MEDICAL RESEARCH REPORTS

Med Res Rep 2019;2(1):9-12

RESEARCH ARTICLE

TITLE: EFFECTS OF IMMUNOTHERAPY ON T-LYMPHOCYTE AND CYTOKINE COMPOSITION

Ali SEYED RESULİ[1]

1 Istanbul Yeni Yüzyıl University, Faculty of Medicine, Department of ENT, Istanbul, Turkey

ABSTRACT

Objective: In this study, we aimed to compare serum IFN-g and T4 and T8 lymphocyte levels before and after immunotherapy in patients treated for allergic rhinitis. Thus, the effects of immunotherapy on these pathways were investigated.

Methods: Five study groups including 40 patients with allergic rhinitis and 10 healthy individuals were included. Group I (n=10): Patients whose IFN-g levels were measured before implementation of IT. Group II (n=10): Patients whose IFN-g levels were measured after implementation of IT. Group III (n = 10): Patients whose IFN-g levels were measured in the 3rd control year after implementation of IT Group IV (n=10): Patients whose levels of T4 and T8 lymphocytes were measured before and after implementation of IT. Group V (n=10): Control individuals.

Results: In our study, IFN-g levels before and after the implementation of IT, and in the 3rd control year after the implementation of IT were compared with the control group. IFN-g levels immediately after and three years after IT were found to be significantly higher compared to pre-IT measured values. According to our findings, T4 lymphocyte counts decreased and T8 cell levels decreased after the IT. According to these results, T4/T8 ratio also decreased.

Conclusion: There was a decrease in T4 level, an increase in T8 and decrease in the rate of T4/T8 after the implementation of IT.

Key Words: immunotherapy, interferon-gamma, T4 and T8 lymphocyte.

Cite this article as: Seyed Resuli A. Effects of Immunotherapy on T-lymphocyte and Cytokine Composition: Medical Research Reports 2019;2(1):9-12.

INTRODUCTION

The aim of immunotherapy for more than a century is to train the immune system and teach the body that allergens are not enemies. Allergic response substances are given to patients in increasing doses and over a long period of time to change the immune response of the patient and to prevent the development of allergies in the next encounter with the allergen. Most drugs used in the medical treatment of allergy successfully suppress symptoms over the long term, but do not cure the disease. Immunotherapy is the only successful treatment modality to eliminate the disease. Immunotherapy can be applied to: i) allergies that cannot be controlled despite the use of allergen prevention methods and medication, ii) inability to continue the drug due to side effects of allergy drugs, and iii) to prevent new allergies and asthma development [1].

Allergic rhinitis is an inflammatory disease of nasal mucosa, that occurs by reacting against a normally harmless antigen. It is characterized by troubled local nasal symptoms and general fatigue and adversely affects quality of life [2,3]. Allergen-specific IT is an important treatment method for patients with allergic rhinitis and is the only curative intervention today that potentially balances the immune system and thus affects the natural course of the allergic disease. The long-term efficacy and safety of allergen-specific IT has been confirmed by many clinical studies [4]. There are significant changes in cellular and humoral immunity composition as a result of the İmplementation of IT. Primary changes occur in the ratio of T4 (T-helper, CD4) and T8 (T-suppressor, CD8) and the types of cytokines they secrete (interferon and interleukin) [5,6].

The way to contact with an allergen and its concentration determine the type and amount of cytokine (interferon and interleukin) secreted by allergen-specific T-lymphocytes. Normally, a contact with the antigen results from inhalation. However, there is a change in the relationship between antigen-presenting cells and T-lymphocytes because there will be a contact in intense concentrations and in a short time through implementation of IT

