EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Regulatory Workshop on Clinical Trials Designs in Neuromyelitis Optica (NMO) and Spectrum Disorders

Clinical view on current Standard of Care in NMO

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Instituts thématiques

Inserm
Institut national de la santé et de la recherche médicale

Level of Evidence for SOC in NMO: State of the Art

- No RCT=No level A evidences
- Most studies are single-arm, open-label, with no control group, in small numbers of people

… but:

- NMO= Rare disease, 0.4 in 10,000 people in the European Union (EU)
- NMO= Well characterized recently (2004-2006)

Treatments for relapse prevention in NMO

Immunosuppressant therapies

- Azathioprine (Aza)
- Mycophenolate Mofetil (MMF)
- Methotrexate
- Mitoxantrone

B-cell Targeting therapy

- Rituximab (RTX)

New therapies

- Eculizumab
- Tocilizumab

Standard of Care for relapse prevention in NMO: Definition

Immunosuppressant therapies

- **Azathioprine (Aza)** : DNA synthesis inhibitor
- **Mycophenolate Mofetil (MMF)**: cytostatic effect on T, B lymphocytes
- Methotrexate
- Mitoxantrone

B-cell Targeting therapy

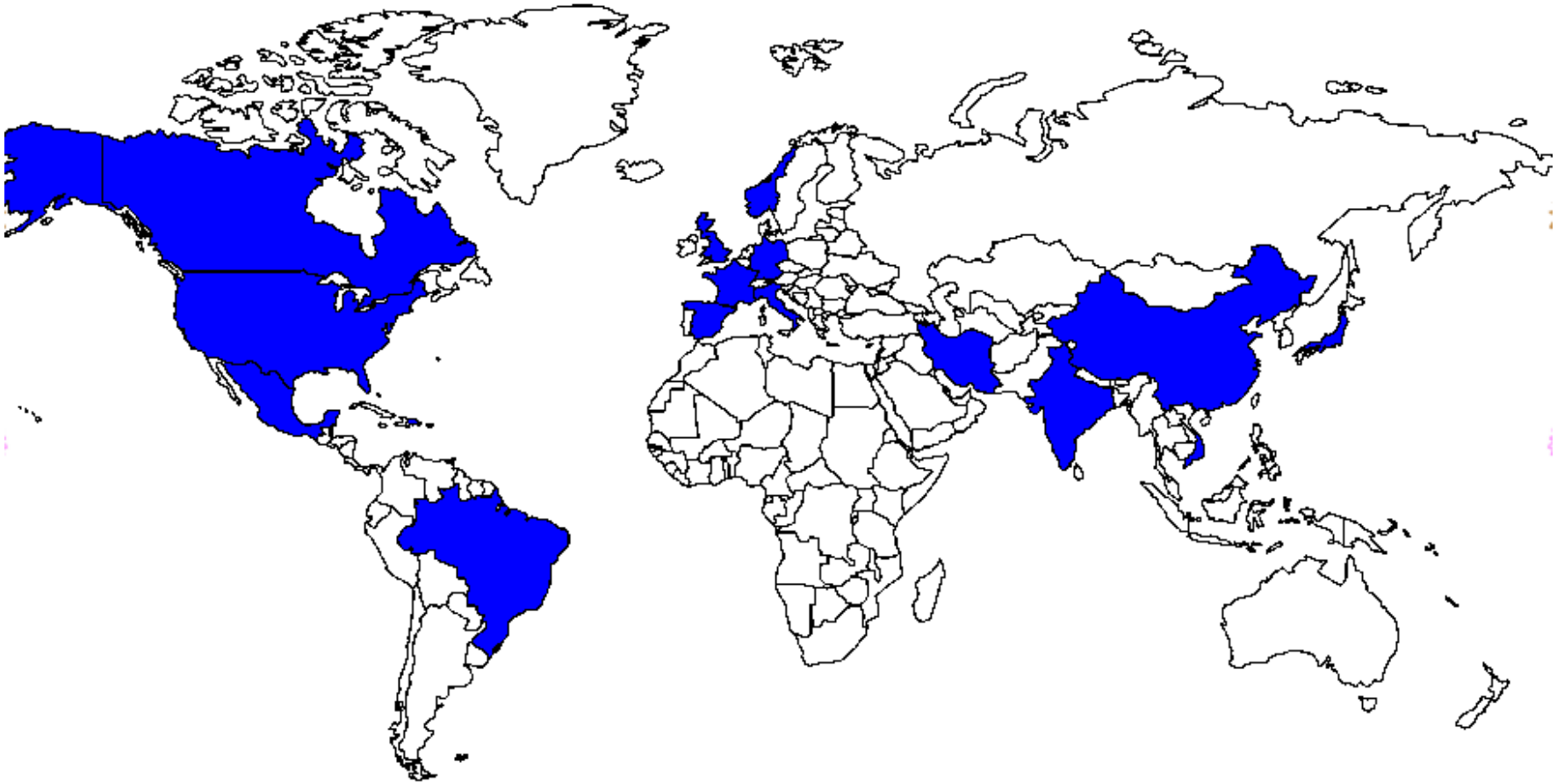
- **Rituximab (RTX)**: chimeric monoclonal antibody against CD 20

New therapies

- Eculizumab
- Tocilizumab

Standard of Care : widespread use in NMO

Reported use of Aza and/or MMF and/or RTX in > 25 patients



Austria: Aboul-Enein et al. 2013; Brazil: Bichuetti et al 2010; China: Yang et al. 2013; France: Papeix et al. 2007; Collongues et al. 2010; Germany: Pelkofer et al., 2011; Jarius et al., 2012; Trebst et al; 2014; India: Barhati et al. 2014; Iran: Etemadifar et al.2014; Italy: Ghezzi et al. 2004; Japan: Kitley et al. 2012; Korea: Kim et al; 2011, 2013; Huh et al. 2014; Mexico: Rivera et al. 2008; Norway: Asgari et al; 2014; Spain: Saiz et al. (in preparation); UK: Kitley et al. 2012, Jacob et al. 2014; USA: Jacob et al. 2008, 2009; Constanzi et al. 2011, Mealy et al. 2014

