시신경척수염스펙트럼질환 치료의 최신 지견

김 수 현
국립암센터 신경과

Current Approaches for the Treatment of NMOSD

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Disclosure of conflict of interest

❖I have given talks, consulted and received honoraria and/or hospitality and/or support for research activities from following companies: Bayer Schering Pharma, Merck Serono, and Teva-Handok

❖I have a working relationship with the National Cancer Center, Korea.

Treatments of NMOSD

❖ **Acute treatment of relapses**
High dose IV methylprednisolone
Plasma exchange

❖ **Prevention of relapses**

❖ **Symptom management**

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

Azathioprine in NMOSD

- Azathioprine is a DNA synthesis inhibitor, as it is converted to a purine analogue with interference in the purine synthesis.

- 9 published studies
- Mean/median 15-47 months
- 2-3 mg/kg/day and/or PD (5-60mg)
- pre-ARR 0.9-2.3 => post ARR 0-0.6
- 74% of improved or stabilized disability

Pros
- Low cost
- High familiarity

Cons
- High risk of insufficient response
- Side effects
- Needs for concomitants PD

Mandler, 1998, Bichuetti, 2010, Constanzi, 2011, Kaegeyamma, 2013, Elsone, 2014, Mealy, 2014, Qui, 2015, Torres, 2015, Jeong, 2015

Mycophenolate mofetil in NMOSD

- Mycophenolate mofetil is a inhibitor of inosine monophosphate dehydrogenase (IMPDH), and inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA
- 4 published studies / median 20-27 months
- Oral 1500-2000mg/day
- Mean/median pre-ARR 1.3-2.6 => post ARR 0-0.3
- 91% of improved or stabilized disability

Pros
- Higher efficacy and less side effects compared to AZT

Cons
- Some patients still have relapses despite MMF therapy
- High cost

Jacob, et al. 2009, Huh, et al. 2014, Mealy, et al. 2014 Torres, et al. 2015

Rituximab in NMOSD

- Rituximab is a chimeric monoclonal antibody against the protein CD 20
- 17/ 19 published studies have reported significant effect for prevention of relapse in NMOSD.
- Mean/median 12-67 months
- Mean/median pre-ARR 1.3-2.9 => post ARR 0-0.9
- 89% of improved or stabilized disability

Pros
- High efficacy with tolerable safety

Cons
- High cost
- No standard regimen

Cree, 2005/Capobianco, 2007/ Jacob, 2008/ Pellkofer, 2011/ Bedi, 2011/ Kim, 2011/ Mashmodd, 2011/ Lindsey, 2012/ Kim, 2013/ Gredler 2013/ Kim, 2015/ Ip, 2013/ Yang, 2013/ Longoni, 2014/ Mealy 2014/ Zephir, 2014/ Torres, 2015/ Nosadini 2016,/ Annovazzi, 2016/ Radaelli, 2016

Mitoxantrone in NMOSD

- Mitoxantrone intercalates DNA and inhibits topoisomerase II, interfering with DNA repair.
- 3 published studies in total 76 patients
- Mean/median 12-41 months
- Mean/median pre-ARR 1.8-2.8 => post ARR 0.37-0.7
- 96% of improved or stabilized disability

Pros
- High efficacy
- Cheap

Cons
- Risk of serious side effects
- Limitation in cumulative dose (up to 72mg/m²)

Weinstock-Guttman, et al. 2006/ Kim, et al. 2010/ Cabre, et al. 2012

Tocilizumab in NMOSD

- Tocilizumab is a humanized monoclonal antibody against the interleukin-6 receptor.
- 6 case series (n=21)
- Mean treatment duration 6-31 months
- 8mg/kg IV every 4 weeks and/or steroid or AZT
- Relapse free rate 52%
- Stabilized disability 100%
- IL-6 blockade treatment may alleviate chronic pain in NMOSD

Araki, 2012/ Kieseier, 2012/ Ayzenger, 2013/ Lauenstein, 2014/ Ringelstein 2015

Summary of studies of immunosuppressive therapies for preventing relapse of NMOSD

	AZT	MMF	Rituximab**
Number of studies	9	4	19
Number of patients	427	121	428
Treatment duration, m	15-47	20-27	12-67
Relapse free rate (%)	51%	58%	63%
Disability worsening (%)	26%	9%	11%
Persistence (%)	71%	77%	92%
Sum of patient/year	747	236	1489

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

Comparison of treatment outcome in patients with NMOSD

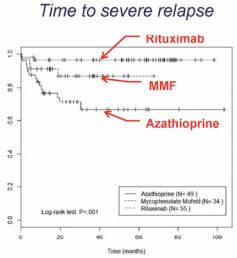
❖ **Treatment efficacy in NMOSD**
Rituximab > MMF > Azathioprine

Treatment associated relapse rate

Medication	Pretreatment ARR	Posttreatment ARR	Change From Pretreatment to Posttreatment, %
Azathioprine	2.26	0.63	72.1
Mycophenolate mofetil			
Optimal dosing	2.55	0.25	90.2
Rituximab			
Optimal dosing	3.25	0.20	93.9

