

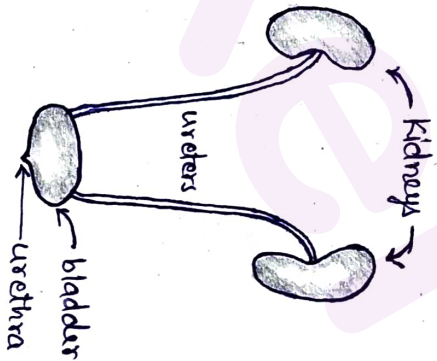
UNIT-4

Chemotherapy of UTIs

A Urinary Tract Infection (UTI) is an infection in any part of urinary system - kidneys, ureters, bladder and urethra. Infection of lower urinary tract is more common, i.e., of bladder and urethra. Women are at greater risk of developing a UTI than are men. UTIs are about 50 times more common in women.

Urinary tract is divided into 2 parts:

- 1) Upper urinary tract : It comprises of
 - a) Kidneys
 - b) ureters
- 2) Lower urinary tract : It comprises of
 - a) bladder
 - b) urethra



Types of UTIs

UTIs are caused by micro-organisms or germs, usually bacteria. The different types are:

1) Cystitis :- infection of the bladder (most common)
 The symptoms include :- pelvic pressure, lower abdomen discomfort, frequent and painful urination, blood in urine sometimes.

2) Urethritis :- infection of urethra
 The symptoms include :- burning with urination, discharge from penis, itching, swelling in penis.

3) Pyelonephritis :- infection of kidneys
 The symptoms include :- upper back and side pain, high fever, shaking and chills, nausea.

causes of UTIs

→ Bacteria do not normally live in the urinary tract. When bacteria enter urinary tract and multiply, they can cause a UTI.

→ The most common germ causing UTIs is found in our digestive system, E. coli. E. coli can

easily spread to the urethra and stick to the lining of urinary tract.

→ Germs like Mycoplasma and Chlamydia can cause urethritis in both men and women. These germs can be passed on during sexual intercourse.

→ E. coli cause more than 90% of bladder infections.
→ Other causes may be due to poor hygiene.

Treatment of UTIs

The following drugs may be used in the treatment of Urinary Tract Infections:

1) Nitrofurantoin

It is primarily bacteriostatic but may be cidal at higher concentrations. It is effective against E. coli.

→ It is well-absorbed orally, rapidly metabolized in liver.

→ Plasma $t_{1/2}$ is 30-60 minutes.

2) Cephalexin

Active against Proteus, E. coli, and Klebsiella.

3) Gentamycin

→ Only in patients who need parenteral therapy and have severe IgE mediated penicillin allergy.
→ It has ototoxicity/nephrotoxicity concerns.

4) Bactrim

Bactrim is a combination of two antibiotics, sulfamethoxazole and trimethoprim, used to treat UTIs. And also prevent re-infection.

5) Amoxicillin

It is an antibiotic medication belonging to the aminopenicillin class. This drug is used to treat UTIs and also treat ear infection, pneumonia, skin infections, etc.

6) Fosfomycin

Fosfomycin can treat UTIs caused by bacteria that cannot be treated with common antibiotics due to antibiotic resistance.

Chemotherapy of STDs

Sexually transmitted diseases (STDs) are infections that are passed from one person to another through sexual contact. They are usually spread during vaginal, oral or anal sex.

→ STDs can be caused by viruses, bacteria or even protozoans. These organisms spread through blood, semen, vaginal fluids or other bodily fluids.

→ Many STDs like syphilis, hepatitis B, HIV, chlamydia, gonorrhoea, herpes are transmitted non-sexually, like from pregnant mother to foetus.

Syphilis

Syphilis is caused by *Treponema pallidum*.

They cause ulcers in the area where they live usually in the mucous membranes of mouth or genitals.

Treatment

1) Penicillin G, administered parenterally, is the preferred drug for treating patients in all stages of syphilis.

2) Patients allergic to penicillin should be given doxycycline.

