MONOCLONALI NON INDUTTIVI: INTERVALLO STANDARD VS ESTESO

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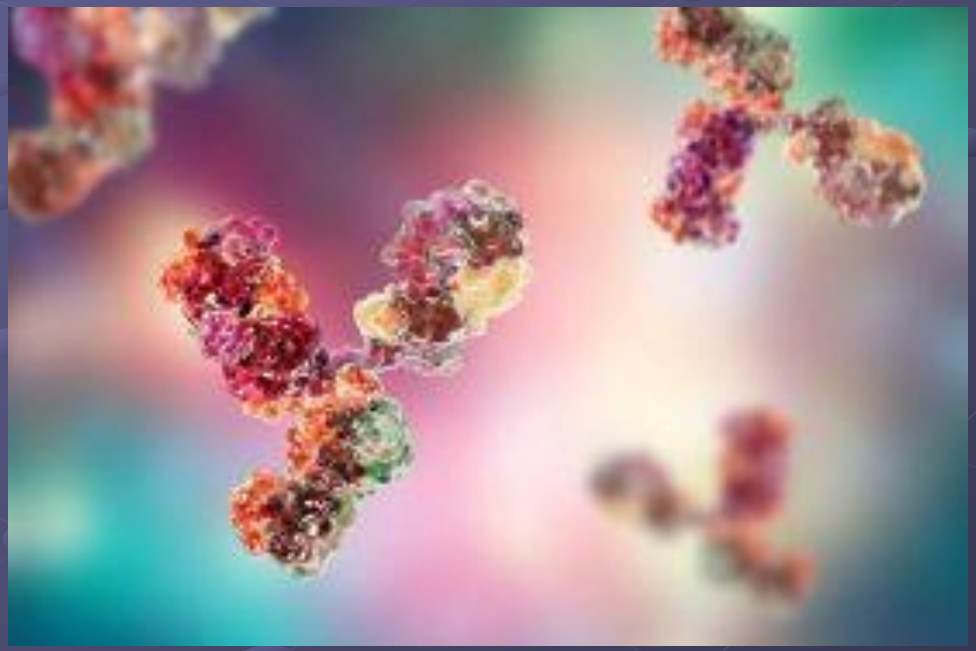
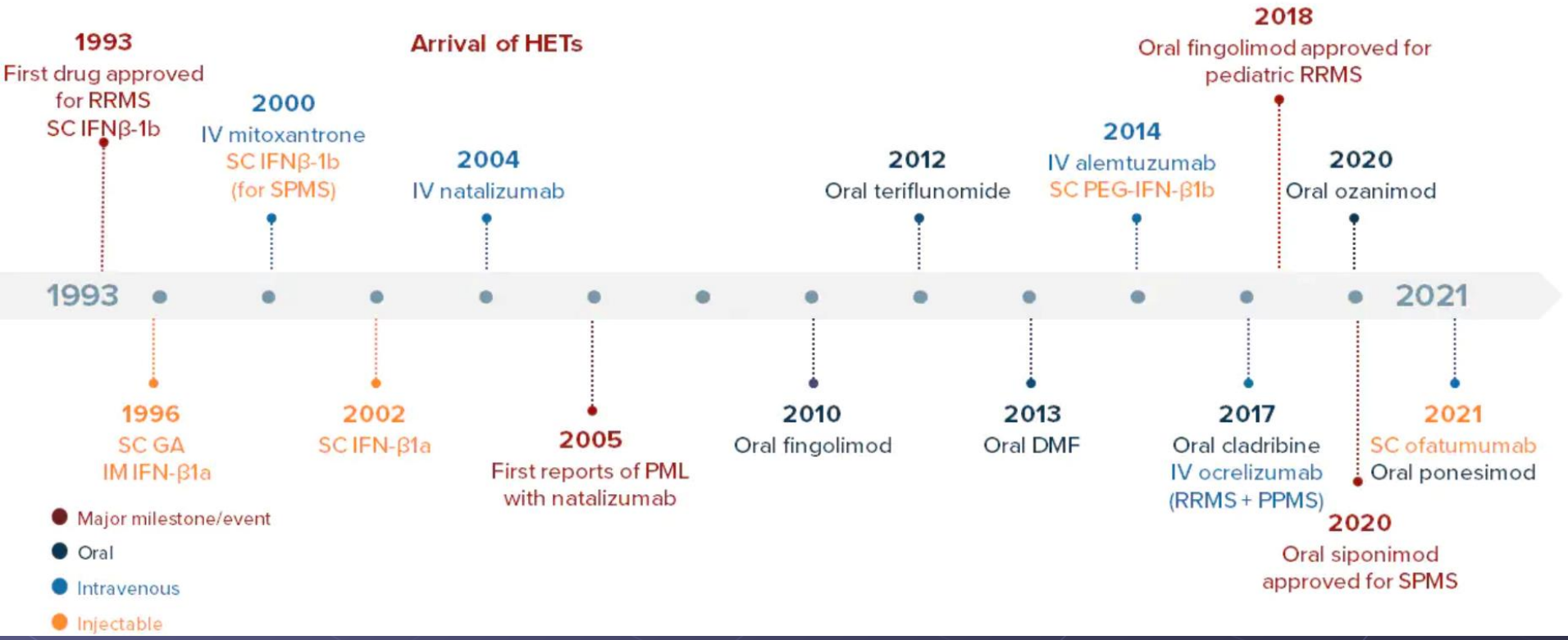


