

# Transverse Myelitis - The MS Connection

Joanne Lynn MD

## Why look at MS?

“There is very little information about the immunologic aspects of ATM. Although this neglect may reflect the rarity of the disease, it more likely reflects a common belief, rightly or wrongly, that ATM is part of a spectrum of CNS demyelination, the cause of which can be unraveled through study of other more common diseases, such as MS.” - Dr. Lael Stone, 1997

# Why discuss MS?

- 1) TM falls within the clinical category of neuroimmunology, so the specialists most interested in investigation will be those who specialize in MS.
- 2) Possible similarities of etiology, pathophysiology and clinical features between TM and MS
- 3) TM may be a first attack of MS

# TM - The MS Connection

“MS is almost certainly not a single disease but a series of IIDD [idiopathic inflammatory demyelinating diseases].”

- Syndromes such as TM may be viewed as a monosymptomatic IIDD and have a poorly defined relationship to MS

# TM and MS - Relative Incidence

- The incidence of MS varies with geography and, in particular, latitude. In the US, the incidence varies from 10 per 100,000 to above 100 per 100,000.
- There are fewer epidemiologic studies of TM but estimates are 1 to 5 per million.

# TM as first attack of MS

- 40 to 50% of first attacks of MS are monosymptomatic
- Spinal cord attacks are common in MS but the syndrome of complete acute TM is unusual as first attack of MS
- Only 0.7% of a Canadian MS population had acute TM as their first attack (Paty and Ebers).

# Optic Neuritis - Monosymptomatic MS

- Acute inflammation/demyelination of optic nerve
- Varies from mild visual blurring or decreased color vision to total blindness
- Prognosis is very good -recovery within weeks to months
- High dose IV steroids hasten recovery

# Development of MS in ON: Studies of Cerebral MRI

<u>Study</u>	<u>Abnml Brain MRI</u>		<u>Nml MRI</u>	
Jacobs	6/23	26%	3/25	12%
Martinelli	7/23	33%	0/16	0%
Frederiksen	7/30	23%	0/20	0%
Miller	12/34	35%	0/19	0%
Morrissey	23/28	82%	1/16	6%
Beck	55/150	37%	19/202	9%

# TM: MS Prognostic Factors

- Complete vs partial myelopathy
- Symmetry vs asymmetry of motor and sensory abnormalities
- Cerebrospinal fluid abnormalities
- Features of magnetic resonance imaging of brain and spinal cord

# TM: MS Prognosticators

## Complete vs Incomplete

- Complete transverse myelopathy means total loss of movement and sensation below the level of the lesion
- Lipton and Teasdale (1973) reported that only 2.9% of patients with complete ATM converted to MS in period of 5 to 42 years
- Ford (1992): 12 of 15 (80%) of patients with partial TM converted in 3.2 years

# TM: MS Prognosticators

## *Symmetry vs Asymmetry*

- Scott (1998) followed patients with acute TM and noted that 15/16 patients with acute myelopathic MS had asymmetric findings while 20/20 acute TM patients exhibited symmetric motor loss and 19/20 symmetric sensory loss
- They concluded that symmetry vs asymmetry was a more important factor than complete vs partial

# TM: MS Prognosticators

## Cerebrospinal Fluid

- In one study of 183 patients with monosymptomatic suspected MS:  
24 % with CSF OCBs versus only 9% without OCBs developed definite MS
- However, patients with monosymptomatic MS without CSF OCBs have been reported to develop MS so their absence does not rule out subsequent development of MS

# TM: MS Prognosticators

## Spinal MRI

- No specific findings that distinguish MS from acute TM
- Swelling of the cord is more common in acute TM but may be seen in MS
- Multifocal lesions are more common in MS compared with acute TM

# Development of MS in TM: Studies of Cerebral MRI

Patients with Monosymptomatic TM  
converting to MS

<u>Study</u>	<u>Abnml Brain MRI</u>	<u>Nml MRI</u>
Ford	12/15 80%	1/3 33%
Morrisey	10/17 59%	1/11 9%

