Neuromyelitis Optica: Is There Treatment Equipoise?

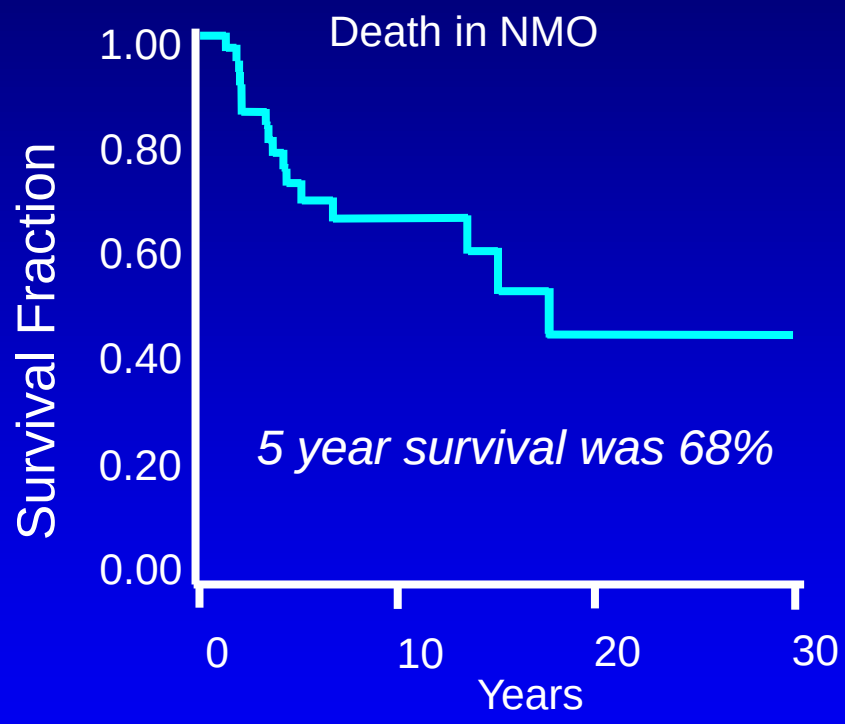
Bruce Cree, MD, PhD, MCR
Associate Professor of Clinical Neurology
Clinical Research Director
University of California San Francisco
Multiple Sclerosis Center

What is Neuromyelitis Optica?

- Syndrome of aggressive inflammatory demyelination afflicting the optic nerves and spinal cord a.k.a. Devic's disease
- Associated with infections and collagen vascular diseases but idiopathic form is considered a variant of central nervous system demyelinating disease (MS)
- Definitions vary but recent experience with modern case series indicate that NMO is characterized by:
  - Recurrent attacks of optic neuritis and acute transverse myelitis
  - Multisegmental spinal cord lesion ≥ 3 vertebral segments
  - Initial brain MRI is often (but not always) normal

NMO Relapses and Disability

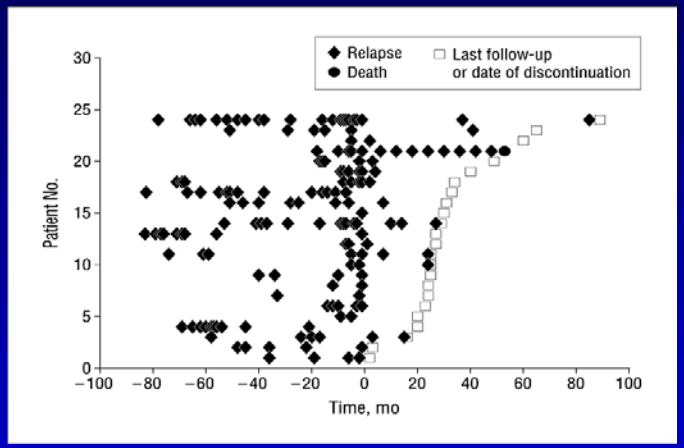
- Despite improvements in function with treatment from high dose corticosteroids and plasmapheresis many patients have residual neurological deficits
- In NMO, few patients experience secondary progressive disease[1]
- Therefore, disability and death are caused primarily by relapses[2]
- Management of NMO focuses on relapse prevention with goal of treatment a relapse free state



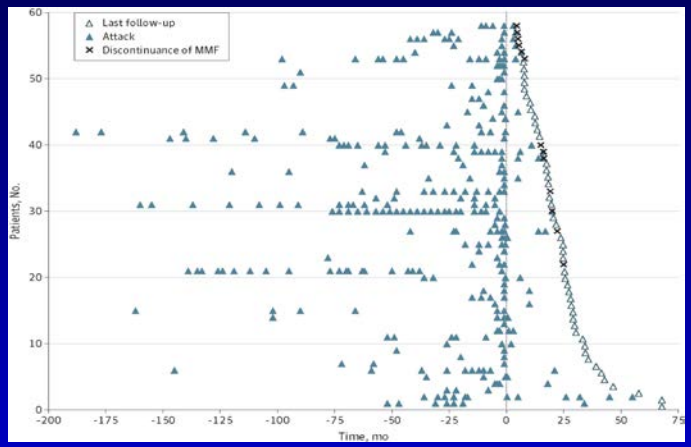
Respiratory failure from acute cervical myelitis occurred in 33% of relapsing NMO patients
93% of patients experiencing respiratory failure died

