Herpetic and other infections with Current and Future DMTs

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Agenda

• Opportunistic vs. other infections
• Data by pharmaceutical
  – Corticosteroids
  – Natalizumab
  – Fingolimod
  – Teriflunomide/leflunomide
  – Anti-CD20
  – Alemtuzumab
  – Daclizumab
Opportunistic infections

- An infection that occurs because of a weakened immune system.
- Opportunistic infections may be caused by bacteria, fungi, viruses, or parasites.
- May be normal flora or pathogenic organism
- Interferon-beta and glatiramer acetate are not associated with opportunistic infections
- Mild, moderate, severe or life-threatening

Hypogammaglobulinemia

- Affects opsonization of encapsulated organisms
- Even low “normal” levels can be risk
- More severe infections
- IVIG is RX choice for primary immunodeficiencies
- IgG subclass and IgA congenital deficiency is risk for IVIG allergy
- High risk
  - Pulmonary: *S. pneumoniae, H. influenzae*
  - GI: *Giardia, Campylobacter*
Pneumonia

Fungal Candidal Yeast infections

- *Candida albicans*
  - Most common, often ill
  - 90% of vulvovaginal
- *Candida glabrata*
  - Diabetics
  - Immunocompromise
  - 10% of vaginal infections
- Normal flora of oral, GI, vagina
- *Cryptococcus neoformans*
- Filamentous fungi
  - Superficial mycosis, dermatophytes
- Pathogenic fungi
  - Coccidiomycosis, *Aspergillus*
Cryptococcal Yeast infections

- *Cryptococcus neoformans*
  - Lungs or skin from pigeons
    - Primary infection is respiratory
  - Smoking risk factor
  - Dissemination to skin, lungs, meninges, brain
  - 8% AIDS, 50% are otherwise healthy
  - Encapsulated organism resistant to phagocytosis

Superficial Fungi

- Black/White piedra *Trichosporon* hair associated
- Tinea veriscolor *Malassezia* normal flora
- True dermatophytes
  - Infect keratinized tissue – skin hair nails
  - Itchy peeling skin
  - *Epidermophyton, Microsporum, Trichophyton, Candida*
  - Species differ with body location
Risk factors for Yeast

• Chemotherapy
• Antibiotics (lactobacillus spp. Affected)
• High estrogen levels (luteal phase)
• HIV 90% thrush
• Esophageal candidiasis in HIV
• Systemic yeast in HIV and neoplastic disease

Treatment for yeast infections

• Polyenes
  – Amphotericin
• Azoles
  – Ketoconazole, fluconazole, et al.
  – Resistance arises due to efflux pumps repeat exposures
• Terbinafine
Herpes Simplex

- HSV is latent in the sensory neuron of the dorsal root ganglion, viral assembly and transport to axon terminals
- HSV1 Most are likely infected early in life by family member
  - 95% prevalent
- HSV2 about 30% post-mortem prevalence in the 1980s
- HSV infection occurs in the sensory terminals of a single neuron, when severe, multiple neurons involved
- May be mistaken for VZV if outside typical location
  - Somatic
  - Smaller vesicles, single receptive field
- May spread centripetally into the brainstem/spinal cord
- Causes a demyelinating type lesion in the CNS experimentally
Varicella - Herpes Zoster

Herpes Zoster

- VZV is latent in the glia of the dorsal root ganglion
- Reactivates to cause ganglionitis then neuronitis with centrifugal viral spread to entire sensory dermatome (e.g. multiple receptive fields)
- May spread centripetally into the spinal cord
- Herpes zoster associated with higher risk of MS in subsequent year (4 fold; Kang et al J Infect Dis 2011;204-188-92)
Treatment for HSV

- Thymidine kinase of HSV/VZV is uniquely susceptible to acyclovir class antivirals
- Treatment prevents viral replication and likely kills infected cells
- Resistance (TK-) can arise with chronic exposure and not all genotypes susceptible
- Prophylaxis lowers incidence and severity of relapses

Comparison of antiherpetic agents

- Acyclovir cost $ - poor bioavailability
  - Prophylaxis 400 mg QD/BID $10-$20/month
  - Treatment 800 mg 5X/day X 5-10 d $20-40/course
- Valacyclovir cost $$ - good bioavailability
  - Prophylaxis 0.5-1 g/day $30-$60/month
  - Treatment 1 g TID X 5-10 d $30-$60/course
- Famcyclovir cost $$$
  - Prophylaxis 250 mg BID $45/month
  - Treatment 500 mg TID X 7-14 days $40-80/course
Corticosteroids

