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Immunosuppressant Drugs

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Abstract:

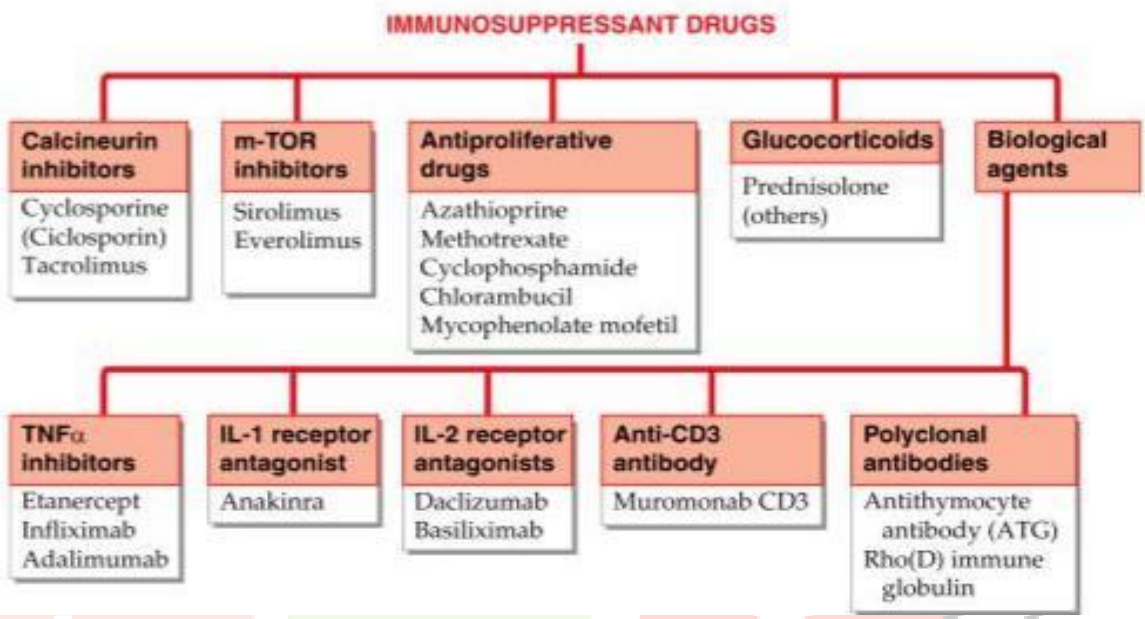
Immunosuppression may worsen severe acute respiratory syndrome coronavirus 2 (SARS- cov2) infection. He conducted a nationwide cohort study of the effect Of exposure to immunosuppressant's on the prognosis of SARS-Cov2 infection in Denmark. He identified an SARS-10 V2 test positive patients. From February 2020 To October 2020 and linked. Healthcare data from nationwide registers, including Prescriptions for the exposure Immunosuppressant drugs? We estimated relative Risks of hospital admission intensive care unit (ICU) admission and death teach Studied independently up to 30 days. From testing) with a 10g linear binomial Regression. Adjusted Fox confounders using a propensity score based matching Weights model.A composite immunosuppressant exposure was associated with a Significantly Increased risk of death adjusted relative risk 1:56 5.95%.] 1.16-2·22) The Increased risk of death was mainly driven by exposure to systemic glucocorticoids Adjusted relative risk 2-38 (95 % CI 1·72-3:30), which were also. Associated with An increased risk of hospital admission adjusted relative risk 1:34 (95% c 1:10 but Not of ICU admission adjusted risk $76 (95%. (1 0.93-3-355), these risks were Greater for high cumulative doses of glucocorticoids than for modern doses. Exposure to selective Immunosuppressant tumour necrosis factor inhibitors or Interleukin inhibition was not associated with an increased risk of hospitalization, ICU admission or death, nor was exposure to calcuineurin inhibitors, other Immunosuppressant's, hydroxychloroquine or chloroquine. This review summaries current knowledge regarding immunosuppressive drug Classes as well as their dosages and application regiments with consideration Species specific drug metabolisation and side effects.

Keywords :- Animal models, immunomodulation, immunosuppression transplantation, translation research