1. Wingerchuk D Neurology 2007;68:603-605. 2. Wingerchuk D. Neurology 1999; 53:1107-1114.

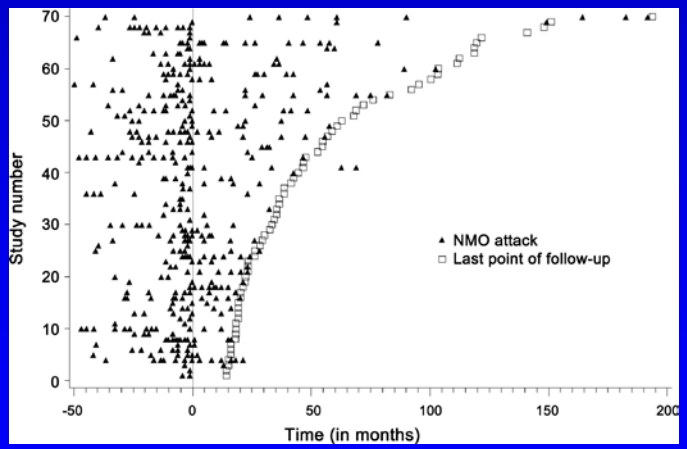
NMO Treatment Case Series



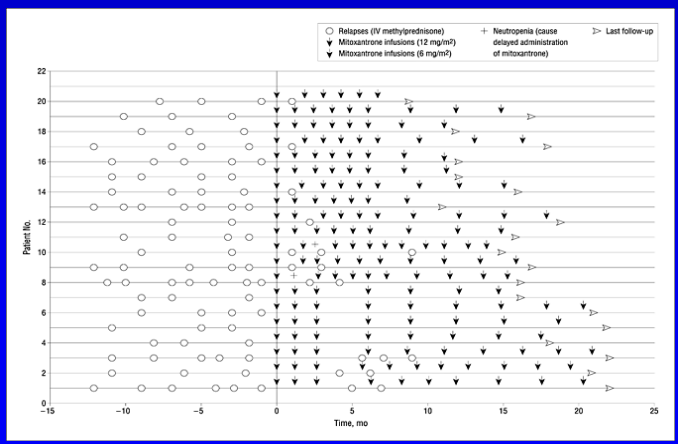
Rituximab



Mycophenolate Mofetil



Azathioprine



Mitoxantrone

Costanzi C. Neurology 2011;77:659-666 Jacobs A. Arch Neurol 2008;65:1443-8
Huh S-Y. et al. *Arch Neurol* 2014;*epub ahead of print* Kim S-H. et al. *Arch Neurol* 2010.

Are case series adequate for determining efficacy?

- A decline in relapse frequency could occur independently from treatment
  - Natural h/o NMO is for attacks to cluster, often around onset
  - “Regression to the mean” following treatment always causes over-estimation of treatment effect
- To make meaningful claims of efficacy a parallel group is needed, either alternate treatment or no treatment
- Treatment selection in all studies is influenced by known and unknown biases from both clinician and patient
- Matching can control for known confounders but unknown confounders can only be accounted for my randomization
- Data acquisition in the majority of case series was retrospective, unblinded and subject to bias
  - NB: eculizumab trial was prospective
- All case series in NMO have a relatively small sample size

Wingerchuk D, et al. Neurology 1999;53:1107

History repeats

- Some examples of observational studies in which randomized trials did not support accepted medical beliefs include:
  - Hormone replacement therapy in postmenopausal women[1]
  - Mycophenolate mofetil in myasthenia gravis[2]
  - Embryonic substantia nigra transplantation for Parkinson's disease[3]
  - Donepezil for memory impairment in MS[4]

1. Hulley S. Jama 1998;280:605-613. 2. Sanders DB. Neurology 2008;71:400-406.
3. Freed CR. N Engl J Med 2001;344:710-719. 4. Krupp L. Neurology. 2011;76:1500-7

