KỶ NGUYÊN ĐIỀU TRỊ MỚI CỦA RỐI LOẠN PHỔ VIÊM TỦY THỊ THẦN KINH (NMOSD)

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Bộ môn Thần Kinh – BV ĐHYD

Rối loạn phổ viêm tủy thị thần kinh (NMOSD)

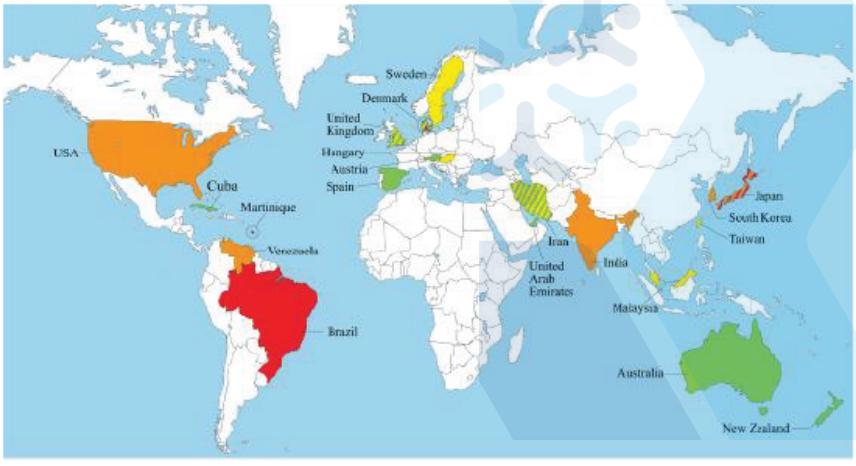


Figure. Global prevalence gradient for neuromyelitis optica spectrum disorders

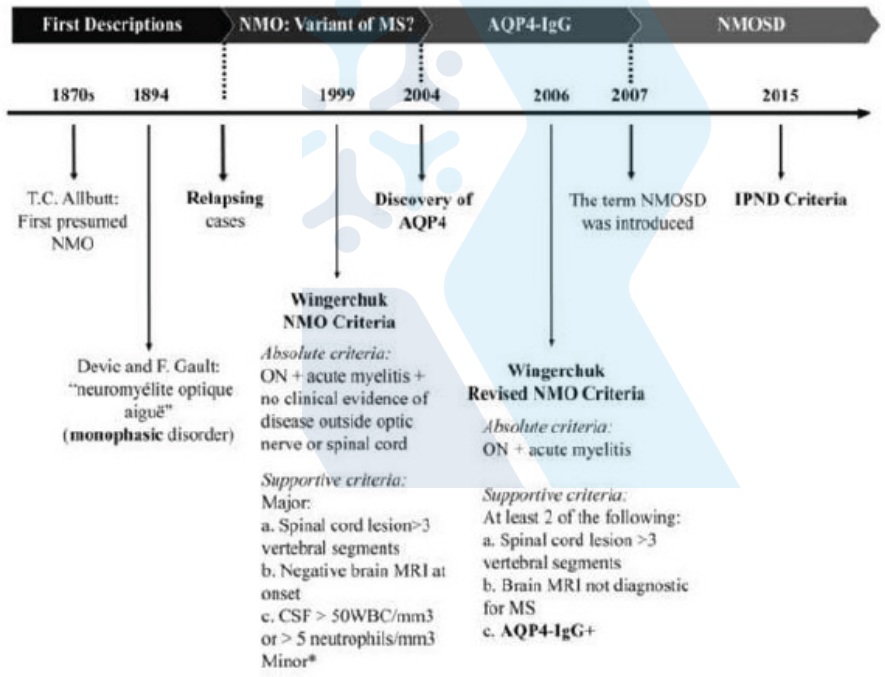
Costello F. Neuromyelitis Optica Spectrum Disorders. *Continuum (Minneap Minn)*. Aug 1 2022;28(4):1131-1170. doi:10.1212/con.0000000000001168

NMOSD thường gặp hơn ở nữ giới gấp năm đến mười lần so với nam giới.

Tỉ lệ hiện mắc ở Đan Mạch 4,4 trên 100.000 người và Nhật Bản ở mức 4,1 trên 100.000 người.
Tỉ lệ lưu hành ở nhóm dân số gốc Phi (Mỹ gốc Phi-Caribe) là 10 trên 100.000 người..

Độ tuổi trung bình khởi phát NMOSD là 39 tuổi.