I. INTRODUCTION

Immunosuppressant disease 2019 (COMID-19), mused by severe acute respiratory syndrome coronavirus CSARS-COV-2), manifests with varying clinical severity Cl. 23. An inflammatory response with virus- specific T-cells. clears the virus and leads to recovery in most patients. however, an aberrant inflammatory response can lead to severe diseases. severe cases are predominantly characterised by Pneumonia and may feature multigrain inflammatory involvement, including elevated pro-inflammatory Cytokines such as interleukin (IL)-IL- and tumour necrosis factor (TNF) [3-5]. Patients receiving immunosuppressant therapies for conditions including instammatory diseases and said organ transplantation are susceptible interment viral and bacterial infections (b.1], and although evidence is lacking regarding their effect on couin-19, expert groups concerned that immunosuppression may worsen the prognosis have advised withholding or reducing immunosuppressant's during intercurrent COUID-19 C8-10).Immunosuppressive treatments me routinely applied to prevent immune bonne damage 01. rejection These interventions continuously regain. importance given the increasing need for solid organ and tissue replacement. In many countries, there has actually been a decline in the availability of appropriate transplants 1 In parallel the development. optimization and implementation of emerging cell and tissue based regenerative therapies are underway to compensate best the paucity of transplantable Organs Regenerative therapies also provide a perspective on causal treatments for degenerative diseases that have been considered untreatable for decades. 2. once proven effective, such regenerative therapies will meet likely on non autologous on the shelf cell of tissue preparations. to meet huge clinical demand. This will in turn require highly developed and effective immunosuppression or immunomodulation protocols to prevent graft rejection importantly regenerative medicine. approaches should be assessed in animal studies. before clinical translation. In many cases, they one even restricted to Cyclosporin A. (CSA) monotherapy, which is frequently reported in experimental transplantation protocols s there may be some room for improvement by taking species specific differences as Hell as Pharmacodynamics and pharmacokinetics into full consideration, as these differences may significantly the biological activity of a particular drug 4 Neglecting these considerations not only leaves. many important research questions unsolved for example, regarding the necessity of graft survival 100 maximum therapeutic effect, Or mitigating the effects emerging from graft decline) but may also severely bias the translatability of preclinical findings themselves on the other hand. Virtually all immunosuppressive strategies are accompanied by undesirable side effects and thus imperatively require a well balanced, recipient and species specific design, including a combination of available protocols or even. Considering options currently under development. This review provides a comprehensive, state of the overview of Immunosuppressive treatments in. relevant animal model species that is non. Human primates (NHPs) frequently investigated transplantation scenarios. Relevant physiological differences between animal species and humans. As well As important differences in pharmacodynamics and pharmacokinetics are Emphasized. In addition, He review promising experimental

immunosuppressive protocols in Potential teams of their potential experimental cell tissue transplantation studies Our compendium thus aims to enable researcher to apply tailored immuno-Suppressive effective, with respect to the experimenter question and on the Particular treatment subject under consideration with the goal of ultimately Ensuring a high predictive value of preclinical study results with respect to the Clinical situation. Immunosuppressant's are drugs which inhibit cellular humoral or both types of Immune responses, and have their major use in organ transplantation and Autoimmune diseases Immunosuppression involves. An ad that seduces the activation a efficacy of the Immune system. Some portions of the immune system. Some have immuno-Suppressive effects on other pants of the immune system and Immunosuppression may occurs as an adverse reaction to treatment of other Conditions. Immunosuppressant's are used to control severe. Of allergic Autoimmune and transplant related diseases. Some thugs have a diffuse offed on. The immune system while others have specific targets. Drugs with diffuse effects Are more likely to cause damaging adverse effects but the effectiveness of the More specific drugs may be reduced is their action can be bypassed by alternative metabolic pathway.



Immunosuppressant drugs are classified into following as

A) Calcineurin inhibition

1. Cyclosporine (cyclosporine)
2. Tacrolimus

B) M – TOR inhibitors

1. Sirolimus
2. Everolimus

Temsirolimus

C) Antiproliferative drugs

1. Azathioprine
2. Methotrexate
3. Cyclophosphamide
4. Chlorambucil
5. Mycophenolate mofetil

D) Glucocorticoids
1 Prednisolone (others)

Biological agents

A) TNF Alfa inhibitors

1. Etanercept
2. Inflximab
3. Adalimumab

B) IL-2 receptor antagonist

1. Anakinra

C) IL-2 receptor antagonists

1. Basilixmab
2. Daclizumab

D) Anti- CD3 antibody

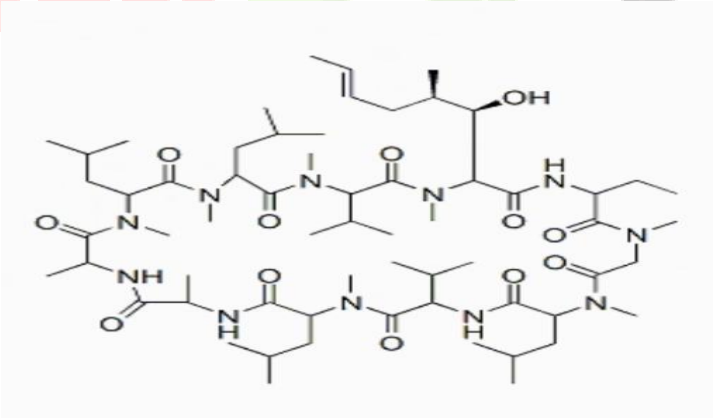
1. Muromonab CD3

E) Polyclonal Antibiotic

1. Antithymocyte antibody (ATG)
2. Rho (D) immune globulin

A) CALCINEURIN INHIBITORS

1) Cyclosporine:- (Ciclosporin)