- Suppress all aspects of inflammation and phagocytosis
- Infections rates on systemic therapy RR 1.6
  - Relative risk in Neurological diseases 2.8 vs. GI diseases 1.4
  - No risk with less than 10 mg/day or 700 mg exposure
    - Stuck et al Rev Infect Dis 1989;11:954-63
- Candida
  - Other infections rare in the pattern in which we use MS, e.g. intermittent
  - Zoster and Herpes simplex can occur
  - Fatal complications in two acute disseminated VZV on fingolimod
- Corticosteroids may cause, worsen, and obscure the infection
- Interaction between corticosteroids and other MS treatment may be important (natalizumab, fingolimod)

Infection and Natalizumab

- Rate of infection is 1.5 per patient year in both natalizumab and placebo
  - Vaginitis is 10% natalizumab and 6% placebo
  - Herpetic infections 8% treated vs. 7% placebo (AFFIRM)
- Serious infections in the trial 3% natalizumab = placebo
- Infection rate treated = placebo 2 MS & 2 Crohn’s trials
- In both AFFIRM and SENTINEL more infections were seen after corticosteroids
- Corticosteroid-associated infections are similar between natalizumab and placebo patients in both patients
Infections with Natalizumab

- PML
  - Constantly evolving information on pathology and risk
  - High risk patients (long term, JCV seropositive, immunosuppression) exceed 1% risk in MS/Crohn’s
  - Similar to HIV/AIDS
  - JCV serology index data in a state of evolution
    - May be helpful in nonimmunosuppressed in classifying risk
    - 1:100, 1:1000, 1:10,000

Herpetic Infections - Natalizumab

- Animal models indicate that CD8 T cells are critical for protection and prevention of CNS infection
- Herpes zoster – no formal series reported
- Herpetic encephalitis or meningitis
  - Encephalitis presents with headache, fever, seizures, altered mental status
- VZV meningoencephalitis or shingles
- Shingles not rare and generally uncomplicated
CNS Herpetic Infections - Natalizumab

- 20 CNS Herpetic infections from FDA post-marketing
  - 18/20 survived, most not previously immunosuppressed
- HSV 16 cases (6 untyped, 5 HSV1, 5 HSV2) – prior IS 6
  - Encephalitis 10 – 4 recovered completely, 2 died
  - Meningitis 5 – Neurological deficits after in 2
  - Meningoencephalitis 1
    - prior AZA MTX with subsequent PML fully recovered
- VZV 4 cases – All recovered – prior IS in 1
  - Retinitis, meningitis, meningomyelitis, meningitis, meningoaradiculitis
  - 2 with zoster and 2 without

Fine et al 2013 Clin Infectious Diseases 2013;57:849-52

Other Infections - Natalizumab

- Toxoplasma CNS
  - One encephalitis in aggressive MS early in the course of natalizumab
  - One ocular case
- Cryptosporidium gastroenteritis
  - Seen in a single patient in a trial
- In Crohn’s <1% have Pneumocystis, pulmonary mycobacterium, and Burkholderia (like Pseudomonas) in some cases with concurrent immunosuppression
Natalizumab Summary

- PML principal opportunistic infection risk
- May be a minor effect on *Candida* infections
- CNS herpetic infections much lower risk but have occurred and very serious
- Other opportunistic infections extraordinarily rare in MS, perhaps increased in Crohn’s
- General infection risk is unchanged.

Teriflunomide/leflunomide

- Cytostatic effect *de novo* pyrimidine synthesis
- Infrequent *Mycobacterium* TB, *Cytomegalovirus*
- PML seen with leflunomide
- Cutaneous symptoms
  - Hypersensitivity vs. Fungal infection
  - Diagnostic problem requires subspecialty
  - Long t½ means drug may cause a protracted hypersensitivity syndrome
Teriflunomide infection risk –
Pooled studies 1226 patient-years

- Serious infections and deaths, placebo = 14 mg
- Intensity of infections same
- Over 80% of infections had normal WBC
- Leukopenia increased with teriflunomide
  - No grade 4 leukopenia
    - WBC < 3 27% 14 mg vs. 11% placebo
- Serious opportunistic infections rare
  - CMV hepatitis recovered with discontinuation
  - Gastrointestinal TB recovered with antibiotics

Singer et al P01.171 AAN 2013 San Diego

Leflunomide – a teriflunomide prodrug

- Comparable infection rates to MTX in RA
  - Singer & Gibofsky *Curr Opin Rheumatol* 2011;23:288-292

- Long term risk/benefit
  - Teratogen
  - Secreted in breast milk
  - Drug induced hepatotoxicity rare 0.02%
  - Sustained clinical response in RA
  - Predisposition to peripheral neuropathy
    - Alcorn et al *Drug Safety* 2009;32:1123-34
- Consideration for treatment of post-PML transplant
Fingolimod