Lịch sử phát triển của NMOSD



Nguồn: Internet

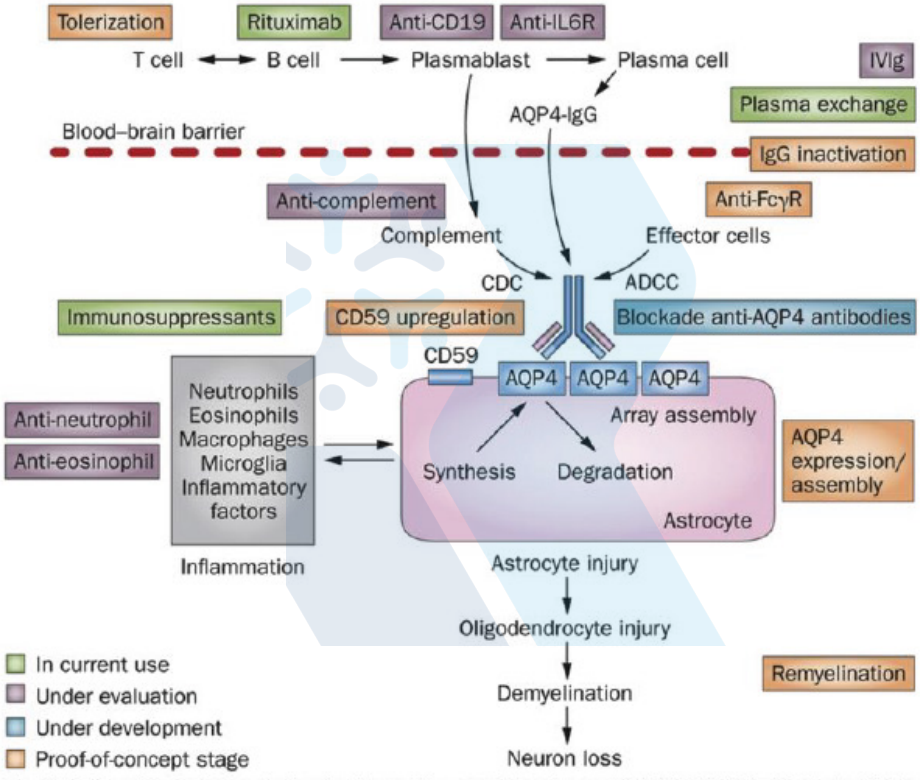


Fig. 21.12. Green boxes show mechanism-based approaches currently used to treat NMO (anti-CD20 antibody (rituximab);

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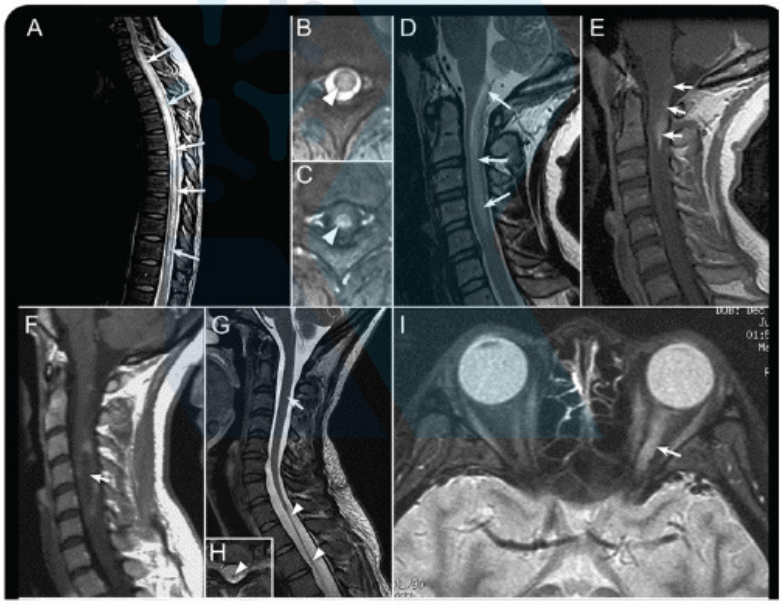
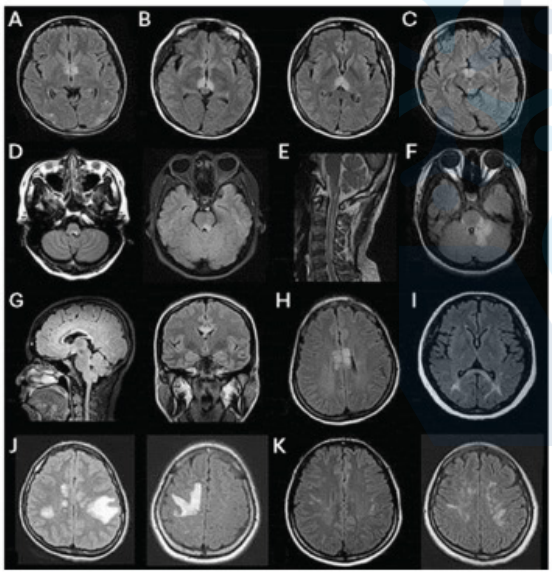
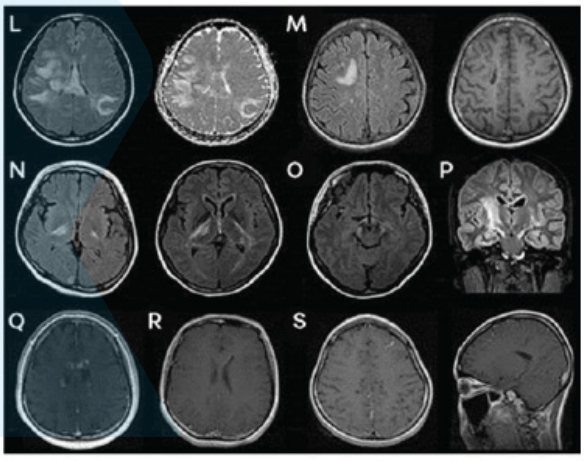
Đặc điểm tổn thương tủy và dây thần kinh thị trên MRI



