Endpoints in a treatment trial in NMO: Clinician's view

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“The greatest challenge to any thinker is stating the problem in a way that will allow a solution”

Bertrand Russell

Much of this presentation is moot as we have 2 trials recruiting and lengthy discussions preceded those

Plan of presentation

- Primary and secondary endpoints
- Definitions of endpoints
- Tools/instruments
- Surrogate markers
- Precision and power in trials of rare disorders
- Quality of life
- Patient reported outcomes

Possible endpoints in an NMO treatment trial ?

- What are the most important, measurable, biological events for a patient with NMO that we are trying to reduce /modify with a drug?

- Relapse
- Disability

- Can we replace these with non clinical/ surrogate endpoints ?

Is that it ?
What about all those we use in MS ?

Relapse related:

- Time to first/second Relapse
- Relapse Rates(ARR)
- Relapse duration severity by Neurologic Rating Scale
- Relapse free proportion

Disability related:

- Sustained
- EDSS change months- years
- Ambulation index
- Arm function
- MSFC

Surrogate:

- MRI related
  - lesion load
  - new T2 lesions
  - hypo intense lesions
  - enhancing lesions
  - lesion volume
  - brain volume changes (atrophy)

Outcome measures in RRMS Lavery 2014 MS International

What is used in spinal cord injury ?

- Traumatic SCI typically has no relapses
- Endpoints are disability measures
  - The ASIA scale (A-E)
  - American spinal injuries association scale
- 2 point improvement in ASIA is the primary endpoint in UK study (STRIVE) in acute transverse myelitis
- Validated
- But cannot measure non spinal cord dysfunction
- Surrogate electrophysiological endpoints in SCI (SSEP) not correlated to clinical improvement

Steeves etal Guidelines for conduct of RCT in SCI Nature 2007

Relapse VS Disability which should be the primary endpoint?

- Disability (of various types)
  - but disability in NMO is a direct consequence of the relapse
  - spontaneous gradual progression of disability like in MS is very rare in NMO
  - we want to avoid disability in patients in trials
- So relapses are the most appropriate choice

