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Sublingual Allergen Immunotherapy in HIV positive patients.

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ABSTRACT

HIV infection is a relative contraindication for allergic immunotherapy (AIT). In the last decade highly active antiretroviral therapy (HAART) has improved immune function and life expectancy in HIV infected patients whose respiratory allergies incidence is similar to the general population.

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We evaluated the safety and clinical effectiveness of sublingual immunotherapy in a group of grass-pollen allergic HAART treated HIV-positive patients. Thirteen patients received sublingual immunotherapy (SLIT) tablet (Oralair, Stallergenes®) and symptomatic therapy and were compared with nine receiving symptomatic therapy alone. Clinical benefits were evaluated by analysis of total combined score (TCS), sum of symptom-medication score and a quality of life (QoL) questionnaire. HIV viral load and peripheral TCD4 lymphocytes were analyzed at the beginning and the end of the study. Clinical efficacy data showed a significant improvement in SLIT treated patients compared to controls (TCS: $p=0.0001$; QoL: $p=0.03$). We did not observe a significant alteration of TCD4 cells counts and viral load (VL) in both groups.

Keywords: grass-pollen, HIV-infection, sub-lingual immunotherapy (SLIT), TCD4, VL

INTRODUCTION

The prevalence of allergic respiratory diseases, asthma and rhino-conjunctivitis, has increased dramatically with the advent of industrialization, both in industrialized and in developing countries.

The allergen-specific immunotherapy is considered the gold-standard treatment of respiratory allergic diseases because it induces symptom control, long-term remission, a prevention of the development of new sensitization to new allergens and asthma progression.

Sublingual immunotherapy (SLIT) for allergic respiratory diseases was first described in 1986 and immediately appeared as a viable alternative to the traditional subcutaneous route.

The incidence of respiratory allergy in HIV infected patients is similar to the general population (1).

In the last decade the introduction of highly active antiretroviral therapy (HAART) has dramatically increased survival of HIV infected patients. The reduction of antiretroviral adverse events, the increased access and adherence to HAART have revolutionized the course of HIV infection improving immune function. In fact the cause of death for most HIV-infected patients has changed from AIDS-related opportunistic infection to chronic diseases with an inflammatory pathogenesis usually associated with the elderly (2).

Considering the proven positive effects of antiretroviral therapy on immune system function, in this pilot study we have evaluated the efficacy and safety of allergen-specific SLIT in a group of treated HIV-positive patients with grass pollen allergy

MATERIALS AND METHODS

Thirty HIV adult positive patients were enrolled by the Allergy and Clinical Immunology Unit of L. Sacco Hospital in Milan. Inclusion criteria were: stable antiretroviral treatment, undetectable viremia (VL<37 copies/ml) and peripheral CD4 T-cells count more than 350 cells/mm³ for at least one year, a clinical history suggesting grass-pollen sensitization, a skin prick test positive to grass pollen, clinical report of rhino-conjunctivitis with or without asthma. Exclusion criteria were: prior diagnosis of AIDS, persistent allergic rhinitis and asthma, severe asthma, previous immunomodulant therapy and other contraindications to immunotherapy. Twenty six patients resulted eligible and were enrolled by a participating physician and attributed 1:1 to immunotherapy: group A = thirteen patients, who received Oralair (Oralair 100 & 300 IR Stallergenes©) sublingual tablets of grass pollen from January to April 2013 (N= 13: 1 female, 12 males), or symptomatic therapy arm: group B= thirteen control patients, who received symptomatic therapy alone (antihistaminic, steroid nasal spray, eye drops, steroid sprays and bronchial beta 2 agonists) (N= 13: 5 females, 8 males), according to a computer generated randomization list, only available to another researcher.

Symptomatic therapy during May 2013 was granted for two groups of patients.

Patients had kept a diary since the previous grass pollen season for the daily evaluation of symptoms severity (rhino-conjunctivitis total symptom score plus asthma score and medication score: total combined score (TCS)

(3) The patients have also filled out a questionnaire on QoL (4).

TCS, peripheral TCD4 counts and plasmatic viremia were performed twice: at the enrollment (T0 May 2012, observational period) and at the end of the study (T1 May 2013, treatment period). All patients signed an informed consent at the time of study entry while the protocol was approved by local Ethics Committee.