Correspondence Address: Eski Edirne Asfaltı No:653 Bahat Hastanesi Sultangazi/İSTANBUL TURKEY **E-mail:** a.s.resul@hotmail.com

subcutaneously. Thus, instead of production of interleukin-4 (IL-4) by T-cells, interferon-gamma (IFN-g) is produced. IL-4 is a cytokine in the form of polypeptide that is synthesized by T8 lymphocytes. IL-4 is an important growth and differentiation factor for B-lymphocytes. Furthermore, it is the activator for mast cells and macrophages [7]. IFN-g is also called as immune or type II interferon. IFN-g is a cytokine in the form of glycoprotein produced by T4 and T8 lymphocytes. T-helper lymphocytes are divided into two main groups based on the cytokines they secrete. Although Th1 lymphocytes secrete IFN-g and lymphotoxin, Th2 lymphocytes secrete IL-4 and IL-5 [8]. As well as functioning as a co-factor in the proliferation of B-lymphocytes, IL-4 which is synthesized from Th2 lymphocytes, provokes the secretion of Ig-G and Ig-E, and B-lymphocytes stimulated by lipopolysaccharide (LPS). IFN-g is secreted by Th1 cells and inhibits B-lymphocyte functions through IL-4 [9-11]. In many cases, IL-4 antagonizes INF-g activity [12,13].

In this hospital-based case-control study, we aimed to compare serum IFN-g and T4 and T8 lymphocyte levels before and after immunotherapy in patients treated for allergic rhinitis. Thus, the effects of immunotherapy on these pathways were investigated.

METHOD

Ten control individuals and 40 patients with allergic rhinitis admitted to the allergic outpatient clinic (Hospital of Cerrahpaşa Medical Faculty, İstanbul University) due to complaints of nasal congestion, nasal itching, sneezing, red eye and watering of the eyes were included in the study. As the results of anamnesis, ear, nose and throat examination, prick test, and laboratory findings, patients were found to be sensitive to dermatophagoides pteronyssinus (Dp) and dermatophagoides farinea (Df). The main distinctions between the patient groups were based on IFN-g and T4-T8 lymphocyte levels before and after implementation of IT. Thus, five groups were formed along with the control group.

Group I (n=10): Patients whose IFN-g levels were measured before implementation of IT.

Group II (n=10): Patients whose IFN-g levels were measured after implementation of IT.

Group III (n = 10): Patients whose IFN-g levels were measured in the 3rd control year after implementation of IT

Group IV (n=10): Patients whose levels of T4 and T8 lymphocytes were measured before and after implementation of IT.

Group V (n=10): Control individuals.

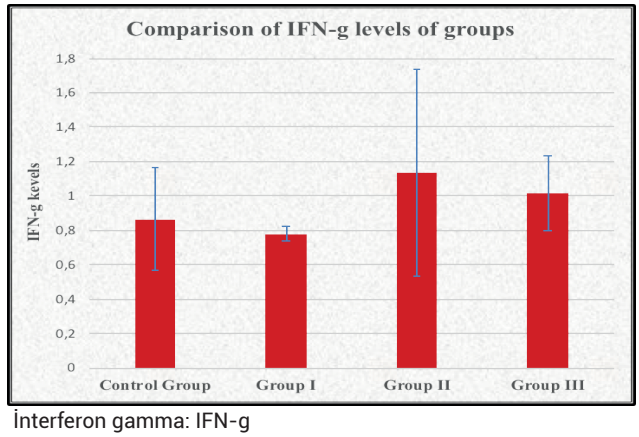
The participants who were included in the study were informed about the study and the Informed Consent Form was signed from the consent of the guardians and the results of the study were used for scientific purposes. The principles of the Declaration of Helsinki and Guidelines for Good Clinical Practices were followed during the study. The ethical approval of study supplied from İstanbul University-Cerrahpasa Medical Faculty.

Immunotherapy was administered subcutaneously Dp (50%) and Df (50%) (HAL Allergy, Haarlem, The Netherlands) at doses of 10 AU, 100 AU, 1000 AU and 10,000 AU each week for the first six months. Subsequently, the classical IT plan (AU 10,000) was implemented once a month for two years. Patients were invited to check for routine follow-up for three years after the IT application.

