Pharmacotherapy of autoimmune diseases

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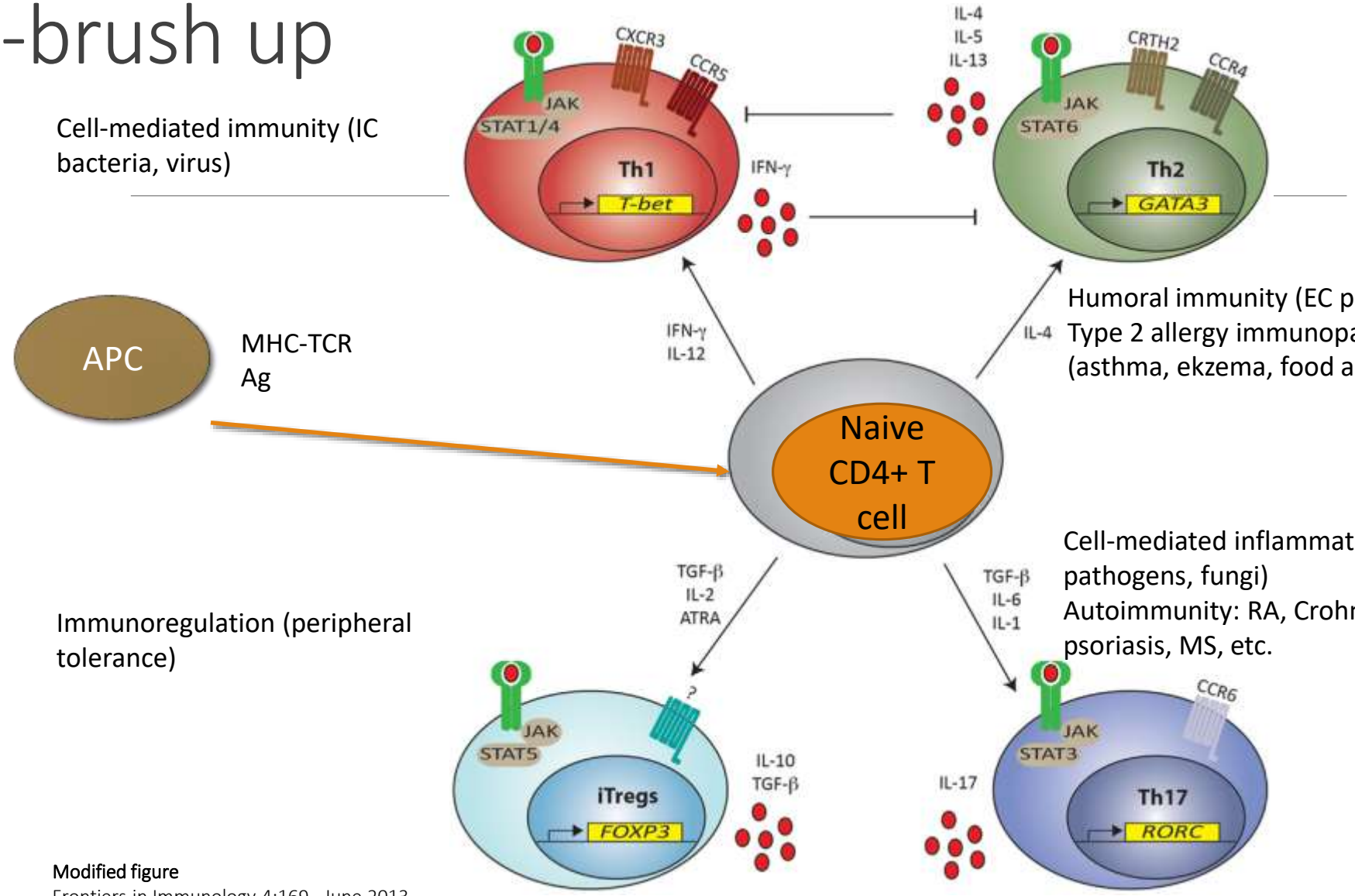
Immunology -brush up

Cell-mediated immunity (IC bacteria, virus)



Humoral immunity (EC parasites)
Type 2 allergy immunopathology (asthma, ekzema, food allergy)

Immunoregulation (peripheral tolerance)

Cell-mediated inflammation, (EC pathogens, fungi)
Autoimmunity: RA, Crohn, psoriasis, MS, etc.

Modified figure
Frontiers in Immunology 4:169 · June 2013
Cellular and Molecular Immunology **volume7**, pages182–189 (2010)

Common inflammatory pathways

Rheumathoid arthritis (RA), inflammatory bowel diseases (IBD) and psoriasis most likely share, - at least partly, - the same inflammatory pathways: **Th17 T-lymphocytes are involved**

Surface damage leads to the appearance of antigens in the tissues – antigen presenting cells produce cytokines that activate T cells producing other inflammtory cytokines – eventually a chronic inflammation develops

The critical pathway: antigen presenting macrophages or dendritic cells induce CD4+ T-cell activation by IL-6 and IL-23 – T-cell differentiation results in Th17 cells that produce several inflammatory cytokines e.g. IL-17A and F, TNFα, IFNγ; macrophages directly stimulate neutrophils by IL-1

Genetic background of Rheumathoid Arthritis

HLA-DRI and the shared ”Susceptibility Epitope” (SE) (also called shared epitope)

SE: conserved amino acid sequence in 70-74 position: they can present citrullinated residues well. The SE with the closest links to RA include DRB*0401, DRB*0404, DRB*0101, and DRB*1402. More than 90% of patients with RA express at least one of.

Functions linked to SE:

- shaping the T cell repertoire in the thymus
- altering intracellular HLA-DR trafficking and antigen loading
- serving as an autoantigen.

