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Review

Immunopharmacology if Autoimmune Disorders in Rheumatiod Arthritis, Myasthenia Gravis and Graves Disease

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Abstract

Immunopharmacology has progressed greatly over the last 25 years with improvements in cell biology and monoclonal antibody technology allowing for the discovery of highly specific antibodies for the treatment of autoimmune disease and organ transplantation rejection. Immunopharmacology has opened up the possibilities for the discovery of new agents and new ways to enhance immune responses, or correct immune deficits, for example by restoring growth factor and cytokine deficiencies through pharmacological therapies. Gene therapy for genetically defective diseases and disorder with defective genes has also become a focus area as a potentially curative long-term treatment pathway. Immunopharmacology can be defined as the science of therapeutic immunoregulation with a focus on selective regulation of the human immune system to achieve clinical benefit. The three categories of drugs under immunopharmacology can be classified as immunosuppressants, tolerogens, and immunostimulants. Immunosuppressants suppress the immune system, while tolerogens induce antigen-specific unresponsiveness. These agents can be utilized in the management of infections, cancer, and in states of immunodeficiency.

Keywords: Immunopharmacology, Autoimmune Disorders, Rheumatoid Arthritis, Myasthenia Gravis, Graves Disease, Immunomodulators

INTRODUCTION

Immunopharmacology is an expanding field of research that examines the complex interactions between drugs and the immune system. The ultimate goal is to understand how drugs modify immune responses, which is critical for developing new therapeutic interventions for a variety of ailments, such as many autoimmune disorders, cancer, and infectious diseases [1]. Improvements in the field of immunopharmacology have been especially strong in the past couple of decades, and reports of biologics and immunotherapies are being developed that are able to intervene in the response from the immune system with unprecedented precision and efficacy. Immunopharmacology will require careful planning and precise drug application due to the many threats and

opportunities included in the anti-immune system activities or immune mediated toxicities and eventual resistance [2]. The dense prism of signalling mechanisms of the immune system presents a vexing landscape for the drug developer, and a considerable amount of detailed investigation in immunological principles, practice and molecular mechanisms will be needed. This research paper serves as an introductory overview to immunopharmacology and is divided into sections detailing the mechanisms of immunomodulation, therapeutic uses and the future of drug development in this field [3]. New therapeutics targeting the immune system have to raise to the table as a target for drug development, with approximately 20% of drug approvals since 2018 that have elements targeting the immune system, and almost 50% of new drug approvals in oncology based on immune system target.

