Điều trị NMOSD: cấp, phòng ngừa và triệu chứng

(Treatment of Neuromyelitis Optica Spectrum Disorder: Acute, Preventive and Symptomatic)

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Điều trị NMOSD

Neuromyelitis optica spectrum disorder (NMOSD):

- ❑. Hiếm gặp
- ❑. Tự miễn

Bệnh hệ tk trung ương tấn công chủ yếu thần kinh thị giác và tủy sống dẫn đến mù mắt và liệt 2 chi dưới

☞ *Đáp ứng tự miễn chuyên biệt đến kênh nước aquaporin-4 trên sao bào*

Quan. điểm hiện nay

☞ *Với nhận thức rộng hơn về NMOSD, điều trị chuẩn mực dựa trên hàng loạt nghiên cứu hồi cứu và tiền cứu*

- ❑. **Điều trị tái phát cấp (treatment of acute relapses)**
- ❑. **Phòng ngừa (preventive approaches)**
- ❑. **Điều trị triệu chứng NMOSD**

Giới thiệu

- . NMO chỉ công nhận như thực thể riêng biệt với multiple sclerosis (MS) trên 10 năm qua sau khi phát hiện biomarker antibody *(> 72 % bệnh nhân NMOSD với specificity > 99 %)*

- . NMOSD ước khoảng 1.5 % demyelinating diseases ở người châu âu, bắc phi, tây á, bắc phi, ấn độ(Caucasian), tỉ lệ hiện mắc 0.52 đến 4.4 /100,000.

❑. NMOSD được quan tâm rất nhiều do những hiểu biết bệnh lý của bệnh và xác định đích sinh học điều trị (druggable targets for therapy)

❑. Năm 2005, đích của NMO antibody được xác định là aquaporin-4 water channel (AQP4) trên sao bào hệ thần kinh trung ương

(Druggability is a term used in drug discovery to describe a biological target (such as a protein) that is known to or is predicted to bind with high affinity to a drug (sự giống nhau về cấu trúc với thuốc cao)

❑. Tấn công AQP4 qua trung gian tế bào B và T

❑**.** Bao gồm neutrophils và eosinophils, complement system, pathogenic antibodies,

(each of which has been successfully targeted for therapy in NMO)

Các nghiên cứu điều trị hiện nay căn cứ trên nc hồi cứu, một số nc tiền cứu mở

Mục tiêu điều trị NMOSD:

- **ức chế đợt viêm nhiễm cấp tái phát (suppression of acute inflammatory relapse)**
- **phòng ngừa tái phát (prevention of future relapses)**

Điều trị cấp

❑. NMOSD là bệnh tái phát, lập lại đợt tấn công dẫn đến tích lũy tổn thương thần kinh và tàn phế

❑. Ở thời điểm tái phát cấp tổn thương hệ tktư: phù, viêm nhiễm thứ phát

❑. Mục tiêu điều trị cấp:

+ ức chế viêm nhiễm (suppress acute inflammatory attack)
+ giảm tổn thương hệ tktư (minimize CNS damage)
+ cải thiện chức năng tk lâu dài
(improve long-term neurological function)

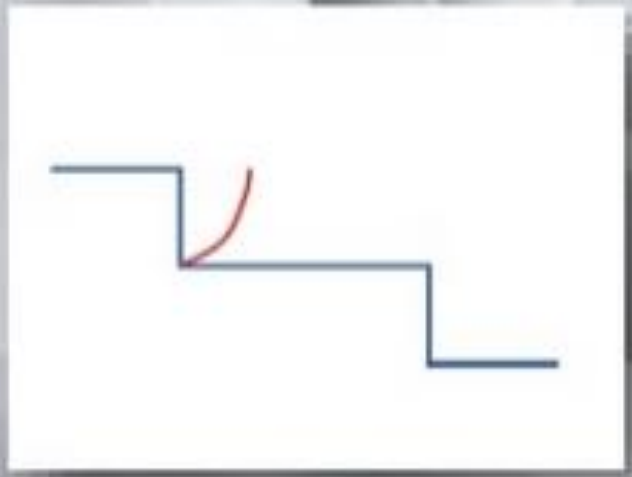
TREATMENT of the NMO relapse

aggressive relapse treatment

reduce permanent disability

Urgent IV Methylprednisolone
1g 3-5 days

poor response
significant disability
4-10 days



Prompt plasma exchang
5-7 days or
IVIG

Acute Treatment of NMO

- ***Currently Available (off-label):***

– IV Methylprednisolone
– Plasma exchange
– Cyclophosphamide
– IVIG???

Greenberg, 2011

❑. **Liều cao tĩnh mạch methylprednisolone được chấp nhận**

(first-line agent to broadly suppress inflammation in acute NMOSD relapses)

(This particular concern does not apply to NMOSD where studies have shown that permanent damage from relapses leads to cumulative disability. Therefore, the consensus among experts in NMOSD is that every relapse needs to be treated and high-dose corticosteroids are good starting agents because they are widely available, are simple to administer, and may provide some benefits in suppressing the acute inflammatory response)

❑. Liều khởi đầu điều trị NMOSD:

1000 mg methylprednisolone intravenously trong 5 ngày, thường theo sau steroid uống giảm dần 2-8 tuần tùy độ năng đợt tấn công

❑. Khởi đầu dùng corticosteroid trong NMOSD tái phát làm giảm phù và viêm nhiễm thứ phát, có thể ảnh hưởng tức khắc từ nhẹ đến trung bình chức năng thần kinh. Tổn thương dài và viêm nhiễm nặng, có thể chỉ định thêm liều steroid.