- Fingolimod MOA should decrease availability of CD8 to the CNS
- Lymphocytes recover to 80% of baseline by 3 months after discontinuation
- No correlation of peripheral counts with infection
  - FREEDOMS infection rates per patient-year
  - 1.4 placebo
  - 1.0 in fingolimod-treated patients
  - who had the lowest lymphocyte counts (< 0.2 x 10^9/l)
    Francis et al Mult Scler J online Aug 15 2013
- FREEDOMS Overall infection rate 72%, serious infections 2%, similar to placebo
- FREEDOMS herpetic infection 9% drug vs. 8% placebo

Herpetic and Other Infections - Fingolimod

- Herpes Simplex – may be increased in FREEDOMS 2
  - Death HSE 1.25 mg in Asian (delayed recognition of encephalitis/corticosteroids)
- Varicella Zoster – ? increased FREEDOMS 2, long-term
  - Primary infection
    - Death disseminated VZV 1.25 mg fingolimod treated corticosteroids
  - Recurrent infection
    - Death from disseminated primary herpes zoster treated as MS relapse with corticosteroids
    - “VZV encephalitis/vasculopathy” Seizure and coma, positive CSF PCR VZV, focal medulla infarcts, in setting of zoster.
  - Zoster
    - Note that serology is not sufficiently sensitive and zoster is evidence of prior infection.
- PML several cases after Tysabri/immunosuppression

Ratchford et al Neurology 2012;79: 2002-4
### Fingolimod Infection Risk (per 100 pt-y)

- **Combined phase II, III and extensions**
  - Zoster
    - fingolimod 1.0 vs. placebo 0.5 vs. IFN 0.2
  - Any herpetic infection
    - fingolimod 6.3 vs. placebo 5.7 vs. IFN 3.0
  - Pneumonia
    - fingolimod 0.5 vs. placebo 0.1 vs. IFN 0.2
  - Lower respiratory
    - fingolimod 0.5 vs. placebo 1.4 vs. IFN 0.2
  - Urinary tract infections
    - fingolimod 8.9 vs. placebo 12.1 vs. IFN 5.1

*Cohen et al P983ECTRIMS October 2012 n = 3916*

### Fingolimod Summary

- Periodic safety data -3 and -4 report to FDA
- PML in transition from natalizumab
- Herpetic infections/pneumonia
- Lymphopenia is not a compelling infection risk in patients on fingolimod
Anti-CD20

• CD-20 is target on naïve and mature B-cells – Anti-CD20 eliminates cells
  – Not Pre Bcell or Plasma Cell
  – Anti-CD20 eliminates circulating cells
  – Oncology patients (lymphoma) are higher infection risk and have greater rates of hypogammaglobulinemia
    Casulo et al *Clin Lymphoma Myeloma Leuk* 12-28-2012
  – Short-term treatment has limited risk in MS

Anti-CD20

• Rituximab
  – PML in other diseases rarer than in natalizumab in MS
    • Cytotoxic chemotherapy more likely responsible
    • Infected stem cells and pre B cells mobilized from bone marrow
    • 2/8000 SLE patients; 2.2/1000 pt-yrs in Non-Hodgkin’s lymphoma
      Bennett *Cleve Clinic J Medicine* 2011;78:S13-17
  – Pneumonia
    • Usually community acquired – see RA data
    • *Pneumocystis* – in heme malignancy treated with rituximab with or without steroids, chemo
      Martin-Garrido et al *Chest* 2013:258-65
• Ocrelizumab
  – Sepsis
  – Pneumonia *Streptococcus Pneumoniae*
• Ofatumumab and others
Infections Ocrelizumab - MS

- Phase II MS trial - 24 weeks only
- Serious adverse events
  - 4% placebo, 4% interferon-beta
  - 2% 600 mg, 5% 2000 mg
- Herpetic infections greatest in placebo (6%)
- Respiratory infections greatest in placebo (4%)
- Urinary tract infections greatest in placebo (9%)

Kappos et al Lancet 19;378:1779-87

Ocrelizumab – related diseases

- Lupus nephritis Study Mylser et al Arthritis Rheum 2013; epub
  - Concomitant treatment with mycophenylate, cyclophosphamide or azathioprine
  - Serious infection rates
    - 19% placebo, 25-29% ocrelizumab
- Japanese RA MTX failures Harigai et al J Rheumatol 39:486-95
  - Serious infections including PCP, all in the treated group
- OCR + MTX vs. MTX RA Stohl et al Ann Rheum Dis 2012; 71:1289-96
  - Serious infections 2.6 OCR vs. 3.0 MTX /100 pt y
- OCR + MTX vs. MTX Rigby et al Arthritis Rheum 2012; 64:350-9
  - 48 weeks, Serious infections 3.5 (placebo), 3.5 OCR 200, 8.6 OCR 500 – dose matters
Rituximab – RA experience

