4th MENACTRIMS CONGRESS

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Dubai, United Arab Emirates

Hosted by

MENACTRIMS
Middle East North Africa Committee for Treatment and Research in Multiple Sclerosis

In collaboration with

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EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

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PALMS

NMOSD therapy Updates

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Consultant Neuroimmunology and Multiple sclerosis
Prince Sultan Medical Military City
Riyadh, KSA

DISCLOSURE

Relevant Financial Relationship(s)

None

Off-label therapy discussion

Methylprednisolone, plasma exchange,azathioprine, mycophenolate mofetil, mitoxantrone, rituximab, intravenous immune globulin, cyclophosphamide, and other immunological therapies for treatment of NMOSD

Agenda

- Therapy
  - Acute attack
  - Prevention of attacks
  - New agents in clinical trials
  - DMDs to avoid
- Pregnancy recommendation
- MOG-related disease
- Symptomatic treatment

Immunology of NMO

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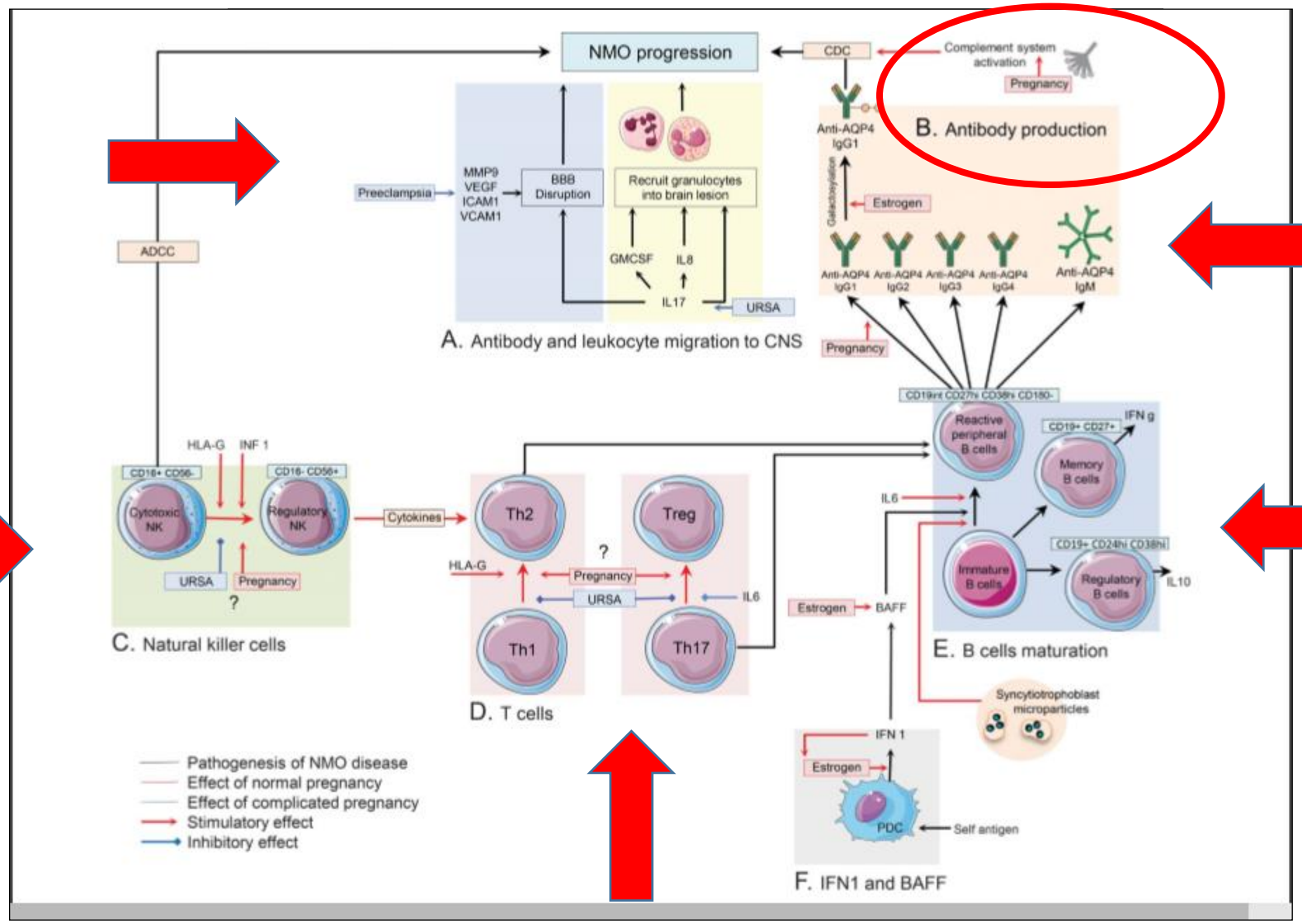