IFN-g activities were determined by commercially available the radioimmunoassay (RAI) test kits (Medgenix Diagnostics SA, Fleurus, Belgium) according to the manufacturer's instructions. T lymphocyte subgroups were counted using Ventrex Reserch Lab. monoclonal antibodies. In all patients, after a significant improvement in clinical allergy symptoms following implementation of IT, the degree to which serum IFN-g and IT change was changed in allergic patients, 1- IFN-g levels before implementation of IT in Group I, 2- IFN-g levels after implementation of IT, 3- IFN-g levels in the 3rd year after implementation of IT in Group III, and 4- IFN-g levels in the control group were investigated. In addition, the changes between IT and cellular immune composition (T4, T8 lymphocyte count and ratio before and after IT) in allergic patients were examined.

The data were analyzed using Mann-Whitney U - Wilcoxon Rank Sum W test, Wilcoxon Matched - Paris Signed - Ranks test and Person Correlation analysis. The variables were examined at 95% confidence level and p value was accepted as less than 0.05.

Figure 1. Comparison of İnterferon gamma (IFN-g) levels of groups. Values were expressed as mean ± SD.



İnterferon gamma: IFN-g

RESULTS

The participants (40 patients and 10 healthy individuals) were 33 females and 17 males. The age of participants were between 15 and 56 years and the mean age was 25.4 years.

The mean and standard deviations of IFN-g levels of the groups are shown in Figure 1. According to this graph, a statistically significant increase was observed in Group II and Group III when compared with Group I (p values 0.047 and 0.007, respectively). Differences observed in other comparisons were not significant.

Before and after implementation of IT, T4 and T8 levels in Group IV are shown in Figure 2. Accordingly, T4 levels decreased significantly (p = 0.014), whereas T8 values increased (p = 0.007).

The rates of T4 and T8 levels in Group IV before and after IT application are shown in Figure 3. Accordingly, T4/T8 ratio decreased significantly after IT application (p=0.028).

DISCUSSION

T-lymphocytes, B-lymphocytes and their products -cytokines which are activated by allergens play a role directly and indirectly in the formation of immunological mechanisms of allergic diseases and emergence of their clinical symptoms. In this study, after the efficacy of the IT was clinically shown, serum IFN-g levels that were measured at specific times before and after the implementation of IT were compared with the non-allergic control group. Also , changes in T-lymphocyte composition (T4, T8) were determined. According to HanGlass et al., IT mainly affects the T-lymphocyte composition and its subgroups. This effect occurs in two ways: 1) an increase in allergen-specific T8 lymphocytes and 2) a change in allergen-specific T4 lymphocyte phenotype [14].

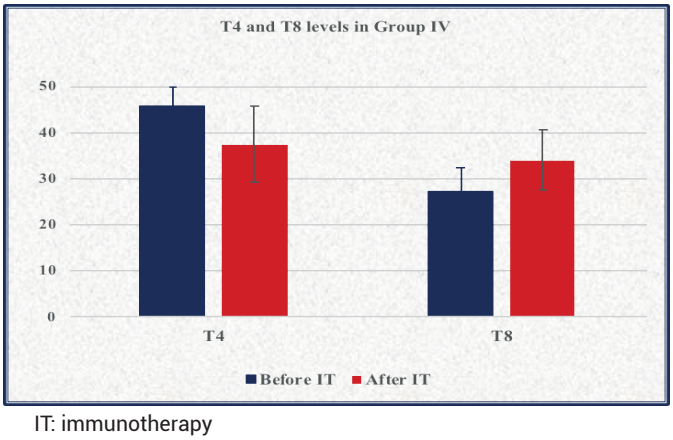
A study showed an increase in IFN-g producing lymphocytes and a decrease in T8 lymphocytes in atopic individuals compared with the normal population. Based on the impact of IT implementation on the T4/T8 ratio, there was a change in favor of T8 [15] and an increase in T8 level from conventional IT management [16)]. In addition, a change in the T4/T8 ratio was found after administration of IFN-g in subjects with hyper-Ig syndrome [17]. A study by Gideon et al. also showed significant changes in the T cell composition resulting from IT administration [18].