MỘT SỐ TÁC GiẢ ĐỀ NGHỊ

Methylprednisolone 1g TM trong 5 ngày tiếp theo uống prednisone(1mg/kg cân nặng cơ thể và giảm dần trên 6-12 tháng

❑. ***Nếu NMOSD không đáp ứng liều cao corticosteroids, thay huyết tương (plasma exchange (PLEX) cho thấy hiệu quả***

(PLEX involves the use of a centrifuge to separate the cells from a patient's plasma, whereupon the cells are returned to the patient and the plasma is replaced with saline±normal serum albumin. PLEX serves to remove plasma components involved in the inflammatory cascade and has the effect of suppressing active CNS inflammatory attack.)

KHUYẾN CÁO THAY HUYẾT TƯƠNG

❑. PLEX: 5-7 lần thay huyết tương thời gian trên 2 tuần
❑. PLEX thực hiện đầu tiên khi bn biết đáp ứng trong đợt tấn công trước và cơn tấn công nặng

- Relapses that do not respond to intravenous steroids could benefit from plasma exchanges (PLEX); typically 5–7 exchanges over a 2-week period.
- If the patient is known to have responded well to TPE during earlier attacks and the present attack is severe, TPE can also be considered as a first measure.
- Improvement - 44%–75% of the NMO patients treated with PLEX .
- Male gender, preserved reflexes and early initiation of treatment are associated with moderate or marked improvement.
- Efficiency of plasma exchange is independent of NMO-IgG seropositivity

Trong cả 2 trường hợp corticosteroids và corticosteroids+PLEX, mong đợi:

- Sau thời gian cải thiện đầu tiên, cải thiện được chức năng thần kinh 6-24 tháng trong quá trình lành bệnh

(In both cases of corticosteroids or corticosteroids plus PLEX, the expectation is that after an initial period of improvement due to resolution of secondary inflammation and edema, there is a period of 6–24 months during which the healing process can lead to further improvement in neurological function.

After the healing process, there can be additional improvements in function due to recruitment of other neurological circuits optimized by physical and occupational therapy)

ĐIỀU TRỊ IVIg

❑. IVIg chưa có báo cáo liên quan điều trị hiệu quả trong đợt cấp NMO

- No report concerning therapeutic efficacy of intravenous immunoglobulin (IVIG) for acute exacerbation of NMO.
- In a retrospective review of 10 patients treated with intravenous immunoglobulins (IVIg) for acute relapses because of lack of response to steroids with/without TPE, improvement was noted in about 50 % of patients

Cyclophosphamide trong giai đoạn cấp

(không đáp ứng steroid/PLEX)
Đặc biệt có bệnh tự miễn hệ thống, lupus….

Small case series also support the use of cyclophosphamide in acute steroid/PLEX-unresponsive NMOSD attacks, especially in the context of systemic lupus erythematosus (SLE) and other systemic autoimmune diseases)

Ức chế dòng thác bổ thể kinh điển

Nhiều điều trị cấp đặc hiệu trong NMOSD đã được nghiên cứu gần đây: ức chế dòng thác bổ thể kinh điển

- *Cinryze*
- *Solirs*

(More specific acute therapies in NMOSD have been trialed recently. Damage in NMOSD relapses is mediated in part by the classical complement system beginning with antibody fixation and ending with the membrane attack process.(hoạt hóa một phần bởi hệ thống bổ thể khởi đầu với cố định kháng thể và chấm dứt với tấn công màng)

An inhibitor of the classical complement cascade,

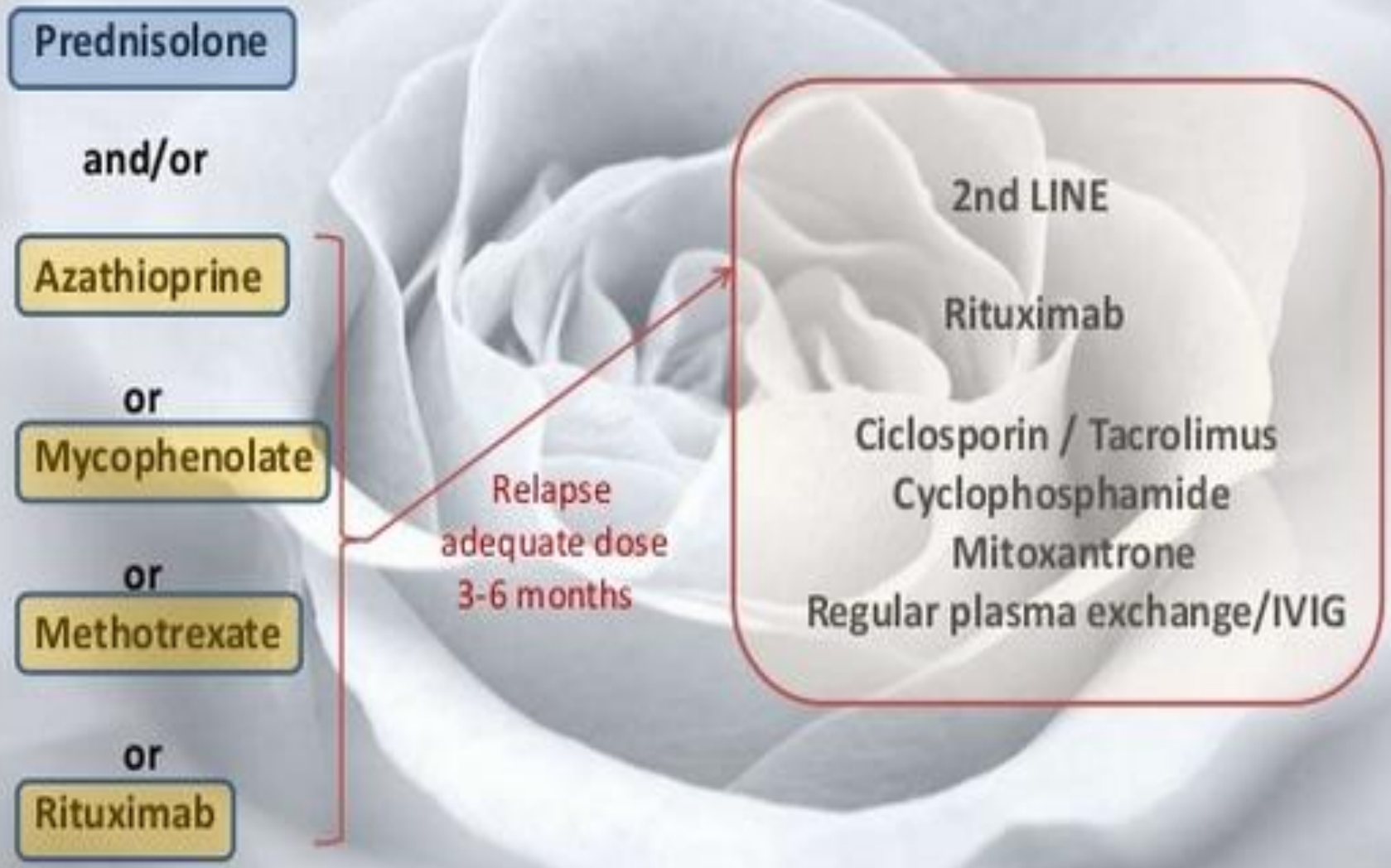
+ C1-esterase inhibitor (Cinryze®) was recently demonstrated to improve outcomes of nine of ten NMOSD subjects back to their baseline neurological function after an acute relapse of either optic neuritis or transverse myelitis in NMOSD.

