CMEO
BriefCase

Transforming MS Care: Advanced Strategies in Multiple Sclerosis Management

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CME OUTFITTERS

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Tanuja Chitnis, MD

Professor of Neurology, Harvard Medical School,
Chief, Division of Neuroimmunology, Mass General Brigham
Boston, MA

Mitzi Joi Williams, MD, FAAN

Medical Director
Joi Life Wellness Center
Smyrna, GA

CME OUTFITTERS

LEARNING OBJECTIVE #1

Assess data on available anti-CD20 therapies to make appropriate recommendations for patients with MS

CME OUTFITTERS

LEARNING OBJECTIVE #2

Utilize evidence-based guidelines for MS management to optimize treatment selection and monitor therapeutic outcomes

CME OUTFITTERS

LEARNING OBJECTIVE #3

Develop tailored MS treatment plans to address the unique physiological and social needs of older and pediatric patients

Patient Case: Emma

14-year-old girl with pediatric-onset relapsing MS (POMS), diagnosed 6 months ago. She has a busy school schedule; caregiver worried about long-term cognition and disability; patient prefers fewer clinic visits.

Recent relapse: **optic neuritis** (painful monocular vision loss) + sensory symptoms

- MRI brain: **> 10 T2-hyperintense lesions; 3 T1 gadolinium (Gd)-enhancing lesions**; cervical spinal cord lesion
- CSF: **oligoclonal bands (OCBs) positive**
- **MS mimic/secondary cause work-up:** serum **MOG-IgG and AQP4-IgG negative**; baseline safety labs/serologies pending or negative

Initiated an oral DMT 6 months ago; now breakthrough disease activity (clinical relapse + new enhancing lesion)

"My parents are worried about my future. I want to keep playing soccer and stay in school with my friends. What treatment will give me the best chance at a normal life?"

AQP4 = aquaporin-4; CSF = cerebrospinal fluid; DMT = disease-modifying therapy; IgG = immunoglobulin G; MOG = myelin oligodendrocyte glycoprotein; MRI = magnetic resonance imaging; MS = multiple sclerosis.

Audience Response

For Emma with highly active relapsing-remitting multiple sclerosis (RRMS) despite adherence to fingolimod, what is the next best step after confirmed breakthrough disease activity?

A. Optimize adherence/support barriers and continue current therapy with close reassessment

B. Intensify treat-to-target monitoring only (e.g., earlier MRI) without changing therapy

C. Refer for escalation planning, including pediatric trial eligibility and implement treat-to-target monitoring

D. Treat the acute relapse and defer any disease-modifying strategy change until later follow-up

E. Other

Pediatric-onset MS

Why Early Control Matters

Pediatric-onset MS is typically more inflammatory than adult-onset MS, with higher relapse rates and greater MRI lesion activity early in disease.

Children have a long disease horizon; early inflammatory activity is associated with later cognitive difficulties and earlier attainment of disability milestones (at a younger chronological age).

Real-world data suggest that starting highly effective therapy (HET) first-line is associated with a lower risk of relapse compared with starting moderately effective therapy.

Practical Implication

For patients with high disease activity or poor prognostic features, aim for rapid disease control using a treat-to-target mindset (e.g., relapse-free and MRI-stable; NEDA where feasible) while proactively managing safety, vaccination timing, and life-stage needs.

NEDA = no evidence of disease activity.

Margoni M, et al. *Front Neurol*. 2021;12:676095. McKay KA, et al. *JAMA Neurol*. 2019;76(9):1028-1034. McKay KA, et al. *Neurology*. 2019;92(24):e2764-e2773. Benallegue N, et al. *JAMA Neurol*. 2024;81(3):273-282. Newsome SD, et al. *Neurol Ther*. 2023;12:1909-1935.

Appropriate & Personalized Treatment Selection in POMS

Step 1 — Confirm inflammatory activity and prognostic risk

- **Clinical**: relapse frequency/severity, recovery, steroid use
- **Imaging**: enhancing lesions, spinal cord lesions, lesion burden; **new/enlarging T2 lesions vs. post-treatment baseline**
- **Patient factors**: adherence, access/logistics, needle aversion, family/caregiver engagement, monitoring burden, growth/puberty considerations; school/social schedule; caregiver capacity

Step 2 — Match therapy intensity to risk (and revisit early)

- **Breakthrough activity** (relapse and/or new/enhancing lesions beyond expected onset) → **reassess** and **switch/escalate within age-approved options** and/or **refer for pediatric MS/clinical trial evaluation**
- **Document SDM**: values (risk tolerance), logistics, and monitoring commitments

Step 3 — Define a monitoring target and timeline upfront

- **MRI plan:** baseline pre-start/switch → **new baseline ~3–6 months** → **annual MRI** (individualize if stable)
- **Triggers to change:** relapse; **new/enhancing lesions after baseline**; unacceptable toxicity/tolerability

SDM = shared decision-making.

Wattjes MP, et al. *Lancet Neurol*. 2021;20(8):653-670. Hacohen Y, et al. *Mult Scler*. 2021;27(13):1970-1976. Margoni M, et al. *Front Neurol*. 2021;12:676095. Benallegue N, et al. *JAMA Neurol*. 2024;81(3):273-282.