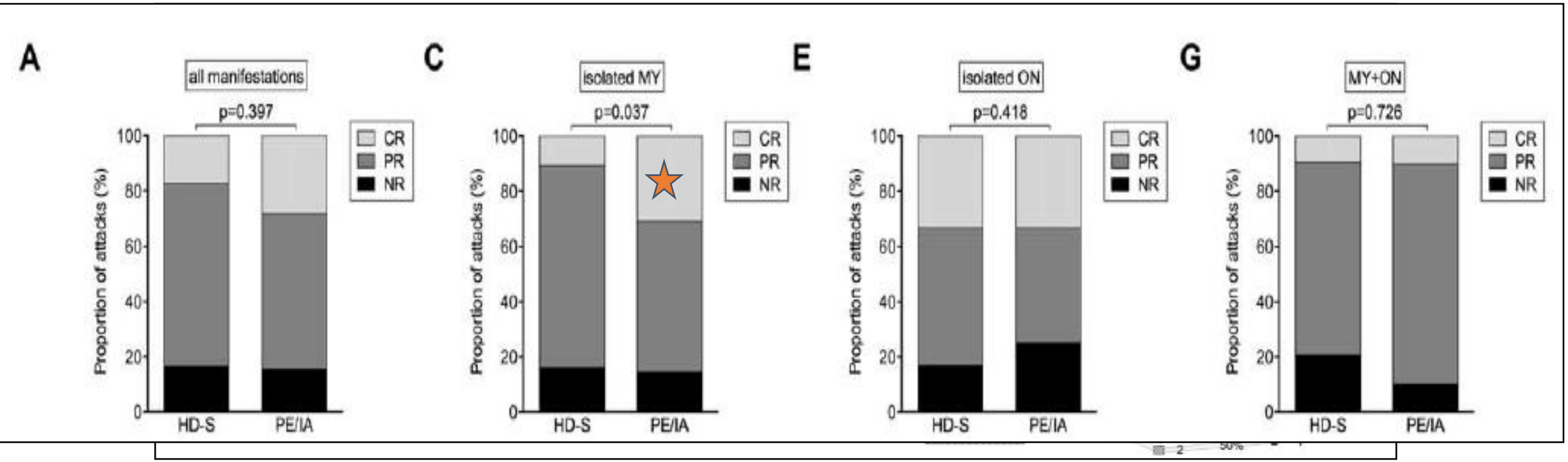
Davoudi et al 2016

Acute attack treatment

- Intravenous methylprednisolone
  - 1g for 5 days
  - Second course can be considered if PLEX is contraindicated
  - Gradual tapering off over a 6–12 month period.

- PLEX
  - 5–7 exchanges every other day
  - Considered as a first measure
    - *Severe attack*
    - *Refractory or known to be resistant to IVMP*

- IVIG
  - Very limited effect *(Jacob et al, 2012)*



Kleiter et, Annals of Neurology2016

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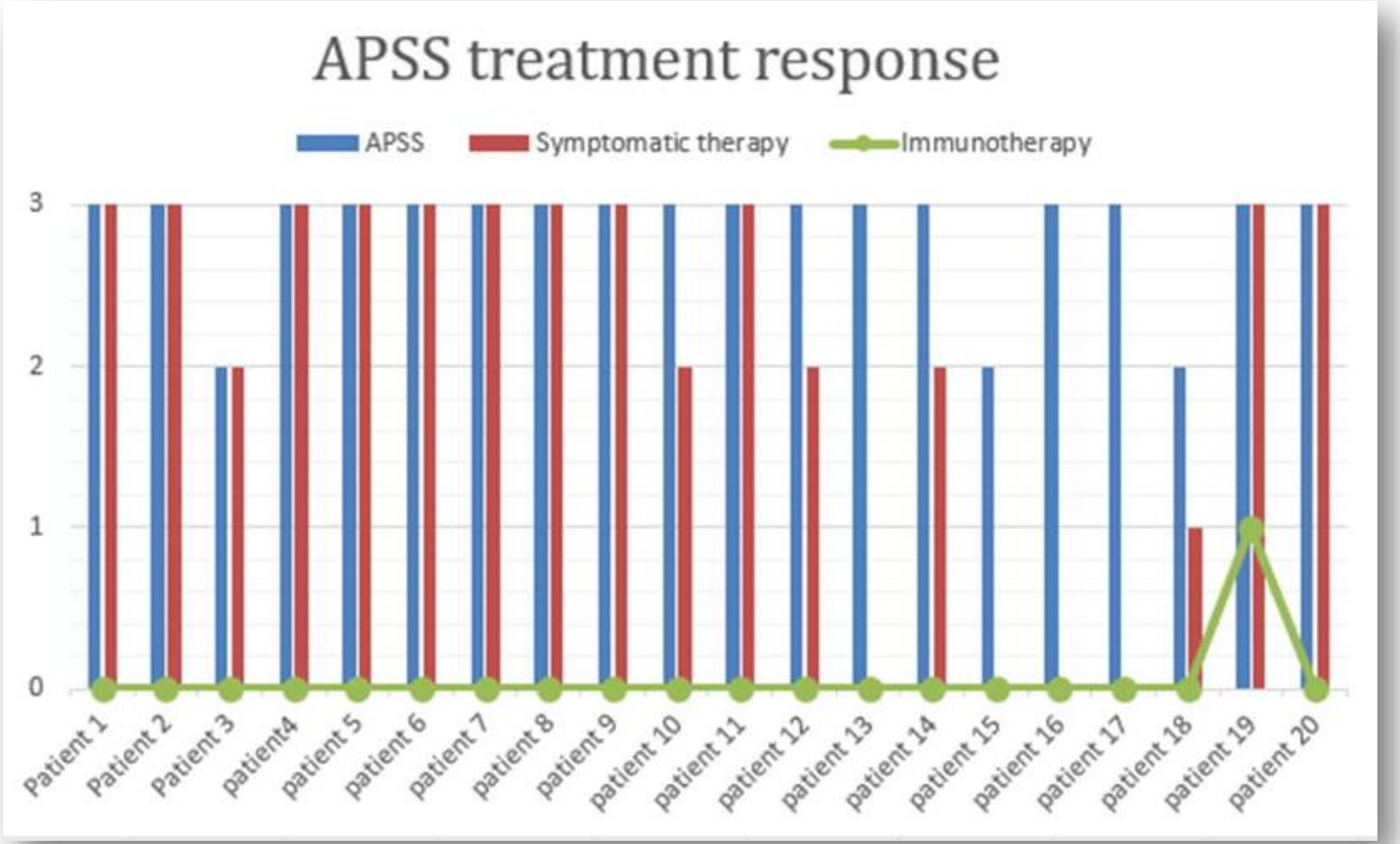

