



# Pediatric onset Multiple Sclerosis in a nutshell, old, new, and upcoming medicines

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Novembre 2nd 2024

<https://www.youtube.com/watch?v=wyQilpw1VwI>

<https://invents-he.eu/>



INVENTS has received funding from the European Union's Horizon Europe Research and Innovation program under grant agreement 101136365.



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# Introduction

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- ❖ Multiple sclerosis (MS) is an autoimmune disease of the Central Nervous System (CNS). The body's immune system mistakenly attacks a substance called myelin, a layer of fat, that surrounds and protects the nerves in the brain and spinal cord.
- ❖ Myelin allows signals to move quickly and smoothly through the nerves. When it's injured, the signals slow down and miscommunicate, causing the symptoms of MS.
- ❖ MS diagnosed in childhood is called pediatric MS. Few people with MS between 3 to 10 percent are diagnosed before 16 years old, and less than 1 percent receive the diagnosis before they're 10 years old.



# Symptoms of MS in children and teens

## Multiple Sclerosis (MS) Symptoms



Symptoms of MS depend on which nerves have been affected.

Because the myelin damage is spotty and can affect any part of the central nervous system (CNS), the symptoms of MS are unpredictable and vary from person to person.

In children, relapsing-remitting MS is almost always the diagnosis.

This means the disease alternates between relapses, in which someone develops new symptoms, and remissions, in which there are only mild or no symptoms.

# Symptoms of MS in children and teens



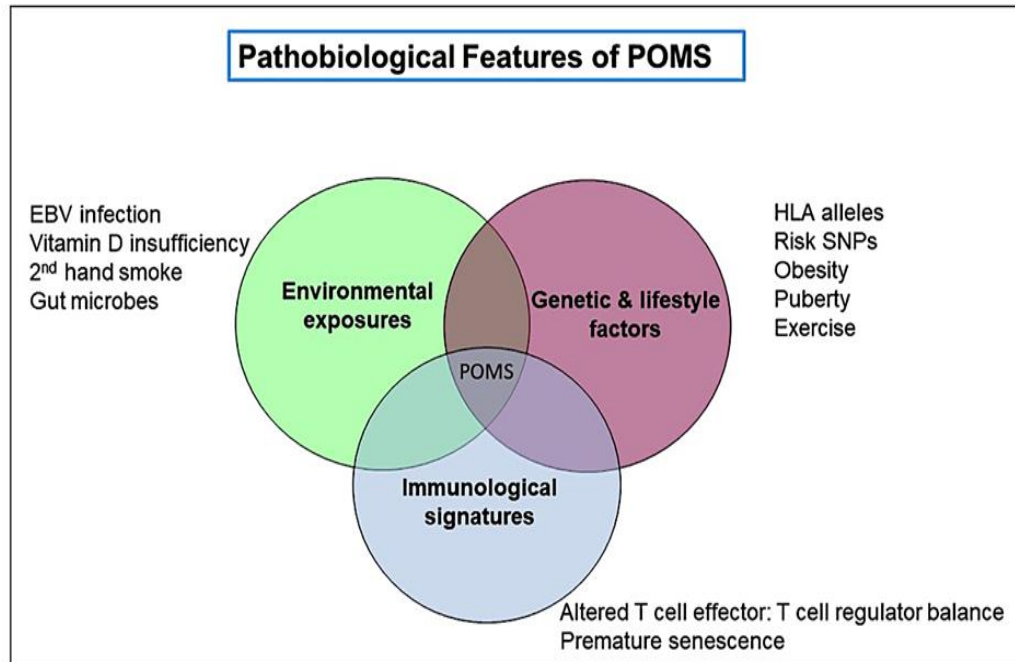
Weakness, tingling and numbness; eye problems, including vision loss, pain with eye movement, and double or blurred vision; balance problems, difficulty with coordination or walking, tremors, involuntary muscle spasms (spasticity) bowel and bladder control problems slurred speech.

Symptoms like weakness, numbness and tingling, and vision loss often happen on only one side of the body at a time.

