Selected Topics in Clinical Immunology - Biologics -

Biomedical Sciences
February 28, 2019
M. Seitz
today´s menu

• lessons regarding pathogenesis
• cytokines
• cytokine inhibitors / cytokine antagonists
• therapeutic antibodies beyond anti-cytokines
• immunoreconstitution
what are we talking about

*p*athogenesis of inflammatory diseases

- rheumatoid arthritis, early
what are we talking about

*pathogenesis of inflammatory diseases*

- rheumatoid arthritis
- joint space narrowing

![Image showing radiographs at time 0 and after 19 months]

*time 0*  
*after 19 months*
what are we talking about

*pathogenesis of inflammatory diseases*

- rheumatoid arthritis, late
Clinical example

*Rheumatoid Arthritis (RA)*

- joint inflammation
- tendons and bursae
- systemic inflammation
- ESR, CrP
- anemia, thrombocytosis
- rheumatoid factor
- CCP-antibodies
pathogenesis of inflammation

- molecular mechanisms rheumatoid arthritis
cytokine production

TNF, IL-6

- ESR, CrP, anemia…

lymphotoxin

- inflammation and joint damage in RA
- lymphoid structures in the synovium
T cell
monozyte
immunological stimulus

B cell

TNF
IL-1

IL-6
IL-8

chemotaxis
CRP
pain
fever

TNF blocking agents
MabThera
Actemra
Orencia
Kineret

Orencia
anti-cytokine mechanisms

Tumor necrosis factor (TNF)
anti-cytokine mechanisms: TNF
activated macrophage

Target cell

Inflammatory reaction
Target cell

activated macrophage

Inflammatory reaction
TNF-blockade by Infliximab

Activated macrophage

Target cell

Infliximab
specificity of monoclonal antibody versus fusion protein

*TNFα and lymphotoxin binding*

<table>
<thead>
<tr>
<th></th>
<th>TNF-a</th>
<th>LT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td><img src="image" alt="Diagram" /></td>
<td><img src="image" alt="Diagram" /></td>
</tr>
<tr>
<td>Etanercept</td>
<td><img src="image" alt="Diagram" /></td>
<td><img src="image" alt="Diagram" /></td>
</tr>
</tbody>
</table>
avidity

reversibility of binding

Etanercept

on-rate
off-rate
cytokine receptor

Infliximab

on-rate
off-rate
mechanisms of inhibition

1. neutralizing antibody
2. receptor-blockade
3. soluble receptor

cytokine

cytokine receptor
mechanisms of inhibition

1. neutralizing antibody

- Infliximab (Remicade®)
  chimeric antibody against TNFα

- Adalimumab (Humira®)
  humanised antibody against TNFα

2. receptor-blockade

3. soluble receptor

- cytokine

- cytokine receptor
mechanisms of inhibition

neutralizing antibody

1

Etanercept (Enbrel®)
fusionprotein (IgG1 + TNFα -receptor)

3

soluble receptor

Infliximab (Remicade®)
chimeric antibody against TNFα

Adalimumab (Humira®)
humanised antibody against TNFα

cytokine

cytokine receptor
treatment goals

• reduction of disease activity

• prevention of joint destruction

• long-lasting remission

• minimalized side effects
**Disease Activity Score**

>3.7 = high disease activity

<2.4 = low disease activity
Median Change from Baseline

- Responders
  - MTX + Placebo: 3.6
  - IFX 3mg q8+MTX: 0.0*
  - IFX 3mg q4+MTX: 0.5
  - IFX 10mg q8+MTX: 4.3
  - IFX 10mg q4+MTX: 2.5*

- Non-Responders
  - MTX + Placebo: N=10
  - IFX 3mg q8+MTX: N=32
  - IFX 3mg q4+MTX: N=38
  - IFX 10mg q8+MTX: N=28
  - IFX 10mg q4+MTX: N=34

* indicates statistical significance.
Other indications:

- Granuloma destruction
  - Wegener’s disease
  - Crohn’s disease
  - Sarcoidosis
  - Tuberculosis
Psoriasis vor und nach Golimumumab
MRI-Verlauf bei AS vor und nach Infliximab
Braun J et al., A&R 2003; 48:1126-36

vor

nach 12 Wo.
9 Tage nach Infliximab
vor Infliximab

4 Monate unter Infliximab
Resultat: Remission innerhalb von 24 h, vollständige Unterdrückung der Entzündung nach 7 d
treatment goals in RA

*how to measure...*

- reduction of disease activity («DiseaseActivityScore»)
  - number of tender joints
  - number of swollen joints
  - ESR/ CrP

