

Systemic treatment in dermatology

MUDr. Eva Březinová, Ph.D.

Systemic treatment - indications

- **Systemic diseases:**
 - infectious, autoimmune, life-threatening diseases
 - single therapy in high risk groups of patients
- **Skin diseases:**
 - large area of disease
 - ineffectiveness of previous therapy
 - inability / unwillingness to apply topical treatment

Systemic treatment in dermatology

- **Systemic treatment – classification:**
- Therapy of infections
- Different systemic medicines
- Immunomodulators and antiproliferative agents
- „Biologic“ treatment

1) Systemic therapy – infectious diseases

- Antibiotics
- Antifungals
- Antivirotics
- Antiparasitics

2) Systemic therapy - different

- Antihistamines
- Vasoactive and antiplatelet drugs
- Antiandrogens and androgens
- Psychotropic drugs
- Intravenous immunoglobulins (IVIg)
- Systemic anticancer drugs

3) Immunomodulatory and antiproliferative treatment

- Systemic corticosteroids
- Methotrexate
- Azathioprine
- Mycophenolate mofetil
- Cyclosporine A
- Dapsone
- Antimalarials
- Systemic retinoids
- Interferons

Glucocorticosteroids

- Adrenal cortex hormones
- immunosuppressive effect
- morbidistatic (suppressing symptoms and development of the disease without its cure)
- antiallergic effect
- anti-inflammatory effect

Glucocorticosteroids - use

- short-term administration of high doses applied in life-threatening conditions
- pulsed corticoid therapy
- prolonged glucocorticoid therapy
- total administration - p.o., i. m., i. v., intranasally
- local application - mucous membranes, skin (corticosteroid dermatology)

Glucocorticosteroids

- dosage:
- according to the type of disease and the patient's weight
- monitoring:
- blood count, urea, creatinine, liver tests, glycemia, ions
- systemic most common side effects: attenuation of the hypothalamic-pituitary-adrenal cortex axis

Glucocorticosteroids

- The half-life $T_{1/2}$ of the biological effect is longer than the plasma $T_{1/2}$:
- - short-acting - biol. $T_{1/2}$ 8-12 h
(hydrocortisone, cortisone)
- - medium-acting - biol. $T_{1/2}$ 18-36 h
(prednisone, prednisolone, triamcinolone, methylprednisolone)
- - long-acting GCC - biol. $T_{1/2}$ about 36-54 h
(dexamethasone, betamethasone)

Corticosteroids - long-term side effects

- formation or perforation of GIT ulcer
- hypertension
- ACTH secretion block
- mineral disorders
- osteoporosis
- Cushing's syndrome
- acneiform rash
- hypertrichosis
- striae
- steroid diabetes
- depression
- psychosis
- thrombosis
- activation of latent infections

Corticosteroids - indications

- Autoimmune bullous diseases (pemphigus, pemphigoid, scarring pemphigoid, linear IgA dermatosis, EBA, herpes gestationis)
- severe allergic reactions (drug allergies, angioneurotic Quincke's edema)
- Vasculitis
- Connective tissue diseases (SLE, dermatomyositis, polyarteritis nodosa)
- Lymphomas
- Sarcoidosis
- Infections with severe inflammation reactions (Jarisch-Herxheimer reaction, generalized atopic eczema)
- XXX CAVE not for psoriasis !!!

Dapsone (sulfone)

- Antimicrobial / antiprotozoal action
- Anti-inflammatory
- Indications:
- dermatitis herpetiformis Duhring (+ gluten-free diet)
- chronic dermatoses with accumulation of neutrophils and / or eosinophils
- leprosy, pneumocystis pneumonia and prevention of toxoplasmosis in AIDS

Dapsone (sulfone)

- Side effects:
- methemoglobinemia... dyspnoea, anemia (glucose-6-phosphate dehydrogenase deficiency) - necessary controls for metHb levels
- hemolysis
- agranulocytosis
- hepatopathy

Aminoquinolones (antimalarials)

- Hydroxychloroquine (Plaquenil)
- It interferes with the function of lysosomes
- Disrupts antigen presentation by dendritic cells
- Anti-inflammatory effect
- Indications:
- SLE and discoid skin LE
- Photodermatoses (polymorphic light eruption, porphyria cutanea tarda)
- (sarcoidosis, dermatomyositis, oral lichen planus, chronic ulcerative stomatitis)
- CAVE! Retinopathy, keratopathy - eye examination!