3) Ceftriaxone and azithromycin, administered orally in the treatment of early syphilis.

Gonorrhoea

Gonorrhoea is a STI caused by bacteria called *Neisseria gonorrhoeae* or gonococcus.

→ It infects epithelium most often of the urogenital tract and secondarily of the rectum, oropharynx, and conjunctiva.

→ In males, it affects urethra, Littre's, Cowper's, Tyson's, perourethral and prostate glands, seminal vesicles and epididymis.

→ In females, it affects urethra, Skene's and Bartholin's glands, cervix and fallopian tubes.

Treatment

- Gonorrhoea is typically treated with an intramuscular (IM) injection of ceftriaxone. It is sometimes given in combination with doxycycline or azithromycin.
- Ampicillin and Amoxicillin are effective but they are of no value in penicillin resistant gonococci.
- Tetracyclines are also effective, given orally. They are of limited value in pregnancy because of their side effects.
- Gentamycin is effective in treatment, its tolerance is excellent and has no side effects.

Herpes Infection

Herpes simplex is a viral infection caused by Herpes simplex Virus (HSV).

HSV infections are caused by two major antigenic types, HSV-1 and HSV-2.

→ HSV-1 is primarily associated with oral infections, while HSV-2 causes genital infections.

→ These viruses can be easily transmitted through direct contact (intimates) from an infected sexual partner or from contact in day to day activities.

Signs and symptoms

- 1) Blisters or ulcers, on lips, mouth, or genitals.
- 2) Fever initially
- 3) Genital lesions starting with a burning or tingling sensation.
- 4) Enlarged lymph nodes in the neck or groin.

Treatment1) For primary infection

a) Herpetic gingivostomatitis :- Acyclovir 5 to 20 mg / Kg body weight

8 hourly for 7 to 10 days.

b) Herpetic whitlow and Kerato-conjunctivitis :

Treated with oral acyclovir 200mg 5 times a day for 7 to 10 days.

2) For recurrent Infection

- a) Acyclovir 200 mg five times a day for 5 days.
- b) Alternative antiviral drugs: valacyclovir and famciclovir

Chemotherapy of Malignancy

Malignancy = Cancer

Cancer is a disease involving abnormal cell growth with the potential to invade or spread to other parts of the body circulating with blood and lymph.

Types of cancer

- 1) Leukemia :- cancer that starts in blood-forming tissue such as the bone marrow and causes large number production of blood cells.

- 2) Carcinoma :- cancer that forms in epithelial tissues. It comprises of skin and internal covering of organs.

- 3) Sarcoma :- cancer that begins in bone and in soft tissues of the body, including cartilage, fat muscles, blood vessels, fibrous tissue.

- 4) Lymphoma and myeloma :- cancer that begins in the cells of immune system.

- 5) CNS cancers :- cancers that begin in the tissues of the brain and spinal cord.

Causes of cancer

- 1) Radiation (UV-radiation, X-rays)
- 2) Chemicals (e.g. benzoyl peroxide)
- 3) Infectious agents (e.g. Human Papillomavirus-HPV, Helicobacter pylori).

