S-11-B-2a Recombinant Granulocyte Colony-stimulating Factor (rG-CSF) in HIV Patients with Zidovudine Related Neutropenia

N.CLUMECK, S.D.WIT, P.HERMANS, P.FRANCHIOLY,
and B.SOMMERIJNS

Division of Infectious Diseases, Saint-Pierre University Hospital,
Brussels, Belgium.

I. INTRODUCTION

In the recent years, therapeutical approach of HIV infected patient has dramatically improved. This includes : prophylactic use of various regimens of antimicrobial agents in order to prevent opportunistic infections; early treatment of HIV infections by specific antiviral drugs (mostly nucleosides analogues) and extensive use of chemotherapeutic agents for neoplasms such as Kaposi's sarcoma and lymphoma. As a result, poor hematologic tolerance to therapies and hematopoietic failure has become serious impediments to the successful treatment of patients with HIV infection.

Fortunately, rescue therapy with hematopoietic stimulants has consequently been developed. In this respect, the use of granulocyte colony-stimulating factor (G-CSF) which has the capability in vitro to stimulate the functional activity of mature neutrophils could represent an important therapeutical progress specially among patients experiencing severe myelosuppressive effects of Zidovudine, currently the only retroviral agent with clinically proven effectivity against HIV infection.

The objectives of the present study were to evaluate the safety, tolerability and the effects of a range of doses of rG-CSF in comparison with vehicle, on the counts of neutrophil granulocytes, in neutropenic AIDS/ARC patients treated with Zidovudine.

II. PATIENTS AND METHODS

The study was a phase II single blind randomized parallel group, vehicle-controlled dose ranging study. Patients with a symptomatic HIV infection (CDC class IV classification) were eligible for the study when they had neutrophil count between 750 and 1000/mm³ on at least two occasions whilst receiving Zidovudine treatment for at least two weeks prior to study entry. Exclusion criteria were the following : age under 18 years, a Karnofsky score under 50, a life expectancy under 3 months, an active uncontrolled infection, or treatment with immunomodulating agents including systemic steroids or any investigational drug for HIV infection. The study was approved by the hospital ethical committee. All patients gave written informed consent.

rG-CSF was provided by Chugai - Rhône-Poulenc Pharmaceutical. rG-CSF is produced in Chinese hamster ovary (CHO) cells after transformation with a vector containing G-CSF-cDNA derived from a human squamous cell carcinoma cell line (CHU-2) producing G-CSF constitutively. Analysis of the amino-acid sequence of the CHO-cell derived rG-CSF has shown that it is identical to native human

G-CSF and is thus not expected to provoke an immune response in human subjects. rG-CSF has a molecular weight of 18000-20000 Daltons and consists of 174 amino-acids and a carbohydrate moiety of approximately 4% [1].

Each patients were randomly assigned to one of the 5 treatments groups and treated with 0.5, 2, 5 or 10 $\mu\text{g/kg}$ rG-CSF or vehicle for a period of 10 days followed by an observation period of 7 days. G-CSF was administered subcutaneously once daily by a physician or a trained nurse. rG-CSF was supplied in vials containing 250 μg of rG-CSF or vehicle.

Study Parameters. At entry a complete history and physical examination were undertaken. Throughout the study the patients were carefully observed for infections and possible side effects. Total white blood cells and differential counts were determined daily during the study period and twice weekly after. Serum HIV-1 p24 antigen levels and peripheral blood CD4-positive lymphocyte counts were determined before and at the end of rG-CSF treatment.

III. RESULTS

Eleven patients were included in the study (8 males, 3 females). Five patients had AIDS, 4 had AIDS-related complex and 2 were HIV asymptomatic. The mean age was 37.3 ± 7.5 years. The mean Zidovudine dose at entry was 812 ± 264 mg/d. The mean duration of Zidovudine therapy was 16 ± 10 months.

One patient received placebo, 2 patients 0.5 $\mu\text{g/kg}$, 2 patients 2 $\mu\text{g/kg}$, 3 patients 5 $\mu\text{g/kg}$, and 3 patients 10 $\mu\text{g/kg}$ of rG-CSF. The mean baseline neutrophil count was $667/\text{mm}^3$ (range : 285-1020). Neutrophil counts increased in all patients except the one who received placebo (Figure).

Fig. Neutrophil count among HIV infected patients treated with various doses of rG-CSF.

The mean neutrophil count after 8 days of treatment was significantly different than pre-treatment values at each dose regimen. Increase in neutrophil count was clearly dose-related (Table).

Table : Mean Neutrophil Count with Various Doses of rG-CSF

Dose rG-CSF .	Neutrophil Count		
	Before Treatment (range)	During Treatment (range)	After Treatment (range)
0 µg/kg	285	160	365
0.5 µg/kg	984 (948-1020)	2590 (1920-3260)	981 (684-1279)
2 µg/kg	634 (540-728)	8596 (6103-11088)	1005 (912-1098)
5 µg/kg	741 (656-798)	11179 (7040-15708)	1181 (900-1479)
10 µg/kg	690 (669-704)	16936 (11603-27192)	714 (583-974)
	Global : 710 (285-1020)		

At the end of therapy drop in neutrophil count was rapid and independant of the pic neutrophil level (Figure).

There were no significant effects on the number of red blood cells, platelets, and eosinophilic granulocytes. P24 antigen remained unchanged.

Subjective tolerance was excellent. No clinical side effect was observed. One patient mentioned disappearance of symptoms of gingivitis and healing of an anal fissure while under therapy.

IV. DISCUSSION

This study demonstrates that rG-CSF is efficient in increasing polymorphonuclear counts among neutropenic HIV infected patients. Increase in the neutrophil count was dose-dependant and transient. This is in accordance with other preliminary studies which showed similar results [2]. In contrast with the study of Vanderwouw, we did not observed any side effects and particularly no bone pain nor thrombocytopenia. The good tolerance of G-CSF might be an argument to use it rather than GM-CSF in HIV patients. Indeed, in an open non comparative study we have observed similar efficacy but higher side effects with GM-CSF including flu-like symptoms, bone pain and fever [3]. These data clearly highlight the need for further randomized double-blind comparative trials.

The optimal dose and schedule of administration of rG-CSF remain to be determined. If the goal is to maintain neutrophil count between 1000 and 2000/mm³, it is then likely that a dose of 0.5 to 2 µg/kg/day will be sufficient. It remains however that in some patients with profound and persistent bone marrow suppression, higher dosage could be necessary [4].

So far, all the studies with G-CSF [2,5] have addressed the problem of Zidovudine related neutropenia which is reversible and dose-related.

In the future, it will be important to study the potential role of rG-CSF among HIV infected patients with neutropenia induced by aggressive chemotherapy of Kaposi's sarcoma or lymphoma or treatment of cytomegalovirus infection with Gancyclovir. In all these situations neutropenia is severe and persistent, and is often the limiting factor to the success of therapy.

In summary, rescue therapy with rG-CSF represents a major therapeutical progress which could particularly be of benefit for HIV infected patients. Further prospective studies are needed in order to clarify the precise indications, and the optimal dose and schedule of G-CSF among these patients.

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