Biologicals (or targeted therapies) – an evergrowing plethora of opportunities for infectious agents

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Possible conflicts of interest

• Speakers and Advisory Boards for: BMS, GSK, Janssen, MSD, Novartis, Roche, Pfizer, ViiV
• Travel-Grants: Pfizer, Novartis
• Study grants: GSK, Biochryst, Actelion
• Others (patents, stock options) none
What is a „biological“?

- Correct: biopharmaceutical = extracted from or synthesized from biological sources
  - Extracted
    - E.g. whole blood or blood components, insulin, fetal microbiota
  - Synthesized
    - E.g. modern insulins, monoclonal antibodies
- Different regulation, additional biologic testing
- Generics: „biosimilars“
BUT.....

• Not all biologicals act relevantly on the immune system (e.g. VGEF-inhibitors)

• In addition, more and more small molecules (not biologicals) acting on the immune system are licensed – e.g. Tofacitinib as a JAK-STAT-inhibitor

• Targeted therapies?
Targets

- Proinflammatory cytokines – TNF, Interferon-y
- Interleukins, Immunoglobulins: IL-1, IgE
- Other soluble targets: Proteins in signalling pathways, e.g. JAK3-Kinase in JAK-STAT pathway
- Lymphocyte/Leukemia cell surface markers: CD19, CD20
- Others: PD-L1 (programmed-death ligand 1), alfa-4-integrins, lymphocyte function associated antigen,
Spectrum of agents

- Etanercept: neutralizing antibody against TNF-a
- Gemtuzumab-Ozogamicin: anti-CD33 antibody, coupled with a potent toxin
- Anti-PDL-1: strong activator of immune reaction (anti-tumor efficacy, risk of autoimmune reactions)
One of the first studies with a "biological" - what was the drug, what was the target?

Fisher CJ; NEJM 1996, 334, 1697ff
ESGICH Initiative

• Evaluate infection risk, preventive and prophylactic strategies for current biologicals

• Regular update

• First version to be published CMI 2017
Drugs and Infections

- Spectrum of disease
- Incidence/risk
- Time frame
- Management
  - Prevention and prophylaxis
  - Diagnostic strategies
  - Therapy
- Problems: time shift to reporting of rare events
Targets in the immune system

- Natalizumab
- Belimumab
- Anakinra
- Tocilizumab
- Infliximab
- Adalimumab
- Golimumab
- Certolizumab
- Etanercept
- Rituximab
- CD20
- CD28
- α4β1
- BLys
- Infliximab
- Adalimumab
- Golimumab
- Certolizumab
- Etanercept

Mod. nach Bodro, CID 2013
Case 1

• 42 yo female, steroid dependent ulcerative colitis ulcerosa,

• Former medical history
  – Breast cancer 2010, operation, adj, chemotherapy, in full remission

• In 9/2013 start of adalimumab (humanized anti-TNF-antibody)

• After three courses full remission of symptoms
Case 2

• Fever and Malaise, starting in 12/2013
• Admission to hospital 19.12.2013

• Lab: LDH 538U/l, CRP 125mg/l, otherwise unremarkable

• What do you want to do/know)
Case 1

- Started on empirical antibiotic therapy (Amoxicillin/Sulbactam)
- Return of team on 29.12.
  - Ongoing fever, no clinical improvement
- CT scan on 30.12.
Case 1

- Return of team 1 on January 8
- Still fever, clinically worse
- Bronchoscopy
  - AFB positive, referral to our clinic
- Start on TB-treatment
Did we miss something?
AE reports from early studies

• 70 MTB cases until 2009 from worldwide studies (146,000 Pt.) analyzed
  – Onset median 12 weeks after first dose (IQR 8-22 W.)
  – 57% extrapulmonary, 24% disseminated (expected without immunodeficiency 18 / 2%)

• Incidence Risk Ratio 5 for Infliximab

• Screening guidelines for latent Tb rapidly developed,

Keane, NEJM 2001; Wolfe, Arthritis. Rheumat 2004
Screening for tuberculosis

A. Initial TST* or IGRA**
Repeat/Rescreen (only if TB risk factors present)

- Negative
  - No latent or active TB (presume uninfected)††

- Positive

B. Chest Radiograph§

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* TST = Tuberculin Skin Test
** IGRA = Interferon-gamma Release Assay
†† Active TB
§ Chest Radiograph
Screening for tuberculosis