Nguồn: *Wingerchuk DM (2015)*

Đặc điểm tổn thương não trên MRI của NMOSD





Nguồn: *Kim HJ (2015)*

Diễn tiến lâm sàng của NMOSD

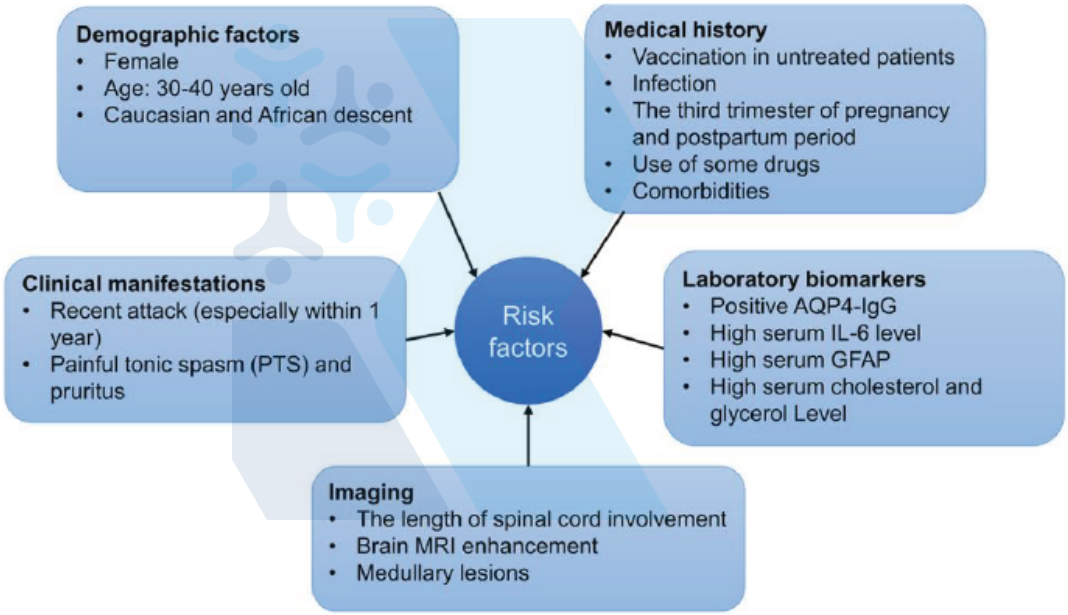
Trên thực tế có # 4% BN có biểu hiện đơn pha. 92% BN có kháng thể AQP4 dương tính bị tái phát.

Nếu không điều trị thuốc ƯCMD thích hợp, 50% NB sẽ phụ thuộc vào xe lăn và mù chức năng trong vòng 5 năm kể từ lần tấn công đầu tiên và một phần ba sẽ tử vong.

