9$/L. Median survival in the 60 patients who received rHuG-CSF was 658 days, compared with a median survival of 511 days in the 104 patients who did not receive rHuG-CSF ($p < 0.01$). A similar analysis by the same authors performed on data from a similar cohort in Denmark found that the 60 patients who had received rHuG-CSF lived for

Table 1 Summary of published papers

Reference no.	Type of study	No. of patients	Condition(s)	Intervention	Results
[89]	Prospective, uncontrolled	14	Neutropenic or scheduled to receive ZDV. Most pt were hemophiliacs; 8 had other infections	Randomly received 100 or 200 μg/m^2/d G-CSF initially, then titrated to keep ANC >3.0 × 10^9/L	Improvement in neutrophil count, even when pt received ZDV. Improvement in control of other infections
[90]	Prospective, uncontrolled	22	Severe HIV; ANC <2.5 × 10^9/L; Hgb <11.5 g/dL; platelet count >50 × 10^9/L	Myelosuppressive drugs stopped; G-CSF 3 μg/kg/d given and dose escalated until ANC maintained >6.0 × 10^9/L for 2 wk; rHuEPO subsequently given	Correlation between blood forming units (BFU-E) and G-CSF dose ($R = 0.65$; $p = 0.02$). Mean Hgb increase 1.04 ± 0.34 g/dL
[91]	Prospective, uncontrolled	22	ANC <2.5 × 10^9/L; Hg <12 g/dL; platelet >50 × 10^9/L	Myelosuppressive drugs stopped; G-CSF 3.6 μg/kg/d and escalated until ANC >6 × 10^9/L for first 11 pts and 1.5–5.0 × 10^9/L for subsequent 11 pts; maintained for 2 wk; Epoetin alfa subsequently given. ZDV administered and titrated to dose 1,500 mg/d as tolerated	No pt required discontinuation of ZDV for neutropenia, but 6 pts required ZDV discontinuation for transfusion-dependent anemia
[108]	Prospective, uncontrolled	12	CDC stage IV AIDS on ZDV with ANC <0.1 × 10^9/L on 2 occasions	G-CSF 0.4 μg/kg/d and titrated upward to achieve ANC >3.0 × 10^9/L. Maintained for 3 wk	Increase in mean ANC from 0.65 to 6.01 × 10^9/L after 1 wk and 5.54 × 10^9/L after 4 wk ($p < 0.01$) of G-CSF therapy; values returned to baseline after cessation of treatment
[92]	Pilot followed by prospective, uncontrolled	6 in pilot phase; 11 in prospective phase	AIDS pt with Kaposi's sarcoma (8 pts), CMV retinitis (8 subjects), or lymphoma (1 pt) and WBC <1.0 × 10^9/L	G-CSF 5 μg/kg until WBC >1.5 × 10^9/L, then maintenance	All 11 pts in prospective with ANC >1.0 × 10^9/L within 24 hr. No bacterial infections seen when WBC >1.5 × 10^9/L or ANC >1.0 × 10^9/L during the subsequent 7 mo

(continued)

Table 1 (continued)

Reference no.	Type of study	No. of patients	Condition(s)	Intervention	Results
[110]	Prospective single-blind randomized dose-varying	11	CDC stage IV AIDS with ANC 0.5–1.0 $\times$ 10^9/L on two occasions while receiving ZDV	G-CSF 0.5–10 μg/kg administered for 10 d	Mean baseline ANC 0.67 $\times$ 10^9/L; ANC increased at all doses except placebo in a dose-dependent manner and decreased rapidly after cessation of therapy
[111]	Case series	6	Pt with ZDV-associated neutropenia (ANC $<1.0 \times 10^9$/L)	G-CSF 300 μg/d for 10 d with cessation of ZDV therapy	Increase in mean ANC from 0.89 $\times$ 10^9/L before G-CSF administration to 1.55 $\times$ 10^9/L after
[112]	Randomized placebo-controlled	8 experimental; 2 control	AIDS pt receiving ZDV with ANC $<1.0 \times 10^9$/L	Placebo or varying doses of G-CSF administered for 10 d	Mean ANC increase from 0.99 $\times$ 10^9/L to 3.81 $\times$ 10^9/L after 8 hr, which reversed after treatment cessation
[112]	Case series	6	AIDS pt receiving ganciclovir for CMV retinitis	G-CSF 5 μg/kg given for 6–117 d	Mean ANC increase from 0.65 $\times$ 10^9/L to 2.17 $\times$ 10^9/L within 24 hr
[113]	Case series	8	Stage IV-A AIDS pt with ANC $<0.75 \times 10^9$/L and concomitant infection	Filgrastim 3–4 μg/kg/d	Filgrastim was well-tolerated and infection was successfully treated in all pt
[114]	Case series	7	CMV end organ disease and ANC $<0.58 \times 10^9$/L	Filgrastim titrated to maintain trough ANC 0.5–1.5 $\times$ 10^9/L range	All 7 pts were successfully treated with a full course of ganciclovir
[115]	Prospective, uncontrolled	19	Children <18 years of age receiving ZDV and with ANC $<0.8 \times 10^9$/L despite ZDV dose reduction	Filgrastim 1 μg/kg/d was begun and titrated to keep ANC in 1.5–5.0 $\times$ 10^9/L range	Increase in median ANC from 1.02 to 2.96 $\times$ 10^9/L ($p = 0.0006$); 17/19 pts were able to continue ZDV therapy