POMS Anti-CD20 Trial Evidence*

Agent	Trial	Phase	Comparator/Design	Status	Key Publicly Reported Findings
Ocrelizumab	OPERETTA 2 (NCT05123703)	3	Ages 10–17; double-blind/double-dummy; noninferiority vs. fingolimod	Ongoing/Completed enrollment	ARR: 0.07 vs. 0.14 (rate ratio 0.52); noninferiority met. MRI: fewer new/enlarging T2 lesions; fewer T1 Gd+ lesions at week 12 (ECTRIMS 2025 presentation).
Ofatumumab	NEOS (NCT04926818)	3	Pediatric MS; multi-arm vs. fingolimod; includes siponimod arm	Active, not recruiting; no results posted	No publicly posted efficacy outcomes to date (trial ongoing; endpoints pending)
Ublituximab	ULTIMATE KIDS I (NCT07220252)	2/3 *(design includes phase 2 dose-finding component)*	Pediatric MS study; dose-confirmation/design posted	Not yet recruiting (per registry)	No efficacy outcomes available yet (trial not recruiting; results pending)

*Anti-CD20 agents are not currently approved for pediatric MS; pediatric use is off-label. Anti-CD = anti-cluster of differentiation; ARR = annualized relapse rate; ECTRIMS = European Committee for Treatment and Research in Multiple Sclerosis; Gd+ = gadolinium-enhancing lesions.

ClinicalTrials.gov. Identifier: NCT05123703. ClinicalTrials.gov. Identifier: NCT04926818. ClinicalTrials.gov. Identifier: NCT07220252.
Etemadifar M, et al. *Mult Scler Relat Disord*. 2024;91:105849.

Guideline Touchpoints

Treatment Selection and Monitoring

Individualize DMT

Match efficacy/safety to disease activity; incorporate comorbidities, access, and patient/caregiver preferences.

Reassess Early

Switch/escalate with relapse and/or new MRI activity after adequate exposure/onset-of-effect.

MRI Monitoring

Baseline (or pre-switch) MRI → "new baseline" MRI **~3–6 months** after start/switch → repeat at **~6–12 months**, then typically **annually** (shorter intervals if high risk).

*For anti-CD20: consider infection risk + Ig monitoring**

Treat-to-Target Example (NEDA-3)

No relapses + no new/enlarging T2 or Gd+ lesions + no confirmed disability worsening.

*Anti-CD20 agents are not currently approved for pediatric MS; pediatric use is off-label. Ig = immunoglobulin.

Rae-Grant A, et al. *Neurology.* 2018;90(17):777-788. Wattjes MP, et al. *Lancet Neurol.* 2021;20(8):653-670. Newsome SD, et al. *Neurol Ther.* 2023;12(6):1909-1935. Benallegue N, et al. *JAMA Neurol.* 2024;81(3):273-282. Kornbluh A, Kahn I. *Semin Pediatr Neurol.* 2023;46:101054. Kalb R, et al. *Mult Scler.* 2018;24(13):1665-1680. McKay KA, et al. *JAMA Neurol.* 2019;76(9):1028-1034.

POMS: Management Considerations

POMS: Treatment Selection & Monitoring — *What's Different?*

- **More inflammatory early course** (higher relapse/MRI lesion burden than adult-onset); evidence supports considering **early high-efficacy therapy** for high-risk patients
- **Cognition/school function**: baseline + periodic screening; refer for neuropsych testing as indicated
- **Disability framing:** slower progression from onset, but milestones can occur at **younger chronological age**
- **SDM** with adolescent + caregiver (logistics, risk tolerance, adherence support)
- **Regulatory reality (US):** fingolimod is FDA-approved for pediatric relapsing MS (≥ 10 years); other strategies may involve referral to specialty centers/trials

If Considering Anti-CD20 in POMS*

- **Evidence status:** pediatric safety/efficacy **not established**; consider **trial enrollment**
- **Vaccines:** update before therapy when possible; responses may be blunted on anti-CD20; avoid live vaccines during therapy/immune depletion
- **Baseline labs/screening: HBV** screening; baseline **Ig** and periodic monitoring as clinically indicated
- **Infection vigilance** + caregiver education; plan follow-up cadence and access needs

*Anti-CD20 agents are not currently approved for pediatric MS; pediatric use is off-label. FDA = US Food and Drug Administration; HBV = hepatitis B virus.

National Multiple Sclerosis Society. 2023. https://www.nationalmssociety.org/for-professionals/for-healthcare-professionals/managing-and-treating-ms/pediatric-ms. Portaccio E, et al. *Brain Sci.* 2021;11(4):442. McKay KA, et al. *Neurology.* 2019;92(24):e2764-e2773. Castillo Villagrán D, Yeh EA. *Curr Neurol Neurosci Rep.* 2023;23(11):657-669. ClinicalTrials.gov. Identifier: NCT05123703. ClinicalTrials.gov. Identifier: NCT04926818. Otero-Romero S, et al; *Eur J Neurol.* 2023. Ublituximab-xiiy [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761238s000lbl.pdf.

