

New Immunomodulators and Invasive Fungal Infections

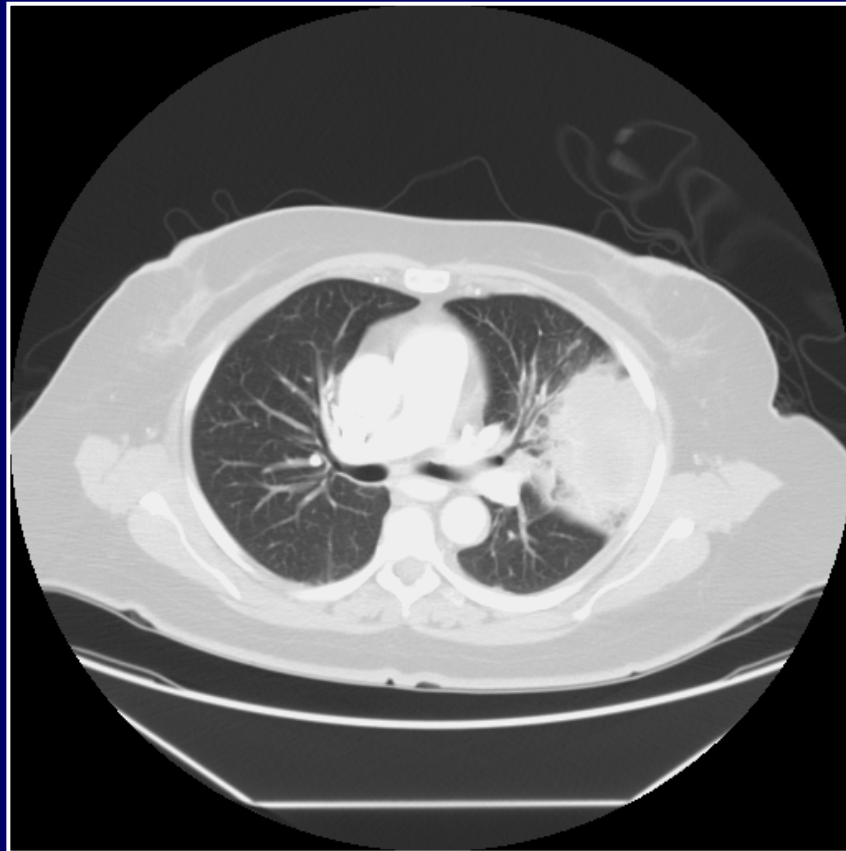
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It starts with a case...

- 59 y/o female with AML, s/p matched unrelated donor alloBMT, refractory GvHD, steroids & Infliximab
- Occasional hemoptysis, no fever
- Receiving:
 - Linezolid
 - Moxifloxacin
 - Cefpodoxime
 - Posaconazole



What are we dealing with?



Finger Bx: Mucor

Newer Immunomodulators: *an expanding list*

- Anti-TNF Ab
- Anti-integrin Ab
- Alemtuzumab (Campath-1H)
- Other anti-lymphocytic agents
- Revlimid

Fungal Infections: Limitation of the Literature

- Isolated cases
- Small series, heterogeneous patient populations
- Potential overreporting or underreporting of events (FDA's AERS is a passive reporting system)
- Unconfirmed diagnoses
- Absence of a control population
- Imprecise calculations of event rates
- Concomitant immunosuppression

Immunosuppression associated with cancer chemotherapy

Barriers

- Breakdown of skin/mucosal integrity
- Changes in endogenous flora
- Indwelling vascular catheters

INNATE IMMUNITY

Impairment of Pattern Recognition Molecules

Impairment of:

- Complement
- Acute phase reactants
- Immunoregulators

Natural Killer Cells

- Deficiency of circulating NK cells
- Dysfunction of NK cells

Phagocytic Cells

- Deficiency of circulating neutrophils, monocytes
- Defects of phagocytic function

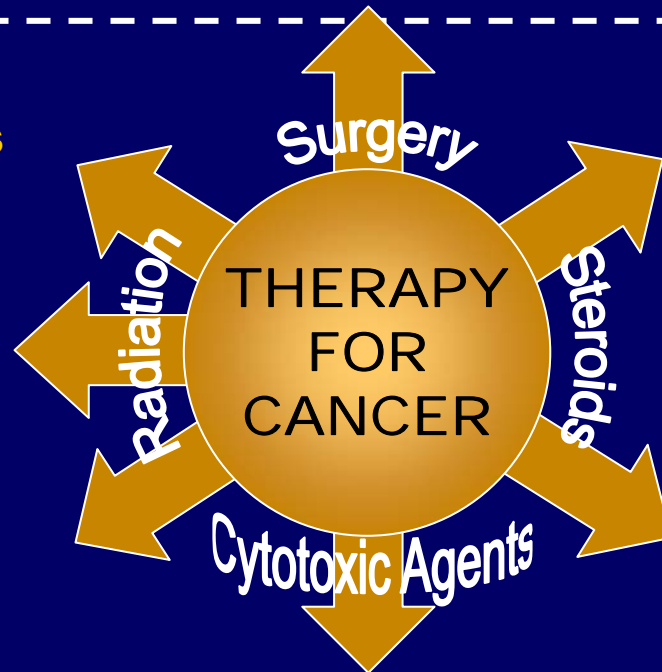
CLONAL/ADAPTED IMMUNITY

Cell-Mediated Immunity

- Deficiency of circulating lymphocytes
- Imbalance and depletion of lymphocyte subsets
- Aberration of function

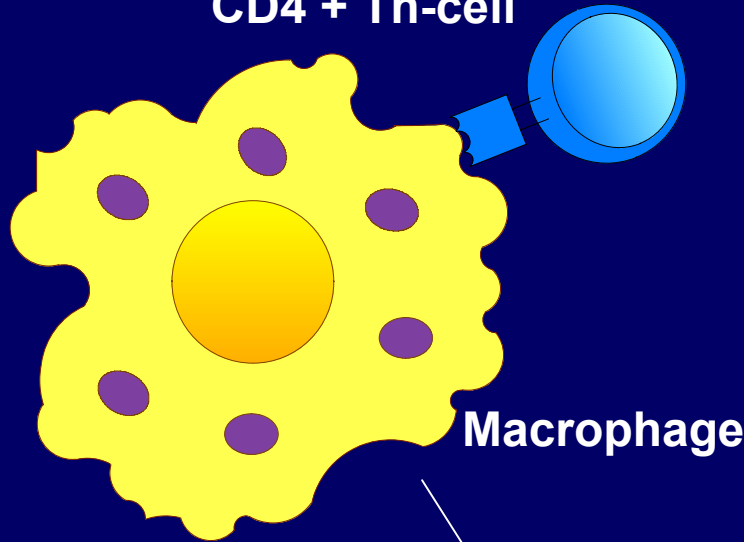
Antibodies

- Deficiency of B cells
- Deficiency of Ig production



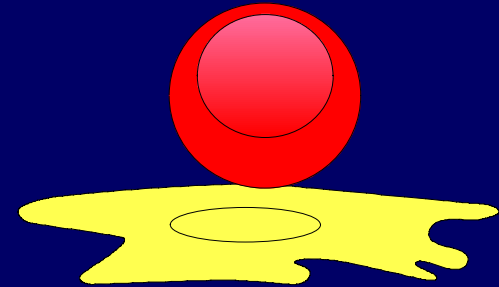
Cell-Mediated Immunity

CD4 + Th-cell



Macrophage

CD8 + Th-cell
(cytotoxic)



Viral-infected cell

Herpes simplex
Varicella zoster
Cytomegalovirus
HHV-6
Epstein-Barr

Adenovirus

Polyomaviruses

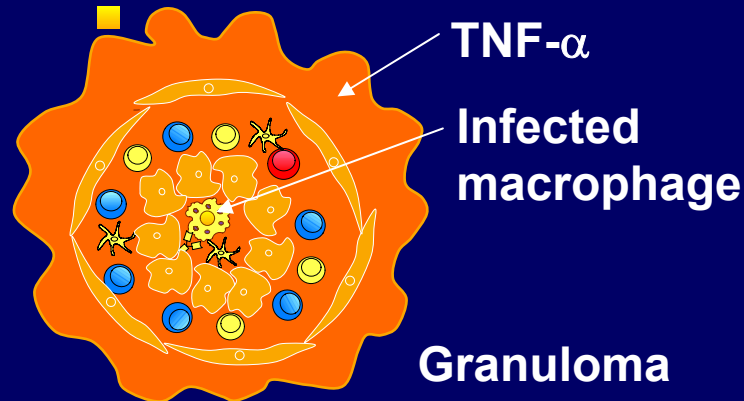
Influenza
Parainfluenzae
RSV

Mycobacterium tuberculosis
Atypical mycobacterium
Legionella spp.
Listeria monocytogenes
Salmonella typhi
Nocardia

Candida spp.
Endemic fungi
Cryptococcus neoformans

P. jiroveci
Toxoplasma gondii
Cryptosporidium
Leishmania

College matrix



TNF- α

Infected
macrophage

Granuloma

TNF- α

- Formation and maintenance of granulomas
- Migration and maturation of inflammatory cells to the site of infection
- Production of
 - cytokines such as IL-1, IL-6, IL-8
 - Monocyte chemoattractant protein type-1
 - Adhesion molecules such as intercellular adhesion molecule-1 and E-selectin