[116]	Prospective, uncontrolled	15	AIDS pt with baseline ANC $<1.0 \times 10^9$/L	G-CSF 300 μg/d with 500 mg/d ZDV for 11 mo	Mean final ANC 2.54×10^9/L. No pt developed a new infection or sepsis during follow-up. One death due to cerebral hemorrhage and one due to lymphoma
[117]	Case series	3	HIV-infected children with leucopenia and anemia	G-CSF 5 μg/kg 3 times wk with Epoetin alfa	Cessation of transfusion requirements and decrease in hospitalizations
[93]	Retrospective cohort	60 experimental; 104 control	AIDS pt with CD4+ count< 50 cells/mm^3 given G-CSF compared with controls who were not given G-CSF	Daily G-CSF given until WBC $>1.5 \times 10^9$/L, then several times wk	Median survival of 658 d in the G-CSF group and 511 d in controls ($p < 0.01$)
[93]	Retrospective cohort	60 experimental; 65 control	AIDS pt with WBC <1,000 cells/mm^3 or ANC $<0.5 \times 10^9$/L given G-CSF compared with controls not given G-CSF	Daily G-CSF given until WBC $>1.5 \times 10^9$/L, then several times wk	Median survival of 248 d in the G-CSF group vs. 145 d in controls ($p = 0.06$)
[118]	Open-label, noncomparative	20	AIDS pt with 2 ANC $<1.0 \times 10^9$/L within 7 d on myelo-suppressive therapy	G-CSF 1 μg/kg daily, with dose escalation to maintain ANC 2.0 to 5.0×10^9/L	One pt died and one withdrew from study. Other pt were able to maintain myelo-suppressive therapy without neutropenia. Mean ANC increased from 0.72×10^9/L to 3.11×10^9/L
[94]	Prospective, open-label, noncomparative	200	AIDS pt with 3 measured ANC $<1.0 \times 10^9$/L not attributable to cancer therapy	Filgrastim 1 μg/kg/d initiated and titrated to maintain ANC $>2.0 \times 10^9$/L	Reversal of neutropenia in 98% of pt, sustainable with maintenance therapy
[119]	Case report	1	38-year-old man with AIDS, neutropenia, and oral ulcers refractory to steroids, acyclovir, and antibiotics	G-CSF 300 μg daily, titrated to maintain ANC $>2.0 \times 10^9$/L	Resolution of neutropenia and of ulceration. Subsequent death from other AIDS-related causes

(continued)

Table 1 (continued)

