IMMUNOLOGICAL EVALUATION OF SUBLINGUAL IMMUNOTHERAPY IN BRONCHIAL ASTHMA

Thesis

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AHR	Air way hyperresponsiveness
ASM	Air way smooth muscle cell
APCS	Antigen presenting cells
BAL	Bronchoalveolar lavage
BHR	Bronchial hyperresponsiveness
CCR	Chemokine receptor
CCL	Chemokine ligand
DBPC-RCTs	Double blind placebo control randomized control trials
DCs	Dendritic cells
D.farinae	Dermatophagoides farina
EAR	Early phase asthmatic reaction
EBV	Epstein Bar Virus
EGF	Epidermal growth factor
FcεRI	High-affinity IgE Fc receptor
FEV	Forced expiratory volume
FGF	Fibroblast growth factor
FLG	Filaggrin
ICS	Inhaled corticosteroid
GM-CSF	Granulocyte macrophage colony stimulating factor
GWA	Genome wide association
HB-EGF	Related molecules to epidermal growth factor
HLMC	Human long muscle cell
HRCT	High resolution completed tomography
HSP	Heat shock protein
IFN-γ	Interferon gamma
IL	Interleukin

LAR	Late phase asthmatic reaction
LABA	Long acting B2 agonist
LTs	Leukotriens
MCP-3	Monocyte chemotactic protein-3
MCP-4	Monocyte chemotactic protein-4
MDC	Machrophage derived chemokine
MHC	Major histocompalibility complex
MIP-1a	Macrophage inflammatory protein
MMP-9	Matrix metallopeptidase-9
mRNA	messenger RNA
NGF	Nerve growth factor
iNKT	Invariant natural killer T cell
OVA	Ovalbumin
PAF	Platelets activating factor
PBMCs	Peripheral blood mononuclear cells
PDGF	Platelets derived growth factor
PGE2	Prostaglandin E2
RANTES	Regulated on activation, normal T-cell expressed and secreted
RDBPC	Randomized double-blind placebo-controlled
SCIT	Subcutaneous allergen immunotherapy
SLIT	Sublingual immunotherapy
SMD	Standardized mean difference
SNPs	Single nucleotide polymorphisms
TARC	Thymus and activation regulated chemokine
TGF-β	Transforming growth factor-β
Th	T helper cell

TLR	Toll-like receptor
TNF-α	Tumor necrosis factor alpha
Treg	T regulatory cell
TSLP	Thymic stromal lymphopiotein

ABSTRACT

Background: Allergen specific immunotherapy is aimed at modifying the natural history of allergy by inducing tolerance to the causative allergen. In its traditional, subcutaneous form, immunotherapy has complete evidence of efficacy in allergic asthma. However, subcutaneous immunotherapy (SCIT) has a major flaw in side effects, and especially in possible anaphylactic reactions, and this prompted the search for safer ways of administration of allergen extracts. Sublingual immunotherapy (SLIT) has met such need while maintaining a clinical efficacy comparable to SCIT.

OBJECTIVES: We aimed to investigate immunological efficacy of mite-specific SLIT and SCIT versus a placebo in asthmatic patients who were sensitized to house dust mite: *Dermatophagoides farinae (D.farinae).*

METHODS: This study is a prospective, randomized, three parallel group studies, comparing the clinical and immunological efficacy of SLIT and SCIT, with *(D.farinae)* allergen to that of placebo in treatment of patients with allergic asthma and a proven allergy to *(D.farinae)* by skin prick test. 60 patients mono-sensitized to *(D.farinae)* were randomized to receive either SLIT (n=30), SCIT (n=15) or Placebo (n=15). Symptom and medication score, serum *(D.farinae*) specific immunoglobulin E (IgE), IL4, IL-10 and IFN-γ levels were evaluated at base line and after three months.

RESULTS: SLIT and SCIT demonstrated a significant reduction in asthma symptom and medication score. A significant reduction of serum-specific D.farinae IgE in SLIT and SCIT were observed. Serum IL-10 and IFN-γ significantly increased in SLIT and SCIT compared with placebo, whereas serum IL-4 significantly decreased. No statistically significant change was observed when SLIT compared to SCIT either in clinical or immunological parameter.

CONCLUSION: Both SLIT and SCIT demonstrated clinical and immunological improvement compared to placebo in asthmatic patients monosensitized to *D. farinae.*

Keywords: Allergic asthma, efficacy, specific immunotherapy, sublingual immunotherapy, interleukine

Introduction

INTRODUCTION

Despite remarkable advances in diagnosis and long-term management, asthma remains a serious public health problem worldwide and is now one of the most common chronic diseases in developed countries. Asthma is characterized by reversible airway obstruction, bronchial hyperresponsiveness, and airway inflammation. The key pathological features of asthma are highly complex with multiple features that include infiltration of the airways by activated lymphocytes, eosinophils, and neutrophils; mast cell degranulation; and mucous gland hyperplasia**.** Asthmatic epithelium exhibits sloughing and/or denudation and cilia dysfunction together with collagen deposition in the epithelial sub-basement membrane area**.** Asthma pathology is associated with the release of pro-inflammatory substances including lipid mediators, inflammatory peptides, chemokines, cytokines, and growth factors. In addition to infiltrating leukocytes, structural cells in the airways, including smooth muscle cells ،endothelial cells, fibroblasts, and airway epithelial cells, are all important sources of asthma causing or enhancing mediators ***(Walsh and McDougall, 2007).***

Inhaled glucocorticoids (ICS) are first-line therapy for asthma due to their potent anti-inflammatory properties that primarily result in reduced numbers of airway inflammatory cells and their associated mediators. The symptoms of most asthmatics are satisfactorily controlled by the regular use of ICS with or without the addition of a long-acting β2-agonist (LABA). They reduce airway hyperresponsiveness (AHR), disease exacerbations, and hospitalizations while improving lung function and quality of life. However, ICS are symptomatic medications requiring life-time therapy for the patient, and are relatively non-specific in their actions while variations