- Negative
  - C. Sputum for AFB (to rule out active TB)
    - Negative
    - Positive
- Latent TB
  - Completion of at least 1 month treatment of latent TB
  - Start (or resume) biologic or tofacitinib immediately
- Active TB
  - Completion of treatment of active TB
  - Start (or resume) biologic or tofacitinib immediately

D. If risk factors for future or ongoing TB exposure, screen annually for latent TB
Some Caveats

• Screening test may be negative on steroids (both TST and IGRA)

• Elispot is probably the most sensitive test in immunocompromised patients (but few data!)

• You can repeat screening after tapering steroids (even less data)
TST, QFT and TB-Elispot in Pts. With RA
Who has the highest risk for TB?

Lee, Plos One 2015
## Is Screening Effective?

<table>
<thead>
<tr>
<th>Period</th>
<th>TNF-Inh. Events/ PY</th>
<th>Rate/ 100.000</th>
<th>IRR vs. population</th>
<th>IRR vs. RA- without TNF-Inh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Screening</td>
<td>27/4780</td>
<td>564 (387-823)</td>
<td>22.6 (12.6-40.6)</td>
<td>6.2 (2.6-16.9)</td>
</tr>
<tr>
<td>Post-Screening</td>
<td>1/1040</td>
<td>95 (13-676)</td>
<td>3.8 (0.1-23.4)</td>
<td>1.0 (0.92-8.2)</td>
</tr>
</tbody>
</table>

Carmona, Arthritis Rheumatism 2005
Spectrum of Infections with TNF-Inhibitors

- Anti-TNF-Substanzen (Infliximab, Adalimumab > Etanercept)
  - Tuberculosis (randomized phase III trials)
  - Aspergillosis, Hepatitis B-Reactivation, PjP, invasive salmonella, Listeriosis, nocardiosis, atypical mycobacteria, toxoplasmosis, Legionella pneumonia, all in multiple case series/reports and FDA –register (OR > 5 vs untreated??)
  - Herpes zoster (rates of severe episodes 5-20% compared to 2-5% with conventional DMARDs) - debated
Case 2: Acute liver failure after Adalimumab

- 41yo female, chronic arthralgias since age 31, provisional diagnosis ANA-pos. polyarthritis
  - Several episodes with treatment by steroids, chloroquine and methotrexate
  - While on holiday in Turkey severe back pain, consulted rheumatologist started adalimumab

- 6 months later presentation with malaise and jaundice

- AST 6500, ALT 5900 U/l, liver necrosis, high urgency liver transplant
Hepatitis B-Serology

- Chronic Hepatitis B diagnosed in 2004, HbsAG+, HbeAG-, HBV-DNA negative on several occasions

- HBV-DNA >10^7 copies/ml

- Reactivation with Adalimumab
Hepatitis B Reactivation and Biologicals

- Reactivation also in patients with
  - HbsAg+/DNA- and
  - Anti-Hbc+ /HbsAg-
- Risk: Rituximab >> Infliximab, Adalimumab > Etanercept (case reports)
- Strategy: serology, vaccination if possible
  - HBsAG+/DNA+: antiviral drug therapy
  - HbsAg +/DNA-: prophylaxis, e.g. lamivudin
  - anti-Hbc+: monitoring? High risk: BMT, Rituximab

Manzano, World J Gastroenterol 2011
Pneumocystis jirovecii - Biologicals

- Rituximab: Case reports/ series
- Risk with anti-TNF-agents: 0.4% Infliximab, 0.3% Adalimumab, 0.18% Etanercept
  - Add. Risk factors: older age, pulmonary comorbidity, additional steroid therapy
- Alemtuzumab: case series/report
- Different to classical DMARD therapy: CD4 cell count not useful for risk stratification

