Combined Recombinant Human Growth Hormone, IL-2 and GM-CSF for Immune Reconstruction in Patients with HIV.

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ABSTRACT

Background: Various studies have investigated the individual roles of recombinant human growth hormone (rhGH) and IL-2 in immune reconstitution for patients with HIV. Additionally, in vitro studies on GM-CSF suggest that it is capable of downregulating the CCR5 co-receptor on the monocyte derived population. We report our experience with HIV patients treated simultaneously with all three of these agents in conjunction with highly active anti-retroviral therapy (HAART).

Subjects: The records of patients who had been treated concomitantly with rhGH, IL-2 and GM-CSF were reviewed. At least five cycles of IL-2/GM-CSF and a follow-up period of at least three months off IL-2/GM-CSF were required. Eight homosexual HIV positive males (average age 42.3; range 33-50) met these criteria.

Methods: Patients were observed on anti-retroviral therapy alone for a period of at least three months. Subsequently, rhGH (Serostim dosages ranged from 3 mg SC three days per week to 6 mg daily) was added to the HAART regimen (>2 nRTI's and >1 PI) and patients were monitored for at least 3 months. Finally, IL-2/GM-CSF was initiated (each cycle: IL-2 7.5 million IU SC BID pulsed for 5 days of each month co-administered with GM-CSF 250 mcg SC BID either pulsed for five days or uninterrupted). Viral RNA, CD4 percentages and absolute counts were averaged for three month intervals during each of the treatment phases. Serum HIV DNA status was also monitored.

Results: The mean baseline CD4 percent/absolute count (prior to addition of rhGH) was 12.1%/281 (range 0.1-25.3%/0.3-724). The patients received an average of 6.4 cycles of IL-2/GM-CSF (range 5-8), with a mean follow up period of 7.1 months (range 3-9 mos). Paired t-tests showed a statistically significant increase over baseline CD4% after rhGH was added to anti-retroviral therapy alone (12.1% vs. 20.4%, p<0.011). CD4% again rose significantly compared with patients on HAART and rhGH after IL-2/GM-CSF was added (20.4% vs. 23.8%, p<0.006). This effect persisted in the follow up period. The same trend was observed for absolute CD4 counts but statistical significance was not achieved. Remarkably, four of the eight patients exhibited negative serum HIV DNA testing at various times during the course of the IL-2/GM-CSF treatment (1/4) or in the follow-up period (3/4).

Conclusion: Prospective studies to determine the role of combined rhGH, IL-2 and GM-CSF for immune reconstruction in HIV patients should be pursued.

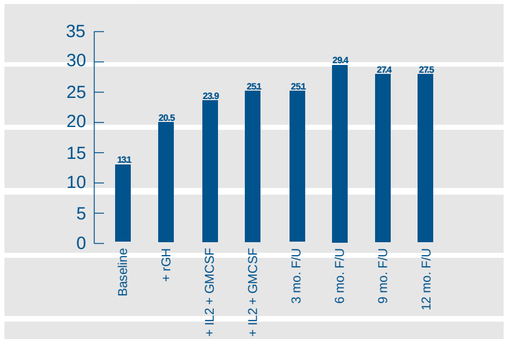
BACKGROUND

Therapeutic modalities for immune reconstruction in patients with HIV are at the forefront of AIDS research. IL-2 induces proliferation of CD4+ T-cells. Highly active anti-retroviral therapy was shown to increase IL-2 producing CD4+ T-cells.(1) Recombinant human growth hormone (rhGH) stimulates lymphopoeisis and maturation of T-cells. In vitro, it has been shown to increase IL-2 receptor expression on T-cells.(2) Granulocyte monocyte-colony stimulating factor(GM-CSF) has been shown to increase CD4 counts in patients with HIV, and the mechanism by which it improves T-cell immunity may be related to the downregulation of macrophage CCR5 surface receptor expression.(3) By reducing the functional activity of the co-receptor that is required for cell entry, infection may potentially be inhibited. The combined effect of these four therapeutic modalities used in combination has not been reported.

