New estimate of MS prevalence in the US

- 2 private health insurance databases and 3 government insurance (Medicare, Medicaid, VA)
- 6.3% increase in lifetime prevalence 2010-2017
- The overall prevalence rate for the US for 2010 is 382.46 per 100,000 which corresponds to 899,624 people with MS, and was estimated at 947,484 in 2017.
- Female to male prevalence ratio is 2:82
New diagnostic criteria

• **2017 revisions to McDonald criteria**

Misdiagnosis
• NMOSD should be considered
• CSF should be considered in nonclassical presentation

Revisions
• 1) CSF counts toward DIT (2+ OCBs)
• 2) symptomatic lesions count toward DIS
• 3) cortical lesions count as well as juxtacortical lesions count
• 4) ON lesion on MRI is not counted toward DIS
• 5) provisional course (Lublin 2013) should be determined and then periodically evaluated

• PPMS criteria not changed, but can use symptomatic and nonsymptomatic lesions
Value of OCBs in patients meeting 2010 DIS criteria

- Catalonia cohort n=164 pts, 1995-2010
- 67% converted to CDMS within avg 7 years
- Including OCB into criteria increased the specificity (80 to 88%), but decreased the sensitivity (60s to 47%)
- Cutoff used was 2 or more bands.
- CSF testing was completed within 3 months of presentation.
- Only OCBs were included in this testing (not IgG index, presumably due to the fact that it varies with steroid treatment.)
CMSC consensus statement on gadolinium use

- Group consensus:
- GBCA remain essential in the diagnostic evaluation of a patient suspected of having MS to demonstrate inflammatory lesions.
- GBCA should be used judiciously, minimizing gadolinium exposure and dose when possible, with preference given to macrocyclic agents.
- Routine monitoring with GBCA may be useful in the following circumstances:
  - Selection of or obvious clinical activity for which confirmation may modify therapy
  - Confirmation of lack of disease activity
  - Facilitating selection of disease modifying therapies
Prognosis

EDSS course by outcome at 30 years

Of the 132 originally recruited, at 30 years: We were unable to trace 9; ~23% remained CIS; ~24% had an EDSS ≤3.5; ~20% had SPMS (all with an EDSS >3.5); and ~12% EDSS 10.
Neurofilament light (NfL) serum levels at CIS, and future outcomes
CSF soluble CD27 at CIS predicts conversion to MS.
High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (HALT-MS) is a phase II clinical trial of HDIT/HCT for patients with relapsing-remitting (RR) MS who experienced relapses with disability progression (Expanded Disability Status Scale [EDSS] 3.0–5.5) while on MS disease-modifying therapy.

- 24 patients
- Event-free survival was 69.2 %
- Progression-free survival, clinical relapse-free survival, and MRI activity-free survival were 91.3%(90%CI 74.7%–97.2%), 86.9%(90%CI 69.5%–94.7%), and 86.3% (90% CI 68.1%–94.5%), respectively.
- Improvements were noted in neurologic disability with a median change in EDSS of -0.5 (interquartile range -1.5 to 0.0; p=0.001) among participants who survived and completed the study.
5-year HALT-MS results
Long-term outcomes of AHSCT for MS

- 281 patients (218 progressive forms of MS)
  - 25 centers, 13 countries
- Median EDSS 6.5
- 8 deaths (2.8%) within 100 days, considered related to transplant
- 5-year outcomes
  - Overall survival 93%
    - Worse for higher EDSS, HR 2.03
  - Probability of progression-free survival 46%
    - Poor prognostic factors:
      - Progressive form of MS (HR 2.33)
      - More than 2 prior DMTs (HR 2.03)
      - Older age (HR 1.03)
Long-term outcomes of AHSCT for MS

Muraro et al. JAMA Neurology (2017) 459-469
Comparative Effectiveness of RTX and Other Initial Treatment Choices for Multiple Sclerosis

- 494 patients in 2 areas of Sweden
  - 215 (43%) injectable DMT
  - 86 (17.4%) DMF
  - 17 (3.4%) fingolimod
  - 50 (10.1%) natalizumab
  - 120 (24.3%) rituximab
- Comparison of discontinuation rates and reasons

Granqvist et al. JAMA Neurology 2018
Figure 2. Drug Survival and Reasons for Therapy Discontinuation for Treatment Groups

A Drug survival

Granqvist et al. JAMA Neurology 2018
Reasons for DMT discontinuation

Granqvist et al. JAMA Neurology 2018
Results Announced from Phase 2 Clinical Trial of Ibudilast Suggest Reduction of Brain Atrophy (Shrinkage) in People with Progressive MS

October 26, 2017

SUMMARY

› Top-line results were announced of a phase 2 clinical trial testing an oral therapy ibudilast (MN-166, MediciNova, Inc.) in people with progressive forms of MS.
› The results announced in a press release concluded that ibudilast was well tolerated and significantly slowed the rate of brain atrophy compared to placebo. Brain atrophy (shrinkage) has been linked to cognitive and physical disability in MS.
› The trial was conducted at the Cleveland Clinic and 27 other sites across the U.S., and involved 255 people with primary or secondary progressive MS.
› The study was principally funded by NeuroNEXT Network, a clinical trials initiative of the National Institutes of Health, with additional support by MediciNova, the company that supplied ibudilast. The National MS Society also provided funding support.
› Further details are scheduled to be presented Saturday, October 28th at the MSParis2017 – 7th Joint ECTRIMS-ACTRIMS Meeting.
› These phase 2 results may lead the way to the testing of ibudilast in larger phase 3 trial(s), which would be needed before the company could apply for marketing approval from the FDA, the European Medicines Agency or other regulatory agencies. Ibudilast was designated by the FDA as a “Fast Track Product” which could speed its future development as a possible treatment of progressive MS.