Disclosures

E Cocco received speaker fees and consultancies from:

- Aldmirall, Biogen Idec, BMS, Janssen, Sanofi, Merck, Novartis and Roche

Decades of MS Drug Development



Tintorè M et al., *Nat Rev Neurol* 2019; Siponimod, EMA Jan 2021; Ozanimod, EMA Oct 2020; Ponesimod, EMA Jun 2021; Ofatumumab, EMA Jun 2021

Which is the true induction in MS?

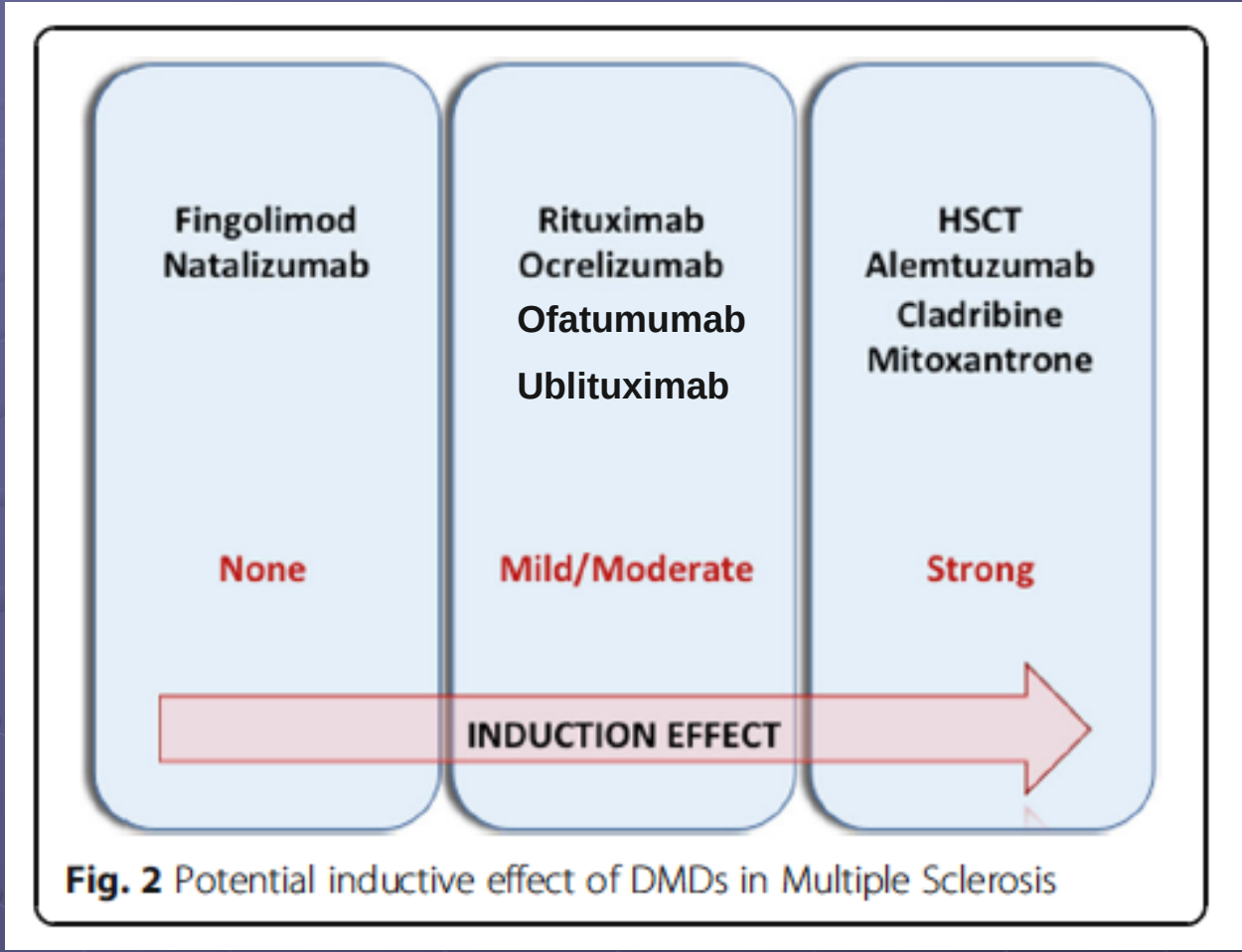


Fig. 2 Potential inductive effect of DMDs in Multiple Sclerosis

AN EVOLVING CONCEPT…..

Ruggieri *et al. Multiple Sclerosis and Demyelinating Disorders* (2018) 3:5
https://doi.org/10.1186/s40893-018-0037-7

EARLY INTENSIVE THERAPY

Early Intensive therapy (EIT):[1]	
Induction treatment	Mitoxantrone Cyclophosphamide Stem cell transplantation Alemtuzumab Cladribine*
Sustained HET	**Natalizumab** Fingolimod* **Anti-CD20 treatment**

MAbs are currently taking a leading role among HET for MS

Therefore, it is a timely topic to discuss how to optimize these treatments without decreasing drug efficacy by

