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Low-dose Prednisolone Has a CD4-Stabilizing Effect in Pre-treated HIV-patients during Structured Therapy Interruptions (STI)

A. Ulmer, M. Müller, B. Bertisch-Möllenhoff, B. Frietsch

HIV-Schwerpunktpraxis, Stuttgart, Germany

Abstract:
Background: A favorable development of CD4+ T cells was firstly noticed in therapy-naïve HIV-patients without antiretroviral therapy (ART) taking 5 mg prednisolone daily. This observation led to the prescription of prednisolone during structured therapy interruptions (STI).
Objective: To evaluate the effect of low dose prednisolone on pre-treated patients during STI.
Methods: A retrospective analysis including all pre-treated patients with prednisolone therapy for ≥6 months during STI has been conducted. The patients with prednisolone onset right at the beginning of STI (n = 95) were compared with all patients without prednisolone therapy during their first 6 months of STI (n = 49). Patients with prednisolone were divided into two subgroups: the ongoing STI-group and the patients with ART-restart. Additionally, the development of all 33 patients from the control group having started prednisolone later during STI was documented. Irrespective of the time of initiation of prednisolone therapy during STI, the development of CD4+ T cells in all patients with prednisolone for >12 months during STI was analyzed (n = 108).
Results: The mean daily CD4+ T cell decrease during STI was significantly less pronounced in the prednisolone-group (-0.50 vs. -0.74 cells/day; p = 0.0361). The daily CD4+ T cell decline of the 33 patients from the control subgroup including patients with a later onset of prednisolone therapy was only -0.11 during a mean time of 715 days under prednisolone. The CD4+ T cell count of the STI-patients treated with prednisolone for >12 months (n = 108; mean: 837 days ± 64.6 (366-1,756 days)) decreased from 677/µl to 504/µl.

51 of 81 patients (63%) included in 2-year-analysis showed stable CD4+ T cell counts (mean daily CD4+ T cell decrease: 0.08) and continued ART interruption.
Conclusion: This retrospective evaluation provides evidence that low dose corticosteroids are associated with less decrease of CD4+ T cell count in pre-treated HIV patients resulting in prolongation of the potential time of structured treatment interruptions for many HIV patients.

Key words: HIV, prednisolone, corticosteroids, CD4+ T cell, STI, antiretroviral therapy

Introduction

Structured treatment interruptions (STI) have been subject of controversial discussions. Our own experience was predominantly encouraging. Mainly following other promising studies dealing with strategies to prevent or overcome multidrug resistances (19) or to reduce toxicities (9, 27), we induced STI in selected patients. Additionally we observed treatment interruptions being initiated by patients.

In accordance to advantageous experiences with prednisolone for therapy-naïve HIV patients (33) we also prescribed prednisolone during STI.

Methods

Of 145 HAART pre-treated HIV patients in STI receiving a daily dose of 5 mg prednisolone for ≥6 months, 95 patients were treated with this low dose prednisolone right from STI-initiation (mean CD4+ T cell count: 698 ± 251.1 (200 – 1,550)/µl, mean duration from nadir to STI-baseline: 1,511 ± 798.9 (0 - 3,735) days, CD4+ T cell nadir: 275 ± 127.3 (17 - 820)/µl).

CD4+ T cell profiles of these patients were compared to CD4+ T cell profiles of all non-prednisolone STI-patients (n = 49, mean CD4+ T cell count: 823 ± 359.8 (150 – 2,250)/µl, mean duration from nadir to STI-baseline: 1,243 ± 667.4 (99 – 3,088) days, CD4+ T cell nadir 361 ± 179.4 (120 – 1,210)/µl) using the unpaired t – test. As either the differences in CD4+ T cell nadir and CD4+ T cell count at baseline, i.e. at STI-initiation, or the CD4+ T cell increase based on ART might influence the degree of CD4+ T cell decreases during STI, 5 further analyses were conducted:

1. matched-pair analysis (n = 39 matched for CD4+ T cell counts at baseline)
2. division of the STI-patients with prednisolone into two subgroups: Ongoing and finished STI (i.e. restart of HAART)
3. Correlation between CD4+ T cell nadir and degree of CD4+ T cell decreases during STI
4. Correlation between CD4+ T cell count at STI-baseline and degree of CD4+ T cell decline during STI
5. Correlation between degree of the CD4+ T cell increases from nadir during or before HAART to STI-baseline and CD4+ T cell decrease during STI.