Mealy ,2014 JAMA Neurol

Time to severe relapse



Jeong, 2015 Mult Scler

Concerns on the use of rituximab in NMOSD

What is the optimal 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/

ORIGINAL CONTRIBUTION

ONLINE FIRST

Repeated Treatment With Rituximab Based on the Assessment of Peripheral Circulating Memory B Cells in Patients With Relapsing Neuromyelitis Optica Over 2 Years

Su-Hyun Kim, MD; Woojun Kim, MD, PhD; Xue Feng Li, MD, MSc; In-Ja Jung, RN; Ho Jin Kim, MD, PhD

Research

Original Investigation

A 5-Year Follow-up of Rituximab Treatment in Patients With Neuromyelitis Optica Spectrum Disorder

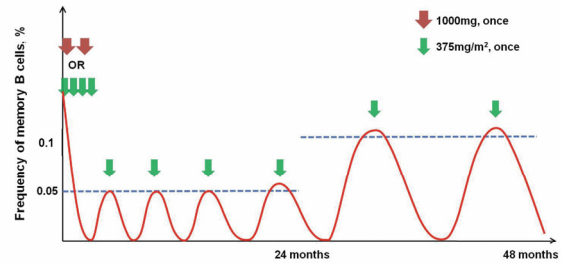
Su-Hyun Kim, MD; So-Young Huh, MD; Sun Ju Lee, MS; AeRan Joung, RN; Ho Jin Kim, MD, PhD

Original Investigation

Treatment Outcomes With Rituximab in 100 Patients With Neuromyelitis Optica
Influence of *FCGR3A* Polymorphisms on the Therapeutic Response to Rituximab

Su-Hyun Kim, MD; In-Hye Jeong, MD; Jae-Won Hyun, MD; AeRan Joung, RN; Hyo-Jin Jo, BS; Sang-Hyun Hwang, MD, PhD; Soolin Yun, MS; Jungnam Joo, PhD; Ho Jin Kim, MD, PhD

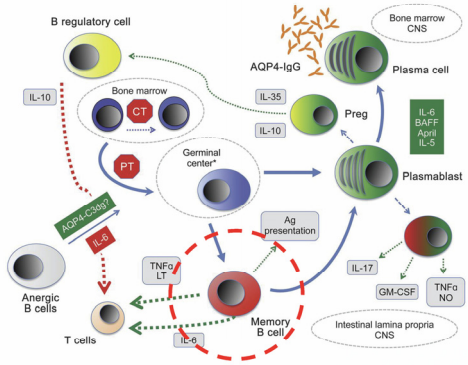
Repeated treatment protocol of rituximab



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

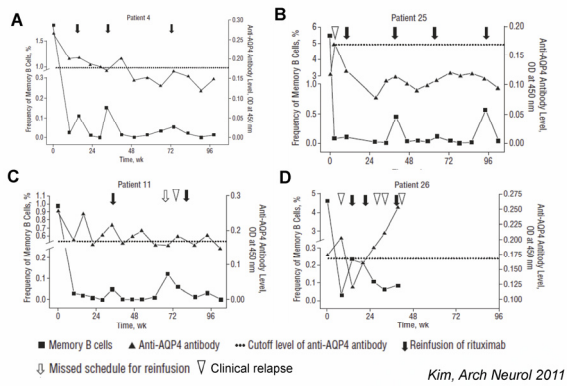
Kim, Arch Neurol 2011
Kim, JAMA Neurol 2013
Kim, JAMA Neurol 2015

Why are memory B cells important?



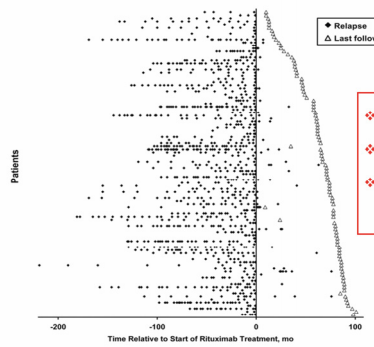
Bennett, 2015 Neurol Neuroimmunol Neuroinflamm

Depletion of memory B cells correlates with clinical response



Kim, Arch Neurol 2011

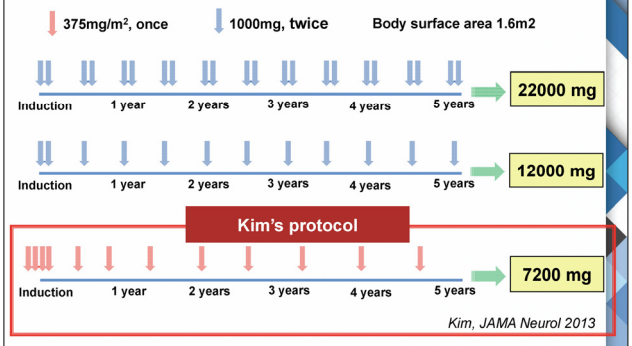
Relapses in 100 patients with NMOSD before and after median 67 months of rituximab treatment.