Revisit The Case: The Right Fit For The Right Patient

Clinical Reasoning

- High inflammatory activity (clinical relapse and/or enhancing/new lesions) → prioritize rapid disease control
- Long disease horizon → protect cognition/school function and reduce cumulative burden
- Strong caregiver support → leverage for **adherence + follow-up**

Treatment Pathway

- SDM with adolescent **and** caregiver (risk tolerance, logistics, adherence support)
- **On-label pediatric option (US):** fingolimod (≥ 10 years) for pediatric relapsing MS
- Cognitive/school function: screen; **neuropsych testing as indicated**
- Vaccines/infection risk counseling; monitoring burden and access
- Match route/visit burden to school schedule + family capacity (infusion access vs. frequent dosing/monitoring)

Approach

- Confirm breakthrough activity + adherence; set treat-to-target goals (clinical + MRI)
- Refer to pediatric MS specialty center to discuss age-appropriate DMT strategy escalation and clinical trial options (including investigational anti-CD20 studies where available)
- Establish MRI timeline and cognitive follow-up expectations
- If considering anti-CD20*: **screen for clinical trials** and counsel on visit burden/infusion vs. SC logistics

*Anti-CD20 agents are not currently approved for pediatric MS; pediatric use is off-label. SC = subcutaneous.

Benallegue N, et al. *JAMA Neurol*. 2024;81(3):273-282. ClinicalTrials.gov. Identifier: NCT05123703. ClinicalTrials.gov. Identifier: NCT04926818. ClinicalTrials.gov. Identifier: NCT07220252.

Tools for Monitoring Treatment Response

Clinical (Every Visit/Periodic)

- Relapse screen + neurologic exam; document severity/recovery
- Disability/functional: EDSS or equivalent q6–12 mo; consider T25FW + 9HPT as indicated
- Vision + cognition check-ins; SDMT baseline + periodic screening; school-function check-in
- PROs: fatigue/QoL, adherence barriers, caregiver observations

MRI (Treat-to-Target Support)

- Baseline MRI (brain ± spine) **before** start/switch
- "New baseline" MRI **~3–6 mo** after initiation/switch
- Ongoing MRI **annually if stable** (earlier with clinical concern)
- Track new/enlarging T2 lesions and Gd+ lesions; standardize protocol/reporting

Laboratory

- Baseline (anti-CD20* example): HBV screening + quantitative immunoglobulins
- Ongoing: periodic immunoglobulins during/after therapy; CBC/LFTs per selected DMT/protocol
- Consider CD19 counts only for specific clinical questions / per protocol

Adherence & Follow-up Strategies (POMS-Practical)

- Shared plan with adolescent + caregiver; clear escalation steps
- Home dosing: reminders/calendar, refill checks, teach-back technique
- Clinic/infusion dosing: schedule next visit before leaving; transportation + school note templates
- Team check-ins/patient support programs; coordinate with school for missed time

*Anti-CD20 agents are not currently approved for pediatric MS; pediatric use is off-label.
9HPT = Nine-Hole Peg Test; CBC = complete blood count; EDSS = Expanded Disability Status Scale; LFTs = liver function tests; PROs = patient-reported outcomes; QoL = quality of life; SDMT = Symbol Digit Modalities Test; T25FW = Timed 25-Foot Walk.

Wattjes MP, et al. *Lancet Neurol.* 2021;20(8):653-670. Kalb R, et al. *Mult Scler.* 2018;24(13):1665-1680. Benedict RH, et al. *Mult Scler.* 2017;23(5):721-733.
Multiple Sclerosis Outcome Assessments Consortium (MSOAC). *EMA Qualification Opinion (Clinical Outcome Assessments in MS).* 2019. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-qualification-opinion-multiple-sclerosis-clinical-outcome-assessment-mscoa_en.pdf.
Ocrelizumab and hyaluronidase-ocsq [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2025/761371Orig1s000ChemR.pdf.
Ofatumumab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/125326Orig1s070.pdf.
Ublituximab-xiiy [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761238s000lbl.pdf.

Strategies for Shared Decision-Making

Pediatric MS

Key Principles (POMS-Specific)

- **Triadic SDM:** include adolescent **and** caregiver; support emerging autonomy
- Use **age-appropriate language + visuals**; confirm understanding (teach-back)
- Review all treatment options with pros/cons; use visual aids when helpful
- Discuss realistic expectations: what treatment can and cannot do
- Start with goals/values: **school, sports, fatigue/cognition, risk tolerance, visit burden**
- Surface fears early: **needles, safety concerns, missed school, travel, coverage delays**

A Simple SDM Flow (3-Talk)

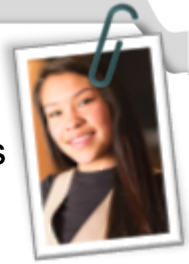
- **Team talk:** name the decision + who's involved + goals
- **Option talk:** compare reasonable options (efficacy, safety/monitoring, route/cadence, impact on life)
- **Decision talk:** document the "why," and schedule the next monitoring steps before they leave

Close the Loop

- Give a written plan: what to watch for, who to call, when MRI/labs/visits occur
- Build adherence supports: reminders, refill checks, injection/infusion teaching, early check-ins
- For patients of reproductive potential: raise contraception/pregnancy planning early (as relevant to DMT choice)
- Connect families with support resources (MS societies, peer support groups)

Elwyn G, et al. *BMJ*. 2017;359:j4891. Opel DJ. *Pediatrics*. 2018;142(Suppl 3):S149-S156. Duffy LV, et al. *J Pediatr Nurs*. 2021;61:404-409. Hillert J, et al. *Mult Scler*. 2024;30(9):1093-1106.