Patient characteristics	Prednisolone group N	%	Control group n	%
total	95	100.0	49	100.0
male	65	68.4	38	77.6
female	30	31.6	11	22.4
homosexual	47	49.5	26	53.1
bisexual	4	4.2	1	2.0
heterosexual	19	20.0	7	14.3
Africa	9	9.5	3	6.1
Asia	2	2.1	2	4.1
context of drug use	16	16.8	10	20.4
transfusion	1	1.1	1	2.0
No information	1	1.1	0	0.7
CD4+ T cell nadir (mean)	275/µl ± 127.3/µl		361/µl ± 179.4/µl	
Mean time between nadir and STI-baseline (days)	1,511 ± 798.9		1,243 ± 667.4	
STI-baseline CD4 + T cell (mean)	698/µl ± 251.1/µl		823/µl ± 359.8/µl	

In the non-prednisolone-group were either patients who refused prednisolone treatment (including the five patients initiating STI without consultation), or patients for whom the treating physicians - partly due to lack of experience with prednisolone for HIV-patients - were hesitant to start prednisolone treatment. One patient suffered from mild diabetes mellitus, two patients from chronic hepatitis B and one patient from a previous Kaposi-sarcoma.

Additional analysis was conducted including a subgroup of STI-patients with prednisolone treatment for >12 months (n = 108, mean treatment duration: 837 (366 – 1,756) days), irrespective of the initiation date of prednisolone treatment during STI. Their latest measured CD4+ T cell counts during STI and prednisolone treatment were correlated a) with CD4+ T cell nadir prior to HAART interruption and b) with CD4+ T cell count at baseline prior to prednisolone.

Results

STI-related loss of CD4+ T cells was slower in the prednisolone group (n = 95): Mean daily decrease was 0.50 cells/day equivalent to an absolute decrease from 698 to 461/µl observed in 627 days (mean), compared to a daily decrease of 0.74/day equivalent to an absolute decrease from 823 to 510/µl during a mean of 480 days in the control group (n = 49) (p = 0.0361, Fig. 1).

There was no correlation between CD4+ T cell decline and baseline, nadir or the profile of prior increase. Among the prednisolone group the subgroup of patients with ongoing STI had higher nadir, slightly steeper increase and higher CD4+ T cell count at STI-baseline, but – in contrast to the comparison between prednisolone- and control group – showed a flatter decrease than the subgroup of patients with terminated STI and HAART-restart (Fig. 2). Obvious differences between the 2 prednisolone-subgroups led to several further analyses designed to find predictive parameters for a distinction of groups prior to STI, like sex, age, inflammatory signs, prior treatment and viral load. So far no parameters have become apparent.

After a mean STI of 440 ± 231.3 days, prednisolone treatment was initiated in 33 (67.3%) patients from the control group without prednisolone treatment: Under

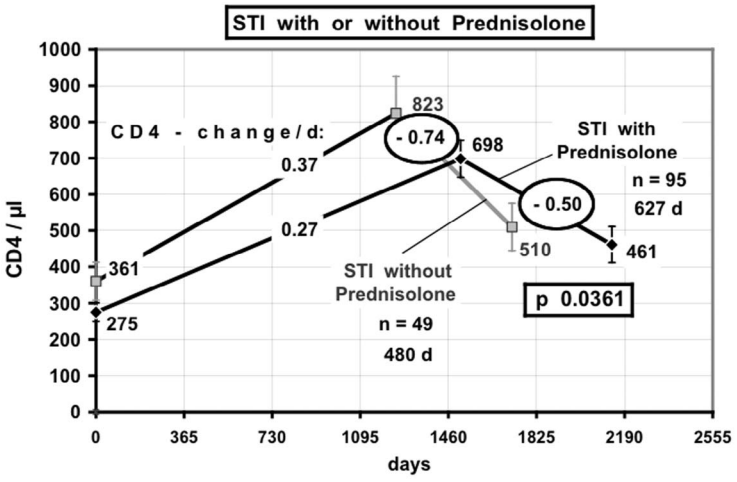

Fig. 1. CD4 profile of STI-patients: Prednisolone group (Treatment at least during first 6 months of STI) vs. Control group. 275 – 698 - 461 = Nadir - STI-baseline - last count during STI with prednisolone (95 patients), 361 – 823 – 510 = Nadir - STI-baseline - last count during STI without prednisolone (49 patients).