- prevention of joint destruction / disease damage
  - ultrasound
  - X-rays
  - MRI (magnetic resonance imaging)
summary anti-cytokine strategies

- *neutralization of*
  - TNF
  - IL-1
  - IL-6
  - IL-17
  - IL-12/23

- *competitive blocking of receptor*
  - IL-1 receptor antagonist (IL-1ra)

- *use of soluble receptor*
  - TNF R
  - abatacept
beyond anti-cytokine strategies
pathogenesis of RA

*B-cells as important factors*

- abundance of B-cells in the synovium of affected joints organized into lymphoid structures

- 3 critical roles of B-cells
  - antigen presentation and T-cell activation
  - autoantibody production
  - cytokine production
autoantibody production

autoreactive B cells

- produce autoantibodies including RF
- => formation of immune complexes
- => production of pro-inflammatory cytokines
Steps in the maturation of B cells

Stem cells  Pro-B cells  Pre-B cells  Immature B cells  Activated B cells  Memory B cells  Plasma B cells

CD10
CD19
CD20
CD24
CD38
CD39
Rituximab (MabThera®/Rituxan®)

Rituximab

- novel
- genetically engineered
- anti-CD20 therapeutic monoclonal antibody
- *selective* depletion of CD20+ B-cells
CD20: an ideal B cell target

CD20

- 297-amino acid phosphoprotein
- highly expressed on B cells but not on stem, dendritic or plasma cells
- no known natural ligands for CD20
complement-dependent cytotoxicity

Rituximab bound to CD20

- interacts with C1q
- triggers activation of the complement system
- leads to B cell lysis via formation of pores in the membrane
pachymeningitis in a patient with RA
pachymeninigitis in a patient with RA
pre-post rituximab therapy

CD20 stain
example: gastric MALT- lymphoma
summary cell-targeted strategies

- depletion of B lymphocytes
- depletion of CD20+ lymphocytes

- classical immunosuppressive agents
ciclosporine
  => inhibit function / activity of T-lymphocytes
  => used in organ transplantation
mechanisms of co-stimulation
how are T cells recruited?

- **signal 1 (TcR)**
- **signal 2 (co-stimulation)**
- **signal 3 (cytokines)**
**first signal:**

TCR binds to MHC complex on APC

**second signal:**

CD28 binds to B7 on APC

T cell proliferation
**CTLA4:** Cytotoxic T cell Leukocyte Antigen 4

- **CTLA4 binds to B7 on APC!**
- **TCR binds to MHC complex on APC**
- **First signal:**
- **T cell receives no second signal from B7!**
- **T cell apoptosis/anergy**

**Diagram:**
- T cell
- APC
- MHC II
- B7
- TCR
- CTLA4
- Ig

**Text:**
- T cell
- Antigen-presenting cell (APC)
- Cytotoxic T cell
- Leukocyte Antigen 4

**Note:**
- CTLA4 binds to B7 on APC.
- T cell receives no second signal from B7.
- T cell apoptosis/anergy.
blockade of the CD28 pathway
Anti-TNF antibodies and the risk of malignancies  *JAMA 2006, 295 (19): 2275*

- systematic review and meta-analysis in randomized controlled trials
- 144 trials, 9 suitable for analysis
- Etanercept excluded (why?)
- RA patients only
- 3493 patients, 1512 controls
- Infliximab up to 10mg/kg, every 4 wk
- Adalimumab up to 40mg per wk
- Duration of therapy until diagnosis of malignancy: 2 -114 weeks (!!)
Anti-TNF antibodies and the risk of malignancies  

*JAMA 2006, 295 (19): 2275*

**Results**

- 29 malignancies in verum, 3 in placebo
- **OR 3.3 (1.2 – 9.1)**
- however:
  - Low dose: OR 1.4 (0.3 – 5.7)
  - High dose: OR 4.3 (1.6 – 11.8)
- number needed to harm (NNH): **154** (91 - 500)
relation: risk of malignoma / disease activity

is inflammation itself (or are genetic factors) propagating malignancies?

case control study showing an increased lymphoma risk of up to 25 (BMJ 1988)
after review of the existing literature and thorough discussion:

• screening for Tbc and latent Tbc infection should be performed in all patients prior to any anti-TNF-α therapy

• screening should be based on history, chest X-ray and an IGRA test.
  – history: detailed history of exposure to or prior treatment for Tbc, considering the risk associated with birthplace or country of origin
  – chest X-ray: for detecting past or present Tbc
  – IGRA test
Questions ?