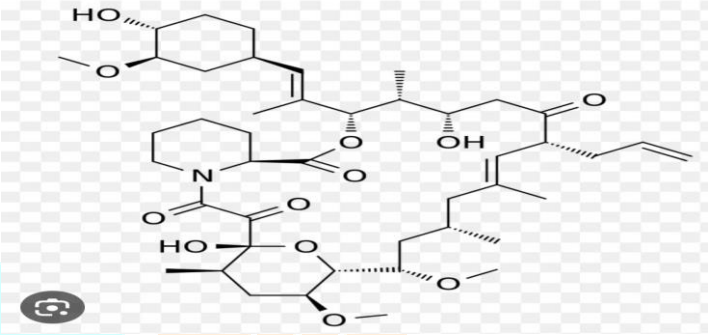
Synonyms :- Ciclosporin, Ciclosporina, Ciclosporine, Cyclosporin etc
IUPAC Name :- cyclo[((2S)-2-aminobutyryl)-sarcosyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-N-methyl-(4R)-4-[(E)-but-2-enyl]-4-methyl-L-threonyl
Chemical Formula :- C62H111N11O12

Pharmacology :- Cyclosporine is approved for a variety of conditions. Firstly, it is approved for the prophylaxis of organ rejection in allogeneic kidney, liver, and heart transplants. It is also used to prevent bone marrow transplant rejection. For the above indications, cyclosporine can be used in conjunction with azathioprine and corticosteroids. Finally, cyclosporine can be used in patients who have chronic transplant rejection and have received previous immunosuppressive therapy20 and to prevent or treat graft-versus-host disease (GVHD)

Pharmacodynamics:- Cyclosporine exerts potent immunosuppressive actions on T cells, thereby prolonging survival following organ and bone marrow transplants.24 This drug prevents and controls serious immune-mediated reactions including allograft rejection, graft versus host disease, and inflammatory autoimmune disease.24Some notable effects of cyclosporine are hypertrichosis, gingival hyperplasia, and hyperlipidemia. There is also some debate about this drug causing nephrotoxicity.

Mechanism of action :- Cyclosporine is a calcineurin inhibitor that inhibits T cell activation.2,5,12 Its binding to the receptor cyclophilin-1 inside cells produces a complex known as cyclosporine-cyclophilin. This complex subsequently inhibits calcineurin, which in turn stops the dephosphorylation as well as the activation of the nuclear factor of activated T cells (NF-AT) that normally cause inflammatory reaction.

2). Tacrolimus



Synonyms :- Anhydrous tacrolimus, Tacrolimus , Tacrolimus anhydrous
IUPAC Name :- (1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-17-Allyl-1,14-dihydroxy-12-{(1E)-1-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-propen-2-yl}-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-Aztar ;icyclo[22.3.1.04,9]octacos-18-en-2,3,10,16-tetron
Chemical Formula. :- C44H69NO12

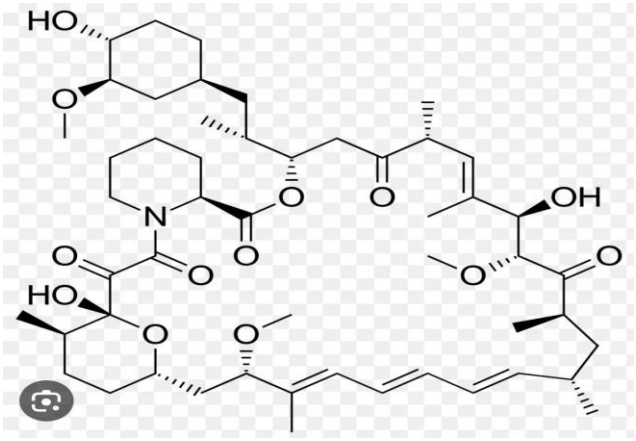
Pharmacology :- Immediate-release formulations of tacrolimus are indicated for the prophylaxis of organ rejection in adult and pediatric patients receiving allogeneic liver, kidney, heart, or lung transplants, in combination with other immunosuppressants.7 Extended-release formulations of tacrolimus are indicated for the ophylaxis of organ rejection in adult and pediatric patients receiving kidney transplants, in combination with other immunosuppressants,8,9 and may be used in patients converted from immediate-release formulations.

Pharmacodynamics :- Tacrolimus acts by reducing peptidyl-prolyl isomerase activity by binding to the immunophilin FKBP-12 (FK506 binding protein) creatinga new complex. This inhibits both T-lymphocyte signal transduction and IL-2 transcription. Tacrolimus has similar activity to cyclosporine but rates of rejection are lower with tacrolimus. Tacrolimus has also been shown to be effective in the topical treatment of eczema, particularly atopic eczema. It suppresses inflammation in a similar way to steroids, but is not as powerful. An important dermatological advantage of tacrolimus is that it can be used directly on the face; topical steroids cannot be used on the face, as they thin the skin dramatically there. On other parts of the body, topical steroid are generally a better treatment.