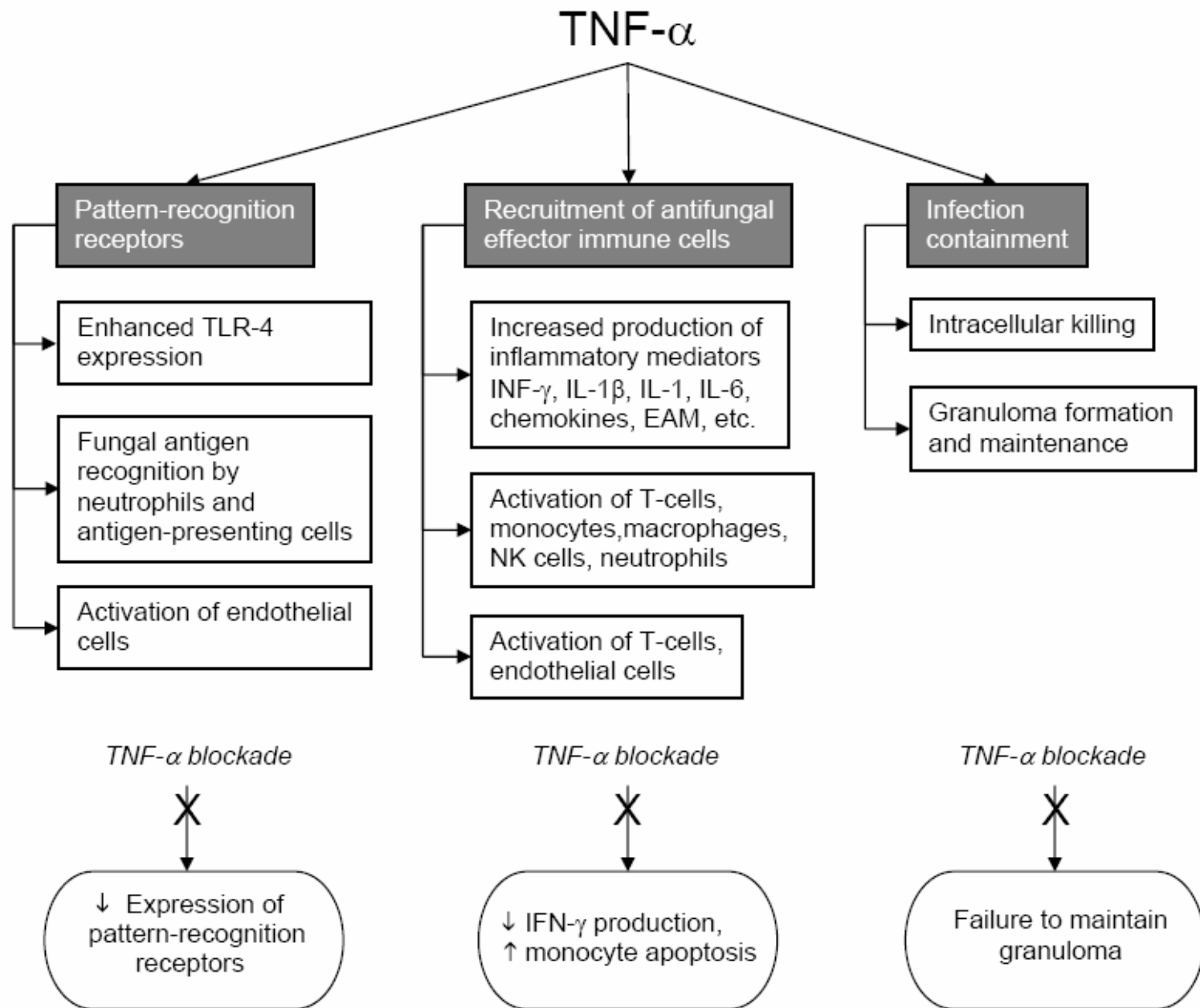


Figure: R Lewis

TNF- α inhibitors: Indications

- Reduce disease severity in
 - Rheumatoid arthritis
 - Crohn's disease
- Varying efficacy
 - Juvenile rheumatoid arthritis
 - Spondyloarthritides
 - Psoriasis
 - Hidradenitis suppurativa
 - Steroid-refractory graft-versus-host disease reactions in allogeneic hematopoietic cell transplant patients
 - Sarcoidosis
 - Wegener's granulomatosis

Anti-TNF- α Ab therapies

- Biologic agents targeting TNF- α –mediated immunomodulatory effects
 - Infliximab (Remicade): chimeric IgG1 κ monoclonal antibody
 - Etanercept (Enbrel):
 - protein composed of two p75TNF- α receptors fused to the Fc portion of IgG1
 - binds both TNF- α and lymphotoxin- α
 - Adalimumab (Humira): fully humanized IgG1 κ monoclonal antibody

Pharmacology

| | Half-life | Dosing |
|------------|------------|------------------------|
| Infliximab | 8-9.5 days | every 15-60 days IV |
| Etanercept | 4-5 days | every 3-4 days SQ |
| Adalimumab | 12-14 days | every 7-14 days SQ |

Serious side effects

- Lymphoma
- Heart failure
- Granulomatous infections: tuberculosis attack rate was deemed high enough to lead to formal recommendations regarding skin testing in all patients before initiation of infliximab treatment

Immunity against fungi

- Exposure to a fungal antigen
- Naïve T cells differentiate into distinct Th cell subsets
 - Th1 cells: IFN- γ , IL-2, lymphotoxin, and stimulates cell-mediated effector responses and IgG2a production
 - Th2 cells: IL-4, IL-5, IL-9, IL-13, mastocytosis, eosinophilia, IgE, IgG1
- Expression of Toll-like receptor 4 (TLR-4)
 - Important for recognition of fungi including *Candida albicans* and *Aspergillus fumigatus*

Infliximab use in allogeneic BMT patients with severe GvHD

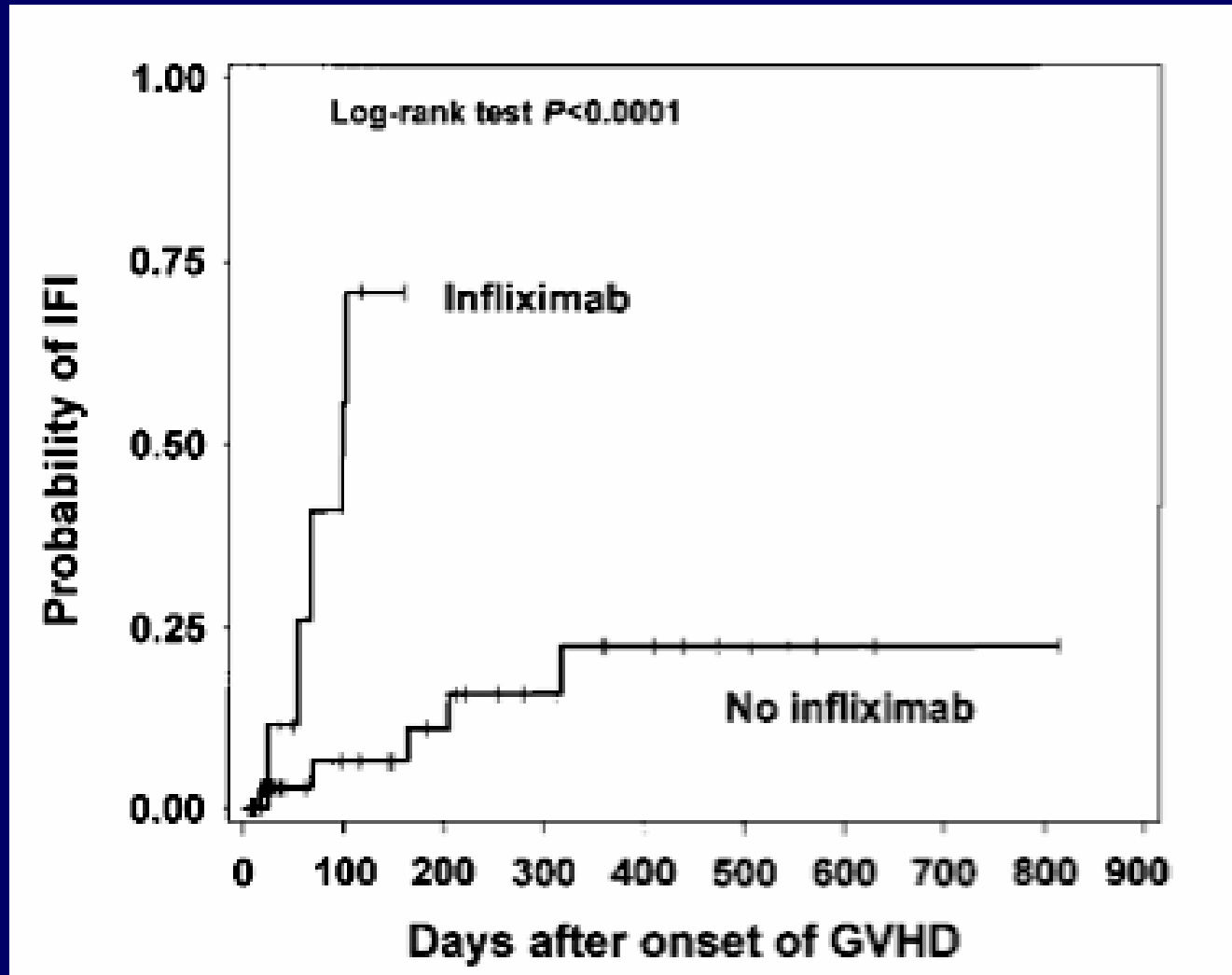


Table 5. Infections after infliximab

| Type of infection | No. patients (%) | No. positive cultures (%) |
|-------------------------|------------------|---------------------------|
| Bacterial | 17 (81) | 45 (52) |
| Gram-positive | 11 (52) | 32 (37) |
| Gram-negative | 5 (24) | 8 (9) |
| Others | 4 (19) | 5 (6) |
| Fungal | 10 (48) | 18 (21) |
| <i>Aspergillus</i> spp | 6 (29) | 7 (8) |
| <i>Candida glabrata</i> | 5 (24) | 5 (6) |
| <i>Candida</i> spp | 4 (19) | 6 (7) |
| Viral | 14 (67) | 24 (28) |
| Cytomegalovirus | 11 (52) | 16 (18) |
| Respiratory viruses | 5 (24) | 5 (6) |
| Others | 3 (14) | 3 (3) |
| Total | 21 (100) | 87 (100) |

Literature, 1999 to mid-2006

- 251 reported cases of IFI associated with TNF- α inhibition
 - 215 (86%) associated with infliximab
 - 36 (14%) with etanercept
 - none associated with adalimumab
- Median age 59 years (IQR: 49-70)
- 64% were male

Tsiodras & Kontoyiannis: Fungal Infections Complicating TNF- α Blockade Therapy: A Review of Reported Cases. IDSA 2006

Other Immunosuppression

- Use of at least one other immunosuppressant medication, typically a systemic corticosteroid, was reported during the course of the fungal infection in 86 (99%) of the 87 patients.