Bodra, CID 2013, online publ. 13.03
Case 3

- 52 yo male with severe destructive RA
- No response to MTX, Leflunomide, initially remission on Infliximab, on recurrence change to Adalimumab (no change), then to Tocilizumab (anti-IL6)
- Rapid remission
- Presentation after 4 months with abdominal pain, diarrhea and fever
- Tender lower right abdominal quadrant, otherwise unremarkable physical
Case 3

- Leukocytes 2500/µl, Thrombocytes 130.000/µl, AST 63, ALT 84, bilirubine 0,8mg/dl, s-creatinine 1,3mg/dl, CRP 25mg/l, PCT 0,1ng/ml
- Thoracic X-Ray: no pathology
- Abdominal ultrasound: right colonic wall thickening and inflammation, no sign of perforation or abscess
- Waiting for results on blood and stool cultures
- What to do else?
Case 3

• Some further information
• Current immunosuppressive therapy
  – Tocilizumab
  – Prednison 5mg/d (taper after long term steroids)
• Vaccines all according to guidelines:
  – Influenza, Pneumococcal, Hepatitis A, B
• Serology for HSV, VZV, CMV positive
Case 3

- CMV-DNA in Serum $3 \times 10^{\exp 4}$
- On colonoscopy several ulcerations, biopsy not seen typical for CMV
- What do we do?
Case 3

• Options
  – Immunohistochemistry in biopsy (highest specificity for CMV GI disease)
  – CMV-DNA from biopsy (highest sensitivity)
  – CMV-DNA from stool (non invasive)
CMV disease in the immunocompromised host

- HIV-Infection
  - Severe immune deficiency (<=100 CD4/mcl)
  - Retinitis>GI>CNS-Manifest.>> pneumonia

- Allogeneic SCT:
  - Highest risk R+D-, very low risk R-D-
  - High risk first 100 days, rapid decrease if no GvHD
  - GI-Manifestationen >Pneumonie >> Retinitis

- SOT
  - Highest risk R-D+
  - Lung> heart> kidney> liver, long term risk
  - CMV-syndrome> GI-Manifestation >> others
CMV and Targeted Therapies

• Alemtuzumab (anti-CD52, therapy of lymphoma, organ rejection, multiple sclerosis – lower dose)
  – complement-induced lysis of lymphocytes, long term reduction of CD4-cells (80%)
  – CMV-manifestations in phase II/III studies of lymphoma therapy
  – Case reports in therapy of MS, not in phase III (<<1%)

• Tocilizumab (RA) – case reports from RA-Tregister data

• Very (unusually?) rare with anti-TNF-agents
Case 4

- 35yo female with highly active relapsing-remitting multiple sclerosis, failure on IFN-β
- Therapy mit Tysabri® (Natalizumab)
- Remission and decrease in recurrences

- At 6 months memory loss, cognitive dysfunction, left sided spastic paresis
Case 4
Case 4

- PML with Natalizumab initially seen in drug therapy of CED 2004
- Agent was retracted and relicensed for MS
- 212 cases with 99,000 treated patients until 2012
- What actually does Natalizumab?
Targets in the immune system

- Infliximab
- Adalimumab
- Golimumab
- Certolimumab
- Etanercept

- Natalizumab
- Bevimab
- Anakinra
- Tocilizumab
- BLys
- TNFα
- IL-1
- IL-6
- CD20
- CD28
- CD52
- B-Lymphozyt
- T-Lymphozyt
- α4β1
- Abatacept
- B7
- Alemtuzumab

Mod. nach Bodro, CID 2013
PML and Drugs

• Natalizumab
• Case reports
  – Alemtuzumab
  – Rituximab
  – Fingolimod (MS-Therapie)
  – No cases yet for Vedolizumab (another anti-adhesion molecule)
• Risk factors: positive serology, long term therapy, others (?)
Small but relevant differences: Natalizumab vs. Vedralizumab

McLean, Exp Opin Invest Drug 2016
Case 5

• 72 yo female with severe RA, on therapy with Adalimumab for 2 years with good clinical result

• Presents with sudden back pain, lower thoracic region, somehow itching..
Case 5
HZ and Targeted Therapies

• Incidence higher in placebo controlled studies
• Incidence not higher compared to DMARDS nicht erhöht (12/1000 patient years – similar to > 70 yo.)
• But: incidence higher in RA compared to CED and psoriasis

• One substance is different – do you know which one?

