Biological therapy
What is biological therapy?

- Biological therapy is defined as an application of substances of variable composition and mode of action, interfering with immune and inflammatory processes accompanying initiation and development of treated diseases.
What is „biological remedy“?

- Remedies manufactured by means of biotechnology process - modifying biologic response on molecular level
- Aim of biological therapy is targeted regulatory intervention into biological processes accompanying origin and development of treated diseases
- Highly effective biological compounds are either same or very similar to the compounds produced by the organism itself.
Biological therapy

• Employs biological products – (c.f. pharmacological therapy – synthetic compounds)
• Medicinal biological products are – toxins, antitoxins, therapeutic sera and products of alive or dead microorganisms
• Vaccines or some produced manufactured from human blood are an example
• Recipient may perceive as heterologous proteins – they may act as antigens and induce production of antibodies in treated organism
• Problem of biological therapy – potential to allergic reactions and/or decrease of efficacy of the therapy
Representatives of biologic therapy

- **Monoclonal antibodies against cytokines** (e.g. anti-TNFalpha)
- Native biologic products and isolates (e.g. hyperimmune gamma globulin, coagulation factors)
- **Recombinant peptides** and proteins (e.g. recombinant cytokines, antagonists of cytokine receptors)
- **Synthetic oligonucleotides** (e.g. antisense oligodeoxynucleotide alicaforsen used in therapy of ulcerous colitis)
- Gene therapy
System of biologic therapy

A) Focused on target molecule, Biol. Therapy act as inhibitor of:
   • cytokine TNF-alpha:
     – adalimumab
     – etanercept
     – infliximab
     – golimumab
   • interleukin 12/23:
     – ustekinumab
   • interleukin receptor 6 (IL6):
     – tocilizumab
   • B cell:
     – rituximab
   • T cell:
     – abatacept

B) According to active ingredient we distinguish:
   • monoclonal antibodies:
     – fully human (adalimumab, ustekinumab, golimumab))
     – humanised i.e. 5-10% of murine protein(tocilizumab)
     – chimerical i.e. 25% murine protein (infliximab)
   • fusion protein of receptor and Fc fragment of IgG
     – etanercept
Properties of biological therapy

• Less AE and no drug interaction in comparison with current systemic therapy, no risk of cumulative toxicity in long-term application

• *never the less clinical experience is still limited*

• Relatively expensive therapy.

• In comparison with current therapy does not require expensive lab tests and clinical examination in the course of therapy.

• Improves ability to work, decrease hospitalization and risk of invalidity and decrease indirect costs connected with therapy
Monoclonal antibodies
Monoclonal antibodies – structure of immunoglobulin

V = variable domain (antigenic variability)

C = constant domain (link of complement, link on Fc receptor immunocompetent cells ...)

1-3 – hyper-variable segment (antigenic specificity)

$V_L - V_H = F_v$ (link of antigen)

$\mu, \delta, \alpha, \gamma, \varepsilon =$ isotopes of heavy chains (IgM, IgD, IgA, IgG, IgE)
Terminology of monoclonal antibodies

- **Murine** monoclonal antibodies – high production of HAMA;
  generic ending: „-mab“.
- **Chimerical** monoclonal antibodies – 60–70 % of human protein (constant domains) + 30–40 % murine antibodies;
  generic ending: „-ximab“.
- **Humanized** monoclonal antibodies – 5–10 % murine antibodies;
  generic ending: „-zumab“
- **Human** monoclonal antibodies (100% human)
  generic ending: „-mumab“
Monoclonal antibodies

Murine MAb
- 100% murine
- Hypersensitivity (not in use)

Chimeric MAb
- 34% murine
- Hypersensitivity
  (rituximab, infliximab)

Humanised MAb
- 5-10% murine
- Hypersensitivity
  (trastuzumab, certolizumab)

Human MAb
- 100% human
- Hypersensitivity
  (panitumumab, adalimumab)
Mode of action of monoclonal antibodies

1. Cytotoxicity depends on CFR complement fixation reaction
   – Link of antibody with tumor or other targeted cell
   – C5-C9 complement attacks membrane
   – Penetration into the cell and killing the cell