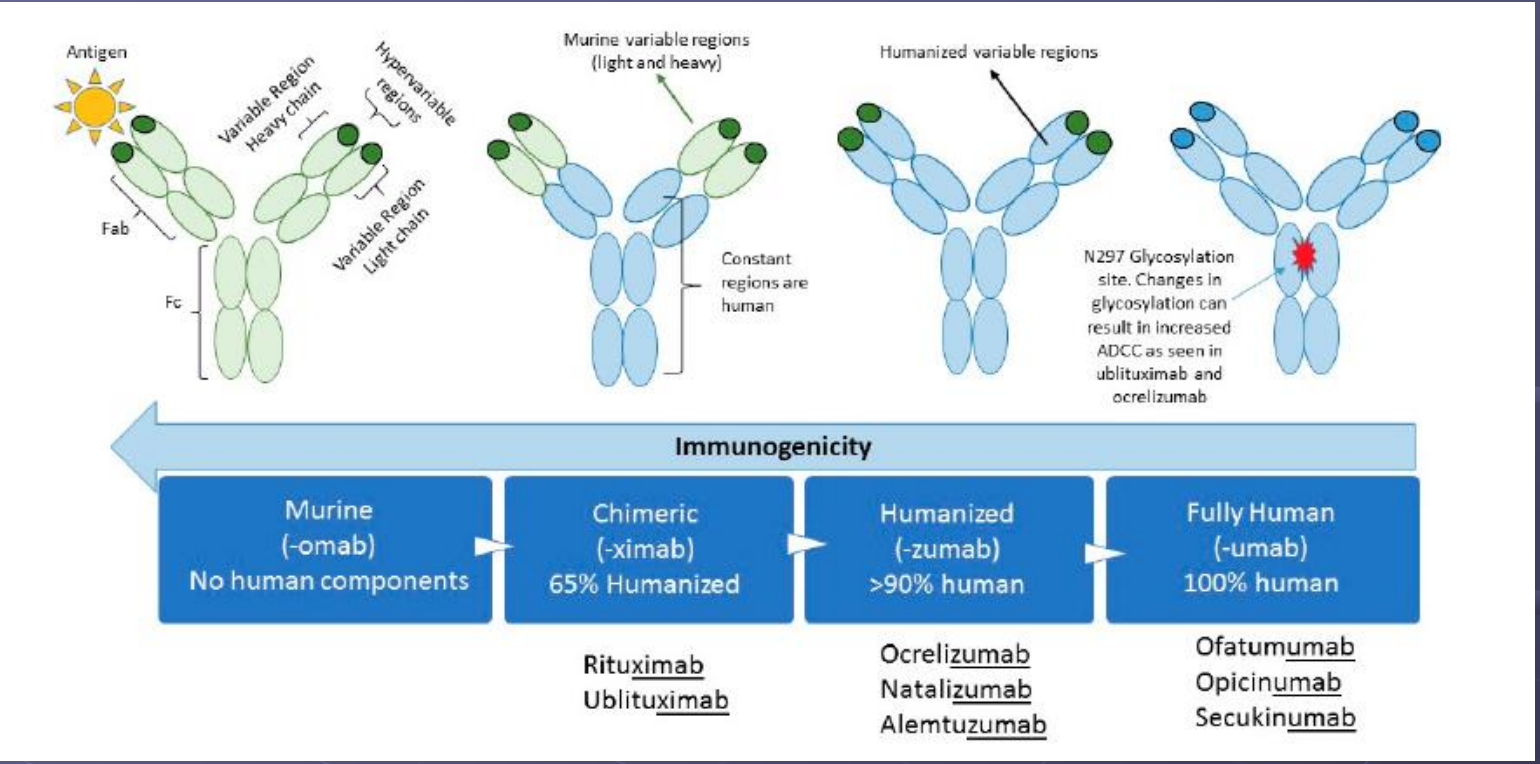
- extended (when infusion intervals are prolonged to a set interval)
- personalized dosing (based on pharmacokinetic and/or pharmacodynamic measurements).

*There is currently no consensus for cladribine and fingolimod; some authors consider them HET and some do not.

CD20, B-lymphocyte antigen CD20; HET, high-efficacy therapy; HSCT, haematopoietic stem cell transplantation; IFN, interferon; IRT, immune reconstitution therapy.