Case Conclusion



Practical Plan

1. **Reassess**: confirm relapse vs. pseudo-relapse; review adherence/access barriers and tolerability
2. **Re-stage disease activity**: brain MRI (± spine per phenotype) and establish a post-switch baseline
3. **Escalate thoughtfully (POMS context)**: align efficacy needs with family logistics; discuss **FDA-approved pediatric options** and **refer for specialty center/clinical trial evaluation** when higher-efficacy strategies are needed
4. **Safety essentials (apply per therapy)**: vaccine review/timing; reproductive counseling as indicated
5. **If anti-CD20* is being considered (trial context)**: HBV screening + baseline quantitative immunoglobulins; infection counseling; define lab/MRI follow-up cadence
6. **Make adherence realistic**: match the regimen to the patient's daily life; caregiver-supported calendar, refill/visit planning, school coordination/accommodations

Key takeaway: Breakthrough activity in POMS should trigger explicit reassessment + timely escalation, paired with a realistic adherence/monitoring plan and caregiver + school supports.

Individualized Treatment Optimization and Addressing the Needs of Older Patient Populations with MS

Patient Case: Robert

Robert is a 68-year-old male with relapsing MS diagnosed at 45 years; clinically and radiographically stable on ocrelizumab, but with increasing fatigue and falls. Recently, two hospitalizations in the past 6 months for pneumonia/bronchitis; shingles episode in the past year.

- **Stable** disease for 8 years on ocrelizumab; no relapses or new MRI lesions
- **Recent**: Hospitalized twice in 6 months for respiratory infections (pneumonia, bronchitis)
- **Comorbidities**: hypertension, type 2 diabetes, mild cognitive impairment, chronic sinus disease; polypharmacy
- **EDSS**: 3.5 (stable)

Current medications: ocrelizumab, lisinopril, metformin

Labs: IgG = 480 mg/dL (low); CD19+ B cells undetectable

Goal: maintain independence and avoid hospitalization; prefers fewer clinic visits

"I'm worried about these infections. My wife helps me with everything, but she's getting older too. Should I keep taking this medicine if my MS has been stable for so long?"

mg/dL = milligrams per deciliter.

Audience Response

Given Robert's scenario, what is the best NEXT step?

A. Continue anti-CD20 on the same schedule and monitor
B. Hold or extend the next anti-CD20 dose (e.g., extended-interval dosing) and reassess infection risk, IgG trend, and B-cell reconstitution before re-dosing
C. Switch to a lower-risk DMT (de-escalate) and monitor closely
D. Discontinue DMT with a structured follow-up plan (clinical + MRI) and restart if activity returns
E. Refer to immunology/infectious disease and consider Ig replacement depending on severity

Older Adults With MS

Shifting Biology and Treatment Benefit–Risk

With aging and longer disease duration, relapses/new MRI lesions often decline, while disability accrual increasingly reflects progression independent of relapses and neurodegeneration.

Immunosenescence, plus greater comorbidity and polypharmacy, increases vulnerability to infections and other adverse outcomes; important context for treatment risk discussions.

As inflammatory activity wanes, incremental benefit of high-efficacy DMT may be smaller in selected stable older patients, while serious infection risk and anti-CD20–associated hypogammaglobulinemia may rise.

Clinical Implication:

Reassess benefit–risk periodically and after key events (new comorbidities, disability progression, serious infection). For selected patients ≥ 55 years with prolonged clinical/MRI stability, consider de-escalation or discontinuation discussions with a monitoring plan, balancing recurrence/rebound risk and agent-specific safety.

van der Walt A, et al. *Nat Rev Neurol*. 2025;21:432-448. Siddiqui A, Hua LH. *Neurotherapeutics*. 2025;22(4):e00603. DiMauro KA, et al. *J Neurol*. 2024;271(7):3794-3805. Langer-Gould AM, et al. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(6):e200164. Smolik K, et al. *Mult Scler Relat Disord*. 2025;93:106191. Corboy JR, et al. *Lancet Neurol*. 2023;22(7):568-577. Jouvenot G, et al. *JAMA Neurol*. 2024;81(5):490-498.