Cancer cell cycle

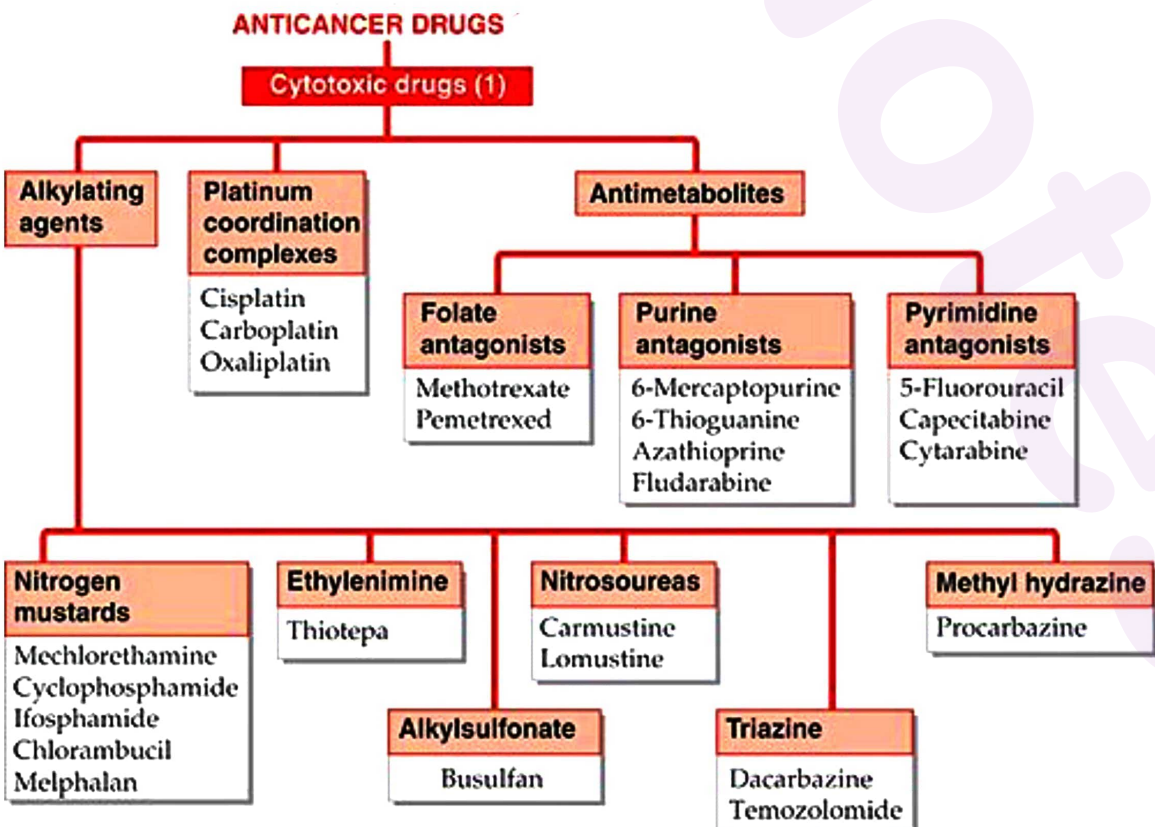
The process of cell division occurs through 5 phases:

- 1) G₀ (Gap₀ or Resting Phase)
- 2) G₁ (Gap₁ or pre-synthetic phase)
- 3) S (Synthetic phase)
- 4) G₂ (Gap₂ or Post-synthetic phase)
- 5) M (Mitotic Phase)

- 1) G₀ Phase :- It is a non-proliferative phase.
- 2) G₁ Phase :- cell synthesize protein and enzymes.
 - Replication of most of cell organelles occurs.
 - cell size get increased.
- 3) S-Phase :- phase of DNA synthesis (replication).
 - Between G₁ to S phase, there are check points which regulate cell division.
- 4) G₂ Phase :- This phase determines the accuracy of DNA replication.
 - Replication of remaining cell organelles.
 - Fully grown cell.
- 5) M-Phase :- During this phase, the replicated chromosomes divide itself into two nuclei for the two daughter cells.
 - These daughter cells further re-enter the cell cycle.

Classification of anticancer drugs

Anticancer drugs are also called as antineoplastic or antitumor drugs.



Alkylating Agents

The alkylating agents show their mechanism of action as follows:

- 1) Alkylating agents produce carbonium ion which is electron deficient.
- 2) Guanine has two extra electrons, that's why the carbonium ions forms a covalent bond with N-7 guanine.
- 3) In this way, they do cross-linking/ abnormal base pairing.
- 4) It results in DNA strand breakage.
- 1) Mechlorethamine → It is the first nitrogen mustard. It is highly reactive and is administered intravenously.
- 2) Cyclophosphamide → It gets activated only after getting metabolised in the liver. Its metabolites produce antitumor action.
- 3) Ifosfamide → It is used in breast, testicular, bladder, head, and neck carcinomas, osteogenic sarcoma and certain lymphomas.

