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. influenza*
  - 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
  - *Epidermaphyton, 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 $t_{1/2}$ 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 teri
  - 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 × 10⁹/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 Mysler 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%


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 anti-thymocyte 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?