Cytostatics

- substances that stop the growth of tumor cells
- inhibition of cell proliferation
- inhibition of nucleic acid biosynthesis (antimetabolite group)
- microtubule damage
- inhibition of cell division
- damage of the function and structure of nucleic acids

Methotrexate

- antimetabolite - blocking of the enzyme dihydrofolate reductase, preventing the reduction of folic acid, and thus the synthesis of RNA and DNA
- effect:
 - immunosuppressive
 - antiproliferative
- indications:
 - severe form of psoriasis vulgaris
 - neoplasia

Methotrexate

- dosage:
- - once a week 7.5 mg in a weekly dose (approx.), ev. according to the patient's disability and weight
- - concomitant administration of folic acid is necessary, due to the risk of anemia and reduction of gastrointestinal and hepatic toxicity
- monitoring:
- - control of hematological functions (at least once a month)
- - liver and kidney function (once every 1-3 months)

Methotrexate

- side effects:
 - - hepatotoxicity
 - - myelotoxicity
 - - methotrexate pneumonitis
 - - nausea
 - - stomatitis
 - - diarrhea
 - - defluvium
 - - excessive fatigue
 - - chills and fever
 - - dizziness
 - - reduced resistance to infections

Cyclophosphamide

- indications:
 - - neoplasia
 - - psoriasis vulgaris severe forms
 - - autoimmune diseases
 - - vasculitis
- dosage:
 - - the average dose is between 50 and 100 mg a day, early in the morning and the bladder should be emptied often
 - - sufficient hydration of the patient is necessary, maintaining fluid balance to prevent the development of cystitis

Cyclophosphamide

- monitoring:
 - - control of hematological functions (at least once a month)
 - - liver and kidney function (once every 1-3 months)
- side effects:
 - - nausea and vomiting
 - - anorexia and uncommon abdominal discomfort, abdominal pain and diarrhea
 - - haemorrhagic colitis, ulceration of the oral mucosa
 - - headache
 - - disorders of gonadal function (azoospermia, amenorrhea)

Azathioprine

- imidazole derivative of 6-mercaptopurine (6-MP)
- the effect of the therapy is not apparent until several weeks or months of treatment
- immunosuppressive antimetabolite alone or in combination with other medicinal products (corticosteroids)

Azathioprine

- Indication:
- severe rheumatoid arthritis
- **systemic lupus erythematosus**
- **dermatomyositis and polymyositis**
- autoimmune chronic active hepatitis
- **pemphigus vulgaris**
- **polyarteriitis nodosa**
- autoimmune hemolytic anemia
- chronic refractory idiopathic thrombocytopenic purpura
- relapsing multiple sclerosis
- transplanted
- intestinal inflammation

Azathioprine

- dosage:
- - 1 to 3 mg / kg body weight / day
- monitoring:
- - once a week blood count and differential (8 weeks), then once a month (bone marrow suppression)
- - urea, creatinine, liver tests

Azathioprine

- side effects:
 - - infectious and parasitic diseases
 - - benign and malignant neoplasms (including cysts and polyps)
 - - blood and lymphatic system disorders - bone marrow suppression
 - - immune system disorders
 - - respiratory, thoracic and mediastinal disorders
 - - very rare: reversible pneumonitis
 - - skin disorders and subcutaneous tissue
 - - alopecia
- CAVE: live vaccine must not be given - atypical potentially harmful reactions!

