

# Lecture-X

## IMMUNOSUPPRESSANTS (Part-II)

### 4) Glucocorticoids

- Glucocorticoids have potent immunosuppressant and anti-inflammatory action, inhibit several components of the immune response.
- They particularly inhibit MHC expression and activation/proliferation of T lymphocytes.
- Expression of several IL and other cytokine genes is regulated by corticosteroids and production of adhesion molecules is depressed.
- Accordingly, they have marked effect on CMI but effect on humoral immunity.

#### a) Dexamethasone

- Initial dose 0.75 mg to 9 mg orally per day.
- 0.5 mg to 9 mg i.v. or i.m. per day in divided doses every 12 hrs.

#### b) Prednisolone

- 5 to 60 mg orally per day

#### Side effects:

- Aggression
- Agitation
- Anxiety
- Blurred vision, decrease the amount of urine
- Dizziness
- Arrhythmia
- Headache

#### Uses:

- Corticosteroids are widely employed as companion drug to cyclosporine or other immunosuppressants in various organ transplant.
- In case graft rejection sets in –large doses of corticosteroids i.v. are employed for short periods.
- They are used practically in all cases of severe autoimmune diseases,

especially during exacerbation.

## 5) Biological agents

- These are biologically produced recombinant proteins or polyclonal/monoclonal antibodies directed to cytokines or lymphocyte surface antigens which play a key role in immune response.
- They are important recent additions, mostly as supplementary/ reserve drugs for severe and refractory cases of autoimmune diseases and graft versus host reaction.

### a) TNF- $\alpha$ inhibitors

- TNF- $\alpha$  is secreted by activated macrophages and other immune cells to act on TNF receptors (TNFR1, TNFR2) which are located on the surface of neutrophils, fibroblasts, endothelial cells as well as found in free soluble form in serum.
- TNF- $\alpha$  amplifies immune inflammation by releasing other cytokines and enzymes like collagenases and metalloproteinases.
- The TNF- $\alpha$  inhibitors are mainly used in autoimmune diseases, and are briefly described with disease modifying drugs for rheumatoid arthritis.

#### i) Etanercept

- The fusion protein of human TNF receptor and Fe portion of human IgG1 neutralizes both TNF- $\alpha$  and TNF- $\beta$ .
- It prevents activation of macrophages and T-cells during immune reaction.
- It is used mostly in combinations with methotrexate in rheumatoid arthritis patients who fail to respond adequately to the latter.

### b) IL-1receptor antagonist

- Stimulated macrophages and other mononuclear cells elaborate IL-1 which activates helper T-cells and induces production of other ILs, metalloproteinases etc.
- An endogenous IL-1 receptor antagonist has been isolated and several of its recombinant variants have been produced for clinical use.

**i) Anakinra**

- This recombinant human IL-1 receptor antagonist prevents IL-1 binding to its receptor and has been approved for use in refractory rheumatoid arthritis not controlled by conventional DMARDs.
- Anakinra along with continued methotrexate has been used alone as well as added to TNF- $\alpha$  antagonists, because its clinical efficacy as monotherapy appears to be lower.

**c) IL-2 receptor antagonist**

- The CD-25 molecule is expressed on the surface of immunologically activated, but not resting T-cells.
- It acts as a high affinity receptor for IL-2 through which cell proliferation and differentiation are promoted. Some anti CD-25 antibodies have been developed as IL-2 receptor antagonist to specifically arrest the activated T-cells.

**i) Daclizumab**

- It is highly humanized chimeric monoclonal anti CD-25 antibody which binds to and act as IL-2 receptor antagonist.
- Combined with glucocorticoids, calcineurin antagonists and/or azathioprine/MMF, it is used to prevent renal and other transplant rejection reaction.
- The plasma  $t_{1/2}$  of daclizumab is long (3 weeks), and it has also been used in combination regimens for maintenance of graft.

**d) Anti-CD3 antibody**

**i) Muromonab CD3**

- It is a murine monoclonal antibody against the CD3 glycoprotein expressed near to the T cell receptor on helper T-cells.
- Binding of muromonab CD3 to the CD3 antigen obstructs approach of the MHCII antigen complex to the T-cell receptor.
- Consequently, antigen recognition is interfered and participation of T-cells in

the immune response is prevented.

- Muromonab CD3 is the oldest (developed in the 1980s) monoclonal antibody that is still occasionally used clinically.

### **Uses:**

- Induction therapy of organ transplantation is infrequent now, since better alternatives are available.
- It has also been used to deplete T cells from the donor bone marrow before transplantation.

### **Side effects:**

- Chills
- Rigor
- High fever
- Wheezing
- Malaise
- Life threatening pulmonary edema
- Seizures and shock like state

## **e) Polyclonal antibodies**

### **i) Antithymocyte globulin (ATG)**

- It is a polyclonal antibody purified from horse or rabbit immunized with human thymic lymphocytes which contains antibodies against many CD antigens as well as HLA antigens.
- It binds to T lymphocytes and depletes them. It is a potent immunosuppressant and has been used primarily to suppress acute allograft rejection episodes, especially in steroid resistant cases, by combining with other immunosuppressants including steroids.
- It can also be used in induction regimens, but this has potential to produce serum sickness or anaphylaxis.

- Dose- 100mg inj: 200 mg i.v./day

### j) Anti-D immune globulin

- It is human IgG having a high titer of antibodies against Rh (D) antigen.
- It binds to Rho antigens and does not allow them to induce antibody formation in Rh negative individuals.
- It is used for prevention of postpartum/ post-abortion formation of antibodies in Rho-D negative, Du negative women who have delivered or aborted an Rho-D positive, DU positive baby/foetus.
- Administered within 72 hrs of delivery abortion, such as treatment prevents Rh haemolytic disease in future offspring.
- It has also been given at 28<sup>th</sup> week of pregnancy.
- Dose: 250-350 µg i.m. of freeze dried preparation.

## Summary