Shosha et al, Neurology 2018

Other - potential adjunctive acute therapies

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- Cell-depleting therapies
  - Rituximab (*Kimbrough et al, 2012)*
  - Cyclophosphamide *(Greenberg, Thomas et al. 2007)*
- Uncontrolled observational studies
  - Cetirizine (antihistamine) (*Zhang et al, 2013)*
  - Bevacizumab (anti-vascular endothelial growth factor (VEGF)) *(Mealy et al, 2015)*

Preventive Therapy

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Medication	Dose	Route	Schedule	Monitoring	Treatment Change Considerations	ARR/ EDSS
*Azathioprine (+ prednisone)	2 - 3 mg/kg/ day (+ 30 mg/ day)	Oral	1-2 daily doses (prednisone taper after 6 – 9 months)	Initial: TPMT activity assay. Periodic: Mean corpuscular volume (MCV) increase of at least 5 points from baseline; monthly liver function tests for first 6 months, then twice yearly; maintain absolute neutrophil counts > 1000 cells/μL.	If MCV did not rise on initial dose, consider increase by 0.5 – 1 mg/kg/day. Or consider increasing dose or duration of prednisone. *Switch to:* Rituximab or mycophenolate mofetil.	2.1 to 0.60 *Bichuetti et al(2010)* Stable EDSS
*Mycophenolate mofetil (+ prednisone)	1000 – 3000 mg/day (+ 30 mg/ day)	Oral	Two daily doses (prednisone taper after 6 months)	Absolute lymphocyte count (ALC) target of 1.0 – 1.5 k/μL; monthly liver function tests for first 6 months, then twice yearly	If ALC goal cannot be reached at maximum dose of 3000 mg/day, observe closely for relapse. *Switch to:* Rituximab	1.29 to 0.09 *(Jacob, Matiello et al. 2009).* Stable EDSS
*Rituximab	1000 mg for adults; 375 mg/m^2 for children	IV	Two doses of 1000 mg 14 days apart or 4 weekly doses of 375 mg/m^2 for children; each pair can be given routinely q6 months without monitoring of CD19 counts, or by following CD19+ cell counts and dosing as soon as it exceeds 1%.	Monthly CD19+ B cells starting immediately post-infusion; if CD19+ count exceeds 1% of total lymphocytes, re-dose with rituximab. If suppression of CD19+ count does not occur, consider switching to alternative. Monitor immunoglobulins yearly.	Relapses during first 3 weeks of initial dosing are not failures. Relapses when CD19+ count is greater than 1% are failures due to undertreatment. *Switch to:* Azathioprine or mycophenolate mofetil.	2.6 to 0.0 *Cree et al (2005)* Stable or improved EDSS

IG depletion with Rituximab

- Recurrent infections associated with Ig depletion
- Sinopulmonary and urinary tract
- Consider IgG(mg/dl) repletion with IVIG
  - < 150: replace
  - 150-300: usually replace, especially if clearly documented history of recurrent infections
  - 300-500: heavily dependent on infection history; may use responses to vaccines to judge
  - > 500: rarely needs replacement
- Dosage:
  - IVIG 400 mg/kg every 4 weeks to start
  - After 3 doses check IgG trough and adjust to get IgG >800-1000

Preventive Therapy

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*Prednisone	15-30 mg	Oral	Daily dose; taper after 1 year	Blood sugar to avoid hyperglycemia, blood pressure; DEXA scans as appropriate for osteoporosis; vitamin D and calcium supplementation as needed; consider proton pump inhibitors for gastric protection	Prednisone monotherapy not recommended for long-term use beyond 1.5 years. *Switch to:* Azathioprine, mycophenolate or rituximab.	**ARR/EDSS** 1.48 to 0.49 *(Watanabe, Misu et al. 2007* EDSS stable
Methotrexate	15 – 25 mg	Oral	Weekly	Check for liver toxicity every 3 months; recommend folate 1 mg supplementation; avoid non-steroidal anti-inflammatory drugs.	*Switch to:* Azathioprine, mycophenolate mofetil or rituximab	1.39 to 0.18 *Minagar et al,(2000)* EDSS stable
Mitoxantrone	12 mg/m^2	IV	Monthly ×6, followed by monthly maintenance dose of 6 mg/m^2. Total cumulative dose no greaterthan 120 mg/m^2.	Baseline and monthly echocardiogram to exclude patients and discontinue drug if left ventricular ejection fraction < 50%.	Only recommended as second line agent. The maximum cumulative dose is 140 mg/m^2. *Switch to:* Azathioprine, mycophenolate mofetil or rituximab	2.8 to 0.7 *Weinstock-Guttman et al (2006).* EDSS 5.8 to 4.4