Other AIDs linked to HLA patterns

Type I DM – DR3, DR4, DQB1 position β57

Grave's disease – DR3, DRB1*08

Hashimoto's thyreoiditis – DR4, DR3

Myasthenia Gravis – DR3

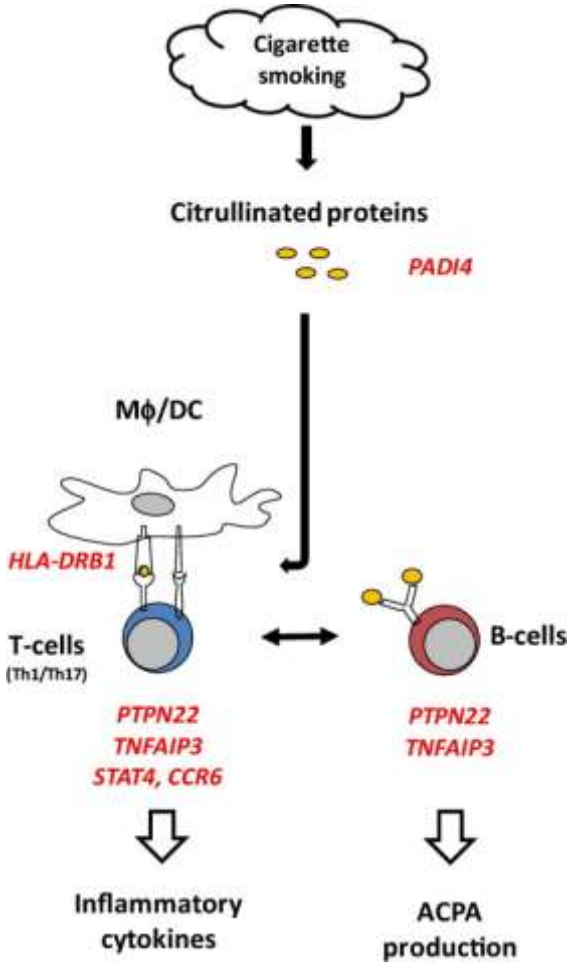
Addison's disease – DR3

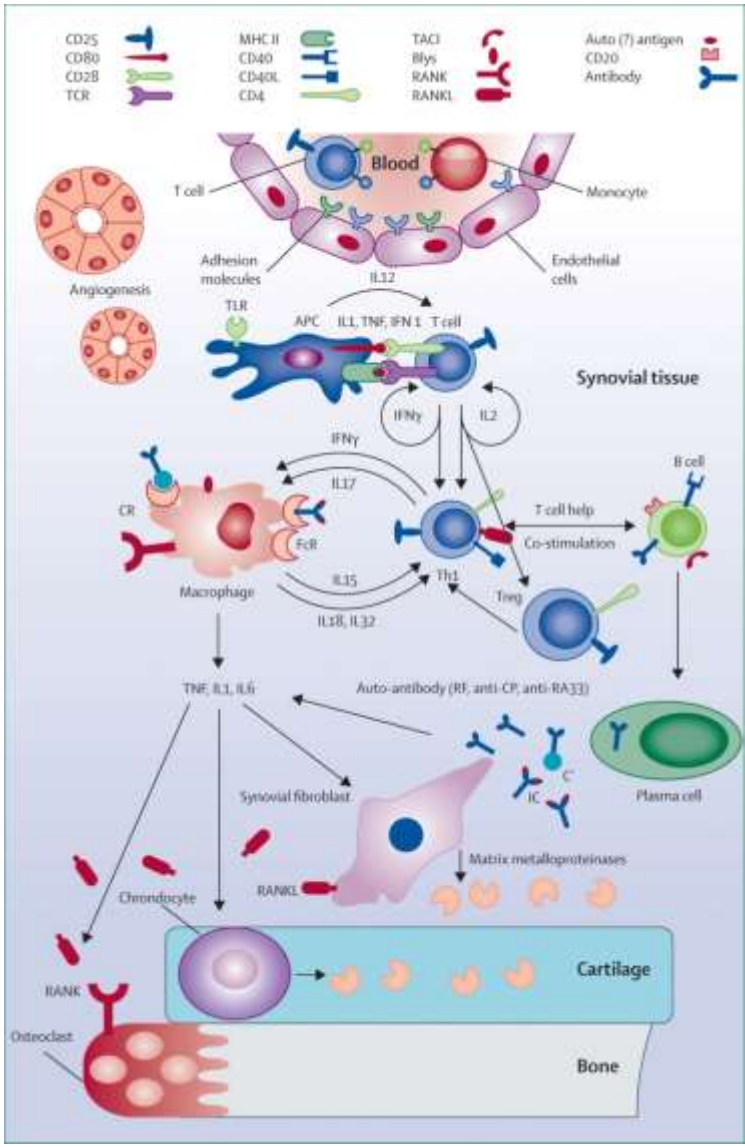
Multiple sclerosis – DR15

SLE – DR3, DR8, DR15

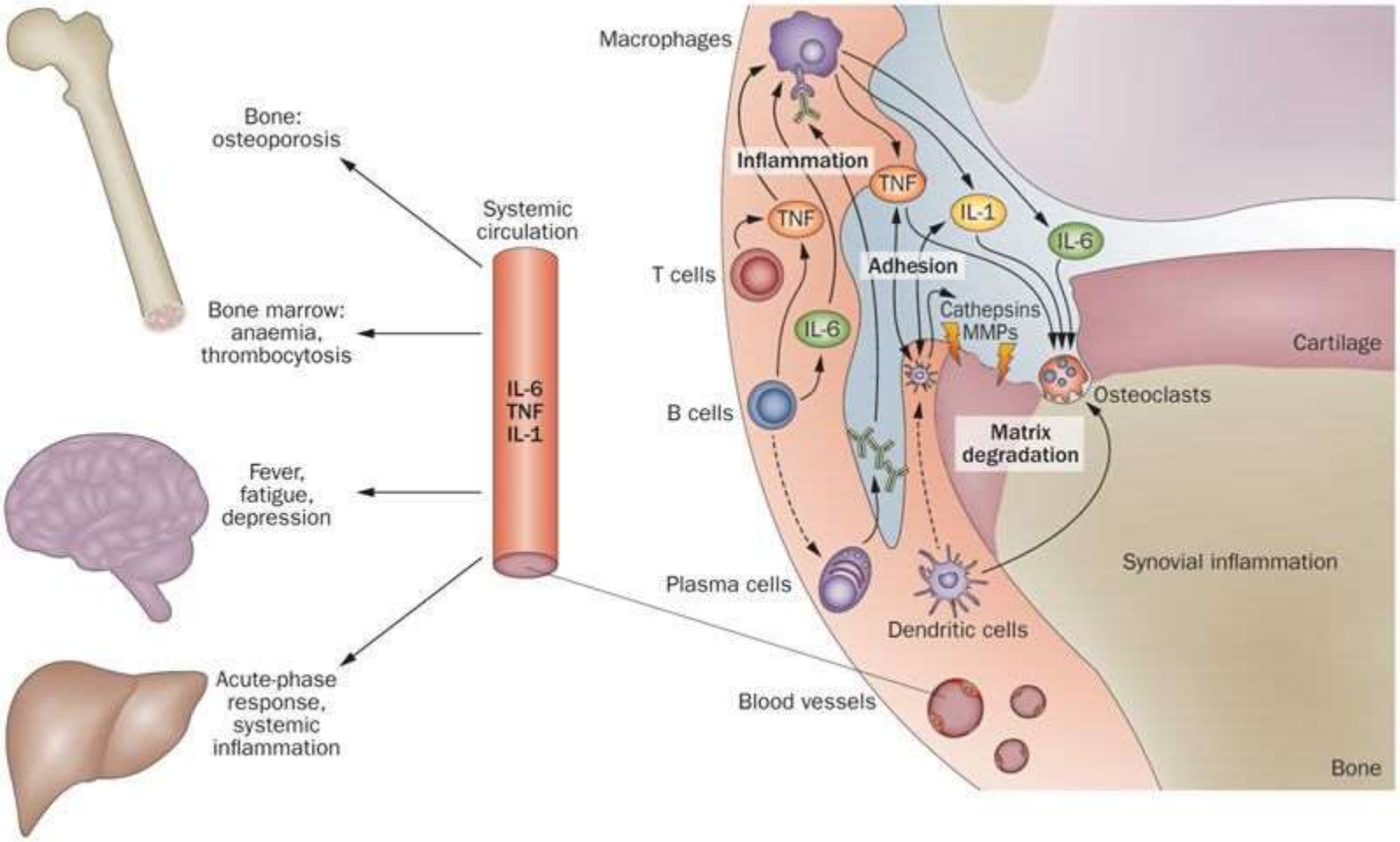
Source: S.C.L. Gough and M.J. Simmonds: The HLA Region and Autoimmune Disease: Associations and Mechanisms of Action, Current Genomics, 2007, 8, 453-465

Pathomechanism of Rheumathoid Arthritis





Pathomechanism of Rheumathoid Arthritis



Nature Reviews Rheumatology
ISSN 1759-4804

Rheumathoid Arthritis – symptoms

Prevalence: 1% - 3-4x more often in females

It starts mainly between 20 and 40 years of age

Symptoms:

- Morning stiffness, swelling, pressure pain over articulations (early)
- Tenosynovial and bursal inflammation, destruction of cartilage and bone erosion and myasthenia (later)
- Fibrous and bony ankilosis
- Small joints (metacarpophallangeal, proxymal interphallangeal) are more targeted, but also large joints can be affected
- Can cause also extraarticulal inflammation and fibrosis (heart, vessels, lungs, eyes etc.). Very specific: rheumatoid nodule in the skin
- Increased cardiovascular risk can be detected among RA patients

2010 ACR/EULAR Classification Criteria for RA

JOINT DISTRIBUTION (0-5)	
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
>10 joints (at least one small joint)	5
SEROLOGY (0-3)	
Negative RF AND negative ACPA	0
Low positive RF OR low positive ACPA	2
High positive RF OR high positive ACPA	3
SYMPTOM DURATION (0-1)	
<6 weeks	0
≥6 weeks	1
ACUTE PHASE REACTANTS (0-1)	
Normal CRP AND normal ESR	0
Abnormal CRP OR abnormal ESR	1

≥6 = definite RA

What if the score is <6?

Patient might fulfill the criteria…

→ **Prospectively** over time (cumulatively)

→ **Retrospectively** if data on all four domains have been adequately recorded in the past

American College of Rheumatology
Education • Treatment • Research

eular

https://www.eular.org/recommendations_eular_acr.cfm

Similarity to other autoimmune diseases

RA diagnosis is established over 6 points
New criteria are more sensitive for early diagnosis

Similar symptoms:

- Viral polyarthritis
- **Systemic rheumatic diseases (SLE)**
- Palindromic rheumatism
- Hypermobility syndrome and fibromyalgia
- **Reactive arthritis and arthritis of IBD**
- Lyme arthritis
- **Psoriatic arthritis**
- Polymyalgia rheumatica
- Crystalline arthritis
- Infectious arthritis
- Osteoarthritis
- Paraneoplastic disease
- Multicentric reticulohistiocytosis
- Sarcoid arthropathy
- Fibroblastic rheumatism

Treatment of psoriasis, juvenile idiopathic arthritis, ankylosing spondylitis and even IBDs have many overlap with RA

Treatment goals (T2T: treat to target) in Rheumathoid Arthritis

Slow down inflammation process (achieve remission)

Relieve symptoms

Prevent joint and organ damage

Improve physical function and overall well-being

Reduce long-term complications

Treatment options in Rheumathoid Arthritis

Conventional synthetic Disease Modifying Antirheumatic Drugs (csDMARDs) as soon as possible:

- **Methotrexate** is usually the first option
- Alternatives: **leflunomide, sulfasalazine, chloroquine, cyclosporin-A, cyclophosphamide**
- Short-term, tapered **glucocorticoids**, or local steroids

If necessary: adding **biological** and so-called **targeted synthetic** (ts) **DMARDs**

In case of inefficiency other **biologicals** and **tsDMARDs** can be used

Source: Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update [published online March 6, 2017]. Ann Rheum Dis. 2017; doi: 10.1136/annrheumdis-2016-210715

EULAR: European League Against Rheumathism

Non DMARDS used in Rheumathid Arthritis

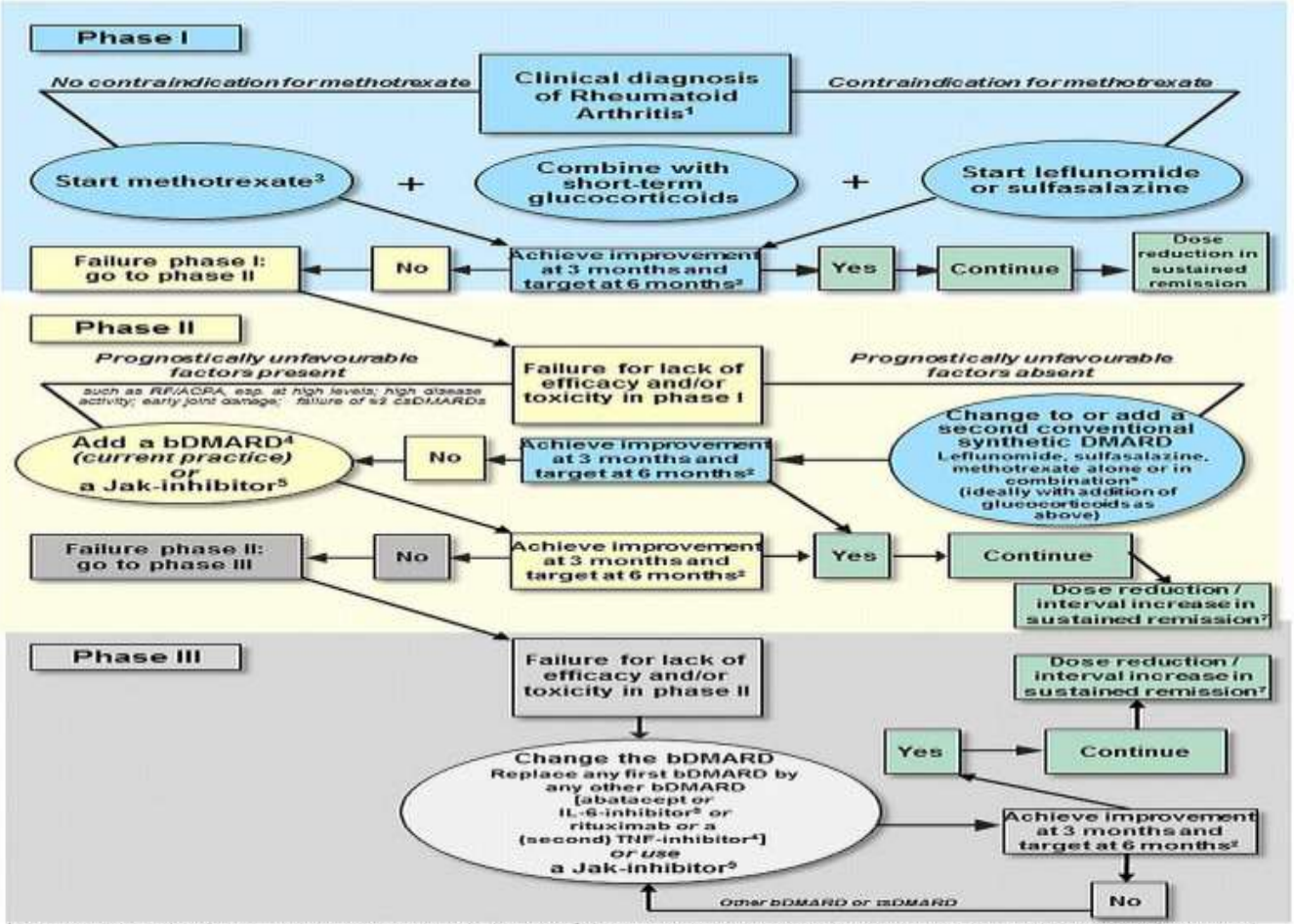
NSAIDS

- They are also essential in the treatment but only symptomatic: they improve the symptoms, but do not slow the progression (even they could facilitate it)
- The long term safetyness is problematic
  - GI ulcerations
  - Cardiovascular risk in RA increased – COX2 inhibition could worsen it

Corticosteroids

- In acute exacerbation they are the most effective drugs
- They can also suppress the progression
- High dose transient treatment, low dose maintained treatment and intraarticular local treatment is also used
- Side effects!!! (see detailed in the specific lecture)

Algorithm based on the 2016 European League Against Rheumatism (EULAR) recommendations on rheumatoid arthritis (RA) management.



[1]2010 ACR-EULAR classification criteria can support early diagnosis. [2]The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if no sufficient improvement is seen after 3 months. [3]"Methotrexate should be part of the first treatment strategy"; while combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs. [4]TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6-inhibitors, or rituximab; in patients who cannot use csDMARDs as comedication, IL6-inhibitors and tsDMARDs have some advantages. [5]Current practice would be to start with a bDMARD (in combination with MTX or another csDMARD) because of the long-term experience compared with tsDMARDs (Jak-inhibitors). [6]The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine. [7]Dose reduction or interval increase can be safely done with all bDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD. [8]Efficacy and safety of bDMARDs after Jak-inhibitor failure is unknown; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. [9]Efficacy and safety of a Jak-inhibitor after insufficient response to a previous Jak-inhibitor is unknown.

Josef S Smolen et al. Ann Rheum Dis 2017;76:960-977

Conventional synthetic (cs) DMARDs in Rheumathoid Arthritis

Methotrexate

- Inhibits several enzymes, including:
  - dihydrofolate-reductase
  - 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) formyltransferase (ATIC) $\rightarrow$ accumulation of AICAR intracellularly and adenosine extracellularly $\rightarrow$ inhibition of both B and T-cell activation (interestingly TNFα upregulates adenosine receptors)
- In RA and other AIDs orally given, in case of oral intolerance sc.
  - Variable dose, recently recomended rapid uptitration (10-15mg weekly)
  - Usually well-tolerated
- Adverse effects
  - Hepatotoxicity, bone marrow suppression, teratogenic
  - Long-term use may lead to lung fibrosis

Conventional synthetic (cs) DMARDs in Rheumathoid Arthritis

Leflunomide

- Inhibits dihydroorotate-dehydrogenase:
  - Pirimidine base synthesis is inhibited
  - It leads to inhibited function of both B and T-cells
- Orally given
- Adverse effects
  - Hepatotoxicity
  - Diarrhea
  - Exanthemas

Conventional synthetic (cs) DMARDs in Rheumathoid Arthritis

Azathioprine / 6-merkaptopurine

- Mechanims of action:
  - Inhibit phosphoribosyl-pyrophosphate-amido-transferase (purine synthesis)
  - Inhibit purine-base salvage
  - Incorporates into nucleic acids
- Orally given (1-3mg/kg sometimes less than 1mg/kg)
- Adverse effects
  - BM suppression, liver toxicity (rarely: liver vein occlusion syndrome)

Biologicals in the treatment of Rheumathoid Arthritis

TNFα antagonists:

- **infliximab, adalimumab, certolizumab pegol, etanercept, golimumab**
  - Inhibit inflammatory processes, apoptosis/cell death
  - May increase the risk of infections (viral, latent viral, tuberculosis)

CTLA4-containing fusion protein

- **abatacept**
  - Prevents the costimulation of T-cells (binds to CD80/86 of the antigen-presenting cell thus T-cell CD28 cannot bind, inhibits T-cell activation)

Biologicals in the treatment of Rheumathoid Arthritis

IL1-receptor antagonist: **anakinra**

- Inhibits the activation of neutrophil granulocytes

IL-6-receptor antagonist: **tocilizumab, sarilumab**

- Inhibit B-cell activation, differentiation of naive CD4+ T cell → Th17 systhesis of acute phase proteins
- Very efficient in monotherapy, without csDMARDs
- SE: High risk of infections, GI perforations, LDL ↑, neutropenia, thrombocytopenia, hepatotoxicity
- Broad off-label use for immunology diseases