SOC in NMO: Guidelines and Recommendations

REVIEW

Update on the diagnosis and treatment of neuromyelitis optica: Recommendations of the Neuromyelitis Optica Study Group (NEMOS)

Corinna Trebst · Sven Jarius · Achim Berthele · Friedemann Paul · Sven Schippling · Brigitte Wildemann · Nadja Borisow · Ingo Kleiter · Orhan Aktas · Tania Kümpfel · Neuromyelitis Optica Study Group (NEMOS)

J Neurol (2014) 261:1–16
DOI 10.1007/s00415-013-7169-7

European Journal of Neurology 2010

doi:10.1111/j.1468-1331.2010.03066.x

EFNS GUIDELINES

EFNS guidelines on diagnosis and management of neuromyelitis optica

J. Sellner[a], M. Boggild[b], M. Clanet[c], R. Q. Hintzen[d], Z. Illes[e], X. Montalban[f], R. A. Du Pasquier[g], C. H. Polman[h], P. S. Sorensen[i] and B. Hemmer[a]

MULTIPLE SCLEROSIS AND RELATED DISORDERS

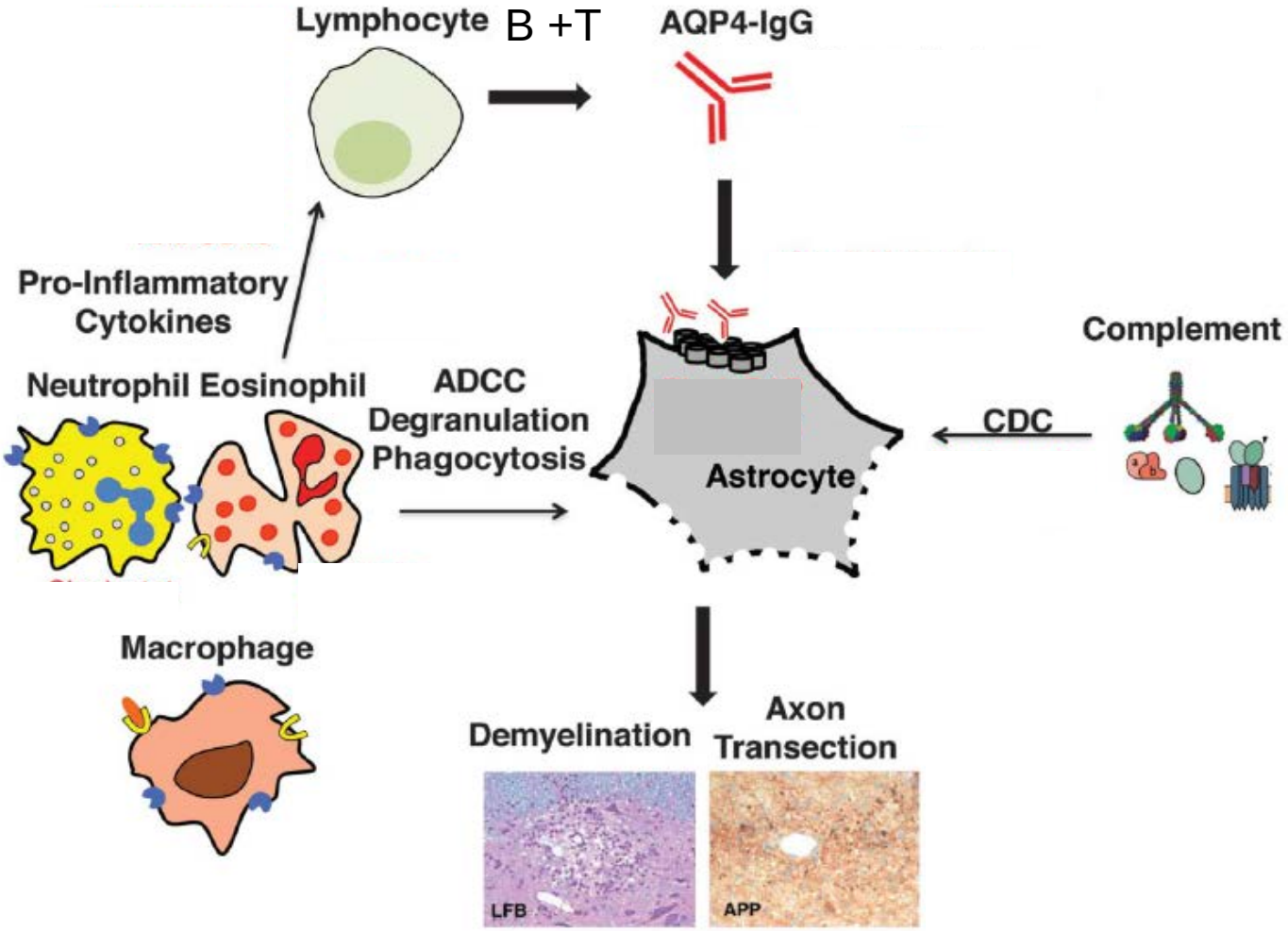
Treatment of Neuromyelitis Optica:
Review and Recommendations
Kimberley et al. for the Guthy Jackson Foundation (WorldWide)

Standard of Care in NMO: Standardized regimen?

Medication	Dose	Route	Schedule	Monitoring	Treatment Change Considerations
*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.
*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
*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.