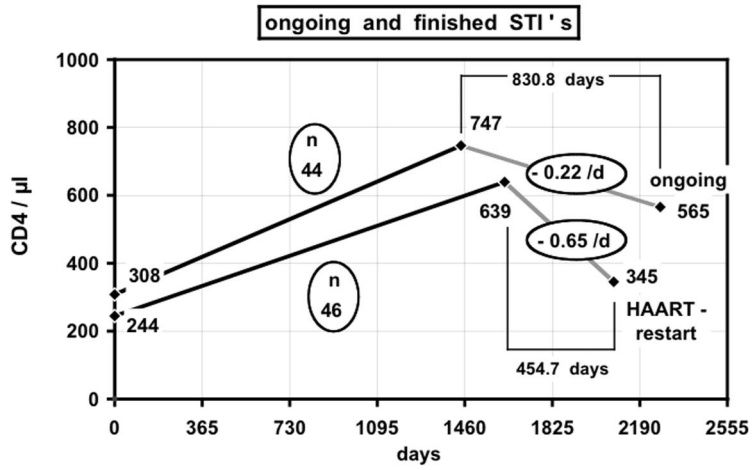

Fig. 2. CD4+ T cell profile of 90 patients treated with prednisolone during STI, subdivided into a subgroup with ongoing prednisolone treatment and a subgroup with HAART-restart. (5 of 95 prednisolone-patients noted in Fig. 1 stopped taking prednisolone or are lost to follow up.)

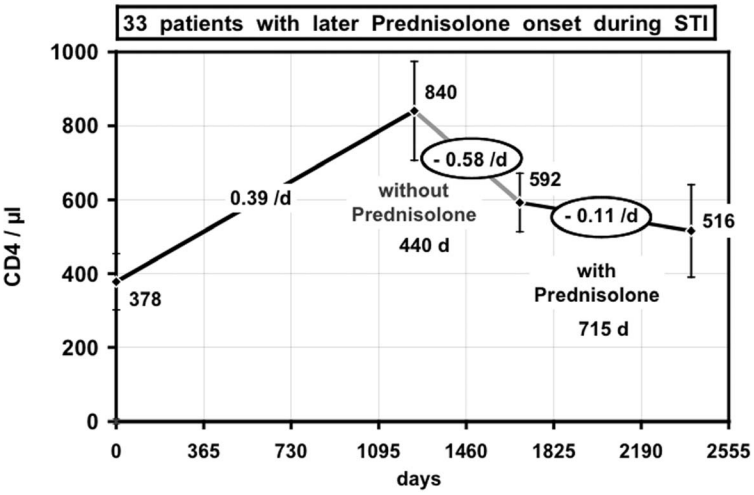

Fig. 3. CD4 profile of STI-patients (n = 33, control group; see Fig. 1) with later prednisolone onset during STI.

prednisolone therapy CD4+ T cell count decline from 0.58 cells/day to 0.11 cells/day equivalent to a further absolute decrease of 76 cells (592 to 516/µl) in 715 (115 – 1,696) days was observed. Overall, a structured treatment interruption is documented in these 33 patients for a mean time of 1,155 ± 464 days - more than 3 years, with an actual CD4+ T cell-count 138/µl above nadir (mean; Fig. 3).

A matched-pair-analysis was conducted in 39 pairs with similar CD4+ T cell counts. CD4+ T cell development was favourable in 74.4% (n = 29/39), likewise mean loss of CD4+ T cells was lower in all prednisolone patients (mean: 0.25/day).

The stability of CD4+ T cell count under low dose prednisolone allows for relatively long interruptions of ART in part of the observed STI patients: Up to date, data are available for STI >2 years (n = 61), >3 years (n = 24) and >4 years (n = 7). Fig. 4 shows the CD4+ T cell development of all patients (n = 108) with >1 year prednisolone treatment during STI: mean CD4+ T cell count decreased from 677 ± 237.7/µl to 504 ± 246.7/µl (166/µl above nadir) in 837 ± 344.7days.