- A benchmark of upper limits for MS?
- Concomitant MTX use common standard
- Highly treatment-experienced cohort
- ~12,000 patient years, 627 patients >5 years,
  - up to 17 cycles over 9.5 years
- Rituximab+MTX >5 years
  - 75 infections/100 patient years (90 with MTX alone)
  - 3.3 Serious infections/100 patient years (3.79 MTX)
- Most common infections
  - URI, nasopharyngitis, UTI, bronchitis, sinusitis, diarrhea, influenza, gastroenteritis
  - Most frequent serious infection pneumonia 2%


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Rituximab – RA experience

- Serious opportunistic infections rare
  - 0.06 rituximab vs. 0.09 MTX per 100 patient years
  - 2 atypical pneumonia
  - 1 each: PML, PCP, Scedosporium pneumonitis, Candida sepsis, de novo hepatitis B,
  - 2 pulmonary TB, No hep B reactivation
- Herpes Zoster
  - 108 in 100 patients 9.0/1000 pt yrs
  - Comparable to general RA 11.5 and MTX 11.7

Rituximab – RA experience
Risk of Hypogammaglobulinemia

- Low Ig levels at screening were excluded
- 22.4% low IgM and 3.5% low IgG after 1 or more cycles
- Serious infections
  - similar before and after hypogammaglobulinemia
  - associated with older age, longer disease, lower CD19, lower mean IgG level
  - IgG 8.4 serious infection vs. 13.2 mg/ml noninfections
  - Little change over time ~4-5/100 pt years


Rituximab – RA experience - Hypogammaglobulinemia

RA clinical trial data rituximab up to 9.5 years of follow-up (n=3194) patients

- Substantial number of patients with >5 years’ observation,
- No new safety signals.
- Peripheral B cell depletion with rituximab did not give rise to any increased safety risk over time of infections or serious events.
- Overall, these results are encouraging and should provide clinicians with reassurance regarding the long-term safety of rituximab in RA.

Ofatumumab 48 weeks RA phase I/II

- Small dose finding trial
- Concomitant MTX and prednisolone
- No infection issues

Anti-CD20 Summary

- Significant risk of hypogammaglobulinemia
- Evidence is not compelling that this identifies those who will have infections
- RA data reassuring
Anti-CD52 Alemtuzumab

• “Hit-and-run” type immune reconstitution
• Fewer infections with the 12 mg dose (likely approval)
• Herpetic infections – higher in first month
  – VZV zoster (up to 10% without prophylaxis)
  – HSV mucocutaneous
• *Listeria* mild case
  – phase II trial with unpasteurized cheese
• Dermatophytes
• *Candida* mucocutaneous and gastroesophageal
• Filamentous fungi
• TB – 1 case of pulmonary TB, one with positive PPD.
• *Histoplasma capsulatum*

Wray et al P01.172 AAN, 2013;

Infection risk of ALE in CARE-MS 1-2

• Most common: nasopharyngitis, URI, mucocutaneous herpes, urinary, gastroenteritis and localized fungal, increased by ALE
• Herpes simplex
  – 13% ALE vs. 2% IFN CMS1
  – 9.7% ALE vs. 2.0% on IFN CMS2
  – Case of herpetic meningitis on ALE CMS1
• Herpes zoster
  – 3% ALE vs. 0% CMS1
  – 6.0% ALE vs. 1.5% on IFN CMS2
• Cystitis
  – 17% ALE vs. 4% IFN CMS1
  – 2.8% ALE vs 1.0% IFN CMS2
• Herpetic infections greatly decreased by prophylaxis
• No effect of lymphocyte count on infection risk
• Most infections in post-infusion 3 month epoch

Cohen et al and Supplement to Cohen et al Lancet 2012 pub online Nov 1 2012; Wray et al P01.172 AAN, 2013 – n=798, mean age 35 years, mean EDSS 2.7
Alemtuzumab Summary

- Infections are increased
  - Mostly mild to moderate
  - Few serious or life-threatening
- Prophylaxis of herpetic infections is warranted in the immediate post-infusion period

Daclizumab

- IL-2 receptor antagonist (Anti-CD25) immunomodulator not cytotoxic
- Expansion of regulatory NK cell population
- Infections not higher than placebo in renal transplant
- More severe infections (10% vs. 7%) after 12 months in cardiac transplant
- CMV not increased, less deaths from infection on daclizumab
  - IV daclizumab ZENAPAX PI
- Death due to corticosteroid-treatment related psoas abscess and sepsis in Phase II SELECT trial in MS
  - Gold et al Lancet 2013;281:2167-75
- In organ transplant daclizumab had fewer infections than antithymocyte globulin
  - Hao et al Transplant Proc 2012; 44:2955-60
Summary

• Serious common infections more of a problem than opportunistic infections in MS, RA
• Appropriate to be aware of infectious liabilities
• A 3 or 5-day rule of observation prior to routine relapse corticosteroid treatment
• A tool box for management of common infections is needed
• Risk mitigation with vaccination?