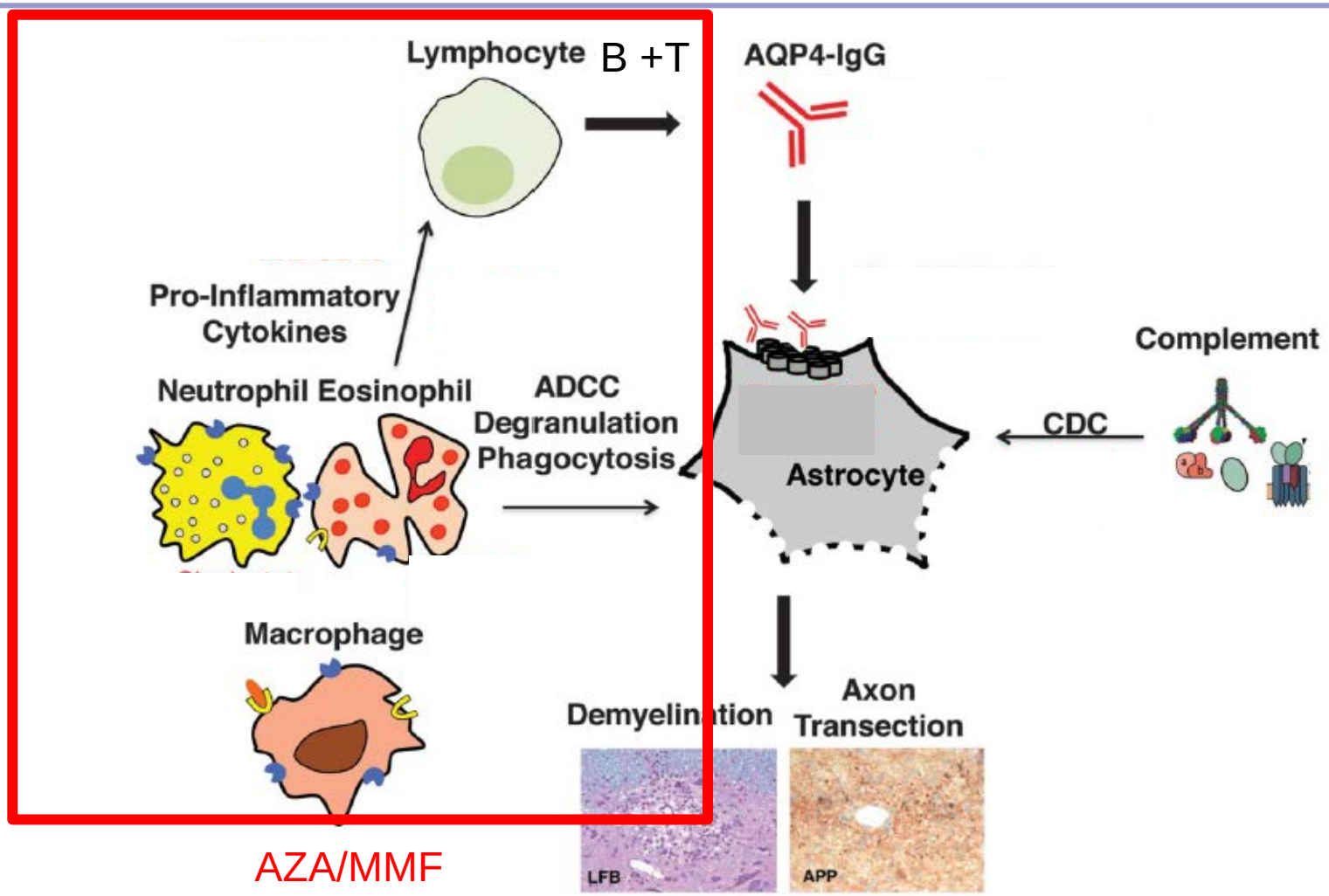
Kimbrough et al. 2012

SOC: physiopathological rationale in NMO



Human Pathology: Lucchinetti et al. 2002, Roemer et al. 2007, Misu et al. 2007, 2013
Animal Model: Bradl et al. 2009, Bennett et al. 2009,Saadoun et al., 2010, Kinoshita et al. 2010, Ratelade 2011
In vitrro model: Hinson et al. 2007, 2008, 2012; Sabater el al. 2009; Marignier et al. 2010, Tradtrantip el al. 2012a, 2012b

Standard of Care : rationale in NMO?



