Newer Perspectives of Childhood Asthma

Dr Keya Lahiri*, Dr Mrunalini Chavarkar⁺

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Introduction

Childhood asthma has been currently linked with the Allergic cascade and as a step in the “Allergic March”. The major atopic diseases viz, Atopic Eczema, Food Allergy, Allergic Rhinitis and Bronchial Asthma can develop in sequence or simultaneously in the same child, however in majority of them, the disorders appear at different ages. Atopic eczema occurs in early childhood followed by food allergy. Subsequently child develops allergic rhinitis and asthma.

The concept of “United Airways” or “One Airway One Disease”

It must be known that asthma and rhinitis occur as co-morbidities [1]. It is supported by their common epidemiological, pathological and physiologic characteristics. Further on, quality of life relating to child's health is called “Health Related Quality Of Life (HRQOL)”. The objectives would be learning impairment, school performance, reading, comprehension and non-sedating antihistamine. The child may also exhibit absent mindedness, pre-occupation, daytime somnolence, fatigue and school absenteeism.

With the rising trend in asthma and related allergic diseases, the past four decades have witnessed dramatic increase in the understanding of both the immunology and the mechanism of inflammation related to asthma and its co-morbidities, further on leading to major new approaches to treatment. These approaches include, avoiding the causes, preventing the immune response, blocking every aspect of the inflammatory response and reversing bronchospasm. Still, large numbers continue to get exacerbations requiring hospitalization. Acute inflammation manifesting as broncho-constriction produces symptoms; chronic inflammation leads to non-specific hyperactivity and airway remodelling culminates in persistent airflow obstruction [2]. Is remodelling reversible? Do the anti inflammatory measures make any difference to the long term outcome? Can a relevant marker be found to identify this process? We need

answers to the above queries. The co-existence of asthma and allergic rhinitis have been conclusively shown and hence one begets the other [1].

The presentation of cough variant asthma should be always borne in mind because it leads to early diagnosis and decreasing morbidities. Another objective modality of assessing the severity and predicting outcome with necessary changes in individual therapies is “Ventilation-Perfusion scan in chronic persistent asthma” [3-6]. Our pilot study, the first of its kind in children shows promising results.

Future aspects of therapeutic strategies

Most therapies are based on improvements in existing therapies or on a better understanding of the cellular and molecular aspects in atopic diseases. Many new therapies in development are aimed at inhibiting components of the allergic inflammatory response but there are possibilities of preventive and curative treatment.

Bronchodilators

This class is used for symptom relief but have no effect on underlying inflammatory process. Inhaled β_2 agonists are safe and effective and there is no parallel to this drug. They relax smooth muscle by increasing the concentration of cyclic AMP and by opening up potassium channels. Hence, the attention has shifted to the development of treatment that suppresses or prevents the atopic inflammatory process.

Corticosteroids

Steroids provide the standard against which new therapies are judged, however, high doses of oral steroids lead to septicemic side effects. Inhaled steroids have revolutionized the treatment of asthma [7], nasal steroids for the management of allergic rhinitis and topical steroids for atopic dermatitis, but dermal atrophy has restricted its use.

New generation steroids viz. budesonide, fluticasone propionate and mometasone furoate have minimal side

*Professor & Head, Department of Pediatrics, Seth GS Medical College & KEM Hospital, Parel, Mumbai, ⁺Lecturer, Department of Pediatrics, TNM College & BYL Nair Charitable Hospital, Mumbai.

effects as the swallowed fraction of the drug is removed by hepatic metabolism. However, these drugs are absorbed from the lung or nasal mucosa and may have side effects at high doses; hence the need for steroids that are metabolized locally viz, "SOFT STEROIDS" i.e. "CICLESONIDE" seems promising as it has less side effects [8,9]. Steroids inactivated in the plasma are now in development.

Mediator antagonists

Antihistamines:

Older antihistamines caused sedation whereas the new generation viz, fexofenidine and terfenadine cause no sedation and improve health related quality of life. They are of immense benefit in allergic rhinitis and atopic dermatitis.

Antileukotrienes :

SLO inhibitor i.e. ZILEUTON and apelinyl leukotriene receptor (apt-LT1) antagonists (pranlukast, zafirlukast, and montelukast) have been developed as an adjuvant [10-17]. They improve symptoms, exercise induced asthma [18], lung function and reduce the need for rescue bronchodilator and useful in aspirin sensitive asthma. They are effective orally and have no specific side effects. They have no benefit over nasal corticosteroids in allergic rhinitis. Selective inhibitors of inducible nitric oxide synthase (iNOS) are now in development.

Tryptase inhibitor 9APC 366 is poorly effective in asthmatic patients. More potent tryptase inhibitors and PAR2 antagonists are now in development.

Cytokine modulators

Anti-IL-5(19):

Interleukin (IL-5) is crucial in orchestrating the eosinophilic inflammation of asthma. Humanised monoclonal antibodies to IL-5 can be used as a single injection, reducing blood eosinophils for several weeks.

Anti-IL-4(20):

IL-4 is critical for synthesis of IgE by B lymphocyte and also eosinophil recruitment to the airways. Inhibition of IL-4 may be effective and soluble IL-4 receptors are in clinical development.

