Effects of Prednisolone on CD4 Counts and HIV Disease Progression: A Two-Year Clinical Trial

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Abstract

BACKGROUND: Chronic immune activation has been identified as a correlate with HIV-associated CD4+ T cell loss and progression to AIDS. Comparative studies between pathogenic HIV infection in humans and nonpathogenic SIV-infection in natural hosts suggest that chronic immune activation may play a central role in disease pathogenesis, and patients with elevated immune activation progress more rapidly than patients with lower levels of immune activation. However, despite convincing association of the two phenomena, a causal link between immune activation and disease progression still remained to be shown.

METHODS: Here we assessed the effects of the immunosuppressive corticosteroid prednisolone on CD4+ T cell counts and HIV disease progression in a randomized, double-blinded, placebo-controlled clinical trial. A total of 326 HIV-infected patients not yet eligible for antiretroviral therapy in Mwanza, Tanzania, were randomly assigned to receive either 5 mg prednisolone per day or placebo for 24 months (Fig. 1). Patients were clinically evaluated and laboratory markers were determined, including immune activation markers (sCD14, suPAR), CD4 and CD8 counts. The primary end point of the study was progression to an AIDS-defining condition and/or a drop of CD4 counts below 200 cells per µ l, or death from any cause. The study is completed. (ClinicalTrials.gov; NCT01299948)

RESULTS: Prednisolone treatment caused a reduction in chronic immune activation (sCD14 and suPAR) (Fig. 2 A,B,C) and a two-fold increase in HIV viral load (Fig. 3 D) after 12 months. CD4-counts increased under prednisolone treatment (+39.12 (± 19.59) cells/µl for prednisolone and -29.76 (± 19.28) cells/µl for placebo) (Fig. 3A, B) and the CD4/CD8 ratio increased significantly (Fig. 3 C). Prednisolone attenuated progression to the primary study endpoint (Fig. 4 A, B) and developed significantly fewer AIDS-defining conditions (4 patients versus 11; p = 0.0196) (Fig. 5C). Immune activation (sCD14) correlated with disease progression (Fig. 4 A, B, C). Adverse events were not elevated under prednisolone treatment and no deaths occurred during the study.

CONCLUSIONS: This study demonstrates that therapeutic interventions that target chronic immune activation attenuate HIV disease-progression despite persistence of high-level virus replication, demonstrating for the first time that chronic immune activation is a causative factor in HIV disease progression. We suggest that corticosteroids such as prednisolone should be explored as an early treatment option for asymptomatic HIV infection in resource-limited countries. Moreover, low-dose corticosteroids might prove beneficial as an adjunct to classical HAART in patients with high levels of residual immune activation and suboptimal immune reconstitution ("immunological nonresponders").

Introduction

HIV infection is associated with a chronic, general immune activation that correlates with disease progression. One of its markers is sCD14 [(1)].

	Virus Replication	Immune Activation	Progression AIDS
Untreated infection			
SIV in African monkeys[(2)]	yes	no	no
SIV in Asian monkeys[(2)]	yes	yes	yes
HIV in humans[(2)]	yes	yes	yes
some elite controllers[(3)]	no	yes	yes
treated HIV infection			
HAART responders[(3)]	no	no	no
Immunological Nonresponders[(4)]	no	yes	yes

Despite good correlation, a causal link between immune activation and HIV disease progression remained to be shown.

Rationale of the Study

Corticosteroids such as prednisolone reduce HIV-immune activation[(5,6)].
If immune activation is a factor in HIV pathogenesis and not just a correlate, prednisolone may attenuate HIV disease progression.

Methods

Study design:
- 326 Patients
- Placebo-controlled
- Double blind
- Randomization 1:1

Study drug:
- Prednisolone (5 mg/day)

Treatment duration:
- 2 years

Inclusion criteria:
- HIV positive
- CD4 ≥ 300
- no previous HAART
- no AIDS

Primary endpoint:
- Time to progression to AIDS (CD4 < 200 and/or AIDS-defining condition)

Second. endpoint:
- CD4 counts
- immune activation

Baseline Characteristics

n=326	Prednisolone	Placebo	p-value
Age (years)	34.09 ± 0.66	34.09 ± 0.66	p=0.221
Gender	81.0% female	80.4% female	p=0.888
CD4 counts	484 [506-607]	535 [410-651]	p=0.143
HIV diagnosis	414 ± 53 days	408 ± 47 days	p=0.938

Results

Fig. 1: Consort Diagram

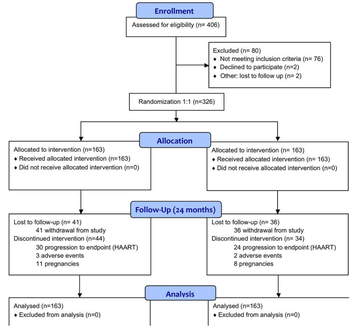
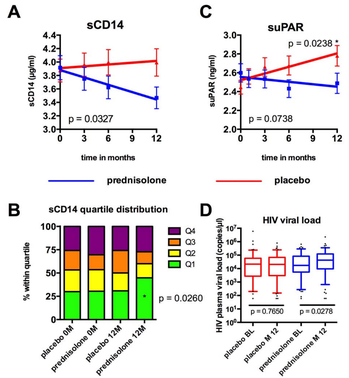


Fig. 2: Immune Activation and Viral Load



Prednisolone treatment (5 mg per day)...

- ...Reduces HIV-associated Immune Activation (Fig. 2)
- ...Increases HIV viral load by factor 2 (Fig. 2)
- ...Increases CD4 counts (Fig. 3)
- ...Improves CD4/CD8 ratio (Fig. 3)
- ...Attenuates Progression to AIDS-defining conditions (Fig. 4)

Fig. 3: CD4 Counts and CD4/CD8 Ratio

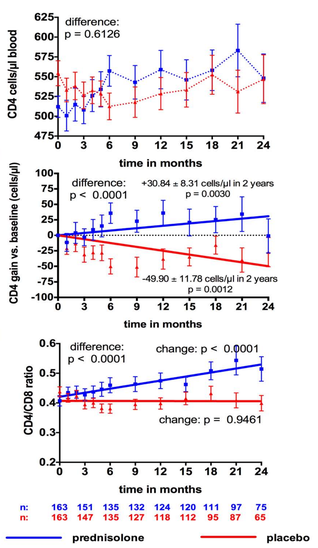
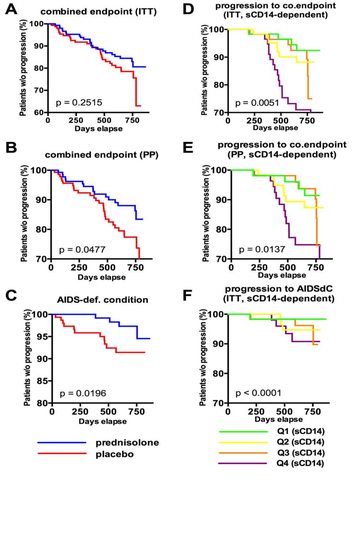


Fig. 4: Disease Progression



Conclusion

- **Reduction of HIV immune activation attenuates HIV disease progression, despite high-level virus replication**
- **This trial demonstrates that HIV immune activation is a causal factor in HIV pathogenesis**
- **Attenuation of HIV pathogenesis with immunomodulating substances may be further explored, e.g. in:**
  - **Immunological Nonresponders (prednisolone plus HAART)**
  - **HIV patients in resource-limited countries (prednisolone preceding HAART)**
  - **Patients with HAART failure in resource-limited countries (prednisolone as a salvage therapy)**

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