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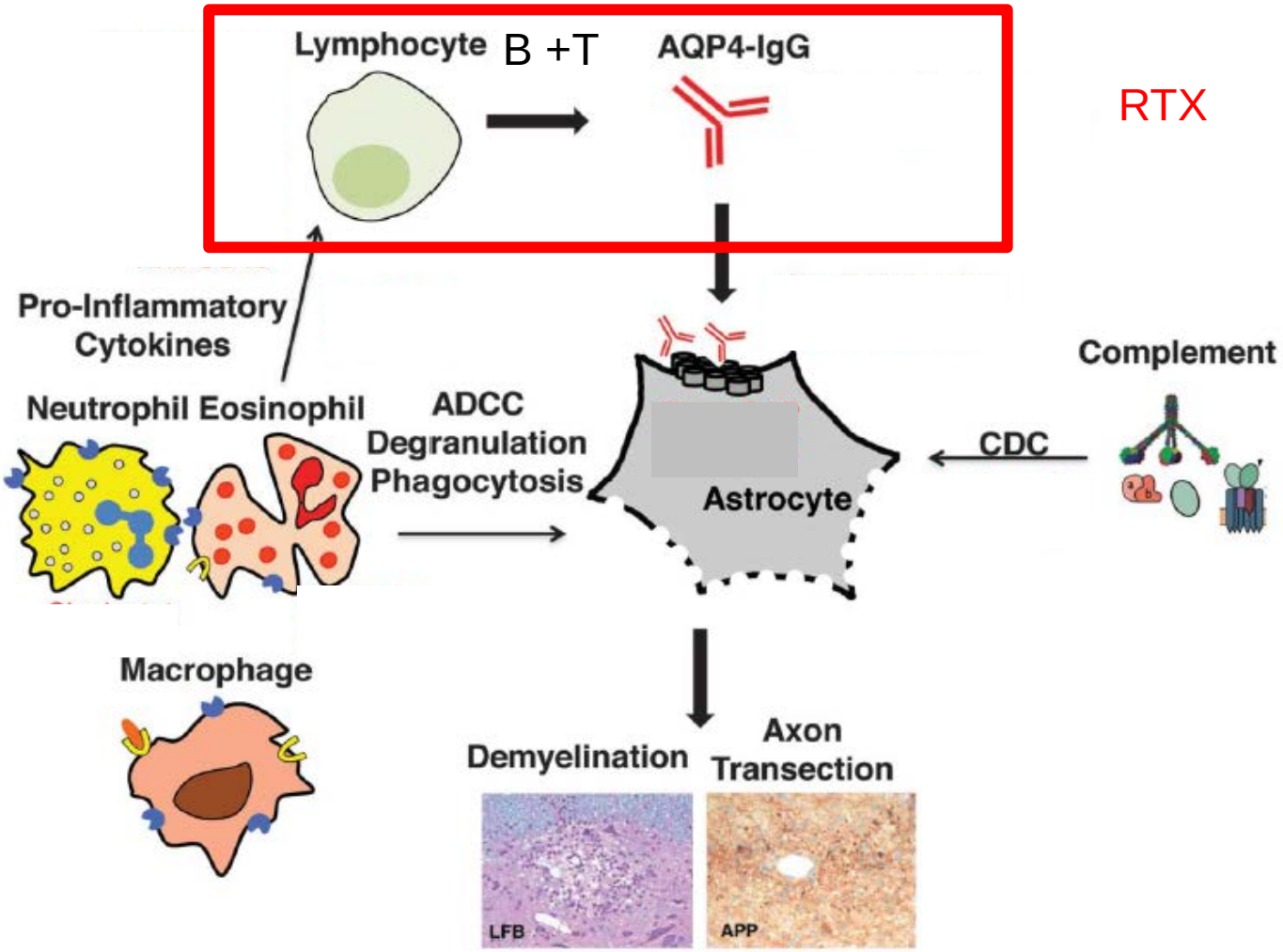
Standard of Care : rationale in NMO?



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SOC: level of evidence in other indications

Approved

AZA:

- an adjunct for the prevention of rejection in renal homotransplantation
- management of active rheumatoid arthritis to reduce signs and symptoms

MMF (in combination with steroids and cyclosporine) :

- prevention of organ rejection assessed in randomized, double-blind, multicenter trials in renal (3 trials), in cardiac (1 trial), and in hepatic (1 trial) adult transplant patients.

Rituximab

- Two forms of non-Hodgkin's lymphoma
- Chronic lymphocytic leukaemia (a cancer of the B-lymphocytes)
- Severe rheumatoid arthritis together with methotrexate
-Rare autoimmune condition anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis

SOC: level of evidence in other indications

Official recommendation

AZA (NICE-UK and HAS-FRANCE)

- Severe or moderately severe inflammatory intestinal diseases (Crohn's disease or ulcerative colitis),
- Systemic lupus erythematosus
- Dermatomyositis and polymyositis
- Auto-immune hepatitis
- Polyarteritis nodosa
- Refractory warm auto-immune haemolytic anaemia
- Chronic refractory idiopathic thrombocytopenic purpura

SOC: level of evidence in other indications

Myasthenia Gravis experience

Auto-antibody mediated neuro-inflammatory disorder

Pathogenic auto-antibody

Rare but life-threatening

Long time experience of immunosuppressive agents

AZA

- Several retrospective and prospective case series Witte et al. 1984; Kuks et al. 1991
- 1 RCT, 46 patients, 3 years FU: better than placebo, in addition to steroids (Palace for the Myasthenia Gravis Study Group 1998)