In another study, it was found that there were allergic reactions and that the changes caused by implementation of IT were indirectly mediated by cytokines released from T-lymphocytes [19]. IL-4 stimulates allergen-specific Ig E production of B-lymphocytes, allowing eosinophils differentiation and maturation in bone marrow in IL-5. T-helper 2 lymphocyte subgroup synthesizes IL-4 and IL-5 which are responsible for allergic reactions. But, T-helper 1 lymphocytes produce IFN-g which causes the suppression of allergic reactions [20-23].

In their study, Gajewski et al. found a significant increase in the level of IFN-g resulting from the IT. They showed that while this process inhibits proliferation of the allergen-specific T-helper 2 lymphocyte clones selectively, it activates the proliferation of T-helper 1 lymphocyte clones [24]. Jutel et al. found a decrease in antigen-specific IL-4 production in mononuclear cell cultures taken from the peripheral blood of patients undergoing implementation of IT and an increase in IFN-g synthesis [25].

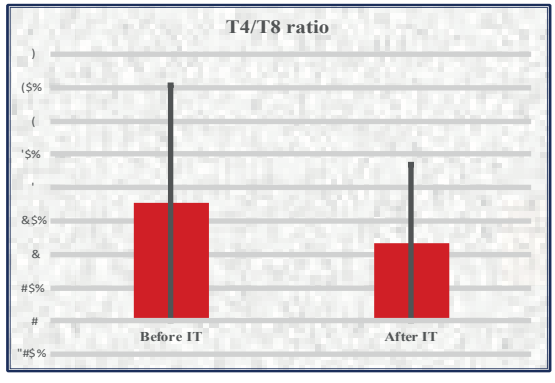
In our study, IFN-g levels before and after the implementation of IT, and in the 3rd control year after the implementation of IT were compared with the control group. IFN-g levels immediately after and three years after IT were found to be significantly higher compared to pre-IT measured values. That is, IT raises the IFN-g level. These findings

Figure 2. Mean and standard deviations of T4 and T8 levels in group IV before (dark navy blue) and after (dark red) immunotherapy



IT: immunotherapy

Figure 3. Mean and standard deviations of T4 / T8 ratio in group IV before and after immunotherapy.



IT: immunotherapy

were consistent with the literature. According to our findings, T4 lymphocyte counts decreased and T8 cell levels decreased after the IT. According to these results, T4/T8 ratio also decreased.

Conclusion

There was no significant difference in the serum IFN-g levels between the allergic patients whom IT was not implemented and that of the control group. There was a significant increase in the serum IFN-g levels of the patients' IT was administered compared to the levels before the implementation of IT and levels of the control group. There was a decrease in T4 lymphocytes in the peripheral blood, an increase in T8 lymphocytes and a decrease in the rate of T4/T8.

Acknowledgements : The author would like to thank Bahat Hospital chief physician Dr. Hamza Bahat, İstanbul University, Cerrahpasa Faculty of Medicine Department of ENT and İstanbul Yeni Yüzyıl University, Faculty of Medicine, Department of ENT.

Disclosure of funding sources: The authors received no financial support for the research and/or authorship of this article.

Disclosure of potential conflict of interest: The authors declare that they have no conflict of interest in the publication of this article.