2. Cell mediated cytotoxicity
   – Express of Fc receptor of some population of leukocytes
   – Followed by fagocytosis of tumor and other targeted cells

3. Cytotoxic activity of antiidiotop antibodies
   – Idiotop = specific binding site for specific antibody
   – Antiidiotopic antibody act against specific binding site
   – Mimic previous antibody = has identical epitop

   – Combination of chemotherapy and MAb (breast cancer)
   – Antitumor vaccines (therapeutic vaccines – e.g., HPV – Cerivarix)
Target of monoclonal antibodies

- Target structure - specific antigen, frequently antigen presented on surface blood cell or hematopoietic stem cells
  - Various types of CD antigens (cluster of definition or cluster of differentiation),
- Antibodies may target practically against any antigen:
  - epidermal growth factor, EGFR (cetuximab, trastuzumab)
  - tumor necrotizing factor, TNF-alpha (infliximab, adalimumab)
  - vascular endothelial growth factor, VEGF (bevacizumab)
  - interleukin IL-2 (daklizumab)
  - alfa4-beta1-integrin (natalizumab)
  - complement C5 (ekulizumab)
  - IgE (omalizumab)
Forms monoclonal antibodies

- Non-conjugated antibodies
  - Cf. Previous mode of action
  - Direct (antitumor) activity
    - Induction of apoptosis
    - Interference with receptor and ligand
    - Influence of activity of classical cytostatics

- Conjugated antibodies
  - Chemical or genetic conjugates
    - Toxins (pseudomonadal, difteric, ricin)
    - Cytokines
    - Radionuclides
    - Cytostatics
Forms of monoclonal antibodies

1. Naked MAb
   - ADCC
   - CDC
   - Biotinylated radioactive ligand
   - Streptavidin

2. Immunoconjugates
   - Radioimmunoconjugate
   - Cytokine
   - Immunocytokine
   - Immunotoxin
   - scFv-enzyme
   - ADEPT
   - Prodrug
   - Drug
   - Liposome
   - scFv

3. Multistep Targeting
   - Bispecific MAb
   - Cellular Immunoconjugates
   - Killer cell
   - Immunoliposome
Monoclonal antibodies

- Adverse events
  - Acute cytokine reaction – (temperature, shivering, malaise) caused by releasing IL-6 and TNF. Occurs in 50 – 90% cases
  - Creation of antibodies
  - Toxic manifestation of toxin linked to antibody
  - Depletion of physiological cells expressing same antigen
### Monoclonal antibodies in oncology

<table>
<thead>
<tr>
<th>INN</th>
<th>brand</th>
<th>target structure</th>
<th>use</th>
</tr>
</thead>
<tbody>
<tr>
<td>trastuzumab</td>
<td>Herceptin</td>
<td>HER-2-neu</td>
<td>Ca prsu</td>
</tr>
<tr>
<td>cetuximab</td>
<td>Erbitux</td>
<td>EGFr</td>
<td>NSCLC, ORL</td>
</tr>
<tr>
<td>bevacizumab</td>
<td>Avastin</td>
<td>VEGF</td>
<td>různé nádory</td>
</tr>
<tr>
<td>rituximab</td>
<td>Mabthera</td>
<td>CD-20</td>
<td>NHL, B-CLL</td>
</tr>
<tr>
<td>ibritumomab</td>
<td>Zevalin</td>
<td>((^{90})Yt) CD-20</td>
<td>NHL</td>
</tr>
<tr>
<td>tositumomab</td>
<td>Bexxar (^{131})I</td>
<td>(^{131})I CD-20</td>
<td>NHL</td>
</tr>
<tr>
<td>epratuzumab</td>
<td></td>
<td>CD-22 human.</td>
<td></td>
</tr>
<tr>
<td>apolizumab</td>
<td></td>
<td>HLA-DR</td>
<td>NHL</td>
</tr>
<tr>
<td>alemtuzumab</td>
<td>MabCampath</td>
<td>CD-52</td>
<td>B-CLL</td>
</tr>
<tr>
<td>gemtuzumab</td>
<td>Mylotarg</td>
<td>CD-33</td>
<td>AML</td>
</tr>
<tr>
<td>oregovomab</td>
<td>Ovarex</td>
<td>CA-125</td>
<td>Ca ovaria</td>
</tr>
<tr>
<td>edrecolomab</td>
<td>Panorex</td>
<td>CO-17-1A</td>
<td>Ca kolorekta</td>
</tr>
<tr>
<td>panitumomab</td>
<td></td>
<td>EGFr</td>
<td>Ca ledvin (RCC)</td>
</tr>
</tbody>
</table>
Overview of biologic therapies in rheumatology, in the therapy of nonspecific gut inflammation and dermatology

