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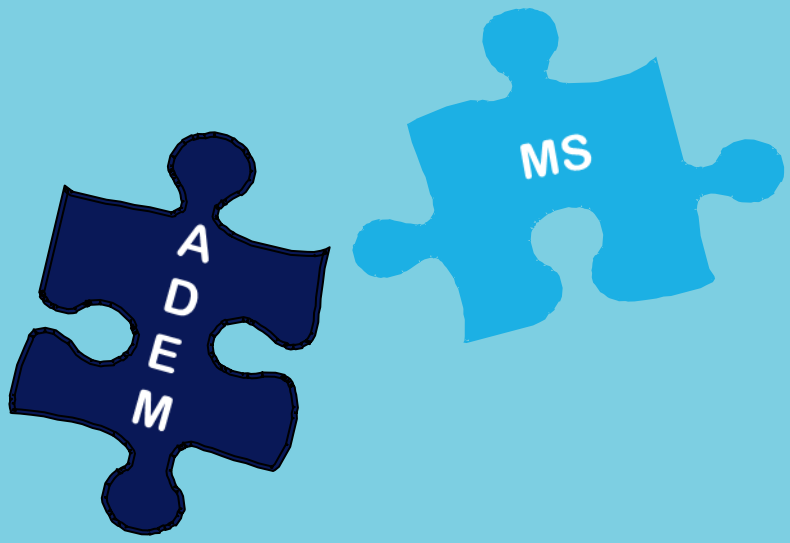

New and old treatments in recurrent demyelinating diseases

Coriene Catsman-Berrevoets

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treatments in recurrent demyelinating diseases

- Prevention / reduction environmental risk factors
- Treatment of acute relapse
- Prevention of relapses
  - 1st line treatment
  - 2nd line treatment
- New treatments
- Treatment of complications

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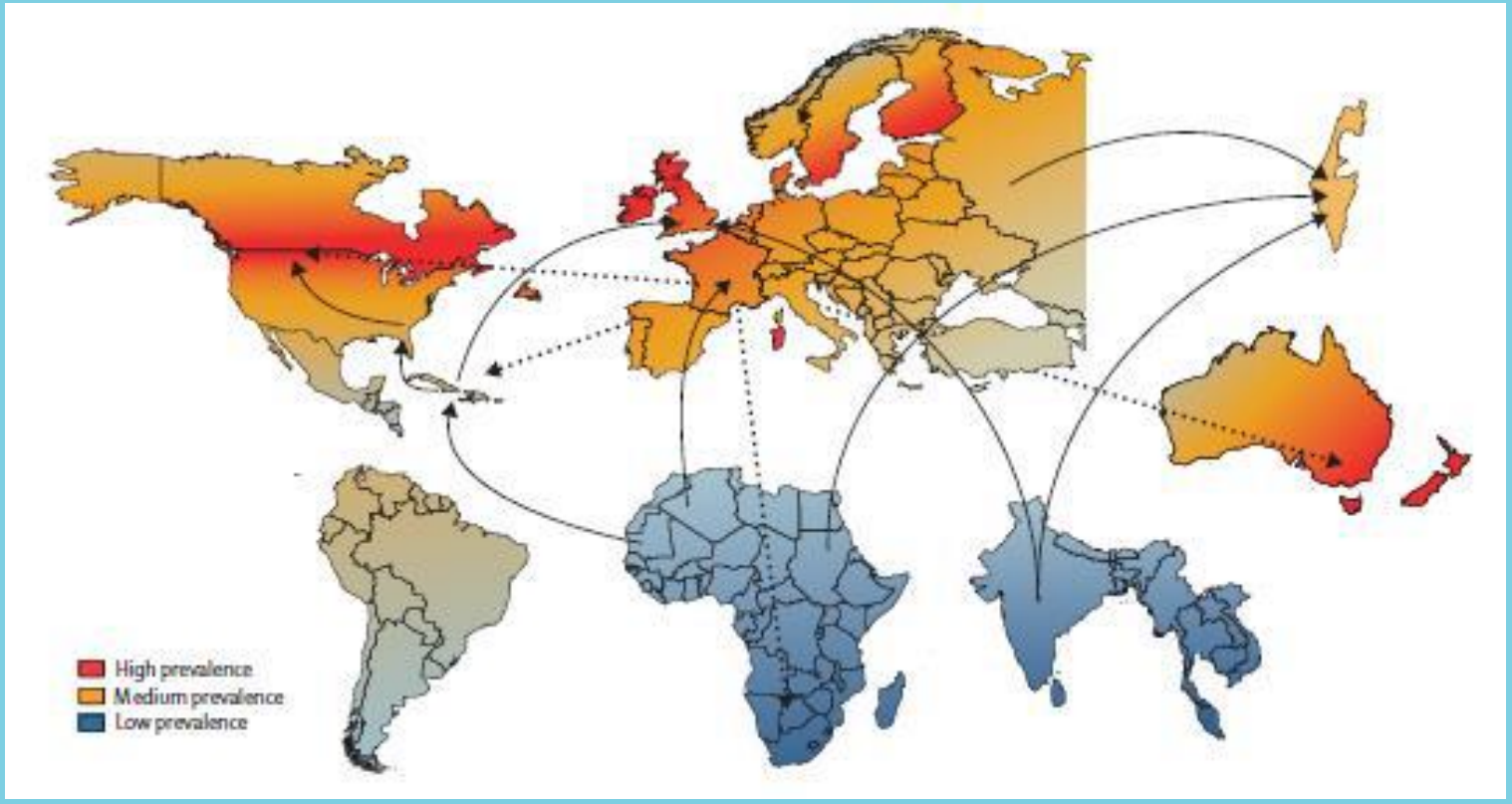
Environmental factors