CD20 antagonist: **rituximab**

- Depletes autoantibody producing B-cells – regeneration after 6 months!
- High risk of infections, malignancies, infusion reaction, arrhythmias, angina, late onset neutropenia
- Broad off-label use

Targeted synthetic (ts) DMARDs

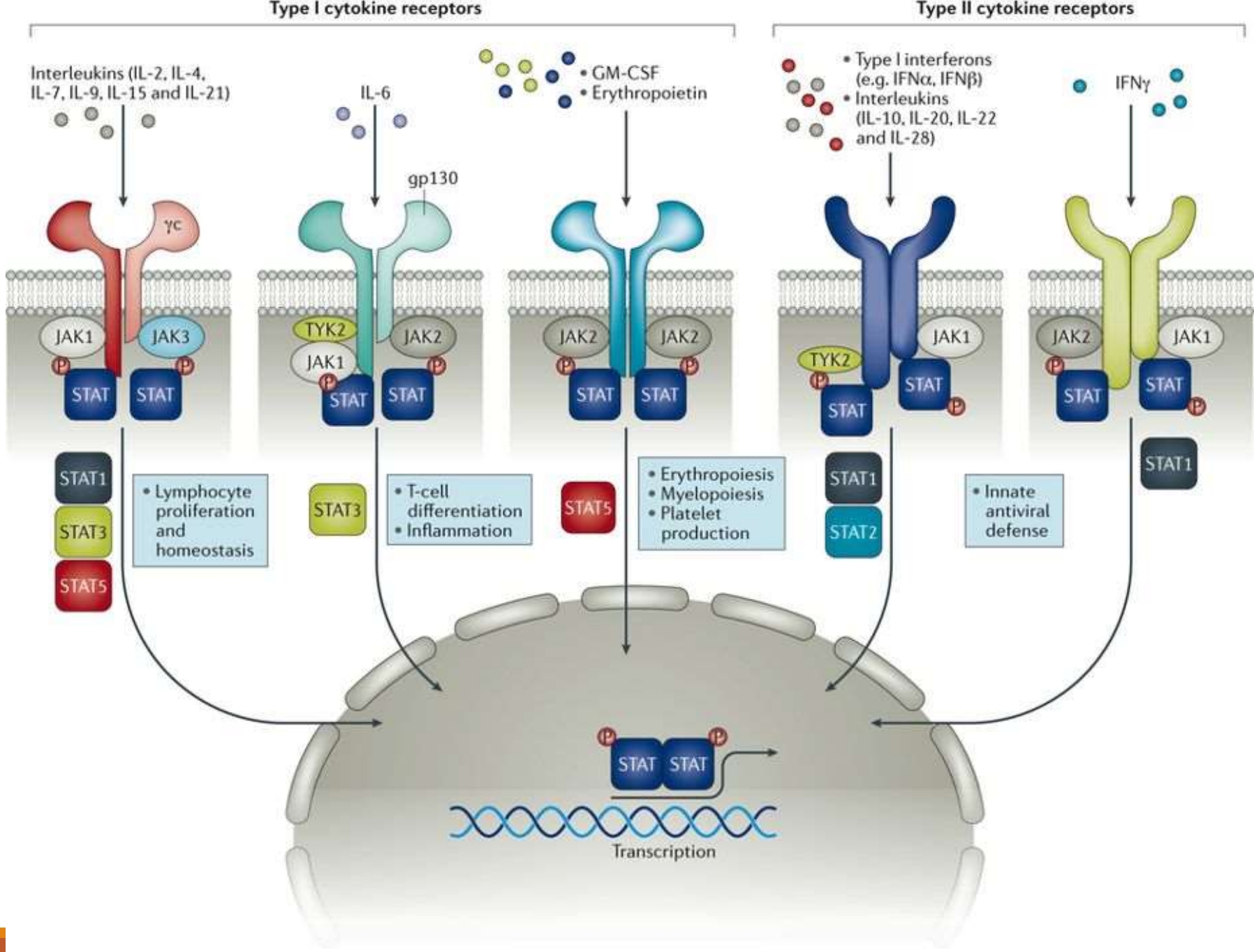
JAK (Janus Kinase) inhibitors

- **tofacinitib**
  - Inhibits JAK-1 and 3
- **baricitinib**
  - Inhibits JAK-1 and 2
- **upadacitinib**
  - Inhibits JAK-1

They inhibit many cytokine-related intracellular mechanisms, very efficient drugs

High risk of infections, virus reactivation (HZV), TBC, LDL-level↑, malignancies (e.g. lymphomas, etc.), thromboembolism, hepatotoxicity, anemia, thrombocytosis (*baricitinib*), neutropenia, GI perforations, intersticial lung disease (*tofacitinib*)

Drug interactions (tofacitinib is metabolized by CYP3A4)


Type I cytokine receptors
Type II cytokine receptors
Interleukins (IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21)
IL-6
• GM-CSF
• Erythropoietin
• Type I interferons (e.g. IFNα, IFNβ)
• Interleukins (IL-10, IL-20, IL-22 and IL-28)
IFNγ
gp130
γc
JAK1
JAK3
TYK2
JAK2
STAT
STAT1
STAT3
STAT5
STAT2
• Lymphocyte proliferation and homeostasis
• T-cell differentiation
• Inflammation
• Erythropoiesis
• Myelopoiesis
• Platelet production
• Innate antiviral defense
Transcription

Inflammatory Bowel Disease (IBD)

Factors behind the pathomechanims:

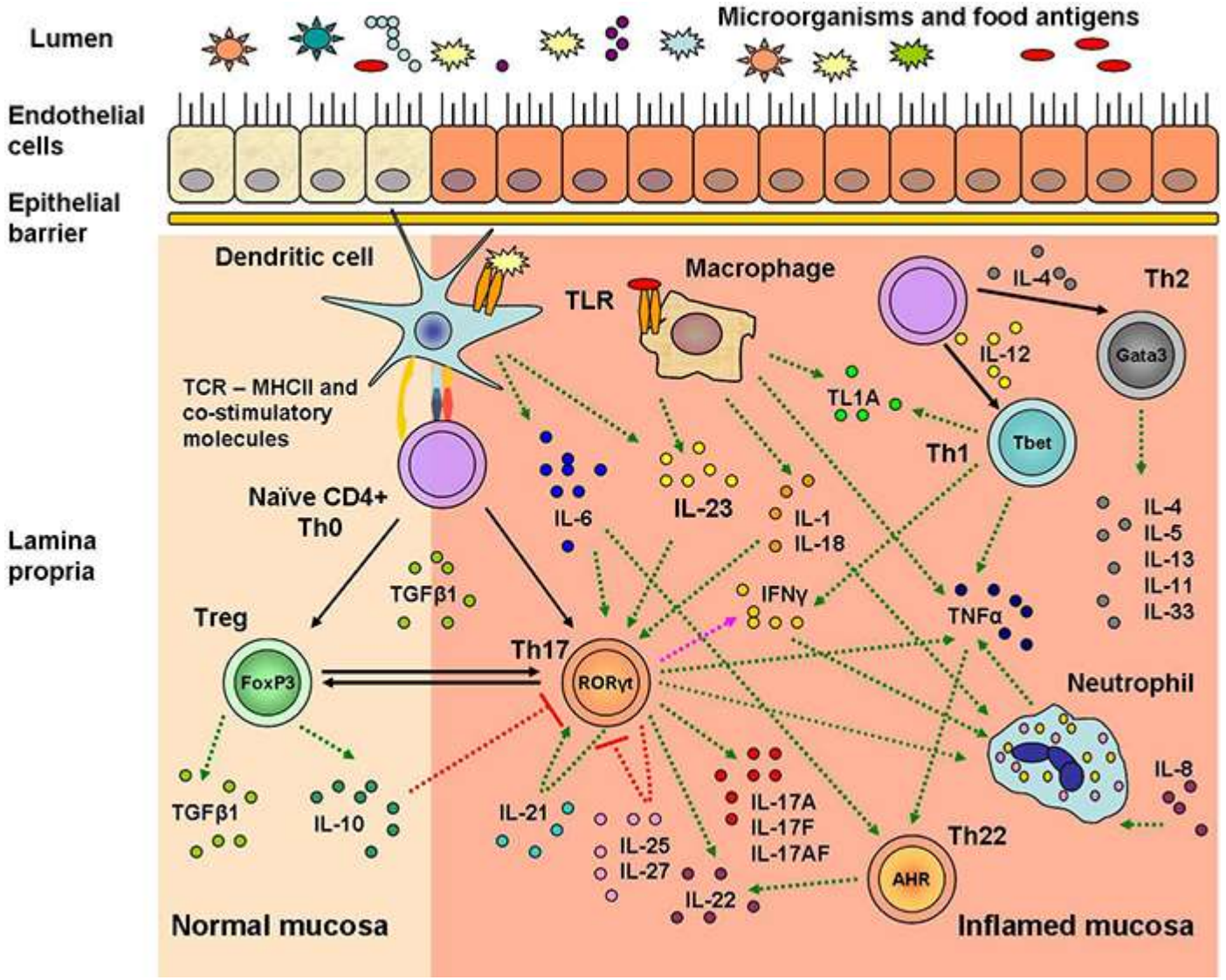
- Genetic, immune regulatory problems, barrier dysfunction, changes in the intestinal bacterial flora
- **Diet**, antibotics, **smoking**, better hygiene
- $\rightarrow$ overproduction of inflammatory cytokines (e.g. IL-1, IL-6, IL-17, IL-23, TNFα) $\rightarrow$ intestinal inflammation