...but where the  
disease come from?

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# Risk factors



**Figure 1.** The interplay between genetic, environmental, and life-style risk determinants for pediatric-onset MS.

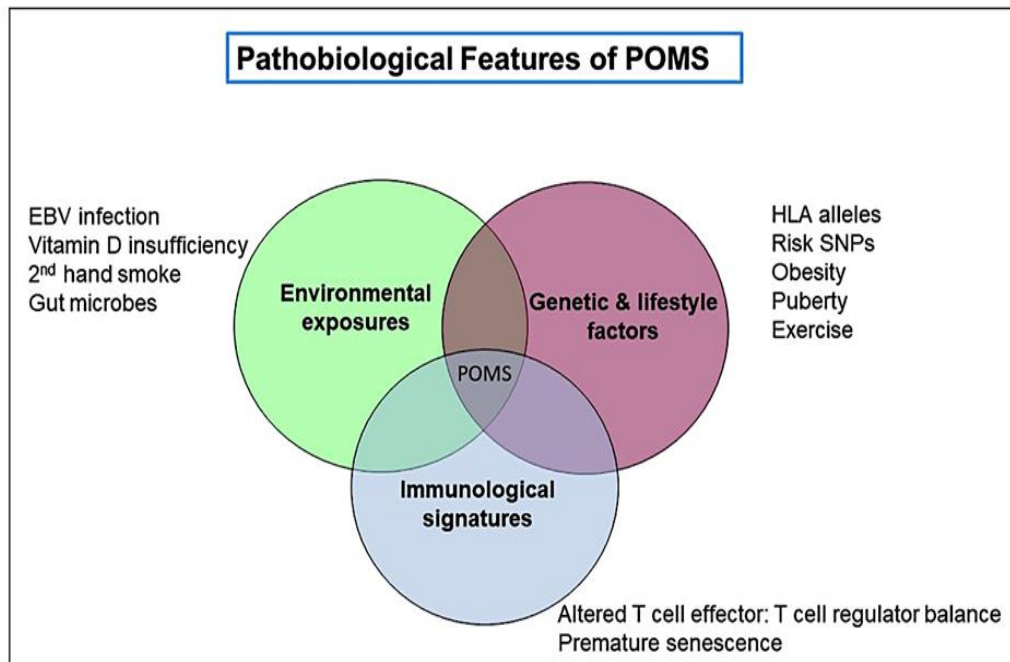
**MS appears to be resultant of a complex interplay between genetic predisposition, environmental exposures, and aberrant host immune responses**

**Serological evidence of remote infection with Epstein–Barr Virus (EBV) is highly associated with MS risk**

# Risk factors

Another strong environmental association exists between low serum vitamin D concentrations and MS risk in both POMS and adult

Lifetime MS risk is increased by childhood obesity serum from POMS patients induced an adiponectin-driven pro-inflammatory response characterized by activation of CD4 and CD8 T cells as well as reduced microglial senescence.



**strongest genetic association is the presence of HLA-DR15 alleles. Relapse rates are higher in POMS patients with at least one HLA-DRB15 allele**

Figure 1. The interplay between genetic, environmental, and life-style risk determinants for pediatric-onset MS.



# Pathogenesis

- T-cells (immune cells) develop in the thymus.
- In the thymus, there are mechanisms known as central tolerance, which prevents the generation of autoreactive T-cells.
- In multiple sclerosis, this tolerance mechanism fails.
- There are too many autoreactive T-cells in the circulation. They can ultimately cross the blood-brain barrier and can enter the brain. So the brain is no more immune privileged.
- In the myelin sheath, there are antigens such as myelin basic protein, proteolipid protein, myelin oligodendrocyte, glycoprotein.
- All of these antigens are detected by these autoreactive T-cells. Autoreactive T-cells actually get activated and affect the myelin sheath.

# Diagnosis

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Diagnosing MS in children can be difficult for several reasons.



Other childhood diseases can have similar symptoms and are hard to differentiate.