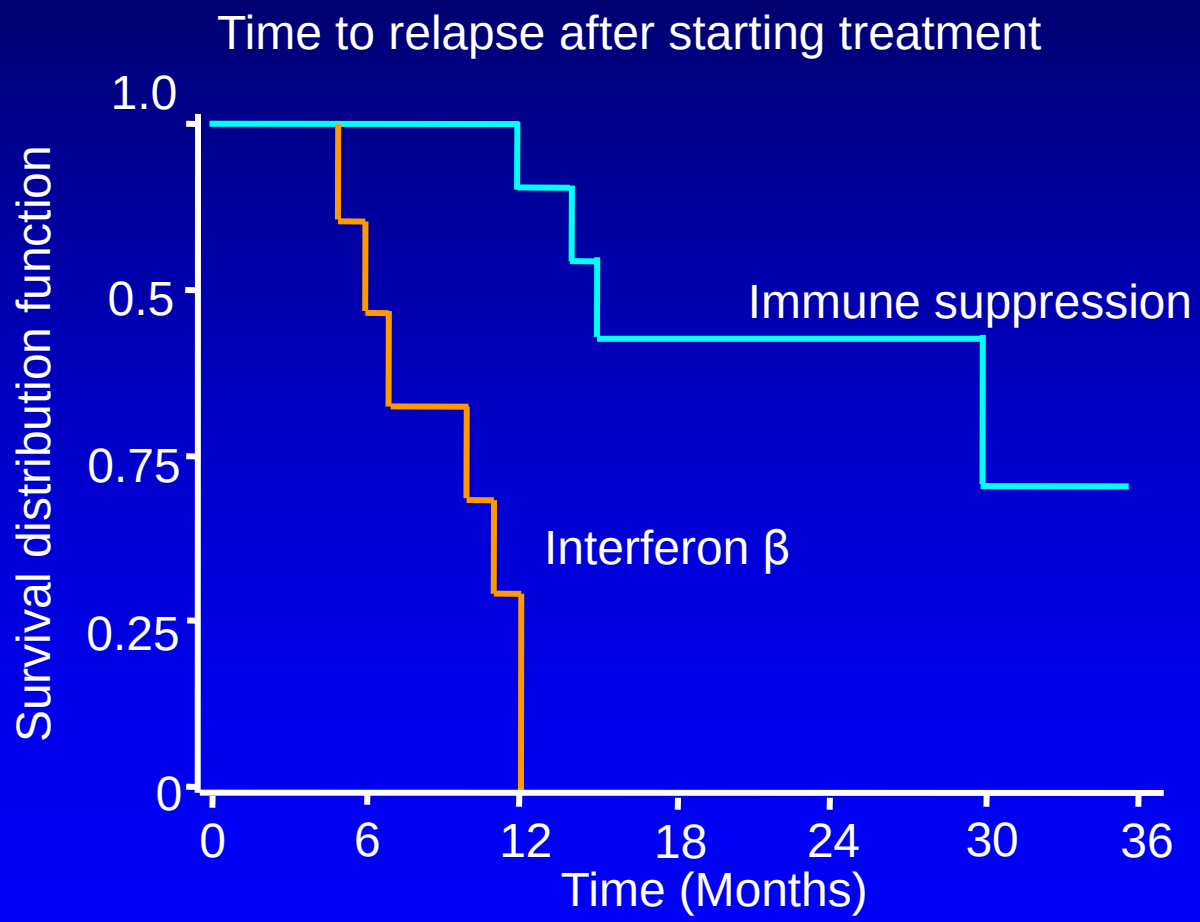
The case for equipoise in NMO treatment

- Case series provide suggestive evidence of efficacy
- Proof requires randomized controlled trials with validated endpoints
- What about using an active comparator?
- There are no proved treatments, therefore any comparisons made against a treatment that is actually harmful could result in assigning benefit to a treatment that had no effect and only appeared to be beneficial because the alternate treatment caused harm
  - Example: flecainide or encainide in the cardiac arrhythmia suppression trial (CAST)

Echt DS. N Engl J Med 1991;324:781-788.

Immune Suppression versus Interferon beta (IFN)

- Interferon β is a proved treatment for relapsing multiple sclerosis
- A retrospective study of 26 NMO patients comparing interferon β to broad spectrum immune suppressants in France suggested that immune suppression was superior to interferon[1]



Papeix C. Mult Scler 2007;13:256-259

A Cautionary Note About Interferon and NMO

- 56 Japanese patients with RRMS were treated with IFN β-1b
- 14 patients subsequently tested seropositive for anti-AQP4 antibody
- 7/14 anti-AQP4 seropositive patients (NMO and NMO spectrum disorder) had severe transverse myelitis relapses (EDSS ≥7) within 3 months of starting treatment
- Interferon β may even exacerbate NMO
- If so, then relapse rates reduction with immune suppression versus IFN reported in the Papeix study may be caused by harm from treatment with IFN β rather than benefit from immune suppression

1. Warabi Y. J Neurol Sci 2007;252:57–61 2. Shimizu J. Neurology 2010;75:1423-1427

The case for no treatment

- Placebo control can provide unequivocal evidence of proof of efficacy
- The number of subjects participating in a placebo controlled study will be smaller than for an active comparator trial
- The number of events needed to prove efficacy will also be smaller for a placebo controlled trial
  - All trials require events: someone is going to get hurt
- Not all placebo controlled trials are unpalatable
- The details of the study design are all important for assessing individual participant risk
  - Unequal allocation, time to first event, rescue therapy, limited duration of placebo exposure and availability of open-label active treatment extension study until approval may make participation attractive for some patients
- Use of placebo reduces potential treatment related harm due to unexpected off-target effects

Placebo-controlled trials and the logic of clinical purpose

- When may the control be a placebo?
  - no standard therapy
  - standard therapy no better than placebo
  - doubt regarding the net therapeutic advantage of standard therapy, e.g. uneven risk:benefit
  - standard treatment is unavailable (cost, supply).
  - standard treatment is placebo

Freedman B. IRB. 1990;12:1-6.

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  - standard treatment is placebo- not the case for NMO

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