Cyclosporine A

- cyclic polypeptide
- suppresses the body's natural immune response
- suppresses the body's inappropriate response to its own cells and tissues

Cyclosporine A

- indications:
- - prevention and treatment of immune reactions to transplanted organs and tissues
- - autoimmune diseases
- - intraocular inflammation (endogenous uveitis)
- - nephrotic syndrome
- - rheumatoid arthritis
- - psoriasis vulgaris
- - atopic dermatitis

Cyclosporine A

- Dosage:
 - - total dose 2.5-5 mg / kg body weight per day divided into two doses
- Monitoring:
 - - level of cyclosporine in the blood
 - - blood pressure - regularly during treatment
 - - liver and kidney function, blood lipid level

Cyclosporine A

- side effects:
 - - manifestations of temporary damage to the nervous system - tingling in the hands and feet, headache - migraine, limb tremor
 - - formation of fine hairs or highlighting of existing hair - hypertrichosis
 - - damage to kidney function and high blood pressure
 - - growth of breasts and mammary glands

Retinoids

- vitamin A analogues
- normalization of proliferation, differentiation and keratinization of epidermal cells
- CAVE:
 - - co-administration of tetracycline antibiotics increases the risk of intracranial hypertension
 - - reduces the effect of low doses of progestins used as contraceptives

Acitretin

- synthetic aromatic analog of retinoic acid
- indications:
 - - severe forms of psoriasis
 - - palmoplantar keratoderma
 - - congenital ichthyosis
 - - lichen ruber planus
 - - follicular keratosis
 - - pityriasis rubra pilaris
 - - palmoplantar pustulosis

Acitretin

- dosage:
 - - start of therapy 25 mg daily, further depending on the condition
 - - the maximum recommended daily dose is 75 mg
- monitoring:
 - - liver tests, lipids, glycaemia

Acitretin

- side effects:
 - - severe headache
 - - inflammation of the lining of the mouth, abdominal pain, diarrhea, nausea, vomiting
 - - fragility of the skin, feeling sticky skin or rash, inflammation of the skin, changes in hair structure, brittle nails, skin infections around the nails, reddening of the skin
 - - joint, muscle, swelling of the ankles
 - - blurred vision
 - - increased sensitivity of the skin to sunlight (photosensitivity reactions)
 - - fetal malformations (necessary protection against pregnancy during therapy and 2 years after termination)

Isotretinoin

- 13-cis-retinoic acid
- the ability to bind to a retinoic acid binding protein

Isotretinoin

- effect:
- - direct inhibitory effect on sebaceous gland and sebocyte maturation
- - specific action on proliferating sebaceous epithelium
- - reduces keratinization in follicles
- - indirectly reduces bacterial flora
- - ability to inhibit neutrophils and monocytes
- - fatty food, milk - increased bioavailability
- - main metabolic product 4-oxo-isotretinoin

Isotretinoin

- indications:
- - cystic forms of acne unresponsive to adequate treatment with systemic antibiotics and topical drugs
- dosage:
- - 0.5–1 to 2 mg / kg / day
- - once or twice a day with food
- - to the cumulative dose (120–150 mg / kg / therapy, exceptionally up to 180 mg)
- - cumulative dose over 180 mg / kg / therapy has no better a therapeutic effect

Isotretinoin

- monitoring:
- - liver enzymes and fats (CHOL, TAG) before the start of treatment, after 1 month of treatment and then every 3 months, ev. according to results

Isotretinoin

- side effects:
- - **teratogenicity** (not transmitted by ejaculate or sperm)
embryotoxicity
- - dryness of the lips (almost 100% of patients - indicator of correct absorption of the drug), dryness of the skin, mucous membranes, burning of the eyes
- - increased sensitivity to UV radiation (thinning of the skin not photosensitivity)
- - pain of muscles, joints
- - increased fatigue
- - night vision disorders
- - increased serum lipids, liver enzymes
- - depression - no direct link

Bexarotene

- 3rd generation retinoid - "rexinoid"
- activator of RXR receptors
- it affects the gene expression of premalignant and malignant cells
- Indications: advanced T-cell lymphomas

Antihistamines

- In dermatology H1 antihistamines
- **1st generation** - lower selectivity to H1 rec, penetrate through HEB
- - sedative effect, cardiotoxicity, mucosal dryness
- - bisulepin (Dithiaden)
- - dimethindene (Fenistil)
- - promethazine (Prothazine)

Antihistamines

- **2nd generation** - selective, do not penetrate HEB
 - non-sedative, safe
- - cetirizine (Alerid, Analergin, Cetirizin, Zodac, Zyrtec)
- - desloratadine (Aerius, Dasselta, Desloratadine)
- - fexofenadine (Ewofex, Fexigra)
- - levocetirizine (Analergin, Cezera, Xyzal, Zenaro)
- - loratadine (Clarinase, Claritine, Flonidan)
- - rupatadine (Tamalis)
- - bilastine (Xados)