REFERENCES

1. Durham S. ABC of allergies. Summer hay fever. BMJ. 1998;316(7134):843-5.
2. Arebro J, Ekstedt S, Hjalmarsson E, Winqvist O, Kumlien Georén S, Cardell LO. A possible role for neutrophils in allergic rhinitis revealed after cellular subclassification. Sci Rep. 2017;7:43568. doi: 10.1038/srep43568.
3. Steinsvaag SK. Allergic rhinitis: an updated overview. Current allergy and asthma reports 2012;12:99-103.
4. Jiang Z, Xiao H, Zhang H, Liu S, Meng J. Comparison of adverse events between cluster and conventional immunotherapy for allergic rhinitis patients with or without asthma: A systematic review and meta-analysis. Am J Otolaryngol. 2019; pii: S0196-0709(19)30486-7. doi: 10.1016/j.amjoto.2019.07.013.
5. Gurka G, Rocklin R. İmmunologic responses during allergen-specific immunotherapy for respiratory allergy. Ann Allergy 1988;61:239-43.
6. Dullaers M, Schuijs MJ, Willart M, Fierens K, Van Moorleghem J, Hammad H, Lambrecht BN. House dust mite-driven asthma and allergen-specific T cells depend on B cells when the amount of inhaled allergen is limiting. J Allergy Clin Immunol. 2017;140(1):76-88.e7. doi: 10.1016/j.jaci.2016.09.020. Epub 2016 Oct 13.
7. Specific Review of İmmunology 5:429-460-,1987 50.
8. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA. Two types of murine hepler T cell. I. Definition according to profiles of lymphokine activities and secreted proteins. J. Immunol. 136:2348
9. Brown MA, Hural J. Functions of IL-4 and control of its expression. Crit Rev Immunol. 2017;37(2-6):181-212.
10. Rabin E, Mond J, Ohara J, Paul W. İnterferon-g inhibits the action of B cell stimulatory factor (BSF)-1 on resting Bcells. J Immunol. 1986;137:1573.
11. Reynolds D, Boom W, and Abbas KA. Inhibition of B lymphocyte activation by interferon-g J. Imumunol. 1987;139:767-73.
12. Reeves R, Magnuson NS. Mechanisms regulating transient expression of mammalian cytokine genes and cellular oncogenes. Progress in Nucleic Acid Research and Molecular Biology 1990;38:241-82.
13. Van Snick J. Interleukin-6: an overview. Annual Review of Immunotherapy 1990;8:253-78.
14. HayGlass KT, Stefura BP. Anti interferon-g treatment blocks the IgE responses. J Exp Med 1991;173:279-85.
15. Canorica GW, Mingari MC, Melioli G, Colombatti M, Moretta L. Imbalance of T cell subpopulations in paients with atopic diseases and effect of specific immunotherapy. J Immunol 1979;123:2669-72.
16. Walker C, Bode E, Boer L, Hansel TT, Blasen K, Virchow JC. Allergic and non-allergic asthmatics have distinct patterns of T-cell activation and cytokin production in peripheral blood and bronchoalveolar lavage. Am Rev Respir Dis 1992;146:109-15.
17. Robinson LD. Gamma interferon induced changes in CD4/CD8 populations in hyper IgE syndrome J Allergey Clin Immunol 1993;91:141.
18. Gideon Lack, Harold S. Nelson. Rush immunotherapy results in alergen-specific alterations in lymphocyte function and interferon-g production in CD4 T cells. J Allergy Clin Immunol 1997;99:530-8.
19. Secrist H, Chelen CJ, Wen Yan, Marshall JD, Umetsu DT. Allergen immunotherapy decreases interleukin-4 production in CD4 Tcells from allergic individuals. J Exp Med 1993;178:2123-30.
20. Kay AB. Mechanisms and treatment of allergic rhinitis. In Kerr, A.G.; Scott-brown's otolaryngology, vol 4, pp:93-114, Butterworth, 1987.
21. Gajewski TF, Fitch FW. Anti-proliferative effect of INF-g inhibits the proliferation of Th2 but not Th1, murine hepler T lymphocyte clanes. J Immunol 1988;140:4245-52.
22. Moore KW, Vieira P, Fiorention DF, Trounstine ML, Khan TA, Mosmann TR. Homology of cytokine synthesis inhibitory factor (IL-10) to the EBV gene BCRFI. Science 1990;248:1230-4.
23. Mosmann TR, Bond MW, Coffman RL, Ohana J, paul WE. T cell and mast cell lines respond to B cell stimulatory factor-1. Proc Natl Acad Sci 1986;83:5654-8.
24. Fenkelman FD, Holmes J., Katona ID et al. Lymphokine control of in vivo immunglobulin isotype selection. Annu Rev Immunol 1990,8:303-33.
25. Jutel M, Hichler WF, Skrbic D, Urwyler A, Dahinden C, Muller UR. Bee venom immunotherapy results in decrease of IL-4 and IL-5 and incresase of İFN-g secretion allergen-stimulated T cell cultures. J Immunol 1995;154:4187-94.