MS Nurse Learning Program

UNDERSTANDING THE IMMUNE SYSTEM AND PROPOSED MECHANISM OF ACTION OF MAVENCLAD® (CLADRIBINE) TABLETS

GET STARTED

IMPORTANT SAFETY INFORMATION

INDICATION

MAVENCLAD® (cladribine) tablets is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS.

Limitations of Use: MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.

IMPORTANT SAFETY INFORMATION

WARNING: MALIGNANCIES and RISK OF TERATOGENICITY

- **Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy. In patients with prior malignancy or with increased risk of malignancy, evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis. Follow standard cancer screening guidelines in patients treated with MAVENCLAD**
- **MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the potential for fetal harm. Malformations and embryolethality occurred in animals. Exclude pregnancy before the start of treatment with MAVENCLAD in females of reproductive potential. Advise females and males of reproductive potential to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. Stop MAVENCLAD if the patient becomes pregnant**

CONTRAINDICATIONS

- Patients with current malignancy.
- Pregnant women, and women and men of reproductive potential who do not plan to use effective contraception during and for 6 months after the last dose in each treatment course. May cause fetal harm.
- Patients with human immunodeficiency virus (HIV).
- Patients with active chronic infections (e.g., hepatitis or tuberculosis).
- Patients with a history of hypersensitivity to cladribine.
- Women intending to breastfeed while taking MAVENCLAD tablets and for 10 days after the last dose.

WARNINGS AND PRECAUTIONS

- **Malignancies:** Treatment with MAVENCLAD may increase the risk of malignancy. After the completion of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years. In clinical studies, patients who received additional MAVENCLAD treatment within 2 years after the first 2 treatment courses had an increased incidence of malignancy. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after the completion of 2 treatment courses has not been studied. Follow standard cancer screening guidelines in patients treated with MAVENCLAD.
- **Risk of Teratogenicity:** MAVENCLAD may cause fetal harm when administered to pregnant women. In females of reproductive potential, exclude pregnancy before initiation of each treatment course of MAVENCLAD and prevent by the use of effective contraception during MAVENCLAD dosing and for at least 6 months after the last dose of each treatment course. Women who become pregnant during treatment with MAVENCLAD should discontinue treatment.
- **Lymphopenia:** MAVENCLAD causes a dose-dependent reduction in lymphocyte count. In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. The lowest absolute lymphocyte counts occurred approximately 2 to 3 months after the start of each treatment course and were lower with each additional treatment course. Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects. Monitor lymphocyte counts before and during treatment, periodically thereafter, and when clinically indicated.
- **Infections:** MAVENCLAD can reduce the body's immune defense and may increase the likelihood of infections. Infections occurred in 49% of MAVENCLAD-treated patients compared to 44% of patients treated with placebo in clinical studies. The most frequent serious infections included herpes zoster and pyelonephritis. Single fatal cases of tuberculosis and fulminant hepatitis B were reported in the clinical program. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD. Screen patients for latent infections; consider delaying treatment until infection is fully controlled. Vaccinate patients antibody-negative to varicella zoster virus prior to treatment. Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. Monitor for infections. In patients treated with parenteral cladribine for oncologic indications, cases of progressive multifocal leukoencephalopathy (PML) have been reported. No case of PML has been reported in clinical studies of cladribine in patients with MS.
- **Hematologic Toxicity:** In addition to lymphopenia, decreases in other blood cells and hematological parameters have been reported with MAVENCLAD in clinical studies. In general, mild to moderate decreases in neutrophil counts, hemoglobin levels, and platelet counts were observed. Severe decreases in neutrophil counts were observed in 3.6% of MAVENCLAD-treated patients, compared to 2.8% of placebo patients. Obtain complete blood count (CBC) with differential including lymphocyte count before and during treatment, periodically thereafter, and when clinically indicated.
- **Risk of Graft-versus-Host Disease With Blood Transfusions:** Transfusion-associated graft-versus-host disease has been observed rarely after transfusion of nonirradiated blood in patients treated with cladribine for non-MS treatment indications.
- **Liver Injury:** In clinical studies, 0.3% of MAVENCLAD-treated patients had liver injury (serious or causing treatment discontinuation) compared to 0 placebo patients. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment. Discontinue if clinically significant injury is suspected.
- **Hypersensitivity:** In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Hypersensitivity reactions that were serious and/or led to discontinuation of MAVENCLAD, occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. If a hypersensitivity reaction is suspected, discontinue MAVENCLAD therapy. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine.
- **Cardiac Failure:** In clinical studies, one MAVENCLAD-treated patient experienced life-threatening acute cardiac failure with myocarditis, which improved after approximately one week. Cases of cardiac failure have also been reported with parenteral cladribine used for treatment indications other than multiple sclerosis.

Adverse Reactions: The most common adverse reactions with an incidence of >20% for MAVENCLAD are upper respiratory tract infection, headache, and lymphopenia.

Drug Interactions/Concomitant Medication: Concomitant use of MAVENCLAD with immunosuppressive or myelosuppressive drugs and some immunomodulatory drugs (e.g., interferon beta) is not recommended and may increase the risk of adverse reactions. Acute short-term therapy with corticosteroids can be administered.

Avoid concomitant use of certain antiviral and antiretroviral drugs. Avoid concomitant use of BCRP or ENT/CNT inhibitors as they may alter bioavailability of MAVENCLAD.

Use in Specific Populations: Studies have not been performed in pediatric or elderly patients, pregnant or breastfeeding women. Use in patients with moderate to severe renal or hepatic impairment is not recommended.

Please see the accompanying full Prescribing Information, including **boxed WARNING** for additional information.

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INTRODUCTION

UNDERSTANDING THE IMMUNE SYSTEM AND THE PROPOSED MECHANISM OF ACTION OF MAVENCLAD® (CLADRIBINE) TABLETS

THE ROLE OF THE IMMUNE SYSTEM IN MS

HOW MAVENCLAD IS THOUGHT TO TARGET AND AFFECT THE IMMUNE SYSTEM

THIS SLIDE DECK AIMS TO HELP YOU:

01

Understand how the immune system is involved in the pathogenesis of MS and the differences between the innate and adaptive immune responses[1,2]

02

Understand the effect of MAVENCLAD treatment on the immune cells and lymphocyte counts of RMS patients[3,4]

03

Be comfortable explaining the immune system to patients and answering patient questions in a level of detail appropriate for each patient

Although MS is often described as a neurological condition, the immune system is critical to the pathology of the disease and, therefore, to disease management and treatment.[1,2]

02

THE ROLE OF THE IMMUNE SYSTEM IN MS

BEFORE COMPLETING THIS LEARNING SESSION, PLEASE TAKE A FEW MOMENTS TO CONSIDER THE FOLLOWING QUESTIONS

You may want to note your answers and then revisit the questions after completing the learning.