Pathophysiology and Immunopharmacology of Myasthenia Gravis

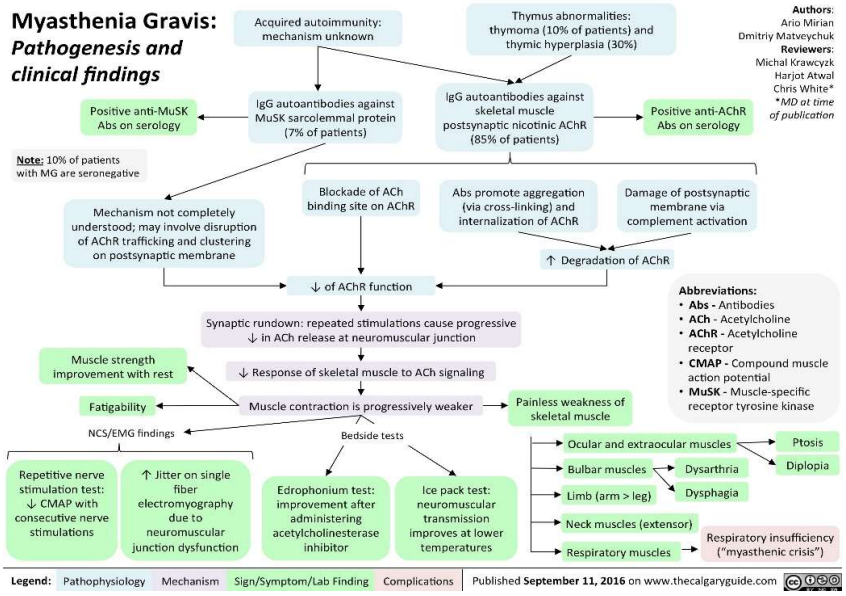

Fig 1: Immunopharmacology of Myasthenia Gravis

Immunopharmacology of Myasthenia gravis class of drugs

Acetylcholinesterase inhibitors

Drugs involved Pyridostigmine and Neostigmine is commonly and most widely used drugs in this. Acetylcholine (ACh) is produced from nerve impulses at the neuromuscular junction and is broken down by the enzyme acetylcholinesterase (ACh) [4]. Pyridostigmine and other acetylcholinesterase inhibitors work by blocking ACh from being rapidly broken down by AChE in the synaptic cleft (i.e. inhibits or slows the breakdown of ACh). In summary, there will be more ACh to bind to the remaining healthy acetylcholine receptors. Increased muscle contraction efficiency leads to stronger muscular contractions and also less muscle tiredness [5]. Because AChE inhibiters do not interrupt the production of the anti-AChR antibodies, blocks the T or B cells that activate the autoimmune response, or halt the progression of immune-mediated injury/damage to the neuromuscular junction, they have an indirect effect on the immune system. under AChEIs the ACh levels are raised to create a better nerve-muscle connection [6]. The goal of AChE inhibitors is symptom management rather than improvement of the overall state of health.

Immunosuppressants and corticosteroids

The drugs used in immunosuppressants in MG are- prednisone, Azathioprine, Cyclosporine and Methotrexate. Immunosuppressants are drugs that reduce the activity of immune cells, suppress antibody formation, reduce T cell activation, and reduce the overall immune response as a whole [7]. There are common immunosuppressants associated with MG (i.e., Prednisone, Azathioprine, Mycophenolate mofetil, Cyclosporine/Tacrolimus, and Rituximab). These medications can improve muscle strength, decrease autoimmunity, reduce the production of harmful antibodies, and have helped manage disease over the long-term.

Corticosteroids, Prednisone for example, are high potency, non-selective immunosuppressants that are used to reduce inflammation and suppress immune cell activity, and, in MG, calm symptoms of muscle weakness. They suppress the hyperactive immune system by having a general "suppressive" effect on both innate and adaptive immune responses [8]. Due to serious side effects from long-term use, most conventional non-steroidal

immunosuppressants, including, Methotrexate, Cyclosporine, Mycophenolate mofetil, Azathioprine, and Tacrolimus are used as "steroid-sparing" medications.

These drugs selectively target the proliferation of T and B lymphocytes to decrease the immune response and decrease the production of autoantibodies [9]. They also inhibit calcineurin, an enzyme that activates the T-cell response, to suppress T-cell activation and proliferation.

Monoclonal Antibodies

Eculizumab, Ravulizumab and Rituximab are widely used. Monoclonal antibodies, which are laboratory-generated proteins, are designed to target different components of the immune system. In multiple sclerosis (MG) are essentially intended to inhibit the generation of autoantibodies, inhibit the complement system, and inhibit the circulation of IgG autoantibodies. Examples of monoclonal antibodies that are used in MG are Rituximab, Eculizumab, Ravulizumab, and others. These allow for long-term management of the disease, improved muscle strength, reduced fatigue, and diminished immune-mediated components [10].

Rituximab targets B cells, the cells that generate harmful antibodies in MG, and reduces B cell populations involved in the generation of autoantibodies targeting MuSK or AChRs. Eculizumab and Ravulizumab inhibit complement proteins that help destroy the neuromuscular junction in MG [11]. Furthermore, these drugs inhibit damaging complement activation at the neuromuscular junction by inhibiting the C5 component of the complement cascade. The neonatal Fc receptor (FcRn) blockers reduce the total "load" of harmful antibodies by inhibiting the circulation of IgG antibodies. These targeted therapies offer better efficacy, greater specificity, and improved patient quality of life [12].