Migration studies: factor X somewhere in the first 15 years of life

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Influence environmental factors

- UV light / sun light
- vitamine D
- Diet
- Smoking (parents)
- Hormones
- Infections during childhood
  - more infections during early childhood protect against MS
  - but: EBV infection increases risk (relative risk 2.3, 95% CI 1.7-3.0)*

*Thacker et el. Ann.Neurol. 2006;59:499

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Vitamin D Deficiency in 6 year olds

- 4167 6 year old children (generation R study)
  - 30% vit D deficiency
  - Prevalence: 17.6%: dutch or western ethnic
- 54.5%: african or mediterranean background
- Risk factors:
  - Household income
  - Television watching
  - Playing outside
- Voortman er al 2015, J of Nutrition

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Acute treatment CIS or MS relapse

- Methylprednisolon 20-30 mg/kg/day IV
- (maximal dosis 1000 mg/day, 3-5 days)

- Purpose
  - Diminishing Inflammation
  - Faster clinical recovery
  - No difference in outcome after 6 months

- Side effects: flushing, hypertension, sleep disorder, irritability, increased appetite, hyperglycemia, gastro-intestinal bleeding

- Pohl ea Neurology 2007
- Ghezzi ea Mult Sler 2010

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Treatment CIS or new MS episode

- No or insufficiënt response to first MP cycle
- Severe neurological symptoms

- • 2nd MP cycle
- • Intraveneus Immunoglobulin 2 g/kg during 2-5 days
- • (Plasmaferesis)

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Disease modifying therapie

- Reduction of disease activity and number (and severity) of relapses
- No cure

- No double blind placebo controled trials
- Treatment is based on expert opinion, small observational studies
- Follows adult treatment regimens

Review

Multiple Sclerosis

The management of multiple sclerosis in children: a European view

Multiple Sclerosis
16(10) 1258–1267

DOI: 10.1177/1352458510375568
msj.sagepub.com
SAGE

Angelo Ghezzi[1], Brenda Banwell[2], Alexey Boyko[3], Maria Pia Amato[4], Banu Anlar[5], Morten Blinkenberg[6], Maartje Boon[7], Massimo Filippi[8], Sergiusz Jozwiak[9], Immy Ketelslegers[10], Barbara Kornek[11], Ming Lim[12], Eva Lindstrom[13], Congor Nadj[14], Rinze Neuteboom[10], Maria A Rocca[8], Kevin Rostasy[15], Marc Tardieu[16], Evangeline Wassmer[17], Coriene Catsman-Berrevoets[10] and Rogier Hintzen[10]