Two types: Crohn's disease (CD), ulcerative colitis (UC)

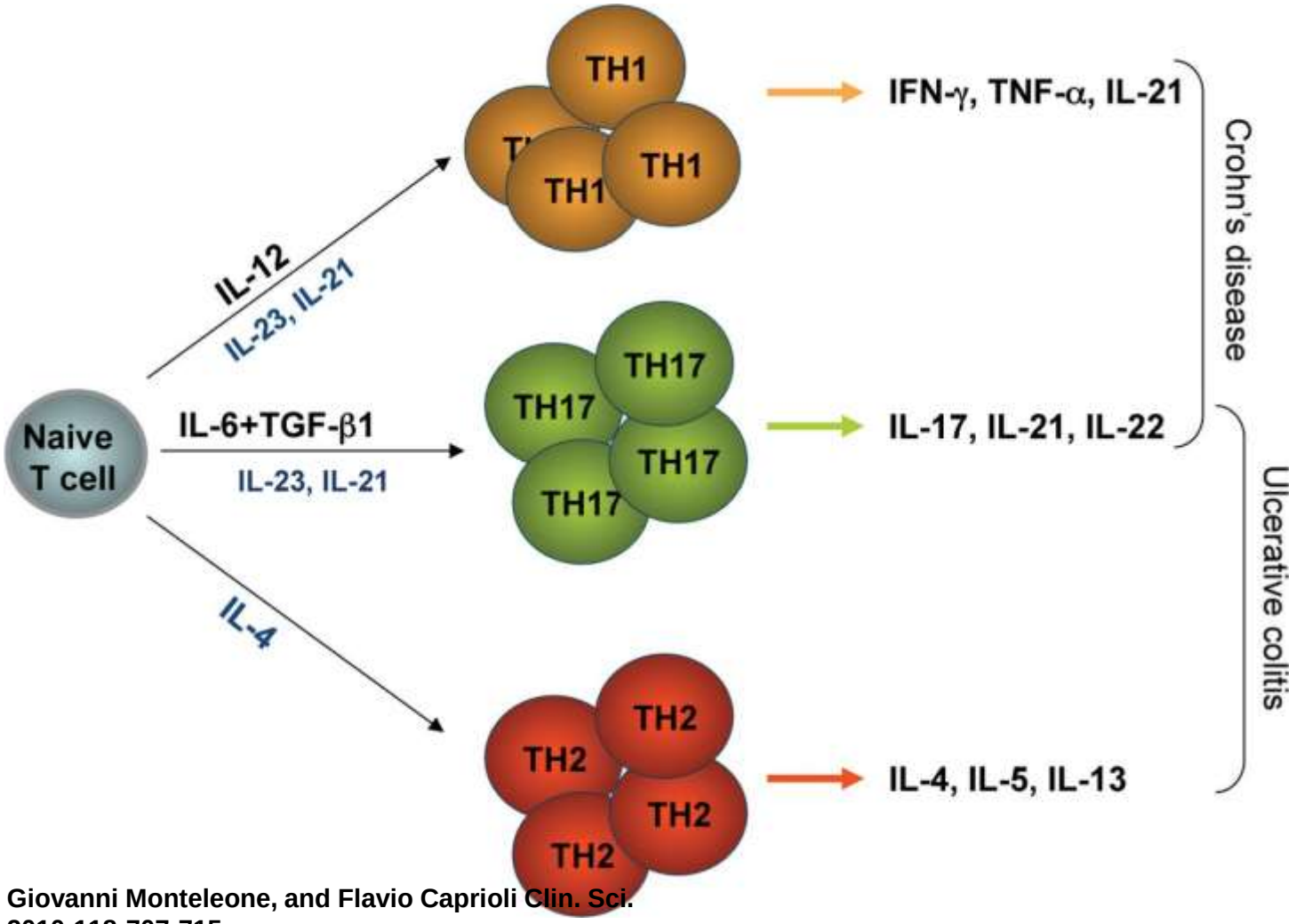
Differences and similarities between Crohn's disease and ulcerative colitis

Crohn's disease	Ulcerative colitis
Anywhere in the GI – skip lesions	Colon, rectum - continous
The whole intestinal wall is affected	Inflammation is localized to the mucosa
Periodic flare-ups of symptoms followed by remissions	Bowel ulcerations
Granulomas, bowel fistulae	Bloody stool
Diarrhea (may be bloody)	Tenesmus (painful defecation)
Wieght loss, fever	Weight loss, fever
Anemia, skin rashes, arthritis, eye inflammation	Anemia, arthritis, eye inflammation, primary sclerosing cholangitis
Leads to strictures (bowel obstruction)	Megacolon
High risk of cancer	Colon cancer

Pathomechanism of IBDs



Pathomechanism of IBDs



Giovanni Monteleone, and Flavio Caprioli Clin. Sci. 2010;118:707-715

PORTLAND PRESS

Therapeutic approach of IBDs

Mild
- **5-aminosalicylic acid** (5-ASA) (both in CD and UC)
- Locally applied 5-ASA, glucocorticoids (UC)
- **Budesonid** (both in CD and UC)

Moderate (or refractory to the above)
- Oral glucocorticoids (both in CD and UC)
- **Azathioprine/6-merkaptopurine** (both in CD and UC)
- **Methotrexate** (CD)

Severe (or refractory to the above)
- Intravenous glucocorticoids
- TNFα antagonists (**infliximab, adalimumab, golimumab**)
- **Cyclosporine** (UC) – not licensed for this in Hungary
- IL12/IL23 antagonist (**ustekinumab**) (CD) – see details in psoriasis
- Integrin antagonists (natalizumab, **vedolizumab**) (CD)

Surgery

5-aminosalicylic acid (5-ASA)

Mechanism of action:

- Inhibition of cyclo-oxygenase
- Modulation of inflammatory cytokines from arachidonic acid
- Inhibition of inflammatory cytokines (NF-κB)

Preparations

- Action is exerted loacally therefore early absorption must be avoided – either prodrugs or special formulations are used (sulfasalazine, mesalazine, olsalazine – microgranules, suppositories, enema)

Adverse effects

- Headache, nausea, diarrhea (sulfazalazine has more)

Glucocorticoids in IBDs

Usually short term treatment to avoid adverse effects

If possible locally acting glucocorticoids (e.g. hydrocortisone enema) or drugs with high first pass metabolism (budesonide controlled release preparations) are preferred

If necessary prednisolone (predenisone in the U.S.) per os or methylprednisolone (oral or injection) are given