Ngày nay người bệnh NMOSD có dự hậu tốt hơn do được chẩn đoán sớm hơn, chính xác hơn và phương pháp điều trị hiệu quả hơn. 5 năm sau khi khởi phát, ít hơn 28% người bệnh NMOSD cần dùng gậy để đi lại và dưới 8% phải ngồi xe lăn.

Weinshenker BG, Wingerchuk DM. Neuromyelitis spectrum disorders. Mayo Clin Proc 2017;92(4): 663-679. doi:10.1016/j.mayocp.2016.12.014
Vincent S.J. Pittock and A. (2016), *"Handbook of Clinical Neurology"*.

Các yếu tố nguy cơ liên quan đến tái phát

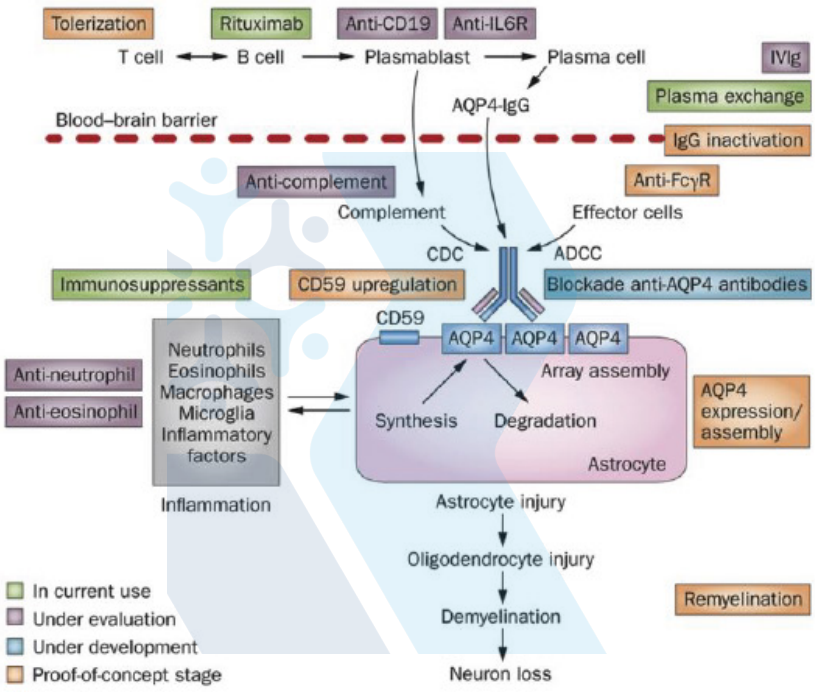


Ma X, Kermode AG, Hu X, Qiu W. Risk of relapse in patients with neuromyelitis optica spectrum disorder: Recognition and preventive strategy. *Mult Scler Relat Disord*. Nov 2020;46:102522. doi:10.1016/j.msard.2020.102522

Điều trị đợt cấp

Treatment	Typical dose	Mode of action
For acute exacerbation		
Methylprednisolone	1 g daily, for 3–5 days	Multiple
Plasma exchange	Five to seven cycles	Depletion of AQP4-IgG and cytokines
Intravenous immunoglobulin	0.7 g/kg for 3 days; treatment period 8 weeks	Multiple
Cyclophosphamide	2 g daily for 4 days	Inhibits mitosis

Papadopoulos MC, Bennett JL, Verkman AS (2014).Treatment of neuromyelitis optica: state-of-the-art and emerging therapies. Nat Rev Neurol 10: 493–506



Papadopoulos MC, Bennett JL, Verkman AS (2014).Treatment of neuromyelitis optica: state-of-the-art and emerging therapies. Nat Rev Neurol 10: 493–506

Điều trị phòng ngừa tái phát

TABLE 12-4 Common Maintenance Immunotherapy Regimens for Neuromyelitis Optica Spectrum Disorder[a]