Onset of IFI after TNF blockade

- Infliximab

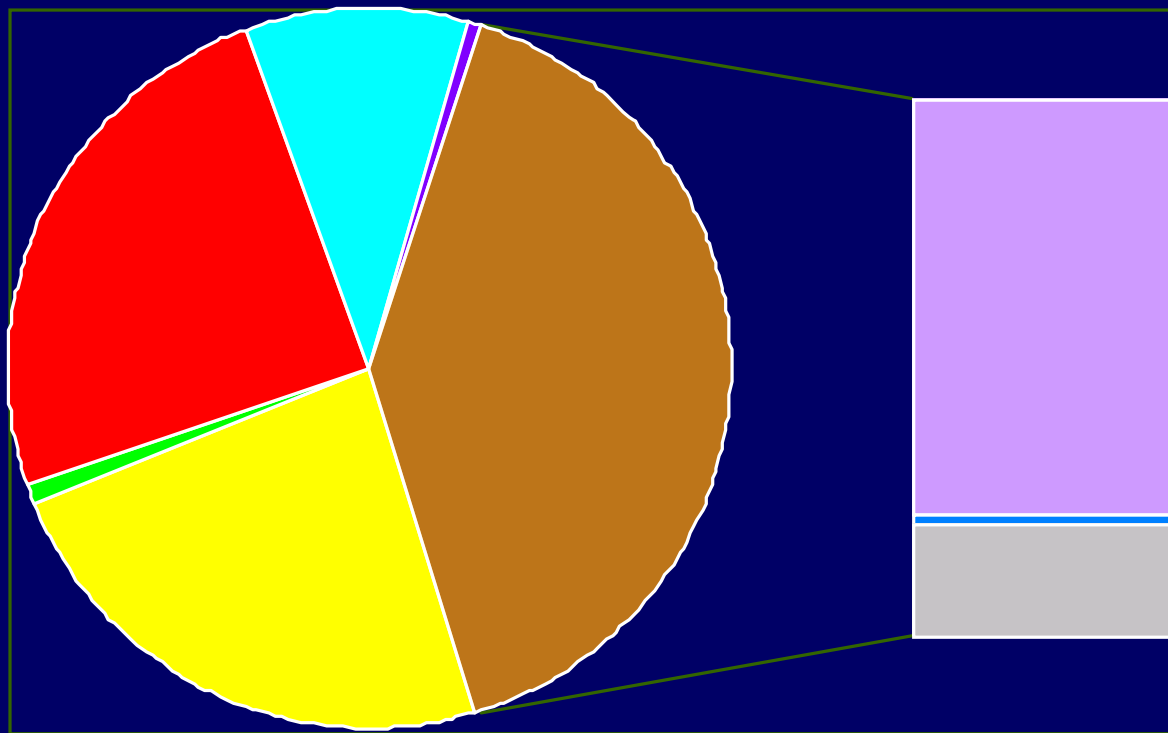
- Median of 55 days (IQR, 15-140 d)
- 3 infusions (IQR, 2-5)

- Etanercept

- Median of 144 days (IQR, 46-240 d)

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Invasive fungal infections



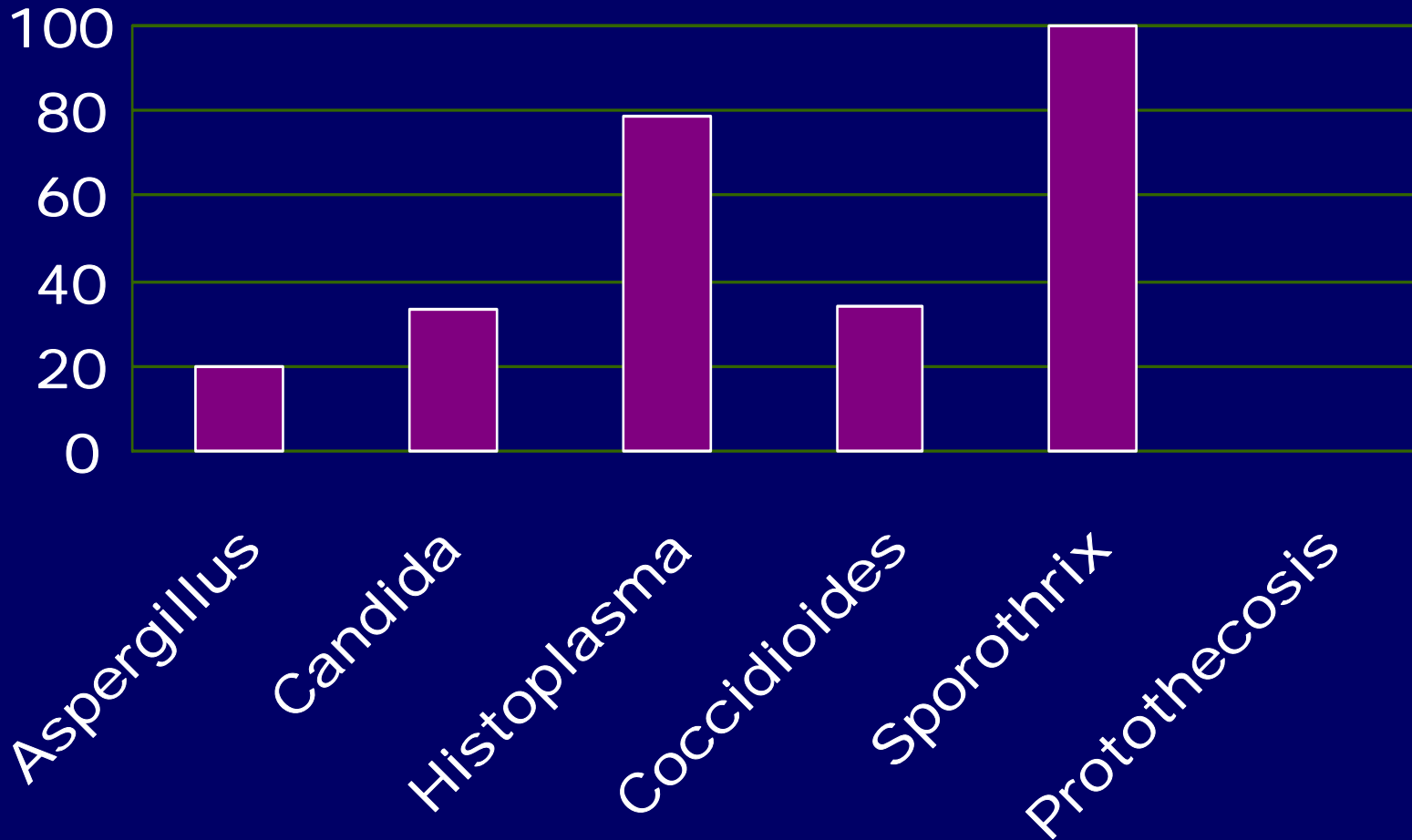
- Aspergillus
- Zygomycetes
- Candida
- Cryptococcus
- Sporothrix
- Histoplasma
- Blastomyces
- Coccidioides

Tsiodras & Kontoyiannis: Fungal Infections Complicating TNF- α Blockade Therapy: A Review of Reported Cases, IDSA 2006

Invasive fungal infections

- Histoplasmosis (n =78, 31%)
- Candidiasis (n = 62, 25%)
- Aspergillosis (n=59, 24%)
- Cryptococcosis (n=25); pneumonias
- Coccidioidomycosis (n=21)
- Zygomycosis (n=2)
- Blastomycosis (n=2)
- Survival 53/80 (66%)

Survival



Tsiodras & Kontoyiannis: Fungal Infections Complicating TNF- α Blockade Therapy: A Review of Reported Cases, IDSA 2006