Cytotoxic drugs in IBDs

Azathioprine or 6-merkaptopurine in both types

Methotrexate in Crohn’s disease only

Integrin antagonists

Mechanism of action

- Inhibit T-cell trafficking to the tissues

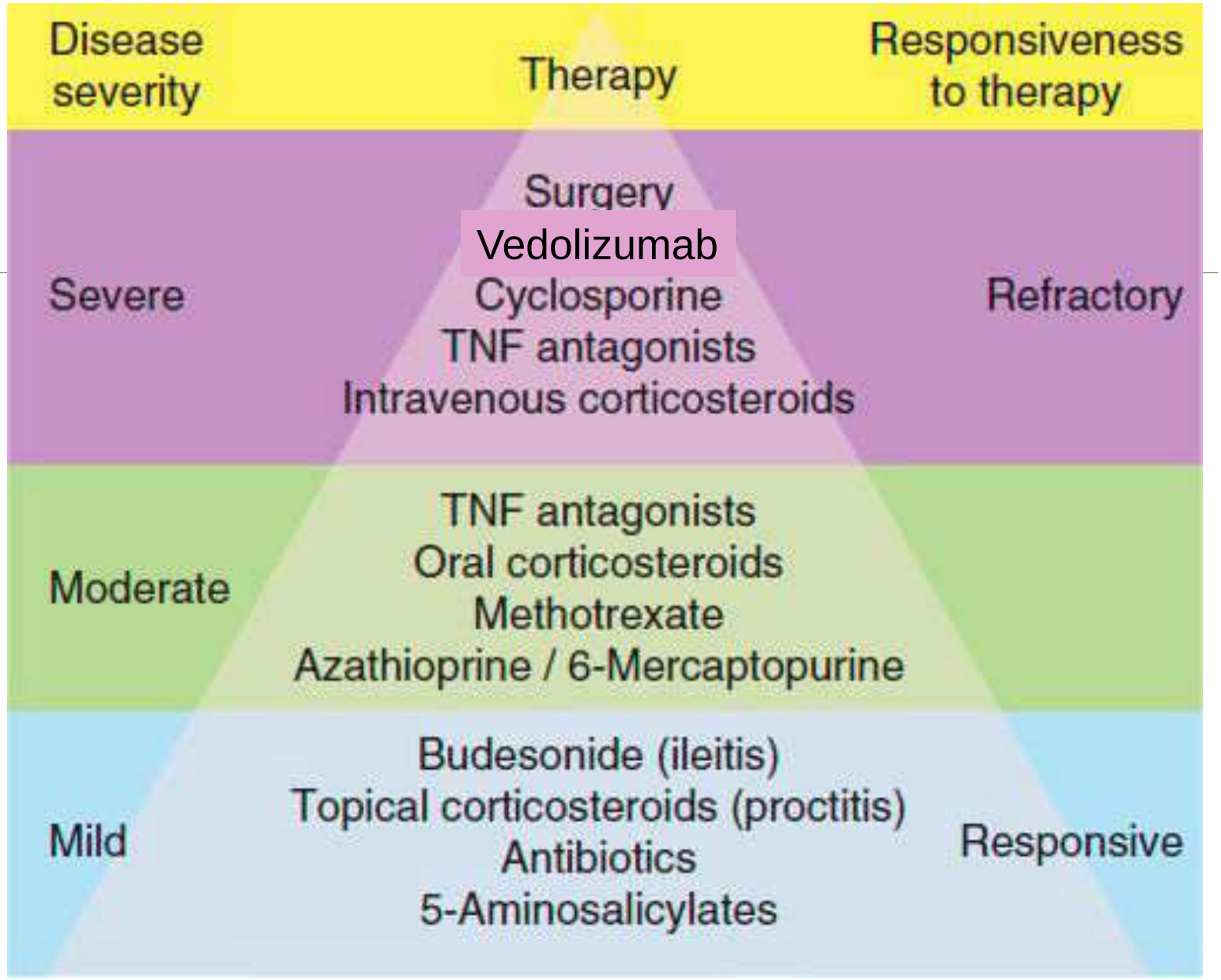
Natalizumab

- *Binds to the α4 subunit of both the α4β1 (VCAM-1 binding is inhibited) and α4β7 (MadCAM-1 binding is inhibited) integrins*
- *Primarily used in multiple sclerosis*

Vedolizumab

- Binds to the β7 subunit of α4β7 integrin (MadCAM-1 binding is inhibited)
- SE: infections (nasopharyngitis, bronchitis, influenza, sinusitis), headache, nausea, fever, fatigue, cough, joint pain

Natalizumab may cause progressive multifocal leukoencephalopathy


Disease severity
Therapy
Responsiveness to therapy
Surgery
Vedolizumab
Severe
Cyclosporine
TNF antagonists
Intravenous corticosteroids
Refractory
TNF antagonists
Oral corticosteroids
Methotrexate
Azathioprine / 6-Mercaptopurine
Moderate
Budesonide (ileitis)
Topical corticosteroids (proctitis)
Antibiotics
5-Aminosalicylates
Mild
Responsive

Psoriasis – background and symptoms

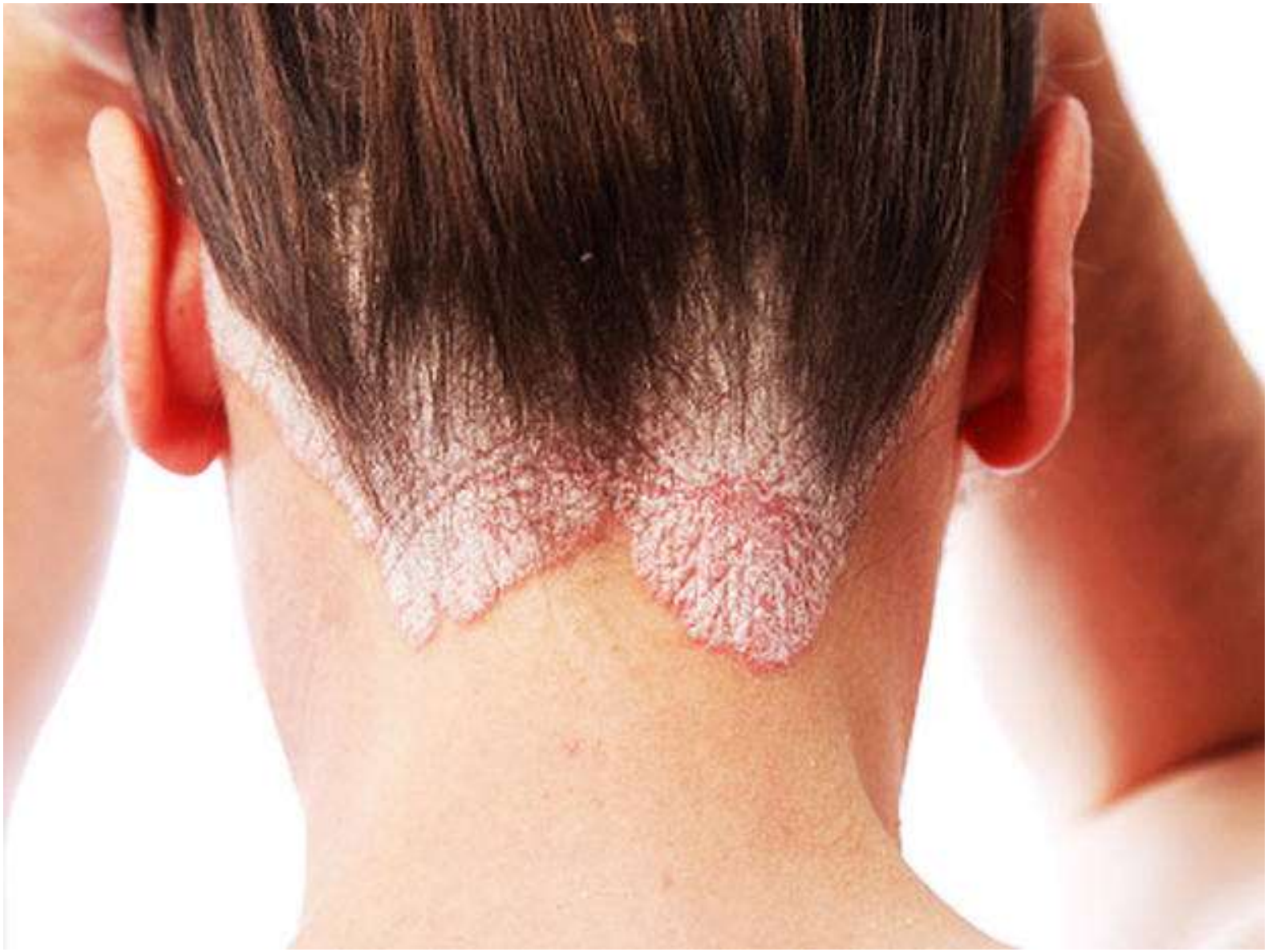
Prevalence: 0.09% (Tanzania) - 11.43% (North Norway) depending on regions,