Antiandrogens

- effects: blocking the effects of androgens in the target tissue
- indications:
 - - treatment and control of benign prostatic hyperplasia (BPH) in patients with an enlarged prostate
 - - treatment of androgenetic alopecia in men (young)

Finasteride

- competitive inhibitor of human 5-alpha-reductase type II, formation of a stable enzyme complex
- - reduction of dihydrotestosterone production
- dosage: - 1 mg daily
- monitoring: - fPSA

Finasteride

- systemic most common side effects:
 - - sexual dysfunction
 - - breast tenderness to touch or breast enlargement, rash, breast discharge
 - - testicular pain, allergic reactions

Antibiotics

- **Penicillins**
- Indications:
- Syphilis and other treponematoses
- Inflammation of the skin and soft tissues caused by *Streptococcus sp.* - impetigo, erysipelas
- Lyme disease
- Actinomycosis
- Listeriosis
- Insect sting infections

Antibiotics

- **Cephalosporins:**
- Broad spectrum, 1.-4. generation (the higher the generation, the lower the efficiency on G + and increases on G-)
- Indications:
- Uncomplicated inflammation of the skin and subcutaneous tissue caused by *Staph. aureus* and *Streptococcus sp.* - impetigo, erysipelas
- Gonorea
- Lyme disease
- Bacterial meningitis

Antibiotics

- **Tetracyclines**
- Indication:
 - - actinomycosis
 - - morsus insecti
 - - anthrax
 - - Lyme disease
 - - chlamydial infections
 - - MRSA
 - - syphilis
 - - tularemia
 - - acne vulgaris

Antibiotics

- **Clindamycin (lincosamides)**
- Good permeability to tissues and body fluids
- Indications:
- Staphylococcal and streptococcal infections
- Anaerobes
- Hidradenitis suppurativa

Antibiotics

- **Macrolides**
- - in case of hypersensitivity to beta-lactams
- Indications:
- Uncomplicated skin inflammations (folliculitis, erysipelas, cellulitis)
- Bartonellosis
- Morsus insecti
- Lyme disease
- Chlamydial infections
- Infection with atypical mycobacteria

Antibiotics

- **Fluoroquinolones**
- Indications:
- 1st choice: anthrax, complicated skin inflammation (G-bacteria), *Pseudomonas aeruginosa* infection (otitis externa, ecthyma gangraenosum)
- 2nd choice: bartonellosis, chlamydial infections, erysipelas, gonorrhoea, granuloma inguinale

Antibiotics

- **Sulfonamides:**
trimethoprim/sulfamethoxazole
- Indications:
- Community MRSA infection
- Uncomplicated inflammation of the skin and subcutaneous tissue
- Granuloma inguinale, ulcus molle
- Urinary tract infections

Antivirotics

- **Acyclovir**
- p.o., i.v., locally
- Control of renal function (dose reduction)
- Indications:
- Symptomatic primary or recurrent mucocutaneous HSV-1 or HSV-2 infection
- Suppression of recurrent HSV-1/2 infections
- Perinatal prevention and treatment of neonatal HSV infection
- Treatment of VZV in adults and immunocompromised

Antivirotics

- **Valacyclovir**
- Indications:
- Treatment of primary or recurrent genital HSV infection
- Prevention of recurrent genital HSV infection
- Treatment of VZV infection

Interferons

- Proteins - cytokines of non-specific immunity, acting in antiviral defense, act paracrine, increase cellular toxicity against viruses and malignancies
- **Interferon α** - adjuvant therapy in malignant melanoma, therapy of mycosis fungoides, granulomatous inflammation
- **Interferon γ** - is not registered in the Czech Republic
- Adverse reactions: flu-like symptoms, leukopenia

Antifungals

- Extensive fungal infections of the skin, skin adnexa, mucous membranes
- Prophylactically in immunocompromised
- p.o., i.v.
- 1. polyenes
- 2. azoles
- 3. allylamines