Medication/Dose/Regimen (Adults)	Precautions/Monitoring/Prophylaxis	Common/Important Side Effects
Corticosteroids: prednisone/ methylprednisolone		
1 mg/kg prednisone orally once daily initially If adding rituximab, use prednisone concurrently for 1 month and then taper If adding azathioprine or mycophenolate mofetil, use prednisone concurrently for 6 months and taper over next 6 months; consider low doses (10-20 mg) in addition to azathioprine or mycophenolate mofetil to maintain remission if necessary Induction therapy of 1 g IV methylprednisolone daily for 5 days may be used before starting oral prednisone	Precautions/monitoring: assess for hyperglycemia if diabetic/at risk, baseline bone density scan in those at risk Prophylaxis: calcium 1500 mg/d and vitamin D 800 IU/d, trimethoprim-sulfamethoxazole one double-strength tablet (800 mg/160 mg) 3 times per week, proton pump inhibitor/histamine-2 receptor blocker in those at high risk for gastrointestinal ulceration	Infection, osteoporosis, avascular necrosis of the hip, cushingoid appearance, skin thinning and easy bruising, insomnia, psychosis, depression, cataracts, hypertension, weight gain and edema; addisonian crisis with abrupt discontinuation

Drug	Mechanism	Dosing options (regimens may vary)	Adverse effects	Indication
Off-label immunosuppressive (induction and maintenance) therapies				
Rituximab	Monoclonal antibody that binds to CD20+ B-lymphocyte surface antigen and depletes B cells	Suggested induction therapies: 375 mg/m^2/wk × 4 weeks or 1000 mg × 2 doses given over 2 weeks; followed by maintenance therapy of 375 mg/m^2 every 6 months	Late-onset neutropenia, hypogammaglobulinemia, reactivation of hepatitis B virus (leading to fulminant liver failure), infections (upper respiratory tract viral infections, nasopharyngitis, bronchitis, pneumonia, and sepsis), severe infusion reactions, tumor lysis syndrome, and mucocutaneous reactions; rare cases of progressive multifocal leukoencephalopathy have been reported	Has been shown to be more effective at suppressing relapses than many other off-label agents including azathioprine and mycophenolate mofetil
Azathioprine	A purine analogue that disrupts synthesis of DNA and RNA and induces T-cell apoptosis	Suggested dosing: 2 mg/kg/d to 3 mg/kg/d combined with oral prednisone initially (30 mg/d which is tapered after 6-9 months)	Neutropenia, leukopenia, pancytopenia, and severe myelosuppression; opportunistic viral, bacterial, and fungal infections	Has been shown to be inferior to rituximab and tocilizumab on relapses and disability progression in neuromyelitis optica spectrum disorders (NMOSD)
Mycophenolate mofetil	An inhibitor of inosine-5′-monophosphate dehydrogenase, a key enzyme in the de novo guanosine nucleotide synthesis	Suggested dosing: 1000 mg/d to 3000 mg/d (can be given in divided doses) combined with prednisone (30 mg/d tapered after 6-9 months)	Neutropenia, leukopenia, pancytopenia, and severe myelosuppression; opportunistic viral, bacterial, and fungal infections	Has been shown to be inferior to rituximab and tocilizumab on relapses and disability progression in NMOSD

Drug	Mechanism	Dosing options (regimens may vary)	Adverse effects	Indication
Off-label immunosuppressive (induction and maintenance) therapies				
Methotrexate	A folic acid analogue that increases extracellular release of adenosine to mediate anti-inflammatory effect	Suggested dosing: 15 mg/wk to 25 mg/wk	Gastrointestinal symptoms such as nausea or diarrhea, bone marrow depression, and an increase of liver enzymes	Retrospective studies in NMOSD showed a decrease of annual relapse rates between 64% and 87%
Mitoxantrone	A type II topoisomerase inhibitor that disrupts cellular DNA synthesis and repair by intercalation between DNA bases; inhibits proliferation of macrophages, B and T cells; induces apoptosis of B cells, monocytes, and dendritic cells; and decreases secretion of proinflammatory cytokines	Suggested dosing: 12 mg/m^2/mo for 6 months, followed by monthly maintenance dose of 6 mg/m^2; total cumulative dose <120 mg/m^2	Because of the side effects (cardiotoxicity, therapy-related acute leukemia) and the limited duration of the therapy, mitoxantrone use is generally not recommended; the maximum cumulative dose should not exceed 100 mg/m^2 body surface area	Has been associated with improved relapse rates and disability