Because MS is so uncommon in kids and teenagers, doctors may not be looking for it.

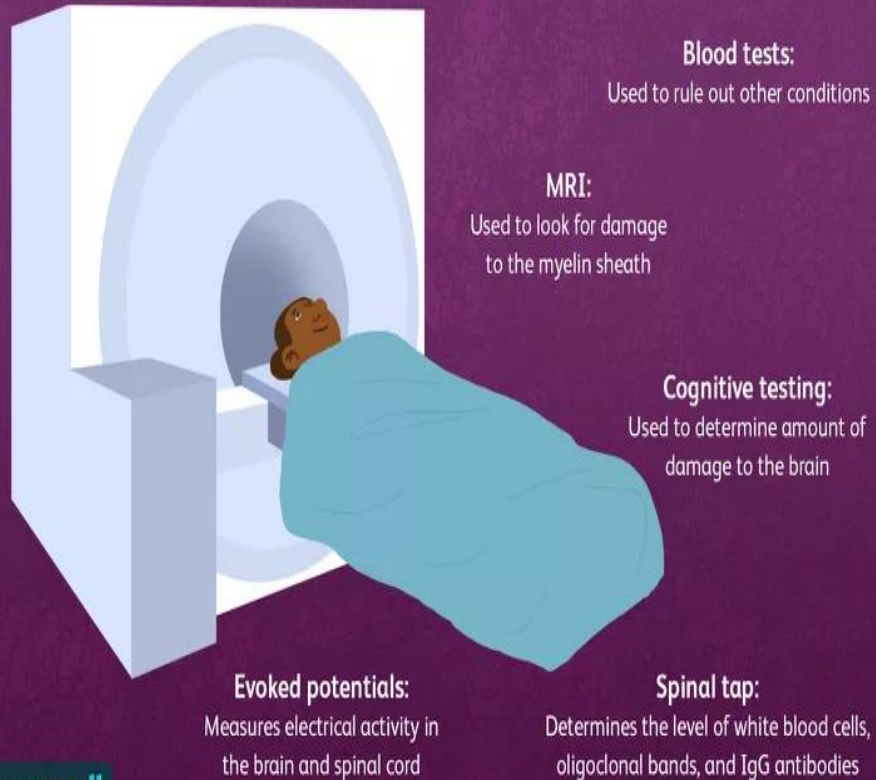
There isn't a specific test for diagnosing MS.

Instead, a doctor uses information from the history, exam, and several tests to confirm the diagnosis and rule out other possible causes of the symptoms.

To make a diagnosis, a doctor needs to see evidence of MS in two parts of the CNS at two different times.

A diagnosis can be made after only one episode with abnormalities seen on magnetic resonance imaging (MRI) if there's evidence of MS in the spinal fluid and all other possible causes of symptoms and MRI findings are ruled out.

## Testing for Multiple Sclerosis





## Testing for Multiple Sclerosis



**Blood tests:**  
Used to rule out other conditions

**MRI:**  
Used to look for damage  
to the myelin sheath

**Cognitive testing:**  
Used to determine amount of  
damage to the brain

**Evoked potentials:**  
Measures electrical activity in  
the brain and spinal cord

**Spinal tap:**  
Determines the level of white blood cells,  
oligoclonal bands, and IgG antibodies

The tests a doctor may use to diagnose MS include: **History and exam.** A doctor will ask detailed questions about the kinds and frequency of the child's symptoms and perform a thorough neurologic examination.

**MRI.** An MRI shows whether any parts of the brain and spinal cord are damaged. It can also show if there's inflammation in the optic nerve between the eye and the brain, which is called optic neuritis.

**Lumbar puncture.** This is also known as a spinal tap. For this procedure, a sample of the fluid that surrounds the brain and spinal cord is collected and examined for signs of MS.

**Evoked potentials.** This test shows how fast the signals move through the nerves. These signals will be slow in children with MS if there's a history of optic neuritis.

**Optical coherence tomography.** This is a test that takes a picture of the optic nerve and can look for thinning. This can pick up a history of optic neuritis that might not have caused any symptoms.