+ Another complement inhibitor, eculizumab (Soliris®) is also in trials for benefit in prevention of relapses in NMO)

Phòng ngừa tái phát
(Preventing relapses)

- Mục đích điều trị NMO là giảm và phòng ngừa tái phát
- Immunotherapies (steroid: prednisolone)
- . Thêm vào azathioprine, methotrexate hay mycophenolate cho phép giảm steroids.
- Khi điều trị ức chế hệ thống miễn dịch, nguy cơ cao nhiễm trùng, theo dõi công thức máu, chức năng gan, thận

IMMUNOSUPPRESSANT ALGORITHM



NC điều trị phòng ngừa NMOSD năm 1998, dùng azathioprine trong 7 trường hợp. Từ đó thêm 6 NC azathioprine trên thế giới trên 03 trường hợp.

Từ năm 2006, NC retrospective và prospective với 2 nhóm thuốc ức chế chống miễn dịch khác: mycophenolate mofetil và rituximab, cho thấy ích lợi

Methotrexate, mitoxantrone và prednisone cũng đã được nghiên cứu trong NMOD

Azathioprine

(***Azathioprine is a purine analog that interferes with DNA synthesis of rapidly proliferating cells, especially B and T lymphocytes***.
(Can thiệp sự tổng hợp DNA của tế bào sinh sôi nhanh chóng, đặc biệt tế bào lymphocytes B vàT)

It was first used in heart and kidney transplants in the early 1960s and quickly adopted for treatment of a range of autoimmune diseases from hemolytic anemia to SLE and rheumatoid arthritis. It has been widely considered a first-line immunosuppressant medication for autoimmune diseases in combination with low-dose oral corticosteroids.

The first series of seven such subjects with NMOSD was published in 1998 by Dr. Mandler and colleagues who demonstrated that this combination of 2 mg/kg/day of azathioprine plus oral prednisone at 1 mg/kg/day for the first 2 months tapered works to improve neurological function after relapses and to prevent future relapses, at least over 18 months.

In this study, patients were enrolled shortly after a relapse so their baseline disability scores were high: the mean Expanded Disability Status Scale score (EDSS) was 8.2, which then improved to a mean of 4.0 at the conclusion of the trial).

This initial success with azathioprine plus prednisone prompted widespread use in NMOSD that continues to this day. Larger series have since supported the initial observations in both children and adults with doses of azathioprine at the higher range of 3 mg/kg/day plus concurrent prednisone showing more benefit than azathioprine monotherapy.

In three large NMOSD cohorts of 99 (Mayo), 103 (UK), and 77 (China) subjects treated with azathioprine for at least 1 year, treatment with azathioprine was successful in preventing relapses in 37–57% of subjects.

The annualized relapse rate (ARR) in the Mayo cohort dropped from 2.20 to 0.52 in those taking more than 2 mg/kg/day and dropped from 2.09 to 0.82 in those taking less than 2 mg/kg/day, suggesting a dose-response effect.

In all three large azathioprine studies, the effect of prednisone was less clear because concurrent prednisone was usually weaned down in subjects who were doing well while purposely maintained or increased among those who relapsed despite azathioprine

Side effects occurred in up to 60 % of patients taking azathioprine in these studies. The most common side effects were gastrointestinal and hematological, as with other diseases. In the Mayo cohort of NMOSD subjects, three of them (3 %) developed treatment-related lymphoma, a known risk of azathioprine use

.

The combined experience with azathioprine in NMOSD suggests the medication has an approximately 50/50 chance of preventing additional relapses.

Concurrent prednisone use helps to keep patients in remission while azathioprine takes effect, which can take up to 12 months. There are no reliable biomarkers of azathioprine effect used in common clinical practice but consensus opinion recommends increasing the dose of azathioprine closer to 3 mg/kg/day if initial treatment fails. And if the higher dose fails to keep the disease in remission, switching to another medication class, such as rituximab, is suggested

Mycophenolate

Mycophenolate mofetil, like azathioprine, is a purine analog anti-metabolite which interferes with lymphocyte proliferation.

But unlike azathioprine, it was developed to be a specific immunosuppressive agent with limited side effects by targeting guanosine more than adenosine.