Emerging NMO Therapies

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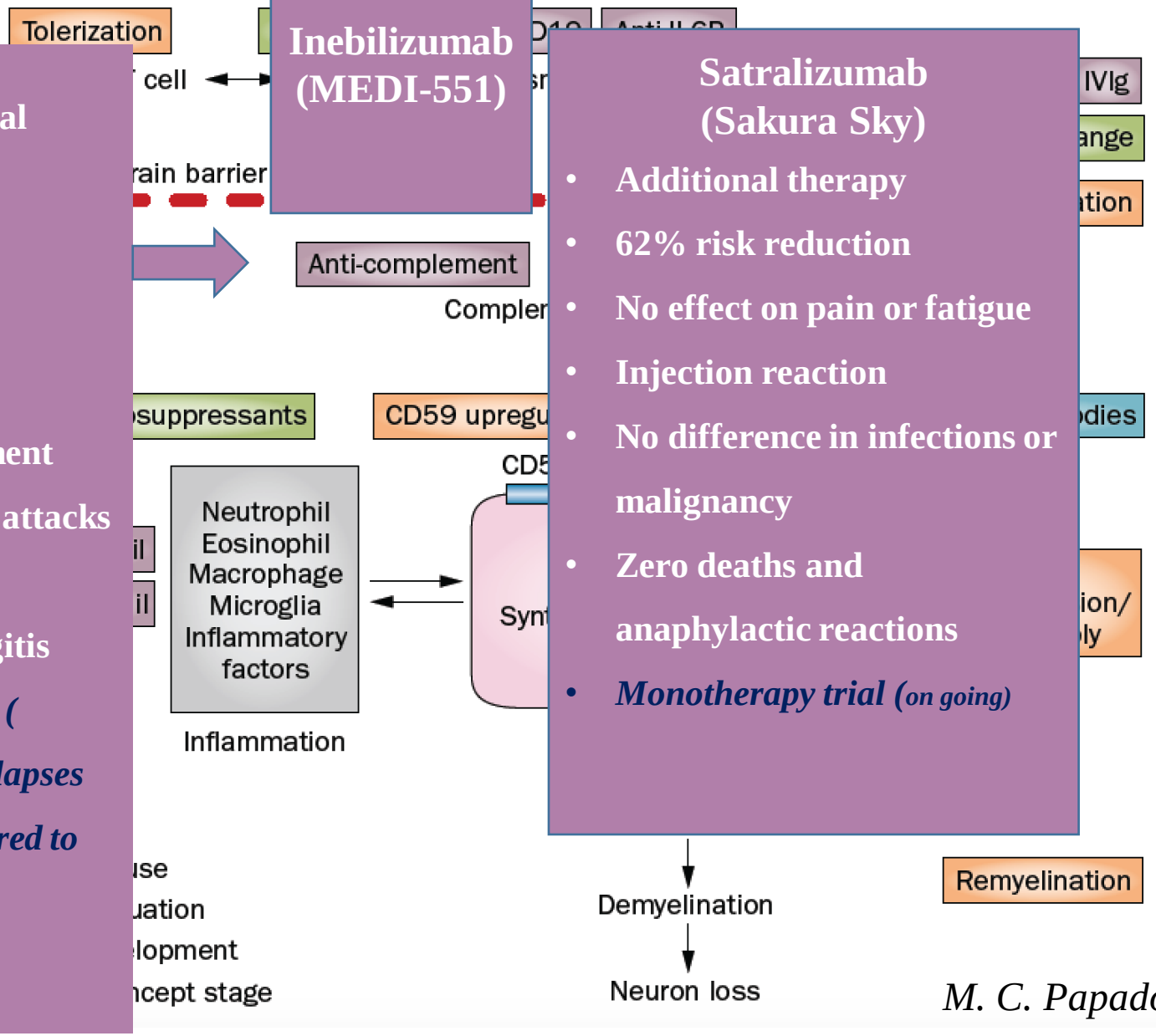
Eculizumab
(Anti C5 monoclonal antibody)

- **Blocking CDCC**
- **14 patients**
- **1-4 to 0 relapses**
- **EDSS improvement**
- **5 patients had 8 attacks after withdrwal**
- **One had meningitis**
- ***PREVENT trial (reduce risk of relapses by 94.2% compared to placebo)***

Inebilizumab (MEDI-551)



Satralizumab (Sakura Sky)

- **Additional therapy**
- **62% risk reduction**
- **No effect on pain or fatigue**
- **Injection reaction**
- **No difference in infections or malignancy**
- **Zero deaths and anaphylactic reactions**
- ***Monotherapy trial (on going)***