<table>
<thead>
<tr>
<th>INN</th>
<th>Efalizumab</th>
<th>adalimumab</th>
<th>etanercept</th>
<th>adalimumab</th>
<th>ustekinumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td>Blok of activation of T lymphocytes</td>
<td>Anti-TNF</td>
<td>Anti-TNF</td>
<td>Anti-TNF</td>
<td>Anti-IL</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>Humanized. mondkl. Ab against CD 11a (T lymphocytes)</td>
<td>Fusion protein Fc fragment IgG, a of TNF receptor</td>
<td>Chimerical monoc. Ab against TNFα</td>
<td>Human monoc. Ab against TNFα</td>
<td>Human monoc. Ab against IL-12/23</td>
</tr>
<tr>
<td><strong>MoA</strong></td>
<td>Inhibition of activation of T lymphocytes, migration and adhesion to keratinocytes</td>
<td>Link with solub. TNFα, block of interaction with surface receptors</td>
<td>Link with solub. and bound TNFα and block of interaction with surface receptors</td>
<td>Link with solub. and bound TNFα, and block of interaction with surface receptors</td>
<td>Link of p40 subunit IL-12 a IL-23 block of interaction with surface receptors</td>
</tr>
<tr>
<td><strong>Application</strong></td>
<td>1. Wk 0,7 mg/kg, then 1 mg/kg, max. 200 mg/d, s.c., 1x wk</td>
<td>25 mg (50 mg max.) s.c., 2x wk</td>
<td>5 mg/kg, i.v., in 0., 2. and 6. wk; Maintenance infusion 5 mg/kg after 8 wk.</td>
<td>Introduction 80 mg s.c., after wk. 40 mg, á 2 wk 40 mg</td>
<td>45 mg s.c., in wk. 0, 4 and then every 12 &gt;100 kg–90 mg</td>
</tr>
<tr>
<td><strong>T1/2</strong></td>
<td>5-10 days</td>
<td>3-5 days</td>
<td>8-9 days</td>
<td>12-14 days</td>
<td>3 weeks</td>
</tr>
<tr>
<td></td>
<td>adalimumab</td>
<td>etanercept</td>
<td>infliximab</td>
<td>certolizumab</td>
<td>golimumab</td>
</tr>
<tr>
<td>----------------</td>
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<td>------------</td>
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<td>-----------</td>
</tr>
<tr>
<td><strong>Structure</strong></td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>Type</strong></td>
<td>Fully human monoclonal antibody</td>
<td>Fully human fusion protein</td>
<td>Chimerical monoclonal antibody</td>
<td>Humanised pegylated Fab fragment</td>
<td>Fully human monoclonal antibody</td>
</tr>
<tr>
<td><strong>Aim</strong></td>
<td>TNF-α</td>
<td>TNF-α</td>
<td>TNF-α</td>
<td>TNF-α</td>
<td>TNF-α</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>40 mg EOW</td>
<td>50 mg/mL 1QW or 25 mg/mL 2QW</td>
<td>3–7.5 mg/kg Q8W</td>
<td>200 mg Q2W or 400 mg Q4W EOW</td>
<td>50 mg month</td>
</tr>
<tr>
<td><strong>Application</strong></td>
<td>Autoapplication by patient (PFS a pen)</td>
<td>Autoapplication by patient (PFS a pen)</td>
<td>120 min infusion</td>
<td>Autoapplication by patient</td>
<td>Autoapplication by patient (Pen), IV 30 min infusion</td>
</tr>
</tbody>
</table>
## Biological therapy in rheumatology and other fields (I)