Also, mycophenolate avoids production of thioguanosine which is incorporated into DNA and leads to treatment-related lymphomas with azathioprine.

In head-to-head studies *in autoimmune disease studies, mycophenolate is safer and slightly more effective than azathioprine*

Many autoimmune diseases in which azathioprine have shown a benefit have been tested for improved safety and efficacy with mycophenolate, and NMOSD is no exception.

The first series of 24 NMOSD subjects controlled on mycophenolate was published in 2009 and validated by additional groups in the US and Korea cohort sizes between 28 and 59 subjects.

Compared to azathioprine, these three studies suggest mycophenolate is more effective at achieving remission in 60–75 % of subjects with fewer side effects and adverse events, most of which were not serious

The recommended starting dose for mycophenolate is 500 mg twice daily with up-titration every 6 weeks until the absolute lymphocyte count reaches the stable target of 1000–1500 cells/μl of blood without causing a rise in liver enzymes.

Concurrent prednisone of 20–30 mg daily is typically used until the target lymphocyte count is reached, and then the prednisone is weaned off. In a few patients, a small dose of prednisone between 2.5 and 10 mg daily is continued if clinically indicated.

Rituximab

B cell depletion with anti-CD20 monoclonals *as a treatment for autoimmune disease was first demonstrated in rheumatoid arthritis using rituximab in 2004, and since then has been used to treat a wide number of autoimmune conditions including myasthenia gravis, lupus, and multiple sclerosis that share immunopathogenic mechanism with NMOSD.*
(làm suy yếu tế bào B kháng -CD20 ĐƠN DÒNG)

In 2005, the first open-label series of rituximab in NMOSD showed promise that has since been supported by 14 additional prospective and retrospective studies around the world with a total patient cohort of well over 300 subject.

Although none of these studies were placebo controlled, they all show a sustained and powerful benefit in the treatment of NMOSD. In studies with persistent B cell depletion, remission rates up to 83 % were achieved.

In retrospective head-to-head studies comparing azathioprine, mycophenolate, and rituximab in NMO, rituximab was the most effective option, followed by mycophenolate and then azathioprine

The proposed mechanisms of action of rituximab in NMOSD include removal of B cells as antigen-presenting cells and reduction in the CD20+ early plasmablast population generating anti-aquaporin-4 antibodies (ref).

Infusion of either 375 mg/m2 or 1000 mg of rituximab leads to rapid depletion of circulating CD20+ mature B cells within a few hours.

Additional doses of rituximab (375 mg/m2 ×4 total weekly doses or another 1000 mg 2 weeks after the initial 1000 mg dose) provide long-lasting B cell depletion for 6–8 months.

The goal of therapy is to keep B cells depleted at all times, which can be achieved either by scheduled infusions every 6 months or based on CD19/20 B cell counts tested monthly

B cells in peripheral organs and the CNS cannot be reached by intravenous rituximab and may explain why the risk of opportunistic infections in patients with autoimmune disease on rituximab is not statistically increased compared to placebo.

The most common and serious adverse reaction with rituximab is allergy due to lysis of circulating lymphocytes and release of cytokines and is greater in patients with replete B cell counts.

True anaphylactic reactions mediated by IgE have been reported, but most allergic infusion reactions to rituximab can be prevented by starting with a slow infusion rate and using preventive medications such as diphenhydramine (25–50 mg), methylprednisolone (100 mg), and acetaminophen (650 mg) up to 45 min prior to infusion

Các thuốc ức chế miễn dịch khác

*+ **Corticosteroids** have been used extensively in the treatment of autoimmune disease for decades. They are an effective add-on agent to prevent relapses in NMOSD when used with anti-metabolite such as azathioprine or mycophenolate and may be useful as monotherapy as well.*

However, the use of prednisone in NMOSD is limited by serious complications including hyperglycemia, hypertension, insomnia, mood swings, truncal weight gait, osteoporosis, and glaucoma

Dùng corticosteroids

Liều: 0,5-1mg/kg trong 3 tháng sau đợt tấn công và giảm dần trong 6-12 tháng

- Since the biological effects of many corticosteroid-sparing agents take months to have an effect, corticosteroids may be needed in many patients at doses 0.5–1 mg/kg for up to 3 months after an attack, and then slowly tapered off over further 6–12 months.

Liều thấp steroid lâu dài (Low dose long term steroids)

❑ Steroids là immunosuppressants tốt. Sau khi chẩn đoán NMO, steroid dùng cho đến khi thay thế điều trị khác
(thí dụ azathioprine có thể 3-6 tháng có hiệu quả). Trong nhiều bn tái phát có thể xảy ra ngay khi giảm từ từ steroids, thường dùng liều thấp trong thời gian dài, đòi hỏi liều duy trì

❑ Điều tri lâu dài chú ý tác dụng phụ: weight gain, acne, indigestion, cataracts, osteoporosis (thinning of the bones), deterioration of the head of the thigh bone and diabetes

.

❑ Bổ sung antacid (omperazole, lansoprazole) và bone protection (alendroic acid và calcium supplements).

Methotrexate , Mitoxantrone

+ Methotrexate is another anti-metabolite (like azathioprine and mycophenolate) that has been studied in NMOSD. Weekly methotrexate at a dose of 50 mg used as monotherapy or in combination with corticosteroids/cyclophosphamide led to remission in about two thirds of subjects. Methotrexate was generally well tolerated in these cohorts.

+ Mitoxantrone, an anthracenedione antineoplastic medication that intercalates DNA and inhibits topoisomerase II, has been studied in three patient populations and can lead to NMOSD disease remission in up to 70 % of subjects when dosed appropriately.