- Itraconazole, fluconazole, terbinafine

Antifungals

- **Itraconazole:**
- Against dermatophytes, yeasts, saprophytic and dimorphic fungi
- Dosage:
- Onychomycosis:
- 200 mg daily for 12 weeks
- or pulse regimen 2x200 mg 1 week, then 3 weeks without therapy and then another pulse, repeated 2x to 3x

Antifungals

- **Fluconazole:**
- Dermatophytes and yeasts except *Candida Krusei*
- The first choice for mucocutaneous candidiasis
- 150 mg once, for chron. infections once a week for up to 6 months
- More serious infections: Day 1 200-400 mg / d, then 100-200 mg / d for 2-3 weeks
- Onychomycosis: 150 mg once a week until the nail grows up (up to 12 months)

Antifungals

- **Terbinafine:**
- Lipophilic, keratophilic
- After absorption it is distributed in the skin and adipose tissue
- Onychomycosis, tinea capitis, refractory tinea corporis, tinea pedis
- CAVE hepatopathy, renal dysfunction
- 250 mg / d 6 weeks (tinea capitis) to 12 weeks (onychomycosis)

Targeted anti-inflammatory and anti-tumor drugs (immunobiology)

- They interfere with the pathogenetic process in cells at the molecular level
- The target is both tumor cells and non-tumor cells
- Targeted drugs can be used in such pathogen. states where it is known:
- **Specific biomarker** (cytokine, cytokine receptor, growth factor)
- **Aberrant ligand or signaling pathway**

Targeted anti-inflammatory and anti-tumor drugs (immunobiology)

- **Classification by structure:**
- Recombinant cytokines and growth factors
- Monoclonal antibodies
- Fusion proteins
- Small molecules

- **Classification according to effects on biomarkers:**
- Inhibitors of TNF- α , interleukins, enzymes, receptors, lymphocyte surface antigens, T-cell immunomodulatory receptors and transduction signals

Targeted anti-inflammatory and anti-tumor drugs (immunobiology)

- Indications: **Psoriasis**
- **TNF α inhibitors** (etanercept, adalimumab, infliximab, certulizumab pegol)
- **Inhibitor IL-12/23** (ustekinumab)
- **Inhibitor IL -17A** (secukinumab, ixekizumab)
- **Inhibitor IL-17-AR** (brodalumab)
- **Inhibitor IL-23** (guselkumab)
- **Inhibitor IL-23p19** (tildrakizumab, risankizumab)
- **Phosphodiesterase (PDE4) inhibitor** (apremilast)

Targeted anti-inflammatory and anti-tumor drugs (immunobiology)

- **Atopic dermatitis**
- IL-4R inhibitor (dupilumab)

- **Lupus erythematoses**
- IL-6 inhibitor (tocilizumab)

- **Hidradenitis suppurativa**
- TNF α inhibitors (adalimumab)

- **Chronic spontaneous urticaria**
- IgE receptor inhibitor (omalizumab)

Targeted anti-inflammatory and anti-tumor drugs (immunobiology)

- **Pemphigus vulgaris, Wegener's granulomatosis, microscopic polyangiitis**
- Anti-CD20 (rituximab)

- **Acute SLE**
- anti- B-lymphocyte activating protein (belimumab)

Targeted anti-inflammatory and anti-tumor drugs (immunobiology)

- **CD30 + cutaneous lymphoma**
- Anti CD30 (brentuximab vedotin)

- **Malignant melanoma**
- Anti CTLA-4 (ipilimumab), anti PD-1 (pembrolizumab, nivolumab)
- BRAF and MEK tyrosine kinase inhibitors (vemurafenib, dabrafenib, trametinib, cobimetinib)

Targeted anti-inflammatory and anti-tumor drugs (immunobiology)

- **Dermatofibrosarcoma protuberans**
- Bcr-Abl tyrosinase inhibitors (imatinib)

- **Metastatic BCC, locally advanced BCC**
- Inhibitor of hedgehog pathway (vismodegib), inhibitor of signaling pathway (sonidegib)

- **Metastatic Merkel cell carcinoma**
- Inhibitor of PD-L1 T-cell immunomodulatory receptor (avelumab)