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First line disease modifying drugs

- 1.Interferon:
  - •interferon beta-1a (Avonex en Rebif)
  - •Interferon beta-1b (Betaferon)
- 2.Glatirameer acetate (Copaxone)
  - all injectables.
  - •Efficacy: reduction relapses 30% for all

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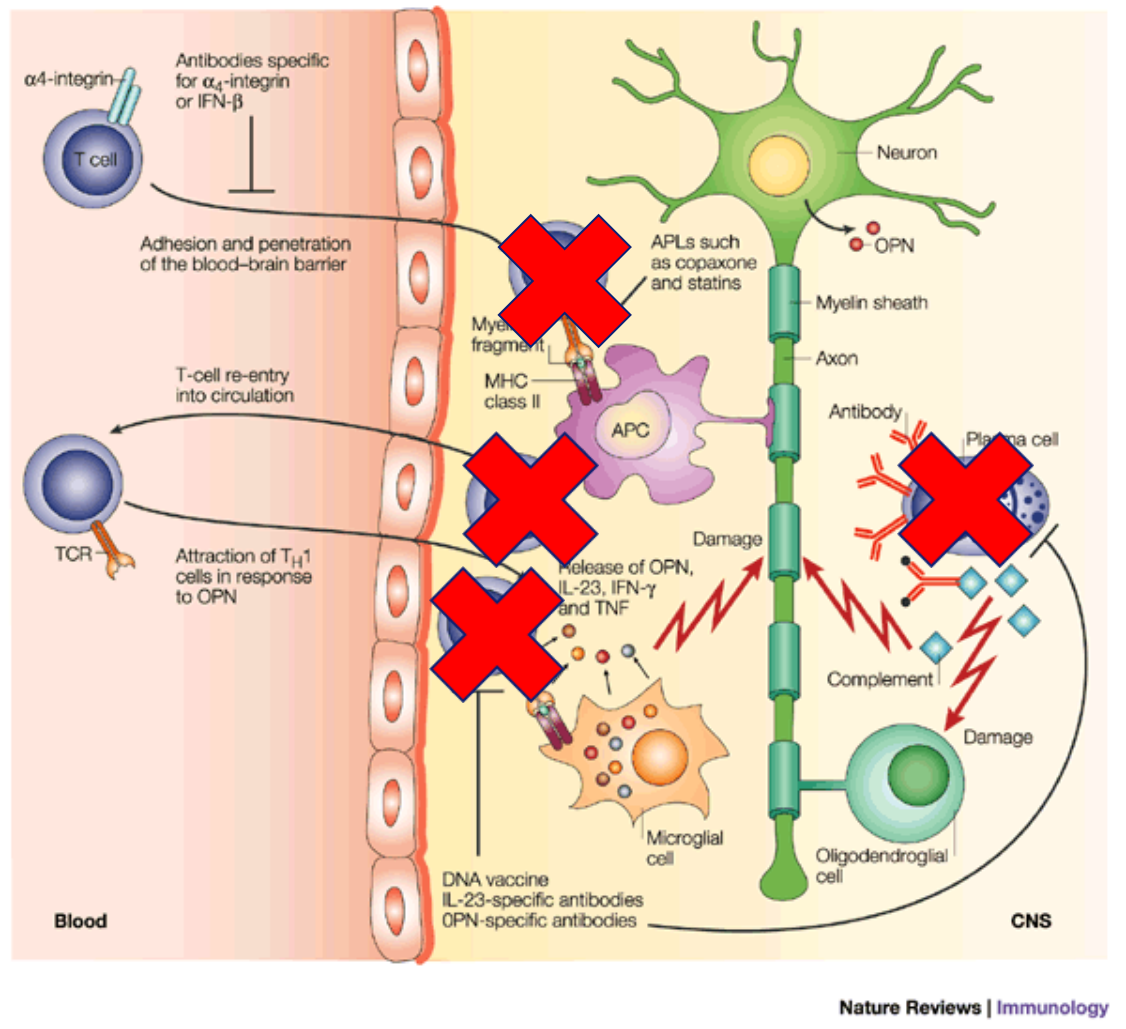
First line disease modifying drugs

modulate the functioning of antigen-presenting cells and effect the cytokine secretion of CD4+ T helper cells



