Farmacotherapy and farmacomodulation of immunity

Lecture 14
MUDr. Elena Nováková, PhD
Reasons

• I. Increase – stimulation of immunity – in case of immunedefficiency, - in case of necessity to improve the healing process
• II. Decrease – normal immunity – transplantation
• III. Modification – hypersensitivity – therapy of allergy
I. Immunotherapy – to increase immunity

• Therapeutical stimulation of immune functions
  
  • A. ADJUVANCE – non specific immune system stimulation
  
  • B. CYTOKINES – specific stimulation of immune processes
  
  • C. ANTISERA – contain antibodies (normal, hyperimmune)
A. Adjuvances

- Non specific stimulation of immune reactions
- Adjuvant substances in vaccines – increase effectivity – attraction of APC
  - stimulation of expression of costimulating molecules

**BCG** – vaccine – stimulate specific but also non specific T cell immunity, (used as adjuvans of other vaccinesn, imunotherapy of bladder tumor – instilation – stimulation of antitumor immunity via inflammatory reaction

**Levamisol** – antihelminticum, increases cellular immunity. – therapy of Ca of colon – stimulation of antitumor cytokines production by macrophages and T cells
B. Cytokines

• Regulate – inborne and adaptive immunity, 
  - induction and intensity of reactions: 
    - cellular growth, differentiation, activation, inflammation and tissue repair

Interferones - Type I (IFN – α, β) Type II (IFN – γ) – immunotherapy in viral infections – VHB, VHC

Side effects – sever flu-like sy
Therapy by cytokines

- IFN-\(\alpha\)2b + ribavirin (antivirotckum) – VHC (in 50% influence clinical course of infection cases)
- IFN - \(\gamma\) chronical granulomatouse disease – proinflammatory cytokine

Tumors
- IFN -\(\alpha\) hairy cell leukemia
- IL-2 Ca of kidney, melanoma (activation of NK cells)
- IFN – \(\gamma\), TNF – \(\alpha\) tumor of ovaria
Therapy of immunoedefficiency in Ca 1

• Isolation of T cells from TU and their proliferation in vitro by application of IL-2 to cell culture
• Production of specific substances against Ca antigens by T cells
• Proliferation of these tumor infiltrating cells in vitro
• Reinstilation – stimulised cells specifically target tumor. IL-2 can increase proliferation of anti tumor T cells in vivo
Immunotherapy in Ca - 2

• Transfection in vitro
  – infection of TU cell by active gene for cytokines, for expression of different CD molecules
  - changes of TU cells to APC, presenting tumor antigens
  - in vivo cell can cooperate with specific T cell and elicit its activation and tumor cell death

• Cytokine - can act as adjuvans – IL-2 and peptide vaccine against melanoma
C. Antibodies

• Normal human immunoglobulin
• IVIG – intraveous Ig
  – generalised agamaglobulinemia, hypoglobulinemia
  – from pooled plasma, contains IgG and small amounts of IgM and IgA
  – half time of elimination is 23 days – aplication every one month
  - alteration of production of Ig, of activation of C’ and production of proinflamatory subsatancies

Autoimmune thrombocytopenia, BC-CLL, Kawasaki sy,
• Hyperimune globuline – ( anti tetanus, rabies, VHB, VZV, CMV...)
• Monoclonal antibodies – antipeptope Ab – anti CD20 in B-NHL non Hodgkin lymphoma
II. Decrease of immune reactions-1

• Prevention and control of processes responsible for rejection of transplantation grafts, for activation of autoimmune processes

A. Antiinflammatory treatment – corticosteroids, NSAID,

B. Immunesupresive therapy:
   Rheumatoid arthritis– inhibitors of TNF α, IL -1 inhibitors, immunemodulation
   (methotrexate, azathioprin, imunoadhesines)
II. Decrease of immune reactions - 2

• **Asthma** - atopy, IgE, (mastocytes, neutrofils, eosinofils, CD4+Th2)  
  - bronchodilatators, theophilin, agonist of β2 - adrenergic receptors, anticholinergic drugs, antiinflamation drugs(CS), inhibitors of degranulation, monoclonal anti IgE (omalizumab)

