

Safety and Efficacy of Allergen Immunotherapy in Patients with HIV and Allergic Rhinitis: Facts and Fiction

Saima Alam, MBBS, MD, MRCP^{1,*}
Moises A. Calderon, MD, PhD²

Address

^{1,2}Department of Allergy and Clinical Immunology, Royal Brompton Hospital, London, UK

Email: sam_alam7@yahoo.co.uk

²Section of Allergy and Clinical Immunology, Imperial College London, NHLI, Royal Brompton Hospital, London, UK

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Opinion Statement

Allergic disorders are increasing, and more than a quarter of the global population have allergies. The belief that individuals infected with human immunodeficiency virus (HIV) are less likely to develop allergic disorders has been disproved. Approximately 33.3 million individuals younger than 25 years of age are living with HIV. Allergic rhinitis is a poorly controlled, chronic disorder in this group of patients. The burden of disease related to allergic rhinitis, both personal and global, has challenged the experts in the field to improve currently available treatments. Allergen immunotherapy is the only recognised treatment which can modulate the immune system and develop tolerance. It has been available for the past 100 years, and although improvements have been made to make it more effective and a relatively safe treatment option, it is poorly used for treating patients with HIV who have allergic rhinitis. This article explores the limited information available in the literature to help highlight the urgent need to address this issue which remains a complex management dilemma for physicians.

Introduction

Human immunodeficiency virus (HIV) infection can severely affect the immune system leading to loss of functional CD4⁺ T lymphocytes. Patients infected with HIV have Th1/Th2 cytokine imbalance, polyclonal

hypergammaglobulinemia, and increased levels of total serum IgE levels [1].

Immunotherapy with allergen extracts is a well-known treatment modality in use since 1911 [2] for managing poorly controlled allergies due to seasonal and perennial aeroallergens and hypersensitivity to insect venom. It involves gradually increasing doses of allergen extract administered via the subcutaneous or sublingual route resulting in immunologic tolerance to a specific allergen. Allergen immunotherapy (AIT) is the only disease-modifying intervention in use for treating allergic disorders [3, 4].

CD4+ T lymphocytes produce IL-4, which is an essential step for the production of IgE antibody. CD4 Th2 cells can switch the production of IgM to IgE or IgG2 and IgG4 in humans [5]. Some researchers have investigated the effect of the loss of CD4+ cells in patients infected with HIV on the development of IgE production and the associated symptoms of allergic disorders [6•].

The World Health Organisation (WHO) and various allergy, asthma, and immunology societies across the world have proposed guidelines for administering AIT to treat allergic rhino-sinusitis and

conjunctivitis, allergic asthma, and Hymenoptera hypersensitivity. The guidelines aimed to improve techniques for better outcomes and most importantly to reduce the risks associated with administering allergens as immune modifiers.

The first ever published list of indications and guidelines for AIT against inhalant allergens and hypersensitivity to venoms, was published in 1987 by the expert working group of the European Academy of Allergy and Clinical Immunology (EAACI) [7]. Since then, clinical guidelines have been revised and published by experts belonging to well-known organisations such as the European Academy [8, 9], World Health Organisation [10, 11], British and American Societies of Allergy and Clinical Immunology [12, 13], the Global Strategy for Asthma Management and Prevention [14], and the International Consensus Report on Rhinitis [15].

The main focus of this commentary is to highlight and discuss the facts versus assumptions based on limited evidence available in the literature for the HIV infected population cohort being considered for AIT.

Guidelines for allergen immunotherapy (AIT): facts and fiction

HIV infection has been traditionally considered a relative contraindication to AIT. We have endeavoured to include all the relevant guidelines and position papers on this subject to highlight the evidence available in the literature at present time.

Facts

1. (a) The European Academy on Allergy and Clinical Immunology (EAACI) working group published their position paper on immunotherapy in 1993 [8]. The guidance suggested immuno-pathologic conditions and malignancies as absolute contraindications to receiving AIT. The position paper on immunotherapy to treat hypersensitivity to Hymenoptera venom, also published in 1993, by the European Academy, agreed with their peers on the contraindications and special circumstances to be considered for AIT [9].
- (b) In 1997, scientists and physicians from various countries met in Geneva to review the indications for AIT and discuss new forms of therapy under development for AIT [16]. It was decided to keep the contraindications suggested in the position paper published in 1993 [17], by the working group of the European Academy of

Allergy and Clinical Immunology (EAACI) without any suggested changes.

