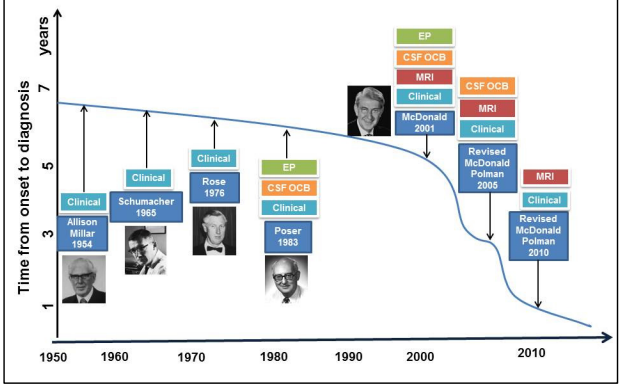
Demyelinating Disorders

김 수 현
국립암센터 신경과

Diagnosis of Multiple Sclerosis

History of diagnostic criteria for MS



MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines

Massimo Filippi, Maria A Rocca, Olga Ciccarelli, Nicola De Stefano, Nikos Evangelou, Ludwig Kappos, Alex Rovira, Jaume Sastre-Garriga, Mar Tintoré, Jette L Frederiksen, Claudio Gasperini, Jacqueline Palace, Daniel S Reich, Brenda Banwell, Xavier Montalban, Frederik Barkhof, on behalf of the MAGNIMS Study Group*

2016 MAGNIMS MRI DIS criteria

At least 2 of five areas of the CNS as follows:
- 3 or more periventricular lesions
- 1 or more infratentorial lesion
- 1 or more spinal cord lesion
- 1 or more optic nerve lesion
- 1 of more cortical or juxtacortical lesion

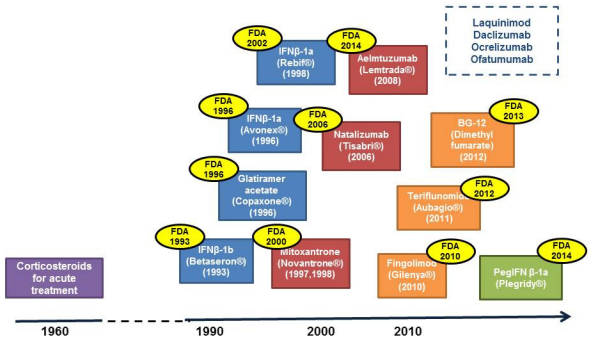
**No distinction needs to be made between symptomatic and asymptomatic MRI lesions for DIS and DIT.

2016 MAGNIMS MRI DIT criteria

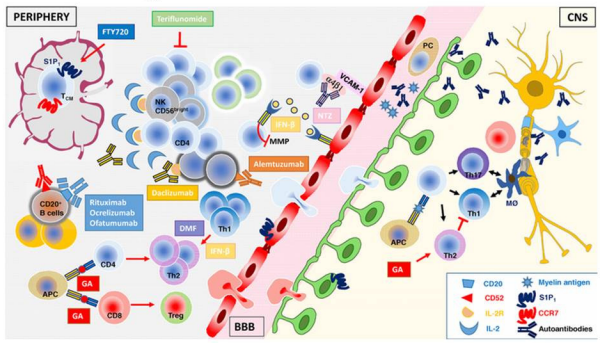
One new T2 or gadolinium enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI
or
Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions

Treatment of Multiple Sclerosis

History of MS Treatment

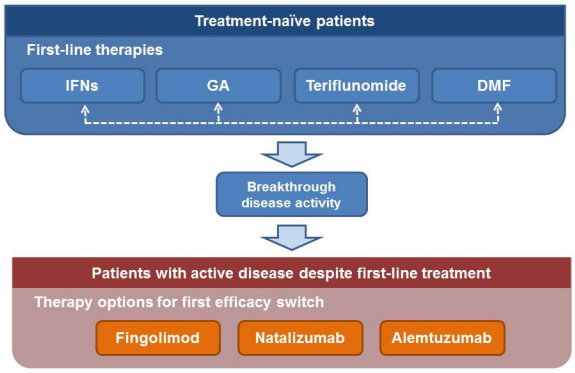


Putative cellular and molecular therapeutic targets used in the MS treatment.