1. Casanova B, et al. *J Pers Med* 2022;12:119;

Monoclonal Abs in MS

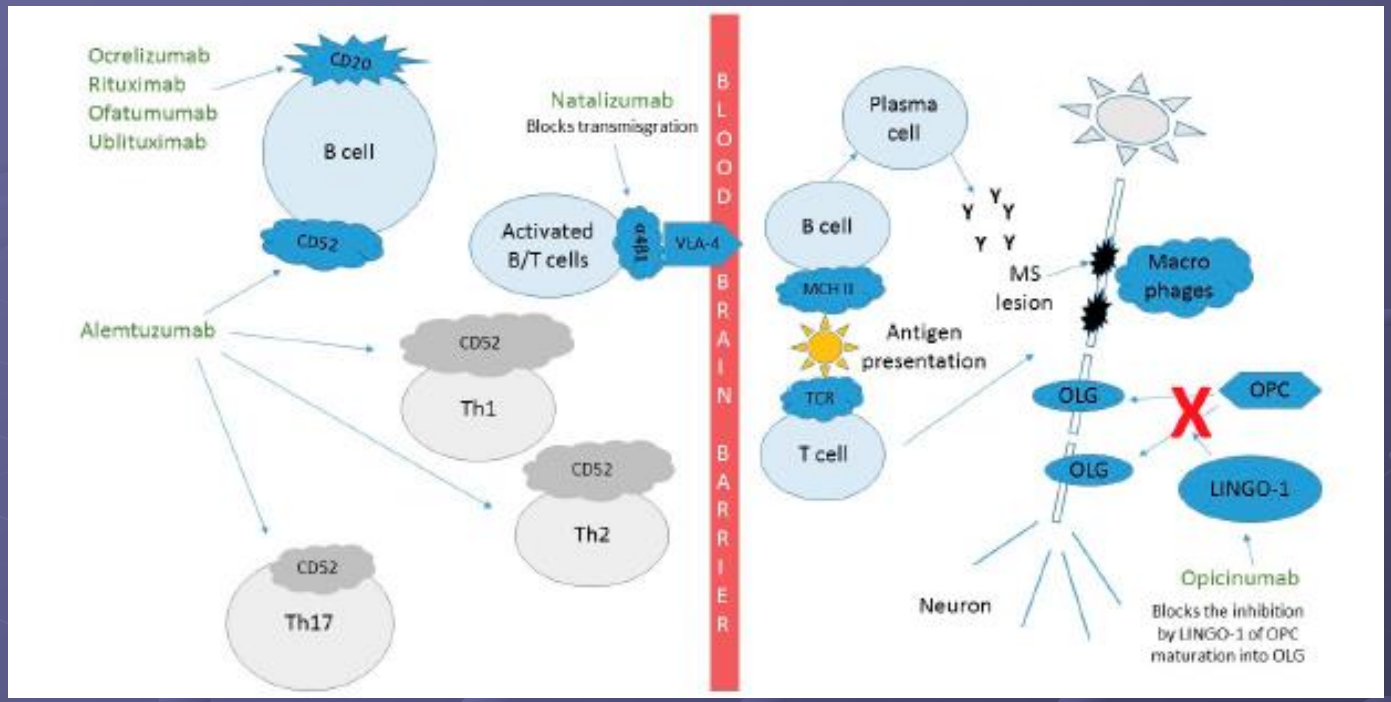


- mAbs belong to the immunoglobulin G (IgG) isotype which bind specifically with their fragment antigen-binding (Fab) region to the epitope of the target molecule.

- mAb are characterized by a relatively long pharmacologic half-life (IgG subclasses up to 30 days) and long pharmacodynamic e ffects.

Voge NV et al 2022

Monoclonal Abs in MS



Currently, four monoclonal antibodies (natalizumab, alemtuzumab, ocrelizumab, and ofatumumab) are approved for the treatment of MS.