Pathophysiology and Immunopharmacology of Rheumatoid Arthritis

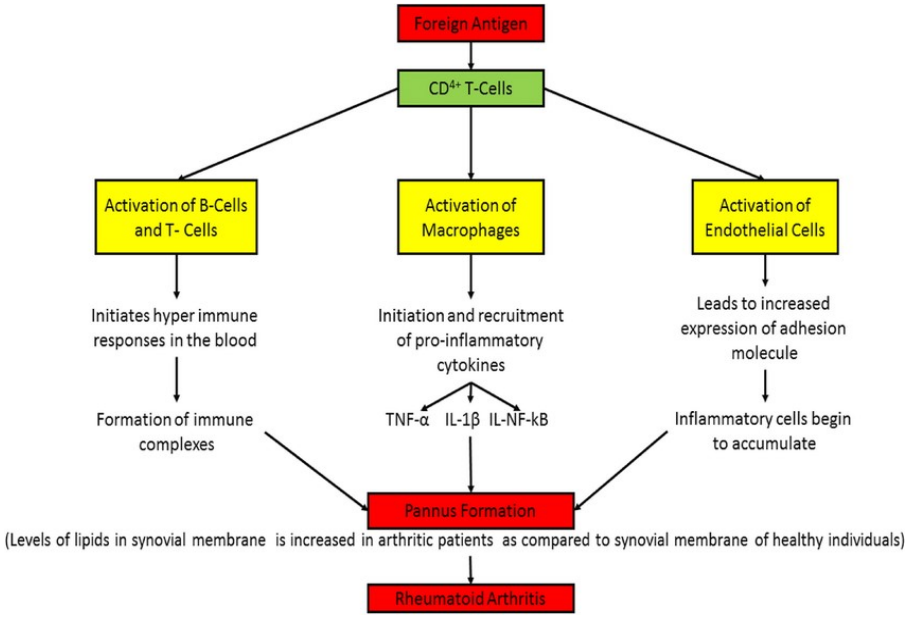

Fig 2: Immunopharmacology of Rheumatoid Arthritis

Immunopharmacology of rheumatoid class of drugs

Corticosteroids

In corticosteroids includes prednisolone and other glucocorticoids Rheumatoid arthritis (RA) is caused by an overactive immune system that is attacking the joints. Corticosteroids can help control this aberrant immune response by reducing immune cell activity, inflammatory cytokines, inflammatory gene expression and antigen presentation [13]. They are also reducing the number and function of immune cells involved in the pathophysiology of RA via glucocorticoid receptors. They also decrease adhesion molecules, inhibit phospholipase A2 (PLA2), decrease pro-inflammatory mediators, and increase anti-inflammatory gene and protein transcription. They reduce the time course of the disease and diminish pain and swelling in the joints. They are quite effective for controlling sudden exacerbations of RA symptoms [14]. Some of the serious side effects are high blood pressure, increasing blood sugar, mood swings, thinning of skin, cataracts, weight gain, fluid retention, osteoporosis, and risk of infection. Corticosteroids play an important role in reducing joint damage and

inflammation in RA. Some of the serious side effects are high blood pressure, increasing blood sugar, mood swings, thinning of skin, cataracts, weight gain, fluid retention, osteoporosis, and risk of infection [15].

DMARD'S

In non-biological agents

which includes immunosuppressants it includes Methotrexate, Azathioprine and cyclosporine drugs. These drugs are a broad class of drugs known as immunosuppressive agents are used to treat rheumatoid arthritis (RA), which is associated with an overactive immune system that attacks the body's own joints and other organs [16]. These help to suppress the immune response by inhibiting antigen presentation, reducing inflammation, affecting the metabolism of DNA and cellular replication and inhibiting T and B lymphocytes that are over-reactive. Some examples of immunosuppressive agents include methotrexate, leflunomide, azathioprine, cyclosporine, and biologics such as TNF inhibitors [17].