# Cerebral MRI findings strongly suggestive of MS - UBC criteria

- Four white matter lesions
- Three white matter lesions, one of which is periventricular
- Diameter of all lesions  $> 3$  mm and predominantly in the white matter

## Other Cerebral MRI findings that add specificity for MS

- Diameter  $> 6$  mm
- Ovoid shape of long axis of lesion usually 90 degrees to the plane of the lateral ventricle
- White matter lesions in the brainstem
- Lesions along the corpus callosum
- An open ring appearance on enhanced MRI

*Controlled High-Risk  
Avonex Multiple  
Sclerosis Prevention  
Study*

*a.k.a. CHAMPS*

Intramuscular Interferon Beta-1a  
Therapy Initiated during a First  
Demyelinating Event in Multiple  
Sclerosis

Jacobs LD et al and the CHAMPS Study  
Group. NEJM 2000;343:898-904

# *CHAMPS*

## *Specific Aims:*

*In patients with monosymptomatic:*

- 1. Optic neuritis*
- 2. Brainstem / cerebellar or*
- 3. Spinal cord*

*AND*

*At least 2 T2 MRI lesions > 3 mm with at least 1 ovoid or periventricular*

*Does Avonex significantly delay the time to a second clinical attack?*

# *CHAMPS*

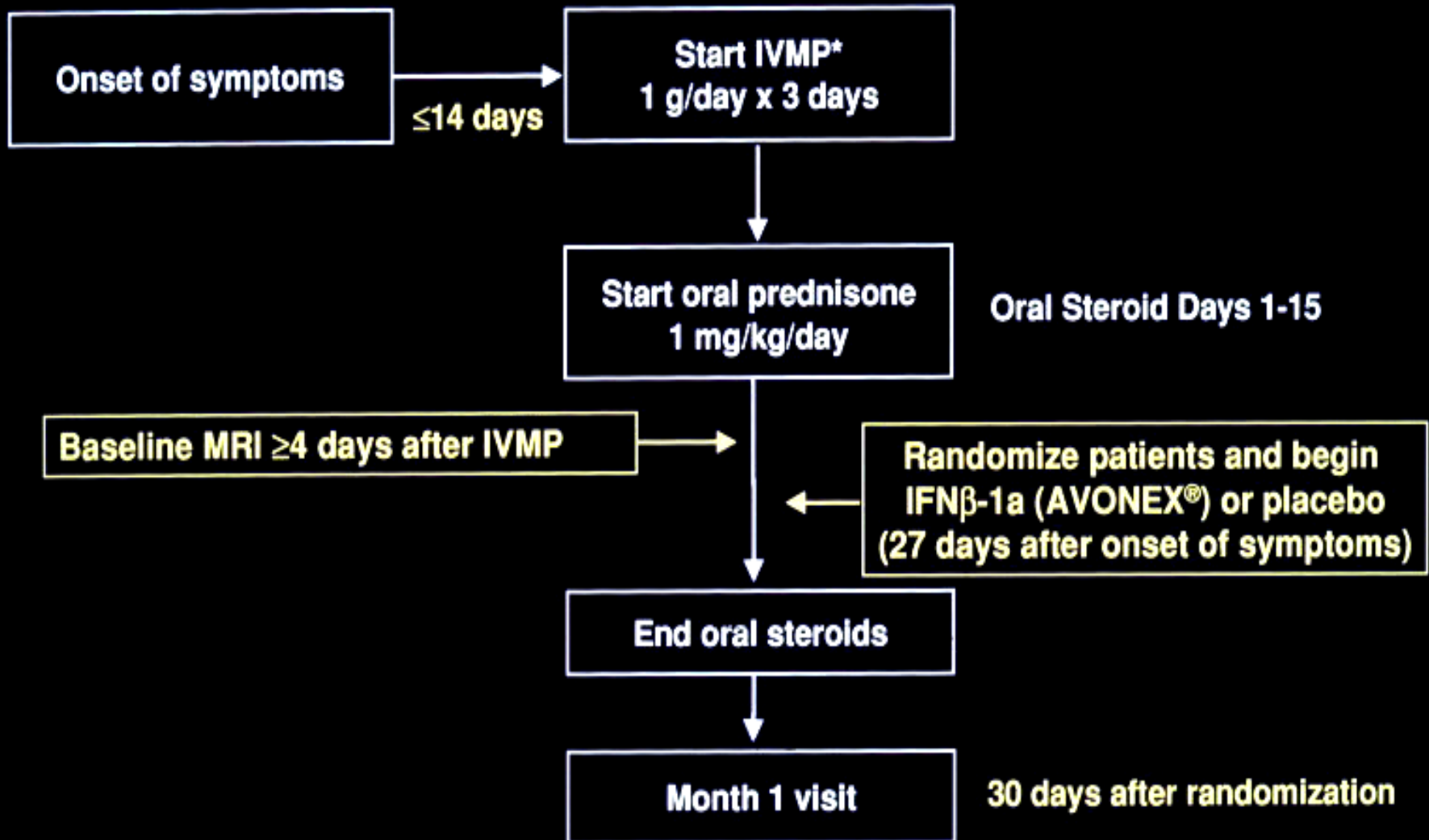
## *Methods:*

- *383 patients ( incidence study)*
- *50 Centers in U.S and Canada*
- *A priori termination:  $p < .029$*

