Pediatric MS treatments: What do you start with, when do you switch?

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Disclosures

- Clinical research funding regarding pediatric demyelinating disease from NMSS and NIH (no treatment related funding)
- There are no currently FDA approved multiple sclerosis treatments for persons under 18 years of age
  - Recommendations for all medications discussed here is based upon small trials and expert opinion
  - European Medicines Agency (EMA) has approved use of IFN-β and glatiramer acetate in patients ≥ 12 years of age
Objectives

- Know the indications for starting disease modifying therapy (DMT) for Pediatric onset multiple sclerosis (POMS)
- Describe a strategy for initiating and monitoring response to first line DMT
- Describe current definitions and considerations of treatment failure in POMS
- Describe second line agents used for the treatment of POMS
Currently approved MS Treatments

“First line” therapies

• Injectable medications
  – Avonex (interferon beta-1a)
  – Betaseron (interferon beta-1b)
  – Extavia (interferon beta-1b)
  – Copaxone (glatiramer acetate)
    • Glatopa (generic equivalent of Copaxone 20mg dose)
  – Plegridy (peginterferon beta-1a)
  – Rebif (interferon beta-1a)

“Second line” therapies

• Oral medications
  – Aubagio (teriflunomide)
  – Gilenya (fingolimod)
  – Tecfidera (dimethyl fumarate)

• Infused medications
  – Lemtrada (alemtuzumab)
  – Novantrone (mitoxantrone)
  – Tysabri (natalizumab)
  – Zinbryta (daclizumab)
Who should be started on a DMT for multiple sclerosis?

- Definitely: multiple sclerosis
- Probably: clinically isolated syndrome with high MS risk
  - MRI with additional asymptomatic MS-like lesions
    - Positive CSF: positive oligoclonal bands and/or elevated IgG index
    - Positive FMH for MS
- Treatment not indicated: ADEM or multiphasic ADEM
- Special considerations: interferons not effective in NMO
Why should pediatric multiple sclerosis be treated with DMTs?

- Neurodegenerative disease with no natural remission
- Higher annualized relapse rate (vs. adults) in POMS
- DMT action targets MRI inflammatory aspects of POMS lesions
- Brain growth and cognition are adversely affected by POMS
- Disabled at a younger age compared to adult disease
  - There is no treatment for secondary progressive MS
  - Longer interval between onset and accumulation of disability
  - Greater compensation for disease in pediatrics
  - No time difference between adults and pediatrics in disability progression: mild to severe is 10 years
What is the goal of DMT: Minimal Progression or No Evidence of Disease Activity (NEDA)?

• There is no therapy that has shown 100% efficacy
• Minimal disease progression
  – < 1 attack per year
  – < 3 new lesions on yearly MRI
  – no progression of disability
• NEDA: absence of clinical and MRI evidence of disease
  – 50% of adults achieve NEDA at 2 years in most trials
  – 7% of adults have NEDA at 7 years of disease
• No clear difference in long term outcomes
What is the current evidence for efficacy and safety of DMTs in POMS?

- No current evidence of superiority of one drug
- Positive results of phase 4 observational studies for safety and efficacy of “Platform therapies”: Interferon-β (IFN-β) and glatiramir acetate (GA)
  - Populations ranging from less than 10 years to 17 years of age
  - Decreased relapse rate, stabilized disability, reduced accrual of new lesions
  - No major adverse events
    - Common side effects (>50%): flu-like symptoms and injection site reaction
    - Potential side effects: elevated liver enzymes, blood cell abnormalities, GI symptoms, thyroid disease
    - No apparent affect on body development
    - Cautionary use of interferon-β in co-morbid mood disorder
What is the current evidence for efficacy and safety of DMTs in POMS?

- Pediatric trials for other non-platform agents (oral agents, etc.) underway
- **Current IPMSSG recommendation**: Use of non-platform agents in POMS should be considered with extreme caution in selected cases at this time
First-line treatment guidelines for POMS

- **IPMSSG recommendation**: all patients should start first-line therapy (IFN-β or GA) soon after diagnosis
  - Before treatment
    - Counseling: purpose, side effects, and expectations
    - Baseline liver function, CBC, and thyroid function
  - Drug initiation
    - IFN-β: 25-50% of full dosing and titrate to full adult dosing over 4-6 weeks
    - GA: begin with full adult dosing- 20 mg SC daily or 40 mg SC TIW
  - Follow-up
    - Clinical evaluation every 3-6 months
    - MRI every 6-12 months
      - New “baseline” MRI on DMT at 6 months of therapy
    - IFN-β neutralizing antibody test at 12-24 months
Important considerations at follow-up appointments