M. C. Papadopoulos, Rev Neurol 2014

Emerging NMO Therapies

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Tolerization

Anti-CD20

T cell ↔ B cell

Blood–brain barrier

Anti-compl

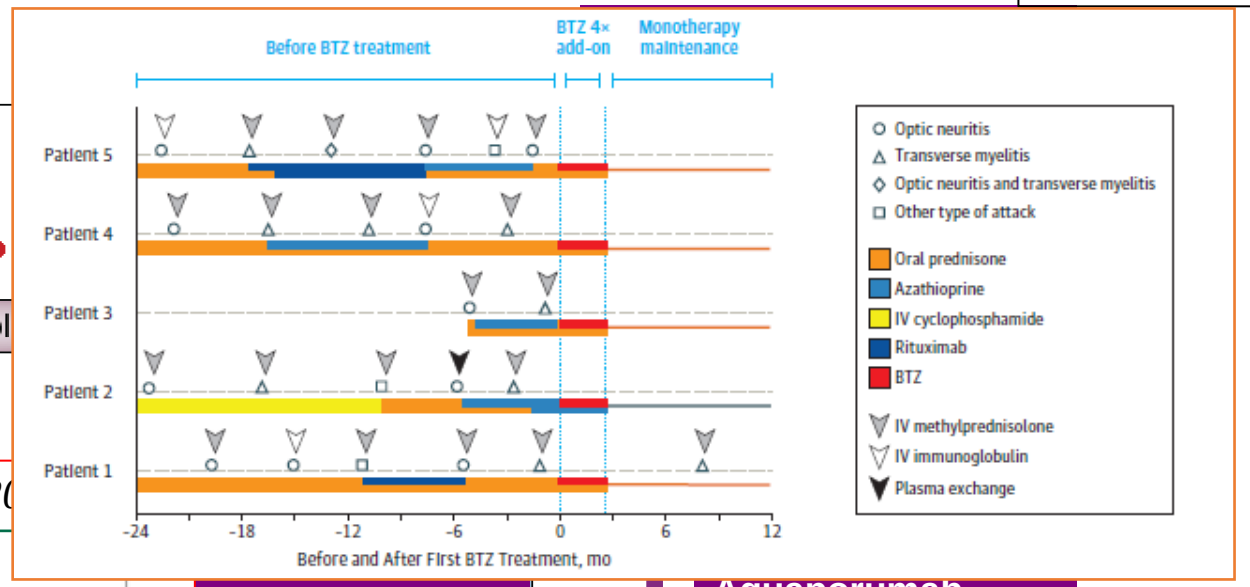
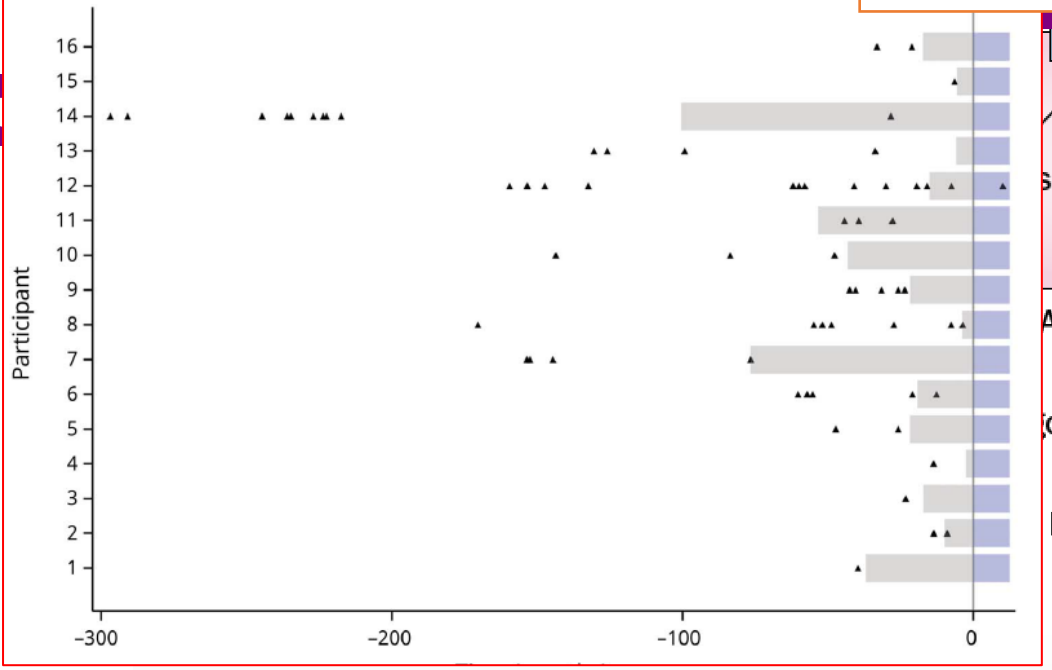


Figure 1 Relapses before and after cetirizine

Katz et al, 20



Siveles

AQP4 AQP4 AQP4

Array assembly

sis Degradation

Astrocyte

Astrocyte injury

odendrocyte injury

Demyelination

Neuron loss

Remyelination

Aquaporumab

- Competitive Inhibitors of NMO IgG Fc portion

M. C. Papadopoulos, Rev Neurol 2014

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Table 2 | Current therapeutic trials in NMO

Company	Intervention	Mode of action	Type of trial	Recruitment	Purpose of trial
Alexion	Eculizumab (Soliris®)	Inhibits C5	Phase III	Not yet started	Long-term safety and efficacy for relapse rate reduction in AQP4-IgG$^+$ NMO
Nihon	Intravenous immunoglobulin (NPB-01) combined with steroids	Multiple	Phase II	Recruiting	Safety and efficacy in AQP4-IgG$^+$ NMO
Mayo Clinic	Plasma exchange	IgG depletion	Phase I	Recruiting	Feasibility, tolerability, safety and preliminary efficacy as maintenance therapy in NMO
Viropharma	C1inh (Cinryze®) as an add-on therapy	C1 inhibition	Phase I	Completed	Tolerability, safety and preliminary efficacy in acute NMO/NMOSD
Genentech	Bevacizumab (Avastin®) as add-on therapy	Inhibits VEGF	Phase II	Not yet started	Tolerability, safety and preliminary efficacy in acute NMO/NMOSD
Chugai	SA237	Anti-IL-6 receptor	Phase III	Not yet started	Safety, efficacy; pharmacodynamic, pharmacokinetic and immunogenic profiles in NMO/NMOSD
ONO	Sivelestat (Elaspol®) combined with methylprednisolone	Anti-neutrophil	Phase I, II	Recruiting	Safety and efficacy in acute NMO
Genentech	Tocilizumab (Actemra®, Toactemra®)	Anti-IL-6 receptor	Phase I, II	Completed	Safety and efficacy in intractable NMO; exploration of mechanisms of action

Abbreviations: AQP4, aquaporin-4; AQP4-IgG$^+$, AQP4-IgG-seropositive; C, complement protein; NMO, neuromyelitis optica; NMOSD, NMO spectrum disorder; VEGF, vascular endothelial growth factor.

M. C. Papadopoulos, Rev Neurol 2014

Table 3 | Compounds in the pipeline

Compound	Target molecule	Mechanism of action
Anti-CD19[34,118]	B-cell surface marker	Depletion of naive and memory B cells, plasmablasts, and some plasma cells
Anti-IL-17[54,183]	Cytokine	Blocks IL-17 signal transduction
Aquaporumab[144]	AQP4	Binds to AQP4 on CNS astrocytes and blocks AQP4-IgG binding
IdeS[153]	AQP4-IgG	Cleaves circulating AQP4-IgG
EndoS[152]	AQP4-IgG	Deglycosylates AQP4-IgG to eliminate CDC and ADCC function
Small-molecule blockers[145]	AQP4-IgG	Competitive inhibition of AQP4-IgG binding
Peptoid inhibitors[184]	AQP4-IgG	Competitive inhibition of AQP4-IgG binding

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; AQP4, aquaporin-4; CDC, complement-dependent cytotoxicity; NMO, neuromyelitis optica.