Serious adverse events including heart failure and leukemia observed in these small cohorts have curbed widespread enthusiasm for mitoxantrone in NMOSD

Có thể điều trị thêm (Further treatments available)

❑. Nếu điều trị trong nhóm đầu tiên không thuyên giảm, có thể cố gắng điều trị nhóm 2 (“second line”)

❑ Nhóm này ức chế miễn dịch manh hơn điều trị cơ bản

❑ Phần lớn thuốc hiệu quả nhiều hơn, nguy cơ tác dụng phụ cao hơn

Đang nghiên cứu về NMOSD

Three promising trials have launched in the NMOSD preventive therapy space, two of which have been tested in pilot studies in NMOSD, eculizumab and tocilizumab.

***+ Eculizumab is a C5 complement inhibitor** that blocks the terminal activation of complement and the membrane attack complex. The rationale behind testing a complement inhibitor in NMOSD is based on the pathology of NMO lesions showing extensive complement deposition.*

The success of this trial prompted a worldwide, placebo-controlled registrational trial of eculizumab in seropositive NMOSD, which is expected to complete enrollment in 2016.

In an open-label study of 14 subjects, of which 8 subjects proved unresponsive to other immunosuppressants, eculizumab appeared to suppress nearly all disease activities. Only two relapses occurred to all subjects over the year of treatment, and both of them were mild in severity. One subject became infected with meningococcal bacteremia, a known risk with eculizumab, but was treated and continued in the study.

+ ***Tocilizumab is a blocker of the interleukin-6 (IL-6) receptor*** *and has been approved for treatment of rheumatoid arthritis and juvenile idiopathic arthritis. The rationale behind testing an IL-6 receptor antagonist in NMOSD is based on the reportedly high levels of the pro-inflammatory IL-6 measured in the blood and spinal fluid of relapsing, actively inflamed NMOSD patients.*

In a pilot study of seven Japanese NMOSD patients, tocilizumab added to background immunosuppressants such as azathioprione or prednisone provided additional reduction in relapse rates . Plus, tocilizumab reduced pain scores in these subjects due to the role of IL-6 in spinal cord pain pathways.

The dual pain/immunosuppressive benefit was confirmed in a German study of eight NMOSD patients on tocilizumab monotherapy. These studies have prompted a worldwide, placebo-controlled registrational trial of SA237, an anti-IL-6 receptor blocking monoclonal antibody applied with recycling antibody technology that extends the dosing frequency to once monthly by intramuscular injection. This study is also expected to complete enrollment in 2016.

A third worldwide, placebo-controlled, registrational trial has launched in NMOSD testing the ability of MEDI-551, a CD19 monoclonal antibody, to prevent relapses. Based on the success of rituximab, a CD19+ B cell-depleting medication would be expected to perform as well or better because earlier B cells and more mature plasmablasts would be depleted compared to rituximab

Điều trị triệu chứng

Điều trị triệu chứng trong NMOSD:

+ bất động (immobility)
+ đau thần kinh (neuropathic pain),
+ co cứng(spasticity),
+ rối loạn tiểu(urinary retention/incontinence),
+ trầm cảm, mệt mỏi, rối loạn chức năng nhận thức(depression, fatigue, and cognitive dysfunciton)

CHƯA CÓ ĐẦY ĐỦ NGHIÊN CỨU

Biến chứng nghiêm trọng NMOSD: tổn thương tủy sống, thân não, thần kinh thị ảnh hưởng chất lượng cuộc sống. Hậu quả năng nề của viêm nhiễm hệ thần kinh trung ương thường gặp là "đau"

(Manifesting as a combination of neuropathic pain described as a constant burning, tingling, and electrical discomfort, and spastic pain described as an intermittent muscular tightening pain).

Nhận ra sự tái phát

Nhận ra sự tái phát và làm gì ?

Tái phát hay cơn tấn công NMO xảy ra khi:

- viêm nhiễm trong hệ thần kinh
- Trong NMO xảy ra ở tk thị và tủy sống
- viêm nhiễm gây triệu chứng mới hay triệu chứng tái phát

Tại sao tái phát xảy ra?

- ❑ Chưa biết nguyên nhân nào gây tái phát.
- ❑ Thường không tiên đoán
- ❑ Đôi khi có thể do nhiễm trùng hay stress

Triệu chứng tái phát.

- ❑ Bn NMO, tái phát thường cả tk thị và tủy sống

Viêm thần kinh thị giác

- Khi tk thị tái phát gây rối loạn thị giác, thường vài giờ hay vài ngày, triệu chứng vào buổi sáng thức dậy.
- Đau mắt khi nhìn, phía sau mắt, có thể kéo dài vài ngày, mù màu, những đợt nặng thị lực có thể mờ hay mất hoàn toàn.
- Đau nhói ngắn xung quanh mắt kéo dài ngắn vài giây hay vài phút không giống tái phát. Nhiều bn NMO thay đổi thị giác từng ngày

Viêm tủy cắt ngang

- Bn NMO có thể tái phát ở tủy sống, các triệu chứng:
  + yếu tay chân
  + bất thường cảm giác tê bì, châm chích tay chân, thân
  + đau vùng cổ, vai
  + rối loạn cơ vòng,

- Các triệu chứng có thể xảy ra riêng biệt hay kết hợp, thường tiến triển trong nhiều giờ hay nhiều ngày

- Đáng kể nếu kéo dài trên 24 giờ

Bn phải làm gì khi có tái phát ?

❑ Quan trong bn NMO tái phát cần đánh giá nhanh chóng

❑ Xin vui lòng theo hướng dẫn sau đây

+ Nếu cảm thấy có sự tổn thương thị giác hay bất cứ triệu chứng kể trên kéo dài hơn 24 giờ

"Please contact your NMO doctor Specialist"
VN ???

- Mỗi bn, mỗi tái phát sẽ có hình ảnh khác nhau và điều trị tùy thuộc vào nhu cầu từng cá nhân

.