# Treatment of MS in children and teens

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# Treatments targets

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- Relapse prevention
- New MRI lesion prevention
- Disability progression prevention
- Preservation of cognition

**High compliance and tolerability of DMT**

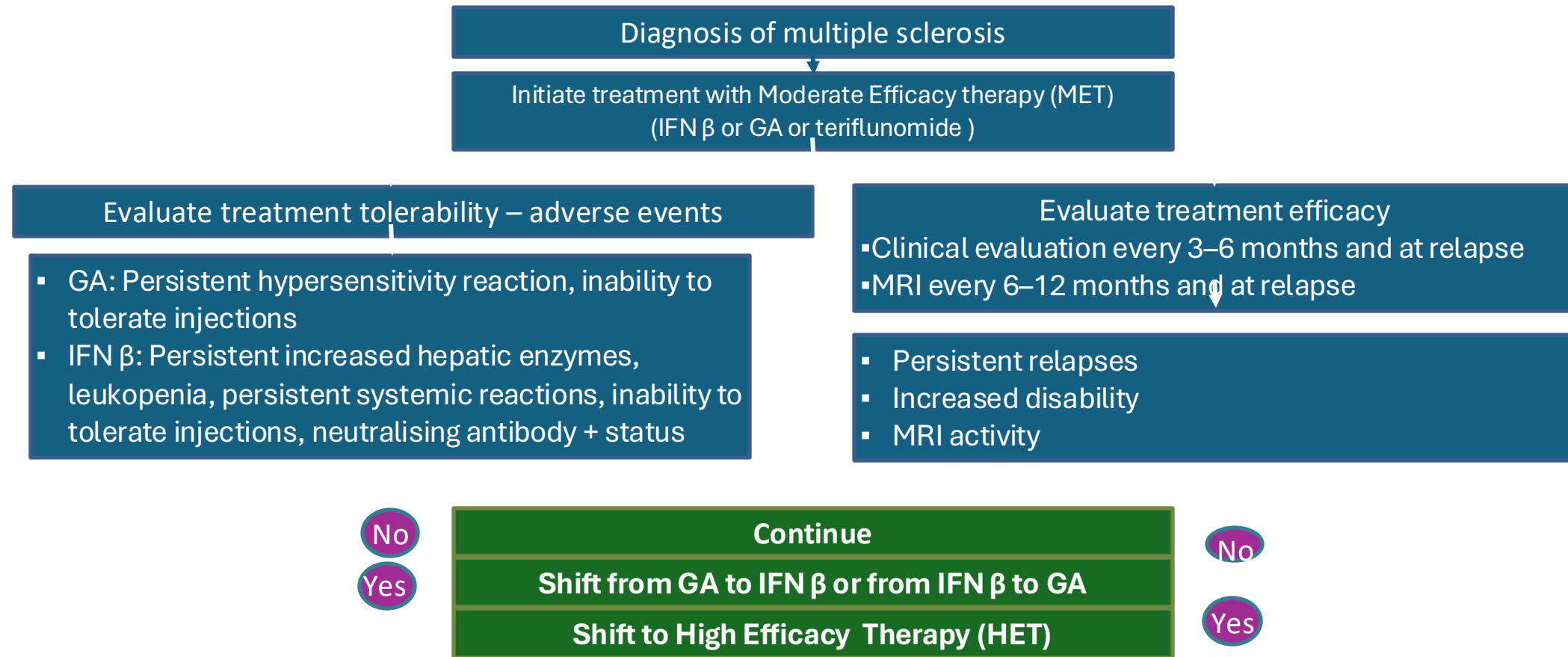
# ACUTE TREATMENT FOR A RELAPSE

- **IV methyl prednisolone 20–30mg/kg (maximum 1g daily) for 3–5 days.**
- **Possible need for an oral taper.**
- **If there is an incomplete response or in case of a severe attack, intravenous immune globulin (IVIg) at 0.4g/kg/day for 5 days or plasmapheresis should be considered**