Rituximab is commonly used off-label and ublitixumab in under investigation.

As natalizumab, rituximab, ocrelizumab, and ofatumumab are regularly administered therapies, these agents are **suitable for extended dosing.**

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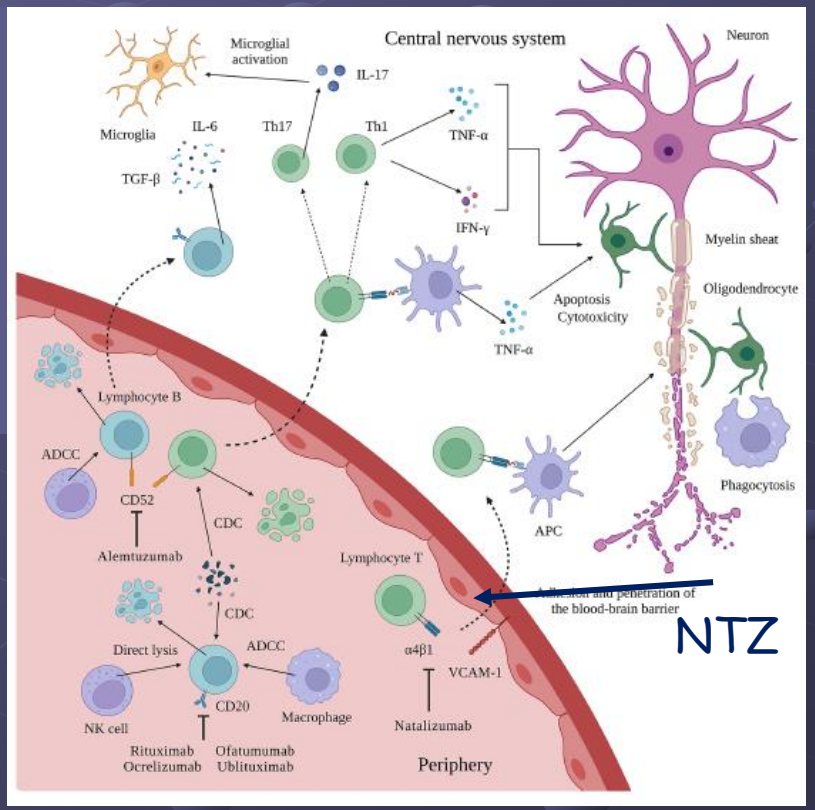
Natalizumab

NTZ is a humanized mAb that binds to 4 integrin receptors on endothelial cells lining blood vessels, disrupting the interaction of 4 1 integrin (VLA-4) expressed on lymphocytes and monocytes with its ligand vascular cell adhesion molecule 1 (VCAM1) on endothelial cells.