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First line disease modifying drugs

AVONEX® (interferon beta-1a) — 1x/week 30 µg IM

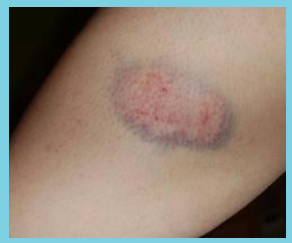
Rebif® (interferon beta-1a) sc injection — 3x/week 22 or 44 µg sc

BETAFERON® — alt. day 250 µg sc

Interferon beta 1B

COPAXONE® (glatiramer acetate for injection) — every day 20 mg sc

- Flue like symptoms
- Mood disorder
- Injection site



- Injection site,

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Predosing with aminoacetophen or iboprufen helps !!

First line disease modifying drugs

Information is important!

- Effect
- Side effects (if necessary prescribe paracetamol, iboprufen)
- Compliance

- Independent of choice of type interferon (beta 1a/1b) or glatitameer acetaat
  - Start with ¼ - ½ of the normal adult dose and slowly raise the dose
  - Lab. controls BB, Liver Functions

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Consider changing type of first line treatment modality

- Severe side effects
- Insufficient compliance
- Poor responder

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Definition of poor response:

- Minimal treatment period of 6 months
- 100% compliance
  - AND
- Either same number of relapses as before treatment or new abnormalities on MRI
- ≥ 2 relapses in preceding 12 months
  -

Chitnis ea Mult Scler 2011

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Poor response

- Options
- 1. Switch 1st line treatment (interferone/GA)
- 2. Switch to 2nd line treatment
  - Higher efficacy (reduction relapses 68%
  - BUT
  - Possible severe side effects!!

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What if first line treatment options fail?

- - what are the treatment options in adults:

- Natalizumab:	PML, melanoma
- Mitoxantrone:	leukemia, infertility, cardiomyupathy
- cyclophosphamide:	nausea, vomiting, osteoporosis,
	amenorrhoea, bladder cancer (mesna)

- No evidence in children on efficacy and safety, only case reports or small series

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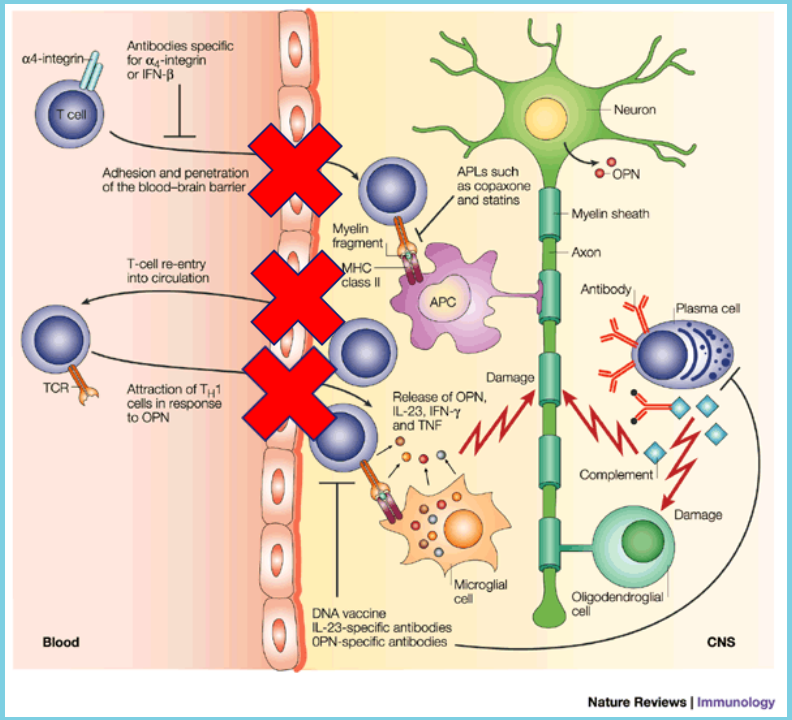
Second line disease modifying drugs

