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(CASE REPORT)

Role of immunomodulation in childhood asthma and pediatrics: A case series

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Abstract

The definition of immunomodulation refers to the action undertaken by the medication on autoregulating processes that steer the immunological defense system. Immunomodulation is modulation (regulatory adjustment) of the immune system. It has natural and human-induced forms, and thus the word can refer to the following:

- Homeostasis in the immune system, whereby the system self-regulates to adjust immune responses to adaptive rather than maladaptive levels (using regulatory T cells, cell signaling molecules, and so forth)
- Immunomodulation as part of immunotherapy, in which immune responses are induced, amplified, attenuated, or prevented according to therapeutic goals

Keywords: Immune modulation; Childhood Asthma; Therapy

1. Introduction

A substance that stimulates or suppresses the immune system and may help the body fight cancer, infection, or other diseases. Specific immune system modulators, such as monoclonal antibodies, cytokines, and vaccines, affect specific parts of the immune system.

2. Definition

- Pediatric asthma is a chronic lung disease that often starts in childhood and is characterized by airflow obstruction and airway hyper-responsiveness.
- The 2018 Global Initiative for Asthma (GINA) report defines two major long-term goals of asthma management:
- to maintain good control of symptoms with no restrictions on activity level and
- to limit future exacerbation risk, adverse effects, and fixed airflow limitation.
- Additional goals of therapy include minimizing the necessity for short-acting β2-agonist (SABA) use and preventing progressive loss of lung function.

3. Methods

Two Children from the department of Paediatricsand Child Health at Masaka Regional Referral Hospital with Childhood onset Asthma are presented:

L.K 12yr male, known asthma patient for 4 years now on unknown inhaler medication presented with history of sudden chest pain described as heaviness, non-radiating associated with shortness of breath and wheezing.Reported history of

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restlessness in the night and failure to sleep. Mother reports that child was given 2 puffs of the inhaler which eased the patient's restlessness.

Report no history of cough, no hemoptysis. A diagnosis of Acute Asthma exacerbation was made. Child was treated with salbutamol Nebs and i/v Hydrocortisone. With resolution of symptoms.

N.h 3yr female presented with history of dry cough for 3 days, no associated chest pain, and no hemoptysis. A day prior to admission, child developed shortness of breath with audible wheezing. No associated chest pain or heaviness.A diagnosis of Acute Asthma exacerbation was made.She was treated with salbutamol Nebs and i/V Hydrocortisone. Discharged on salbutamol inhaler and oral prednisone for 3 days.

4. Results

4.1. Immune Modulation

- Clinical diseases resulting from dysregulation or defects in immunomodulation
- Commonly used or new immunomodulatory therapies
- Adverse effects of immunomodulatory drugs

4.2. Definition of Immune Modulation

- Term referring to a wide range of drug or biologic interventions that alter normal or abnormal immune responses via diverse mechanisms, including:
- altering immune cell proliferation or survival
- modification of cytokine signaling
- changing intracellular signaling responses
- induction of peripheral tolerance

4.3. Examples of Immune Modulation

- Monoclonal antibodies that bind cytokines or cytokine receptors, thereby enhancing or limiting lymphocyte responses
- Inhibiting immunoregulatory transcription factors that regulate expression of pro-inflammatory cytokines
- Preferentially inhibiting cell cycle progression in immunologic cell targets

5. Discussion

5.1. Clinical Diseases Resulting From Dysregulation or Defects in Immunomodulation

5.1.1. Selected Examples

- Allergic/Atopic (e.g., allergic asthma, atopic dermatitis)
- Hypersensitivity, inflammatory (e.g., hypersensitivity pneumonitis, psoriasis)
- Autoimmune (e.g., rheumatoid arthritis, systemic vasculitides)
- Autoinflammatory (disorders involving the inflammasome; e.g., pyrin, cyropyrin).

5.1.2. Asthma: Proposed "Immunophenotypes"

- Non-inflammatory or minimally inflammatory (bronchospastic)
- Th2 predominant
- Th2/Th17 predominant
- Type 2 CD8 (IL13+) predominant
- ILC2 predominant
- Neutrophil predominant
- Mixed lymphoid

5.2. Commonly Used and New Immunomodulatory Therapies

5.2.1. Immunomodulatory Strategies

Molecular immunology-based

- DNA vaccines
- oligopeptides that interfere with chemokine/cytokine

Antibody-based

- soluble antibodies against chemokine/cytokine
- antibodies against chemokine/cytokine receptors

Small molecule - antagonists designed to block receptor function

Transcription factor inhibition using antagonists.

