Selected Topics in Clinical Immunology - Biologics -

Biomedical Sciences
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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

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
TNF blocking agents

MabThera

Actemra

chemotaxis

CRP

pain

fever

B cell

monocyte

T cell

TNF

IL-1

IL-6

IL-8

Kineret

Orencia

Orencia

MabThera

Actemra

chemotaxis

CRP

pain

fever

immunological stimulus
anti-cytokine mechanisms

Tumor necrosis factor (TNF)
TNF-blockade by Infliximab

Activated macrophage

Infliximab

Target cell
specificity of monoclonal antibody versus fusion protein

**TNFα and lymphotoxin binding**

- **Infliximab**
  - TNF-α binding
  - LT binding

- **Etanercept**
  - TNF-α binding
  - LT binding
avidity

reversibility of binding

Etanercept

Infliximab

cytokine receptor

on-rate

off-rate
mechanisms of inhibition

neutralizing antibody

1

Etanercept (Enbrel®)
fusion protein (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
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
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

Cell surface antigens:
- CD10
- CD19
- CD20
- CD24
- CD38
- CD39
Rituximab (MabThera®/Rituxan®)

Rituximab

- novel
- genetically engineered
- anti-CD20 therapeutic monoclonal antibody
- *selective* depletion of CD20+ B-cells
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
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 CD+ lymphocytes

• classical immunosuppressive agents
  ciclosporine
  => inhibits 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)
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:
风险 of 恶性肿瘤 / 疾病活动

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