51 (63.0%) of 81 patients included in 2-year-analysis had stable CD4+ T cell counts (mean daily CD4+ T cell decrease: 0.08) and continued the ART interruption.

The majority of STI-patients were clinically stable. However, even with normally safe CD4+ T cell counts (e.g. > 400/µl), considerably more patients in the pre-treated compared to the therapy naïve group (either with or without prednisolone), showed - mostly moderate - evidence of immunodeficiency: in total 49.2% of patients under prednisolone during a mean time of 600 days (evaluation: 8/04) versus 38.6% of the control group during 486 days. Fig. 5 shows similar rates for both groups over time.

Under prednisolone therapy more oral hairy leukoplakia (OHL) (12/118 vs. 2/45) and candidiasis (6/118 vs. 0/45) was observed. Serious events in the prednisolone group were pneumonia (n = 2), meningitis (n = 1) and candida esophagitis (n = 2, included in the candidiasis group). One patient with an earlier splenectomy died after pneumococcal sepsis (CD4+ T: 560 cells/µl). One patient developed rectal cancer after >2 years STI with intermittent prednisolone therapy; however, 3 patients on HAART developed rectal cancer during the same observation period. In the smaller group without prednisolone one possible pneumocystis carinii-associated pneumonia (CD4+ T cell >1,000/µl; clinic and microbiology) was observed.

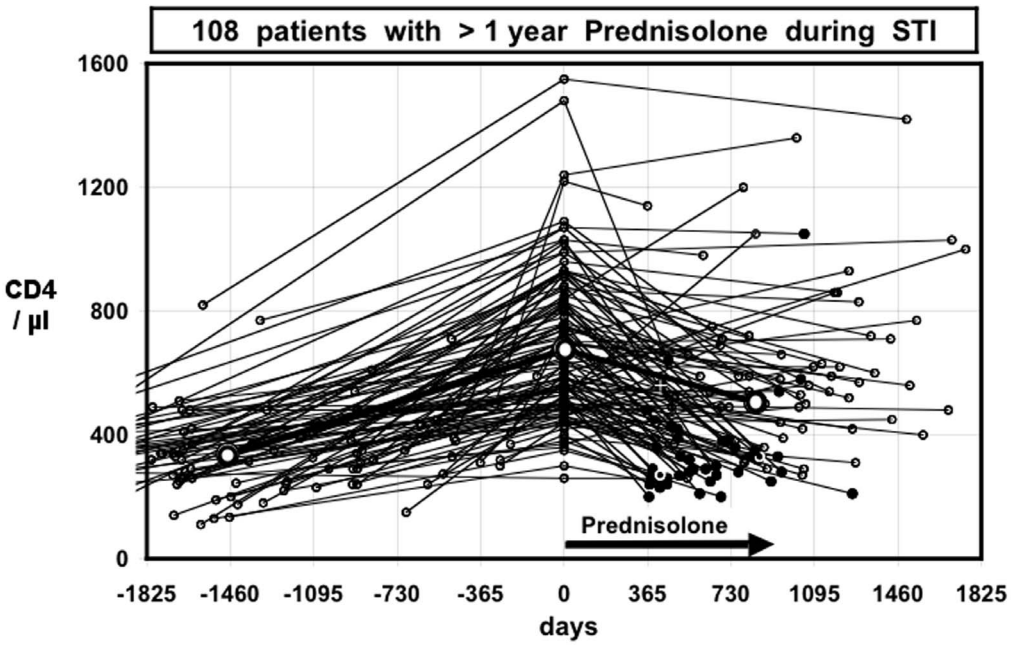

Fig. 4. CD4+ T cell profile (Nadir, partly outside the diagram, cell count prior to prednisolone treatment without ART, actual count under prednisolone without ART) of 108 STI patients with >1 year prednisolone treatment. The figure shows that the CD4+ T cell count in some patients achieved a degree rendering HAART-restart indispensable (black filled circles at the end of STI), partly due to clinical or other reasons like thrombocytopenia and partly due to patients' wish. However, stable CD4+ T cell counts without signs of immunodeficiency can be observed in many patients for years (24 patients >3 years, 7 patients >4 years)