Mechanism of action :- The mechanism of action of tacrolimus in atopic deratits is not known. While the following have been observed, the clinical significance of these observations in atopic dermatitis is not known. It has been demonstratedthat tacrolimus inhibits T-lymphocyte activation by first binding to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin is inhibited This prevents the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines. Tacrolimus also inhibits the transcription for genes which encode IL-3, IL-4, IL-5, GM-CSF, and TNF-, all of which are involved in the early stages of T cell activated.

B) M – TOR INHIBITORS

1) Sirolimus



Synonyms :- Sirolimusum, Sirolimus , Sirolimús , Rapamycin etc .

IUPAC Name :- (1R,15R,16E,18R,19R,21R,23S,24Z,26E,28E,30S,35R)-1,18-dihydroxy-12-[(2R)-1-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]propan-2-yl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo[30.3.1.04,9]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentone

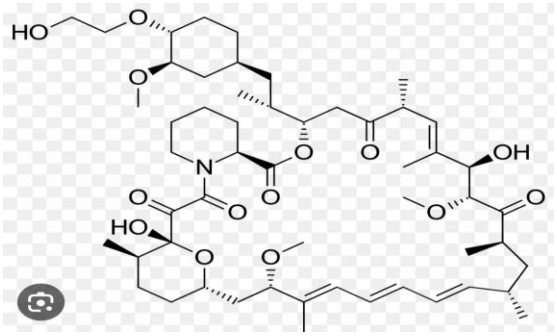
Chemical Formula :- C51H79NO13

Pharmacology :- Sirolimus is indicated for the prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants. In patients at low-to Oderate-immunologic risk, it is recommended that sirolimus be used initially in Egimen with cyclosporine and corticosteroids; cyclosporine should be withdrawn Two to four months after transplantation. Topical sirolimus is indicated for the treatment of facial angiofibroma associated with tuberous sclerosis in adults and pediatric patients six years of age and older.

Pharmacodynamics :- Sirolimus is an immunosuppressant drug with antifungal And antitumour effects. In animal models, sirolimus prolonged allograft survival following various organ transplants and reversed an acute rejection of heart and kidney allografts in rats. Upon oral administration of 2 mg/day and 5 mg/day, Sirolimus significantly reduced the incidence of organ rejection in low- to moderate-immunologic risk renal transplant patients at six months following transplantation compared with either azathioprine or placebo. In some studies, the immunosuppressive effect of sirolimus lasted up to six months after discontinuation of therapy: this polarization effect is alloantigen-specific. Sirolimus potently inhibits antigen-induced proliferation of T cells, B cells, and antibody production.

Mechanism of action :- Sirolimus works by inhibiting T-lymphocyte activation and proliferation stimulated by antigens and cytokines such as interleukin (IL)-2, IL-and IL-15. In target cells, sirolimus binds to the cytoplasmic receptor FK506-Nding protein-12 (FKBP12), an immunophilin, to form an immunosuppressive co

2) Everolimus



Synonyms :- Everolimus , 40-O-(2-hydroxyethyl)-rapamycin, Everolimus I

UPAC Name :- Dihydroxy-12-[(2R)-1-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycy Clohexyl]propan-2-yl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aZatricyclo[30.3.1.0hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentone

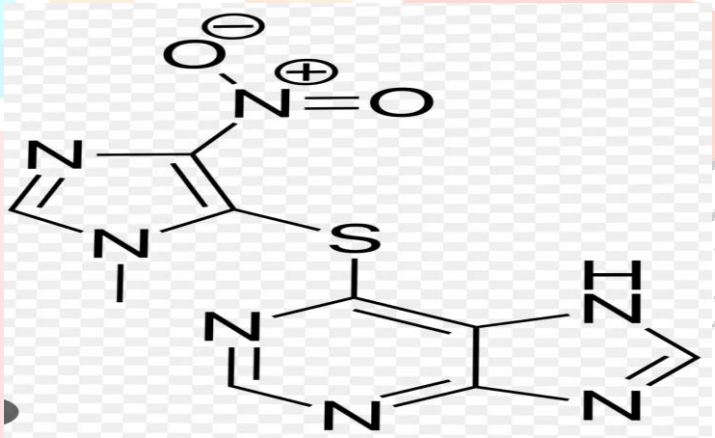
Molecular formula :- C53H83NO14

Pharmacology:- Everolimus is indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole. Indicated for the treatment Of adult patients with progressive neuroendocrine tumors of pancreatic origin (PNET) with unrespectable, locally advanced or metastatic disease. Indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of treatment with sentinel or sorafenib. Indicated for the treatment of adult patients with renal angiomyolipoma and tuberous Sclerosis complex (TSC), not requiring immediate surgery. Indicated in pediatric and adult patients with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected

Mechanism of action :- Everolimus is a mTOR inhibitor that binds with high affinity to the FK506 binding protein-12 (FKBP-12), thereby forming a drug complex that inhibits the activation of mTOR. This inhibition reduces the activity of effectors downstream, which leads to a blockage in the progression of cells from G1 into S phase, and subsequently inducing cell growth arrest and apoptosis. Everolimus also inhibits the expression of hypoxia-inducible factor, leading to a decrease in the expression of vascular endothelial growth factor. The result of Everolimus inhibition of mTOR is a reduction in cell proliferation, angiogenesis, and glucose uptake

C) ANTIPROLIFERATIVE DRUGS

3 Azathioprine



Synonyms :- Azathioprine, Azathioprinum , Azatioprina , Azamun etc.