Reference no.	Type of study	No. of patients	Condition(s)	Intervention	Results
[120]	Randomized, controlled, double-blinded	10 experimental; 10 control	Asymptomatic HIV infection with $CD4^+$ count <500 cells/mm^3	ZDV (500 mg/d) with G-CSF (10 μg/kg biweekly) and Epoetin alfa in trial group; ZDV alone in controls	Significant increase in experimental group in Hgb, ANC, and $CD4^+$ count compared with controls ($p < 0.01$)
[121]	Prospective, uncontrolled	6	Class IV AIDS with lymphocyte count <4,300 cells/mm^3 and ANC $<1.9 \times 10^9$/L	Filgrastim 3–5 μg/kg 3 times wk for 2 wk or until recovery of counts	Statistically significant increase in WBC, total lymphocyte, $CD3^+$, $CD4^+$, $CD8^+$, and NK^+ counts
[122]	Prospective, uncontrolled	11	HIV-infected children	G-CSF 5 μg/kg 2–3 times wk with concomitant Epoetin alfa	Increased leukocyte ($p = 0.003$) and neutrophil ($p = 0.009$) counts
[123]	Retrospective cohort	71 experimental; 157 control	HIV-infected pt with ANC $<1.0 \times 10^9$/L given G-CSF or GM-CSF compared with controls not given G-CSF or GM-CSF	G-CSF 300 μg or GM-CSF 250 μg administered per physician discretion	Improved survival in multiple logistic regression model associated with G-CSF or GM-CSF administration (OR 4.2)
[98]	Retrospective cohort	25 experimental; 66 control	HIV-infected pt with disseminated MAI infection	G-CSF as per physician discretion	G-CSF usage associated with improved survival in Cox proportional hazards model (HR 0.22; $p = 0.01$)
[124]	Retrospective cohort	71 experimental; 81 control	HIV-infected pt with ANC $<1.0 \times 10^9$/L	G-CSF 300 μg 5 times wk initiated when ANC$<0.5 \times 10^9$/L and titrated to maintain ANC $>1.0 \times 10^9$/L	In both bivariate and multivariate analysis, G-CSF administration was associated with a decreased risk of bacteremia and death

[95]	Prospective, randomized, unblinded	172 experimental; 86 control	HIV-infected pt with $CD4^+$ count <200 cells/mm^3, ANC 0.75–1.0 × 10^9/L, and platelet >50 × 10^9/L	Daily or intermittent filgrastim titrated to maintain ANC between 2.0 and 10.0 × 10^9/L in intervention group. Controls received filgrastim only if ANC <0.5 × 10^9/L persistently	Decreased incidence of severe neutropenia and severe bacterial infections (RR 0.46; $p < 0.01$) associated with filgrastim usage
[125]	Prospective, randomized controlled	5 experimental, 5 control	HIV-infected pt with disseminated MAI infection	Intermittent filgrastim titrated to maintain WBC >5.0 × 10^9/L	Clearance of infection and survival in all 5 pts in experimental group; death in all 5 pts in control group
[126]	Randomized, single-blind, controlled	55 experimental; 15 control	HIV-infected pt with CMV infection and ANC <1.0 × 10^9/L during first 12 d ganciclovir treatment	Lenograstim 25–150 μg/m^2 daily or placebo administered concomitantly with ganciclovir 5 mg/kg every 12 hr	Higher median ANC was noted in the intervention groups compared with the control group. No additional effect was noted for doses >50 μg/m^2/d
[109]	Pre- and post-intervention	71 pre-intervention; 81 post-intervention	HIV-infected pt who met detailed guidelines for initiating G-CSF therapy	Pharmacist-driven protocol for G-CSF dosing in the intervention group vs. standard dosing in the control group	Decrease in mean number of daily G-CSF doses given (0.51 to 0.29) and quarterly cost of G-CSF to HIV-infected pt ($90,000 to $22,000) without increase in number of neutropenic days
[127]	Prospective randomized, double-blinded, controlled	6 experimental, 5 control	HIV-infected pt with $CD4^+$ count <350 cells/mm^3 initiating HAART	Filgrastim 300 μg 3 times wk or placebo with HAART for 12 wk	Trial terminated due to adverse event. HIV viral load decreased less rapidly in filgrastim group compared with placebo group

(continued)

Table 1 (continued)