CME OUTFITTERS

Personalized Treatment Optimization

Older Adults with MS

A Balancing Framework

Confirm Current Inflammatory Activity

- Relapse history (≈ past 5 years) and MRI activity (new T2/Gd+ lesions ≈ past 3 years)
- Disability trajectory: relapse-associated worsening vs. PIRA / progression
- Recent steroids/clinical concerns; phenotype/context

Quantify Vulnerability (Baseline Risk)

- Age, disability, comorbidity burden, polypharmacy, frailty/falls, cognition
- Infection history + vaccines; labs as relevant (IgG especially with anti-CD20)

Match Action + Monitoring Plan

- Active disease: continue/optimize effective DMT + risk mitigation
- Stable + rising risk: consider de-escalation (dose-spacing/switch) or structured discontinuation in selected patients; counsel that risk of recurrence is agent-specific (higher after natalizumab/S1P modulators)
- Monitoring + restart criteria (clinical + MRI at defined intervals)

PIRA = progression independent of relapse activity; S1P = sphingosine-1-phosphate.

Graves JS, et al. *Lancet Neurol.* 2023;22(1):66-77. Fernández O, et al. *Front Immunol.* 2024;15:1379538. Weideman AM, et al. *Front Neurol.* 2017;8:577. Langer-Gould A, et al. *Neurol Neuroimmunol Neuroinflamm.* 2023;10(6):e200164. Smolik K, et al. *Mult Scler Relat Disord.* 2025;93:106191. Corboy JR, et al; *Lancet Neurol.* 2023;22(7):568-577. Jouvenot G, et al. *JAMA Neurol.* 2024;81(5):490-498. Androdias G, et al. *Brain.* 2025;148(5):1459-1478. Wattjes MP, et al. *Lancet Neurol.* 2021;20(8):653-670.

Overview of Anti-CD20 Therapies

Older Patient Populations

Expected Benefit with Age

- Anti-CD20 therapies strongly reduce relapses/MRI activity in relapsing MS, but inflammatory activity (and average treatment effect on disability outcomes) generally declines with age and longer disease duration. Risk rises with age, disability, comorbidity, and cumulative exposure, individualize benefit–risk

Key Class Safety Signals

- Infusion/injection reactions; serious infections (incl. herpes virus infections); **HBV reactivation risk**
- Gradual declines in **IgM** (and sometimes **IgG**) over time; lower IgG is linked to higher serious infection risk; vaccine antibody responses are often blunted during B-cell depletion

Practical Mitigation & Monitoring

- **Before start:** HBV screen; baseline Ig; update vaccines (no live vaccines during therapy)
- **During:** periodic Ig monitoring; hold/delay for active infection; if recurrent/severe infections + low IgG, reassess (space/hold/switch) and consider ID/immunology ± IVIG/SCIG

ID = infectious diseases; IgM = immunoglobulin M; IVIG/SCIG = intravenous/subcutaneous immunoglobulin.

Weideman AM, et al. *Front Neurol*. 2017;8:577. Cohen JA, Sweitlik C. *J Neurol*. 2024;271:3794-3805.
Ocrelizumab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761053s036lbl.pdf.
Ofatumumab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/125326Orig1s070.pdf.
Ublituximab-xiiy [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761238s000lbl.pdf. Otero-Romero S, et al. Mult Scler. 2023;29(8):904-925. Bar-Or A, et al. *Neurology*. 2020;95(14):e1999-e2008. Rempe T, et al. *Mult Scler Relat Disord*. 2023;79:105028.

Anti-CD20 Therapies in MS

The Current Landscape

	Ocrelizumab (RMS, PPMS)	Ofatumumab (RMS)	Ublituximab (RMS)	Rituximab (off-label for MS)*
MOA	IV: Humanized anti-CD20; B-cell depletion SC: Same molecule + hyaluronidase for SC delivery	Fully human anti-CD20; B-cell depletion	Chimeric anti-CD20 IgG1; B-cell cytolysis/depletion	Chimeric anti-CD20; long experience in other conditions
Route	IV: 300 mg day 1 + day 15; then 600 mg q6 mo SC (HCP): 23 mL abdomen over ~10 min q6 mo	SC self-injection: 20 mg wks 0/1/2; then monthly starting wk 4	IV: 150 mg day 1; 450 mg day 15; then 450 mg q24 wks	IV, various regimens
Key Practical Considerations	Infusion center; premeds; observe ≥ 1 hr post-infusion; HBV + serum Ig screening SC: Short clinic time; In-clinic; premeds; observe 1 hr (initial), 15 min (subsequent); HBV + serum Ig screening	Home administration; first dose under HCP guidance; HBV + serum Ig screening; caregiver support; cold-chain supply	Premeds; infusion ~4 hr (1st), ~1 hr (2nd+); observe ≥ 1 hr after first 2 infusions; HBV + serum Ig screening	Not FDA-approved for MS; dosing protocols vary by center/payer; evidence largely observational/registry; do not infer equivalence across agents

*Rituximab is not currently indicated for the treatment of MS; prescribed off-label.
HCP = healthcare professional; IV = intravenous; MOA: = mechanism of action; PPMS = primary progressive MS, RMS = relapsing forms of MS.
Ocrelizumab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761053s029s030lbl.pdf. Ocrelizumab and hyaluronidase-ocsq [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2025/761371Orig1s000ChemR.pdf.
Ofatumumab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/125326Orig1s070.pdf.
Ublituximab-xiiy [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761238s000lbl.pdf.

