Farmacotherapy and farmacomodulation of immunity

Lecture14

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Reasons

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

I. Imunotherapy – 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 – stimulise specific but also non specific T cell immunity, (used as adjuvans of other vaccinesn, imunotherapy of bladder tumor – instilation – stimulation of antitumor immunity via inflamatory 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, inflamation and tissue repaire

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

Side effects – sever flu-like sy

Therapy by cytokines

- IFN-α2b + ribavirin (antivirotckum) – VHC (in 50% influence clinical course of infection cases)
- IFN - γ chronical granulomatouse disease – proinflamatory cytokine

Tumors

- IFN -α hairy cell leukemia
- IL-2 Ca of kidney, melanoma (activation of NK cells)
- IFN – γ, TNF – α tumor of ovaria

Therapy of immunedefficiency in Ca 1

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

Immunetherapy 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 immuneglobulin
- IVIG – intraveouse 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 – antiepitope 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. Antiinflamatory treatment – corticosteroids, NSAID,

B. Immunesupresive therapy:
Rheumatoid arthritis– inhibítors 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...

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

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 harmfull reaction (allergy, anaphylaxy)

A. Prevention – in case of imminent harmfull reaction
   - 1. ATB – prevention of poststreptococcal sequelaes

B. Modification of on-going process

B Modification of on-going process - to minimalise devastation

1. cytokines

– *IFN* α - therapy of TU,

- *IFN* β – Sclerosis multiplex

- *IFN*–γ 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 – stimulses CD8+ activity,

IFN-α/IFN-γ – increase activity ofCTL,

GM-CSF – activity of monocytes and macrophages

G-CSF – increase number of myeloid precursors

III. Modificaton of immune reactions

2. Alergen immunetherapy – desensibilisation – subcutaneous application of water extractes of alergen during weaks and months in increasing quantities.

Aim – reduction of alergic reaction, increase of inflamation 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 alergic rhinitis, asthma, hypersensitivity to insects)

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

20 minutes

carefull survey,

prepared for acute therapy with antihistamines, epinephrine, resuscitation