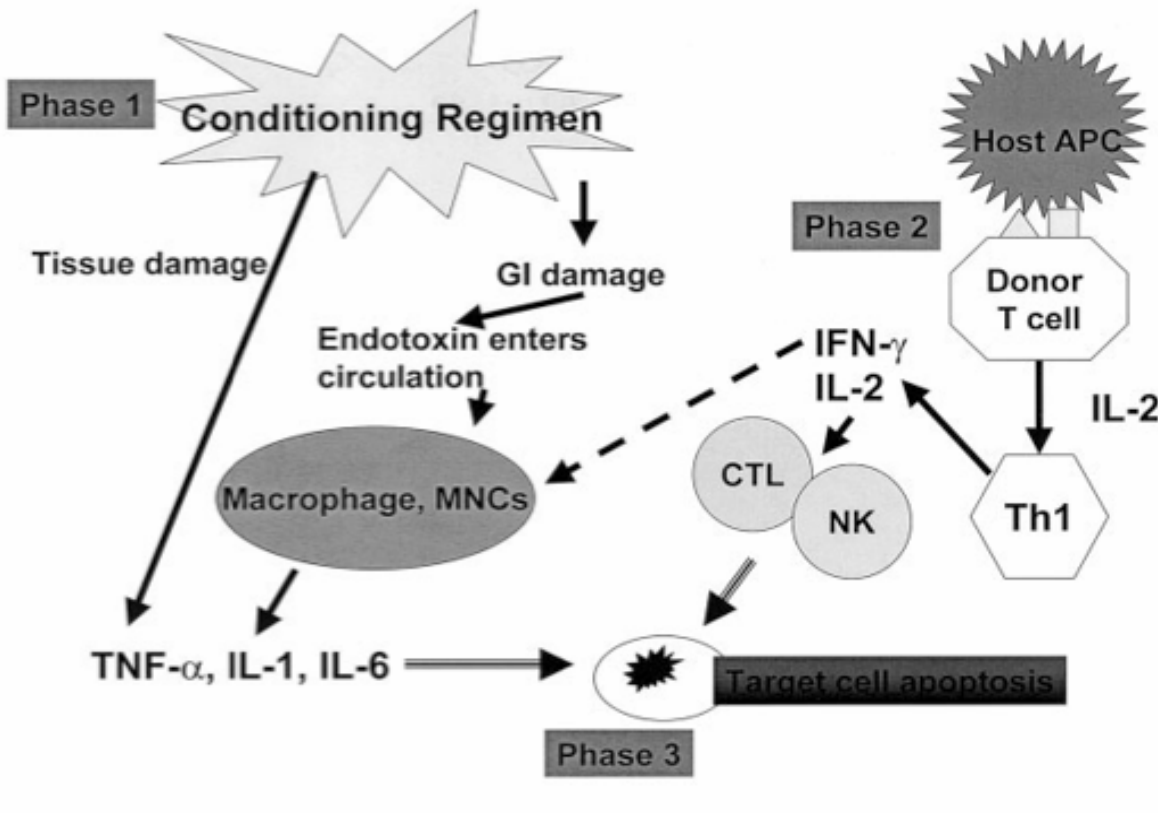
59 cases of aspergillosis

| | Cases | Survival |
|-----------------|-------|-------------------|
| GvHD after HSCT | 15 | “grave prognosis” |
| RA | 3 | 2 |
| IBD | 2 | 0 |

Tsiodras & Kontoyiannis: Fungal Infections Complicating TNF- α Blockade Therapy: A Review of Reported Cases, IDSA 2006

- Is the poor outcome of opportunistic IFIs following TNF inhibition in alloBMT a reflection to profound net state of immunosuppression in these patients or it is specifically related to these agents?
- Is the risk outcome of IFIs following TNF blockade dependant on the underlying disease?

Pathophysiology of GvHD



Acute GvHD



Methylprednisone (MP) 2 mg/kg + tacrolimus



Response 3-7 days into MP?



Yes (50%)

No



Steroid taper



ATG

Pentostatin (adenoside deaminase)

Daclizumab (anti-IL-2 receptor)

Visilizumab (anti-CD3)

Infliximab (anti-TNF- α)

Denileukin diftitox (anti-IL-2, dip toxin)

ECP
Photopheresis

Rheumatoid arthritis

Meta-analysis

- Randomized, placebo-controlled trials of the 2 licensed anti-TNF antibodies (infliximab and adalimumab) used for 12 weeks or more.
- Nine trials
 - 3493 patients received anti-TNF antibody
 - 1512 patients received placebo

Pooled odds ratios

- Malignancy
 - POR = 3.3 (95% CI, 1.2-9.1)
 - Malignancies were significantly more common in patients treated with higher doses compared with patients who received lower doses
 - Number needed to harm was 154 (95% CI, 91-500) for 1 additional malignancy within a treatment period of 6 to 12 months.
- Serious infection
 - OR = 2.0 (95% CI, 1.3-3.1)
 - Number needed to harm was 59 (95% CI, 39-125) for serious infections within a treatment period of 3 to 12 months.

Infliximab and PCP: review of 84 cases

Kaur et al.

Dig Dis Sci.

2007;52(6):1481-4

| | Number of patients |
|-------------------------------------|--------------------|
| <hr/> | |
| I. Demographics | |
| Men | 27 |
| Women | 47 |
| Mean age = 55 ± 15 years | |
| II. Indications for infliximab | |
| Rheumatoid arthritis | 49 |
| Crohn's disease | 14 |
| Ulcerative colitis | 2 |
| Ankylosing spondylitis | 2 |
| Wegener's granulomatosis | 2 |
| Psoriatic arthritis | 1 |
| Dermatomyositis | 1 |
| Polymyositis | 1 |
| Still's disease | 1 |
| III. Concomitant immunosuppressants | |
| Methotrexate | 38 |
| Prednisone | 37 |
| Azathioprine | 6 |
| Leflunomide | 6 |
| 6-Mercaptopurine | 5 |
| Cyclosporine | 4 |
| IV. Comorbid diseases | |
| Anemia | 3 |
| Asthma | 3 |
| Pulmonary fibrosis | 2 |
| Bronchitis | 2 |

PCP Post Infliximab: Temporal Relationship

| | |
|--|-------------------------------|
| Mean time between infliximab infusion and onset of pneumonia | 21 ± 18 days ($n = 40$) |
| Number of infusions before onset of symptoms | 2.1 ± 1.3 ($n = 76$) |

Mortality: 23/84 pts (27%)

Conclusions RE: TNF blockade

- Increased risk of serious IFIs
- Risk, timing for IFIs differs among anti-TNF drugs (infliximab >> etanercept, adalimumab)
- Could be reactivation of latent infection or progression of newly acquired IFI
- Impossible to calculate specific risk for IFIs or the period at risk for IFIs (no laboratory surrogate marker, no ascertainment of exposure periods)

High risk scenarios for IFI following TNF blockade

- GvHD
- History of IFIs
- Colonization with pathogenic fungi
- Environmental exposures
 - High risk travel in endemic areas
 - High risk outdoor activities
 - Construction

Recommendations for new courses of TNF blockade

- High index of suspicion
- No anti-TNF agents in patients with active IFI
- Patients with history of mold infections:
Contraindications for anti-TNF agents
vs prophylaxis & intense monitoring?
- Develop pharmacovigilance database
- Study immunopathogenesis

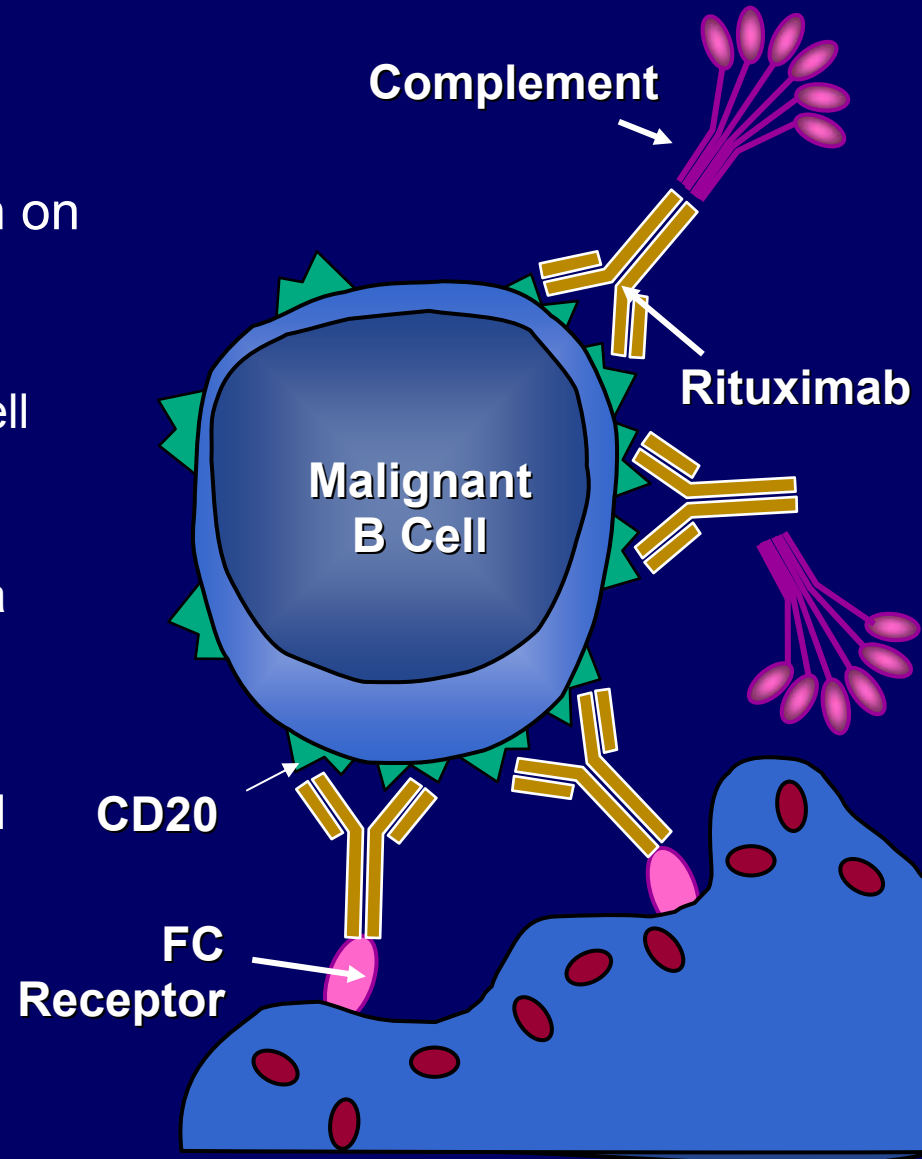
Other Immunomodulators

Principles of Monoclonal Antibody-Based Therapy

- Cytotoxicity
 - ADCC: Antibody dependent cell-mediated cytotoxicity
 - CDC: Complement-dependent cytotoxicity
- Direct effect on tumor cells
 - Growth inhibition
 - Cell cycle arrest
 - Induction of apoptosis
- Synergy with conventional chemotherapies

Rituxan (Rituximab)

- Chimeric murine/human antibody
- Binds specifically to CD20 antigen on normal and malignant pre-B and mature B lymphocytes
 - CD20 expressed by >90% of B-cell NHL
 - No CD20 on human stem cells, progenitor cells, or normal plasma cells
- Lyses lymphocytes via:
 - Antibody dependent cell mediated cytotoxicity
 - Induction of apoptosis

