**New Immunosuppressants and Invasive Fungal Infections**

Andreas H. Groll, M.D.
Infectious Disease Research Program
Center for Bone Marrow Transplantation and
Department of Pediatric Hematology/Oncology
University Children’s Hospital Muenster

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**Macromolecular Immunosuppressants**

- Engineered antibodies and proteins
- Target extracellular structures
  - Inactivate soluble factors
  - Block receptors / signalling pathways
  - Cause cell lysis / phagocytosis
- Applications as immunosuppressants, antiinfectives and as anticancer agents

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**Monoclonal Antibodies**

- A MAB name has 4 components:
  - A random prefix for the individual product
  - A disease / target sub-stem [immuno-modulary,-li(m); tumor,-tu(z); viral,-vi(z)]
  - A source-stem (chimeric,-xi; human,-u; mouse,-o; rat,-a)
  - The stem for monoclonal antibodies (-mab)
- Examples: Inf-li-xi-mab, Gem-tuz-u-mab

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**Immunomodulatory Proteins**

- Fusion proteins
  - Humanized anti-cytokine Fab fragments linked to PEG
  - Soluble cytokine receptors linked to constant region of IgG heavy chain or PEG
  - Toxins linked to cytokines
- Engineered non-MAB receptor antagonists
Clinical Indications

- **Immunosuppression**
  - Rheumatoid arthritis, ulcerative colitis, Crohn’s disease, plaque psoriasis, MS
  - Autoimmune disorders, asthma and PTLD
  - Transplant rejection and GVHD
- **Anticancer treatment**
  - B-/T-cell Lymphoma, B-CLL, AML
  - Breast and colorectal cancer
- **Antinfective treatment**
  - RSV prophylaxis, Candida, C. difficile, Anthrax...

Adverse Effects

- **Class specific**
  - Immunogenicity
    - Hypersensitivity reactions
    - Decreased efficacy over time

- **Target specific**
  - Cytokine release / capillary leak syndromes
  - Tumor lysis syndrome
  - **Immunosuppression**
    - Infection
    - Secondary cancers

Macromolecular Immuno-suppressants and Infections

Assessing Infection Rates

- Assessing infectious complications in patients is difficult
  - Patients are already immunosuppressed and thus at greater risk of infection
  - Available clinical data often of insufficient power to detect rare infections or differences between drugs
- More than 20 compounds approved
- Focus on TNF-inhibitors, IL-2 receptor antagonists, alemtuzumab and rituximab

Anti-TNFα Treatment

- TNF / IL-1 proinflammatory cytokines, produced by macrophages and lymphocytes in response to infectious and immune stimuli
- Inhibition of TNFα approved in rheumatoid and psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, ulcerative colitis, psoriasis
- Also used to combat steroid-refractory GVHD
Anti-TNFα Treatment

**Anti-TNFα MABs**
- Infliximab (Remicade®)
- Adalimumab (Humira®)

**Fusion protein**
- TNF-receptor/IgG-FC
  - Fusion protein
  - Anti-TNFα MABs

Anti-TNFα Treatment: Infection Risks

- Infections among the most commonly reported AEs of TNFα inhibition
  - Tuberculosis (screening / monitoring mandatory)
  - Intracellular and other bacteria, respiratory viruses
  - Pneumocystis, endemic and opportunistic fungi

- Difficult to quantitate in RCTs: metaanalysis of MABs in RA shows 2-fold increased risk for serious infections vs. placebo
  - Infection risk greater with MABs vs. etanercept/anakinra
  - Combination of anakinra with etanercept associated with increased infection rates and no added benefit in RA

Anti-TNFα Treatment: Fungal Infections

- Literature search for reports of IFI associated with infliximab, etanercept and adalimumab
- No selection for underlying disease (all inclusive)
  - 281 cases, most (80%) associated with infliximab
  - Median time to occurrence 55 days (IQR, 15-140)
  - Use of at least 1 other immunosuppressant, typically a corticosteroid, reported in 102/104 pts with data
  - IFIs included histoplasmosis (n=184; 30%), candidiasis and aspergillosis (n=164; 23% each)
  - Pneumonia most common pattern of infection
  - 29 fatalities (32%) among 90 cases with outcome data