It appears in all ages, mainly between 50 and 69 year age

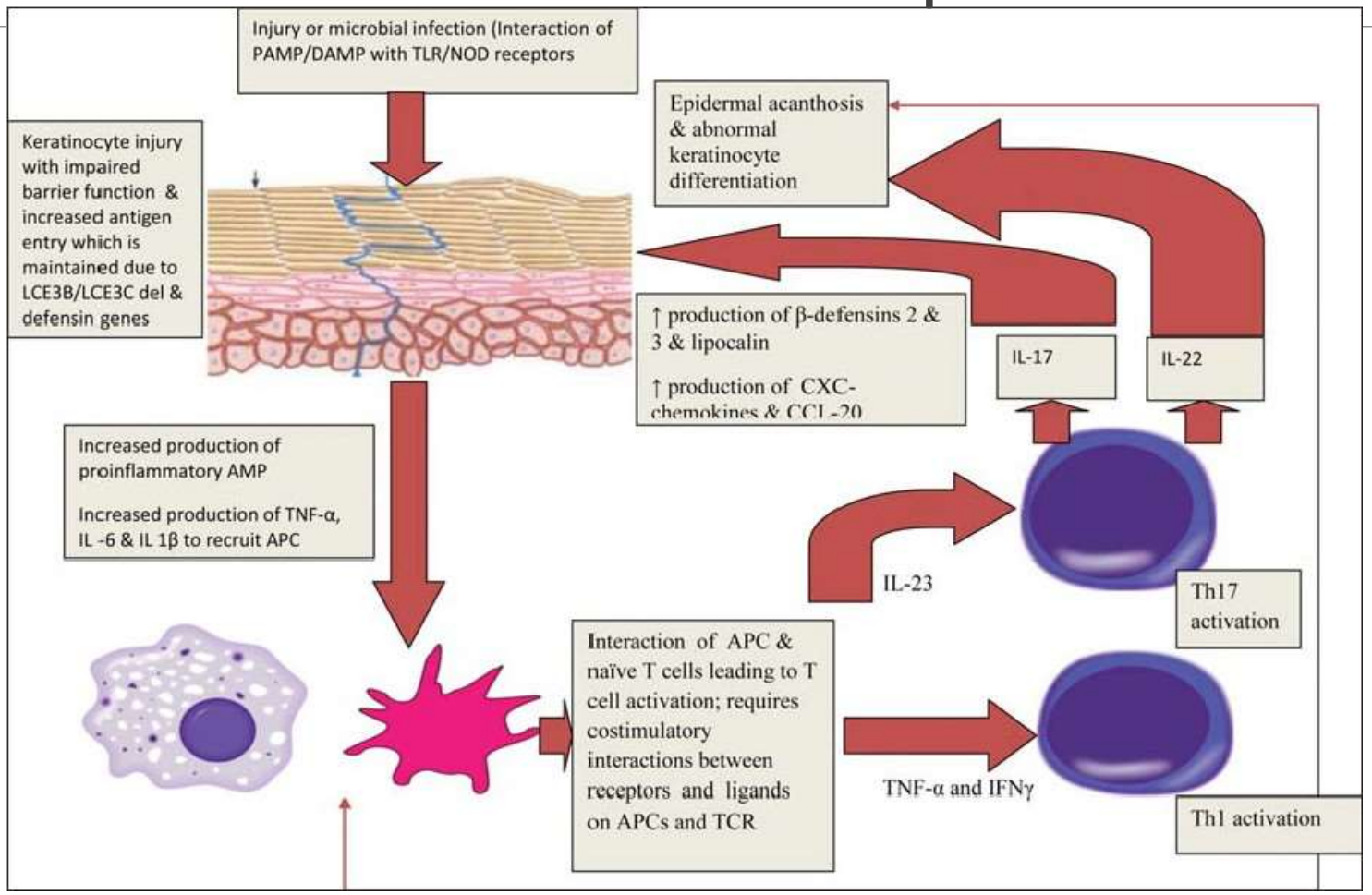
Genetic background – can be provoked by mild trauma, sunburn, infections, systemic drugs (e.g. β-blockers), stress

Symptoms:

- Red patches of abnormal skin (symmetrical, sharply demarcated, red papules and plaques)– from localized to general forms
- Five types: plaque, guttate, inverse, pustular, and erythrodermic
- May be associated with arthritis (psoriatic arthritis), depression, higher risk of Crohn's disease, cardiovascular diseases, lymphomas



Pathomechanism of psoriasis



Pathomechanism of psoriasis

Keratinocyte injury with impaired barrier

↓

Increased production of TNFα, IL-6, IL-1β

↓

Recruitment of antigen presenting cells (dendritic cells) leading to activation of naive T-cells

↓

TNFα and INFγ activates the Th1 pathway, **IL-23** activates Th17 pathway leading to the production of **IL-17** (A and F) and IL-22

↓

Accelerated proliferation of abnormal keratinocytes

Treatment goals in psoriasis

Successful treatment: decrease in the Psoriasis Area and Severity Index (PASI) score of 75 percent or greater

Unsuccessful treatment: improvement is lower than 50% in the PASI score → change in the treatment

Treatment options of psoriasis

PUVA = UV beam after taking 8-methoxypsoralene orally or applying a cream or bath. The drug makes the plaques photosensitive

Topically applied drugs

- **Glucocorticoid creams** alone or with tar or Vitamin D3 analogs (**calcipotriol with betamethasone**, cream or gel, **tacalcitol** emulsion)
- Vitamin D analogs inhibit keratocyte proliferation, used only in localized plaque psoriasis
- Retinoids: **tazaroten** (not in whole Europe)

Treatment options of psoriasis

Systemically applied drugs

- **Acitretin** (inhibits synthesis of keratin precursors, decreases hyperkeratosis)
- Immunosuppressive drugs: **cyclosporin, methotrexate, leflunomide**
- **Dimethyl-fumarate** (stimulates transcription factors)
- PDE-4 inhibitor: **apremilast** (inhibits expression of TNF-α, IL-23, IL-17 and other inflammatory cycokines)
- Biologicals
  - IL-23 antagonists – **ustekinumab** (IL-12/IL-23), **guselkumab** (IL-23), **risankizumab** (IL-23)
  - IL-17 antagonists – **ixekizumab**, **secukinumab**
  - IL-17R antagonist – **brodalumab**
  - TNFα antagonists – **adalimumab**, **etanercept**, **infliximab**

Retinoids in psoriasis

Mechanism of action

- Inhibition of cell proliferation and differentiation (they bind to nuclear retionoid receptors RAR and/or RXR)

Tazaroten – locally applied

Acitretin – systemic

- Can be used in more severe psoriasis
- Adverse effects may include dry mucosa (e.g. xerophtalmia=dry eyes), itching, several skin problems (e.g. hair loss, exfoliation, dermatitis, pyogen-granuloma)
- **Extremely teratogenic - !!! Getting pregnant must be avoided during and 3 years after terminating the treatment!!!**

Biological treatment in psoriasis

IL-23 antagonists
- **ustekinumab** (IL-12/IL-23), **guselkumab**, **risankizumab**

IL-17 antagonists
- **ixekizumab**, **secukinumab**

IL-17R antagonist
- **brodalumab**

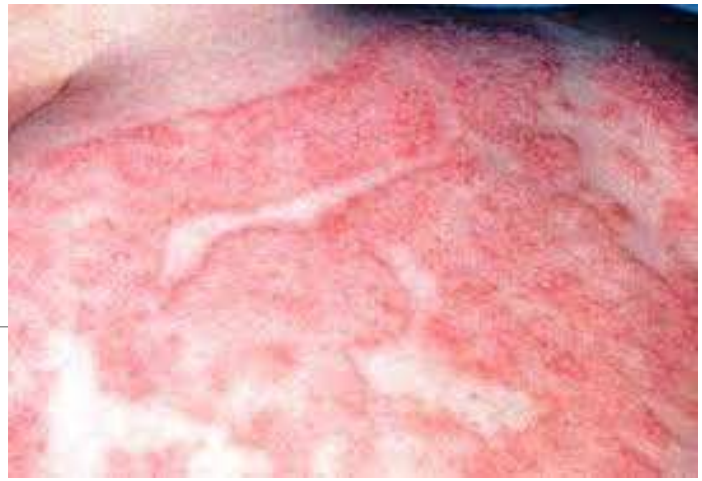
TNFα antagonists
- **adalimumab**, **etanercept**, **infliximab**

Usually highly efficient, older ones are indicated in psoriathic arthritis as well

Higher incidence of suicide – but this may be simply due to the common comorbidity depression

SE: infections like TBC, virus activation (HZV, hepatitis), hematological malignancies

Atopic dermatitis



Chronic autoimmune dermatitis

Concomitant appearance with other atopic manifestations (asthma, food allergy, sinusitis/nasal polyposis)