To what extent do you feel you can apply your understanding of the immunology of MS to your practice in general, and in regard to educating patients with RMS?

What are your main areas of uncertainty?

A patient with RMS asks you how MAVENCLAD works. What would you say?

What are your main areas of uncertainty?

An RMS patient considering MAVENCLAD wants to know how the treatment has affected the immune systems of RMS patients.

What would you say to this patient? What are your main areas of uncertainty?

THE IMMUNE SYSTEM AND MS

01

MS is an autoimmune disease, which means the immune system mistakenly attacks healthy cells, tissues, and organs in the body[2,5]

02

B and T cells normally protect us against infections and other diseases. In certain conditions, such as MS, the immune system attacks healthy cells[2,5]

03

In MS, B and T cells attack a substance in the nerves called myelin, causing inflammation and damage in the central nervous system and leading to the symptoms of MS[6]

04

Although there is currently no cure, **there are multiple treatments approved for relapsing forms of MS[7]**

THERE ARE 4 TYPES OF MS

CIS

Clinically isolated syndrome[8]

RRMS

Relapsing-remitting multiple sclerosis[8]

PPMS

Primary progressive multiple sclerosis[8]

SPMS

Active secondary progressive multiple sclerosis[8]

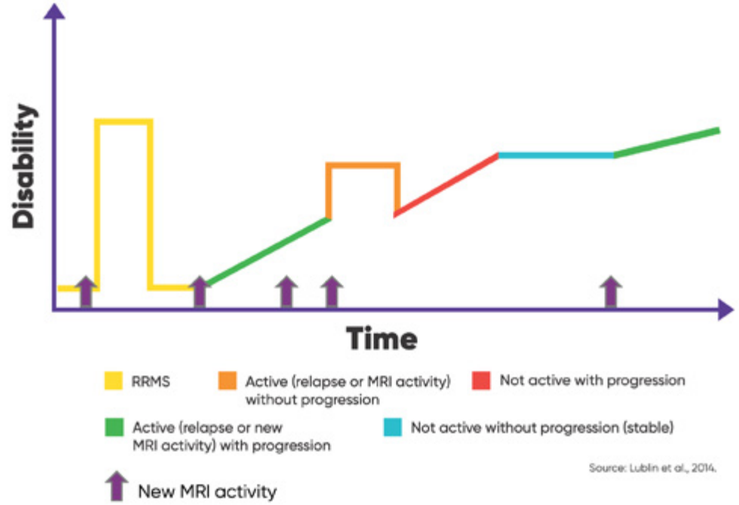
MAVENCLAD is not recommended for use in people with CIS and is not approved in people with PPMS.

MAVENCLAD is approved to treat relapsing forms of MS to include relapsing-remitting and active secondary progressive. Because of its safety profile, MAVENCLAD is generally used in people who have tried another MS medicine that they could not tolerate or that has not worked well enough.[3]

LET'S TAKE A LOOK AT THE 2 TYPES OF MS THAT MAVENCLAD IS INDICATED FOR[6,9,10]

Relapsing-remitting multiple sclerosis (RRMS)

Active secondary progressive multiple sclerosis (SPMS)



KEEP IN MIND THAT EACH PERSON'S SYMPTOMS AND EXPERIENCES ARE UNIQUE

Relapsing-remitting multiple sclerosis (RRMS) is the most common type of MS. Approximately 85% of people with MS are initially diagnosed with RRMS.[6,8,10]

- It is characterized by clearly defined attacks of new or worsening MRI activity. These attacks—also called relapses or exacerbations—are followed by periods of partial or complete recovery (remissions). During remissions, all symptoms may disappear, or some symptoms may continue and become permanent
- New lesions on MRI may develop as part of a relapse. New MRI lesions indicating MS activity may also occur without symptoms of which the person is aware

Active secondary progressive multiple sclerosis (SPMS) follows an initial relapsing-remitting course.[11]

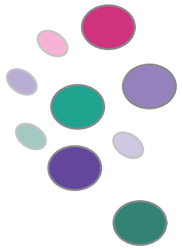
- Many people who are diagnosed with RRMS will eventually transition to an active secondary progressive course in which neurologic function (accumulation of disability) gets worse over time
- SPMS can be characterized at different points in time as either active or not active, as well as with progression or without progression
- MAVENCLAD is only for patients with active SPMS who continue to have relapses[3]

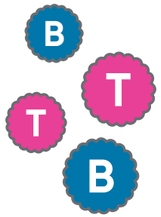
THE IMMUNE SYSTEM IS A COMPLEX NETWORK OF CELLS THAT WORK TOGETHER TO DEFEND THE BODY FROM INFECTION

These cells fall into 2 main groups: innate and adaptive

INNATE

Innate cells are the immune system's first line of defense, but their response is nonspecific. Their job is to recognize harmful agents in the body and respond to them immediately.[1,2]





ADAPTIVE

Adaptive immune cells called T and B cells (also known as lymphocytes) listen to the innate cells and respond over days or weeks to eliminate the specific virus or infection.[1]

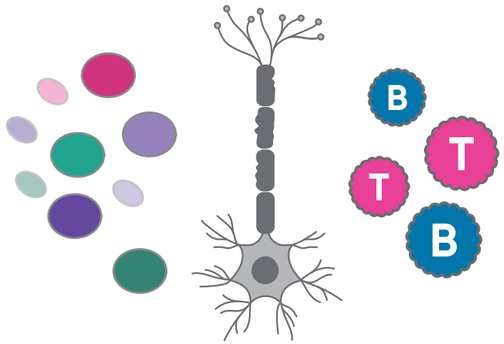
These cells also develop a memory so that the body is prepared the next time the harmful agent threatens the body.