- Pre-ARR 2.4 -> post-ARR 0.1
- Relapse-free rate 70%
- Improved or stabilized disability 96%

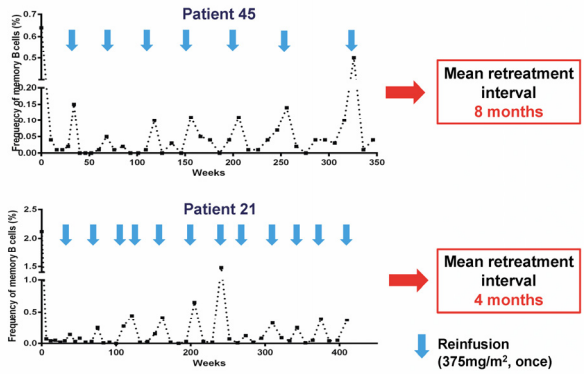
Kim, JAMA Neurol 2015

Tighter control of disease activity by predefined therapeutic target can enable control of the disease activity with a lower dose

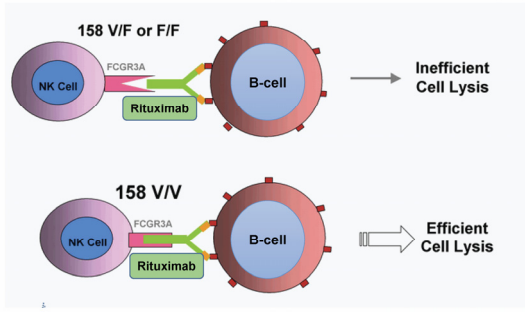


Kim, JAMA Neurol 2013

Individual variation of mean retreatment interval of rituximab treatment in NMOSD



FCGRIIIA variant affect efficiency of B cell depletion by rituximab



Dall'Ozzo,2004 Cancer Research

Biological response according to FCGR3A genotype

	Insufficient memory B cell depletion at 6–10 weeks after rituximab		Mean time to retreatment for initial 2 years	
FCGR3A	OR	p	Coefficient Estimate	p
Additive VF vs. VV	4.99	0.034	-3.48	0.027
FF vs. VV	24.87		-6.96	
Recessive V carriers vs. FF	0.18	0.032	5.12	0.011

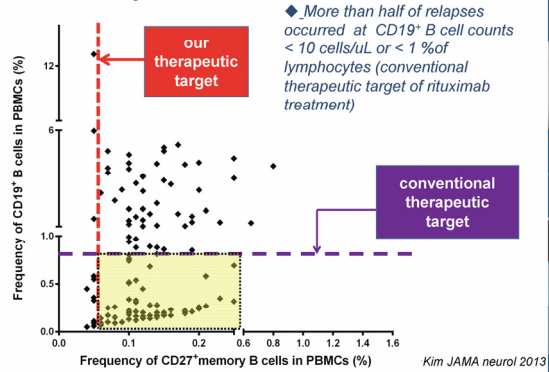
Kim, 2015 JAMA Neurol

Clinical Outcome according to *FCGR3A* Genotype

	Relapse ≥1		Relapse ≥2		Post-ARR		EDSS worsening	
	OR	p	OR	p	Coefficient Estimate	p	OR	p
FCGR3A								
Additive VF vs. VV	2.35	0.047	1.37	0.58	0.12	0.202	-	0.994
FF vs. VV	5.50		1.88		0.24			
Recessive V carriers vs. FF	0.35	0.038	0.88	0.847	-0.16	0.188	-	0.995

Kim, JAMA Neurol 2015

The reconstitution of CD19⁺ B cells is not necessarily proportional to repopulation of CD27⁺ memory B cells

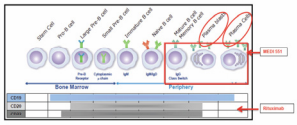


◆ *More than half of relapses occurred at CD19⁺ B cell counts < 10 cells/uL or < 1 %of lymphocytes (conventional therapeutic target of rituximab treatment)*

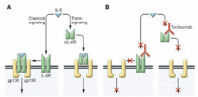
Kim JAMA neurol 2013

Current clinical trials in NMOSD

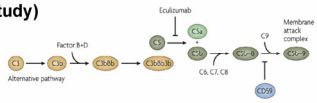
◆ MEDI-551-anti-CD19 (N-Momentum)



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

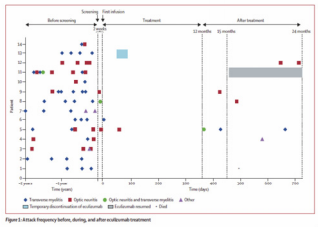


◆ Eculizumab (PREVENT Study)



Eculizumab in AQP4-IgG-positive relapsing neuromyelitis optica spectrum disorders: an open-label pilot study

- 14 patients with NMOSD received eculizumab for 52 weeks
- Relapse free rate: 86%
- Median ARR 3.0 (2-4) => 0.0 (0-1)
- Disability stabilized or decreased: 100%
- One patient had menigococcal sepsis, but recovered completely.



Pittock, 2013 Lancet Neurol

Current therapeutic options for NMOSD