Lattanzi S, Cagnetti C. et al. Oral and intravenous steroids for multiple sclerosis relapse: a systematic review and meta-analysis. J Neurol. 2017; 264



# Current algorithm to treating children with MS



# MODERATE EFFICACY TREATMENTS (MET) VS HIGH EFFICACY TREATMENTS (HET)



- MET: Infb, ga, teriflunomide, dimetilfumarate

Safety and efficacy of teriflunomide in paediatric multiple sclerosis (TERIKIDS): a multicentre, double-blind, phase 3, randomised, placebo-controlled trial

Tanuja Chitnis, Brenda Banwell, Ludwig Kappos, Douglas L. Arnold, Kivilcim Gücüyener, Kumaran Deiva, Natalia Skripchenko, Li-Ying Cui, Stephane Saubadu, Wenruo Hu, Myriam Benamor, Annaig Le-Halpere, Philippe Truffinet, Marc Tardieu, on behalf of the TERIKIDS Investigators

- HET: fingolimod, natalizumab, ocrelizumab, rituximab.

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Trial of Fingolimod versus Interferon Beta-1a in Pediatric Multiple Sclerosis

Tanuja Chitnis, M.D., Douglas L. Arnold, M.D., Brenda Banwell, M.D., Wolfgang Brück, M.D., Angelo Ghezzi, M.D., Gavin Giovannoni, M.D., Benjamin Greenberg, M.D., Lauren Krupp, M.D., Kevin Rostásy, M.D., Marc Tardieu, M.D., Emmanuelle Waubant, M.D., Jerry S. Wolinsky, M.D., Amit Bar-Or, M.D., Tracy Stites, Ph.D., Yu Chen, M.Sc., Norman Putzki, M.D., Martin Merschhemke, M.D., and Jutta Gärtner, M.D., for the PARADIGMS Study Group\*

JAMA Network | Open



Original Investigation | Neurology

## Effect of Dimethyl Fumarate vs Interferon $\beta$ -1a in Patients With Pediatric-Onset Multiple Sclerosis: The CONNECT Randomized Clinical Trial

Patrick Vermersch, MD, PhD; Matthew Scaramozza, MS; Seth Levin, MD; Raed Alroughani, MD; Kumaran Deiva, MD, PhD; Carlo Pozzilli, MD, PhD; Jennifer Lyons, MD; Oksana Mokliatchouk, PhD; Joe Pultz, PhD; Fatou N'Dure, MBA; Shifang Liu, PhD; Runda Badwan, PharmD; Filipe Branco, MSc; Valencia Hood-Humphrey, MS; Nathalie Franchimont, MD, PhD; Jerome Hanna, MBBCh, BAO; Amir-Hadi Maghzi, MD



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# Phase-3 Trials in POMS (Fingolimod)