MMF

- Recommended as steroid-sparing medication

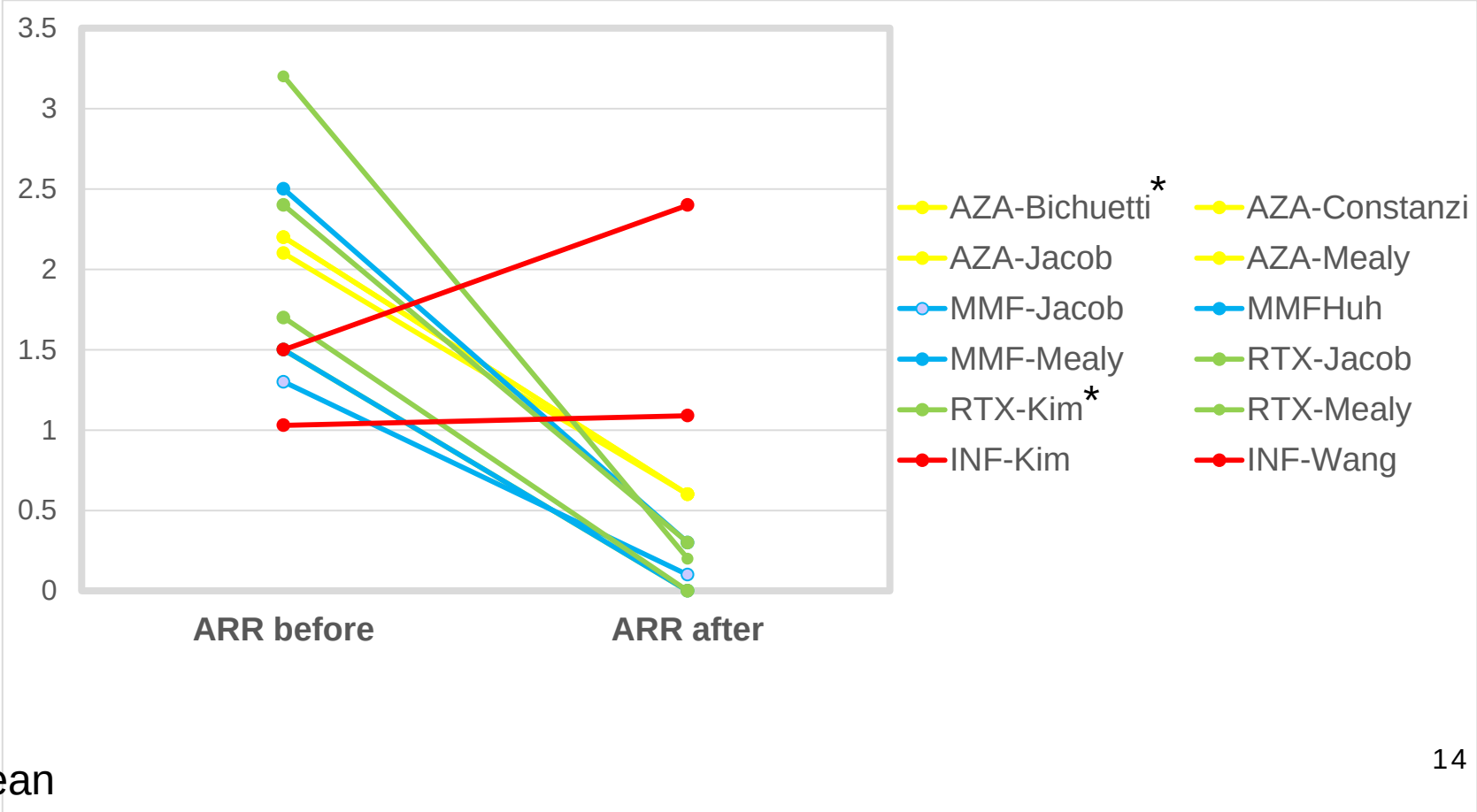
Rituximab

- Recommended for refractory MG
- MG associated to MuSK auto-antibodies Thakre et al. 2007; Baek et al., 2007

SOC: evidence of efficacy in NMO

Median ARR

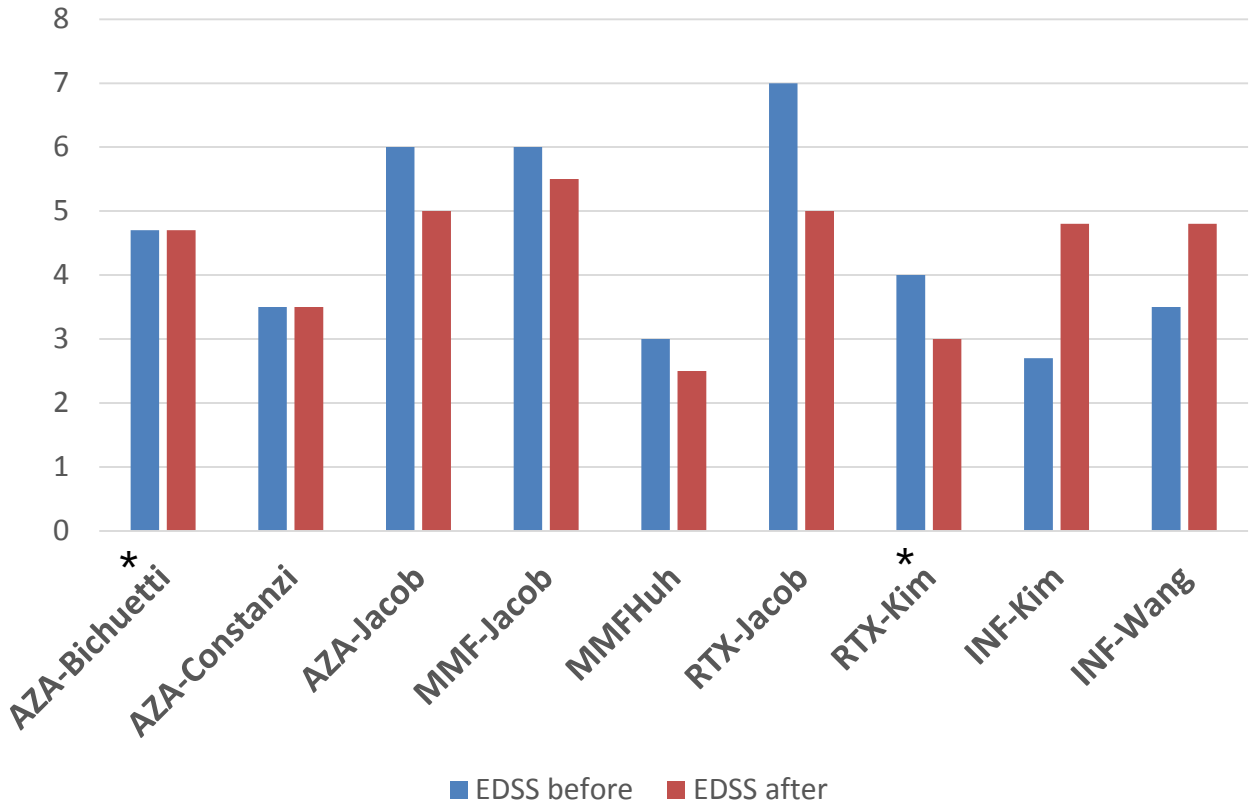
10 open-label retrospective studies
Number of patients > 25
Duration of follow-up > 18 months
Same endpoints