IUPAC Name :- 6-[(1-Methyl-4-nitro-1H-imidazol-5-yl)sulfonyl]-7H-purine

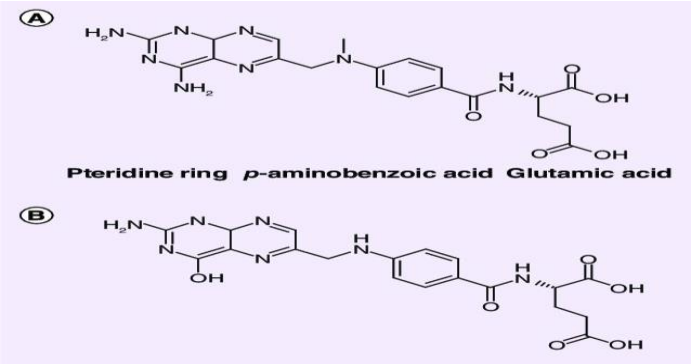
Molecular formula :- C9H7N7O2S

Pharmacology :- Azathioprine is indicated to treat rheumatoid arthritis and prevent renal transplant rejection

Pharmacodynamics :- Azathioprine is an immunosuppressive agent which function's through modulation of rac1 to induce T cell apoptosis, as well as other unknown immunosuppressive functions. It has a long duration of action as it is given Daily, and has a narrow therapeutic index.12 Patients should be counselled regarding the risk of malignancies of the skin and lymphomas.

Mechanism of action :- Azathioprine's mechanism of action is not entirely Understood but it may be related to inhibition of purine synthesis, along with Inhibition of B and T cells. 6-thioguanine triphosphate, a metabolite of Azathioprine, modulates activation of rac1 when stimulated with CD28, inducing T cell apoptosis.5 This may be mediated through rac1's action on mitogenativated protein kinase NF kappa B.

2) Methotrexate



Synonyms :- Methotrexate, Methotrexate, 4-amino-10-methylfolic acid etc.

IUPACName:-:(2S)-DiaminopteridYl)methyl](methyl)amino}benzoyl)amino]pentanedioic acid

Molecular formula :- C20H22N8O5

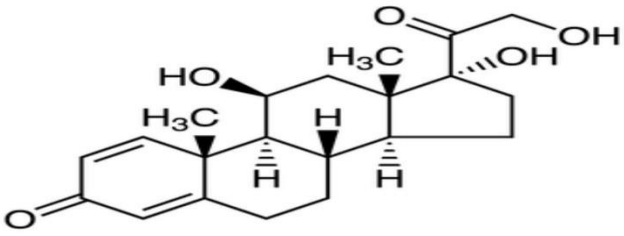
Pharmacology :- Methotrexate oral solution is indicated for pediatric acute Lymphoblastic leukemia and pediatric polyarticular juvenile idiopathic Arthritis.4 Methotrexate injections for subcutaneous use are indicated for severe Active rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and severe, Recalcitrant, disabling psoriasis. Other formulations are indicated to treat Gestational choriocarcinoma, chorioadenoma destruens, hydatiform mole, breast Cancer, epidermoid cancer of the head and neck, advanced mycosis fungoides, Lung cancer, and advanced non-Hodgkin's lymphoma.7It is also used in the Maintenance of acute lymphocytic leukemia.7 Methotrexate is also given before Treatment with leucovorin to prolong relapse-free survival following surgical Removal of a tumour in non-metastatic osteosarcoma.

Pharmacodynamics :- Methotrexate inhibits enzymes responsible for nucleotide Synthesis which prevents cell division and leads to anti-inflammatory actions.1It Has a long duration of action and is generally given to patients once Weekly.1,4,5,6 Methotrexate has a narrow therapeutic index.2Do not take methotrexate daily.

Mechanism of action:- Methotrexate enters tissues and is converted to a Methotrexate polyglutamate by folylpolyglutamate.1Methotrexate's mechanism of Action is due to its inhibition of enzymes responsible for nucleotide synthesis Including dihydroorotate reductase, thymidylate synthase, aminoimidazole Caboxamide ribonucleotide (AICART),phosphoribosyl transferase Inhibition of Nucleotide synthesis prevents cell division. In rheumatoid arthritis, methotrexate Polyglutamates inhibit AICART more than methotrexate.1 This inhibition leads to Accumulation of AICART ribonucleotide, which inhibits adenosine deaminase, Leading to an accumulation of adenosine triphosphate and adenosine in the Extracellular space, stimulating adenosine receptors, leading to anti-inflammatory action

D) GLUCOCORTICOIDS

1) Prednisolone



Synonyms :- delta-dehydrocortisol, delta-dehydrohydrocortisone, Prednisolona , Prednisolonum etc.