M. C. Papadopoulos, Rev Neurol 2014

Drugs to avoid

- INF *(Shimuzu et al, 2010, Okada et al 2010)*
- Natalizumab *(Kleiter et al, 2012)*
- DMF *(Popiel et al, 2018)*
- Alemtuzumab *(Gelfland, et al 2014)*
- Fingolimod *(Min et al, 2012)*

Pregnancy recommendation

- Acute relapse
  - IVMP: avoid repeated courses.
  - PLEX:
  - IVIG: risk of low birth weight/ monthly doses as maintainace

Shosha et al, MSJ 2018

Azathioprine:

- Continue; alone or with small dose of steroid.

- Leukocyte evaluation
  - Leukocyte count monitored every 1-2 weeks
  - Halve dose at 32 week, if leukocyte <8.6 X 10(9)/l) so as not to affect fetal haemopoiesis

Shosha et al, MSJ 2018

Rituximab:

- B-cell depletion persists approximately 9-12 months

- For planned pregnancy:
  - Two doses of 1000 mg IV separated by 2 weeks
  - Consider single 1000 mg IV dose if B cell already depleted

- For unintended pregnancies:
  - Consider remaining duration of effect
  - Decide based on recent NMOSD activity

Shosha et al, MSJ 2018

Pregnancy recommendation

- Immunosuppresive therapy
  - MMF: stop it 6 weeks prior conception
    - *use reliable contraceptive methods*
  - MTX: stop it 3 months prior conception

Shosha et al, MSJ 2018

MOG-Associated Disease

- Corticosteroid and PLEX-responsive
  - IVMP followed by oral corticosteroids
  - PLEX for more severe/refractory attacks
- Prolonged corticosteroid treatment after first attack associated with lower relapse risk
  - Prednisone >20mg/d
  - Continue treatment for 3-6 months
- Who requires treatment?
  - Established relapsing disease
  - Persistent MOG-IgG antibodies beyond 6 months?

Symptomatic treatment

- Spasticity
- Urinary retention/ incontinence
- Fatigue
- Depression
- Cognitive Dysfunction
- Neuropathic pain

Tha

From left: B lymphocyte; Eosinophil; Platelet; Neutrophil; Macrophage; T lymphocyte; Monocyte; NK cell; Dendritic cell; Basophil; Mast cell

Factors affecting treatment of relapse

- Age less than 40
- IVMP vs PLEX
- Shorter disease duration
- Complete vs partial remission

Can we stop IS?

Journal of Child Neurology
2015, Vol. 30(10) 1366–1370

DOI: 10.1177/0883073814553974
jcn.sagepub.com
SAGE

Prolonged Remission in Neuromyelitis Optica Following Cessation of Rituximab Treatment

Kelley Weinfurtner, BA[1], Jennifer Graves, MD, PhD[2], Jayne Ness, MD[3], Lauren Krupp, MD[4], Maria Milazzo, RN, MS[4,5], and Emmanuelle Waubant, MD, PhD[2,6]

Abstract

Neuromyelitis optica is an autoimmune disease characterized by acute episodes of transverse myelitis and optic neuritis. Several small, open-label studies suggest rituximab, a monoclonal antibody against CD20, prevents relapses in neuromyelitis optica; however, there is little consensus on timing or duration of treatment. Here we report four patients with severe relapsing neuromyelitis optica who were stabilized on rituximab and, after discontinuing treatment, continued to experience prolonged remission of their disease. Remission ranged from 4.5 to 10.5 years total, including 3 to 9 years off all therapies. The patients had sustained clinical responses despite normal B-lymphocyte levels and, in at least 2 patients, continued seropositivity for aquaporin-4 antibodies. These cases suggest that rituximab may induce prolonged remission in certain neuromyelitis optica patients, and they highlight the need for further elucidation of rituximab's mechanism in neuromyelitis optica.

GA

- Effective in two patients
  - [Bergamaschi et al. 2003].
  - Gartzen et al.2007].

OPEN

Efficacy and safety of tacrolimus treatment for neuromyelitis optica spectrum disorder

Received: 21 December 2016
Accepted: 15 March 2017
Published online: 11 April 2017

Bo Chen[1], Qian Wu[1], Gaotan Ke[2] & Bitao Bu[1]

Neuromyelitis optica spectrum disorder (NMOSD) is a severe inflammatory autoimmune disease that mainly involves the optic nerves and spinal cord, causing blindness and paralysis. Although some immunosuppressants such as rituximab and azathioprine have proven to be effective in relapse prevention, the high costs or intolerable adverse events preclude their wide application. Thus, we have conducted a retrospective study in 25 NMOSD patients who were treated with tacrolimus, an immunosuppressant with high efficacy and good tolerance in other autoimmune diseases, to assess its efficacy and safety in NMOSD treatment during the last five years (2011–2016). The results revealed that tacrolimus could reduce the relapse rate by 86.2% and improve the Expanded Disability Status Scale (EDSS) scores (4.5 vs 2.3; $P < 0.001$) significantly. Relapses in tacrolimus treatment were associated with serum titers of aquaporin 4 antibody (AQP4-IgG) ($P = 0.028$). Further Cox proportional analysis demonstrated that patients with high titers of AQP4-IgG ($\geq$1:64) had a significantly higher risk of relapse than those with low titers after tacrolimus therapy (HR:5.665; CI_{95}: 1.012–31.705; $P = 0.048$). Tacrolimus tended to be superior to azathioprine (29 patients) in terms of efficacy and safety during the same period. Our study suggests that tacrolimus may be another promising immunosuppressant for NMOSD.