As data were normally distributed, procedures were based on parametric analyses. Comparisons between different groups were made using a two-tailed T-test. Possible relationships were evaluated using Pearson's or Spearman's correlation tests. Changes from baseline were evaluated using a general linear model: gender and baseline values for the variables were included in the final equations. Statistical analysis was performed using the SAS/STAT statistical package (SAS Institute Inc., Cary, NC, USA).

RESULTS

Twenty-two patients (13 in the group A and 9 in the group B) concluded the study.

Epidemiological, clinical and therapeutic characteristics of patients enrolled in the study are showed in Table 1.

Four patients in the group A reported mild adverse events (1 oral aphthosis, 2 sublingual edema and 1 epigastric discomfort), but they did not interrupt SLIT treatment. Four males in the group B were lost for poor compliance and were excluded by final analyses.

At baseline, groups were similar as regards age (43.2 ± 9.7 in group A and 45.5 ± 6.0 in group B) but different in female proportion (7.7% vs 38.5% respectively, $p=0.06$). This difference increased after 4 males in the group B were lost to follow-up (7.7% vs 55.5%, $p=0.01$). Subsequently, gender was included in the final adjusted analysis and was not significantly related to our findings. To be as conservative as possible, although the differences were not statistically significant, baseline TCS and QoL values were included in the final equations, as appropriate, comparing TCS and QoL changes from baseline between groups.

After the treatment period, we observed a significant reduction of TCS in SLIT treated HIV positive patients compared to controls (group A T0 vs T1: 376 ± 133 vs 204 ± 155 $p<0.0001$ group B T0 vs T1: 277 ± 147 vs 278 ± 150 $p=ns$).

A similar significant reduction was evident for the QoL (group A T0 vs T1 94 ± 29 vs 46 ± 23 $p<0.0001$ group B T0 vs T1 78 ± 22 vs 80 ± 15 $p=ns$) (fig. 1 panel B).

In addition, the TCS and the QoL at T1 were significantly lower in group A compared to group B (TCS group A vs group B $p<0.0001$; QoL group A vs group B $p=0.0003$) (fig 1 panel A and B). In the multivariate analysis, QoL change from baseline was also significantly associated to baseline value ($p=0.002$).

During the study period we did not observe a significant alteration of peripheral TCD4 lymphocytes counts (group A T0 vs T1: 684 ± 350 vs 696 ± 266 , $p=ns$; group B T0 vs T1: 598 ± 232 vs 704 ± 228 , $p=ns$) in both group of patients. The VL remained undetectable (<37 copies/ml).

DISCUSSION

The main purpose of this study was to evaluate if even in antiretroviral treated HIV patients with respiratory allergies, allergic immunotherapy (AIT) represents a safe and effective therapeutic tool. Our preliminary data, in

a small group of HIV positive patients, show that not only the SLIT therapy is clinically effective but it is safe and does not change any immune-virological parameter.

In particular SLIT therapy in our grass-pollen allergic HIV virologically-suppressed antiretroviral treated patients induced: 1) significant improvement of TCS and QoL, 2) no change in the peripheral TCD4⁺ cells count, 3) no change in the HIV viremia compared to controls. In addition in our pilot study Oralair is shown to be safe for HIV positive patients since there were no serious adverse events or dropouts due to intolerance.

HIV-infection represents a relative contraindication for AIT. The 2011 Task Force Report on AIT considers the possibility to treat even patients with acquired immunodeficiency (5), though still lacking solid clinical data to support this claim. The two most important concerns are the limited information on the response to therapy and the potential stimulus on viral replication by maintenance AIT.

The therapeutic approach for the pharmacological control of allergic manifestations in HIV positive patients is similar to that of immuno-competent patients, with the exception of the possibility to prescribe immunotherapy (generally contraindicated in all states of immuno-suppression).

However, the use of steroids could be disadvantageous in HIV-patients because it can induce systemic or local immuno-suppression. In addition, from the pharmacokinetic point of view, certain antiretroviral drugs and the use of medications used in the treatment of allergy may cause interaction of clinical significance. Moreover the incidence of atopy and allergic reactions in general is similar or even increase in HIV-positive patients (6-8).

There were concerns about the role of immunotherapy in the context of HIV infection. Different studies in patients with HIV have demonstrated that vaccinations have a minimal effect on peripheral lymphocytes TCD4⁺ cells counts and plasmatic VL (9-10). Furthermore, as stated in a survey conducted by the American Academy of Allergy and Clinical Immunology, 40% of physicians surveyed said that they would treat with AIT HIV positive patients like any immunocompetent patient (11).