Attack related disability

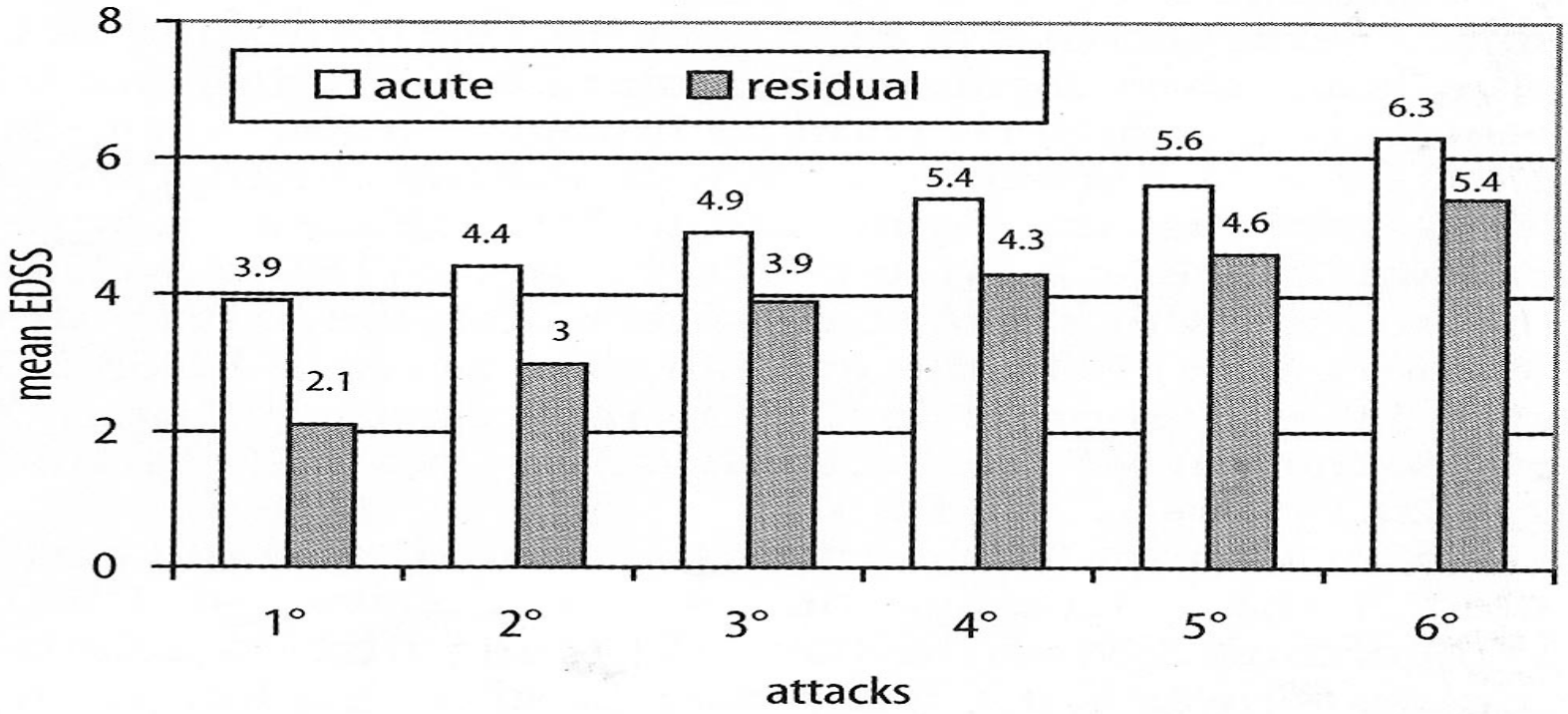

Fig. 2 Mean EDSS score during and after the acute phase of the first six attacks

Ghezzi A et al. J Neurol 2004: 251; 47-52

What are the characteristics of a relapse that needs consideration?

- Definition of relapse
  - Strict protocol definitions or investigator discretion?
- What measure of relapse rate reduction ?
  - Time to first relapse or annualised relapse rates?
- Severity of relapse
  - Are all relapses equal ?
- Types of relapse
  - myelitis, optic neuritis, brainstem events
  - Are they all equal?

Definition of relapse

- Clinical practice:
  - new onset neurologic deficit or worsening of existing one with an objective change (no specific degree for at least 24 hours , related to NMO on a background of stability of >1 month
- Practicable in clinical trials too
  - allows for clinician's judgment (**investigator defined**)
- But
  - can be biased by experience, knowledge and other subjective elements

Allow only protocol defined relapses ?

- Adds further objectivity/quality in addition to above :
  - Specific change in EDSS e.g. 1 point
  - Or on the FSS of EDSS e.g. 2 points
- Should suffice for vast majority of relapses
- But occasionally may not capture a true relapse

Example 1

- Clinical trial of drug X
- Patient presents with severe neuropathic pain and severe itch in leg
- MRI shows unambiguous new inflammatory lesion
- It's a relapse in clinical practice; but protocol defined relapses does not include pain

Example 2

- 3 week history of intractable nausea and vomiting (not part of any FSS)
- Exam normal
- MRI abnormal with area postrema lesion
- Relapse in practice but not in trial

Is the solution to think of a variety of such scenarios and make objective definitions with the addition of MRI criteria ?

Time to first relapse or annualised relapse rates?

Time to first relapse (TFR)	Annualised relapse rates (ARR)
Pros Patients can exit study if treatment ineffective Reduces disability accumulation	**Pros** Standard familiar measure
Recruitment better	Long term effects identifiable
Shorter studies	
Cons :	**Cons**
long term effects not demonstrable	Unless all patients stay in for a minimum period (denominator), skewed ARR
Slow acting drugs may not have chance to become effective ; need time to second relapse or such	
1 patient contributes only one event	

Personal view: TFR is the most appropriate measure to limit exposure to an ineffective drug in a disabling disease

Grading severity of a relapse

- Attack severity can vary
  - Patient and physician factors
  - Treatment factors
- Should all attacks be considered the same ?
- What scales to assess severity
  - EDSS functional scale
  - Optic spinal impairment scale
  - ASIA

Can we develop an attack severity score e.g no of relapses X severity?

- In a study of drug X
- Relapse severity scale of grades 1-5 ;
  - placebo arm has 25 relapses
  - 1 (n=5), 2 (n=5), 3(n=5), 2(5), 4(n=5), 1(n=5)
  - total score = 65
  - active arm 25 relapses
  - 1(n=10), 2(n=5), 3(n=3), 4(n=2)
  - total score = 34
- Clinically meaningful difference if scores used
- But no difference if relapses are merely counted

Secondary end points

- Disability
- The main categories:
  - Spinal cord/ brainstem related
    - motor (weakness, spasticity)
    - sensory (numbness and pain)
    - bladder , bowel, sexual function
  - Vision
    - Acuity
    - Field

- How do we measure these ?