Reference no.	Type of study	No. of patients	Condition(s)	Intervention	Results
[128]	Prospective randomized, double-blinded, controlled	12 experimental; 15 control	HIV-infected pt with $CD4^+$ count<350 cells/mm^3 on stable HAART regimen	G-CSF 300 μg 3 times wk or placebo for 12 wk	Significant increases in lymphocyte count ($p = 0.002$), $CD4^+$ count ($p = 0.03$), $CD8^+$ count ($p = 0.004$), and NK cell count ($p = 0.001$) in the G-CSF group. Increases were reversed after termination of study
[129]	Prospective, uncontrolled	18	HIV-infected pt on no or stable HAART regimen	Filgrastim 10 μg/kg daily for 7 d to stimulate mobilization for stem cell transplantation	9/18 pts experienced at least one significant increase in HIV-1 RNA viral load
[130]	Prospective randomized, double-blinded, controlled	12 experimental; 15 control	HIV-infected pt with $CD4^+$ count <350 cells/mm^3 on stable HAART regimen	G-CSF 300 μg 3 times wk or placebo for 12 wk	Significant increase in $CD34^+$ ($p = 0.006$) and $CD4^+$ counts
[96]	Retrospective cohort study of data from multiple prospective clinical trials	398 experimental; 311 control	HIV-infected pt receiving anti-CMV therapy who received filgrastim compared with controls who did not	Filgrastim with dose varying between studies	56% reduction in risk of death associated with filgrastim use in regression model ($p < 0.001$). Marginal benefit in same model on risk of bacterial infection (OR 0.48; $p = 0.062$)
[131]	Retrospective cohort study of data from prospective clinical trial	36 experimental; 36 control	HIV-infected pt receiving anti-CMV therapy who received filgrastim compared with controls who did not	Filgrastim given at physician discretion	Viral load 1.7-fold higher in pt receiving filgrastim ($p = 0.12$) after adjustment for confounders
[132]	Secondary analysis of prospective, uncontrolled trial	18	HIV-infected pt undergoing stem cell mobilization	Filgrastim 10 μg/kg daily for 7 d	In 7 pts whose HIV RNA viral load increased with filgrastim usage, an increase in quasispecies noted

[133]	Secondary analysis of prospective, uncontrolled trial	6	HIV-infected pt undergoing stem cell mobilization	Filgrastim 10 μg/kg daily for 7 d	2/3 pts with HHV-8 antibodies experienced reactivation of HHV-8 viremia after receiving filgrastim, compared with 0/3 pts without HHV-8 antibodies
[134]	Prospective, uncontrolled	32	HIV/HCV coinfected pt receiving IFNα 2b and ribavirin	Filgrastim 300 μg/week initiated when ANC $<0.75 \times 10^9$/L and titrated to keep ANC $>0.75 \times 10^9$/L	50% of pt required filgrastim during therapy. Baseline ANC $<2.25 \times 10^9$/L was predictive of requiring filgrastim usage while receiving anti-HCV therapy

ANC absolute neutrophil count; *d* day; *HAART* highly active antiretroviral therapy; *HCV* hepatitis C virus; *Hgb* hemoglobin; *hr* hour; *IFN* interferon; *MAI* *Mycobacterium avium* infection; *mo* month; *NK* natural killer cell; *pt* patients; *wk* week; *WBC* white blood cell; *ZDV* zidovudine

a median of 248 days, compared with a median survival of 145 days in the 65 patients who did not receive rHuG-CSF [93].

Also notable for both its size and its prospective nature is the multicenter trial conducted by the G-CSF 92105 group and published in 1996. Patients were eligible if, on at least three occasions within a 2-week period, their measured ANC was found to be $<1.0 \times 10^9$/L. Filgrastim dose was titrated to maintain ANC $>2.0 \times 10^9$/L, a target obtained in 98% of patients. Patients received filgrastim for at least 28 days, but could receive it for a longer duration at the discretion of their physicians. The number of patients receiving what were considered to be the drugs most associated with neutropenia (zidovudine, trimethoprim-sulfamethoxazole, ganciclovir, and pyrimethamine) increased 20% over the course of the study [94].

The results of the largest prospective randomized control trial to investigate the outcome of filgrastim administration to neutropenic patients with HIV were published by Kuritzkes et al. in 1998. Of note, patients were accrued in the pre-HAART era. Eligibility requirements for this multicenter, nonblinded study included at least one measured ANC between 0.75 and 1.0×10^9/L, $CD4^+$ lymphocyte count <200 cells/mm^3, platelet count $>50.0 \times 10^9$/L, Karnovsky score $>50\%$, and life expectancy >6 months. Malignancy was the most notable exclusion criterion. In all, 258 patients were randomly assigned to daily, intermittent, or no filgrastim administration for 24 weeks, with filgrastim dose subsequently titrated to maintain white cell count in the $2.0–10.0 \times 10^9$/L range. Control patients receiving no filgrastim who developed an ANC $<0.5 \times 10^9$/L were censored and subsequently re-randomized to one of the two treatment groups, an event which occurred in 18 patients. In all, 34.1% of patients who were assigned to receive no filgrastim developed the primary endpoint of severe neutropenia or death, compared with 12.8% of patients in the intermittent filgrastim group and 8.2% of patients in the daily filgrastim group. Patients who received filgrastim were 54% less likely than controls to develop a serious bacterial infection ($p = 0.005$) [95].