4) Chlorambucil → It acts particularly on lymphoid tissue and acts very slowly when compared to other alkylating agents. It is also used in treating lymphatic leukaemia as a maintenance therapy.

Antimetabolites

Antimetabolites inhibit DNA or RNA synthesis by interfering with normal purine or pyrimidine nucleotide precursor's availability.

1) Methotrexate

Methotrexate inhibits the enzyme dihydrofolate reductase which converts folic acid to its active form. Folic acid plays a vital role in cell replication.

2) 6-Mercaptopurine → It is a purine analogue which is beneficial for treating neoplastic disease.

3) 5-Fluorouracil → It is a pyrimidine analogue which has a stable fluorine atom at 5th position of uracil ring. It inhibits DNA synthesis.

Vinca Alkaloids

Vinca alkaloids are obtained from the plant *Vinca rosea*.

1) Vincristine (Oncovir)

- It is a spindle poison and acts by causing arrest of mitotic cycle.
- Drug used in leukemia and lymphomas.

2) Vinblastine

- It acts by binding the microtubular proteins of the mitotic spindle, it leads to metaphase arrest.
- often a substitute of vincristine in treating lymphomas.
- used in the management of malignant teratoma.

Taxans

The drugs include:

1) Paclitaxel (Taxol)

- It acts as a mitotic spindle poison.
- It is used in the treatment of ovarian cancer and breast cancer.

2) Doxetaxel (Taxotex) → It is an antibiotic used

in the treatment of advanced breast cancer.

Antibiotics

Most antibiotics blocks the transcription of new RNA, DNA and cell replication by binding with the DNA. These antibiotics are cytotoxic in nature.

1) Dactinomycin → It is an antineoplastic antibiotic

obtained from *Streptomyces parvullus*.

- It acts by binding to DNA to inhibit the synthesis of mRNA, DNA-dependent RNA and rRNA synthesis in nucleus.

2) Anthracycline antibiotics

The anthracycline antibiotics include: doxorubicin and daunorubicin obtained from *Streptomyces peucetius*

- Doxorubicin is used in the treatment of non-Hodgkin's lymphomas, and acute leukemia.
- Daunorubicin is primarily used in acute myeloid leukemia.

Enzymes

certain enzymes such as Asparaginase are used in the treatment of cancer.

→ Asparaginase is derived from *E. coli* or *Erwinia carotovora* culture.

Asparaginase catalyses the hydrolysis of asparagine to aspartic acid and ammonia which leads to depletion in the amount of asparagine in blood and tumor cells. Depletion of asparagine leads to interference with protein, DNA and RNA synthesis in tumor cells, thereby killing them.

Radioactive Isotopes

Radioactive isotopes emit beta particles or ionising radiations that destroy living tissues near them.

1) Sodium Phosphate (P^{32} , Phosphotope)

Radioactive phosphorus gets accumulated in hemopoietic tissue (it produces blood) to produce reduced concentration of red and white blood cells,

→ It is effective in chronic lymphocytic and granulocytic leukemia.

2) Sodium Iodide (I^{131} , Iodotope)

This radioactive isotope of iodine accumulates in the thyroid gland, where it destroys thyroid tissue.

→ It is used to treat hyperthyroidism and thyroid carcinoma.

Hormones

There are some specific hormones used in the treatment of cancer, like endocrine-related tumors (carcinoma of breast, prostate) and non-endocrine malignancies (leukemia, lymphomas).

MOR → The steroid hormones form a steroid-receptor complex by binding to receptor proteins in the cytoplasm of cancer cells which directly binds to DNA and alters the transcription of structural genes.

The most useful hormones include:

Adrenocorticosteroids, Androgens, Oestrogens, Progestogens, LH-RH.

Immunostimulants

Immunostimulants are the drugs that stimulate the immune system or boost it against the infections.