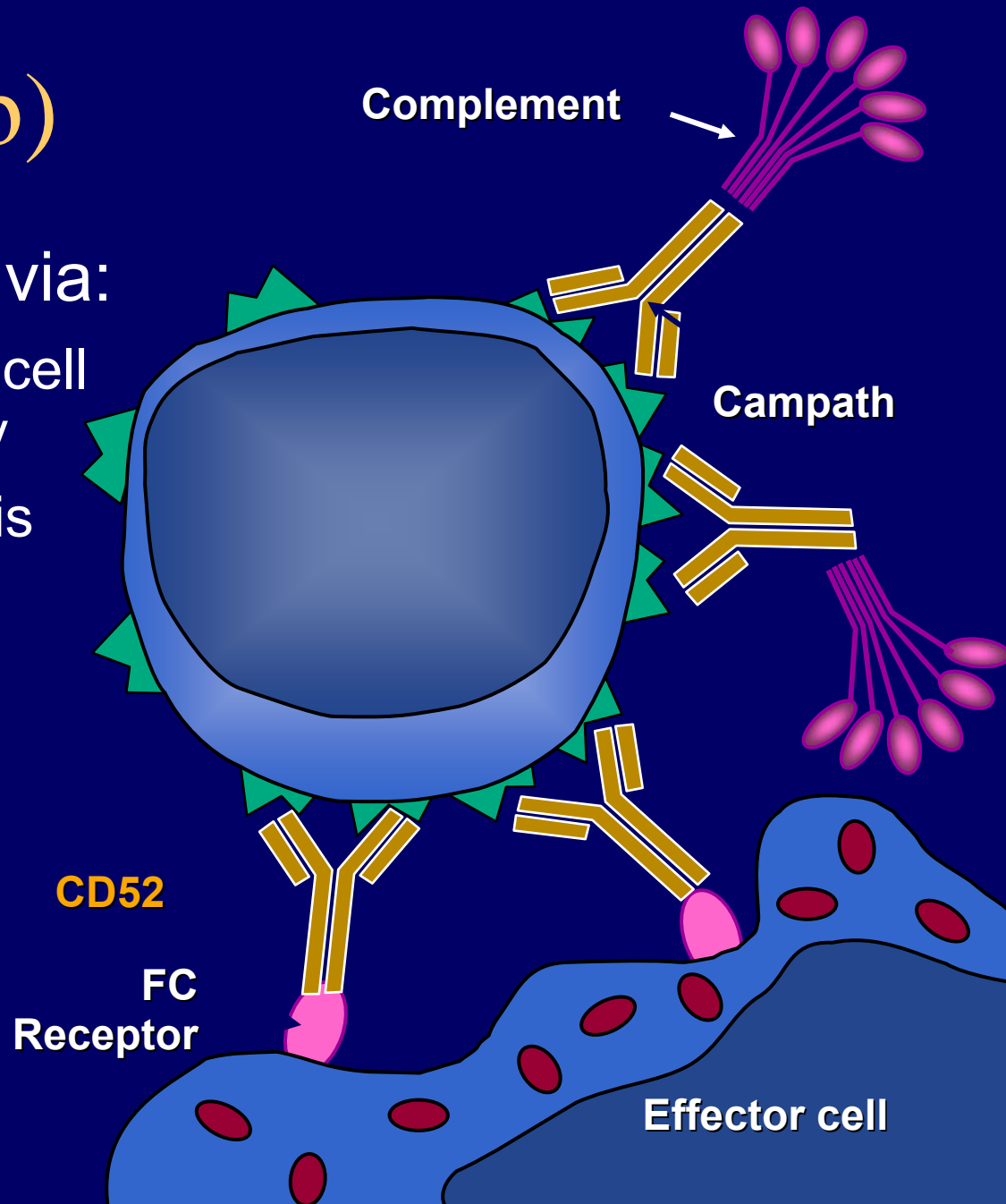


Rituxan- Immune suppression

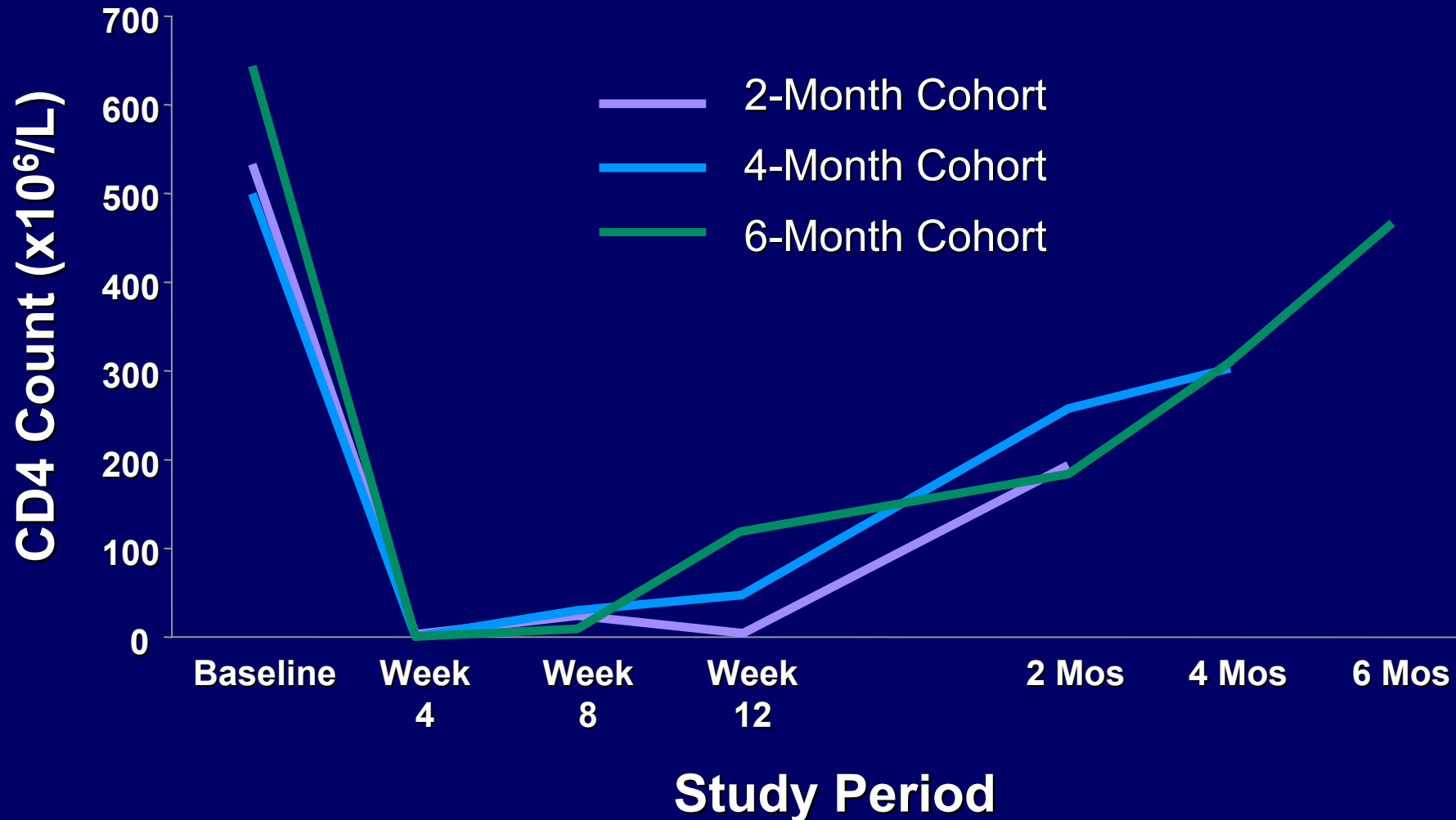
- Results in a 90% reduction in peripheral B-lymphocyte counts in 3 days
 - Recovery occurs slowly over 9-12 months
- Despite B-cell depletion, minimal decrease in serum immunoglobulin levels, and no effect on serum complement
- Neutropenia may be seen if used with fludarabine
- Infection incidence and severity is often less than seen with other therapies

Campath-1H (alemtuzumab)

- Lyses lymphocytes via:
 - Antibody dependent cell mediated cytotoxicity
 - Induction of apoptosis

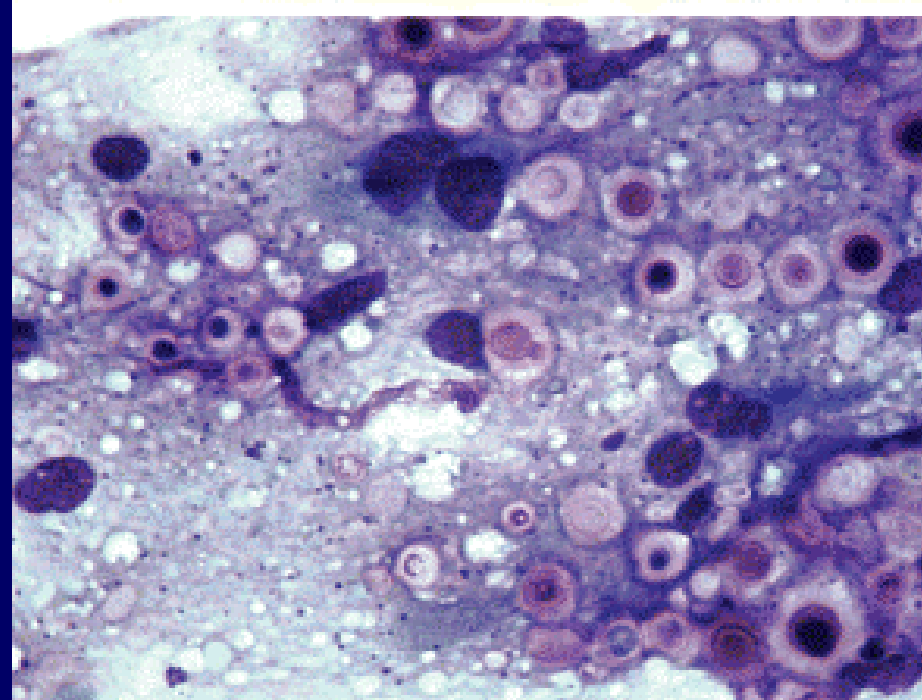


Median CD4 Cell Counts Over Time (Campath-1H, alemtuzumab)