Martin. Eur J immunol 2016

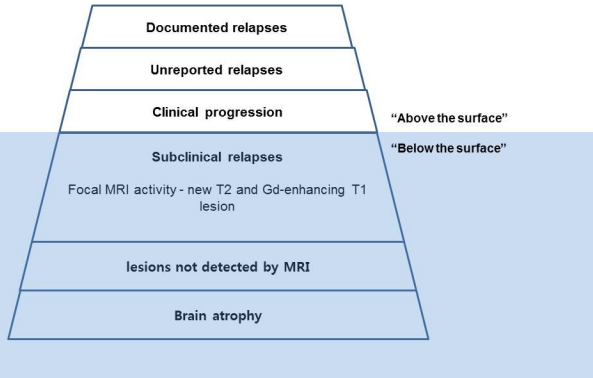
Treatment algorithm for first- and second-line therapies based on their use in clinical practice



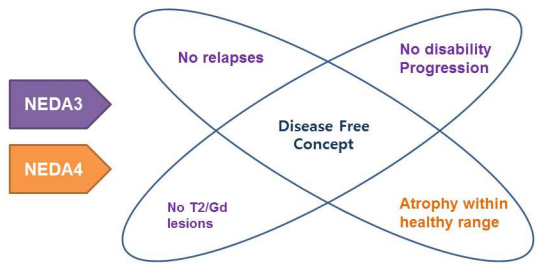
New FDA Approved Drugs for RRMS

	Dosage	Adverse effects	Monitoring
Natalizumab (Tysabri®)	300mg IV every 28 days	Headache, fatigue, **PML**, hypersensitivity reaction	CBC, LFT, JC virus antibody index
Alemtuzumab (Lemtrada®)	12mg IV daily for 5 days at month 0, then 12 mg IV daily for 3 days at month 12	**Secondary autoimmunity,** ITP, autoimmune thyroid disease, malignancy, **infusion reactions,** headaches, flushing	CBC, serum creatinine, thyroid function, urinalysis
Fingolimod (Gilenya®)	0.5mg PO daily	**AV block, bradycardia, macular edema,** zoster, liver enzyme abnormalities, PML	Cardiac monitoring, CBC, LFT, macular edema screen
Teriflunomide (Aubagio®)	14mg PO daily	Headache, diarrhea, fatigue, hair thinning, LFT abnormalities **pregnancy-category X,** severe skin reaction	CBC, LFT
Dimethyl fumarate (Tecfidera®)	240mg PO b.i.d.	**Flushing, abdominal pain, diarrhea, lymphopenia,** liver enzyme abnormalities, PML	CBC, LFT

The MS Iceberg



No Evidence of Disease Activity



Bevan CJ. JAMA Neurol 2014

Is it achievable?

Figure 1. No Evidence of Disease Activity (NEDA) During 7 Years in the Overall Cohort

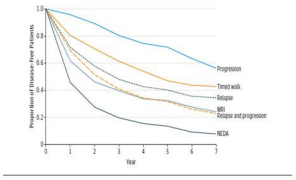


Table 3. NEDA in Clinical Studies

Clinical Study	Study Duration, y	Patients With NEDA Status, %
ADVANCE	1	Placebo, 15%; pegylated interferon beta-1a every 2 weeks, 34%
AFFIRM	1	Placebo, 15%; natalizumab, 47%
SELECT	1	Placebo, 11%; daclizumab, 39%
AFFIRM	2	Placebo, 7%; natalizumab, 37%
CARE-MS I	2	SC interferon beta-1a, 27%; alemtuzumab, 39%
CARE-MS II	2	SC interferon beta-1a, 13%; alemtuzumab, 32%
CLARITY	2	Placebo, 16%; cladribine, 46%
CLIMB	2	Early MS, 24%; established MS, 31%
FREEDOMS	2	Placebo, 13%; fingolimod, 33%
DEFINE	2	Placebo, 15%; dimethyl fumarate, 28%
CombiRx	3	IM interferon beta-1a alone, 21%; glatiramer acetate alone, 19%; glatiramer acetate and IM interferon beta-1a, 33%
CLIMB	7	Early MS, 6%; established MS, 10%