YOUR IMMUNE SYSTEM IS A COMPLEX NETWORK OF CELLS THAT WORK TOGETHER TO DEFEND THE BODY FROM INFECTION

The immune system and MS

INNATE

For people with MS, some innate immune cells work as they should, but a few may play a role in the development and progression of MS.[5,13,14]



ADAPTIVE

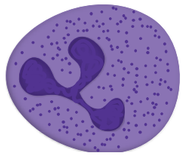
In MS, T and B cells do not communicate properly and become overactive, leading them to mistakenly attack the nerves in the central nervous system. This causes damage and inflammation, which show up as lesions and MS-related symptoms.[2]

UNDERSTANDING THE ROLES OF IMMUNE CELLS IS IMPORTANT TO RECOGNIZING THE PATHOLOGY OF MS[12]

Innate immune cells: First line of defense, serve as immune surveillance

NATURAL KILLER (NK) CELLS

- Induce cell death (apoptosis) in virus-infected cells[12]
- May play a role in MS pathogenesis[13]



NEUTROPHILS

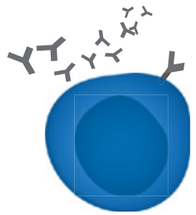
- Phagocytose bacteria and fungi[12]
- The role of neutrophils in MS is still emerging[14]

MONOCYTES

- Phagocytose pathogens and present antigens[12]
- May have a pro-inflammatory role in MS[5]

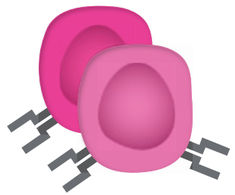
UNDERSTANDING THE ROLES OF IMMUNE CELLS IS IMPORTANT TO RECOGNIZING THE PATHOLOGY OF MS

Adaptive immune cells: Second line of defense, key drivers of neuroinflammation in MS



B CELLS

- Differentiate into antibody-secreting plasma B cells, including in response to vaccines[2,15]
- In MS, can produce antibodies that lead to myelin damage and present antigen to activate T cells



CD4+ HELPER T CELLS, CD8+ CYTOTOXIC T CELLS

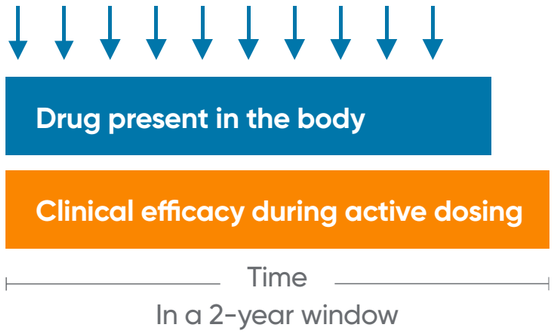
- Attack cells (eg, virus-/bacteria-infected cells, tumor cells), able to respond quickly to re-exposure[12]
- Help regulate the immune response and release pro-inflammatory proteins
- In MS, contribute to central nervous system inflammation and damage and do not function correctly[5,16]
- Widely implicated as pro-inflammatory cells

03

UNDERSTANDING HOW MAVENCLAD TARGETS AND AFFECTS THE IMMUNE SYSTEM

IN RMS, THERE ARE MULTIPLE TREATMENT APPROACHES TO CONSIDER THAT HAVE VARYING EFFECTS ON THE IMMUNE SYSTEM

IMMUNOMODULATION

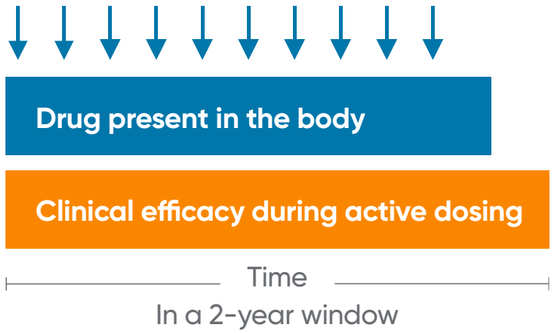


- Continuous administration[7]
- Ongoing modulation of immune function during active treatment without immunodepletion

Drug Administration

IN RMS, THERE ARE MULTIPLE TREATMENT APPROACHES TO CONSIDER THAT HAVE VARYING EFFECTS ON THE IMMUNE SYSTEM

CHRONIC IMMUNOSUPRESSION

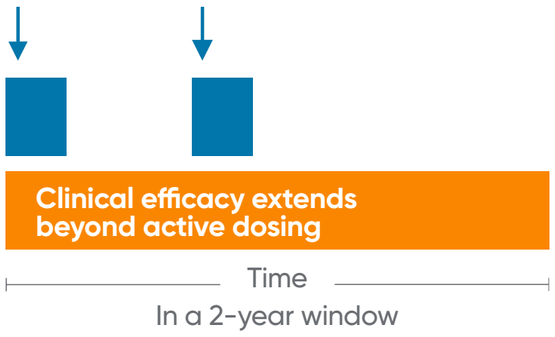


- Continuous administration[7,17]
- Ongoing suppression of immune function during active treatment

Drug Administration

IN RMS, THERE ARE MULTIPLE TREATMENT APPROACHES TO CONSIDER THAT HAVE VARYING EFFECTS ON THE IMMUNE SYSTEM

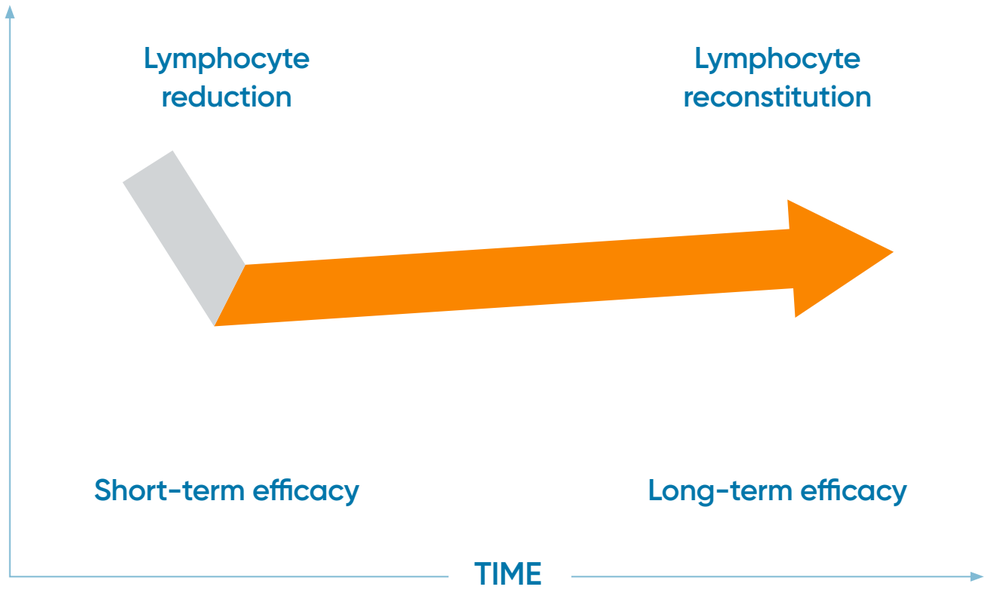
IMMUNODEPLETION FOLLOWED BY REPOPULATION