<table>
<thead>
<tr>
<th>INN</th>
<th>BRAND</th>
</tr>
</thead>
<tbody>
<tr>
<td>adalimumab</td>
<td>HUMIRA</td>
</tr>
<tr>
<td>infliximab</td>
<td>REMICADE</td>
</tr>
<tr>
<td>golimumab</td>
<td>SIMPONI</td>
</tr>
<tr>
<td>etanercept</td>
<td>ENBREL</td>
</tr>
<tr>
<td>kertolizumab-pegol</td>
<td>CIMZIA</td>
</tr>
</tbody>
</table>
Adalimumab – mode of action

- recombinant **human** Mab produced be means of ovarian cells Chinese hamsters
- **specific link with TNFα** and neutralizing biological function of TNF by means of bloc its interaction with p55 and p75 TNF receptor on cell surface.
- also modulates biologic response induced or being regulated by TNF, including changes of adhesion molecules levels responsible for leukocyte migration (ELAM-1, VACM-1 and ICAM-1 with IC50 0,1-0,2 nM).
Adalimumab – indication

- Active rheumatoid arthritis
- Between 13 – 17 years: polyarticular juvenile idiopathic arthritis.
- Active and progressive psoriatic arthritis
- Serious active ankylosing spondylitis
- Serious active Cohn's disease
- Psoriasis

*Without therapeutic answer to other therapeutic options*
Infliximab – mode of action

• Chimerical human-murine MAb
• High affinity link with soluble and transmembrane forms of TNFα, not on lymfotosoxin α (TNFβ).
• Inhibits functional activity of TNFα in broad spectrum in vitro biological methods.
• Prevents in development of polyarthritis in transgenic mice
Infliximab – indication

- Rheumatoid arthritis
- Cohn's disease, serious form or in case of fistula formation
- Ulcerous colitis
- Serious active ankylosing spondylitis
- Psoriatic arthritis
- Psoriasis

*Without therapeutic answer to other therapeutic options*
Golimumab – mode of action

- **human IgG₁κ** Mab produced by murine hybridoma cells line - DNA recombinant technology
- Creates high affinity, stable complexes with soluble and transmembrane bioactive forms of human TNF-α, prevents link of TNF-α with receptors
Golimumab – indication

- Active rheumatoid arthritis
- Active and progressive psoriatic arthritis
- Serious active ankylosing spondylitis

*Without therapeutic answer to other therapeutic options*
• Majority of pathological processes in rheumatoid diseases, in the skin affected by psoriasis are influenced by pro-inflammatory molecules – the TNF system.

• **Competitive inhibitor of TNF link on surface cellular receptors** – creation of biologically non-active TNF prevents cellular answer

• Etanercept may also influence cellular answer directed by other molecules induced by TNF (e.g., cytokines, adhesive molecules or proteinases).
Etanercept – mode of action

- Link and neutralization of soluble TNF-α; link also with TNF-β (lymfotoxin)
Etanercept – indication

- Rheumatoid arthritis
- Between 13 – 17 years: polyarticular juvenile idiopathic arthritis
- Psoriatic arthritis
- Serious active ankylosing spondylitis
- plaque psoriasis

*Without therapeutic answer to other therapeutic options*

- Potential indication – Alzheimer disease
Kertolizumab-pegol – indication

- Cohn's disease
- Rheumatoid arthritis
• PEGylated TNF inhibitor
  – Block the effect of TNF and substances created by the cells of immunity system responsible for inflammation
  – PEGylation extends effect i.e. application possible every 4 weeks
Biological therapy in rheumatology and other fields (II)

<table>
<thead>
<tr>
<th>INN</th>
<th>BRAND</th>
</tr>
</thead>
<tbody>
<tr>
<td>tocilizumab</td>
<td>ROACTEMRA</td>
</tr>
<tr>
<td>anakinra</td>
<td>KINERET</td>
</tr>
<tr>
<td>ustekinumab</td>
<td>STELARA</td>
</tr>
<tr>
<td>efalizumab*</td>
<td>RAPTIVA</td>
</tr>
</tbody>
</table>