NTZ inhibits migration of leukocytes through the BBB into the brain and spinal cord.
While preventing invasion of autoreactive lymphocytes from peripheral blood into the CNS, cells are not depleted from the circulation.

The median relative bioavailability following administration is:
- IV 100%
- SC 82.4%

The median half-life:
- IV 27.1 days,
- SC absorption half-life around 2.6 days



Neurotherapeutics
https://doi.org/10.1007/s13311-022-01224-9

Natalizumab

DMT	Mechanism of action	Dose, administration and interval of application	Efficacy	Important safety issues	Risk management
Natalizumab	$\alpha_4\beta_1$ integrin antagonist	Dose: 300 mg iv. or sc Every 4 weeks (SID) to every 6 weeks (EID)	Phase 3 clinical trials: AFFIRM, SENTINEL Clinical outcomes • 24–42% decrease in the risk of sustained disability progression • 54–68% reduced ARR at year 1 MRI outcomes • 83% and 89–92% reduction of the number of new and/or enlarging T2L, and Gd-enhancing lesions at year 2, respectively	PML	Monitoring anti-JCV antibody index, MRI monitoring

Neurotherapeutics
https://doi.org/10.1007/s13311-022-01224-9

- Phase I trial with single IV doses ranging from 0.03 to3.0 mg/kg.
  - 1.0 and 3.0 mg/ kg had detectable drug concentrations 3–8 weeks after infusion.
- Phase II trial, with a single dose of 1.0 and 3.0 mg/kg IV NTZ,
  - both dosages resulted in a comparable decrease of GD
- Second Phase II trial randomized vs placebo, IV NTZ 3.0 or 6.0 mg/kg every 28 days for 6 months.
  - Both doses showed comparable efficacy.

A fixed 4 weeks IV dose of 300 mg was chosen for subsequent phase III trials, resulting in a 3.0–6.0 mg/kg dose for patients with weights ranging from 50 to 100 kg.

In 2011 and 2014 (DELIVER & DEFINE), two studies were completed evaluating 300 mg dosing of NTZ SC and IV every 4 weeks, with comparable pharmacokinetics and efficacy.

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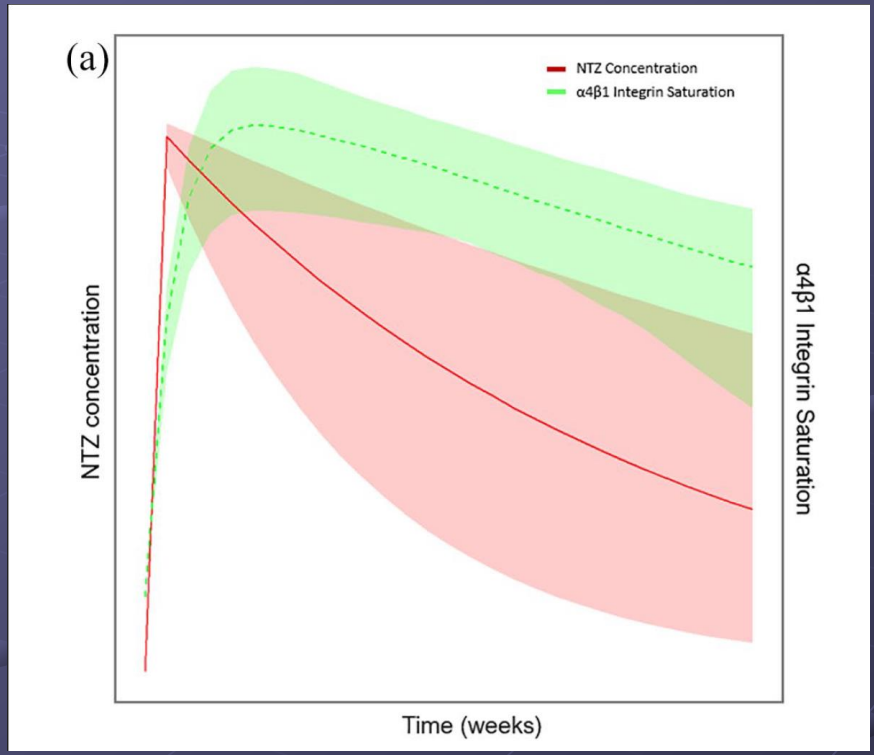
Natalizumab