**Qualifying:**  
**About 12 total lesions**



# Conduct of Trial: CHAMPS

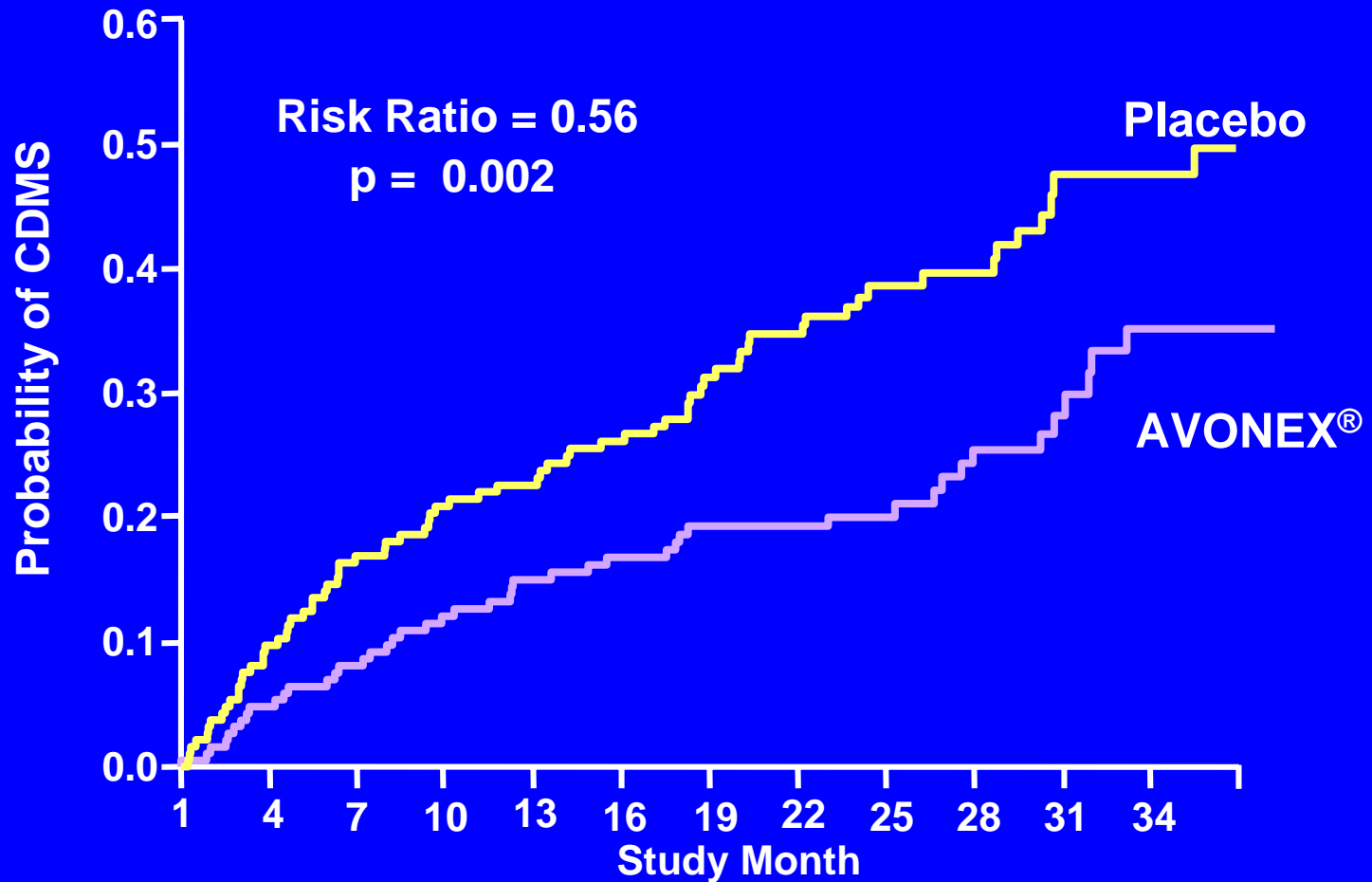


\*IVMP = intravenous methylprednisolone.