5.2.2. Mycophenolate

Primary effect: reversibly inhibits the enzyme (inosine monophosphate dehydrogenase) used in the de novo pathway of purine synthesis needed for growth of B and T cells (effects naïve, memory and plasma cell differentiation).

Secondary effects: decrease CD83 and CD205 expression on DCs, decrease expression of IL-2R, HLA-DR, adhesion molecules, transferin receptors, IL-1Ra, TGF-a and IL-10.

Clinical uses: prevent organ transplant rejection, steroid sparing in autoimmune disease, Behcet's disease, Pemphigus vulgaris, SLE, psoriasis, IgA nephropathy, lupus nephritis, Crohn's disease.

5.2.3. Methotrexate

Primary effect: inhibits the enzyme (dihydrofolate reductase) used in the metabolism of folic acid.

Secondary effects: decrease ICAM, CXCR3 and IL-12R expression, inhibit methyltransferase activity, inhibit T cell activation, block IL-1b binding to surface receptor, increase IL-10 expression and CD95 sensitivity on T cells

Clinical uses: cancer chemotherapy drug, rheumatoid arthritis, juvenile dermatomyositis, psoriasis, psoriatic arthritis, lupus, sarcoidosis, Crohn's disease, eczema, vasculitis

5.2.4. Glucocorticoids

Primary effect: generally thought of as anti-inflammatory and immunosuppressive. Increases expression of anti-inflammatory genes by binding to receptor and activating genes directly in the nucleus. Can repress pro-inflammatory genes either by repressing genes directly or binding factors in the cytosol and preventing translocation to the nucleus.

Secondary effects: inhibition of bone formation, suppression of calcium absorption, delayed wound healing, muscle weakness, increased risk of infection

Clinical uses: allergies, asthma, autoimmune diseases, sepsis, cancer, prevent acute transplant rejection, prevent graft-versus-host disease

5.2.5. Rituximab

Primary effect: kills all CD20+ B cells except terminally differentiated plasma cells by binding to surface-bound CD20 and inducing antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

Secondary effects: decrease B cell receptor levels, increase shedding CD23, increase MHC II, LFA-1 and LFA-3 expression

Clinical uses: Cancer-leukemia and lymphomas, rheumatoid arthritis, prevent kidney transplant rejection, other autoimmune diseases including MS, SLE, chronic inflammatory demyelinating polyneuropathy .

5.3. Proposed Mechanisms of Allergen Immunotherapy

Subcutaneous Immunotherapy (SCIT)

- Influences on IgE

Inhibition of seasonal increase in specific IgE

- Blocking antibodies (allergen-specific IgG, IgG4, secretory IgA)

No correlation with clinical efficacy

FcγRII engagement

- Induction of mast cell / basophil "non-releaser" phenotype
- Clonal deletion / anergy of allergen-specific $CD4^+$ cells
- Induction of IL-10 producing regulatory T (Tregs) and B cells (Bregs).

5.4. Intravenous immunoglobulin (IVIG)

- Designed for the treatment of humoral immune deficiencies by supplementing insufficient antibody quantity (or quality)
- Of note, at higher doses (2 mg/kg) IVIG has immunosuppressive properties
- IVIG is also effective in idiopathic thrombocytopenic purpura, Kawasaki's disease, and polymyositis.

5.5. Adverse Effects of Immunomodulatory Therapies

- Hypersensitivity reactions (local reactions, anaphylaxis, rash, urticaria, infusion reaction, cutaneous reactions, serum sickness)
- Potential side effects/risks (GI intolerance, headache, liver toxicity, autoimmune-like disorder, neurologic symptoms, cancer, death)
- Immunosuppression (secondary immunodeficiency: decreased vaccination responses, increased risk of infections)

5.6. Immunosuppression

5.6.1. Rituximab (RTX)

- Common immunosuppressive effects: hypogammaglobulinema and severe neutropenia.
- Symptoms: mostly bronchitis, sinusitis, and pneumonia; fatality associated w/ enteroviral meningoencephalitis

6. Conclusion

- When to consult a specialist/ allergist/immunologist for altered immune response:
- Patients with unusually frequent or severe infections or infection involving unusual organisms without clear explanation
- Chronic use of high dose systemic steroids or other immunosuppressive therapies with evidence for hypogammaglobulinemia, lymphopenia, or poor vaccine response
- Live vaccinations are generally avoided in patients on chronic immunosuppression or chronic oral steroid (>20 mg daily prednisone/equivalent for more than 2 weeks).
- Prophylactic antimicrobials should be considered for patients on chronic steroids plus immunosuppressive therapy.

Supplemental IgG should be considered in patients with symptomatic hypogammaglobulinemia, including post B-cell depleting therapy.

Compliance with ethical standards

Disclosure of conflict of interest

Authors declare no conflict of interest..

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