Efficacy Outcomes*

Pivotal Trial Snapshots

Trial (agent vs. comparator)	Annualized relapse rate (ARR)	MRI lesion activity	Disability outcomes (selected)**
OPERA I/II (Phase 3) Ocrelizumab vs. IFNβ-1a — RMS	0.16 vs. 0.29 (~46–47%↓)	↓ New/enlarging T2 lesions and ↓ Gd+ lesions vs. IFNβ-1a	Pooled: ↓ risk of 12-wk CDP (HR ~0.60); also ↓ 24-wk CDP
ORATORIO (Phase 3) Ocrelizumab vs. placebo — PPMS	N/A (PPMS) (relapse rate not the primary efficacy endpoint)	↓ T2 lesion burden/accumulation and ↓ brain volume loss vs. placebo	↓ 12-wk CDP (HR 0.76) and ↓ 24-wk CDP (HR 0.75) vs. placebo
ASCLEPIOS I/II (Phase 3) Ofatumumab vs. teriflunomide — RMS	0.10–0.11 vs. 0.22–0.25 (~51–58%↓)	↓ New/enlarging T2 lesions and ↓ Gd+ lesions vs. teriflunomide	Pooled: 3-mo CDW 10.9% vs. 15.0% (HR 0.66); 6-mo CDW 8.1% vs. 12.0% (HR 0.68)
ULTIMATE I/II (Phase 3) Ublituximab vs. teriflunomide — RMS	0.08–0.09 vs. 0.18–0.19 (~51–59%↓)	↓ Gd+ lesions and ↓ new/enlarging T2 lesions vs. teriflunomide	Pooled: No significant difference in 12-wk disability worsening (5.2% vs. 5.9%; HR 0.84; P =0.51)
RIFUND-MS (Phase 3) Rituximab vs. dimethyl fumarate; RRMS/CIS	0.015 vs. 0.087 (rituximab vs. dimethyl fumarate)	Any new T2 and/or Gd+ lesion: 21% vs. 37% (lower with rituximab)	Confirmed EDSS worsening; 10% vs. 5% (NS) (trial not powered for disability separation)

*Populations, endpoints, and comparators differ; no completed head-to-head RCTs comparing FDA-approved anti-CD20 MS therapies—interpret descriptively.
**Trial programs shown; disability outcomes reflect published pooled analyses where available. CDP = confirmed disability progression; CDW = confirmed disability worsening; CIS = clinically isolated syndrome; IFNβ-1a = interferon beta-1a. RRMS = relapsing-remitting multiple sclerosis.

Hauser SL, et al. *N Engl J Med.* 2017;376(3):221-234. Hauser SL, et al. *N Engl J Med.* 2020;383(6):546-557. Hauser SL, et al. *N Engl J Med.* 2022;387(8):704-714. Montalban X, et al. *N Engl J Med.* 2017;376(3):209-220. Svenningsson A, et al. *Lancet Neurol.* 2022;21(8):693-703.

Guidelines in Treatment Selection

Older Adult Patients

Vaccination & Infection Prevention

- Review immunization status at diagnosis/therapy change; prioritize non-live vaccines (e.g., influenza, pneumococcal, recombinant zoster, COVID-19)
- Before anti-CD20: give needed vaccines ≥ 4 w (live-attenuated) or ≥ 2 w (non-live) before first dose when feasible; HBV screen = HBsAg + anti-HBc (± anti-HBs)
- During therapy: avoid live vaccines; counsel responses may be blunted; coordinate timing (prefer before initiation/next dose when feasible)

Treatment Reassessment / De-Escalation

- AAN DMT guideline provides limited stopping guidance and no age-based thresholds → individualize benefit–risk.
- DISCOMS (≥ 55, stable): discontinuation did not meet noninferiority; more new MRI lesions vs continuation; relapses uncommon.
- Selected older, stable patients with rising safety risk: consider de-escalation/ discontinuation with monitoring + restart criteria; avoid abrupt stopping of rebound-prone agents

AAN = American Academy of Neurology; Anti-HBc = hepatitis B core antibody; Anti-HBs = hepatitis B surface antibody; DISCOMS = discontinuation of disease-modifying therapies in multiple sclerosis; HBsAg = hepatitis B surface antigen.

Otero-Romero S, et al. *Mult Scler.* 2023;29(8):904-925. Farez MF, et al. *Neurology.* 2019;93(13):584-594. Zettl UK, Rommer PS. *Nat Rev Neurol.* 2023;19(9):509-510. Bar-Or A, et al. *Neurology.* 2020;95(14):e1999-e2008. Ocrelizumab and hyaluronidase-ocsq [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2025/761371Orig1s000ChemR.pdf. Conners EE, et al. *MMWR Recomm Rep.* 2023;72(1):1-25. Rae-Grant A, et al. *Neurology.* 2018;90(17):777-788. Corboy JR, et al. *Lancet Neurol.* 2023;22(7):568-577. Androdias G, et al. *Brain.* 2025;148(5):1459-1471. Jouvenot E, et al. *JAMA Neurol.* 2024;81(5):490-498.