Anti-IL-3:

IL-3 causes AHR and mucus hypersecretion and may be an important target for the development of new therapies.

Anti TNF:

Tumour necrosis factor (TNF) 2 amplifies asthmatic inflammation; hence soluble TNF receptors are a logical approach to asthma therapy.

Chemokine inhibitors

Chemokine are rantes, MCP-3, MCP-4 and eotaxins may be crucial in the recruitment of eosinophils in atopics.

Anti-inflammatory cytokines

They have anti-inflammatory activity in atopic inflammation. IL-10 inhibits synthesis of proteins. IFN inhibits Th2 cells, thereby inflammation. IL-12 determines the balance between Th1 and Th2.

New anti-inflammatory drugs

These are PDES, transcription inhibitors, MAP kinase inhibitors, tyrosine kinase inhibitors, immunosuppressants and cell adhesion blockers.

Specific anti-allergy drugs

Cromones (Sodium cromoglycate and nedocromil sodium) are the most specific anti-allergy drugs [21,22]. Topical application is effective in asthma, rhinitis, and conjunctivitis, but effects are less marked and effective only in mild disease.

Th2 cell inhibitors - Cyclosporin A and tacrolimus are relatively less effective. CD4+ (Keliximab) which reduces circulating CD4+, seems to have some effect on asthma [23-25].

Anti-IgE-Rhu-Mab-E25 (humanized monoclonal murine Ab) reduces early and late responses to inhaled allergen [26].

Immunotherapy

One of the most novel, yet effective treatment modalities available to the medical professional is "immunotherapy" for allergic diseases (also termed "specific immunotherapy" or SIT). Other synonyms for this treatment are desensitization, hyposensitization, allergy shots, allergy vaccines and allergen injection therapy. Discovered in 1911 by Leonard Noon (27) at St. Mary's Hospital in London, SIT has stood the test of time for the past 89 years and has now come to be accepted as the cornerstone of treatment for allergic diseases. Approximately 64 million patients received SIT in Europe and North America in a survey published in 1991 [28] and this figure is steadily increasing every year.

SIT involves the subcutaneous injection of allergen extracts in increasing concentrations and decreasing frequency, starting about twice a week, then once a week and later once in two weeks. The aim of SIT is to introduce a state of "hyposensitization" with a diminished clinical response on natural re-exposure to the allergen. Few medical treatments have been shrouded in as much controversy as the practice of SIT. The only compelling argument in favour of establishing a specific diagnosis in allergic diseases is that when the offending allergen

is identified, a specific treatment can be instituted. Only two specific treatments are available to the allergic patient; allergen avoidance and SIT. Medication although useful, will only suppress symptoms but does little to modify the long term disease process. SIT is at present the only specific, disease modifying, cost effective treatment option [29]. Immunotherapy is an important part of our treatment of allergic diseases. Its importance in our treatment plans will increase as we recognize the potential for subtle complications from pharmacotherapy [30].

Preventive strategies

Atopy seems to be due to deviation from Th1 to Th2 cells which may arise because of failure to inhibit the normal Th2 preponderance at birth which in turn may result from environmental factors such as Th1 response to infectious agent.

- Immunotherapy : Specific allergen vaccine.
- Peptide immunotherapy : Peptide fragments block T-cell response.
- Vaccination : Induces protective Th1 responses to prevent sensitization and thus prevent atopy. BCG vaccination has been associated with a reduction in atopic diseases in Japan, but this has not been confirmed in Swedish population.

Gene Therapy

Atopy being polygenic, there is no role of gene therapy in long term treatment. One needs to target genes in IL4 and IL5 cluster. Advances in therapy will be facilitated through development of more specific anti-allergy drugs that lack side effects. If it can be taken orally, it would treat asthma, rhinitis and eczema which often coincide. The possibility of developing a cure is remote but strategy to inhibit the development of sensitization in early childhood offers such a prospect in future.

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From the Editor's Desk

From the response of the readers and contributors, it is heartening to know that the new look MJAFI has had the desired impact by stirring up readers' interest and authors' enthusiasm. This is a great source of inspiration for the Editorial Board. In our constant endeavour to meet quality standards and time deadlines, certain impediments, inherent to our environment have to be overcome. We wish to share some of the most commonly occurring ones with an aim to minimize their impact through mutual understanding.

From receipt of an article to its final publication takes 6 months to one year, if the article is of good quality. Every article received is sent for peer review, provided it meets all the criteria laid down in the "Instructions to Authors" of January 2004 issue. When an article falls short of these criteria, it is returned to authors for rectification and resubmission. On the other hand, an article meeting these criteria is reviewed by the Editorial Board and sent to referees for peer review. Observations and queries raised by Editorial Board and referees are then again routed to authors for reply. Once a satisfactory reply has been received and accepted by referees, articles are screened by Editorial Board for selection. Hence, it is obvious that transit time is one major factor in delay. Transfers, postings, temporary duties and annual leave of authors and referees further delay processing. In order to minimize this time lag, a few simple solutions will go a long way and benefit all. Towards that end, we request authors and referees to carefully follow all the instructions, be always aware that spoken and written language differ considerably and be prompt and precise in their replies to raised issues. We are confident that with a more responsive attitude the time lag can be further trimmed down and participative enthusiasm shored up.

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