Immunostimulants can increase or stimulate the immune system response to treat cancer and HIV infection,

→ Based on action, there are two types of immunostimulants:

1) Specific Immunostimulants → these drugs provide immune response against specific antigens, e.g. vaccine

2) Non-specific Immunostimulants → These drugs act irrespective of antigen specificity, so act against all antigens.
e.g. Immunoglobulins.

→ Reasons for using immunostimulants:

- 1) antibiotic resistance of the bacteria.
- 2) allergic reactions to antibiotics.
- 3) immunosuppressive effects of antibiotics.
- 4) Poor effects of the antibiotics.

Classification of Immunostimulants

- 1) Vaccines - BCG, Polio, Rota virus
- 2) Adjuvants
- 3) Immunoglobulins
- 4) other stimulants
 - Levamisole
 - Thalidomide
 - Isoprinosine
 - Immunocyanin

Vaccines

Vaccines are suspensions of dead microorganisms (inactivated) or attenuated but live microorganisms. → In general, attenuated vaccines are more potent than the inactivated vaccines.

How does vaccines work in our body?

Vaccines introduce weak or dead antigens to our body, it triggers our immune system.

This way, if we encounter the real antigen later, our body knows how to fight it off, preventing our body from infection.

Some vaccines used are:

1) BCG (Bacillus Calmette - Guerin) :- It has an attenuated mycobacterium bovis strain.

This vaccine is used to provide immunity against Mycobacterium tuberculosis and has also been approved as a treatment for bladder cancer.

2) Poliomyelitis vaccine :- Polio vaccines are used to prevent polio disease against polio virus.

Two types of polio vaccines are used:

- 1) an inactivated poliovirus given by injection.
- 2) a weakened poliovirus given by mouth.

3) Rotavirus vaccine :- This vaccine prevents against rotavirus infection.

→ These viruses cause severe diarrhoea among young children.

Adjuvants

An adjuvant is a substance that increases immune response to foreign antigens. OR,

An adjuvant is an ingredient in a medicine that increases the activity of other ingredients.

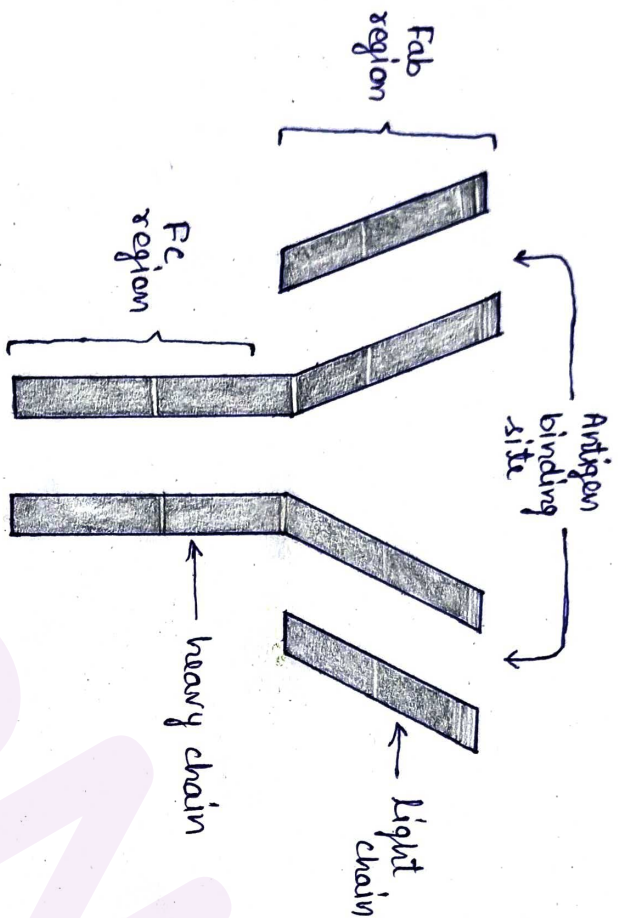
→ Adjuvants may be added to a vaccine to boost immune system so as to produce higher amount of antibodies.