The most recent large study to examine the effect of filgrastim administration on outcomes in patients with HIV was the retrospective cohort study published by Davidson et al. in 2002. This study was a retrospective analysis of data from several prospectively conducted studies of HIV-infected patients with CMV retinitis. Of note, significant heterogeneity in the use of filgrastim was present in the original trials. In an analysis made complex by the need to correct for the inherent biases of a retrospective analysis, filgrastim use was associated with a 56% reduction in death in a multivariate model ($p < 0.01$). Associations between filgrastim use and such outcomes as catheter-associated bacteremia and repeat bacterial infection were significant in unadjusted analysis but not after adjustment for confounders [96].

Other interesting uses for rHuG-CSF which single reports have explored include the use of filgrastim as an adjunct to a tagged white blood cell scan in a neutropenic HIV-infected patient in the workup of postoperative fever [97], and the use of filgrastim concomitantly with antimicrobials in the treatment of disseminated mycobacterial infection [98].

7 The Use of Filgrastim in Malignant Conditions in HIV Infection

The benefits of more widespread use of colony-stimulating factors in HIV-negative patients undergoing chemotherapy are now widely accepted, as demonstrated by recently written clinical guidelines which expand the criteria for their use [99]. This change in practice applies to HIV-infected patients as well. Although no randomized trial specifically has addressed the use of filgrastim in HIV-associated malignancy, several nonrandomized comparative studies looking at the benefits of adding rHuG-CSF to a chemotherapy regimen in patients with HIV-associated lymphoma have been published. In a pre- and postintervention trial where 65 HIV-infected patients with non-Hodgkin's lymphoma (NHL) either received a dose-reduced variant of the CHOP regimen (chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone) or full-dose CHOP augmented by filgrastim, grade 3 or 4 neutropenia occurred in fewer patients receiving full-dose CHOP with filgrastim (13% vs. 25%), a nonsignificant difference. The study was neither intended to nor powered to measure the effect of filgrastim independently [100]. A similar, nonrandomized study by Rossi found that HIV-positive patients receiving rHuG-CSF during chemotherapy were more likely than those who did not to receive full doses of chemotherapy and to receive cycles without delays, although the likelihood of complete response was actually lower in those who received rHuG-CSF [101]. A third study, also nonrandomized, compared the outcomes of HIV-positive patients undergoing chemotherapy for NHL, finding a decrease in mean duration of treatment delays between cycles from 9d to 4d ($p = 0.01$). Again, however, mean duration of survival was worse in the group receiving rHuG-CSF, which also trended toward having more advanced HIV [102]. Further discussion of the role of rHuG-CSF in HIV-associated malignancies is beyond the scope of this chapter; a review of the use of hematopoietic growth factors in HIV-associated malignancies has been previously published [103].

8 Adverse Effects of Use

The most common side effect of filgrastim is bone pain, with headache, nausea, and vomiting also frequently reported [104]. Although generally safe, filgrastim usage in HIV patients has been associated with disseminated intravascular coagulation [105], hepatitis, and pancreatitis [106]. In non-HIV patients, a review of case reports of adverse effects of filgrastim noted a number of rare adverse events, many of which were attributed to increased inflammation (ARDS, shock, worsening autoimmune disease) or leukostasis (arterial thrombosis or myocardial infarction, interstitial nephritis, bone marrow necrosis) [107].

Nevertheless, the adverse effect of filgrastim that serves as the biggest barrier to its use is its cost. However, filgrastim may be effective in HIV-infected patients at

doses lower than those traditionally used for patients with chemotherapy-induced neutropenia [108]. One center developed a clinical pharmacist-driven protocol for dosing filgrastim in HIV-infected inpatients based on ANC; subsequently, the quarterly cost for filgrastim for the HIV service decreased from US$90,000 to US$22,000 [109].

9 Conclusion

The incidence of neutropenia in HIV-infected patients has decreased with the advent of therapies that arrest and reverse the progression of AIDS. In the future, most patients with HIV who develop neutropenia will likely do so from oncologic disease and its treatment, not HIV itself. However, the inability of all HIV-infected patients to benefit from the advances in HIV treatment means that filgrastim will continue to play a role in the management of complications of advanced HIV and its treatment.

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