Rotstein DL. JAMA Neurol 2015

- NEDA-3 status was observed in 40.1% of CIS and 20.4% of RRMS patients after 1 year.

  Only 4.6% of CIS and 1.0% of RRMS patients maintained NEDA-4 status after 4 years.

Uher T. Mult Scler 2017

What are the consequence of NEDA?

- NEDA-3 at 2 years had a positive predictive value of **78.3%** and negative predictive value of **40-43%** for no progression at 7 years.

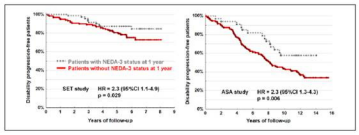
Rotstein DL. JAMA Neurol 2015

- The NEDA-3 2-year endpoint was not a predictor of long-term stability

Cree BA. Ann Neurol 2016

- Loss of NEDA-3 status after the first year was associated with a higher risk of disability progression (hazard ratio (HR) = 2.3-4.0; p = 0.005-0.03) over 6 years

Uher T. Mult Scler 2017



How do you decide WHEN to escalate?

Ref	Criteria (1st year of Tx)	N	Results	Outcome
Rio 2008	≥3 active lesions	152	OR 8.3 71% sensitivity, 77% specificity	Disability progression over 1-2 years
Rio 2009	Rio score, ≥2 parameters from • 1 ≥ relapse; • 1 ≥ point confirmed EDSS score increase; • 3 ≥ active lesions	222	OR 3.3-9.8 for relapses OR 6.5-7.1 for progression	Relapse or disability progression over 1-3 years
Horakova 2012	≥ 3 new T2-weighted lesions	172	42% sensitivity, 79% specificity	Relapse or disability progression over 1-5 years
Sormani 2013	Modified Rio score, 1 relapse and > 5 new T2-weighed lesions, or ≥ 2 relapses	365	HR 4.60 24% sensitivity, 97% specificity	Disability progression over 1-3 years
Prosperini 2014	• ≥ 1 relapse and ≥ 9 T2 lesions or ≥ CEL • ≥ 1 relapse or ≥ CEL • ≥1 CEL or ≥2 new T2 lesions	370	• 34% sensitivity, 90% specificity • 68% sensitivity, 80% specificity • 61% sensitivity, 83% specificity	Relapse or disability progression over 1-4 years
Sormani 2016	MAGNIMS score > 0 • Score 0: 0 relapse and 0-2 new T2 lesions • Score 1: 0 relapses and ≥3 new T2lesions or 1 relapse and 0-2 new T2 lesions • Score 2: ≥ 2 relapses or 1 relapse and ≥3 new-T2 lesions	1,280	50% sensitivity, 70% specificity	Disability progression over 1-3 years

CEL, contrast-enhancing lesions

When do we have to escalate ?

- The risk of failure had a relevant increase with 1 relapse (hazard ratio [HR] 1.84, 95% CI 1.39-2.44, p<0.001) and 3≥ new T2 lesions (HR 1.55, 95% CI 0.92-2.60, p=0.09).