→ The most commonly used adjuvants include aluminium hydroxide and paraffin oil.

Immunoglobulins

Immunoglobulins (Ig) or antibodies are glycoproteins produced by plasma cells.

An antibody molecule consists of two light and two heavy chains.



Structure of Antibody

Antibodies bind to specific antigens on the surfaces of bacteria, viruses and other invaders triggering body's immune response to destroy them.

Miscellaneous

1) Ivermectin

- It is available as ivermectin or ivermectin.
- It is used to treat worm infections.
- It is used in the treatment of tumors.

→ It acts by stimulating cell-mediated immunity.

2) Thalidomide

Thalidomide exhibit anticancer and immunostimulating effects.

→ It is used with dexamethasone for the treatment of multiple myeloma.

3) Isoprinosine

→ It is useful as immunostimulant in immunodeficient patients.

→ It is an antiviral agent.

→ It is most commonly used to treat rare measles complications.

MOA

1) It triggers cell-mediated immunity by stimulating the differentiation of T-lymphocytes into Helper-T cells and thereby increasing production.

2) It increases humoral immune response by stimulating the differentiation of B-lymphocytes into plasma cells and increases antibody production.

3) It inhibits viral growth by suppressing RNA synthesis.

Immunosuppressants

Immunosuppressants are drugs that prevent your immune system from attacking healthy cells and tissues by mistake.

Immunosuppressants are used to treat certain autoimmune diseases and prevent the chances of rejection of organ transplant.

→ But these medications also increase the risk of infection because of our immune system is not working at its full potency.