Mitoxantrone

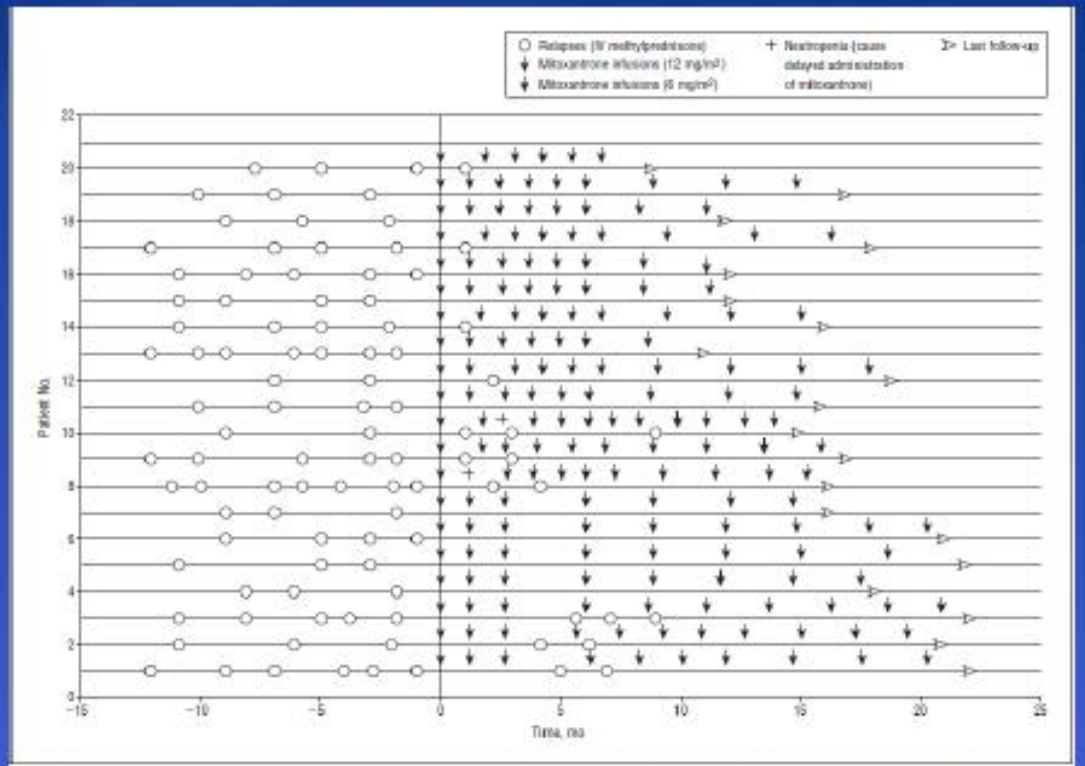
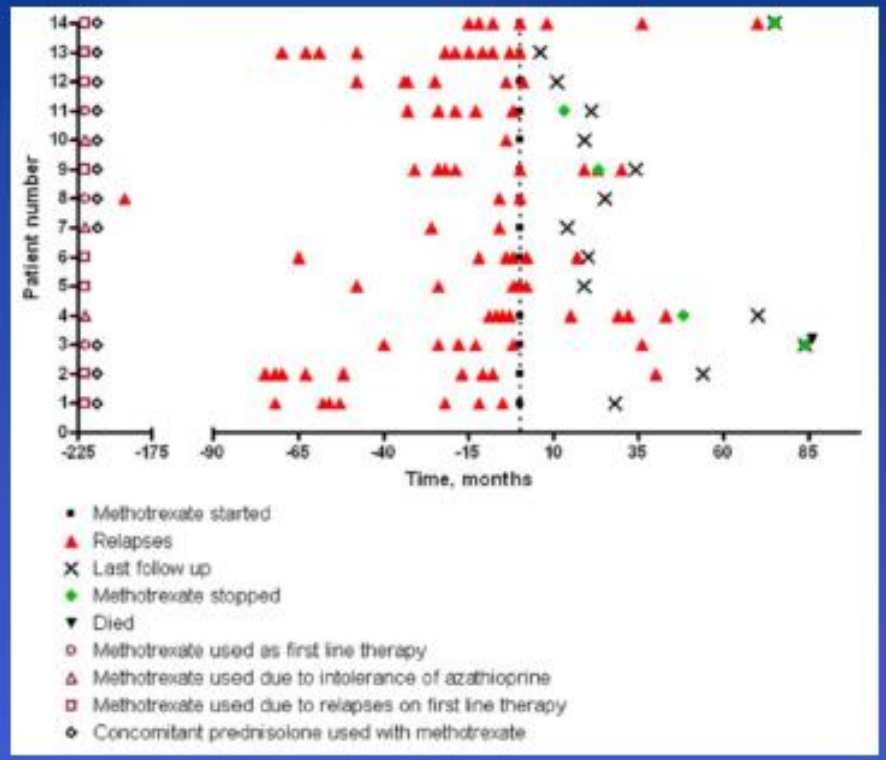


Figure 1. Relapses in patients with neuromyelitis optica before and after treatment with mitoxantrone. When the frequency of relapses is compared between 1 year preceding the start of mitoxantrone therapy and 1 year after mitoxantrone therapy, a significant decrease in relapses is observed. On the x-axis, 0 indicates the start date of treatment. Each interrupted line on the y-axis represents a patient.