Figure 1 Treatment failure-free survival

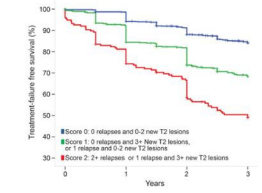
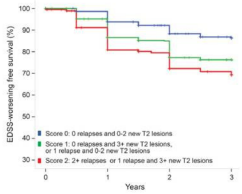


Figure 2 Expanded Disability Status Scale (EDSS worsening)-free survival



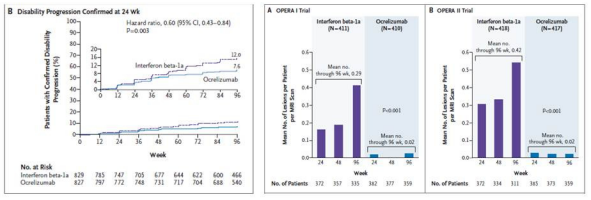
Sormani MP. Neurol 1016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis

S.L. Hauser, A. Bar-Or, G. Comi, G. Giovannoni, H.-P. Hartung, B. Hemmer, F. Lublin, X. Montalban, K.W. Rammohan, K. Selmaj, A. Traboulsee, J.S. Wolinsky, D.L. Arnold, G. Klingelschmitt, D. Masterman, P. Fontoura, S. Belachew, P. Chin, N. Mairon, H. Garren, and L. Kappos, for the OPERA I and OPERA II Clinical Investigators*



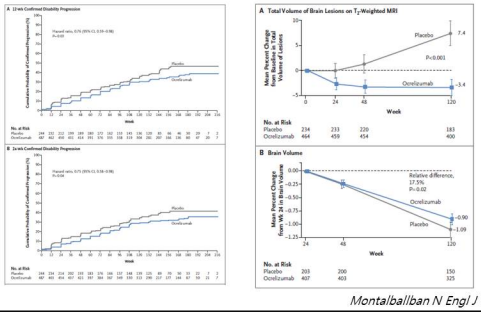
Hauser N Engl J Med 2017

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 19, 2017 VOL. 376 NO. 3

Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis

X. Montalban, S.L. Hauser, L. Kappos, D.L. Arnold, A. Bar-Or, G. Comi, J. de Seze, G. Giovannoni, H.-P. Hartung, B. Hemmer, F. Lublin, K.W. Rammohan, K. Selmaj, A. Traboulsee, A. Sauter, D. Masterman, P. Fontoura, S. Belachew, H. Garren, N. Mairon, P. Chin, and J.S. Wolinsky, for the ORATORIO Clinical Investigators*



Montalbalban N Engl J Med 2017

Diagnosis of NMOSD

VIEWS & REVIEWS

International consensus diagnostic criteria for neuromyelitis optica spectrum disorders

OPEN

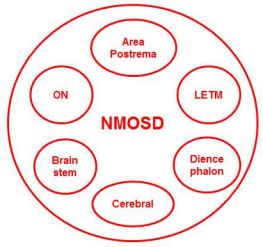
Table 1 NMOSD diagnostic criteria for adult patients

Diagnostic criteria for NMOSD with AQP4-IgG
1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses*

Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status
1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements
   a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
   b. Dissemination in space (2 or more different core clinical characteristics)
   c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses*

Core clinical characteristics
1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions (figure 3)
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions (figure 3)

Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status
1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm (figure 1)
2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis (figure 1)
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions (figure 2)
4. Acute brainstem syndrome: requires associated periependymal brainstem lesions (figure 2)