There are also some case reports in the literature that would seem to indicate that specific AIT is safe in HIV-positive patients, at least in the early stages of the disease or in patients on antiretroviral therapy with low VL and discrete CD4 count (12-15). A review article (1) suggests guidelines for allergy treatment in HIV positive patients with early to middle HIV disease with a CD4 count of 400 or more cells/mm³ with no history of AIDS associated diseases and no evidence of plasma viremia.

These clinical results are even truer if we consider our data, the availability of more effective antiretroviral therapies and the new therapeutic strategies that antiretroviral therapy started earlier to preserve the immunocompetence function of Immune System.

Still under discussion is the effect of long-term stimulation of the AIT on HIV status that should be administered for a period of 3-5 years where a close monitoring over time of immuno-virological parameters is certainly required.

We experienced two main limits in our study: the small number of enrolled patients on one side and the absence of a blinding control group on the other. But this is only a pilot study, with the primary purpose to demonstrate the safety of the allergic immunotherapy in a group of HIV treated patients. Stepping up in this process we need a DBPC study that can confirm our data and therefore show the efficacy and the safety of this therapy even in HIV-seropositive treated population. Considering the potential interaction between symptomatic allergic drugs and protease inhibitors, together with the high incidence of allergy respiratory diseases in HIV population, SLIT could be evaluated in the management of these allergic patients.

Conflict of interest.

The authors declare that they have not conflict of interest.

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FIGURE LEGENDS:

Figure 1: Total Combined Score (panel A), QoL (panel B) in HIV SLIT treated patients (Group A) (dark bars) and HIV control patients (Group B) (light bars) at T0 (May 2012) and T1 (May 2013). Mean values, SE and *p* values are shown.

Tab. 1: Epidemiological, clinical and therapeutic characteristics of the patients enrolled in the study.

REFERENCES:

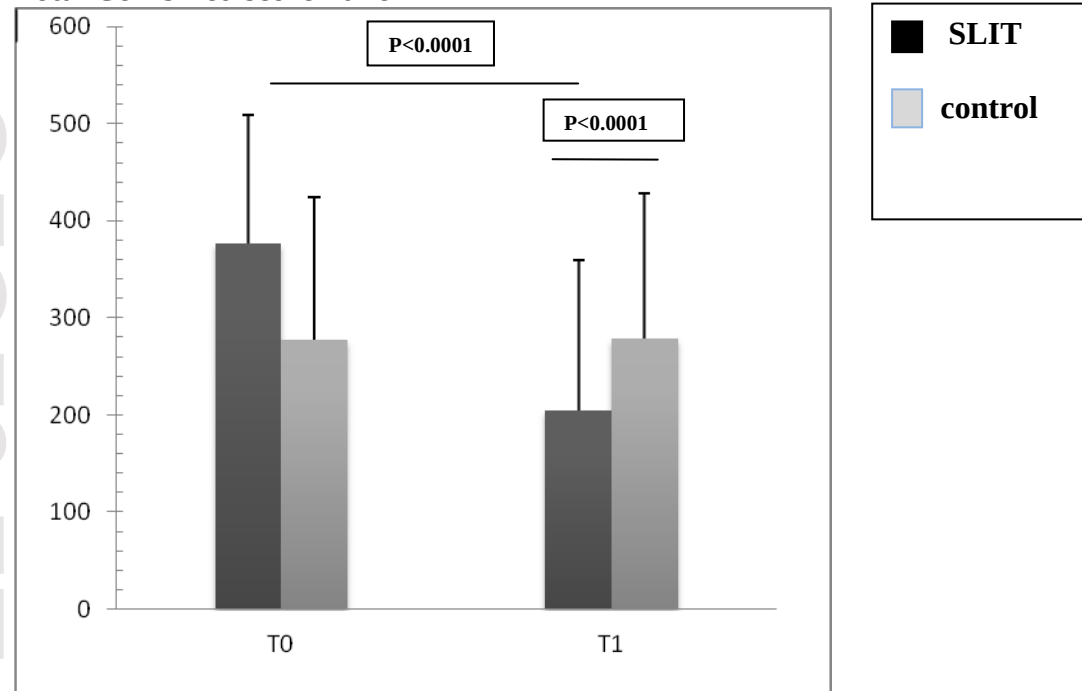
- 1) Marshall GD. AIDS HIV-positive patients and allergies. *Allergy Asthma Proc.* 1999; 20: 301-304.
- 2) Rodger AJ, Lodwick R, Schechter M et al. Mortality in well controlled HIV in the continuous antiretroviral therapy arms of SMART and ESPRIT trials compared with the general population. *AIDS* 2013; 27: 973-979.