Anti-TNFα Treatment: Fungal Infections

- Use of infliximab associated with P. carinii infection:
  - 6-year review of the FDA Adverse Event Reporting System for cases of PCP associated with infliximab
    - 84 cases of PCP following infliximab therapy
    - Concomitant immunosuppressive medications included MTX, PRED, azathioprine, 6-MP, CSA
    - Mean time between infliximab infusion and onset of symptoms of pneumonia was 21 days
    - 23 of the 84 (27%) patients died

Anti-TNFα Treatment: Steroid-Refractory GVHD

- In a small retrospective cohort study including 53 transplant patients with grade III/IV GVHD, infliximab was associated with an increased risk of non-Candida invasive fungal infections
  - 5 of 11 infliximab recipients developed an IFI (6.78 cases/1000 GVHD patient-days), compared with 5 of 42 among nonrecipients (0.53 cases/1000 GVHD patient-days)
  - In a time-dependent Cox regression model, the adjusted IFI hazard ratio of infliximab exposure was 13.6 (P = .004; 95% CI, 2.29-80.2).

T-Lymphocyte Inhibition/Depletion and Infection
Anti-CD3 / IL-2 R Treatment

- Activation of T-cells pivotal mechanism in the immune response against allo-antigens
- T-lymphocyte depletion /inhibition used for prophylaxis and treatment of transplant rejection
- Also explored to manage steroid-refractory GVHD and certain autoimmune disorders

Anti-CD3 Treatment

Anti-CD3 MAB
- Muromonab (Orthoclone OKT® 3)

Anti-CD3ε MAB
- Visilizumab (Nuvion®)

Anti-IL-2 R Treatment

Anti-CD25 MABs
- Basiliximab (Simulect®)
- Daclizumab (Zenapax®)

Approved for acute and chronic rejection prophylaxis in renal transplantation

under investigation for GVHD prevention and treatment

Elimination of activated T-cells that express the α-subunit of the IL-2 R (CD25)

Anti-CD3 / IL-2 R Treatment: Infection Risks

- Muromonab-CD3
  - Lymphocyte depletion and TC-receptor modulation contribute
  - Bacterial infections most common, but assessment confounded by routine administration of prophylaxis against OIs

- Basiliximab, daclizumab
  - Extensively used in solid organ transplantation
  - Individual reports suggest lower infection risk as compared to anti-CD3 and ATG when given as induction
  - Concurrent cytolytic treatment associated with excess death

No signal for increased risk of fungal infections

Daclizumab Treatment: Fungal Infections

- 57 patients, daclizumab alone
  - 54% had improvement, but opportunistic infections in 95%
  - 75% mortality, infection causal in most pts (79%) (relapse: 14%)
- 21 pts, daclizumab plus etanercept
  - 66% responded, but 80% mortality after median of 566 days
  - Infection causal in most pts (65%) (relapse: 17%)
- Daclizumab +/- infliximab/ATG (n=12) compared to ATG/MMF (n=6)
  - Antibacterial and Aspergillus prophylaxis, rapid steroid tapering
  - Complete resolution [12/12 vs. 1/6; P < 0.001].
  - No invasive aspergillosis [9/12 vs. 4/6; P < 0.005]
  - Improved survival at day 200 (73% vs. 17%) and improved overall survival (median 453 vs. 42 days from GVHD onset; P < 0.0001)
  - GVHD-related mortality 17% vs. 89% (P < 0.0001).

T- plus B-Lymphocyte Depletion and Infection
Anti-CD52 Treatment: Alemtuzumab

Alemtuzumab (MabCampath®)
- Complement- and antibody dependent lysis and apoptosis of B- and T-cells and mononuclear phagocytic cells
- Prolonged and profound lymphopenia
- Approved for CLL refractory to fludarabine
- Also used in other hematological malignancies, transplantation medicine and autoimmune diseases

Anti-CD52 Treatment: Infection Risks
- Opportunistic and other infections common, particular in cancer patients
  - Herpes viruses, BK-virus, MTB, MOT, Toxo
  - Intracellular and other bacteria
  - Pneumocystis, endemic and opportunistic fungi
  - PCP and HSV prophylaxis for CD4<200 recommended
- Occurrence of IFIs difficult to quantitate
  - 8/121 (6.6%) pancreas transplant pts
  - 18/547 (3%) unselected organ transplant pts
  - alemtuzumab associated with late aspergillosis following RIC