Activation of Th2 lymphocyte pathway→ increased IL-4, IL-5, IL-13 production

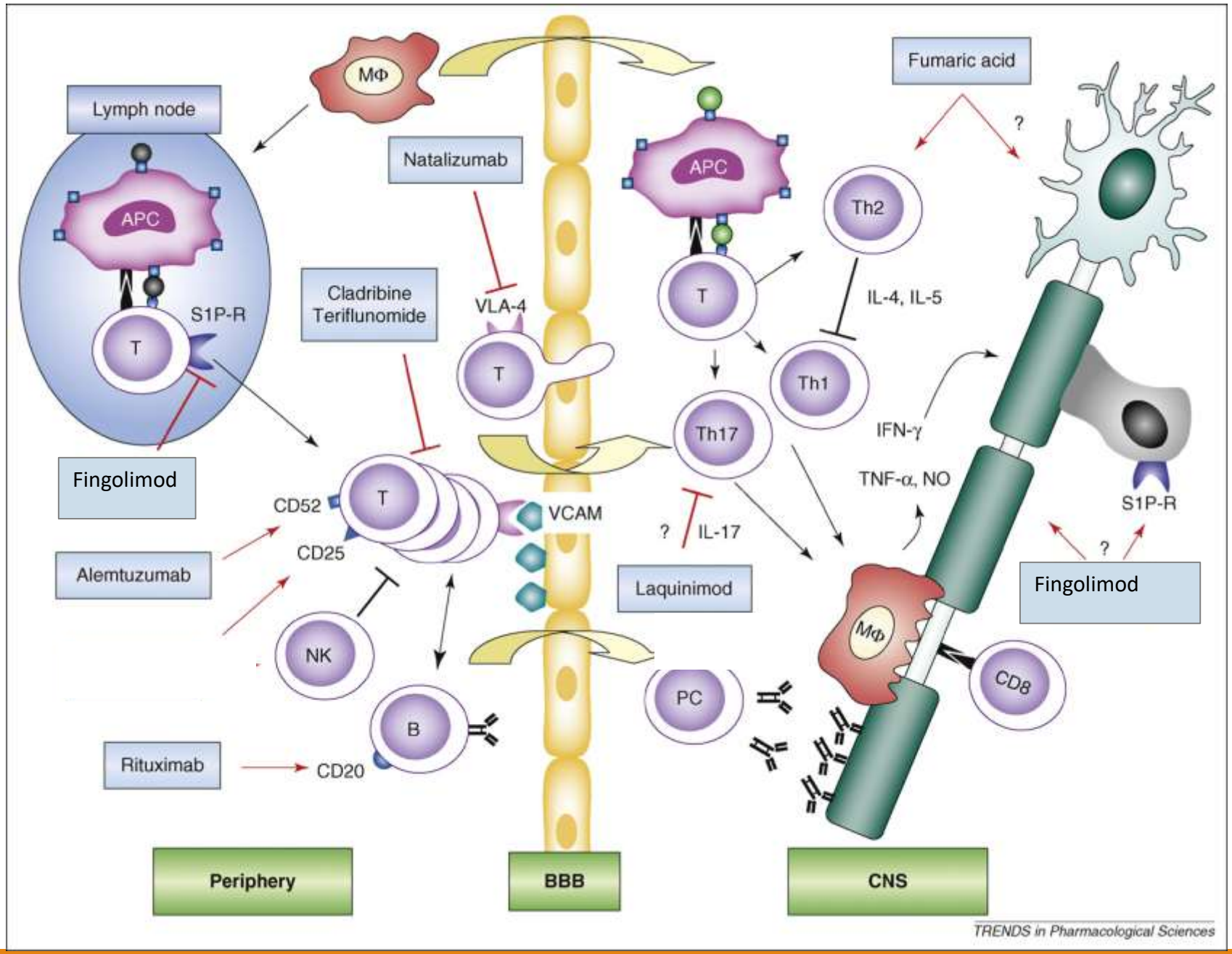
Therapy – depends on severity:

- 1. mild forms: local creams (**emollients**, **pimecrolimus**, **glucocortikoids**)
  - Systemic steroid only in acute exacerbation for a short time
- 2. more severe forms: systemic drugs: **cyclosporin-A** or IL4R/IL13R antagonist **dupilumab**

Multiple sclerosis – MS

Demyelinization of neurons in the CNS – antibodies and lymphocytes attack myelin

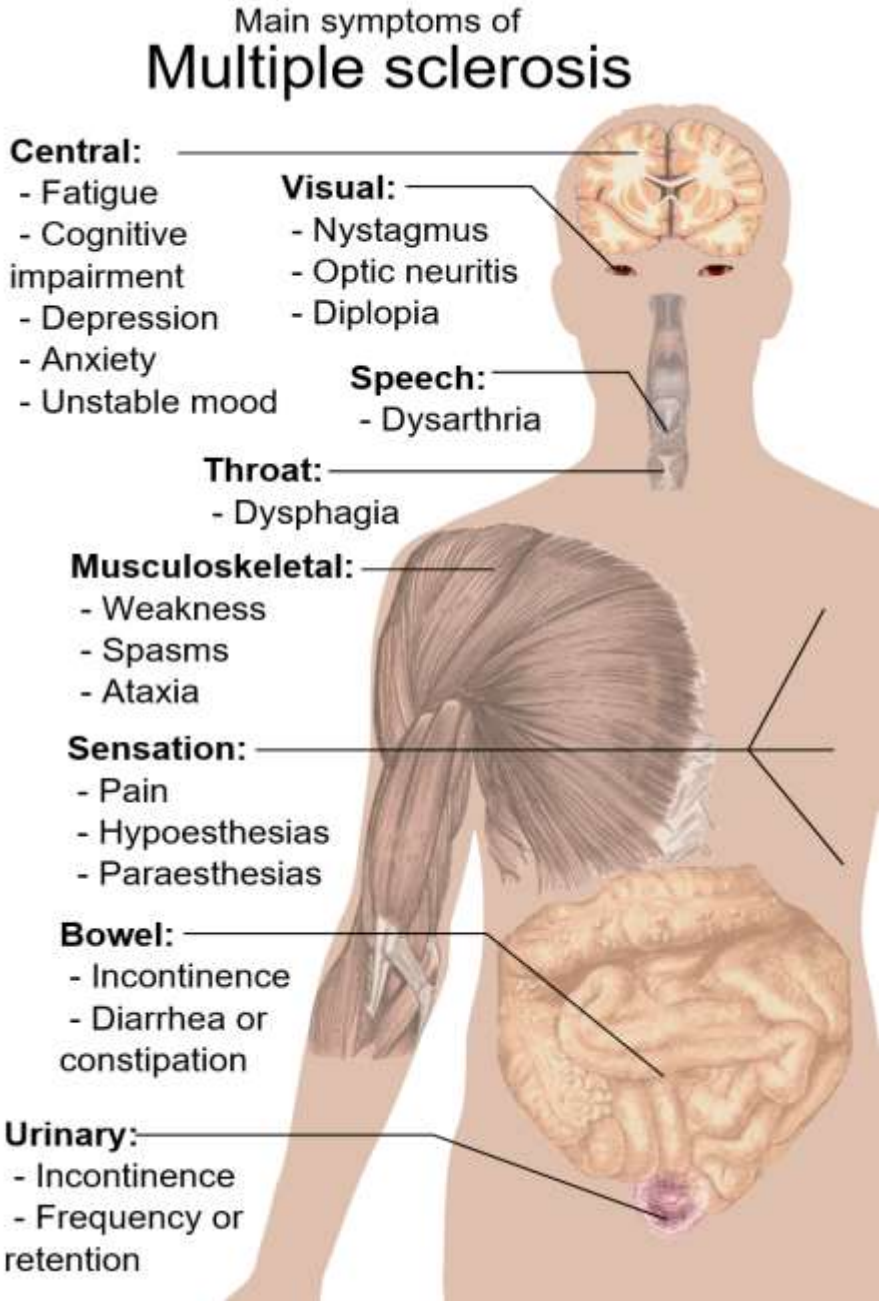
The appearence of immune cells (other than microglia) in the CNS is very unusual – the problem might be initiated by a pathological trafficking of T-cells into the CNS



Módosított ábra

Types of MS

Clinically Isolated Syndrome (CIS)
Relapsing-remitting MS (RRMS)
Primary progressive MS (PPMS)
Secondary progressive MS (SPMS)



Treatment options in MS

Interferons (INF-β1a, INF-β1b)
Glatiramers – mixture of short peptides corresponding myelin building blocks
Antimetabolites (oral)

- **Teriflunomide** - dihydroorotate-dehydrogenase inhibitor
- **Cladribine** -purine analog

Leukocyte depletion

- **Alemtuzumab** – CD52 inhibitor, T and B cell depletion, i.v. induction treatment

Treatment options in MS

T-cell inhibition

- **Natalizumab** (i.v.) - integrin $\alpha 4\beta 1$ inhibitor, prevents BBB penetration – broken trafficking
- **Fingolimod** (oral)-sphingosine-1-phosphate receptor modulator, inhibits lymphocyte mobilization from lymph nodes
- Siponimod (oral)-sphingosine-1-phosphate receptor modulator, inhibits lymphocyte mobilization from lymph nodes, indication: secondary progressive, active MS

B-cell depletion

- **Ocrelizumab** (only licenced drug for primary progressive form)-CD20 inhibitor

Treatment options in MS

Other (oral)

- **Dimethyl-fumarate** - Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcription pathway stimulator – increase the level of antioxidant enzymes

Improving motoric functions

- **Fampridine** – K^+-channel blocker (see 4-amino-pyridine, cholinergic transmission)