- Therapy administered intermittently as a short course[3,17]
- Dosing followed by depletion and repopulation

Drug Administration

MAVENCLAD IS THOUGHT TO WORK THROUGH IMMUNODEPLETION, FOLLOWED BY REPOPULATION



MAVENCLAD is associated with a reduction and subsequent recovery in lymphocyte count.[3]

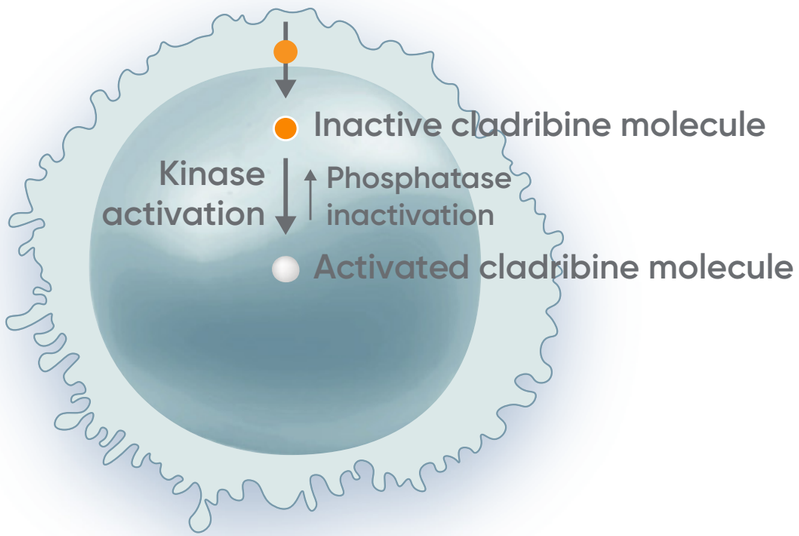
Lymphocytes generally recovered over several months or more and they may not go back to pre-treatment levels. Refer to slide 20 for the effect of MAVENCLAD on total lymphocytes.

Vaccination can be considered until 4-6 weeks prior to starting each MAVENCLAD course only if white blood cell counts are within normal limits. See more vaccine information on slide 30.

In an addition to lymphopenia, decreases in other blood cells and hematological parameters (neutrophils, hemoglobin, and platelets) have been reported with MAVENCLAD in clinical studies.

MAVENCLAD IS THOUGHT TO PREFERENTIALLY TARGET B AND T LYMPHOCYTES[4,18,19]

MAVENCLAD is a prodrug that is preferentially activated in B and T lymphocytes[4,18,19]



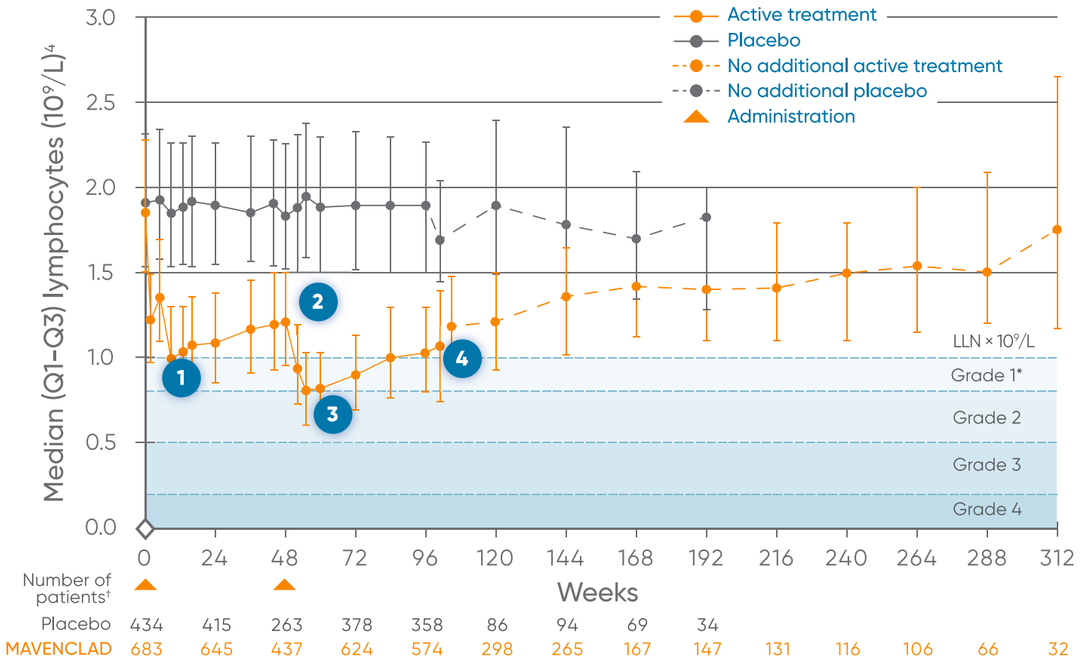
MAVENCLAD is a prodrug that is activated by specific kinases and deactivated by specific phosphatase.[3]

MAVENCLAD becomes active in the cells upon phosphorylation to its 2-chlorodeoxyadenosine triphosphate (Cd-ATP) metabolite.