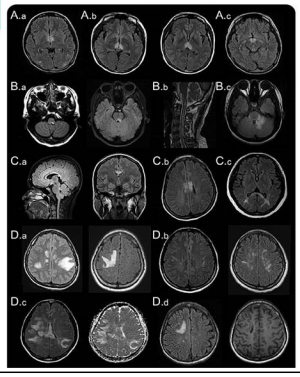
Neurology 2015;85:1-13

VIEWS & REVIEWS

MRI characteristics of neuromyelitis optica spectrum disorder

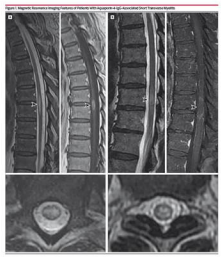
An international update

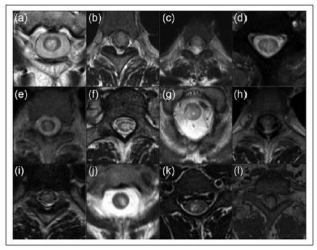
Ho Jin Kim, MD, PhD
Friedemann Paul, MD
Marco A. Lana-Peixoto, MD, PhD
Silvia Tenembaum, MD
Nasrin Asgari, MD, PhD
Jacqueline Palace, DM, FRCP
Eric C. Klawiter, MD
Douglas K. Sato, MD
Jérôme de Seze, MD, PhD
Jens Wuerfel, MD
Brenda L. Banwell, MD
Pablo Villoslada, MD
Albert Saiz, MD
Kazuo Fujihara, MD, PhD
Su-Hyun Kim, MD
With The Guthy-Jackson Charitable Foundation NMO International Clinical Consortium & Biorepository



Neurology 2015;84:1-9

Short segment myelitis does not Preclude the possibility of an NMOSD diagnosis





Flanagan EP. JAMA Neurol 2015

Huh SY, et al. Mult Scler 2017

Treatment of NMOSD

Treatments for prevention of relapse in NMOSD

Recommended

- Azathioprine (AZT)
- Mycophenolate mofetil (MMF)
- Rituximab (RTX)
- Mitoxantrone
- Tocilizumb
- Euclizumab
- Methotrexate

Poor efficacy or harmful effects

- B-interferons
- Glatiramer acetate
- Fingolimod
- Natalizumab

Summary of studies of immunosuppressive therapies for preventing relapse of NMOSD

	AZT	MMF	Rituximab**
Number of studies	10	5	19
Number of patients	532	226	402
Treatment duration, m	15-47	20-27	12-67
Relapse free rate (%)	51% (259/503)	58% (126/226)	62% (251/402)
Disability worsening (%)	20% (64/316)	11% (21/187)	12% (35/302)
Persistence (%)	71%	77%	90%
PML	1	0	0
Sum of patient/year	1115	383	1248

***Repeated treatment with rituximab was conducted in 88% of patients.*

Mandler,1998/Bichuetti, 2010/ Constanzi, 2011/Kaegeyamma, 2013/Elsone, 2014/Qui,2015/Torres 2015 Mearly, 2014/ Jeong, 2015/Chen, 2016/ Jacob, 2009/ Huh, 2014/ Cree, 2005/ Jacob, 2008/ Pellkofer, 2011/Bedi, 2011/ Kim, 2015/ Ip, 2013/ Yang, 2013/ Longoni 2014, Nosadini, 2016/ Collongues, 2015/Zephir,2014/ Annovazzi, 2016/ Radaelli, 2016/ Evangelopoulos 2017

MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Predictors of response to first-line immunosuppressive therapy in neuromyelitis optica spectrum disorders

Multiple Sclerosis Journal
1–7
DOI: 10.1177/1352458516687410
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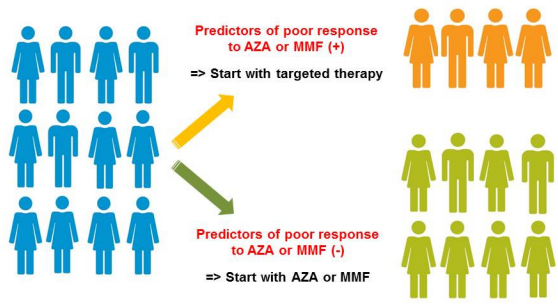
Su-Hyun Kim, Jae-Won Hyun, AeRan Joung, Eun Young Park, Jungnam Joo and Ho Jin Kim

