To the Editor:

In their recent report of granulocyte macrophage colony-stimulating factor (GM-CSF) used in an alternating regimen with azidothymidine (AZT) in human immunodeficiency virus (HIV) patients with leukopenia, Pluda et al reported that six patients with detectable p24 at baseline had significant increases during the period of GM-CSF administration. Although most patients had subsequent decreases in p24 when AZT was later added, this data may raise a safety concern about giving GM-CSF to HIV patients.

The clinical experience suggests that this concern may not be warranted. In a study by Groopman et al, GM-CSF given alone in neutropenic acquired immunodeficiency syndrome (AIDS) patients did not increase HIV as determined by cell culture. Mitsu- yasu et al reported on 15 HIV-infected patients administered GM-CSF for up to 6 months without a consistent change in HIV expression, and we have recently completed a study of GM-CSF with daily AZT in 19 patients with no consistent increase in p24.

In vitro data using HIV-infected mononuclear phagocytes suggests that GM-CSF may stimulate virus production, although this may be dependent on the viral strain and specific cell lines used. In contrast, data from in vitro studies using the combination of AZT and GM-CSF show that GM-CSF enhances the anti-HIV effect of AZT.
The increasing p24 seen in the Pluda study should be of less concern, considering the unusual schedule of AZT that was used. Continuous treatment with a drug such as AZT, that works by inhibiting the replication of HIV and not by its eradication, is imperative to sustain a therapeutic effect. When viewed in this context, the increase in p24 seen in this study is not surprising and may be attributable to the discontinuation of AZT as opposed to GM-CSF treatment.

Clinical and laboratory evidence to date demonstrates that GM-CSF, when used with AZT, does not increase p24 or HIV production and very likely will have a prominent place in the therapeutic armamentarium for the treatment of HIV disease.

ROBERT J. ISRAEL
Schering-Plough Research
Kenilworth, NJ
JAMES D. LEVINE
New England Deaconess Hospital
Boston, MA

REFERENCES


RESPONSE

We agree with the conclusion by Drs Israel and Levine that there is no evidence that granulocyte-macrophage colony-stimulating factor (GM-CSF), when administered to patients with zidovudine (AZT), increases the levels of serum human immunodeficiency virus (HIV) p24 antigen (Ag). GM-CSF is an important therapeutic agent that is likely to be valuable in treating several diseases. However, the interaction between GM-CSF and HIV is a complex issue, and there are several lines of evidence to suggest that GM-CSF, in the absence of AZT, may under certain conditions enhance HIV replication in vitro and possibly in vivo. Our report summarized the results of a pilot study initiated in November 1987 and in no way provides definitive answers. The regimen chosen was intended to obviate concerns at the time regarding the use of GM-CSF simultaneously with AZT (then a newly approved agent).

Several groups have shown that GM-CSF alone stimulates HIV replication in peripheral blood monocyte/macrophages or in a promonocytic cell line in vitro. What is more controversial at this point is whether this finding has clinical significance. Moreover, GM-CSF may also enhance the in vitro anti-HIV activity of AZT (and related thymidine dideoxynucleoside congeners) in these same systems. Our group has shown that GM-CSF may favorably influence the anabolic phosphorylation of AZT in vitro.

In the trial previously reported by our group in Blood, each of six evaluable patients had an increase in p24 Ag during an initial 2-week period of single-agent GM-CSF administration. These patients had been off of AZT for at least 4 weeks before receiving the GM-CSF, and in most cases had been shown to have constant HIV p24 Ag levels before beginning GM-CSF. Therefore, we do not believe that the increases in p24 Ag were simply a rebound from prior AZT therapy. More recently, Kaplan et al have found that patients with HIV-associated non-Hodgkin's lymphoma (NHL) treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy and GM-CSF in the absence of AZT generally had increases in serum HIV p24 Ag during the period of GM-CSF administration. On completion of therapy and cessation of the GM-CSF, the p24 Ag returned to baseline (Kaplan L, personal communication, January 1991). In contrast to the above results, however, Mitsuyasu et al6 did not note consistent changes in p24 Ag in patients receiving single-agent GM-CSF of up to 6 months. Moreover, this same group failed to observe an increase in the ability to culture HIV from stimulated peripheral blood T cells in patients administered intravenous GM-CSF.7 It should be stressed that whereas serum p24 Ag is believed to reflect the production of HIV and HIV protein by a variety of cells, in vitro cultures as performed in that study predominantly assess proviral HIV in circulating T cells, and the two assays may thus not be comparable. Also, this group initially did not report p24 Ag levels in their patients receiving intravenous GM-CSF, although they have since suggested that this parameter did not change. Thus, although changes in parameters of viral production have been observed in certain trials, there is not a consensus on whether GM-CSF enhances HIV replication in vivo. Moreover, any potential stimulation of HIV replication must be balanced against the clinical benefits of GM-CSF in a given setting.

Preliminary results of trials conducted by our group and others have noted evidence of anti-HIV activity in patients receiving a combination of GM-CSF and AZT (Pluda JM, Broder S, Yarchoan R, unpublished data, February 1991).8 The use of GM-CSF in combination with AZT for the treatment of patients with HIV infection is a very promising strategy. However, perhaps more research is warranted regarding the use of GM-CSF as a single agent in patients with HIV infection.

JAMES M. PLUDA
ROBERT YARCHOAN
SAMUEL BRODER
National Cancer Institute
National Institutes of Health
Bethesda, MD
REFERENCES


Granulocyte-macrophage colony-stimulating factor and azidothymidine in patients with acquired immunodeficiency syndrome [letter; comment]

RJ Israel and JD Levine