# *CHAMPS BASELINE*

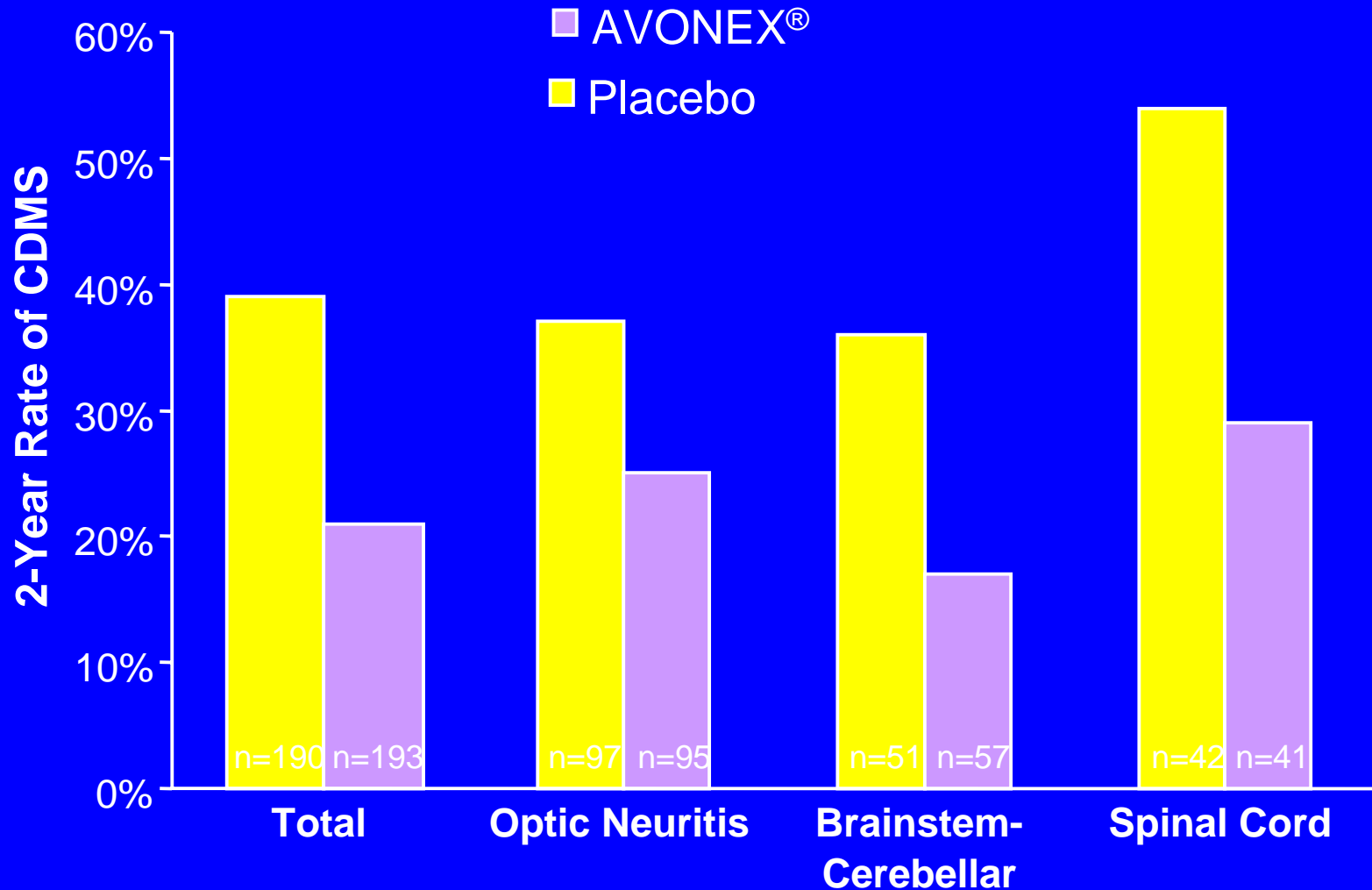
<i>Syndrome</i>	<i>%</i>
• <i>Optic Neuritis</i>	<i>52%</i>
• <i>Brainstem / Cerebellum</i>	<i>27%</i>
• <i>Spinal cord</i>	<i>21%</i>