- N = 20
- Reduced ARR by 75%
- 50% relapse-free
- Clinical stability
- Preferentially affected CD27+CD19+ memory B cells

Kim et al, Arch Neurol 2010

Methotrexate



- Retrospective (n=14)
- Only 3/14 as 1st line
- 11/14 also continued prednisolone
- Median Rx 21.3 mos
- Median ARR reduced from 1.39 to 0.18 ($p<0.005$)
- Cautions: hepatotoxicity, pneumonitis, cytopenias, need for folic acid, contraindicated in pregnancy

Kitley et al, JNNP 2013

Autologous HSCT

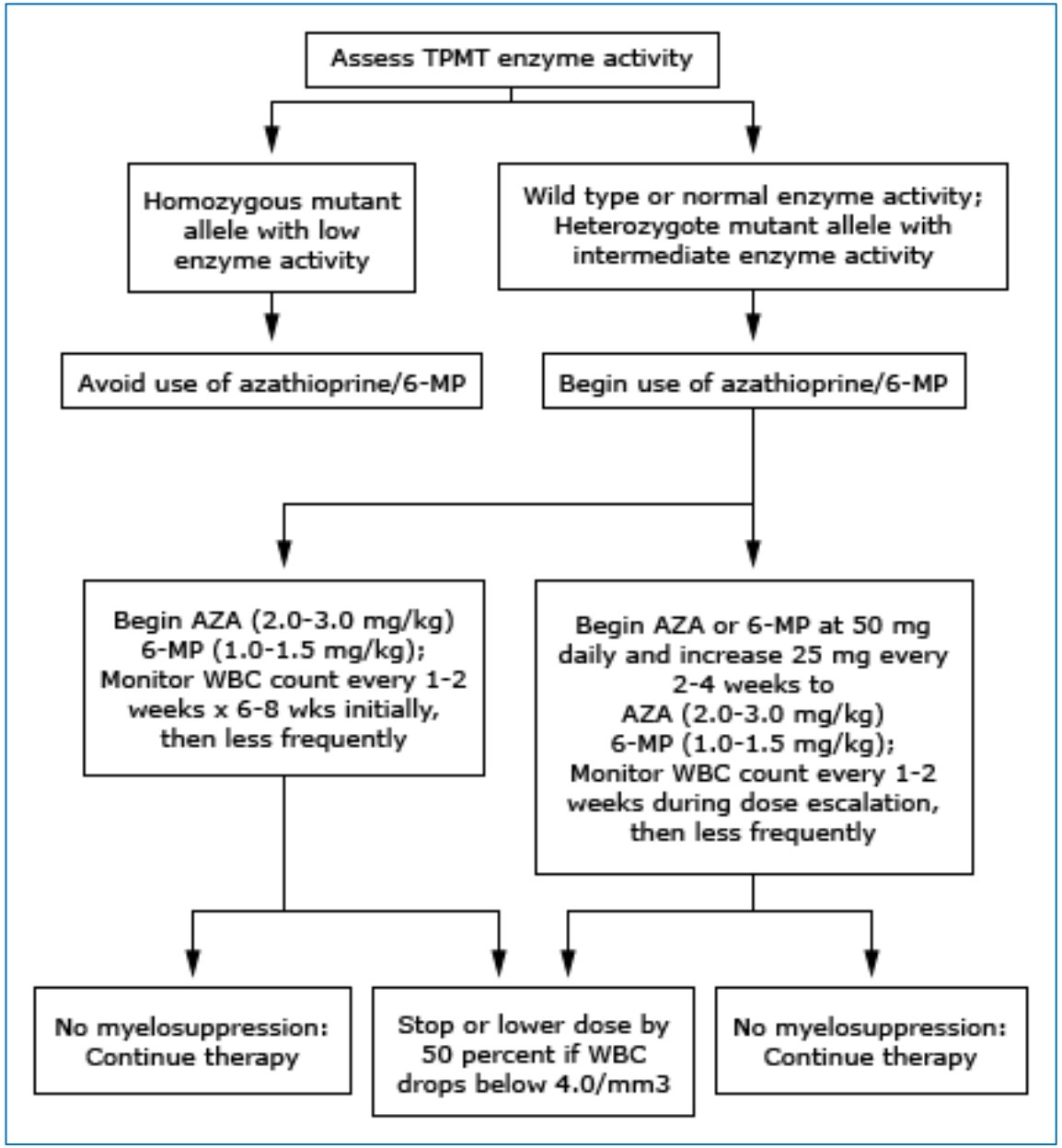
Table 1
Recent reports of hematopoietic stem cell transplant (HSCT) for treatment of refractory neuromyelitis optica

Author	Patients, n (sex)	Median age, years	Type of HSCT	Clinical outcome	Anti-AQP4-Antibodies post HSCT
Greco et al. 2014 [7]	16 (13F/3M)	37	Autologous	Relapse in 13/16 patients (median follow up 47 months) Three patients treatment and relapse free	Only measured in eight patients at follow up, all positive and all of whom relapsed
Greco et al. 2014 [11]	2 (1F/1M)	29	Allogeneic	Relapse free and treatment free (36 and 48 months)	Negative

AQP4 = aquaporin-4, F = female, HSCT = hematopoietic stem cell transplant, M = male.

Drugs umask NMOSD

- Navolumab in non-small cell lung CA
- Ipilimumab in metastatic melanoma


Assess TPMT enzyme activity
Homozygous mutant allele with low enzyme activity
Wild type or normal enzyme activity; Heterozygote mutant allele with intermediate enzyme activity
Avoid use of azathioprine/6-MP
Begin use of azathioprine/6-MP
Begin AZA (2.0-3.0 mg/kg) 6-MP (1.0-1.5 mg/kg); Monitor WBC count every 1-2 weeks x 6-8 wks initially, then less frequently
Begin AZA or 6-MP at 50 mg daily and increase 25 mg every 2-4 weeks to AZA (2.0-3.0 mg/kg) 6-MP (1.0-1.5 mg/kg); Monitor WBC count every 1-2 weeks during dose escalation, then less frequently
No myelosuppression: Continue therapy
Stop or lower dose by 50 percent if WBC drops below 4.0/mm3
No myelosuppression: Continue therapy