- 3) Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol.* 2011; 127 (1): 64-71.
- 4) Juniper EF, Thompson AK, Ferrie PJ, Roberts JN. Validation of the standardized version of the Rhinoconjunctivitis Quality of Life Questionnaire. *J Allergy Clin Immunol.* 1999; 104 (2 Pt 1): 364-9.
- 5) Cox L, Nelson H, Lockey R et al. Task Force Report: Allergen immunotherapy: A practice parameter third update. *J Allergy Clin Immunol.* 2011; 127 (1): S1–S55.
- 6) Rancinan C, Morlat P, Chêne G, Saillour F, Guez D, Lacoste D, Bernard N, Doutre S, Series C, Aubertin J, Beylot J, Salamon R. Prevalence of Clinical Manifestations of Allergic Reactions in HIV infection. Cross sectional study of 115 subjects. *Internal Med Rev.* 1997; 18 (9): 691-4.
- 7) Dikeacou T, Katsambas A, Lowenstein W, Roman C, Balamotis A, Tsianakas P, Carabinis A, Renieri N, Metaxotos N. Clinical Manifestations of allergy and Their Relation to HIV infection. *Int Arch Allergy Immunol.* 1993; 102 (4): 408-13.
- 8) Corominas M, Garcia JF, Mestre M, Fernández-Viladrich P, Buendia E. Predictors of atopy in HIV-infected Patients. *Ann Allergy Asthma Immunol.* 2000; 84(6): 607-11.
- 9) Keller M, Deveikis A, Cutillo-Garcia M et al. Pneumococcal and influenza immunization and human immunodeficiency virus load in children. *Pediatr. Infect Dis J.* 2000; 19: 613-618.
- 10) Castro P, Plana M, Gonzalez R, Lopez A, Vilella A, Argelich R, Gallart T, Pumarola T, Bayas JM, Gatell JM, García F. Influence of a vaccination schedule on immune responses and viral load rebound in HIV-infected Patients Treated successfully. *AIDS Res Hum Retroviruses.* 2009; 25(12): 1249-59.
- 11) Coifman RE, Cox LS. 2006 American Academy of Allergy, Asthma & Immunology member immunotherapy practice patterns and Immunotherapy and Allergy Diagnostics Committee Concerns of the AAAAI. *J Allergy Clin Immunol.* 2007; 119 (4): 1012-3.
- 12) Randhawa I.S, Junaid I, Klaustermeyer WB. Allergen immunotherapy in a patient with human immunodeficiency virus: effect on T-cell activation and viral replication. *Ann Allergy Asthma Immunol.* 2007; 98: 495- 497.
- 13) Fodeman J, Jariwala S, Hudes G, Jerschow E, Rosenstreich D. Subcutaneous allergen immunotherapy in 3 patients with HIV infection. *Ann Allergy Asthma Immunol.* 2010; 105(4): 320-1.
- 14) Lee-Wong A and Kohli M. Allergen immunotherapy in HIV patients with severe allergic rhinitis. *J Allergy Clin Immunol.* 2003; 11(1) suppl 2: S72.
- 15) Wheeler J, Van Stee V, Bayuk JL . Allergen Immunotherapy in a 45 year old Caucasian wrong with 20-year history of severe allergic rhinitis with HIV: Viral load monitoring of HIV and T Cells During Immunotherapy. *J Allergy Clin Immunol.* 2009; 123 (2): S61.