Activated MAVENCLAD accumulates in B and T lymphocytes because they have a higher kinase-to-phosphatase ratio than other cells.[18]

The reduction of B and T lymphocytes by MAVENCLAD is believed to disrupt the immune cascade central to MS.[18]

EFFECTS OF MAVENCLAD ON TOTAL LYMPHOCYTES



For vaccination considerations and their relation to the lymphocytes as part of the white blood cell count, please see slide 30.

Post hoc analysis, percentage of patients who had median ALC at Grade 1 lymphopenia or within normal limits[4*†‡§]

1 Week 13 of Year 1

- Normal to Grade 1: **82.2%**
- Grade 2: 16.4%
- Grade 3: 1.3%
- Grade 4: 0.0%

2 Week 48 of Year 1

- Normal to Grade 1: **89.1%**
- Grade 2: 10.9%
- Grade 3: 0.0%
- Grade 4: 0.0%

3 Week 12 of Year 2

- Normal to Grade 1: **64.5%**
- Grade 2: 28.9%
- Grade 3: 6.7%
- Grade 4: 0.0%

4 Week 48 of Year 2

- Normal to Grade 1: **88.3%**
- Grade 2: 10.4%
- Grade 3: 1.3%
- Grade 4: 0.0%

*Grade 1, <LLN-800/µL; 2, <800-500/µL; 3, <500-200/µL; 4, <200/µL.[20]
†Visits with sample size ≥30 are displayed.[4]
‡Data were derived from a post hoc analysis of the 2 courses in patients receiving MAVENCLAD in CLARITY.[4]
§Percentages were calculated as a proportion of all patients with laboratory values at each time point. A total of 1.7% of patients (3/176) experienced >1 episode of Grade 4 lymphopenia at any time point during the entire trial period.[4]
ALC: absolute lymphocyte count; CLARITY: CLAdRIbine Tablets treating multiple sclerosis orallY; LLN: lower limit of normal.

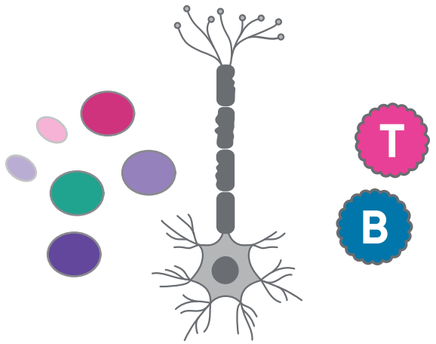
TREATMENT WITH MAVENCLAD HAD THE FOLLOWING RESULTS ON SELECT ADAPTIVE AND INNATE IMMUNE CELLS

MAVENCLAD and the immune system

INNATE

MAVENCLAD has the greatest impact on the adaptive immune system; therefore, there is less disruption of the innate immune cells.

This allows the innate cells to continue to help fight against new infections.[19,21,22] However, low blood cell counts have happened and can increase the risk of infections during treatment with MAVENCLAD.[23]



ADAPTIVE

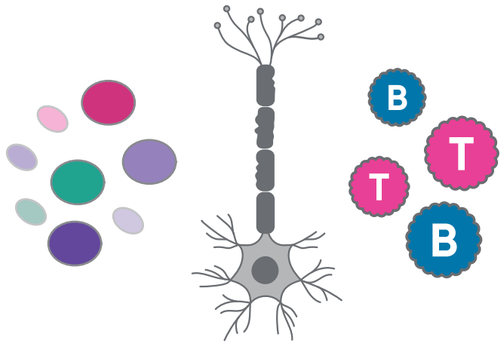
MAVENCLAD is believed to work by targeting and reducing the number of T and B cells in the body so that there are fewer of them to attack the nerves.[3] For most patients, the active ingredient in MAVENCLAD does not remain in the body beyond 1 week.[3,18,24] The numbers of T and B cells reach their lowest level about 2-3 months after the start of each treatment course and are lower with each additional treatment course.[3]

TREATMENT WITH MAVENCLAD HAD THE FOLLOWING RESULTS ON SELECT ADAPTIVE AND INNATE IMMUNE CELLS

MAVENCLAD over time

INNATE

In clinical trials, the average number of innate immune cells remained within normal levels before, during, and after treatment with MAVENCLAD.[4,19,21,22]



ADAPTIVE

Although a majority of patients in clinical trials experienced mild to moderate lymphopenia (low T- and B-cell counts), most had their cell counts return to normal range. It may take several months or more for the recovery of the T and B cells, and they may not go back to pretreatment levels.[3,4]

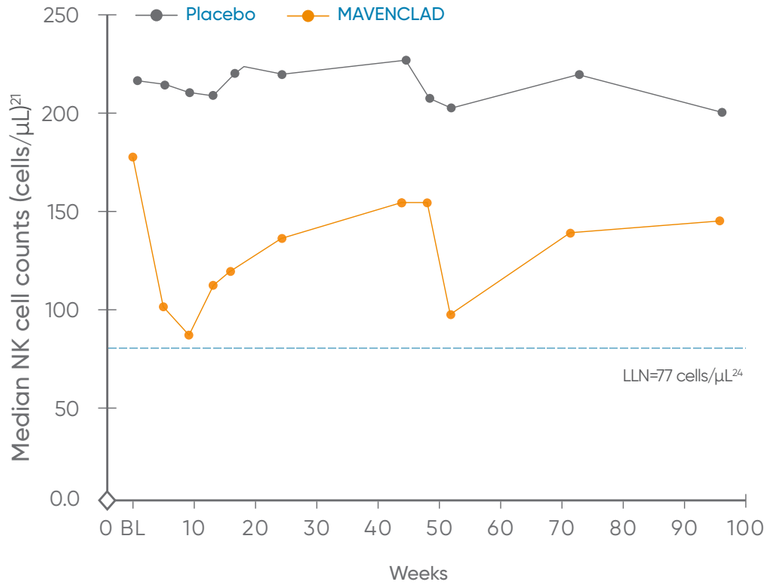
MAVENCLAD AND SELECT NATURAL KILLER (NK) CELLS

Post hoc analysis: median levels of NK cells remained within normal limits throughout MAVENCLAD treatment[21*†‡]

NK CELLS

Induce cell death (apoptosis) in virus-infected cells[12]

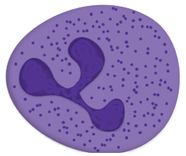
- Reduction in median NK cell counts followed by recovery, but median cell counts remained within normal limits throughout treatment[21]



*204 patients from a post hoc analysis of CLARITY ([n=98] for placebo, [n=101] MAVENCLAD) had lymphocytes and additional blood cells analyzed.
†Decreases in blood cells, other than lymphocytes, and hematological parameters have been reported with MAVENCLAD in clinical studies.[3]
‡In general, mild to moderate decreases in neutrophil counts, hemoglobin levels, and platelet counts were observed. Severe decreases in neutrophil counts were observed in 3.6% of patients treated with MAVENCLAD, compared with 2.8% of placebo patients.[3]
BL: baseline; CLARITY: CLAdRIbine Tablets treating multiple sclerosis orallY; LLN: lower limit of normal.