Multi-system Scales

- Is EDSS suitable ? (0-10)
  - Familiar, well validated in MS world
  - But cerebellar, cerebral FS not really applicable
    - Cognitive and cerebellar dysfunction limited in NMO
  - The other FSS are valuable (brainstem, pyramidal, sensory, bladder bowel, visual)

Multiple Sclerosis Functional Composite (MSFC)

- Composed of
  - Ambulation - Timed 25 ft. walk in seconds
  - Upper extremity function- 9 holed peg test in seconds
  - Cognition - Paced auditory serial addition test (no of correct responses out of 60)
  - Z score
- Potential Problems in NMO :
  - Cognitive element little value
  - spinal cord function poorly assessed

Cutter et al 1999

Optic Spinal Impairment Scale

- Modified from EDSS
- No formal psychometrics
- Not widely used
- Higher sum score- worse disability

Wingerchuk 1999

***Table 1** Quantification of optic nerve and spinal cord impairment*

Function	Score	Description
Visual acuity (V_A)	0	Normal
	1	Scotoma but V_A (corrected) better than 20/30
	2	V_A 20/30–20/59
	3	V_A 20/60–20/199
	4	V_A 20/200–20/800
	5	Count fingers only
	6	Light perception only
	7	No light perception
	8	Unknown
Motor function	0	Normal
	1	Abnormal signs (hyperreflexia, Babinski sign) without weakness
	2	Mild weakness (Medical Research Council grade 5− or 4+) in 1 or more limbs
	3	Moderate weakness (grade 3 or 4) in 1 or more limbs
	4	Severe weakness (grade 2) in 1 or more limbs
	5	Some plegic (grade 0 or 1) muscles in 1 or more limbs
	6	Plegia (grade 0 or 1) of all muscles in 1 or more limbs
	7	Unknown
Sensory function	0	Normal
	1	Mild decrease in vibration
	2	Mild decrease in pinprick/temperature/proprioception or moderate decrease in vibration
	3	Moderate decrease in touch/pinprick/proprioception or essentially lost vibration sense
	4	Loss of all sensory modalities
	5	Unknown
Sphincter function	0	Normal
	1	Mild urinary urgency or hesitancy, constipation
	2	Moderate urinary urgency, hesitancy, or retention of bladder or bowel, infrequent urinary incontinence (less than once per week)
	3	Frequent incontinence or retention requiring intermittent bladder catheterization or aggressive (manual) bowel assistance
	4	Indwelling urinary catheter or absence of sphincter control
	5	Unknown

System specific scales

- Spinal cord specific
  - ASIA scale
  - Spinal cord injury, bladder bowel data sets
- Vision specific scales
  - Numerous but not related to ON

Table I. Summary of vision-specific instruments

Questionnaire	No. of items	Eye condition	Subscales	Item pool development	Psychometrics	Mode of administration
Activities of Daily Vision Scale (ADVS)[9,10,14]	20	Cataract, age-related macular degeneration	Night driving, day driving, distance vision, near vision, glare vision, overall score	CB	IC, TRR, CV, DV, R	Interviewer
American Society of Cataract and Refractive Surgery–Cataract Data Collection Form (ASCRS-ACDCF)[15]	31	Cataract	Mean functional impairment score	NR	NR	Self
Cataract Symptom Scale (CSS)[16]	15	Cataract	Total score	PB	IC, TRR, CV	Interviewer
Catquest[17-20]	37	Cataract	Disability/daily activities, cataract symptoms, activity, driving, employment, global health rating, total score	PB, CB, LB	IC, TRR, CV, DV, R	Self
Daily Living Tasks Dependent Upon Vision (DLTV)[21,22]	22	Cataract, age-related macular degeneration	Total score	PB, CB	IC, CV, DV	Interviewer
Quality of Life in Patients with Graves' Ophthalmopathy (GO-QOL)[23]	16	Graves' ophthalmopathy	Visual functioning, appearance	PB, CB, IB	IC, CV	Self
Houston Vision Assessment Test (HVAT)[24]	11	Cataract	Visual disability, non-visual physical disabilities, total score	PB	IC, CV	Interviewer
Impact of Vision Impairment (IVI)[25,26]	32	Cataract, glaucoma, age-related macular degeneration, diabetic retinopathy	Work and leisure, household and personal care, mobility, consumer and social interaction, emotional reaction to vision loss, total score	PB, IB	IC, TRR, CV	Self and interviewer
Madurai Intraocular Lens Study (MIOLS) – Health-Related Quality of Life (HR-QOL) Questionnaire[27]	12	Cataract	Self-care, mobility, social, mental, total score	PB, CB, IB	IC, TRR, CV, R	Interviewer
Madurai Intraocular Lens Study (MIOLS)-Visual Functioning (VF) Questionnaire[27]	13	Cataract	General, visual perception, peripheral vision, sensory adaptation, depth perception, total score	PB, CB, IB	IC, TRR, CV, R	Interviewer
Miedziak's instrument[28]	54	Stargardt's macular dystrophy	Total score	PB, IB	NR	Self
Measure of Outcome in Ocular Disease (MOOD)[29]	21	Ocular melanoma	Vision, impact, total score	PB	IC, TRR, CV	Self