- Quan trọng là cần nhanh chóng đánh giá trong tái phát và điều trị sớm có thể phòng ngừa tổn thương lâu dài

Hồi phục từ tái phát
(Recovering from a relapse)

- ❑ Thời gian hồi phục chức năng sau khi tái phát có thể rất lớn

- ❑ Yếu tố quan trọng xem xét bất cứ triệu chứng mới hay xấu đi kéo dài các triệu chứng tồn tại (trên 24 giờ) sẽ báo cáo với:

NMO team, neurologist or general practitioner or NMO team for further assessment.

- ❑ Đánh giá sớm và điều trị có thể cải thiện dự hậu và phục hồi sau tái phát

Các triệu chứng kéo dài sau tái phát hồi phục như thế nào ?

- Theo thời gian nhiều triệu chứng có thể hồi phục chức năng

- Triệu chứng cải thiện 2-6 tháng

- Tuy nhiên triệu chứng kéo dài như thay đổi thị lực, viêm tủy cắt ngang có thể xảy ra

- Một số bn sẽ còn lại rất ít triệu chứng từ tái phát, người khác nhiều hơn, độ nặng cũng sẽ khác biệt từng cá nhân

- Triệu chứng có thể dùng thuốc và cải thiện lối sống hàng ngày (‘lifestyle.’)

- ***Thuốc không ngăn ngừa tái phát trong tương lai (?)***

- Ở đây không có thuốc đúng(no ‘right’ drug) khi đáp ứng khác nhau với điều trị khác nhau

❑ Đau thần kinh (Neuropathic pain):

+ Thuốc đề nghị: amitriptyline, gabapentin, pregabalin và carbamazepine

.

❑ Đau thụ thể (Nociceptive (musculoskeletal) pain): trong NMO nguyên nhân áp suất đè trên khớp do thay đổi dáng đi

+ Thuốc đề nghị: paracetamol hay NSAID

There are four general classes of pain medications commonly used in NMOSD patients:

(1) anti-epileptic medications (e.g., gabapentin, carbamazepine),
(2) anti-spasmodics (e.g., baclofen, tizanidine),
(3) anti-depressants (e.g., amitriptyline, duloxetine),
(4) analgesics (e.g., tramadol, opiates).

First-line agents that have been most effective in treating both neuropathic and spastic pain are anti-epileptic medications. Gabapentin dosing is usually started at 300 mg three times daily and titrated up as needed weekly up to a maximum dose of 2400 mg per day.

In the absence of kidney disease, gabapentin monitoring is unnecessary and can be dosed at the minimum effective dose according to patient report of efficacy versus side effects with sedation as the dose-limiting factor. Carbamazepine at 100–200 mg twice daily is also particularly effective at treating both neuropathic and spastic pain in NMO and can be added to gabapentin

When a combination of two anti-epileptic medications is insufficient to manage neuropathic pain, an anti-depressant is usually added to the regimen.

Amitriptyline is a particularly effective agent in this regard starting at a dose of 25 mg nightly and titrating up biweekly to 150 mg nightly as tolerated, also limited by sedation. For those who cannot tolerate the sedation from amitriptyline, duloxetine at a dose of 60 mg twice daily is often an effective substitute.

❑ Tăng trương lực cơ và co thắc(Increased muscle tone and spasms arises): do tổn thương tủy sống ảnh hưởng kiểm soát cơ

+ thuốc đề nghị: baclofen, tizanidine, gabapentin.

❑ Co cứng cơ (Tonic spasms): đau do co thắc cơ từ vài giây đến vài phút, có thể thường xuyên

+ điều trị hiện nay Gabapentin và Carbamazapine

For NMOSD patients with persistent tonic spasms, rather than intermittent spasms, an anti-spasmodic can reduce the spasticity.

Baclofen at doses of 5–20 mg three times daily is good at reducing spasticity, as are other anti-spasmodics, but they can also make patients feel weaker especially while walking.

In a few patients where all efforts have failed to reduce pain to a tolerable level, analgesics can be used sparingly and temporarily while the long-term goal of finding other medications or non-medical interventions continues on a trial-and-error basis

❑ **Cứng khớp** (Joint Stiffness): luyện tập thường giúp ích

❑ **Yếu cơ** (Muscle weakness): không có thuốc cải thiện yếu cơ, luyện tập ích lợi

❑ Triệu chứng bàng quang: do rối loạn cơ vòng *(urgency, hesitancy, frequency and nocturia (passing urine at night) of micturition and retention (unable to pass urine))*

+ thuốc: oxybutynin hay solifenicin có thể giúp ích hay learning intermittent self catheterisation,

❑ Bón: do tổn thương tủy sống và bất động

+ nhuận trường, chế độ ăn nhiều chất xơ, nước(high fibre diet and fluids), abdominal massage

Urinary retention/incontinence

Micturition is initiated by the brain, which sends tracts to the bladder and pelvic floor through the spinal cord. Descending sympathetic and parasympathetic tracts run down the spinal cord in between the corticospinal tracts and the gray matter bilaterally.

Sympathetic nerves destined for the urethra and pelvic floor synapse in the intermediolateral nucleus of the lumbar cord function to close the sphincters to prevent urine leaks.

The parasympathetic serves destined for the bladder wall synapse in the lateral horn of the gray matter in the lumbar cord and function to contract the bladder during voiding.

An acute lesion of the cervical spinal cord would cause loss of function of both autonomic systems which causes both bladder flaccidity and incontinence.

Lower thoracic and lumbar lesions on the spinal cord cause acute urinary retention because of unbalanced sympathetic stimulation to the urethral outlet that exited the spinal cord rostral to the lesion. In these situations, patients are usually unable to sense that their bladder is full which can delay appropriate treatment

There are two options for patients with urinary retention. The most widely recommended option by urologists is clean, intermittent self-catheterization at least three times daily or more often depending on bladder volumes throughout the day.