“These results sound like a very promising step toward a potential new therapy for people with progressive forms of MS, for whom there are few treatment options,” said Dr. Bruce Bebo, Executive Vice President, Research, National MS Society.

DETAILS

Background: Ibudilast (MN-166, MediciNova, Inc.) inhibits an enzyme called phosphodiesterase. While considered a “New Molecular Entity” in the United States and Europe, ibudilast is marketed in Japan and Korea to treat cerebrovascular disorders and asthma. It is also being investigated in the U.S. for its potential to treat ALS and drug addiction.
Lipoic acid in progressive MS

- 51 patients with SPMS and PPMS
- Single center (OHSU/VA Portland)
- Lipoic acid (1200 mg) vs placebo
- Primary outcome=annualized percent change in brain volume (PCBV)
  - -0.21% (LA) vs -0.65% (placebo)
- GI upset, and 1 case of renal failure and glomerulonephritis in LA group
Lipoic acid in progressive MS

Annualized percent change brain volume (PCBV) between LA and placebo cohorts using intention-to-treat analysis of 51 participants with secondary progressive MS (A). Two-year PCBV from study completers is shown and demonstrates significantly less PCBV in the LA cohort ($n = 22$, $-0.45\%$ [95\% CI $-0.78$ to $-0.13\%$, $p = 0.003$]) than controls ($n = 24$, $-1.31\%$ [95\% CI $-1.81$ to $-0.81\%$, $p = 0.001$], B). LA = Lipoic acid; SEE = standard errors of the coefficient estimate.
Siponimod for SPMS

- 1651 SPMS patients, EDSS 5.0-6.5, up to 3 years (event-driven)
- Avg time since conversion to SPMS 3.8 years; 64% had no relapses in prior 2 years; 56% needed walking assistance
- 2:1 oral siponimod:placebo
- Primary outcome=time to 3 month CDP
  - 26% siponimod vs 32% placebo reached this
    - 21% relative risk reduction
  - Lymphopenia, increased LFTs, bradycardia, macular edema, hypertension, VZV reactivation, convulsions more frequently with siponimod than placebo
Siponimod for SPMS
Clemastine for remyelination

- Single-center, 150-day, double-blind, randomized, placebo-controlled, crossover trial (ReBUILD) in patients with relapsing multiple sclerosis with chronic demyelinating optic neuropathy on stable immunomodulatory therapy
- Clemastine fumarate (5.36 mg PO bid) x 90 d, followed by placebo x 60 d vs PLC x 90 d followed by clemastine x 60 d
- N 50 pts
- Primary outcome: VEP latency delay
Figure 3: Association of clemastine fumarate treatment with performance on LCLA testing
Change is in number of letters identified correctly. Mean (SD) shown with both epochs combined. p=0.085, LCLA=low-contrast letter acuity.

Figure 2: Association of clemastine fumarate treatment with VEP latency delay in patients with chronic optic neuropathy
Change from baseline in latency by group and epoch (model-derived estimates of means are represented by dots with the SE from baseline represented by error bars at each relevant timepoint). Solid line is on-treatment and dashed line is on-placebo. Blue line is group 1, orange line is group 2. Blue shaded area is epoch 1 and orange shaded area is epoch 2. p value is for primary analysis including crossover (with assumption of carryover). The inset is the percentage of patients with more than 6 ms improvement in latency delay. VEP=visual-evoked potential. G1=group 1. G2=group 2. E1=first epoch. E2=second epoch. T=treatment period. P=placebo period.
Fingolimod for pediatric MS

- PARADIGMS study (presented at ECTRIMS)
- Ages 10-18, n=215
- 1:1 IFNb IM v. fingolimod, double-blind, double-dummy,
- Primary outcome: ARR
- Safety: more AE on IFNb, however more SAE on fingolimod (17% v 9%)

Chitnis, T. et al., ECTRIMS 2017
Fingolimod effect on ARR in peds MS

**Primary Endpoint: ARR up to Month 24**

Full analysis set (confirmed relapses)

- Fingolimod was superior to IFN β-1a IM in reducing ARR up to Month 24 in paediatric patients with MS

**FDA News Release**

**FDA expands approval of Gilenya to treat multiple sclerosis in pediatric patients**

*First drug approved to treat MS in ages 10 and older*

For Immediate Release

May 11, 2018

Chitnis, T. et al., ECTRIMS 2017
OCR and vaccination

Seroprotection to individual influenza strains

Seroprotection defined as a specific hemagglutination inhibition titer >40.
CI, confidence interval; DM, disease-modifying therapy; IFN, interferon; OCR, ocrelizumab.
Response (IgG) to tetanus toxoid-containing vaccine

Anti-tetanus titer

- Geometric mean titer (IgG IU/mL)
- Pre-vaccination: 1.68
- 4 weeks post-vaccination: 4.13
- 8 weeks post-vaccination: 3.74

Protective titer level:

Proportion of patients with positive tetanus response

- 4 weeks post-vaccination:
  - OCR (all): 24.2% (95% CI: 16.6, 36.0)
  - Control (IFN β or no DMT): 60.6%

- 8 weeks post-vaccination:
  - OCR (all): 23.9% (95% CI: 10.8, 50.5)
  - Control (IFN β or no DMT): 54.5%