Anti-CD52 Treatment: Solid Organ Transplantation
- 547 SOT pts, alemtuzumab as induction therapy or for treatment of rejection, followed until death or 12 months after the last dose
- 56 recipients (10%) developed 62 OIs, including
  - CMV (n = 16), BK virus (n=12), PTLD (n=5), HHV E (n=1), parvovirus infection (n=1), esophageal candidiasis (n=12), cryptococcosis (n=2), invasive mold infection (n=4)
  - Nocardia infection(n=4), mycobacterial infection (n=3), Balamuthia mandrillaris infection (n=1), and toxoplasmosis (n=1)
- Patients who received alemtuzumab for induction were less likely to develop an OI as patients who received it for rejection therapy (4.5% vs. 21%, P<0.001).

Anti-CD52 Treatment: Patients with CLL
- High rate of OIs in early, small scale trials in patients with refractory CLL
- Of 93 fludarabine–refractory patients with CLL treated with alemtuzumab, grade III-IV infections occurred in 27%
  - Eleven pts developed OIs during treatment, and 7 OIs occurred in the follow-up period
  - OIs included PCP (1) in a patient not receiving TMP/SMX; invasive fungal infections (6); herpes zoster (4); and Listeria meningitis (1). The most commonly reported OI was CMV (7)
- Patients who developed OIs had received between 4 and 7 prior regimens

Anti-CD52 Treatment: Steroid-Refractory GVHD
- Safety and efficacy of alemtuzumab in 18 pts with steroid refractory aGVHD (>or=grade II) following HSCT
- 8 patients had grade II aGVHD, 8 grade III, and 2 grade IV.
- Alemtuzumab 10 mg s.c. daily on 5 days, response eval at d 28
- 15 pts (83%) responded to alemtuzumab, including 6 (33%) with complete response. All 3 unresponsive patients died of GVHD
- Ten of 15 responders are alive at median follow-up of 11 months
- Infections occurred in 14 patients, including cytomegalovirus (CMV) reactivation in 11

Anti-CD52 Treatment: B-Lymphocyte Depletion and Infection
Anti-CD20 Treatment: Rituximab

Rituximab (MabThera®)

- targets the B-cell antigen CD20
- standard schedule of 375 mg/m² weekly x 4, results in approximately 90% decrease of B-cells within 3 days; recovery in 9–12 months
- Approved for B-cell malignancies that express CD20 +/- conv. CTX
- Also approved for TNF-inhibitor refractory RA, and increasingly used for autoimmune diseases

Anti-CD20 Treatment: Infection Risks

- Metaanalysis of RCTs in RA pts. showed no increase in serious infections as compared to placebo
- Based on data from 5 RCTs in NHL, no significant increase in infections with addition of rituximab to CHOP
  - However, HIV-positive patients had a 12% increase in infection-related deaths and a higher rate of OIs
- Infections by common bacteria, Pneumocystis, HBV, HCV, CMV, VZV, respiratory viruses, PV B19, and babesiosis reported
  - Role of rituximab confounded by prior and concomitant treatments (f.e., alemtuzumab, purine analogues)

Anti-CD20 Treatment: Fungal Infections

- Higher fungal infection rate reported in elderly patients (more than 80 years old) with diffuse large B cell lymphoma treated with rituximab plus CHOP
- retrospective case-control study
- 34 elderly DLBCL patients treated with rituximab plus CHOP (R-CHOP) and 35 control patients treated with CHOP
- Overall infection rate similar in both groups
- Higher fungal infection rate in R-CHOP (41.7 and 17.1%, P = 0.03)
  - 18/20 Candida, and 16/20 not invasive

Conclusions

- Development of macromolecular immunosuppressants and anticancer agents rapidly evolving
- Some agents associated with increased infection risks
  - TNFα antagonists
  - CD52 antagonist alemtuzumab
- Risk confounded by previous and current therapies, individual and disease-specific factors