- NATALIZUMAB (TYSABRI)
  - monoclonal antibody
  - Reduces entrance activated T lymfocytes to brain



NATALIZUMAB (TYSABRI)

- every 4th week IV – hospital stay!
- Decrease of number of relapses with 68%

- No guidelines concerning treatment child!
- *Ghezzi ea Neurology 2010 (n=19)*
- *Ghezzi ea Mult Scler 2012 (n=55)*
- *Kornek ea JAMA Neurol 2013 (n= 20)*

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NATALIZUMAB (TYSABRI)

- every 4th week IV – hospital stay!
- Decrease of number of relapses with 68%

- Possible side effects
  - Allergic reactions
  - Progressive Multifocal Leucencephalopathy

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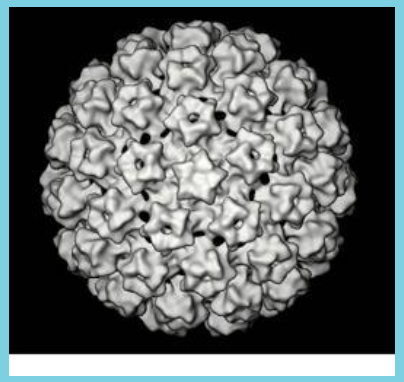
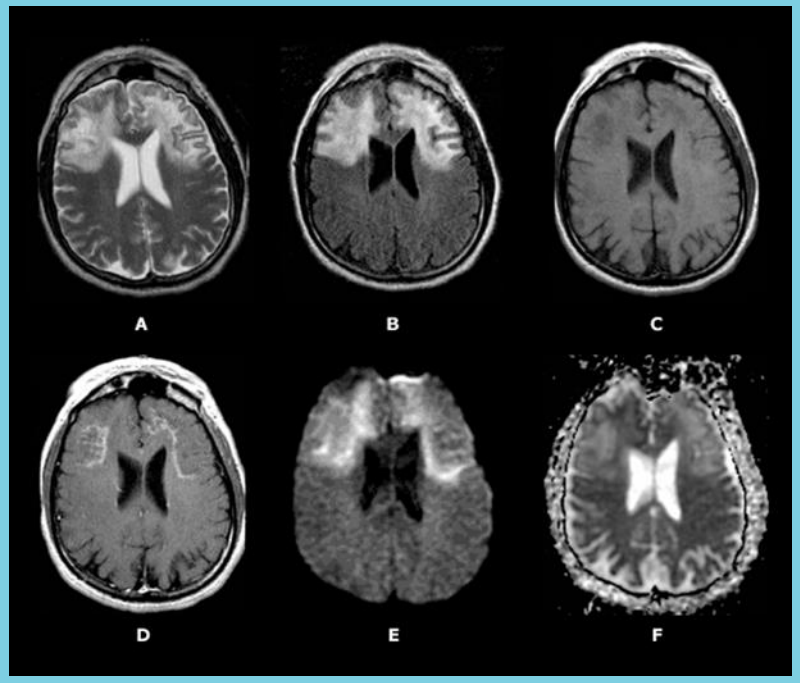
Progressive Multifocal Leucencephalopathy



- PML
- JC (polyoma virus) virus
- 40-60% asymptomatic carriers (86% in adults)
- In case of immunosuppresion (AIDS, cancer, medication) reactivation of the JC virus causes severe progressive demyelinating disease



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Treatment: monophasic disease

- ADEM
- CIS
- Optic neuritis
- Neuromyelitis optica

- - IV corticosteroids
  - Methylprednisolon 10-30 mg/kg/d (3-5 days)
  - (max 1000 mg/d)
- - Plasmaforesis

(severe/ extensive lesions)

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Alternatives for corticosteroids

Corticosteroid sparing drugs:

- Azathioprine
- Mycofenolaatmofetil / Cellcept
- Rituximab
- Less often: cyclofosfamide, mitoxantrone, methotrexate

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AZATHIOPRINE (IMURAN)

- Pro-drug of 6-mercaptopurine.
- inhibits DNA synthesis
- inhibits proliferation B- en T-lymfocytes
- 3-6 months before it has effect (until that time combi with prednisone)
- Side effects:
  - Bonemarrow suppression, leukopenia, thrombocytopenia
  - hepatotoxicity,
  - infections
  - Neoplasma NB Teratogenic!
- Weekly blood test for the first 2 months, after that less frequent
- Gastrointestinal symptoms

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MYCOFENOLAAT MOFETIL (CELLCEPT)

- Pro-drug for mycofenolate
- Inhibits synthesis of guanoside nucleotides >
  - inhibits production B- and T-cells

- Takes 2-3 months to take effect
  - in the mean time corticosteroid treatment.