* Mean

SOC: evidence of efficacy in NMO (2)

Median EDSS **9 open-label retrospective studies**:
Number of patients > 25
Duration of follow-up > 18 months

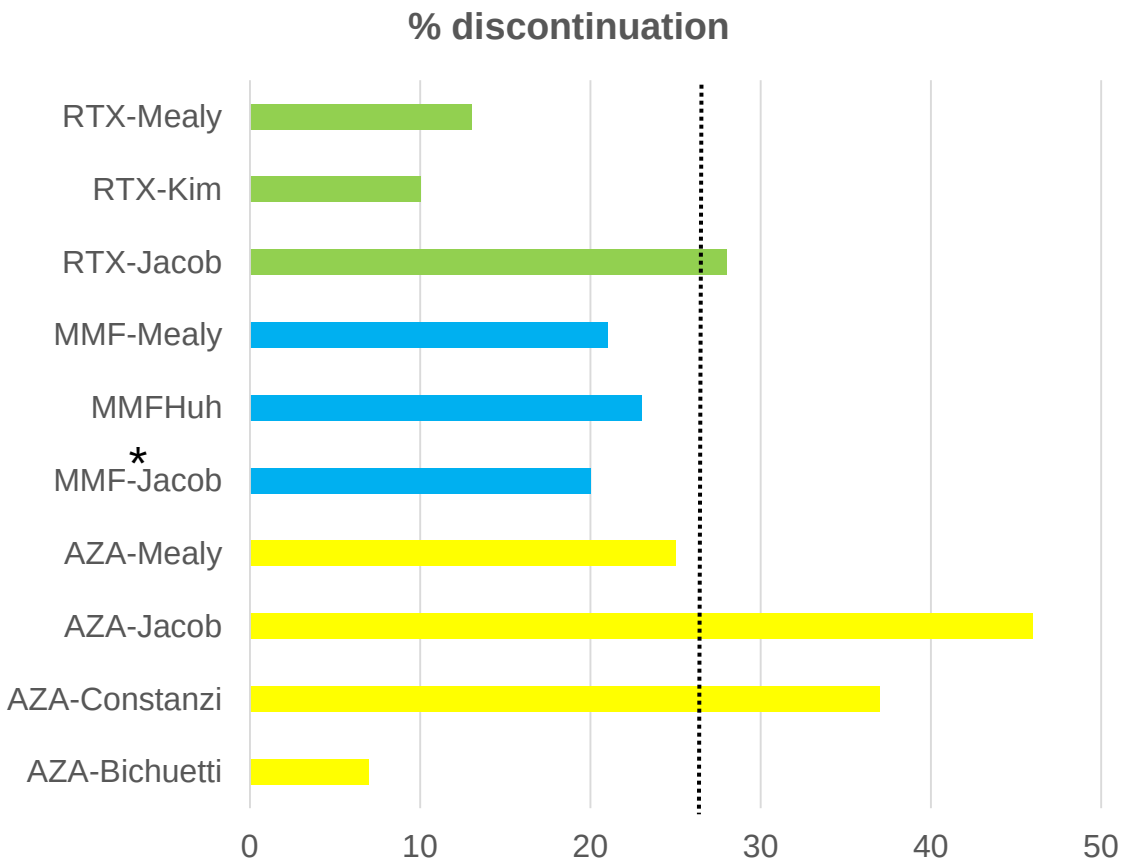


* Mean

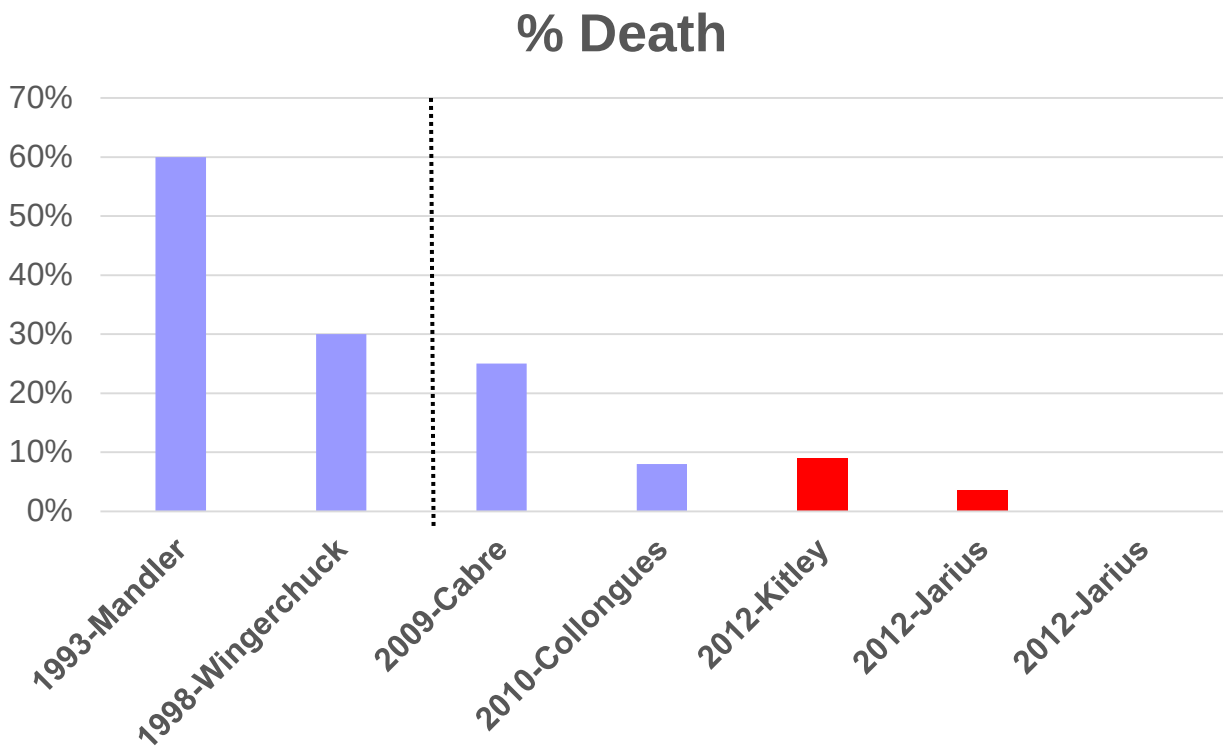
SOC: evidence of efficacy in NMO (3)