Personalized Care Management in Older Adults with MS: *Key Challenges & Practical Approach*

Challenges (Older Adults)

- Comorbidities and polypharmacy can substantially influence symptoms/outcomes and complicate adverse-event attribution
- Functional decline is often multifactorial (progression, frailty/deconditioning, falls risk, mood/sleep disorders, vascular disease, medication effects), not just inflammatory MS activity
- MRI interpretation can be more complex with age (microvascular change, atrophy, incidental findings); use standardized MRI protocols and clinical correlation
- Social determinants (transportation, caregiver support, coverage changes, infusion/specialty access) shape feasibility of care plans

Practical Approach

- Assess: recent relapses/MRI activity vs. progression trajectory; cognition, function, frailty/falls; comorbidities/medications; DMT exposure and safety (e.g., infection history, immunoglobulins)
- Plan: interdisciplinary care, neurology + primary care + rehab (PT/OT) + behavioral health + pharmacy ± social work; involve infectious diseases/immunology for recurrent/severe infections
- Implement: simplify regimen/visit burden when feasible; home safety & falls prevention; coordinate preventive care (vaccines, vascular risk, routine cancer screening)

OT = occupational therapy; PT = physical therapy.

DiMauro KA, et al. *J Neurol*. 2024;271:3794-3805. van der Walt A, et al. *Nat Rev Neurol*. 2025;21(8):432-448. Wattjes MP, et al. *Lancet Neurol*. 2021;20(8):653-670. Thelen J, et al. *Mo Med*. 2021;118(3):239-245. Dobson R, et al. *Nat Rev Neurol*. 2022;18(12):723-734.

Revisit the Case:

A De-escalation Decision Pathway

PT

Robert (68y, 8y stable, recurrent infections/low IgG)

Stepwise Decision Pathway

1. Confirm stability: no relapses and no new/enhancing MRI lesions (past 2–5y)
2. Risk stratify: age, frailty/comorbidities, infection history, IgG trend
3. Match option to risk:
    - Continue anti-CD20 with enhanced prevention/monitoring, or
    - Consider dose-spacing/EID (individualized; observational evidence), or
    - Consider structured discontinuation with monitoring plan
4. Pre-define restart triggers: relapse; confirmed new/enhancing MRI lesions; inflammatory progression
5. Follow-up: clinical q3–6 mo early after change; MRI ~6–12 mo