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Anti-AQP4 antibody (positive)	1.36 (0.40–4.66)	0.621		
Sex (male)	2.13 (0.73–6.17)	0.166		
Onset age	0.97 (0.94–1.00)	0.088	0.95 (0.92–0.99)	0.022
Time interval from onset to treatment (months)	1.00 (0.99–1.01)	0.9		
Severe attack history before AZA or MMF, yes	10.54 (3.42–32.55)	<0.001	12.67 (3.82–42.1)	<0.001
EDSS score before AZA or MMF	0.93 (0.76–1.16)	0.533		
ARR before AZA or MMF	1.03 (0.83–1.27)	0.797		
NMO phenotype				
Definite NMO vs limited form of NMO	2.85 (1.29–6.31)	0.010		
Attack at onset				
Brain attack, yes vs no	0.26 (0.08–0.8)	0.019	0.2 (0.06–0.74)	0.015
Optic neuritis, yes vs no	0.73 (0.33–1.56)	0.406		
Myelitis, yes vs no	0.69 (0.31–1.53)	0.365		
Brain attacks before AZA or MMF, yes	1.07 (0.49–2.3)	0.871		
Brain lesions on MRI before AZA or MMF, yes	1.5 (0.7–3.25)	0.301		
IFN treatment history, yes	2.71 (1.16–6.33)	0.021		
Systemic autoantibodies, yes	0.92 (0.41–2.08)	0.838		

ARR: annualized relapse rate; AZA: azathioprine; CI: confidence interval; CNS: central nervous system; EDSS: Extended Disability Status Scale; MMF: mycophenolate mofetil; NMO: neuromyelitis optica; ON: optic neuritis; OR: odds ratio; IFN: interferon.

Kim. Mult Scler 2017

Personalized Treatment in NMOSD



Rituximab (Mapthera®)

*고시 제 2015-172호(시행일:2015.10.1)

2. 허가사항 범위를 초과하여 아래와 같은 기준으로 투여 시 요양급여를 인정함.

가. ABO 혈액형 부적합 신이식 환자의 거부반응 예방에 375mg/m² 용량으로 1회

나. 패널반응성항체(Panel reactive antibody)>50% 또는 교차반응검사에서 양성에 해당하는 고도 감작된 신이식 환자의 거부반응 예방에 375mg/m² 용량으로 1회

다. 면역글로불린/혈장반출술 등의 치료에 반응하지 않는 신이식 후 발생한 급성 체액성 거부반응에 375mg/m² 용량으로 1회

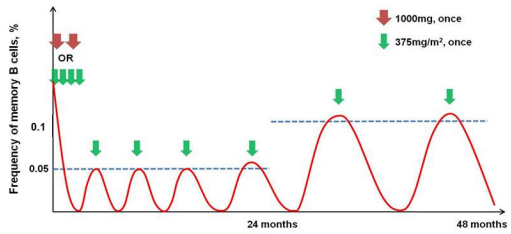
라. 면역억제제 감량에 반응하지 않는 이식 후 발생한 림프증식성 질환 (Posttransplant lymphoproliferative disease)에 375mg/m² 용량으로 4회

마. 소장이식후 거부반응 치료시에 375mg/m² 용량으로 1회

바. 시신경척수염(Neuromyelitis optica)으로 진단된 환자 중 기존 치료제에 부작용이 있거나 반응이 없는 경우

What is the maintenance regimen of rituximab treatment?

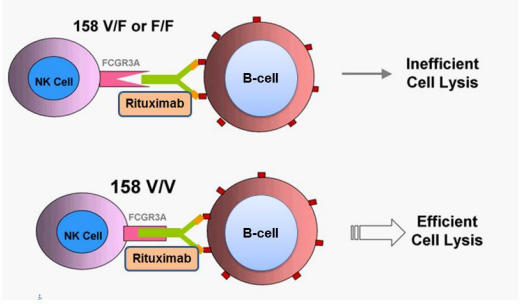
❖**Based on memory B cells in PBMCs**



Median interval of retreatment
1) initial 2 years : 4 months
2) next 3 years: 7 months