MAVENCLAD AND SELECT NEUTROPHILS

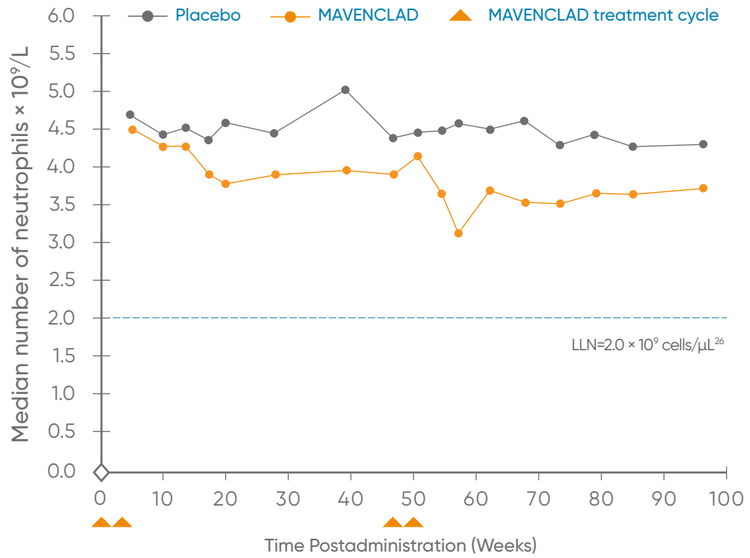
Post hoc analysis: median counts remained within normal limits[19,22]*



NEUTROPHILS

Phagocytose bacteria and fungi[12]

- Mild to moderate effects on neutrophils[19,22]
- Median cell counts remained within normal range throughout the treatment period



*Post hoc analysis of patients taking MAVENCLAD (n=103) and placebo (n=101) from CLARITY had lymphocytes and additional blood cells analyzed.
CLARITY: CLAdRIbine Tablets treating multiple sclerosis orallY; LLN: lower limit of normal.[19,22]

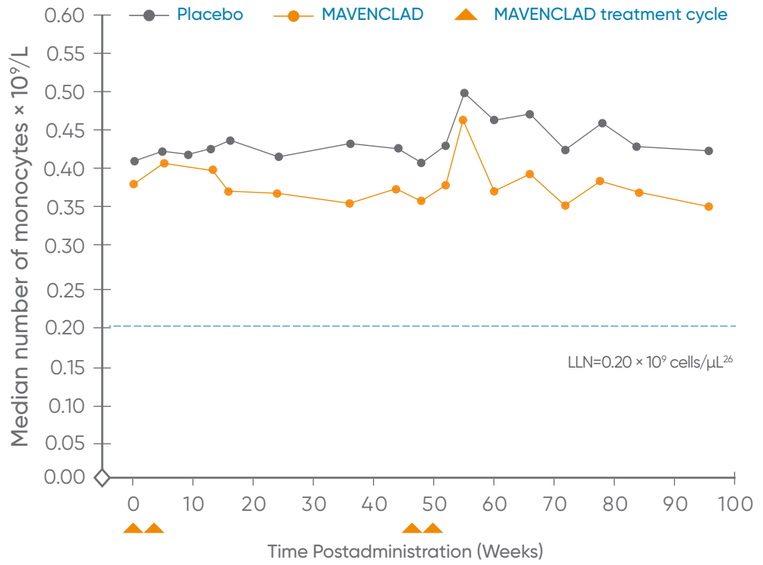
MAVENCLAD AND SELECT MONOCYTES

Post hoc analysis: median counts remained within normal limits[19,22]*

MONOCYTES

Phagocytose pathogens and present antigens[12]

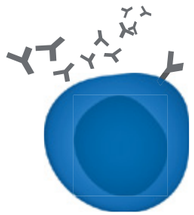
- Mild to moderate effects on platelets and monocytes[19,22]
- Median cell counts remained within normal range throughout the treatment period



*Post hoc analysis of patients taking MAVENCLAD (n=103) and placebo (n=101) from CLARITY had lymphocytes and additional blood cells analyzed.
CLARITY: CLAdRIbine Tablets treating multiple sclerosis orallY; LLN: lower limit of normal.[19,22]

MAVENCLAD AND SELECT B CELLS

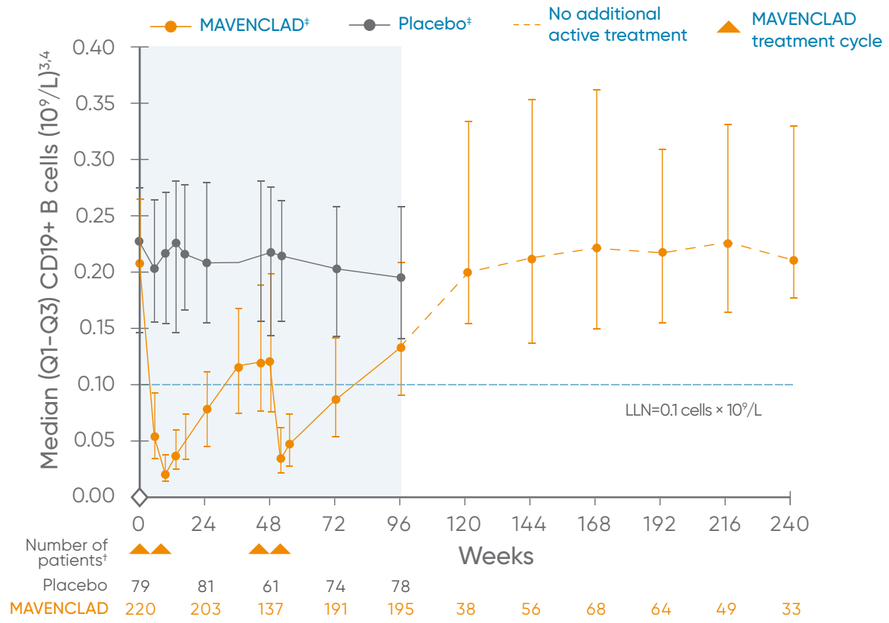
Pooled clinical trial data: MAVENCLAD treatment resulted in sharper depletion, followed by recovery, of CD19+ B cells, compared to T cells[2,15*†‡]