	Age (years)	Sex	HIV positive since (year)	HIV Therapy since (year)	Current HIV therapy	Allergic symptoms	SLIT Side effects	Allergy since (year)
Group A								
1	28	M	2006	2006	NRTI+PI	RC	no	2000
2	37	M	1995	1995	NRTI+PI	RC, A	Aphthosis	2008
3	46	M	2003	2003	NRTI+PI	RC	no	1980
4	60	M	1998	1998	NRTI+PI	RC, A	no	2008
5	42	M	2001	2001	NRTI+PI	RC	Sublingual AE	2005
6	46	M	1996	1996	NRTI+NNRTI	RC	no	2004
7	54	M	1985	1998	NRTI+INI	RC	no	2006
8	38	M	2008	2008	NRTI+NNRTI	RC	Heartburn	1981
9	56	M	1997	1998	NRTI+PI	RC, A	no	1994
10	37	F	1997	1998	NRTI+PI	RC, A	no	1986
11	48	M	1996	1997	NRTI+NNRTI	RC	no	1980
12	40	M	1995	1996	NRTI+PI	RC, A	no	1992
13	30	M	2011	2011	NRTI+INI	RC	Sublingual AE	2001
Group B								
1	55	F	1994	1994	NRTI+INI	RC, A		2006
2	52	M	2002	2002	3NRTI	RC		2000
3	40	F	2000	2000	NRTI+PI	RC, A		2007
4	36	M	2011	2011	NRTI+PI	RC, A		1990
5	48	F	2011	2011	NRTI+NNRTI	RC		2004
6	42	F	2000	2003	NRTI+NNRTI	RC		1981
7	41	F	1996	2002	NRTI+PI	A		1999
8	48	M	1985	1999	NRTI+NNRTI	RC		2003
9	38	M	2000	2000	NRTI+NNRTI	RC		2006
10*	50	M	1996	1998	NRTI+PI	RC		1995
11*	43	M	1999	1999	NRTI+PI	RC		2004
12*	47	M	1994	1996	NRTI+PI	RC, A		1999
13*	52	M	2002	2003	NRTI+INI	RC		2005

TAB 1: Epidemiological, clinical and therapeutic characteristics of the patients enrolled in the study
NRTI: nucleoside reverse transcriptase inhibitors drugs; NNRTI: non-nucleoside reverse transcriptase inhibitors
drugs; I: protease inhibitors drug; RC: Rhino- Conjunctivitis; A : asthma; AE: angioedema , * lost to follow up

Total Combined score Panel A



QoL Panel B

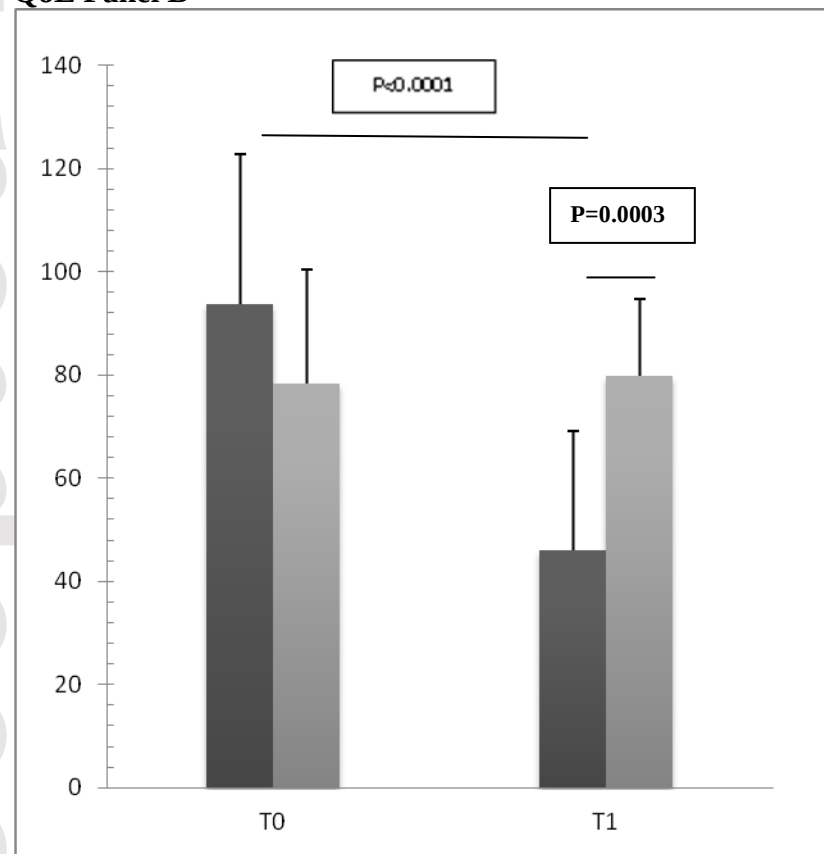


Figure 1: Total Combined Score (panel A), QoL (panel B) in HIV SLIT treated patients (Group A) (dark bars) and HIV control patients (Group B) (light bars) at T0 (May 2012) and T1 (May 2013). Mean values, SE and *p* values are shown.