Multiple Sclerosis Update 2006-7: Past, Present, and Future

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Orlando, FL
September 29, 2007
Disclosures

• Dr. Kantor serves as a consultant or speaker for Bayer, Biogen, Novartis, Pfizer, Questcor, Serono, and Teva Neurosciences.

• Dr. Kantor is a principal investigator of Novartis and Bayer studies.
St. Lidwina (1380-1433): Patron Saint of Ice Skating
Multiple Sclerosis (MS)

- Chronic autoimmune disease
- Central Nervous System (CNS)
  - SC > ON > BS
- Demyelination and axonal loss
- Genetically susceptible individual exposed to environmental trigger(s)
ACT
ACT study: combination

- RRMS, 313 patient on Avonex +
  - IV Solumedrol 1 g daily x 3d monthly
  - Oral methotrexate 20 mg weekly
  - Both
  - Neither

- No statistical differences between the groups
Rituximab
Rituximab (Rituxan)

- Chimeric murine/human monoclonal antibody
- Anti CD20
- IV
- Selective depletion of mature B cells
  - Preservation of B cell precursors and plasma cells
Open label Rituximab in RRMS

- Open label, no placebo, 26 patients
- Rituximab IV 1000 mg once then 2 weeks later and then repeated 6 months later
- Patients followed for 1 year
- Reduction in number of relapses
- >90% reduction in number of Gad+ lesions
Phase II Rituximab in RRMS

- **RRMS**
- **Randomized placebo-controlled**
  - 69 patients received Rituximab
  - 35 received placebo
- **Rituximab IV 1000 mg once then 2 weeks later**
- **Efficacy at 24 weeks (6 months):**
  - Proportion relapse free
    - 58% reduction ($p=0.0238$)
      - Placebo: 65.7%
      - Rituximab: 85.5%
  - 91% relative reduction in mean # of Gad+ lesions ($p<0.0001$)
Rituximab Safety

• Infusion related reactions, mostly on first infusion (fever, rigors, tachycardia), arrhythmias, mucocutaneous reactions
• PML in non-MS patients
  – Lymphoma patients
  – SLE patients
Rituximab in other demyelinating diseases

- Neuromyelitis Optica
- Primary Progressive MS

Questions

- How much will PML be a concern?
- Will antibodies to Rituximab limit its use?
- Will Ocrelizumab (fully humanized) be used or Rituximab?
Alemtuzumab
Alemtuzumab (Campath)

- Humanized monoclonal antibody
- Anti CD52
  - T cells, B cells, eosinophils and monocytes
- IV
- Rapid (2 days) depletion by complement
- T cells recover over 16 months
- B cells recover by 3 months and reach higher than baseline levels by 6 months
- 12-24 mg IV daily x 5 days to deplete secondary lymphoid organs
CD52 is strongly expressed on lymphocytes and not on blood stem cells.
90% reduction in relapse rate after Alemtuzumab.

Alemtuzumab treatments

Months before and after Alemtuzumab

Correct as of 31 December 2003
Phase II Campath in RRMS

- 2 doses of Campath vs. Rebif, 334 patients
- ≥75% Relapse Relative Risk Reduction (p<0.00328)
- ≥65% Relative Risk Reduction in clinically significant disability progression (p<0.01194)
Campath Safety

• **Humoral autoimmunity**
  – Graves disease
  – Goodpasture's syndrome
  – ITP
    • 3% incidence (6 patients)
    • 1 fatal
    • Onset up to 16 months from last infusion
  – Infusion reaction s
Questions

- Will ITP be a major concern?
- Is there a risk for PML?
- Should dosing be annual?
4-Aminopyrididine
4-Aminopyridine (Fampridine SR)

- Centrally acting potassium channel blocker
- Fampridine SR 10 mg PO BID
- **Responder criterion = a consistent improvement in walking speed, as measured with the Timed 25 Foot Walk**
  - 34.8% Fampridine SR
  - 8.3% Placebo
  - $p<0.0001$

- **The mean increase in walking speed over the treatment period from baseline:**
  - 25.2% in drug treated responders vs. 4.7% placebo
  - $P< 0.0001$
Pioglitazone
Pioglitazone (Actos)

- Peroxisome proliferator-activated receptor-gamma inhibitor
  - apoptosis in activated T-lymphocytes and exert anti-inflammatory effects in glial cells

- RRMS, 22 patients
  - Combination Avonex + Actos 30 mg PO
  - Combination Avonex + oral placebo

- No effect on relapses

- Improvement in Paced Auditory Serial Addition Task (PASAT)

- Possible benefit on segmented grey matter at 1 year
Minocycline
Minocycline + Copaxone

- RRMS, 44 patients
- Copaxone + Minocycline vs. Copaxone + placebo
- Primary outcome: total # of Gad+ lesions at months 8 and 9
- Baseline mean Gad+ lesions:
  - 7.62 in the GA + minocycline group
  - 2.43 in the GA + placebo group
- Trend to reduction in the mean total number of Gad+ lesions
  - 1.47 in the combined treatment group
  - 2.95 in the GA + placebo group
  - $p = 0.08$
Statins & Interferons
Statins: more complicated

- 29 RRMS patient stable on Rebif for 6 months
  - Atorvastatin 40 mg, 80 mg, or placebo
- 3 subjects withdrew prior to receiving Lipitor
- 2 subjects withdrew secondary to Lipitor A/E
- 1/9 Rebif + placebo patients worsened
- 10/15 Rebif + Lipitor patients worsened
- Statins may interfere with, not only the interferon gamma cascade, but interferon beta as well
Alternative Medicine
Ashwagandha (*Withania somnifera*)

- Ayurvedic (Indian) herbal medicine
- Trial for the treatment MS related fatigue
- Seeking IRB approval at UF & Shands Jacksonville
- MS patients, regardless of immunomodulatory Rx
- Aged 18-65
- EDSS \( \leq 6 \)
- *16 week prospective double-blind cross-over*
M*STAR

Multiple

Multiple Sclerosis Team

Approach Rule
MS Team

Patient

Friends/community
Significant other
Family
MS Community

Job
PCP
MS Nurse
MS Doctor, Nurse Practitioner, PA

MS Nurse Practitioner, PA
Patient’s Exam

The best teaching is that taught by the patient himself

- Sir William Osler 1903
Multiple Sclerosis Patient Network

Community

Principles

Patient Care

Education

Research
Where We Go From Here

- Oral medicines
- Combinations of medicines
- Higher dose medicines
Together, we can make …
M*STAR

Multiple
*

Sclerosis

Team

Approach

Reality

Patient
Thank You
For Your Attention

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