First line therapies in RA are frequently conventional disease-modifying antirheumatic drugs (cDMARDs), which essentially lower many components of the immune response. Methotrexate inhibits the metabolism of folate and reduced oedema, pain and inflammation while simultaneously preventing joint damage. Leflunomide, inhibits cell proliferation at the level of blocking the enzyme required for the production of pyrimidines in activated T and B cells [18].

Immunomodulators

Which includes the drugs are sulfasalazine, hydroxychloroquine and leflunomide Immunomodulators are used in rheumatoid arthritis (RA) to modify the immune response by either increasing its response (immunostimulants) or reducing it (immunosuppressants). Immunomodulators reduce inflammation and the damage done to joints by the immune system recognizing the body's tissues as foreign and attacking them [19]. Immunomodulators targets T cell, B cell, cytokine, and Treg with the aim to reduce inflammation and changes in cytokine production. Immunomodulators can also affect gene expression to reduce autoimmune responses, and modulate T and B cell activity to reduce their hyperactivity. Ultimately immunomodulators help reduce inflammation in the joint, regulate cytokine of effector T and B cells, and help achieve a balanced immune response [20]. They also reduce autoimmune responses as a result of regulating both T and B cell activity thus reducing their overactivity. Sulfasalazine inhibits immune cell signalling and antigen presentation to decrease pain and inflammation, while hydroxychloroquine, although it appears less effective compared to other DMARDs, may alter immune cell activity. Biologics or biologic DMARDs (bDMARDs) are specifically engineered proteins that inhibit specific molecules or cells that are part of the inflammatory process, thus, inhibiting RA [21]. These can include, but are not limited to B-cell depleting agents, interleukin (IL) inhibitors, TNF-alpha inhibitors, or Janus Kinase (JAK)/targeted synthetic.

In biological agents includes

TNF alpha inhibitors

Rheumatoid arthritis (RA) generates TNF-α, a pro-inflammatory cytokine that induces inflammation of the joint, as well as stimulates other immune cells. TNF-α drugs prevent deterioration and damage of joints, decrease inflammation, prevent activation of immune cells, and block TNF-α activity. TNF-α inhibitors include Etanercept, Infliximab, Adalimumab, Golimumab, and Certolizumab pegol [22].

TNF-α, a pro-inflammatory cytokine, is targeted and neutralized by biologic drugs called TNF-alpha inhibitors will have an effect on the immune system that is attacking the joints in RA. They will block receptor binding, reduce the downstream inflammatory pathways, neutralize TNF-alpha, and modify osteoclast activity [23]. Blocking receptor binding will contribute to reducing downstream inflammatory pathways, and blocking or reducing TNF-alpha modulates osteoclast activity. Inhibitors of TNF-alpha may also affect immune cell subsets in some contexts, such as possibly helping the regulatory T cells (Tregs) of RA patients be functional again. By blocking TNF-α, there are some risks involved, such as either reactivation of latent infections, higher risk of infections, plus other immune modulation adverse effects [24]. Despite this, TNF inhibitors can extend patient's quality of life, decrease inflammation, and modify the disease course of RA.