B CELLS

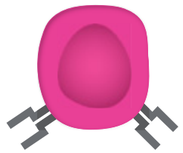
In MS, can produce antibodies that lead to myelin damage and present antigen to activate T cells[2,15]

- Treatment resulted in sharper depletion, followed by recovery of CD19+ B cells, compared to T cells[4,22]



*Pooled data from CLARITY, CLARITY EXT, and PREMIERE.[4]
†Median CD19+ B cells reached a nadir at 2 months (median 0.018 × 10^9 cells/µL) and then gradually increased.[4]
‡MAVENCLAD/placebo were administered as 2 courses separated by 1 year (a maximum of 20 days of treatment). Each course consisted of 2 treatment weeks: 1 at the beginning of the first month and 1 at the beginning of the second month. Data from patients randomized to placebo in CLARITY or who received a cumulative dose of MAVENCLAD for 2 years in CLARITY or CLARITY EXT were included. Any relevant follow-up in CLARITY EXT and PREMIERE are also reported.[3,4]
CLARITY: CLAdRIbine Tablets treating multiple sclerosis orallY; LLN: lower limit of normal.

MAVENCLAD AND SELECT CD4+ HELPER T CELLS, CD8+ CYTOTOXIC T CELLS[4]*

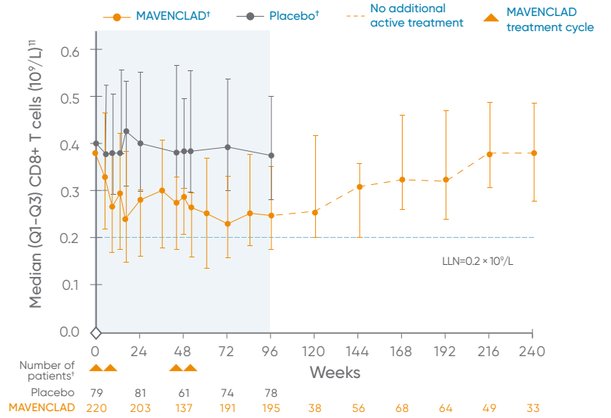


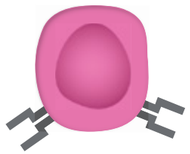
CD8+ CYTOTOXIC T CELLS

In MS, contribute to CNS inflammation and damage[5,16]

MAVENCLAD treatment resulted in[4]:

- Reduction in T cells
- Median CD8+ T-cell counts decreased, followed by recovery



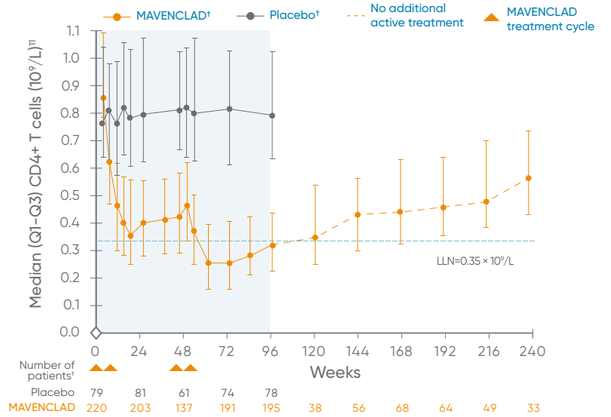


CD4+ HELPER T CELLS

In MS, do not function correctly and are widely implicated as pro-inflammatory cells[5,16]

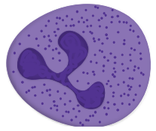
MAVENCLAD treatment resulted in[4]:

- Reduction in T cells
- Median CD4+ T-cell counts decreased, followed by recovery

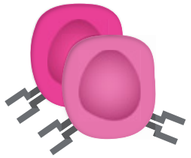


*Pooled data from CLARITY, CLARITY EXT, and PREMIERE.
†MAVENCLAD/placebo were administered as 2 courses separated by 1 year (a maximum of 20 days of treatment). Each course consisted of 2 treatment weeks; 1 at the beginning of the first month and 1 at the beginning of the second month. Data from patients randomized to placebo in CLARITY or who received a cumulative dose of MAVENCLAD for 2 years in CLARITY or CLARITY EXT were included. Any relevant follow-up in CLARITY EXT and PREMIERE are also reported.
CLARITY: CLAdRIbine Tablets treating multiple sclerosis orallY; CNS: central nervous system; LLN: lower limit of normal.[4]

SUMMARY OF MAVENCLAD ACTION ON SELECT IMMUNE CELLS IN CLINICAL STUDIES

	Role of MAVENCLAD in the immune system	MAVENCLAD MOA
	**NATURAL KILLER (NK) CELLS**[12,13] • Induce cell death (apoptosis) in virus-infected cells • May play a role in MS pathogenesis	MAVENCLAD treatment resulted in median NK cells counts remaining within normal limits in patients.[21]
	**NEUTROPHILS**[12,14] • Phagocytose bacteria and fungi • The role of neutrophils in MS is still emerging	MAVENCLAD treatment resulted in a mild to moderate effect on neutrophils. Median cell counts remained within normal range.[19,22]
	**MONOCYTES** (MACROPHAGES AND DENDRITIC CELLS) • Phagocytose pathogens and present antigens • May have a pro-inflammatory role in MS[5,12]	MAVENCLAD treatment resulted in a mild to moderate effect on platelets and monocytes. Median counts remained within normal range.[19,22]

SUMMARY OF MAVENCLAD ACTION ON SELECT IMMUNE CELLS IN CLINICAL STUDIES (CONT'D)