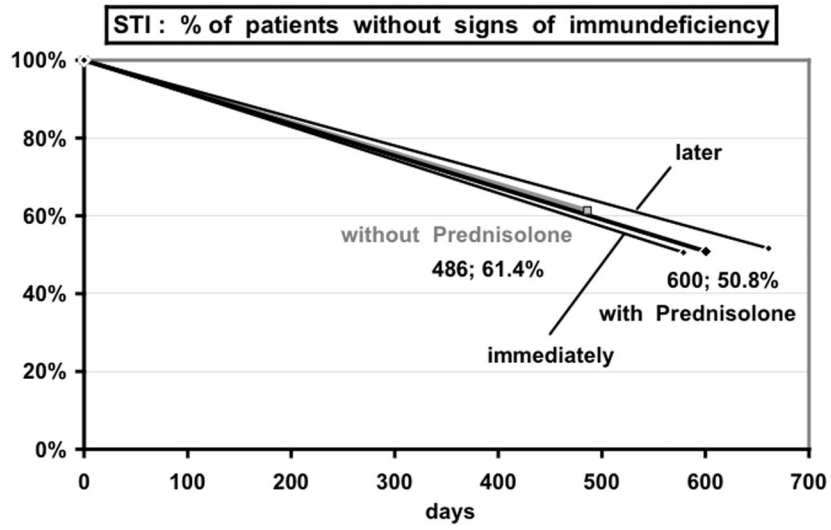

Fig. 5. Percent of patients without signs of immunodeficiency during STI - comparison between patients with prednisolone (without regard to date of onset) and without prednisolone.

Discussion

The use of prednisolone during STI was not yet discussed. Up to date only clinical studies with asymptomatic patients (1, 2) or with prednisolone as an adjunct to antiretroviral therapy (34) were conducted. Data from in vitro studies as well as theoretical considerations (3, 4, 5, 10, 11, 12, 13, 15, 22, 23, 24, 28, 29, 31) and the use of corticosteroids in HIV-related diseases (5, 6, 8, 13, 15, 16, 17, 20, 21, 24, 26, 29, 32, 35) are discussed in our previous paper (33).

The management of HIV by HAART and treatment interruptions is still a subject of controversies. However, the ongoing discussion about STI is not the main topic of this paper. Aim of our study was the description of the impact of prednisolone on the course of STI which should lead to further investigations.

Observed prednisolone- and control-group were not randomly assigned. The groups differ significantly in nadir, CD4+ T cell count at STI-baseline and not significantly in CD4+ T cell increase from nadir to STI-baseline. However, the findings showed no correlation of these parameters and the degree of CD4+ T cell decrease during STI. In the subgroups of the prednisolone-study group, i.e. the ongoing STI- and

the HAART-restart group a tendency to reverse correlations was observed.

Comparing the degree of CD4+ T cell decline over time, we found in 54.2% of STI patients a flatter or similar decline during the first half of STI as compared to the second half. This leads to the assumption that the less extent of CD4+ T cell decrease after starting prednisolone therapy in patients with later prednisolone onset seems to be prednisolone-related. This is supported by the observations in a few patients the CD4+ T cell decrease of whom rose up to 1.3/day after stopping prednisolone intake.

Summing up, data analysis shows a CD4+ T cell-stabilizing effect of low dose prednisolone during STI. In the 2-year-analysis, 63.0% of our STI patients with prednisolone showed CD4+ T cell stability; interestingly the beneficial effect of prednisolone on CD4+ T cells varies considerably between the patients. Up to now, we could not find any predictive parameters.

The probability of signs of immunodeficiency is generally increased during structured treatment interruptions (with or without prednisolone), likewise in the presence of high CD4+ T cell counts. Reconstituted CD4+ T cells do not always have the same functionality as the original CD4+ T cells. Further data is needed – especially with regard to the incidence of OHL and candidiasis in our patients with prednisolone. However, in most cases the observation of potential signs of immunodeficiency didn't result in the necessity of abrupt STI-termination. The risk of potential immunodeficiency should be balanced against the risks of ART and structured treatment interruptions should always be regularly monitored.

However, our findings strongly indicate a potential to prolong ART-free time in part of HIV-patients for many years which means valuable new opportunities in the general concept of treatment.

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Address for correspondence:
Dr. A. Ulmer
HIV-Schwerpunktpraxis
Schwabstr. 26
D-70197 Stuttgart, Germany
Tel.: +49-711- 626308
Fax: +49-711- 610074
e-mail: albrecht.ulmer@gmx.de