Aspects of disability not measured conventionally

Pain in neuromyelitis optica and its effect on quality of life

A cross-sectional study

Y. Kanamori, PhD
I. Nakashima, MD, PhD
Y. Takai, MD
S. Nishiyama, MD

ABSTRACT

Objective: To assess the features of pain and its impact on the health-related quality of life (HRQOL) in neuromyelitis optica (NMO).

Association of Neuromyelitis Optica With Severe and Intractable Pain

Peiqing Qian, MD; Samantha Lancia, MS; Enrique Alvarez, MD, PhD; Eric C. Klawiter, MD; Anne H. Cross, MD; Robert T. Naismith, MD

Short Report

MULTIPLE SCLEROSIS JOURNAL | MSJ

Neuropathic pain in neuromyelitis optica affects activities of daily living and quality of life

Multiple Sclerosis Journal
1–4

DOI: 10.1177/1352458514522103
msj.sagepub.com
SAGE

Sizheng Zhao, Kerry Mutch, Liene Elsone, Turo Nurmikko, and Anu Jacob

:29

Surrogate Markers

- AQP4-IgG:
  - Titers do not correlate with disease severity or relapse in predictable universal manner across patients

- MRI :
  - unvalidated and often no clinical correlates

Should we reduce the precision and power of trials in rare diseases?

- Conventionally
  - 5% type 1 error rate (chance of false + ve result)
  - 10% type 2 error rate (10 % chance of false negative result) i.e. 90% power
- High precision and power need larger patient numbers and longer trials: Are there enough patients?
- Personal view:
  - keep type one error rate unchanged
  - but 80% power is a justifiable compromise

QOL in NMO

- We know QOL poorer in NMO
- But no specific NMO-specific QOL measure
- Use standard measures:
  - SF36
  - EQ5D
- Spinal cord specific measures
  - Spinal cord injuries quality of life
- Vision
  - LVQOL(low vision quality of life)

Patient reported outcome measures

- None in NMO
- But we do know what are the main determinants of QOL

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RESEARCH PAPER

Life on hold: the experience of living with neuromyelitis optica

Kerry Mutch[1], Abigail Methley[2], Phil Moore[3], and Anu Jacob[1]

Mutch et al 2013

Table 2. Themes and subthemes of results.

Themes	Subthemes
Diagnosis and treatment	• Initial symptoms • Getting a diagnosis • Relapse recovery • Treatment and medication side effects • Fear of future relapse
Impact of symptoms on everyday life	• Visual loss • Sensory loss • Continence • Fatigue
Adjustment	• Coping • Frustrations • Life on hold • Mood • Finances
Identity	• Independence • Interests • Image
Support	• Family • Pets • Close friends • Informal societies

Summary

- Primary outcome: time to first relapse
- Disability – no good scale
  - for now EDSS and its FSS
  - Can borrow from SCI : ASIA, SCI of bladder bowel function
  - OSIS
- Pain scales need to be considered
- Specific QOL scales need to be developed
- Health economics a necessary requirement
- PROMS – need to be developed
- Care-giver burden
- Pediatric versions of relevant scales

Thank you !