METHODS

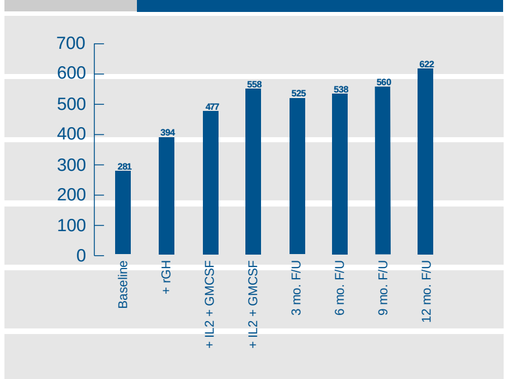
Eight homosexual male patients (average age 42.3; range 33-50) on a stable regimen of antiretroviral therapy with at least three successive monthly undetectable viral loads (<50), were placed on rhGH for three months. At the end of this interval, IL-2 and GM-CSF were added in monthly cycles for an average of 6.4 months. Patients were monitored monthly for viral RNA, CD4 percent and absolute counts, HIV DNA, drug toxicities, and the development of opportunistic infections or AIDS related malignancies. Five of the eight patients on antiretroviral therapy during the three month baseline period were treated with only RTI's (non-HAART). At the time rhGH was started, all eight patients were placed on HAART regimens. Serostim (rhGH) dosages ranged from 3mg SC three days per week to 6mg daily. IL-2 was administered in dosages of 7.5 million IU SC BID pulsed for 5 days of each month. GM-CSF was administered in dosages of 250 mcg SC BID (either pulsed for 5 days or given continuously, 30 days per month without interruption).

Figure 1: **Immune Reconstitution Change in mean CD4%**



At baseline, HIV-RNA was undetectable for a minimum of 3 months at which time Immune Reconstitution was initiated.
Change in Mean CD4 % with addition of GH, IL2 + GM-CSF to Baseline HAART

Figure 2: **Immune Reconstitution Change in mean CD4 count**



At baseline, HIV-RNA was undetectable for a minimum of 3 months at which time Immune Reconstitution was initiated.
Change in Mean CD4 count with addition of GH, IL2 + GM-CSF to Baseline HAART

RESULTS

Eight patients were evaluated. The mean baseline CD4 percent (prior to addition of rhGH) was 12.1%, (range 0.1 to 25.3%). The mean baseline CD4 count was 281(range <1.0 to 724). Patients received an average of 6.4 cycles of IL-2/GM-CSF(range 5 to 8 months). Follow up after discontinuation of IL-2/GM-CSF cycles was observed for 7.1 months (range 3-9 months). Side effects of treatment included mild flu-like symptoms associated with the administration of the IL-2 or GM-CSF. No patients suffered side effects that prompted discontinuation of treatment. No oportunistic infections or AIDS related malignancies occurred during the course of treatment or during the follow up period. Paired t-tests showed a statistically significant increase over baseline CD4% after rhGH was added to the antiretroviral therapy alone (12.1% vs. 20.4%, p<0.011). CD4% again rose significantly after IL-2/GM-CSF was added (20.4 vs. 23.8%, p<0.006). This effect persisted in the follow up period, after discontinuation of IL-2/GM-CSF (See Figure 1). The same trend was observed for absolute CD4 counts, however, statistical significance was not achieved (See Figure 2). Four of eight patients exhibited negative DNA testing on PBMC at various times; one of four patients during the course of combined treatment; three of four in the follow up period (after discontinuation of IL-2/GMCSF).

CONCLUSIONS

- Combined treatment with HAART, rhGH, IL-2 and GM-CSF was well tolerated and provided a durable improvement in CD4 percentages and counts in this pilot study.
- A disproportionately high number of patients became DNA negative during the study, the significance of which may be related to a reduction of infectivity.
- Prospective studies to determine the role of combined HAART, rhGH, IL-2 and GM-CSF in HIV patients should be conducted, including immunologic markers of disease progression.

REFERENCES

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