In longer term, some patients opt for an indwelling suprapubic catheter but all catheters tend to become sources of infection over time. The second option is bethanechol, a parasympathetic agonist that increases bladder muscle tone and contraction at a dose of 25 mg three or four times daily. Bethanechol is best for those who have some retained ability to relax the urethral sphincter.

A trial of bethanechol can be performed within 1–2 h to determine whether it works for an individual patient. Side effects due to parasympathetic overstimulation are generally mild and include upset stomach, dizziness, and sweating/flushing

There are several options for patients with urinary incontinence. One approach involves scheduling frequent bathroom trips to keep the bladder from overfilling and thereby avoid leaks.

In combination with pelvic floor muscle exercises, this method can provide long-term control without medication or intervention. The problem with this approach is that patients cannot always plan a bathroom break especially while at work or traveling.

A second method to treatment urinary incontinence uses anti-cholinergic medications to block the parasympathetic innervation of the bladder wall therapy preventing spasms and allowing the bladder to expand without increasing pressure on the urethral sphincter.

There are six FDA-approved medications that can be tried for patients that work in this way.

A third method involves multiple injections of onabolutinumtoxinA (Botox) into the bladder wall to achieve a 3–6-month period of bladder wall relaxation.

Botox is somewhat more effective in blocking bladder spasms associated with urinary incontinence than medication (ref) and avoids medication side effects, but it does require repeat intervention 2–3 times per year when the Botox wears off.

- Sexual dysfunction

- Osteoporosis (brittle bones) – do dùng steroid kéo dài hay lack of weight-bearing activities

- Depression – thay đổi lifestyle phối hợp biến chứng NMO nguy cơ trầm cảm

- Triệu chứng thị giác (Visual symptoms) – hiện nay chưa có thuốc cải thiện chức năng thị giác sau đợt optic neuritis,

Fatigue/depression/cognition

Psychological issues related to NMO may be due to direct inflammatory influence on higher neuronal circuitry or may be related to complications from optic neuritis and transverse myelitis.

Among the most disabling of these psychological issues are fatigue, depression, and cognitive problems

The work-up for fatigue includes a thorough assessment of sleep habits, medication side effects, and depression.

NMOSD patients can have primary sleep disorders, as well as sleep disorders secondary to repeat awakenings due to nocturia, chronic pain, and obstructive sleep apnea.

Sleep disorders not only lead to fatigue, but they also impact a patient's recovery potential and overall neurological well-being.

Many medications that patients use for pain control and muscle spasticity cause fatigue. Sometimes, a transient side effect of fatigue is worth the benefit provided by the medication, but if not, alternative medications can be considered or the dose of the sedating medication can be reduced.

Stimulants such as modafinil have been used empirically in autoimmune neurological conditions and may be helpful in certain circumstances .

Depression in NMOSD has been recognized as both primary and secondary etiologies . In either circumstance, a combination of behavioral therapy, psychotherapy, and medication may be helpful.

Cognitive problems in NMOSD may be due to depression, fatigue, and medication but may occasionally be due to primary involvement of the subcortical or cortical brain matter.

Research in cognition of NMO patients is ongoing, and specific therapies have not yet been developed

Có thể cải thiện rõ triêu chứng có trong nhiều năm?

+ rất ít xảy ra
+ sự thích nghi cơ thể:

(modifications in house, wheelchair etc) and lifestyle modifications (change of job, moving to a single floor house) should be planned in advance and money spent wisely rather than waiting for 'miracles to happen' or trying out costly alternative medicines or exotic cures.)

+ ***"Sống với NMO"***

Điều trị bổ sung
(What about complimentary therapies?)

- Rất ít nghiên cứu cho thấy hiệu quả các phương pháp điều trị bổ sung

- *Complementary therapies can be used to target a specific physical, mental, emotional or spiritual problem, or as a preventative measure or purely for relaxation, and may increase your feeling of well-being.*

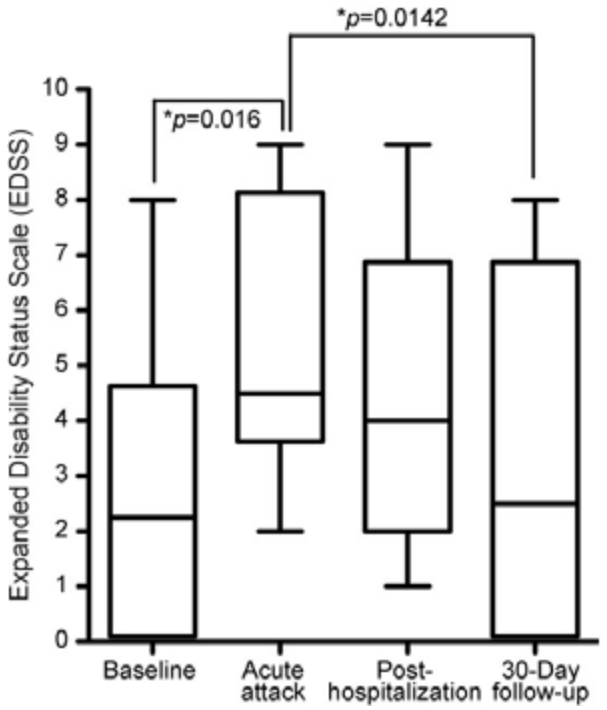
- *Reflexology, Massage, Reiki or Acupuncture may improve relaxation, sleep patterns, relieve pain or reduce stress and tension.*

Tương lai điều trị NMO

NMO is a very rare condition, as such a lot of the research and clinical trials in to the condition and future treatments are carried out at specialist centres like the John Radcliffe and Walton Centre.