*For lack of efficacy registration in EU temporary stopped
Tocilizumab – mode of action

- Specific link with soluble and membrane part of the receptor for IL-6 (sIL-6R and mIL-6R).
- Inhibition of signal transduction facilitated by means of sIL-6R and mIL-6R.
- IL-6 is pleiotropic pro-inflammatory cytokine produced by different types of cells including T and B-cells, monocytes and fibroblasts.
  - IL-6 participates in several physiological processes like activation of T-cells, or acute phase and stimulation of hemopoiesis
  - IL-6 participates in pathogenesis of e.g. inflammatory diseases or tumors, osteoporosis etc.
Tocilizumab – indication

- Moderate to severe active rheumatoid arthritis in adults in combination with methotrexate
  - Previously not responded or not tolerated one or more traditional DMARD or TNF antagonists
Anakinra – mode of action

• Neutralize biological activity of interleukin-1α (IL-1α) and interleukin-1β (IL-1β)
  – competitive inhibitor of the link to receptor type I for interleukin-1 (IL-1RI).

• Interleukin-1 (IL-1) is key pro-inflammatory cytokine
  – Mediates various cellular answers including inflammatory processes in synovial fluid
Anakinra – indication

- Active rheumatoid arthritis combination with methotrexate in patients with unsatisfactory response to methotrexate alone
Ustekinumab – mode of action (I)

• Fully human IgG1κ MAb
  – Binds with high affinity and specificity to protein p40, subunit human cytokines IL-12 and IL-23.
• Inhibits activity of human IL-12 and IL-23
  – bloc cytokines to bind with their receptor protein IL-12Rβ1, exprimed on surface of immune cells
  – Can not bind on IL-12 and IL-23, which are already fixed on IL-12Rβ1 surface cellular receptor
Ustekinumab – mode of action (II)

• IL-12 and IL-23 are heterodimeric cytokines, secreted by activated cells presenting antigen, e.g. macrophages and dendritic cells. IL-12 and IL-23 are involved in immunologic functions, taking part in activation of natural killer (NK) cells and differentiation and activation of CD4+ T cells.
Ustekinumab – mode of action (III)

Fully human IgG1 Mab against IL-12/23 on p40 subunit, binds on p40 protein, which is common for IL-12 and IL-23 and prevent the link with their receptor interleukin-12Rb.
Ustekinumab – indication

• Moderate to severe plaque psoriasis in adults, after the failure of systemic therapy, including cyclosporine and methotrexate application
<table>
<thead>
<tr>
<th>INN</th>
<th>BRAND</th>
</tr>
</thead>
<tbody>
<tr>
<td>palivizumab</td>
<td>SYNAGIS</td>
</tr>
<tr>
<td>basiliximab</td>
<td>SIMULECT</td>
</tr>
<tr>
<td>omalizumab</td>
<td>XOLAIR</td>
</tr>
<tr>
<td>natalizumab</td>
<td>TYSABRI</td>
</tr>
<tr>
<td>abciximab</td>
<td>REOPRO</td>
</tr>
</tbody>
</table>
Palivizumab – mode of action

• Humanized IgG1Kappa Mab focused on epitop in location A antigen of fusion protein in respiratory syncytial virus (RSV).
• Contains 95% human and 5% murine AB.
• Reveals strong neutralizing effect on A and B subtypes of RSV.
• Prevention of serious LRT infections were hospitalization is needed.
• The causative pathogen is RSV – children with high risk of RSV infection
Basiliximab – mode of action

• Murine/human chimerical Mab (IgG1k), active against alpha chain of receptor for interleukin-2 (antigen CD25), (occurs on surface of T-lymphocytes as an answer to antigen trigger)

• Specifically binds with high affinity on antigen CD25 in activated T-lymphocytes with expression of high affinity receptors for interleukin-2 (IL-2R).
Basiliximab – indication

- Prophylaxis of acute GVH reaction - organ rejection in allogenic renal transplantations *de novo* in adults and pediatric patients in age 1-17 y
- *In combination with cyclosporine*
Natalizumab – mode of action

• Selective inhibitor of adhesion molecule
  – Binds on $\alpha_4$-subunit of human integrins, with high expression on surface of all leukocytes with exception of neutrophiles

• Specific binding on $\alpha_4\beta_1$ integrin blocking interaction with its analogical receptor, vascular cellular adhesive molecule - 1 (VCAM-1), and osteopontin ligands and alternatively connected domain of fibronectin, connective segment - 1 (CS-1).