# IFN $\beta$ -1a (AVONEX<sup>®</sup>) Reduced CDMS by 44%



	1	4	7	10	13	16	19	22	25	28	31	34
AVONEX <sup>®</sup>	193	177	164	151	143	139	112	112	73	69	41	36
Placebo	190	165	146	139	131	124	98	90	58	54	26	25

# IFNbeta-1a Reduced the Rate of CDMS in All Subgroups



# Relative Risk of Clinically Definite MS (CDMS)

Presenting Syndrome	AVONEX®		Placebo		Relative Risk†	p Value
	n	% CDMS*	n	% CDMS*		
<b>Optic Neuritis</b>	95	25%	97	37%	<b>0.58</b>	<b>0.05</b>
<b>Brainstem-Cerebellar</b>	57	17%	51	36%	<b>0.40</b>	<b>0.03</b>
<b>Spinal Cord</b>	41	29%	42	54%	<b>0.30</b>	<b>0.01</b>

\*Kaplan-Meier estimates. †From proportional hazards model; adjusted model includes age, log T2 lesion volume, and presence of ≥1 gadolinium-enhanced lesion.

$$\text{group RR} = \frac{\text{Cumulative probability of CDMS in AVONEX®}}{\text{Cumulative probability of CDMS in Placebo group}}$$

# CHAMPS MRI Summary

- AVONEX<sup>®</sup> had significant beneficial effects in Optic Neuritis and Brainstem-Cerebellar subgroups on the following MRI measures at Month 18:
  - T2 lesion volume (p=0.002 and p=0.02)
  - Number of new or enlarging T2 lesions (p=0.004 and p=0.001)
  - Percentage of patients with Gd-enhancing lesions (p=0.001 and p=0.008)

# CHAMPS MRI Summary (*cont*)

In the Spinal Cord Syndrome subgroup:

- Differences were not significant; however, the AVONEX<sup>®</sup> group showed favorable trends for all MRI outcomes
- Lack of significant effects may be due to
  - The low number of patients in this subgroup
  - Active placebo patients reached CDMS early, and were not studied by MRI by study design

# CHAMPS Conclusions

- Supports the recommendation to obtain a cranial MRI scan in people with TM to assess risk of subsequent MS
- Supports early intervention in people with TM and MRI findings that suggest high risk for the future development of MS.