CLL

- 44 year old with CLL
- Refractory to fludarabine
- 6 wks after alemtuzumab (Campath-1H)
- fever $>40^{\circ}\text{C}$
- asthenia
- ANC = 80 cells
- Skin biopsy
- *Cryptococcus neoformans* in blood, urine and stools
- IV lip AmB & 5FC



Infectious complications with Campath-1H / alemtuzumab

- Early experience in CLL patients
 - Opportunistic infections in 10/24 pts (42%)
 - 4 episodes of PCP
 - Invasive aspergillosis
 - 2 cases of *Candida* endophthalmitis
 - CMV
 - Disseminated VZV
 - Legionella

Infectious complications with Campath-1H / alemtuzumab

- This small trial (n=24) found that infections were the major toxicity
 - HSV reactivation 38%
 - Oral candidiasis (17%)
 - Pneumonia (21%) -2 were *PCP*
 - Bacteremia in 3 pts

TMP/SMX prophylaxis recommended in all patients receiving alemtuzumab

Infectious complications with Campath-1H / alemtuzumab

- Fludarabine-refractory CLL (n=94) using TMP/SMX prophylaxis
- Average 4-7 treatments
 - PCP in pt not taking TMP/SMX (n=1)
 - *Aspergillus* (n=2), zygomycosis (n=1) pulmonary cryptococcosis (n=1), invasive candidiasis (n=1)
 - CMV reactivation (n=7)
 - *Listeria* meningitis (n=1)

PCP

- 19 patients with immunodeficiency syndromes (without AIDS)
 - Diagnosed with granulomatous *Pneumocystis* infection
- Index case: 75-year-old woman with CLL treated with Campath-1H / alemtuzumab 3 x weekly for 12 wks.
 - After completion of therapy: dyspnea, hypoxemia, and bilateral infiltrates
 - Responded well to trimethoprim-sulfamethoxazole

OIs

- 547 organ transplant recipients
- At least 1 dose of alemtuzumab
- 9/2002 through 3/2004

| OI | No. (%) of OIs | Time to infection ^a | No. of OIs among transplant recipients receiving alemtuzumab ^b | |
|--------------------------------|-------------------|-----------------------------------|--|-----------|
| | | | Induction | Rejection |
| Any | 62 (100) | 84 (2–328) | 16 | 46 |
| Viral | | | | |
| CMV disease | 16 (26) | 85 (7–254) | 4 | 12 |
| Pneumonitis | 4 | ... | 1 | 3 |
| GI infection | 8 | ... | 1 | 7 |
| Hepatitis | 3 | ... | 2 | 1 |
| Febrile viral syndrome | 1 | ... | 0 | 1 |
| EBV disease | 3 (5) | 95 (42–288) | 2 | 1 |
| PTLD | 3 | | 2 | 1 |
| Febrile syndrome | 0 | | | |
| EBV-negative PTLD | 2 (3) | 24, 169 ^c | 0 | 2 |
| HHV-6 infection | 1 (2) | 222 | 0 | 1 |
| BK virus infection | 12 (19) | 134 (18–328) | 5 | 7 |
| Parvovirus infection | 1 (2) | 325 | 0 | 1 |
| Fungal | | | | |
| Esophageal candidiasis | 12 (19) | 51 (2–265) | 1 | 11 |
| Cryptococcal infection | 2 (3) | 54, 200 ^c | 2 | 0 |
| Invasive aspergillosis | 1 (2) | 34 | 0 | 1 |
| Mucormycosis | 1 (2) | 87 | 0 | 1 |
| <i>Scedosporium</i> infection | 2 (3) | 57, 66 ^c | 0 | 2 |
| Bacterial | | | | |
| <i>Nocardia</i> | 4 (6) | 74 (54–96) | 0 | 4 |
| Mycobacteria | 3 (5) | 77 (63–323) | 1 | 2 |
| Tuberculosis | 1 | | 0 | 1 |
| Nontuberculous | 2 | | 1 | 1 |
| Parasitic | | | | |
| Toxoplasmosis | 1 (2) | 59 | 0 | 1 |
| <i>Balamuthia mandrillaris</i> | 1 (2) | 2 | 0 | 1 |

| Characteristic | Recipients with an OI after receiving alemtuzumab (n = 56) | Recipients without an OI after receiving alemtuzumab (n = 491) | OR (95% CI) | P |
|---|---|---|----------------|-------|
| Age, median (range) | 51 (18–77) | 51 (16–82) | ... | .81 |
| Sex, female | 28 (50) | 195 (40) | 1.5 (0.9–2.6) | .14 |
| Transplant received | | | | |
| Kidney | 16 (29) | 235 (48) | 0.4 (0.2–0.8) | .007 |
| Liver | 8 (14) | 152 (31) | 0.4 (0.2–0.8) | .01 |
| Lung or heart/lung | 12 (21) | 44 (9) | 2.8 (1.4–5.6) | .005 |
| Pancreas or kidney/pancreas | 6 (11) | 44 (9) | 1.2 (0.5–3.0) | .67 |
| Intestinal or multivisceral | 14 (25) | 16 (3) | 9.9 (4.5–21.7) | <.001 |
| Previous transplant received | 8 (14) | 72 (15) | 0.9 (0.4–2.1) | .9 |
| Alemtuzumab received | | | | |
| For induction therapy | 16 (29) | 338 (69) | 0.2 (0.1–0.3) | <.001 |
| For rejection therapy | 40 (71) | 153 (31) | 5.5 (3.0–10.0) | <.001 |
| Doses of alemtuzumab received, no. (range) | 2 (1–5) | 1 (1–5) | 2.3 (1.7–3.1) | <.001 |
| Received pulse methylprednisolone ^a | 15 (27) | 152 (31) | 0.8 (0.4–1.5) | .5 |
| Received >2 pulses of methylprednisolone ^a | 10 (18) | 49 (10) | 2.0 (0.9–4.1) | .08 |
| Received another lymphocyte-depleting antibody ^b | 28 (50) | 117 (24) | 3.2 (1.8–5.6) | <.001 |
| Received both pulse methylprednisolone and another lymphocyte-depleting antibody | 7 (13) | 55 (11) | 1.1 (0.5–2.6) | .8 |
| Received dacluzimab | 2 (4) | 7 (1) | 2.6 (0.5–12.6) | .3 |
| CD4 cell count, median cells/mm ³ | | | | |
| At baseline | 427 | 589 | ... | .2 |
| First month | 6 | 4 | ... | .6 |
| First 3 months | 11 | 8 | ... | .4 |
| First 6 months | 13 | 21 | ... | .6 |
| Second 6 months | 139 | 95 | ... | .6 |
| Death ^c | 12 (21) | 31 (6) | 4.1 (1.9–8.4) | <.001 |
| Allograft failure ^d | 16 (29) | 62 (13) | 2.8 (1.5–5.2) | .002 |

Table 4. Multivariable analysis of independent predictors of the development of an opportunistic infection (OI) in organ transplant recipients who received alemtuzumab.

| Predictor of an OI | OR (95% CI) | <i>P</i> |
|---|----------------|----------|
| Alemtuzumab received as rejection therapy | 3.5 (1.8–6.8) | <.001 |
| Lung or heart/lung transplant received | 3.7 (1.7–8.0) | .001 |
| Intestinal or multivisceral transplant received | 8.3 (3.5–19.5) | <.001 |
| Allograft failure | 2.1 (1.1–4.4) | .04 |

- Transplant recipients who receive alemtuzumab for rejection
 - also exposed to other potent immunosuppressive agents
 - more likely to develop allograft failure than were transplant recipients who did not (27% vs. 7%; $P < .0001$)
 - inherently further out from transplantation & may not have been receiving the same intensive antimicrobial prophylaxis
- No association with CMV found