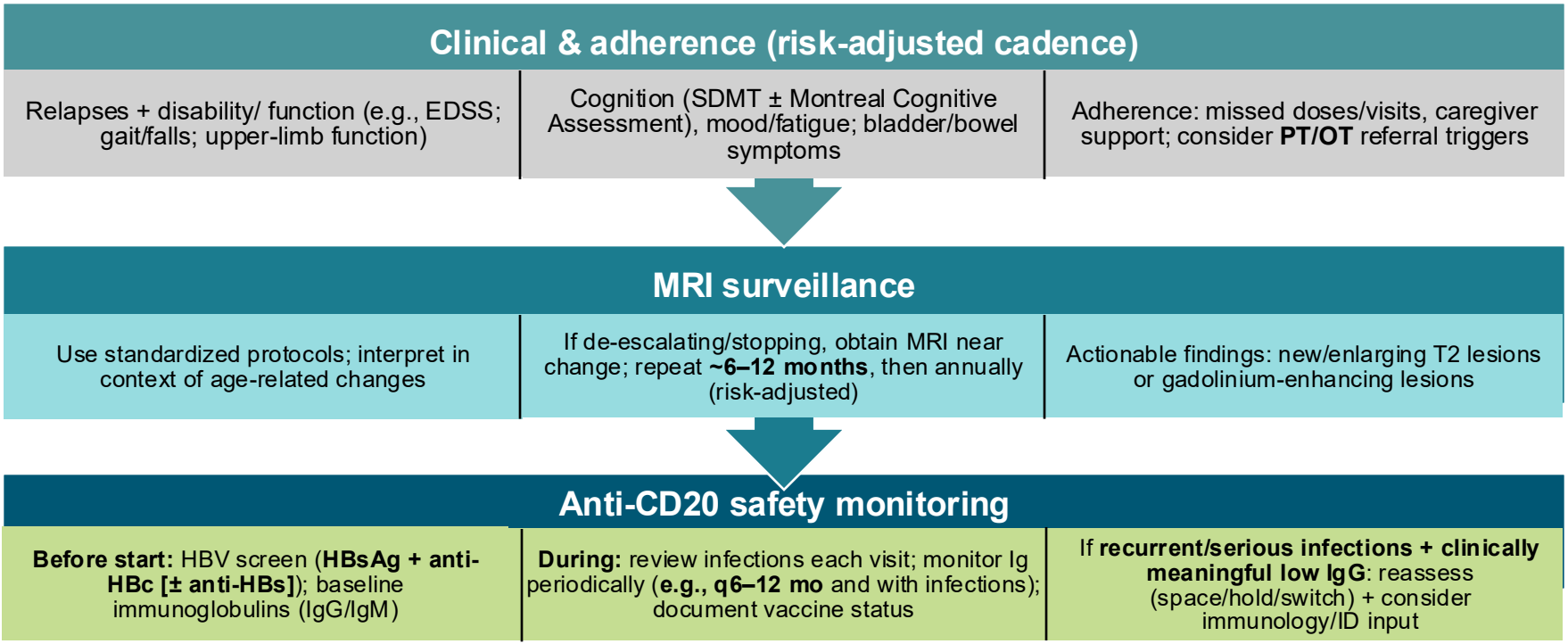
Evidence Snapshot

- DISCOMS (≥ 55, stable): stopping did not meet non-inferiority vs continuing; stopping associated with more new MRI activity (relapses uncommon)
- Observational registry data: relapse risk after stopping varies by agent; rebound risk is higher after natalizumab/fingolimod than after anti-CD20 (interpret cautiously)
- Bottom line: individualize and pair any change with monitoring + restart plan

EID = extended-interval dosing.

Corboy JR, et al. *Lancet Neurol*. 2023;22(7):568-577. Jouvenot G, et al. *JAMA Neurol*. 2024;81(5):490-498.
Rempe T, et al. *Mult Scler Relat Disord*. 2023;79:105028. Androdias G, et al. *Brain*. 2025;148(5):1459-1478.

Tools to Monitor Response, Safety, and Adherence in Older Adults



DiMauro KA, et al. *J Neurol.* 2024;271(7):3794-3805. Wattjes MP, et al. *Lancet Neurol.* 2021;20(8):653-670. Gross RH, Corboy J. *Curr Neurol Neurosci Rep.* 2024;24(9):341-353. Ocrelizumab [package insert]. Ocrelizumab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761053s029s030lbl.pdf. Corboy JR, et al. *Lancet Neurol.* 2023;22(7):568-577.

SDM in Older Adults With MS

Continue, Adjust, or De-escalate?

Framing the Conversation

"You've been stable. Let's review what matters most to you and decide whether continuing, adjusting, or de-escalating treatment best fits your health and goals."

Key Discussion Points

- Review current stability (clinical + MRI) and progression trajectory
- Explain benefit–risk shift with age/comorbidity; use absolute risks when feasible
- Compare options (continue / adjust / de-escalate) + what's known/unknown
- Agree on a written plan: monitoring + clear triggers for action/restart

Patient Values & Supports

- Goals now: mobility/independence, cognition, fatigue, infection avoidance, QoL, visit burden
- Preferences: uncertainty vs simplicity; route/visit burden; costs/access
- Support understanding: plain language + teach-back; caregiver involvement (with consent); consider a decision aid
- Trust and inclusion matter: many MS trials underrepresent some racial/ethnic groups

Key Message: **Changing treatment ≠ abandoning care:** maintain follow-up and a rapid path back if disease activity returns.

DiMauro KA, et al. *J Neurol.* 2024;271:3794-3805. National Institute for Health and Care Excellence (NICE). *Shared Decision Making (NG197).* 2021. https://www.nice.org.uk/guidance/ng197. Stacey D, et al. *Cochrane Database Syst Rev.* 2017;4:CD001431.

CME OUTFITTERS

Case Conclusion

Why reassess now?

- In older patients with stable MS, inflammatory benefit often declines while treatment risks/monitoring burden may rise → **individualize benefit–risk + patient goals**

Options to discuss (structured)

a) Continue anti-CD20 with enhanced prevention/monitoring ± extended-interval dosing (selected stable patients; evidence largely observational)

b) Structured discontinuation with surveillance (document rationale; define restart triggers)

Monitoring & restart triggers (stopping ≠ abandoning care)

- Clinical follow-up + MRI plan; compare to prior baseline
- **Actionable findings:** relapse **or** new/enlarging **T2** lesions **or** gadolinium-enhancing lesions → **revisit treatment**
- If recurrent/severe infections + low IgG → **immunology/ID input; consider Ig replacement if clinically indicated**

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

Put information into action! Consider the following goals; then *set a time frame* that fits with your work environment and *a reasonable improvement target* that aligns with your patient population.

- **Within 1 week,** implement a **standardized anti-CD20 checklist** (HBV serologies, baseline Ig, vaccine timing, logistics). **Target ≥ 80%** completion in eligible visits by week 4.
- **Within 2 weeks,** run a **panel review** to flag: (1) **older anti-CD20** patients with serious infection and/or low IgG, and (2) **breakthrough MS activity**. **Target 100%** of flagged cases reviewed within 30 days.
- **Within 1 month,** document a **monitoring plan** for patients on DMT (clinical function ± cognition + MRI cadence). **Target ≥ 90%** with a documented plan.
- **Within 3 months,** standardize **SDM + de-escalation documentation** (options, patient goals, monitoring + restart triggers). **Target ≥ 75%** of de-escalation discussions include all elements.
- **Ongoing (quarterly),** track 4 metrics: **vaccines, Ig monitoring, missed visits/doses, serious infections**. Set and report a **local improvement target** each quarter.

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