IUPAC Name :- 11β)-11,17,21-Trihydroxypregna-1,4-diene-3,20-dione

Molecular formula :- C21H28O

Pharmacology :- Prednisolone is indicated to treat endocrine, Rheumatic, and hematologic disorders; collagen, dermatologic, ophthalmic, Respiratory, and gastrointestinal diseases; allergic and edematous states; And other conditions like tuberculous meningitis.

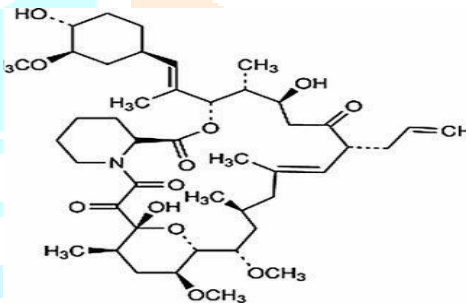
Pharmacodynamics :- Corticosteroids bind to the glucocorticoid receptor, Inhibiting pro-inflammatory signals, and promoting anti-inflammatory Signals.4 Prednisolone has a short duration of action as the half life is 2.1-hours.1 Corticosteroids have a wide therapeutic window as patients make require doses that are multiples of what the body naturally produces.4 Patients taking corticosteroids should be counselled regarding the risk of hypothalamic-pituitary-adrenal axis suppression and increased susceptibility to infections.

Mechanism of action :- The short term effects of corticosteroids are Decreased vasodilation and permeability of capillaries, as well as Decreased leukocyte migration to sites of inflammation.4 Corticosteroids Binding to the glucocorticoid receptor mediates changes in gene expression That lead to multiple downstream effects over hours to days.4Glucocorticoids inhibit neutrophil apoptosis and demargination; they inhibit Phospholipase A2, which decreases the formation of arachidonic acid Derivatives; they inhibit NF-Kappa B and other inflammatory transcription Factors; they promote anti-inflammatory genes like interleukin- 10 . Lower Doses of corticosteroids provide an anti-inflammatory effect, while higher Doses are immunosuppressive.4 High doses of glucocorticoids for an Extended period bind to the mineralocorticoid receptor, raising sodium leves and decreasing potassium levels.

Biological Agents

A) TNE ALFA INHIBITORS

1) Etanercept



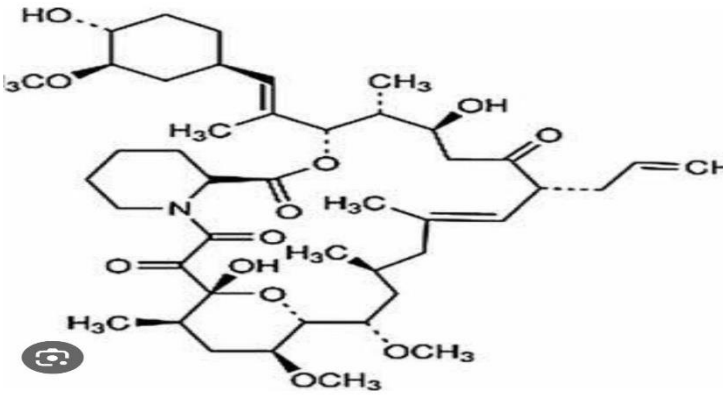
Synonyms :- Etanercept, Etanercept-sizes, TNFR-Immunoadhesin etc.
Molecular formula :- C2224H3475N621O698S36

Pharmacology :- Etanercept is indicated for the treatment of moderately to severely active rheumatoid arthritis in adults and in chronic moderate to severe plaque psoriasis in patients 4 years of age and older.7 It is also used to manage signs and symptoms of polyarticular idiopathic arthritis in those aged 2 years and older. Etanercept is also used to manage the symptoms of psoriatic arthritis and ankylosing spondylitis.

Pharmacodynamics :- Etanercept binds specifically to tumor necrosis factor (TNF) and thereby modulates biological processes that are induced or regulated by TNF.7,5 Such processes or molecules affected include the level of adhesion molecules expressed, as well as serum levels of cytokines and matrix metalloproteinase.

Mechanism of action :- There are two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75). The biological activity of TNF is dependent upon binding to either cell surface receptor (p75 or p55).5 Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind to two TNF molecules, thereby effectively removing them from circulation. Notably, etancerpt is only capable of binding to the active trimeric form of TNF as its binding site is located in the cleft between subunits.6TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses.5 Increased levels of TNF are found in tissues and fluids of those with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis.

