Selected Topics in Clinical Immunology - Biologics-

Biomedical Sciences
April 6, 2017
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today’s menu

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

pathogenesis of inflammatory diseases

- rheumatoid arthritis, early
what are we talking about

pathogenesis of inflammatory diseases

- rheumatoid arthritis
- joint space narrowing

![Images showing comparison of time 0 and after 19 months.](attachment:image1.png)
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
TNF-blockade by Infliximab

Activated macrophage

Target cell
specificity of monoclonal antibody versus fusion protein

TNFα and lymphotoxin binding
mechanisms of inhibition

1. Neutralizing antibody

2. Receptor-blockade

3. Soluble receptor

**Etanercept** (Enbrel®)

**Fusion protein** (IgG1 + TNFα-receptor)

**Infliximab** (Remicade®)

Chimeric antibody against TNFα

**Adalimumab** (Humira®)

Humanised antibody against TNFα

**Etanercept** (Enbrel®)

**Fusion protein** (IgG1 + TNFα-receptor)

**Infliximab** (Remicade®)

Chimeric antibody against TNFα

**Adalimumab** (Humira®)

Humanised antibody against TNFα
treatment goals

- reduction of disease activity
- prevention of joint destruction
- long-lasting remission
- minimalized side effects
treatment goals

how to measure...

• reduction of disease activity («Disease Activity Score»)
  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

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

• *use of soluble receptor*
  - TNF R
  - abatacept
beyond anti-cytokine antibodies
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
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
pachymeninigitis in a patient with RA
summary cell-targeted strategies

• depletion of B lymphocytes
• depletion of CD+ lymphocytes

• classical immunosuppressive agents
  ciclosporine
  => inhibit function / activity of T-lymphocytes
  => used in organ transplantation
CTLA4: Cytotoxic T cell
Leukocyte Antigen 4

**CTLA4 binds to B7 on APC!**

*T cell receives no second signal from B7!*

T cell apoptosis/ anergy

**first signal:**

TCR binds to MHC complex on APC

CTLA4

CTLA4 Ig

B7

TCR

MHC II

Antigen-presenting cell (APC)
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