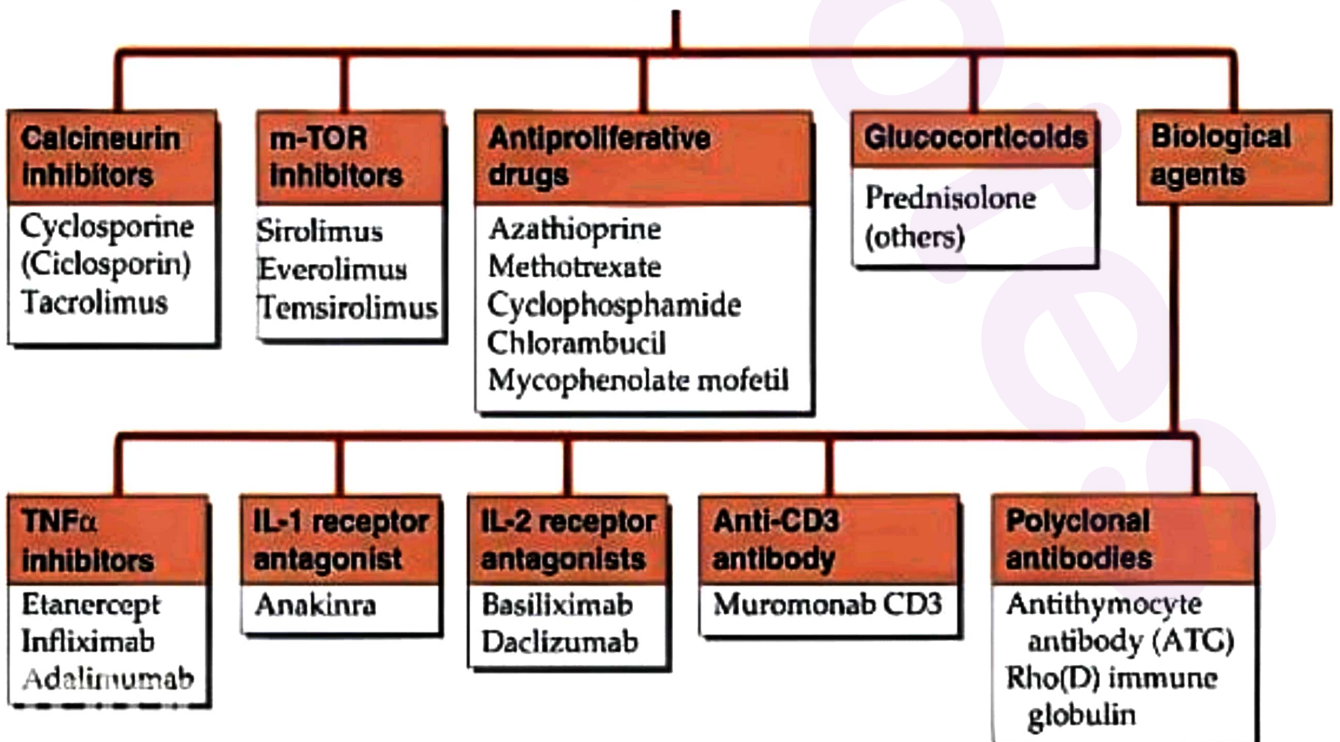
MOA

Immunosuppressants act by suppressing certain T-lymphocyte cells and prevent them from participating in immune response.

→ immunosuppressed patients should avoid taking live vaccines.

→ immunosuppressants may have significant adverse effects. They may increase the risk of certain types of cancers, especially skin cancers.

IMMUNOSUPPRESSANT DRUGS



Cytostatics

Cytostatic drugs act by inhibiting cell division which affects the proliferation of both T cells and B cells. They include the following drugs:

- 1) Alkylating agents → Cyclophosphamide is the most potent immunosuppressive compound used in the treatment of autoimmune haemolytic anaemia, Wegener's granulomatosis and other immune disorders. Other alkylating agents include platinum compounds and nitrosourea.
- 2) Antimetabolites → These drugs act by interfering with nucleic acid synthesis. Drugs of this class include Methotrexate, Azathioprine and Mercaptopurine.
- 3) Cytotoxic antibiotics → Doxorubicin is the first line cytotoxic antibiotic used in transplantation of kidney. Others include bleomycin, mitomycin C, anthracyclines and mitomycin.

Corticosteroids

Corticosteroids were the first agents to be used as immunosuppressives in transplantation and in various auto-immune disorders.

→ They act against various autoimmune disorders including refractory rheumatoid arthritis, temporal arteritis and asthma.

MOA

The exact mechanism is not known. But they mainly affect the T-lymphocytes.

Antibodies

Antibodies inhibit the immune response through various mechanisms, such as blocking immune cells activation or interfering with signaling pathways. This can be achieved through therapeutic monoclonal antibodies which target specific immune components, damaging their function and reducing immune activity.

Monoclonal Antibodies (mAbs)

mAbs act as immunosuppressants by targeting specific molecules involved in immune response, such as cytokines, cell surface receptors or immune cells.

→ mAbs are used to treat autoimmune diseases, organ transplant rejection, and certain cancers by modulating immune responses.

→ Examples include rituximab for rheumatoid arthritis and infliximab for inflammatory bowel disease.

Calcineurin Inhibitors

These are the medicines which inhibit the action of calcineurin. Calcineurin is an enzyme that activates T-cells of the immune system. This way calcineurin inhibitors show their immunosuppressive activity.

Examples -

- 1) Cyclosporine
- 2) Tacrolimus

mTOR Inhibitor Protein Drugs

mTOR inhibitors function by blocking the activity of the mTOR protein, rapamycin which regulates growth and proliferation of cells. By inhibiting mTOR, these drugs suppress immune responses, particularly of T-cells.

Examples - sirolimus, everolimus.

→ They are used to prevent organ transplant rejection and treat certain cancers such as renal cell carcinoma and breast cancer.

Biosimilars

Biosimilar drug is a medicine that is very close in structure and function to a biologic medicine. 'biologic' here means a type of pharmaceutical drug derived from living organisms, such as proteins, antibodies or nucleic acids.

Biosimilars mimic the mechanism of action of the reference biologic targeting the same receptors.

Examples include adalimumab and trastuzumab used in rheumatoid arthritis and breast cancer respectively.