• Prevent interaction $\alpha_4\beta_7$ integrin with mucosal adresin cellular adhesive molecule - 1 (MadCAM-1).
• Recombinant humanized MAb against α4-integrin, produced by murine cell line by means of DNA recombinant technology.

• In monotherapy used as disease modifying medication in patients with high active relapsing-remitting multiple sclerosis
• Binds on IgE, block linkage of IgE to FC\(\varepsilon RI\)* (receptors with high affinity to IgE), reduce free IgE, usable to trigger allergic cascade.
• In atopic patients causes significant decrease of FC\(\varepsilon RI\) receptors on basophiles.
• Histamine release \textit{in vitro} from basophiles isolated from subjects treated with omalizumab was decreased approximately by 90% after allergen stimulation vs. values before the therapy.

\*\(\varepsilon = \text{epsilon}\)
• **Humanized MAb**, derived from recombinant DNA
  – selective binding on human IgE.
  – Ab of the type IgG1 kappa, based on skeleton of human AB and partly derived from murine MAb, binding IgE

• Only for patients with asthma triggered by IgE (lab confirmation mandatory)
Abciximab – mode of action

- **Fab fragment of chimerical Mab 7E3 against glycoprotein IIb/IIIa (GPIIb/IIIa) receptor on human platelet surface.**
  - inhibits platelet aggregation by means of preventing of the binding of fibrinogen, von Willebrand factor and other adhesive molecules on GPIIb/IIIa receptors of activated platelets.
  - Also binds to vitronectin (αvβ3) receptor, located on platelet and endothelia surface. Vitronectin receptor mediates pro-coagulating properties of platelets and proliferative properties ob endothelium and smooth muscle cells in the blood vessels.

- Due to this double specificity blocs more effectively initiation of thrombin cascade, following the platelet activation then substances focused only on GP IIb/IIIa.
Abciximab – indication

- Blocks glycoprotein receptor IIb/IIIa on human platelets surface

Indication

- Percutaneous coronary intervention
  - Prevention of ischemic cardiac complications in patients undergoing percutaneous coronary intervention (e.g. arterectomy, stent application).

- Unstable angina pectoris
  - Short time (1 month) application to decrease risk of AMI in patients with unstable angina pectoris, without the answer to conventional therapy and those who are candidates for percutaneous coronary intervention.
## Biological therapy – summary (I)

<table>
<thead>
<tr>
<th>INN</th>
<th>TM</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>adalimumab</td>
<td>Humira</td>
<td>Rheumatoid arthritis, Psoritic arthritis, Ankylozující spondylitis</td>
</tr>
<tr>
<td>alemtuzumab</td>
<td>Mabcampath</td>
<td>Chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>basiliximab</td>
<td>Simulect</td>
<td>Profylaxis of organ rejection</td>
</tr>
<tr>
<td>bevacizumab</td>
<td>Avastin</td>
<td>Colorectal carcinoma</td>
</tr>
<tr>
<td>cetuximab</td>
<td>Erbitux</td>
<td>Colorectal carcinoma, Spinocellular carcinoma of head and neck</td>
</tr>
<tr>
<td>daklizumab</td>
<td>Zenapax</td>
<td>Prophylaxis of organ rejection</td>
</tr>
<tr>
<td>efalizumab</td>
<td>Raptiva</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>ekulizumab</td>
<td>Soliris</td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
</tr>
</tbody>
</table>
## Biological therapy – summary (II)