	Role of MAVENCLAD in the immune system	MAVENCLAD MOA
	**B CELLS[2,15]** • Differentiate into antibody-secreting plasma B cells, including in response to vaccines • In MS, can produce antibodies that lead to myelin damage and present antigen to active T cells	MAVENCLAD treatment resulted in sharper depletion, followed by recovery of CD19+ B cells, compared to T cells.[4,22]
	**CD4+ HELPER T CELLS, CD8+ CYTOTOXIC T CELLS[12]** • Help regulate the immune response and release pro-inflammatory proteins • Attack cells (eg, virus-/bacteria-infected cells, tumor cells), able to respond quickly to re-exposure • In MS, contribute to central nervous system inflammation and damage, do not function properly[5,16] • Widely implicated as pro-inflammatory cells	**MAVENCLAD treatment resulted in reduction in T cells[4]** • CD4+ cells were more sensitive to MAVENCLAD than CD8+ cells • Median CD8+ counts remained within normal limits throughout the treatment period

CONSIDER THE FOLLOWING ASPECTS AROUND LYMPHOCYTES AND VACCINATIONS FOR PATIENTS

MAVENCLAD can reduce the body's immune defense and may increase the likelihood of infection.[3,22]

A complete blood count must be performed with a differential including lymphocyte count[3]

- Lymphocytes must be within normal limits before initiating the first treatment course and at least 800 cells/µL before initiating the second treatment course. If necessary, delay the second treatment course for up to 6 months to allow for recovery of lymphocytes to at least 800 cells/µL. If this recovery takes more than 6 months, the patient should not receive further treatment with MAVENCLAD

Immunizations: Administer all immunizations according to immunization guidelines prior to starting MAVENCLAD[3]

- Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD because of a risk of active vaccine infection. Vaccinate patients who are antibody-negative for varicella zoster virus, eg, with either an inactivated recombinant vaccine (2 doses) or a live-attenuated virus vaccine (single dose) prior to initiation with MAVENCLAD

Vaccinations: Vaccination can be considered until 4-6 weeks prior to starting each MAVENCLAD course only if white blood cell counts are within normal limits[3]

- Avoid vaccination with live-attenuated or live vaccines during and after MAVENCLAD treatment while the patient's white blood cell counts are not within normal limits
- Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter

04

SUMMARY

SUMMARY

Adaptive and innate immune cells play a major role in MS, with innate immune cells serving as immune surveillance and adaptive immune cells serving as key drivers of neuroinflammation.[1,12]

MAVENCLAD has the greatest impact on the adaptive immune system; therefore, there is less disruption of the innate immune cells.[19,21,22]

MAVENCLAD is thought to preferentially target B and T lymphocytes, and is associated with a **reduction and subsequent recovery in lymphocyte count.**[4,18,19]

AFTER COMPLETING THIS LEARNING SESSION, PLEASE TAKE A FEW MOMENTS TO CONSIDER THE FOLLOWING QUESTIONS

What are 3 of the most important "take-home" messages you have learned during this session?

Have your most important questions been answered? If you answered no, how can you learn more?

Do you feel there are opportunities to use the information in this learning session to improve your consultations, education, and counseling of patients with RMS?

- If you answered no, why?
- If you answered yes, how will you do this?
- What challenges might you experience?
- How will you overcome these challenges?

05

CHECK YOUR KNOWLEDGE

CHECK YOUR KNOWLEDGE

1. B and T cells normally protect us against infections and other diseases. In certain conditions, such as MS, the immune system attacks healthy cells.[1]

- [ ] True
- [ ] False

CHECK

CHECK YOUR KNOWLEDGE

1. B and T cells normally protect us against infections and other diseases. In certain conditions, such as MS, the immune system attacks healthy cells.[1]

True

False

SEE SLIDES 9-13 TO REVIEW

CHECK YOUR KNOWLEDGE

2. Which of the following describes innate immune cells?[14]
Please indicate all that apply

- [ ] Immune surveillance
- [ ] First line of defense
- [ ] Key drivers of neuroinflammation
- [ ] NK cells, neutrophils, and/or monocytes
- [ ] B cells and T cells

CHECK

CHECK YOUR KNOWLEDGE

2. Which of the following describes innate immune cells?[14]
Please indicate all that apply

- Immune surveillance
- First line of defense
- Key drivers of neuroinflammation
- NK cells, neutrophils, and/or monocytes
- B cells and T cells

SEE SLIDE 15 TO REVIEW

CHECK YOUR KNOWLEDGE

3. Which of the following is a feature of immunodepletion followed by repopulation?[3,17]
Please indicate all that apply

- [ ] Continuous administration
- [ ] Therapy administered intermittently as a short course
- [ ] Dosing followed by depletion and repopulation
- [ ] Clinical efficacy extends beyond active dosing
- [ ] Ongoing modulation of immune function during active treatment without immunodepletion

CHECK

CHECK YOUR KNOWLEDGE

3. Which of the following is a feature of immunodepletion followed by repopulation?[3,17]
Please indicate all that apply

- Continuous administration
- Therapy administered intermittently as a short course
- Dosing followed by depletion and repopulation
- Clinical efficacy extends beyond active dosing
- Ongoing modulation of immune function during active treatment without immunodepletion

SEE SLIDES 18-20 TO REVIEW

CHECK YOUR KNOWLEDGE

4. MAVENCLAD has the greatest impact on the adaptive immune system; therefore, there is less disruption to the innate immune cells. This allows the innate cells to help fight against new infections.[19,21]

- [ ] True
- [ ] False

CHECK

CHECK YOUR KNOWLEDGE

4. MAVENCLAD has the greatest impact on the adaptive immune system; therefore, there is less disruption to the innate immune cells. This allows the innate cells to help fight against new infections.[19,21]

- True
- False

SEE SLIDE 24 TO REVIEW

06

ADDITIONAL RESOURCES

CONTINUING THE MAVENCLAD NURSE TOOLKIT

Be sure to review the full Nurse Toolkit, including modules on:

Understanding the immune system and mechanism of action of MAVENCLAD (cladribine) tablets

A review of MAVENCLAD data and product characteristics, coming in 2022

Practical considerations for managing patients with MS taking MAVENCLAD, coming in 2022

07

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REFERENCES

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