2. The British Society of Allergy and Clinical Immunology (BSACI) published guidelines for immunotherapy in allergic rhinitis and for treating hypersensitivity to venoms [18•, 19•].

Immunodeficiency was included under the heading of relative contraindication to AIT. The use of AIT in patients infected with HIV was not mentioned specifically. The guidance for immunotherapy to venom hypersensitivity very briefly touched upon contraindications. Lack of data on the outcome and safety of AIT in immunodeficiency states was highlighted and it was suggested that patients with such conditions should be chosen after risk/ benefit assessment in favour of AIT.

3. The joint task force representing the American Academy of Allergy And Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) published guidelines on immunotherapy in 2010 [20••]. This comprehensive document discussed the contraindications and special considerations for offering immunotherapy in detail. The guidance suggested that patients infected with HIV having middle disease (defined as CD4 count of 400 cells/ μ l or more) were eligible to receive immunotherapy.

The AAAAI guidance on venom immunotherapy published in 1986, stated that there were no absolute contraindications to venom immunotherapy [21].

Fiction

1. The 1993 EAACI position paper on immunotherapy, which was referred to by authors of the later publications on the same subject [8] did not specifically mention HIV infection as an absolute contraindication, but people with allergies also infected with HIV were possibly excluded from receiving immunotherapy based on the suggested guidelines excluding patients with immuno-pathologic conditions from receiving AIT. Evidence in the literature including case reports describing the use of immunotherapy in patients with AIDS and/or HIV are sparse, giving weight to this assumption.
2. The BSACI guidance for the use of immunotherapy to treat allergic rhinitis and venom hypersensitivity lacked specific guidance in relation to patients infected with HIV. This lack in evidence may be perceived as a contraindication for offering AIT to Patients infected with HIV by clinicians with limited experience in the subject.

Published evidence on the use of allergen immunotherapy in patients with HIV and AIDS

In the 1990s, research was conducted to find correlations between total and specific IgE levels, CD4+ lymphocytes, and atopic disease in patients infected with HIV. The results from these studies concluded that there was no correlation

between the raised levels of total IgE found in patients infected with HIV having low CD4 cell counts and the presence of atopic disease [22–25]. It was further suggested that raised levels of total IgE found in HIV patients with low CD4+ cell counts may be a consequence of different IgE regulatory lymphokine production by the T lymphocytes [23].

Some researchers believe that immune-based hypersensitivity disorders such as allergies may develop in patients with HIV even before the manifestation of immunodeficiency [26]. It has been shown that patients with HIV have similar prevalence of allergies to environmental allergens as the general population. It is also suggested that since the advent of the highly effective antiretroviral therapy the life expectancy of patients with HIV has increased considerably.

Allergic rhinitis remains poorly treated due to the lack of safety and efficacy data on AIT in this group of patients. In 2011, a summary on the effects of HIV and AIDS on allergic disorders was published. The authors had reviewed articles from Medline and OVID databases. It was highlighted that HIV infection altered the immune system causing cell-mediated immune deficiency and that the resulting immune dysfunction was the cause for the increased prevalence of allergic diseases in this patient group. Concerns were also raised over the lack of understanding of the interactions between HIV and allergies [27].

A recent study re-examined the effects of loss of CD4+ lymphocytes on allergic symptoms and allergen-specific IgE levels in patients infected with HIV [6•]. It was concluded that allergic patients infected with HIV and who have AIDS with severely reduced CD4 cells continued to produce allergen specific IgE antibodies, resulting in atopic symptoms. It was further concluded that secondary responses in allergen specific IgE does not require functional T cells and should be borne in mind when developing new therapeutic options for IgE-related allergic disorders.

Paediatric HIV populations also show a higher prevalence of allergic disorders. A recent study [28•] evaluated children with HIV under specialist follow-up between the ages of 1 to 18 years in Brazil for the presence of allergies. Twenty-nine subjects were included in the study. The prevalence of allergic disorders was reported as 65.5 %. Allergic rhinitis was the most frequently reported with a prevalence of 44.8 % followed by atopic asthma at 37.9 %. The study lacked details on the treatment that the patients were receiving for their allergic symptoms. The conclusions drawn from this study were that there was no difference in the levels of total IgE in patients with and without allergic symptoms. It was further concluded that children with more advanced HIV disease had higher levels of total IgE. These findings were similar to those observed in the adult HIV patient population.