- Side effects: gastro-intestinal, infections, sepsis, bone marrow suppresion, herpes zoster, flue-like symptoms

- Blood tests every week for the first month, after that every month during the 1st year of treatment

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RITUXIMAB

- Monoclonal antibody against CD20 marker on B- lymfocytes
-
- Depletes functional B cells (antigen precenting cells, production antibodies, production cytokines)

- Rituximab 500 mg/m2, two gifts with 14 days interval
  - (effect 6-10 months)

- Efficacy of 58% reduction of relapse rate

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International cooperation

International Pediatric MS Study Group

Two international studies: oral treatment of paediatric MS

fingolimod

rituximab

ocrelizumab

interferon beta 1b

laquinimod

alemtizumab

mitoxantrone

natalizumab

dimethylfumarate

firategrast

daclizumab

Interferon beta 1a

teriflunomide

azothiaprine

glatirameer acetaat

cladribine

ofatumumab

cyclofosfamide

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Fingolimod: 2nd line MS modulating drug

First oral treatment for MS
1 capsule every day
reduction relapses with 54-60%

First dose should be given under cardiac monitoring
bradycadia

Other side effects:
herpes infections
macula edema

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Fingolimod: 2nd line MS modulating drug

First oral treatment for MS
1 capsule every day
reduction relapses with 54-60%

International Fingolimod study

- *Double blind randomised multicenter study (2 years)*
- *Children 10-18 years with RR – MS and EDSS 0-5,5*
- *Safety and efficacy of fingolimod compared to Interferon B IM 1/week*

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Terikids

- Randomised, double blind, multicentric, placebo controled fase 3 study
- Effect and safety of teriflunomide in children with RR-MS.
- Patiënts: children 10-17 years old with RR-MS and EDSS 0 tot 5.5. (can walk independently or rest for 100 meter
- End point: first relapse after start teriflunomide compared to placebo

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Teriflunomide

- Diminishes frequency of relapses in adult patients with RR-MS and EDSS score 0–5,5.
- Efficacy is similar to interferon β and glatirameer.
- Long term (side) effects are unknown. No information on effect on disability progression
- Mode of action: selective and reversible block of the mitochondrial enzyme dihydro-orotaat dehydrogenase (DHODH), necessary for de novo pyrimidine synthesis. Results in diminishing the proliferation of cells that need de novo pyrimidine synthesis such as lymfocytes

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Symptomatic treatment of MS related symptoms

- Spasticity
  - Baclofen
  - Tizanidine
  - Diazepam, clonazepam
  - Botuline toxine
- Fatigue
  - Amantadine
  - Modafenil
- Urinary inconinence
  - Oxybutine

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Multidisciplinary approach in pediatric MS center

- *Paediatric Neurologist*
- *Rehabilitation specialist*
  - *Fysiotherapist*
  - *Ergotherapist*
- *Paediatric Urologist*
- *Ophtalmologist*
- *Neuropsychologist*
- *Teacher/ school*
- *Social worker*
- *Paediatric MS nurse*

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Take home messages

- First event (NO, CIS, ADEM, ADEM and NO): corticosteroids

- NMO, ADEM +NO : corticosteroid spraing immunesuppressive drugs
  - (imuran / cellcept / rituximab)

- Disease modifying drugs for children morelimited in number
  - 1st line: interferon beta 1A and 1B, copaxone
    - Fingolimod en teriflunomide are under investigation for children
  - 2nd line natalizumab

- Immune mediated demyelinating diseases are chronic diseases with physical and psychological burden for patients and families

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