4) Infliximab



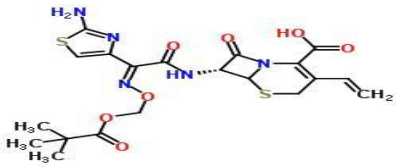
Synonyms :- Infliximab, Infliximab-abda, Infliximab-dyyb, Infliximab-axxq, Infliximab-qbtx etc.
Molecular formula :- C6428H9912N1694O1987S46

Pharmacology :- Indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult or pediatric (≥ 6 years of age) patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy Indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fertilizing Crohn's disease. Indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult or pediatric (≥ 6 years of age) patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

Pharmacodynamics :- Infliximab disrupts the activation of pro-inflammatory cascade signalling. Infliximab has shown to reduce infiltration of inflammatory cells into sites of inflammation. It also attenuates the expression of molecules mediating cellular adhesion {including E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)}, chemoattraction {[IL-8 and monocyte chemotactic protein (MCP-1)} and tissue degradation {matrix metalloproteinase (MMP) 1 and 3}.

Mechanism of action :- Infliximab is a IgG1κ monoclonal antibody that binds to soluble and transmembrane forms of TNF-α with high affinity to disrupt the pro-inflammatory cascade signalling. Binding of the antibody to TNF-α prevents TNF-α from interacting with its receptors. Infliximab does not neutralize TNF-β (lymphotoxin-α), a related cytokine that utilizes the same receptors as TNF-α Label. Blocked actions of TNF-α further leads to downregulation of local and systemic pro-inflammatory cytokines.

B) IL – 1 receptor antagonist
1) Anakinra



Synonyms :- Anakinra, Interleukin-1 receptor antagonist anakinra etc.
IUPAC Name:- Recombinant human Interleukin-1 receptor antagonist protein; syn. N2-l-methionyl-interleukin 1 receptor antagonist (human isoform x reduced)
Molecular formula :- C759H1186N208O232S10.

Pharmacology :- Anakinra is an interleukin-1 receptor antagonist indicated for the reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active rheumatoid arthritis (RA), in patients 18 years of age or older who have failed one or more disease-modifying antirheumatic drugs (DMARDs). Anakinra can be used alone or in combination with DMARDs other than Tumor Necrosis Factor (TNF) blocking agents. Anakinra is also indicated for the treatment of Neonatal-Onset Multisystem Inflammatory Disease (NOMID) and the treatment of Deficiency of Interleukin-1 Receptor Antagonist (DIRA).Anakinra is also used off-label for the treatment of several inflammatory diseases.

Pharmacodynamics :- Anakinra is a recombinant human interleukin-1 receptor antagonist (IL-1Ra) that blocks the biologic activity of interleukin-1 (IL-1) by competitively inhibiting its ability to bind to the IL-1 type I receptor (IL-1RI). IL-1 production is higher in inflammatory diseases such as rheumatoid arthritis, where the amount of naturally occurring IL-1Ra cannot compete with the high level of IL-1 present. Mechanism of action :- Interleukin-1 (IL-1) plays an important role in inflammation and immunological responses. Inflammatory stimuli trigger its production, and it binds to the IL-1 receptor to activate a wide variety of mechanisms. The activity of the IL-1 receptor is also regulated by a naturally occurring IL-1 receptor antagonist (IL-1Ra) that competes for the binding sites of the IL-1 receptor.7 In rheumatoid arthritis (RA) patients, IL-1 levels are elevated, inducing cartilage degradation and the stimulation of bone resorption, and the amount of IL-1Ra in the synovium.

C) IL -2 receptor antagonists

1) Basilixma

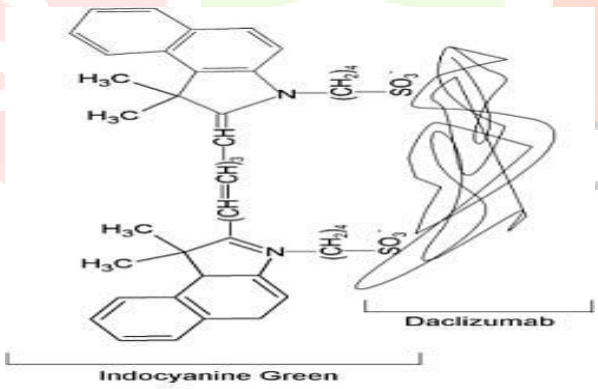
Synonyms :- Basiliximab.
Molecular formula :- C6378H9844N1698O1997S48.
Background:- A recombinant chimeric (murine/human) monoclonal antibody (IgG1k) that functions as an immunosuppressive agent, specifically binding to and blocking the interleukin-2 receptor a-chain (IL-2R alpha, also known as CD25 antigen) on the surface of activated T-lymphocytes. It is a 144 kDa glycoprotein obtained from fermentation of an established mouse myeloma cell line genetically engineered to express plasmids containing the human heavy and light chain constant region genes and mouse heavy and light chain variable region genes encoding the RFT5 antibody that binds selectively to the IL-2R alpha.