There still remains a large gap in literature on the safety and efficacy of allergen immunotherapy in patients infected with HIV. Two case reports have been referred to in the third update on allergen immunotherapy published in 2010 by the joint task force of the American societies of allergy and immunology which are the only case reports available for perusal in peer-reviewed journals.

Steiner et al [29] published a case report following successful desensitisation to birch, hazel, alder, and ash tree pollens over a 3-year period. The patient had well-controlled HIV disease on antiretroviral therapy (HAART) before commencing AIT. His CD4+ count was 307/ μ L with RNA viral load of 50 copies/mL. During the 3-year immunotherapy period, his CD4 count increased to 350

cells/ μ L and remained at this level. His viral load did not change from 50 copies/mL. AIT was tolerated well during both the up-dosing and maintenance phases. The treatment was successful with significant improvement in seasonal symptoms. The patient denied symptoms of allergic rhinitis 3 years after discontinuation of immunotherapy confirming the efficacy of AIT.

Rhandhawa et al. [30] in 2007 reported findings of increase in the RNA viral load and CD4 counts in a patient receiving antiretroviral therapy with stable disease over a 5-year period, following the introduction of AIT to a variety of aeroallergens including tree, grass, and weed pollens as well as a cocktail of mites mix, feather mix, and Hormodendrum and Penicillium antigens. The allergens extracted from the pollens were dispensed in separate vaccines. The remainder of the allergens and antigens were mixed together in one vaccine.

The patient started immunotherapy with four vaccines, which was tolerated well for 6 weeks except for a change in the CD4 count from 540 cells/ μ L to 570 cells/ μ L. At 16 weeks, his viral load increased to 10,900 copies/mL from previously undetectable levels. At the end of 24 weeks of AIT, his viral load became undetectable and his CD4 count was recorded at 356 cells/ μ L. AIT had been tolerated well except for localised reactions at the injection sites. At the time of publishing the report, patient had not yet reached a maintenance dose of AIT.

The investigators concluded that weekly AIT may induce T-cell proliferation and increase RNA viral load. The report was inconclusive since the patient was still in the up-dosing phase of immunotherapy treatment and hadn't yet reached the highest dose used for maintenance therapy. This case highlights the need for vigilance when treating HIV-infected patients with weekly injections of allergen extracts.

Fodeman et al in 2010 [31] published a letter in the *Annals of Allergy, Asthma, and Immunology* on a case series of three patients with HIV receiving AIT who were successfully undergoing treatment at the time of the publication.

Patient 1 had an undetectable RNA viral load at the start of the treatment which remained undetectable during the 153 weeks of treatment. Her CD4 cell count fluctuated between 960 cells/ μ L and 1,045 cells/ μ L. She had tolerated immunotherapy injections well and reported symptomatic improvement during maintenance immunotherapy.

Patient 2 also reported symptomatic improvement with regular AIT. His viral load remained undetectable, and the CD4 count changed from 884 cells/ μ L at initiation to 1,100 cells/ μ L at 53 weeks. He had also tolerated the treatment well.

Patient 3 had received AIT for 158 weeks at the time of the publication. His viral load was undetectable at the start of immunotherapy but fluctuated thereafter between undetectable to >200 copies/mL. He had also reported symptomatic improvement and AIT was well tolerated without any reported adverse events.

The authors concluded that patients with HIV tolerate AIT well. They had observed only minimal effects on CD4 cell counts and RNA viral loads in their patient group. It was also suggested that a larger patient population was required to confirm the safety and efficacy of AIT in HIV infection.

Conclusions

There is a lack of sufficient evidence either in favour or against the use of AIT in patients with HIV with or without AIDS. The issue is further complicated by non-specific statements in guidelines failing to identify any specific factors to be considered when choosing patients with HIV for immunotherapy.

Although it has been repeatedly suggested that acquired immunodeficiency is a relative contraindication for receiving allergen immunotherapy, experts in the field have also highlighted the need to assess patients with HIV requiring immunotherapy on individual basis.

Collaboration between specialists in the field of allergy and HIV medicine could help improve the odds in favour of offering AIT in people with HIV with or without AIDS. It is also desirable to have more reports of such cases in peer-reviewed journals to instil confidence in clinicians dealing with allergy treatment decisions in their clinical practise.

Compliance with Ethics Guidelines

Conflict of Interest

Saima Alam declares that she has no conflict of interest.

Moises A. Calderon declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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