• Assessing adherence
  – Multiple factors affect adherence: DMT side effects/needle anxiety, number of previous attacks, “invincibility” of teens (especially with good disease control), parental involvement
  – Breakthrough disease may relate to non-adherence
  – Directly ask how often the patient/family forgets to take the DMT

• Transition care
  – Starting at age 12 years (or sooner) POMS patients should begin to be able to explain their disease and its treatment

• Adolescent issues: sexual activity, alcohol, drug use
  – Contraindication of DMT in pregnancy
  – Potential interactions of DMT and alcohol/other drugs (e.g. liver function)
Important considerations at follow-up appointments

- Diagnosis of multiple sclerosis
- Initiate treatment with IFNB or GA
  - Evaluate treatment tolerability-adverse events
    - GA: Persistent hypersensitivity reaction, inability to tolerate injections
    - IFNB: Persistent increased hepatic enzymes, leukopenia, persistent systemic reactions, inability to tolerate injections, neutralizing antibody + status
  - Evaluate treatment efficacy
    - Clinical evaluation every 3-6 months and at relapse
    - MRI every 6-12 months and at relapse
      - Persistent relapses
      - Increased disability
      - MRI activity
  - Continue
  - Shift from GA to IFNB or from IFNB to GA
  - Shift to 2nd line treatments
How is treatment failure defined?

• ~30% of POMS do not respond to 1st line therapies

• Considerations
  – Patient age: younger age = higher relapse count
  – Duration of therapy
  – Duration of disease: fewer relapses over time
  – Level of disease activity before treatment
  – IFN-β neutralizing antibody status

• IPMSSG recommendation for defining treatment failure
  – Fully adherent on treatment for at least 6 months but
    • No reduction in relapse rate or new MRI T2 or contrast-enhancing lesions (vs. pre-treatment)
    OR
    • 2 or more relapses (clinical or MRI) within a 12 month period

• Another definition: Ongoing non-adherence due to side effects and/or needle anxiety despite provider and patient attempts to treat these issues
Oral Agents

- **Fingolimod**: 0.5 mg daily
  - Sphingosine-1-phosphate inhibitor blocks egression of lymphocytes from lymph nodes
  - Adverse events: first dose bradycardia, VZV infection, macular edema, herpetic infections, lymphopenia, PML (rare)
  - Requires first dosing observation
- **Dimethyl fumarate**: 240 mg BID
  - Nrf2 antioxidant pathway modulator
  - Adverse effects: flushing, GI upset, lymphopenia, PML (rare)
  - Initial dose titration may help reduce flushing and GI upset
- **Teriflunomide**
  - Pyrimidine synthesis inhibitor affecting T- and B-cell proliferation
  - Adverse effects: hair loss, liver enzyme abnormalities
  - Category X for pregnancy secondary to birth defects
Rituximab

- 750 mg/m²/dose (max 1000 mg); 2 initial doses separated by 14 days and then one dose every 6 months
- Anti-CD20 chimeric monoclonal Ab
  - Ocrelizumab: humanized monoclonal Anti-CD20
- Adult clinical trials demonstrating efficacy in reducing clinical and MRI disease activity
- Pediatric retrospective series demonstrating efficacy and safety in variety of autoimmune and inflammatory disorders of CNS, including POMS
- Follow CD20 counts after treatment and every 3 months
Natalizumab

- 300 mg every 4 weeks
- Humanized monoclonal antibody targeting α4 subunit of α4β1 integrin - blocks T-cell passage across the BBB
- 2004 pivotal RCT: 68% reduction of annualized relapse rate, 83% reduction of new T2 lesions, and 42% reduction of disability progression
- PML risk 4 cases/1000 patients
  - Associated factors: positive JCV Ab status, prior use of immunosuppressants, duration of natalizumab treatment > 24 months
- Pediatric use in retrospective series demonstrate similar efficacy
  - No pediatric PML cases reported to date
- TOUCH risk management program
Rarely used treatments

- Cyclophosphamide 750 mg/m²/dose every 4 weeks x 6-12 months (maximum lifetime dose 80-100 gm)
  - No formal FDA approval in adult MS or POMS
  - Risks of bladder cancer, secondary leukemia, and infertility
- Mitoxantrone 12 mg/m²/dose every 3 months for 2 years (maximum lifetime dose 140 mg/m²)
  - FDA approved for adults with “aggressive” RRMS and SPMS
  - Adverse events
    - 12% of patients develop cardiomyopathy
    - 2.8% with therapy-related acute leukemia
    - Liver toxicity and amenorrhea
My general protocol

“First line” therapy

“Second line” therapy

Oral Agent
- Fingolimod
- Dimethyl fumarate

Reassess at 6-12 months
- Relapse rate
- Disability
- MRI changes
- Adverse events

Treatment failure
- Change to another oral agent
  - Rituximab
  - Natalizumab
Recommended Reading