Adult renal transplant

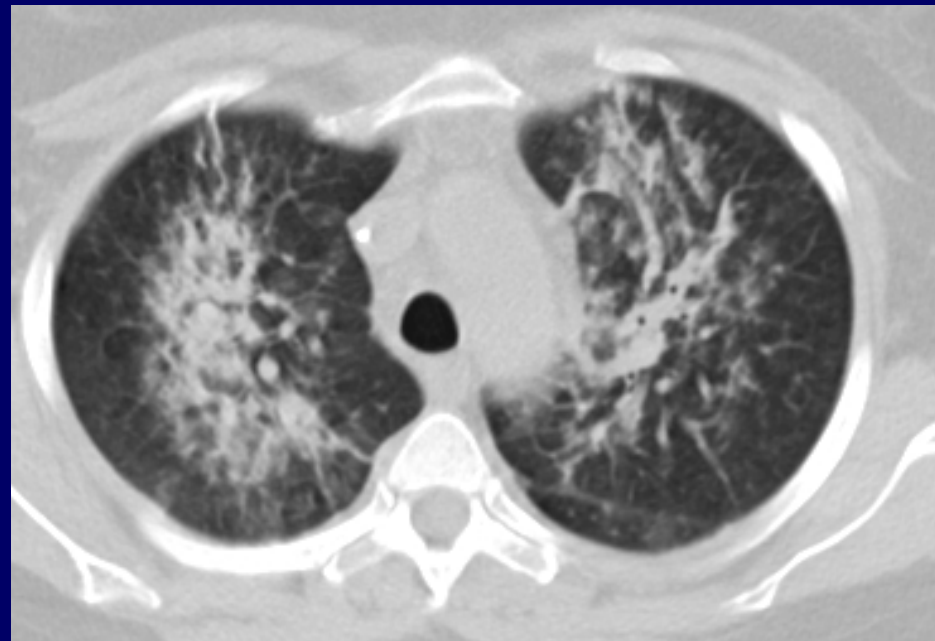
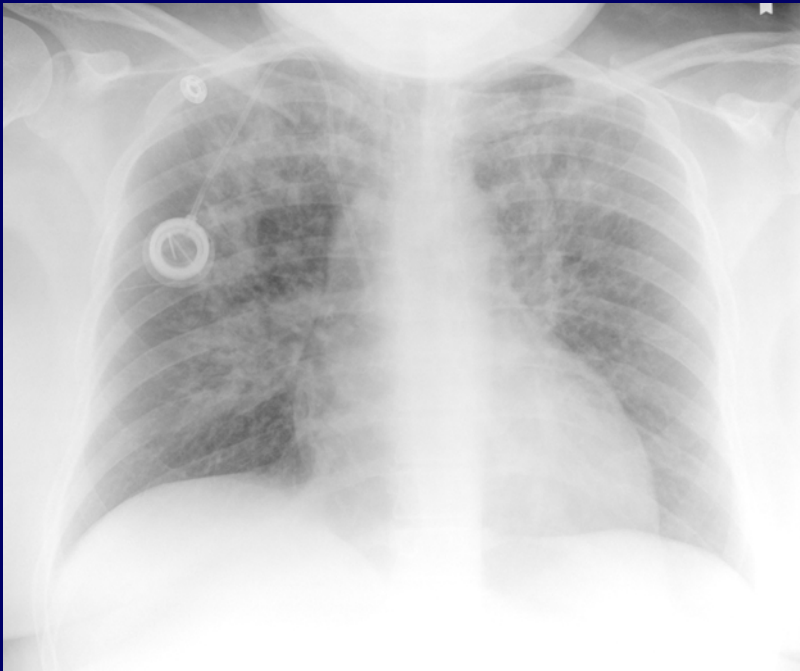
- 49 adult renal transplant patients receiving Campath-1H
 - May 1, 2003 and June 7, 2004
 - Mean follow-up = 13.7 months (range, 10-24 months)
- 8 / 49 (16%) patients in the Campath group had an infectious complication, compared to 18 out of 56 (32%) in the historical group
 - 1 case of CMV viremia
 - 2 cases of CMV disease (pneumonitis and enteritis)
 - 4 cases of UTI
 - 1 cellulitis
 - 1 cryptococcal meningitis

Campath Case 1

- 51 y/o woman with diabetes since the age of 10.
 - Gastroparesis.
 - Hypertension. Status post CVA x 2.
 - Chronic kidney disease with a GFR that runs around 40.
 - Coronary artery disease, atrial fibrillation s/p cardioversion.
- History of seizures when she had hypoglycemic unawareness.
 - Suicidal prior to her pancreas transplant.
- Pancreas transplant in October 1999 with an enteric conversion procedure in July 2002.
 - Campath when ALC > 200 for steroid-free IS

Campath Case 1

- 51 y/o woman is CMV IgG +
- 9/7/04: CMV Ag 205 → 28 → 3
- 10/5/04: GCV level 6.4; 8 → 5 → 1 → 0
- 12/4/04: CXR interstitial opacities



Campath Case 1

- 12/4/04: BAL + PCP
- 1/12/05: GCV level 11.4
- 1/17/05: panc mod aRjxn; CMV HP -
- 1/26/05: Eye fluid + Qual CMV PCR
- 2/05: Ag 2 → 1; bone marrow CMV PCR –
- 5/25/05: Sphenoid sinus Cx + MAI-C
- 6/2/05: BCx + MAI-C
- 6/06: expired from acute leukemia

CMV Infections

University of Minnesota Pancreas Transplants

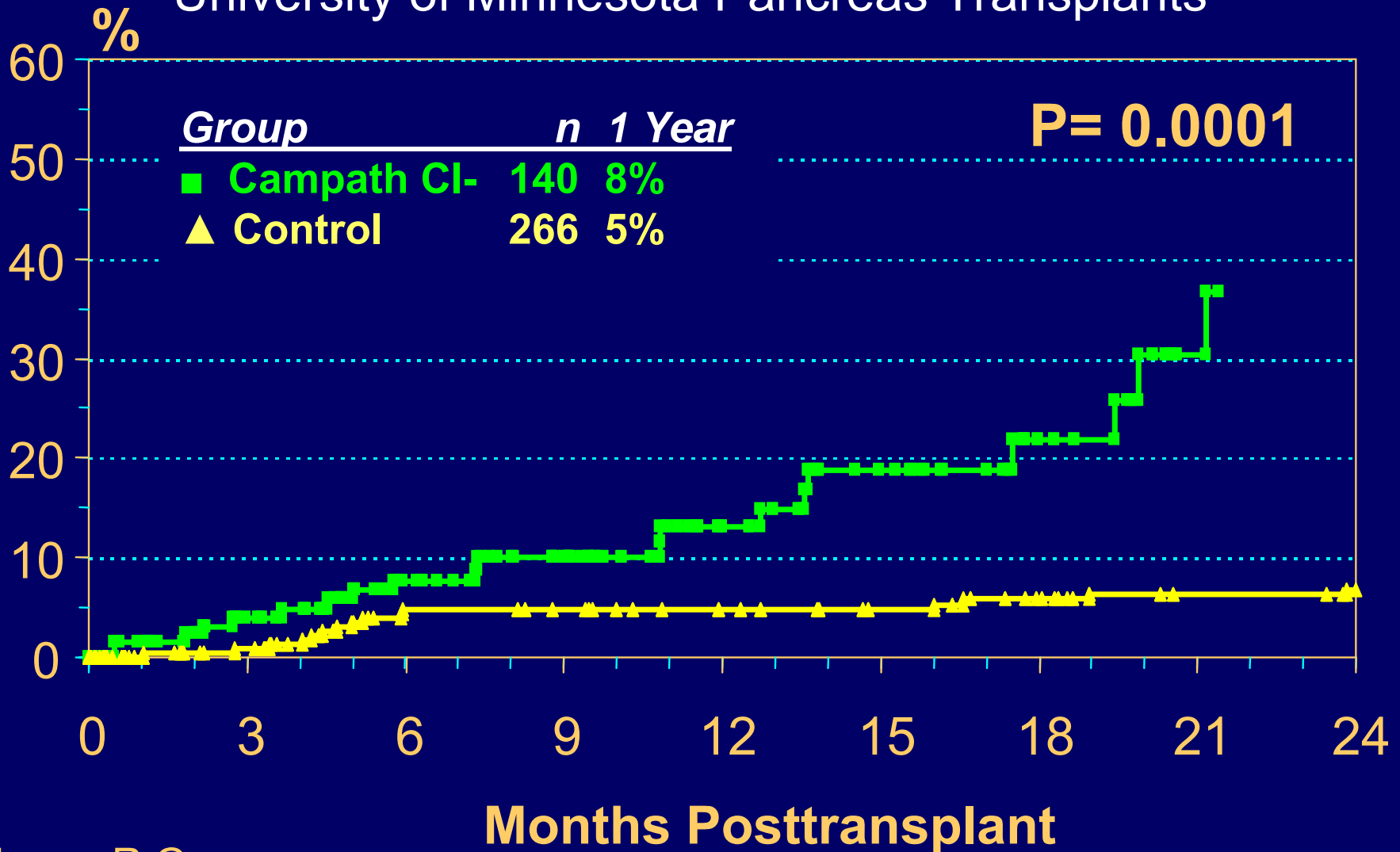


Figure: R Gruessner

Campath Case 2

- 33 y/o man with diabetes for 21 years.
 - Nonproliferative diabetic retinopathy.
 - Epiretinal membranes in both eyes.
 - Anemia.
- Kidney transplant in May 2004.
- Pancreas transplant in November 2004, from deceased donor.
 - Campath when ALC > 200 for steroid-free IS
- February 2005 *Pseudomonas* peritonitis. Followup CT scan of the abdomen demonstrated peripancreatic fluid and phlegmonous changes in March 2005.

Campath Case 2

- 33 y/o man DM, CMV IgG -, k 5/04
- 11/04 R CMV IgG -, donor panc IgG+
 - Valcyte prophylaxis
- 5/3/05: 426 cells, valcyte to IV GCV
- 5/20/05: 1298 cells
- 5/25/05: Foscarnet initiated
- 40 – 3 – 1 – 11 – 21 – 21 – 52 – 8 – 28

Campath Case 3

- 54 y/o man, diabetes mellitus type 1 since childhood with underlying neuropathy, retinopathy requiring retinal photocoagulation, and previous nephropathy.
 - Hypothyroidism.
 - Hypertension.
 - Focal coronary disease. Angiography done on 11-25-03 showed a focal 50-60% stenosis in the mid LAD, a 30% stenosis of the bifurcation of OM1 and OM2, and there were also two focal 50% lesions in the PDA.
- Simultaneous living related donor kidney with deceased donor pancreas graft, which is enterically drained, in July 2004.