Pharmacology :- For prophylactic treatment of kidney transplant rejection.

Pharmacodynamics :- Basilixmab functions as an IL-2 receptor antagonist. Specifically it inhibits IL-2-mediated activation of lymphocytes, a critical pathway in the cellular immune response involved in allograft rejection.

Mechanism of action :- Basiliximab binds with high-affinity to the alpha-subunit (CD25) of the high-affinity IL-2 receptor. This inhibits IL-2 binding, which inhibits T-cell activation and prevents the body from mounting an immune response against the foreign kidney.

5) Dacliximab



Synonyms :- Dacliximab, Daclizumab, Daclizumab beta etc.
Molecular formula :- C6332H9808N1678O1989S42

Background :- Humanized IgG1 Mab that binds to the human interleukin-2 receptor (anti-Tac or anti-CD25). Daclizumab is a composite of human (90%) and murine (10%) antibody sequences. The human sequences were derived from the constant domains of human IgG1 and the variable framework regions of the Eu myeloma antibody. The murine sequences were derived from the complementarity-determining regions of a murine anti-Tac antibody. On 22 April 2008, Roche Registration Limited chose to voluntarily withdraw the marketing authorization for their product Zenapax (daclizumab), as indicated for the prophylaxis of acute organ rejection in de novo allogeneic renal transplantation and used concomitantly with an immunosuppressive regimen like cyclosporine and corticosteroids in patients who are not hight immunized, for commercial reasons and confirmed that this decision was not related to any safety concerns associated with the use of Zenapax (daclizumab)

Pharmacology :- Zenapax is a humanized monoclonal antibody used for prevention of renal transplant rejection.

Pharmacodynamics :- Zenapax functions as an IL-2 receptor antagonist. Specifically it inhibits IL-2-mediated activation of lymphocytes, a critical pathway in the cellular immune response involved in allograft rejection.

Mechanism of action :- Zenepax binds with high-affinity to the Tac subunit of the high-affinity IL-2 receptor complex and inhibits IL-2 binding. The IL-2 receptor (Tac) subunit is expressed on activated but not resting lymphocytes.

D) Anti – CD3 antibody

1) Muromonab CD3
Synonyms :- Anti-CD3, Muromonab-CD3 etc.
Molecular formula :-

Background :- .Murine monoclonal antibody specific to CD3 T-cell lymphocyte antigens. More specifically it is a purified murine (mouse) monoclonal antibody, directed against the CD3 (T3) receptor on the surface of human T-cells (T-lymphocytes) cultured using the murine ascites method.

Pharmacology :- For treatment of organ transplant recipients, prevention of organ rejection.

Pharmacodynamics :- Used in organ transplant prophylaxis, Muromonab or OKT-3 binds specifically to the CD-3 complex, which is involved in antigen recognition and cell stimulation, on the surface of T lymphocytes. Immediately after administration CD-3-positive T lymphocytes are abruptly removed from circulation. It has been effective in reversing corticosteroid-resistant acute rejection in renal, liver, and cardiac transplant recipients

. Mechanism of action :- Muromonab binds to the T-cell surface glycoprotein CD3 epsilon chain. It appears to kill CD-3 positive cells by inducing Fc mediated apoptosis, antibody mediated cytotoxicity and in tissues and fluids of those with rheumatoid arthritis, psoriatic arthritis complement-dependent cytotoxicity.

Conclusion

Immunosuppression is a double-edged sword. While it has been a tool much used by many physicians in combating chronic inflammatory diseases, it does come with significant trade-offs with increased risk of infections being one of them. In this current climate of the COVID-19 pandemic, it is imperative that prescribers of such medications take the time and effort to consider their usage and educate their patients on the actions to take if they unfortunately fall ill. The initial clinical experiences to date seem to allay worries that immunosuppression might increase the risk of patient getting infected with SARS-CoV-2 and developing severe complications. Overwhelmingly, the best practice guidelines worldwide currently recommended the continuation of immunosuppression treatment in patients who require them except for perhaps high- dose corticosteroid therapy, and in patients with associated risk factors for severe COVID-19 disease. There is a pressing need for more research to be done to confirm these preliminary findings and allow refinement of guidelines on the management of immunosuppressed patients during this COVID-19 pandemic. Some immunosuppressive drugs may be beneficial in the treatment of COVID-19, MPA inhibits SARS-CoV-2 replication Empirical finance, 5(3): 221–240.in-vitro, There are indications that corticosteroids and IL-6 inhibitors, like tocilizumab, can reduce mortality and prevent mechanical ventilation in patients with COVID-19. These results have to be confirmed in high-quality dinical trials before these drugs can be implemented as standard care. Based on the positive results of CNI mTOR inhibitors and thiopurine analogues in in-vitro studies with SARS-CoV and MERS-CoV, it would be interesting to investigate their effects on SARS-CoV-2 replication.

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