Your local NMO team will be able to provide you with the most up to date information on the ongoing trials and research.

Acute Treatment of NMO: Block complement



Levy M. *Neurol Neuroimmunol Neuroinflamm. 2014 Apr 24;1(1):e5.*

Acute Treatment of NMO: Minimize BBB disruption

Three Phase III Trials in NMO!
(All preventive)

Actively Enrolling Clinical Trials

Industry Working For You - Cures of Tomorrow Begin Today

ALEXION

CHUGAI

MedImmune

Dự hậu

- Có thể monophasic với một cơn và lui bệnh thường trực tiếp theo.
- 85% bn có thể tái phát lập lại cơn tấn công transverse myelitis hay optic neuritis
- Dạng tái phát: *(usually weeks or months between the initial attacks and better motor recovery after the initial transverse myelitis event)*
- Tái phát sớm *(55% of patients relapse in the first year, 90% in the first 5 years)*
- Bn có thể visual loss và/hay paralysis thường trực

Take home massages:

1. NMO: bệnh mất myelin, gây hoại tử(necrosis) dây tk thị và tủy sống
2. Phối hợp bệnh tự miễn hệ thống hay cơ quan chuyên biệt *(Lupus, Sjögren's syndrome, MG, Celiac etc).*
3. Thường để lại hậu quả nghiêm trọng
4. Anti AQP4 Abs: test tất cả bn có triệu chứng NMO (optic neuritis and/or myelitis) cũng như malignant MS

   (With or without other autoimmune diseases,with neoplasia,with atypical ADEM, with unique symptoms - intractable hiccups or vomiting, symptomatic narcolepsy, olfactory dysfunction and neuroendocrine dysfunctions)

Cảm ơn sự theo dõi

PHỤ LỤC

DRUG	MECHANISM	DOSE	SIDE EFFERCTS	EFFICACY
Corticosteroids	Bind to glucocorticoid receptor, Induce gene expression and modulates immune function	**Acute attack:** methylprednisolone 1,000 mg, 3–5 days **Prophylaxis: prednisone** 2.5–20 mg/d	Insomnia, mood changes, weight gain,glaucoma, osteoporosis, diabetes, hypertension, growth impairment, insomnia	Reduced ARR from 1.48 to 0.49 EDSS was stable
Azathioprine	Acts as immunosuppressive antimetabolite by interfering with proliferation of T and B lymphocytes and alterations in antibody production	2 $mg \cdot kg^{-1} \cdot d^{-1}$	Bone marrow suppression, leukopenia, nausea, hepatotoxicity, diarrhea, hair loss, fatigue	Reduced ARR from 2.20–1.13 to 0.40–0.60 EDSS was stable

DRUG	MECHANISM	DOSE	SIDE EFFERCTS	EFFICACY
Mycophenolate	Reversible inhibitor of inosine monophosphate dehydrogenase that is involved in guanosine nucleotide synthesis Proliferation of T and B lymphocytes is impaired by interruption of guanosine synthesis	2,000 mg/d, range 750–3,000 mg	Leukopenia, skin malignancy, lymphoma, PML, headache, hair loss, diarrhea, constipation, bruising, anxiety	Reduced ARR from 1.28 to 0.09 EDSS was stable
Methotrexate	Inhibitor of dihydrofolate reductase and purine and thymidine synthesis Inhibits proliferation of T and B lymphocytes	17.5–50 mg/wk	Leukopenia, pancytopenia, infections, hepatotoxicity, joint pain, stomatitis, nausea, diarrhea	Reduced ARR from 1.39 to 0.18 EDSS was stable

DRUG	MECHANISM	DOSE	SIDE EFFERCTS	EFFICACY
Mitoxantrone	Intercalates with DNA and inhibits topoisomerase II Suppresses development of T and B lymphocytes and macrophages	max. cumulative doses 120mg/m^2 3–6 monthly cycles of 12 mg/m^2 followed by 6–12 mg/m^2 maintenance doses	Cardiotoxicity, leukemia, hepatotoxicity, leukopenia, nausea, stomatitis, diarrhea	Reduced ARR from 2.8 to 0.7 Reduced EDSS from 5.6 to 4.4
Rituximab	Chimeric anti-CD20 monoclonal antibody Depletes B cells from pre-B cells through memory lineages	Initiation with 375 mg/m^2 weekly for 4 wk, 1,000 mg twice biweekly, maintenance (1,000 mg) either fixed or upon recurrence of B cells	Infusion reactions, infections, (e.g. recurrent herpes zoster, respiratory infections, urinary tract infects), fatigue, transient leukopenia and transaminase elevati on, PML	Reduced ARR from 1.7–2.6 to 0.0–0.93 EDSS stabilized or improved

EFNS guidelines

	Drug name	Regimen
First-line therapy		
	Azathioprine	Oral 2.5–3 mg/kg/day
Plus	Prednisolone	Oral 1 mg/kg/day, tapered when azathioprine becomes effective (after 2–3 months)
OR		
	Rituximab	Option 1: i.v. 375 mg/m^2 weekly for 4 weeks (lymphoma protocol) Option 2: 1000 mg infused twice, with a 2-week interval between the infusions (rheumatoid arthritis protocol) Options 1 and 2: re-infusion after 6–12 months; however, optimal treatment duration unknown
Second-line therapy	Alphabetical order	
	Cyclophosphamide	i.v. 7–25 mg/kg every month over a period of 6 months, especially considered in case of association with SLE/SS
OR		
	Mitoxantrone	i.v. 12 mg/m^2 monthly for 6 months, followed by 12 mg/m^2 every 3 months for 9 months
OR		
	Mycophenolate mofetil	p.o. 1–3 g per day
Other therapies	IVIG, Methotrexate	
Escalation therapy		
AND	Intermittent plasma exchange	