% discontiunation

8 studies:
Number of patients > 25
Duration of follow-up > 18 months

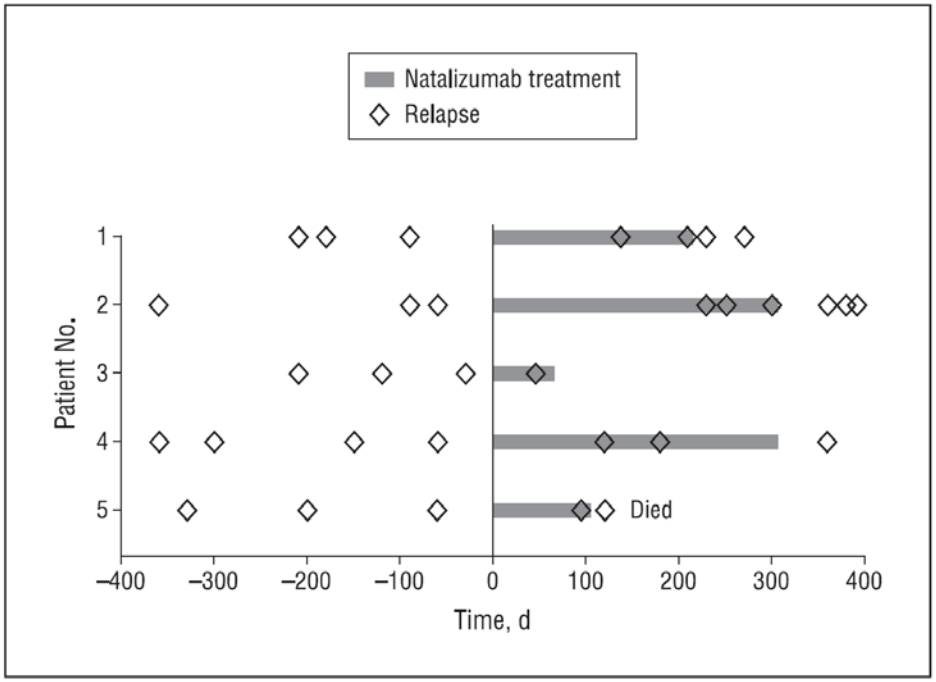


SOC efficacy: Change in NMO natural history

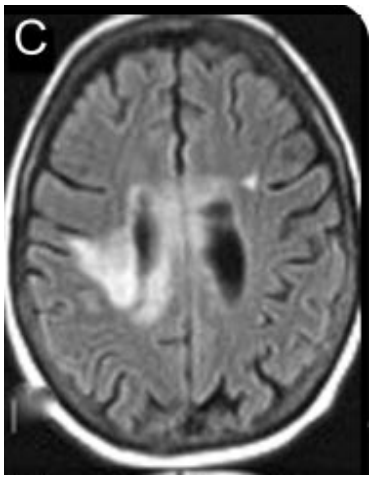


Effect of new diagnostic criteria??? No signal in AQP4+ group
Effect on treatment: Shift from INF Beta/Cyclophosphamide to AZA/MMF/RTX

SOC efficacy: harmful effect of MS-DMT



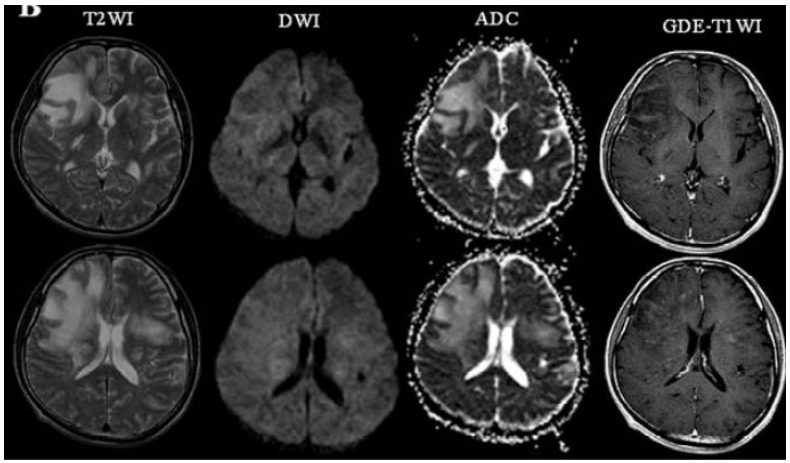
Natalizumab



Jacob et al. 2012 (UK)

Kleiter et al. 2012 (Germany)

Fingolimod



Min et al. 2012 (S Korea)