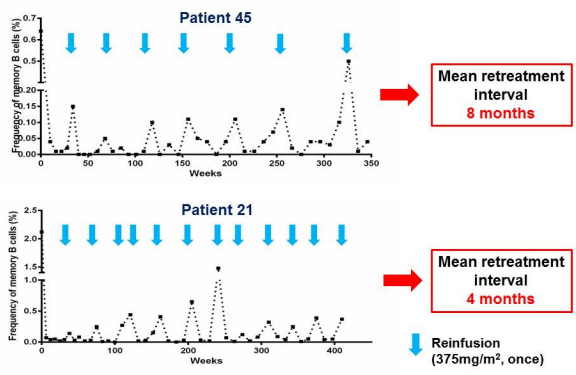
Kim, Arch Neurol 2011
Kim, JAMA Neurol 2013
Kim, JAMA Neurol 2015

FCGRIIIA variant affect efficiency of B cell depletion by rituximab



Dall'Ozzo,2004 Cancer Research

Individual variation of mean retreatment interval of rituximab treatment in NMOSD



What is the maintenance regimen of rituximab treatment?

**Conventional maintenance regimen of rituximab

retreatment (1000mg twice or once)
with every 6 to 9 months interval or
whenever CD19⁺ B cells > 1% of lymphocyte

=> But, these regimen was not sufficient to prevent recurrence of NMO in every patient.

Cree, 2005/ Jacob, 2008/ Pellkofer, 2011

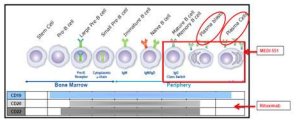
Another possible option for maintenance regimen in clinical practice
Retreatment (375mg/m² or 1000mg once)
with every 4-5 months interval at least initial 2 years or
whenever CD19⁺ B cells > 0.1% of lymphocyte.

Things to Keep in Mind about Rituximab Treatment in NMOSD

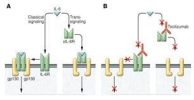
- ❖ 리툭시맙 치료 시작 후 조기 재발 (4-6주 이내)은 치료 실패로 섣불리 고려해서는 안 된다.
- ❖ 리툭시맙 치료에 따른 B-cell depletion은 환자간에 차이가 있으므로 적절한 효과를 위한 재치료 시기는 환자마다 다를 수 있다.
- ❖ 치료 초기 2년 동안 재발시 재치료 간격이 5개월 이상이거나, 말초혈액내 B 세포가 lymphocyte의 0.1%이상이라면 치료 실패가 아니라 불충분한 치료일 가능성을 고려해야 한다.
- ❖ 리툭시맙 치료 전후 혈액 내 면역글로불린 (IgG, IgM, IgA) 수치를 확인하고, 주기적인 모니터링이 필요하다. 치료 전 낮은 IgG 수치를 보이는 경우에는 리툭시맙 치료 후 감염의 위험성에 대하여 근접 감시가 필요하다.

Current clinical trials in NMOSD

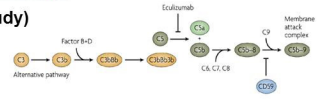
◆ **MEDI-551-anti-CD19 (N-Momentum)**



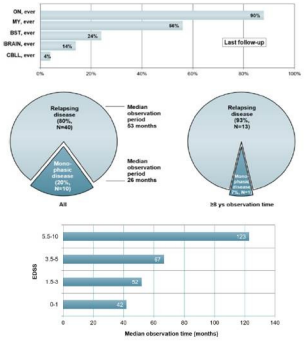
◆ **SA237 (anti-IL-6 receptor antibody) (Sakura Star study)**

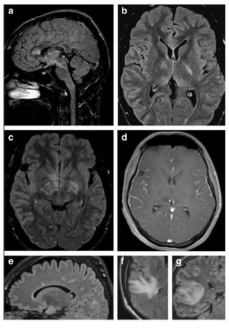


◆ **Eculizumab (PREVENT Study)**



Anti-MOG antibody related disorders





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