<table>
<thead>
<tr>
<th>INN</th>
<th>TM</th>
<th>Indication</th>
</tr>
</thead>
</table>
| infliximab          | Remicade                          | Rheumatoid arthritis
Crohn's disease, Colitis ulcerosa
ankylosing spondylitis
Psoriatic arthritis, Psoriasis |
| kertolizumab-pegol  | Certolizumab Pegol                | Crohn's disease                                                            |
| natalizumab         | Tysabri                           | Sclerosis multiplex                                                         |
| omalizumab          | Xolair                            | Asthma bronchiale                                                           |
| ranibizumab         | Lucentis                          | Neovaskular macular degeneration                                            |
| rituximab           | Mabthera                          | Non-Hodgkin lymphomas
Rheumatoid arthritis |
| trastuzumab         | Herceptin                         | Breast cancer                                                               |
# Traditional DMARD Selection

<table>
<thead>
<tr>
<th>Agent</th>
<th>Time to Benefit</th>
<th>Potential for Toxicity</th>
<th>Toxicities to Monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>1–2 mo</td>
<td>Moderate</td>
<td>Myelosuppression, ↑LFTs, pulmonary infiltrates, teratogenicity</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>1–6 mo</td>
<td>Low</td>
<td>Macular damage</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>4–12 wk</td>
<td>Low</td>
<td>Diarrhea, alopecia, ↑LFTs, rash, headache, risk of immunosuppression, infection, teratogenicity</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>1–3 mo</td>
<td>Low</td>
<td>Myelosuppression, rash</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>4–8 wk</td>
<td>High</td>
<td>Renal insufficiency, anemia, hypertension, immunosuppression</td>
</tr>
<tr>
<td>Gold, parenteral</td>
<td>3–6 mo</td>
<td>Moderate</td>
<td>Myelosuppression, proteinuria</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>2–3 mo</td>
<td>Moderate</td>
<td>Myelosuppression, hepatotoxicity, lymphoproliferative disorders</td>
</tr>
<tr>
<td>Minocycline</td>
<td>1–3 mo</td>
<td>Low</td>
<td>Hyperpigmentation, dizziness, vaginal yeast infections</td>
</tr>
</tbody>
</table>

Specific DMARDs

**Leflunomide**
- Efficacy considered to be almost equivalent to methotrexate
- Used in patients with intolerance to methotrexate
- Time to benefit onset: 1 to 3 months
- Oral administration

**Hydroxychloroquine (HCQ)**
- Demonstrated efficacy in early, mild, and/or seronegative RA
- Time to benefit onset: 1 to 6 months
- Oral administration

**Sulfasalazine**
- Demonstrated efficacy in early, mild, and/or seronegative RA
- May retard radiographic progression
- Time to benefit onset: 1 to 3 months
- Oral administration
Methotrexate (MTX): The Anchor Drug of RA Treatment

- Used in more than 80% of RA patients
- Long-term clinical experience
- Favorable rate of therapy continuation
- Efficacy proven in moderate to severe RA
- Time to onset: 1 to 2 months
- Route of administration: oral, subcutaneous, intramuscular
- Contraindicated in patients with renal insufficiency, liver diseases, or pregnant women
- Side effects:
  - Dose related: nausea, stomatitis, bone marrow suppression
  - Others: fatigue, flu-like symptoms, headache, pneumonitis, hepatic fibrosis
- Toxicities that require monitoring:
  - Myelosuppression
  - Liver fibrosis
  - Cirrhosis
  - Pulmonary infiltrates or fibrosis
Methotrexate: Suboptimal Responses

– Toxicity
  • Ensure folic acid or folinic acid use is appropriate

– Poor efficacy
  • Increase dose (25 mg/week)
  • Switch from oral to SC/IM administration
    – Oral bioavailability variable (20–95%; mean 80%)
    – SC and IM bioavailability similar
  • Combination therapy (MTX + another DMARD)
Is Combination DMARDs More Effective Than Monotherapy?

– 3 types of combination therapies have been studied:
  • 2 or more traditional DMARDs
  • 2 or more traditional DMARDs plus glucocorticoids (low/high dose)
  • Traditional DMARDs (usually MTX) with biologic agents

– DMARD combination strategies
  • Parallel
  • Step-up
  • Step-down
Efficacy of Triple Therapy in RA at 2 Years

MTX, methotrexate; HCQ, hydroxychloroquine; SSZ, sulfasalazine.