Pathophysiology and Immunopharmacology of Graves Diseases

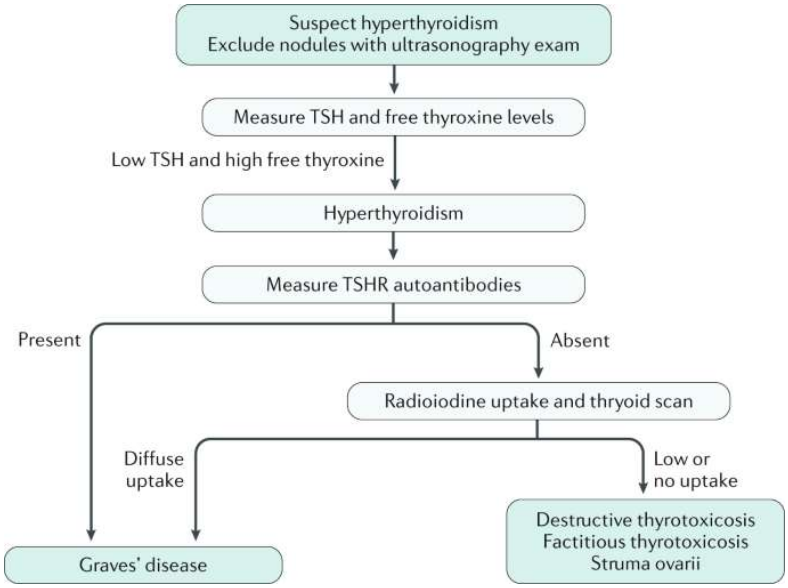

Fig 3: Graves Diseases

Immunopharmacology of Graves disease class of drugs

Antithyroid drugs

Thioamides class of drugs are used as 1st line treatment they are Methimazole and carbimazole.

- TSH receptor antibodies (TRAb) are produced in Graves' Disease, leading to hyperthyroidism.
- Anti-thyroid medications (ATDs) like methimazole and propylthiouracil (PTU) alter the immune system through mechanisms like hormone synthesis inhibition, immunosuppression, T cell modulation, antigen presentation reduction, and oxidative stress reduction [25].
- PTU inhibits peripheral T4 to T3 conversion, leading to rapid T3 levels fall.
- ATDs decrease TSH-stimulating antibodies, improve immune cell balance, and restore immune parameters to normal levels [26].
- Direct immunomodulatory effects include interference with thyroid peroxidase, thyroglobulin iodination, tissue modification, MHC Class I expression inhibition, and apoptosis of intrathyroidal lymphocytes.

Glucocorticoids

Prednisone and Prednisolone are used. Glucocorticoid Effects on the Immune System in Graves' Disease

Immunological Effects

- Suppress T and B cells, thereby inhibiting the generation of autoantibodies.
- Inhibit the release of cytokines to reduce inflammation in the thyroid and orbital tissues.
- Reduces the migration of leukocytes (lymphocytes) to the tissues, and therefore, reduces the infiltration of immune cells in the orbital fat and muscle [27].
- Decrease MHC class II expression to limit antigen presentation.
- Stabilizes blood vessels and decreases oedema to decrease swelling in the orbital tissues [28].

In Graves' Disease:

- High dose injections of glucocorticoids are particularly useful for active and severe GO.
- Glucocorticoids are used in high doses with other medications in Graves' disease thyroid storm to suppress hyperactive immune and inflammatory responses [29].

Appropriate Use and Adverse Effects

Glucocorticoids have adverse effects associated with their use, including increased risk of infections, hyperglycaemia, osteoporosis, weight gain and fluid retention, hypertension, mood effects, skin thinning and easy bruising, muscle weakness, cataracts and glaucoma [30].

CONCLUSION

Immunopharmacology has made major advances over the past twenty five years. Specifically, cell biology and monoclonal antibody technology able to develop high specificity antibodies for the treatment of autoimmune diseases and organ transplant rejection. Immunopharmacology studies drug interactions with the immune system and aims to understand how drugs can induce and modify immunological responses in health and disease. Since 2018, there have been almost 20 % of newly approved drugs that target the immune system. In oncology drug approvals since 2018, almost 50 % are immune system targets. Immunosuppressive agents are used to treat rheumatoid arthritis (RA). RA is an overactive immune system initiating attack against the body, when the immune system attacks the joints and organs in the body. Methotrexate, azathioprine and cyclosporine are Drug Modifying Anti-Rheumatic Drugs (DMARDs) that exert immunosuppressive activity in RA. Immunomodulators induce hypo reactiveness, down regulate production of pro-inflammatory cytokines, or is associated with a normalized immune response. Biologics, or biological DMARDs, inhibit target molecules and cells mediating the inflammatory process. RA is inhibited because the biologics target the inflammatory process.

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