Drug	Mechanism	Dosing options (regimens may vary)	Adverse effects	Indication
Off-label immunosuppressive (induction and maintenance) therapies				
Cyclophosphamide	An alkylating agent that forms DNA crosslinks, which is irreversible, and causes cell apoptosis, eliminates T regulatory cells, and induces T-cell growth factors including type I interferons	The treatment may be applied in immune-ablative doses (2000 mg/d for 4 days) or at a dose of 500 mg/m^2 to 600 mg/m^2 body surface area per administration; the dose should be adjusted according to changes in the total leukocyte count	Bladder cancer, gonadal toxicity, hemorrhagic cystitis; alopecia, nausea/vomiting, transient myelosuppression, and transient azoospermia	Has been associated with improved relapse rates and disability, but results are mixed[82]; it is only recommended when other immunosuppressive therapies fail or are not available

Drug	Mechanism	Dosing options (regimens may vary)	Adverse effects	Indication
Approved NMOSD maintenance therapies				
Eculizumab	Monoclonal antibody that binds to the complement component C5, inhibiting its cleavage and preventing the generation of the terminal complement complex; inhibits AQP4 antibody formation of the membrane attack complex	900 mg/wk IV for 4 weeks, then 1200 mg IV on week 5 and every 2 weeks thereafter	Headaches, leukopenia, and lymphopenia; complement inhibition increases the risk of infection with encapsulated bacteria, especially *Neisseria meningitidis* (meningococcal vaccination is mandatory before starting treatment); upper/lower respiratory tract infections, nasopharyngitis, influenza, pharyngitis, and bronchitis	The PREVENT trial[84] showed that eculizumab reduced the risk of relapse by 94% compared with placebo, and the risk reduction persisted at 48 and 144 weeks

Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. N Engl J Med 2019;381(7):614-625. doi:10.1056/ NEJMoa1900866

Drug	Mechanism	Dosing options (regimens may vary)	Adverse effects	Indication
Inebilizumab	A humanized, affinity-optimized, IgG1 monoclonal antibody that binds to the B-cell surface antigen CD19 with subsequent B cell and plasmablast cell lymphocytolysis; this effect decreases antibody production	300 mg IV 2 weeks apart, then every 6 months	Selective B-cell lymphopenia, rare cases of neutropenia and leukopenia; a 15% reduction in immunoglobulin levels (all types); nasopharyngitis, upper respiratory tract infection, influenza, influenzalike illness, and bronchitis	The N-MOmentum trial[85] showed inebilizumab reduced relapses from 39% vs 12% in all patients regardless of AQP4 serostatus

Cree BAC, Bennett JL, Kim HJ, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a doubleblind, randomised placebo-controlled phase 2/3 trial. Lancet 2019;394(10206):1352-1363. doi:10. 1016/S0140-6736(19)31817-3

Satralizumab	A monoclonal antibody against the IL-6 receptor; blocks the IL-6R and B-cell antibody production	Subcutaneous satralizumab 120 mg at weeks 0 and 2 and every 4 weeks thereafter, has been tested as monotherapy and as add-on therapy in two double-blind placebo-controlled phase 3 trials (SAkuraStar and SAkuraSky)[86,87]	Leukopenia, nasopharyngitis and upper/lower respiratory tract infections	In the SAkuraSky study (satralizumab plus background immunotherapy) 8 (20%) of 41 participants in the treatment arm relapsed over the course of the trial compared with 18 (43%) of 42 controls, resulting in a 62% reduction in adjudicated relapse risk over time; post hoc analysis by AQP4-Ig serostatus revealed a greater effect in the seropositive subgroup, with a 79% reduction in relapse risk compared with seropositive participants in the control group; serum AQP4-IgG-negative participants (n = 28; 14 in each arm) showed no reduction in risk of relapse with satralizumab compared with placebo[11]

Levy M, Fujihara K, Palace J, et al. New therapies for neuromyelitis optica spectrum disorder. Lancet Neurol 2021;20(1):60-67. doi:10.1016/ S1474-4422(20)30392-6

Kết luận

- NMOSD không chỉ đặt ra câu hỏi hóc búa về chẩn đoán mà còn đặt ra những thách thức trong điều trị.
- Trong thập kỷ qua, sự hiểu biết khoa học về các biểu hiện lâm sàng, các yếu tố nguy cơ liên quan đến tái phát và phương pháp điều trị NMOSD đã phát triển nhanh chóng.
- Trong kỷ nguyên điều trị hiện đại, lâm sàng chặt chẽ và khảo sát hướng đến BN sẽ cần thiết để đảm bảo tất cả BN NMOSD đều có thể tiếp cận các liệu pháp điều trị hiệu quả và an toàn.


Thank you for
your listening!