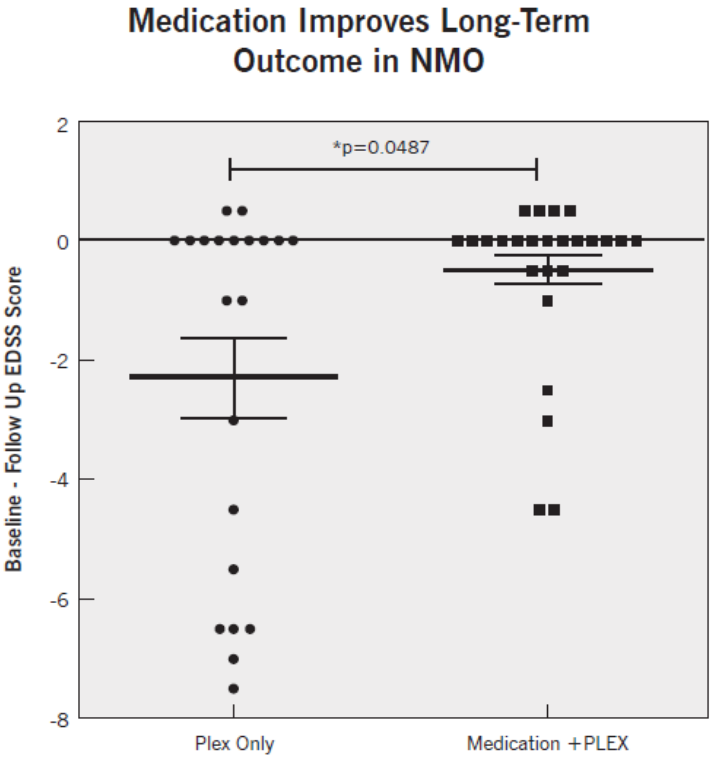
SOC efficacy: lower impact of relapse disability

Residual disability from relapses

Optic Neuritis attacks	off treatment	on treatment	
n	34	17	
Change in VA*, mean (SD)	-0.67 (0.36)	-0.31 (0.40)	p<0.05
% no residual change	17.6	52.9	

TM attacks	off treatment	on treatment	
n	24	12	
Change in EDMUS, mean (SD)	3 (3.17)	0.21 (3.12)	p<0.05
% no residual change	33.3	50.0	

Tackley et al. 2014, ECTRIMS



Abboud et al. 2014, ECTRIMS

SOC in NMO: **differences in approach or effect by major subgroups?**

Pediatric population

- AZA/MMF/RTX has been used in pediatric cohorts (Mc Keon et al. 2008, Lotze et al. 2008, Collongues et al., 2010)
- Recommendation-Guidelines: same than in adults (Tenenbaum 2013)

Overview of immunosuppressive drug use in the treatment of paediatric NMO.

Drug	Date	Lead Author	Location	Population size	Impact on attacks
Azathioprine	2007	Djemal [81]	Tunisia	1	1 attack-free
	2008	McKeon [49]	United States	10	5 attack-free; 2 reduced attack rate
18/24	2008	Lotze [71]	United States	1	1 needed switch to other drug
	2008	Loma [82]	United States	1	1 attack-free
	2010	Collongues [73]	France	4	1/4 needed switch to other drug
	2011	Peña [83]	Venezuela	5	Not reported
	2011	Costanzi [66]	United States	7	6/7 reduced attack rate1/7 discontinued due to SE
Mycophenolate mofetil	2006	Falcini [79]	Italy	1	1 attack-free
6/8	2008	McKeon [49]	United States	3	2/3 attack-free
	2008	Lotze [71]	United States	6	Not reported
	2010	Collongues [73]	France	4	1/4 needed switch to other drug
Rituximab	2008	McKeon [49]	United States	8	7/8 attack-free
9/10	2008	Lotze [71]	United States	5	Not reported
	2010	Collongues [73]	France	1	Not reported
	2011	Mahmood [74]	United States	2	2 attack-free
Methotrexate	2008	McKeon [49]	United States	1	1 attack-free
Cyclophosphamide	2008	McKeon [49]	United States	2	2 needed switch to other drug
	2008	Banwell [48]	Canada and Argentina	2	2 needed switch to other drug
2/9	2010	Collongues [73]	France	5	3/5 needed switch to other drug
Mitoxantrone	2010	Collongues [73]	France	1	1 needed switch to other drug

From Tenenbaum 2013

SOC in NMO: **differences in approach or effect by major subgroups?**

NMO spectrum disorder

Most of the studies included

- genuine NMO (Wingerchuck 1999, Wingerchuck 2006) and NMO Spectrum Disorder (Wingerchuck 2007) AQP4+ LETM, AQP4+ ON
- NMO and NMOSD AQP4-IgG share the same physiopathology (Yanagawa et al. 2009)
- Recommendation –Guidelines (Kimbrough et al. 2012) :

"For NMO or NMOSD patients with established relapsing disease, long term immunosuppression …. are recommended"

AQP4+/AQP4-

- AQP4-IgG negative NMO express some specific features including a possible better outcome (Jarius et al. 2013, Marignier et al. 2013, Marignier et al. 2014)
- AQP4-IgG negative NMO are associated to MOG-IgG (Mader et al. 2011, Reindl 2013)
- MOG-IgG NMO are associated to better outcome (Sato et a. 2014, Kitley et al. 2014)
- No recommendation yet for MOG-IgG but immunoactive treatment might be useful

SOC in NMO: summary

1) Mechanism of action

2) Long-time experience of efficacy and safety in inflammatory disorders and Ab-mediated disorders

3) No harmful signal in NMO (≠MS DMT)

4) Accumulative direct and indirect evidences for efficacy and reasonable safety in NMO

5) Widespread use and access (Asia, Europe, Latin America, USA)

6) Broad range of efficacy: differential diagnosis of NMO (useful in seroneg cases)

7) Practise supported by national and international Guidelines and recommendations

The strength of evidence is related to what the evidence is *for*, and **good evidence for clinical decisions should answer clinically relevant questions**.
What the clinician, patient, or policy maker wants to know (amongst other things) is:
'**Which treatment, from among all the available alternatives, has the most favourable benefit/harm balance**?'

Oxford Centre for Evidence-Based Medicine (OCEBM)

Clinically relevant unmet needs in NMO:

Higher level of evidence for SOC

A new treatment with a more favourable benefit/harm balance than SOC