Winthrop, JAMA 2013
Bortezomib and Herpes Zoster

• Incidence in several studies > 10% (-60%), depending on combination
• Clear recommendation for prophylaxis with ACV/VACV
Prevention and prophylaxis of VZV and HZ

• **Herpes zoster**
  – Think about vaccination (best before immunosuppression is started)
  – Current vaccine live attenuated, new vaccine in late stage development

• **HSV**
  – Antiviral prophylaxis with Aciclovir, also in Alemtuzumab patients, at least 4 weeks after application
Target and Infection – a rare agent

- **Eculizumab**: - Anti-complement-AB, Therapy of PNH, HUS
- Binds to C5, Inhibition of bacterial lysis by complement activation
- Enhanced risk for meningococcal and gonococcal infections with terminal complement deficiency well known – case reports of Gonococcal- and Meningococcal sepsis with Eculizumab
- Recommendation for meningococcal vaccine or drug prophylaxis
# Infection risk and Disease Activity

## Table 1

The prebiologic era: frequency of infections among patients with RA and healthy controls from a Minnesota cohort

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Incidence per 100 Patient-Years RA</th>
<th>Incidence per 100 Patient-Years Non-RA</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>4.0</td>
<td>2.4</td>
<td>1.7 (1.5–1.9)</td>
</tr>
<tr>
<td>Skin</td>
<td>3.0</td>
<td>0.9</td>
<td>3.3 (2.7–4.1)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0.78</td>
<td>0.51</td>
<td>1.5 (1.1–2.1)</td>
</tr>
<tr>
<td>Septic joint</td>
<td>0.40</td>
<td>0.02</td>
<td>14.9 (6.1–73.7)</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>0.22</td>
<td>0.08</td>
<td>2.8 (1.4–6.2)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>0.17</td>
<td>0.01</td>
<td>10.6 (3.4–126.8)</td>
</tr>
</tbody>
</table>

Doran, Arthr Rheum 2003
# Anti-TNFs vs. DMARDs vs Steroids

<table>
<thead>
<tr>
<th>Condition</th>
<th>Infections /100 PY</th>
<th>Hazard Ratio (adj.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoide Arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- DMARDS</td>
<td>7.78</td>
<td>1 (Referenz) 1.015 (0.9c-1.2)</td>
</tr>
<tr>
<td>- Anti-TNF</td>
<td>8.16</td>
<td></td>
</tr>
<tr>
<td>Prednis.-Äquiv.(keine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5mg/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-10mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psoriasis/Spondylarthrop.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMARD</td>
<td>5.37</td>
<td>1 (Reference 1.05 (0.76-1.45)</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>5.41</td>
<td></td>
</tr>
<tr>
<td>Predn.-Äquiv.(kein)</td>
<td></td>
<td></td>
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<tr>
<td>&lt;5mg/</td>
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<tr>
<td>5-10mg/d</td>
<td></td>
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<tr>
<td>&gt;10mg/d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Grijalva, JAMA 2011
Infection Risk with Tofacitinib

- Safety Data from Phase II, III trials and long term observation (> 6000 pts, nearly 20,000 py)
- IR for serious infections 2.7
- IR for Herpes zoster 3.9
- IR for opportunistic infections 0.3
- IR for TB 0.2

- How to evaluate this pattern?
Many questions unanswered

• Long term effects?
  – Randomized studies with strict in- and exclusion criteria, strict protocols
  – Real life data with higher infection rates

• Time pattern
  – Decrease of infection risk after 6 months of therapy?
  – Most probably survivor effect
ESGICH Initiative

• Evaluate infection risk, preventive and prophylactic strategies for current biologicals

• Regular update

• First version to be published CMI 2017
Conclusion

• A number of biologicals and small molecules used in oncology and inflammatory conditions are associated with an increased risk of infection
• Target and spectrum of disease are clearly related
• Mostly opportunistic infections
• Prevention and prophylaxis
  – Established for TB and Hepatitis B, less for Herpesvirus infections