Campath Case 3

- 54 y/o man DM, CMV IgG neg 7/6/04
 - LRD kid & dd panc 7/04
 - Valcyte prophylaxis
- 5/05: BPRPR, Hgb 10, on valcyte
- 5/17/05: random colon bx +HP CMV
- 155 cells; Foscarnet initiated
- 642 – 24 – 6 – 0 – 0 – 0 – 8 – 1
- IgG 444 -> IV IG -> 1090
- Sudden BRBPR at home, xlap

Campath Case 4

- Diabetes mellitus type 1.
 - Proliferative retinopathy.
 - Peripheral neuropathy.
 - Intractable gastroparesis.
 - HTN. CAD, status post PTCA with stenting.
- Seropositive for hepatitis C.
- Status post HLA-identical kidney transplant from his sister in 4/00 for diabetic nephropathy. Ureteral allograft stenosis with hydronephrosis in January 2001.
 - BK virus nephropathy.
- Status post pancreas transplant with bladder drainage 7/01, converted to enteric drainage 3/03.
- 11/04-12/04: nodular skin rash
 - *M. simiae/interjectum*

Campath Case 4

- Campath for steroid-free IS July 2001
- High-grade CMV viremia December 2001.
- CMV duodenitis based on positive biopsies in June 2002.
- 10/30/03: CMV Ag 14 → 3 → 0 → 0 → 0 → 0
- 2/4/05: 4 → 5 → 0 → 0 → 0 → 66 → 24 → 5 → 2
- 5/10/05: liver mass PTLD
- 8 → 0 → 1 → 0; GCV level 5.8; 1 → 1 → 0 → 0 → 0
- Comfort care

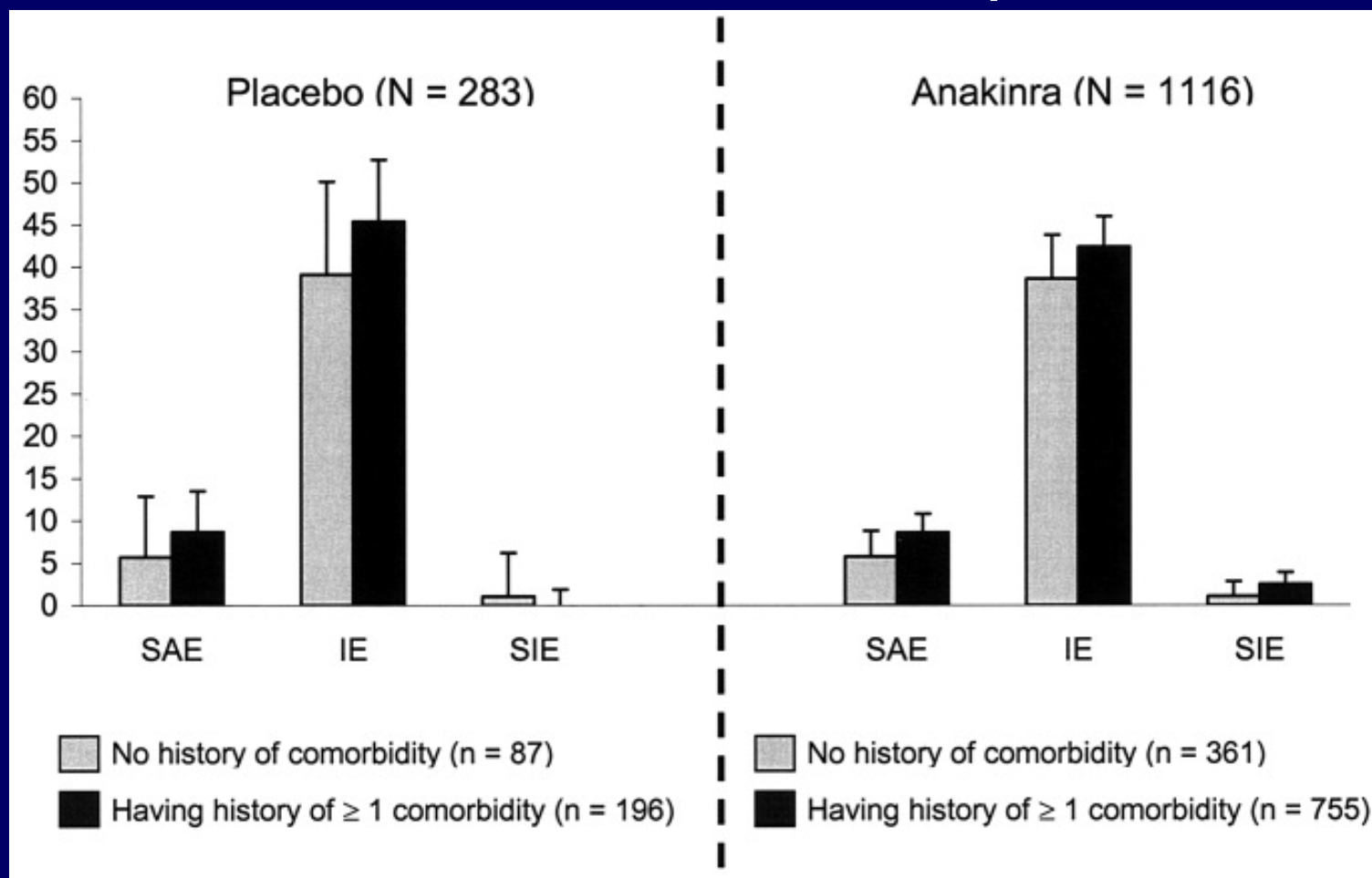
CMV reactivation at MDACC with alemtuzumab

- Heavily pre-treated CLL patients
- CMV reactivation rate consistently 20-25% across all protocols
- Most common manifestation:
 - Persistent fever on broad spectrum antimicrobials, organ involvement uncommon

? Predisposes for subsequent IFIs

Anakinra

Recombinant human IL-1 receptor Ab



Alefacept

- Human lymphocyte function-associated antigen fusion protein
- Psoriasis
- Mycobacterium avium complex olecranon bursitis

Natalizumab

- Humanized monoclonal antibody
- Binds to the $\alpha 4$ chain of the $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins
- In multiple sclerosis, the rationale for natalizumab therapy is the reduction of leukocyte extravasation into the CNS by specifically targeting $\alpha 4\beta 1$ or very-late-activation antigen 4.
- PML has developed in several patients with MS
- ? Role of $\alpha 4\beta 1$ -integrin inhibition by natalizumab in the re-expression of JCV from latent sites and in the inhibition of entry into the brain and peripheral sites.

Stüve et al. Arch of Neurology 2007;64:169-76.

Khalili et al. Neurology 2007;68:985-90.

Treatment of PML induced by Natalizumab

Generation of New Immunocompetent Leukocytes With Unbound VLA-4

Hematopoietic Growth Factors and Leukapheresis and Autotransfusion

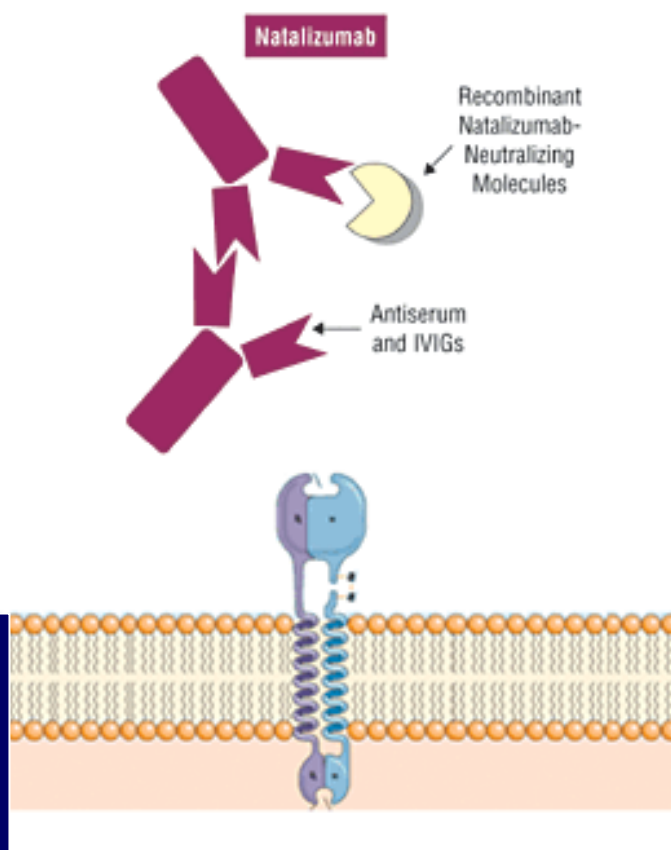


Neutralization of Free Natalizumab

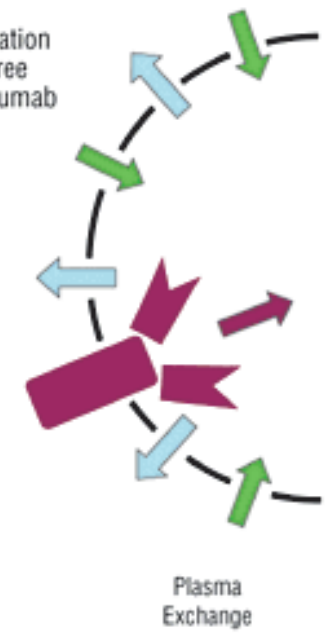
Natalizumab

Recombinant Natalizumab-Neutralizing Molecules

Antiserum and IVIGs



Elimination of Free Natalizumab



Experimental therapies

- Small interfering RNA
- in vivo use of antiserum
- Recombinant natalizumab-blocking molecules

Existing interventions

- Antiviral treatment
- Immunomodulatory therapies
- Hematopoietic growth factors
- Plasma exchange
- IV IG
- Leukapheresis and autotransfusion of leukocytes

Efalizumab

- Anti-CD11a antibody
 - Atopic dermatitis
 - Discoid lupus erythematosus
 - Psoriasis
 - Sjogren's syndrome
- Associated adverse events
 - Lymphoproliferative disease
 - Thrombocytopenia
 - Exacerbation of pityriasis rubra pilaris

Anti-IL-2 receptor antibodies

- Basiliximab, Daclizumab
- *Mycoplasma hominis* septic arthritis in hip 2 months following cadaveric renal transplant
 - Basiliximab
 - Prednisone
 - Tacrolimus
 - Mycophenolate mofetil
 - Thymoglobulin



Conclusions

- Increased risk of serious IFIs
- Risk, timing for IFIs differs among anti-TNF drugs (infliximab >> etanercept, adalimumab)
- Also at risk for PCP, CMV, Mycobacteria
- **TMP/SMX prophylaxis recommended in all patients receiving alemtuzumab**
- Could be reactivation of latent infection or newly acquired infection
- Cannot calculate specific risk for infections
- High index of suspicion
- No immunomodulatory agents in patients with active infections