The NEW ENGLAND JOURNAL of MEDICINE

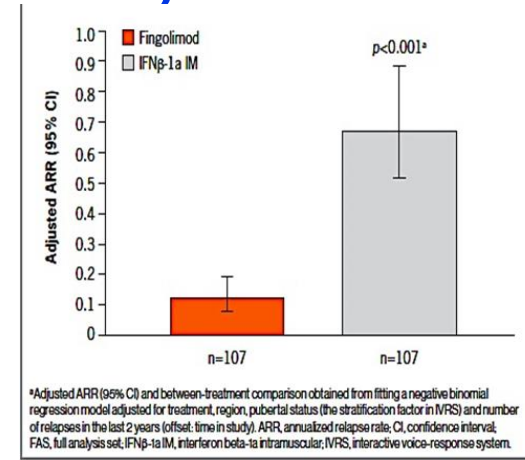
2018

ORIGINAL ARTICLE

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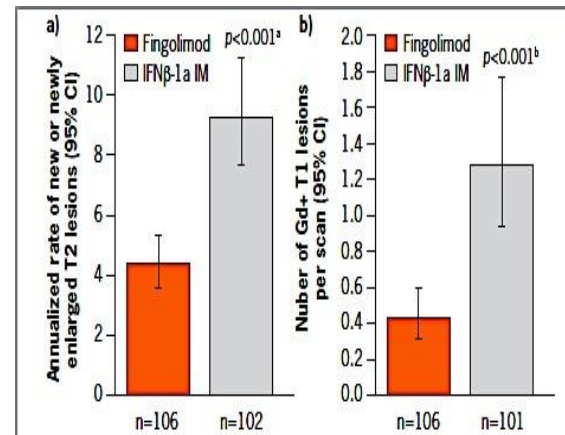
Tanuja Chitnis, M.D., Douglas L. Arnold, M.D., Brenda Banwell, M.D., Wolfgang Brück, M.D., Angelo Ghezzi, M.D., Gavin Giovannoni, M.D., Benjamin Greenberg, M.D., Lauren Krupp, M.D., Kevin Rostásy, M.D., Marc Tardieu, M.D., Emmanuelle Waubant, M.D., Jerry S. Wolinsky, M.D., Amit Bar-Or, M.D., Tracy Stites, Ph.D., Yu Chen, M.Sc., Norman Putzki, M.D., Martin Merschhemke, M.D., and Jutta Gärtner, M.D., for the PARADIGMS Study Group\*

**85.7% vs 38.8%  
of patients did not have relapses**



- 215 patients, across 80 centers worldwide
- 107 fingolimod

❖ **There were more serious AEs with fingolimod (17.8%; IR, 11.0 per 100 PY) than with IFNβ-1a IM (9.3%; IR, 6.2 per 100 PY).**



- 52 % reduction in annualized rate of new or newly enlarged T2 lesions than in IFNβ-1a IM group

- The mean number of Gd+ T1 lesions was lower ( 66 %) than in IFNβ-1a IM



# Phase-3 Trials in POMS (Teriflunomide/ Dimethyl-Fumarate)

*Lancet Neurol* 2021; 20: 1001–11  
Safety and efficacy of teriflunomide in paediatric multiple sclerosis (TERIKIDS): a multicentre, double-blind, phase 3, randomised, placebo-controlled trial

Taruja Chitnis, Brenda Banwell, Ludwig Kappos, Douglas L Arnold, Kivikim Güçüyener, Kumaran Deiva, Natalia Skripchenko, Li-Ying Cui, Stephane Saubade, Wenxuo Hu, Myriam Benamor, Annaig Le-Halpere, Philippe Truffinet, Marc Tardieu, on behalf of the TERIKIDS Investigators

JAMA Network | **Open**™ September 2022

Original Investigation | Neurology  
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- **Median time to first relapse was increased, but not significantly**, in patients treated with teriflunomide (75.3 weeks vs 39.1 weeks)
- **The difference between active treatment vs placebo** was significant only when including the **finding of MRI activity** (72.1 weeks vs 37.0 weeks).
- Active treatment reduced the **number of new or enlarging T2 lesions** by 55% and the number of Gd+lesions by 75%

- Number of patients **free from new or new enlarging T2 lesions** was **significantly higher in DMF arm**;
- Number of **new or enlarging T2 lesions** was **significantly lower in DMF arm**
- Number of **relapses, ARR and changes in disability** were **secondary endpoints** and were in favor of DMF treatment.



## Ongoing RCTs

- **LEMKIDS:** open label **Alemtuzumab** (aimed to evaluate safety and efficacy of alemtuzumab in POMS patients who have failed at least two DMDs is in progress)
- **OPERETTA 2:** A Study To Evaluate Safety And Efficacy Of **Ocrelizumab In Comparison With Fingolimod** In Children And Adolescents With Relapsing-Remitting Multiple Sclerosis





# FUTURE PERSPECTIVES AND GOAL

- 1 Personalized therapies with more target objective (es myelin regeneration)
- 2 Doctors and researchers need to look carefully at how some of these drugs might affect children and teens
- 3 Combined collaboration between researchers, child neurologists and patients





Thank you for your attention

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## SPEAKER'S DETAILS

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### Contact

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