• **Other autoimmune diseases** – humoral or CMI, (Crohn, SM, SLE, myastenia gravis, dermatomyositis, UC, psoriasis, ankylosing spondylitis) – CS, azathioprin, inhibitors of TNF α...
<table>
<thead>
<tr>
<th>Disease</th>
<th>Affected Tissues/Organs</th>
<th>Common Signs And Symptoms</th>
<th>Immunosuppressive/Anti-inflammatory Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn's disease (Fig. 18.5)</td>
<td>Intestinal mucosa layers</td>
<td>Diarrhea, right lower quadrant abdominal pain with an inflammatory mass, fever, and weight loss</td>
<td>Sulfasalazine, corticosteroid, azathioprine, methotrexate, TNF-α inhibitors</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>White matter of brain and spinal cord</td>
<td>Sensory symptoms, optic neuritis, diplopia, limb weakness, ataxia, cognitive and affective abnormalities, fatigue, constipation, urinary urgency/frequency, and sexual dysfunction</td>
<td>IFN-β-1a, IFN-β-1b, glatiramer acetate, mitoxantrone, natalizumab, corticosteroid</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (Fig. 18.6)</td>
<td>Joints, muscle, vasculature, kidneys, skin, mucosa, central nervous system, blood, heart, and lungs</td>
<td>Arthritis, weight loss, fever, fatigue, rash, mouth sores, alopecia, and photosensitivity</td>
<td>Aspirin, NSAIDs, corticosteroid, hydroxychloroquine, cyclophosphamide, mycophenolate mofetil</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Muscle motor end plate (neuromuscular junction)</td>
<td>Muscle weakness (ptosis, diplopia, and dysarthria)</td>
<td>Corticosteroids, cyclosporine, azathioprine</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Skin and muscle</td>
<td>Weight loss, fever, arthralgias, proximal muscle weakness, fatigue, rash, and photosensitivity</td>
<td>Corticosteroid, methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Colonic mucosa and submucosa</td>
<td>Diarrhea and hematoschezia</td>
<td>Sulfasalazine, corticosteroid, azathioprine, methotrexate, TNF-α inhibitors</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Skin</td>
<td>Inflamed, edematous skin lesions covered with a silvery white scale</td>
<td>Topical steroid and retinoids, TNF-α inhibitors</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Joints</td>
<td>Arthritis, arthralgia (oligoarticular joint inflammation)</td>
<td>NSAIDs, corticosteroid, methotrexate, sulfasalazine, TNF-α inhibitors</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Axial skeletal and sacroiliac joints</td>
<td>Inflammatory back pain, and arthritis of the hips and knees</td>
<td>NSAIDs, sulfasalazine, methotrexate, TNF-α inhibitors</td>
</tr>
</tbody>
</table>
II. Decrease of immune reactions-3

- **Transplantation** – usually a certain degree of gene incompatibility – application of therapy to decrease destructive reaction
  - Immunesuppression – whole body (irradiation),
    - more specific:
    - *cyclosporin* – inhibition of T cell immunity, selective alteration of regulation of Th cells and production of IL2 + nefrotoxicity
    - *tacrolimus* – derived from macrolid ATB, 50x stronger
III. Modification of immune reaction

• Prevention, interruption of reaction or deviation to less harmful reaction (allergy, anaphylaxis)

A. Prevention – in case of imminent harmful reaction
   - 1. ATB – prevention of poststreptococcal sequelae

B. Modification of on-going process
B  Modification of on-going process - to minimalise devastation

1. cytokines
   - IFN $\alpha$ - therapy of TU,
   - IFN $\beta$ – Sclerosis multiplex
   - IFN–$\gamma$ atopic dermatitis, decrease production of IL4 and IgE. Side effects – flu-like

   - **anti HIV therapy** – HIV elimination of T CD4+, infection of macrophages, decrease of CD8+: **anti HIV therapeutical process HAART** – to save immunity
   - IL 2 – stops CD4+ lymphopenia,
   - IL12 – specific anti HIV CMI,
   - IL 15 – stimulates CD8+ activity,
   - IFN-\(\alpha\)/IFN-\(\gamma\) – increase activity of CTL,
   - GM-CSF – activity of monocytes and macrophages
   - G-CSF – increase number of myeloid precursors
III. Modification of immune reactions

2. **Alergen immunetherapy** – desensibilisation – subcutaneous application of water extracts of alergen during weeks and months in increasing quantities.

Aim – reduction of allergic reaction, increase of inflammation reaction, inhibition of chronical process

repeated application with alternative application – production of IgG that will bind antigen before it is bound on Fab fragment of IgE anchored on mastocytes (used for allergic rhinitis, asthma, hypersensitivity to insects)

!!!!!! anaphylactic reaction!!!!!!!!!!

20 minutes
carefull survey,
prepared for acute therapy with antihistamines, epinephrine, resuscitation