We can measure drug concentrations in serum and the bound α4β1 integrin on lymphocytes.

- NTZ bound α4β1 receptors, falls between 70%-100% after 4weeks.
- After 3 months α4β1 integrin saturation 20%–40%.
- A concentration of 2–2.5 μg/mL (approximately 50% saturation) could be a safe cutoff.
- In Standard dose (300 mg I/4 weeks) concentrations vary 0.1 and 112 μg/mL,
- NTZ concentrations can increase with consecutive infusions.



As the median trough NTZ concentration is approximately 25–30 μg/mL after a 4-week interval, and considering a therapeutic cutoff of 2 μg/mL, it is plausible **that the majority of patients** could safely be treated with ED intervals with a set 6- or 7-week interval.

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Natalizumab

	Authors	Trial design	*N*	Dosing regimen	Outcome
Natalizumab	Sheremata et al.[1]	Phase I	28	NTZ single dose of 0.03–3.0 mg/kg	NTZ concentration was detectable 3–8 weeks after a single dose of 1.0 and 3.0 mg/kg
	Miller et al.[3]	Phase II	213	NTZ 3 mg/kg or 6 mg/kg every 4 weeks or placebo	Comparable reduction of disease activity of NTZ groups versus placebo group.
	O'Connor et al.[2]	Phase II	180	NTZ single dose of 1 mg/kg, 3 mg/kg, or placebo	Comparable decrease of radiological activity in both NTZ treatment groups versus the placebo group
	Polman et al.[4]	Phase III	942	NTZ 300 mg every 4 weeks or placebo	Significant reduction of relapse rate and sustained disability progression in NTZ group versus placebo group
	Rudick et al. (2006) [48]	Phase III	1171	NTZ 300 mg every 4 weeks with interferon β-1a or interferon β-1a alone	Significant reduction of relapse rate and sustained disability in the add-on NTZ group versus interferon β-1a alone
	Bomprezzi et al.[29]	Retrospective cohort	457	NTZ 300 mg every 4, 6, or 8 weeks	Comparable relapses and MRI activity in patients on 4 weekly dosing in comparison with extended (6 and 8 weekly) dosing
	Trojano et al.[6]	RCT	290	NTZ 300 mg iv or sc every 4 or 12 weeks or NTZ 150 mg iv or sc every 12 weeks (six arms)	The 12-week interval arms were prematurely closed due to recurrence of disease activity.
	Zhovtis Ryerson et al.[34]	Retrospective review	2004	NTZ 300 mg in standard interval dosing (average 4 weeks and 2 days) or extended interval dosing (4 weeks and 3 days up to 8 weeks and 5 days)	Comparable NTZ efficacy of standard interval dosing versus extended interval dosing
	Yamout et al.[31]	Retrospective review	85	NTZ 300 mg with infusion intervals 5–8 weeks	Comparison of former standard dosing in patients on extended dosing with comparable clinical and radiological disease activity
	Clerico et al.[30]	Retrospective cohort	360	NTZ 300 mg in a <5 weeks interval or ⩾5 weeks interval	ARR was comparable between the two groups
	Chisari et al.[35]	Retrospective multicenter study	2092	NTZ 300 mg in standard interval dosing (28–32 days) or extended interval dosing (4 weeks and 5 days to 7 weeks)	Comparable NTZ efficacy of standard interval dosing versus extended interval dosing
	Van Kempen et al.[24]	Prospective multicenter single-arm	61	NTZ 300 mg in personalized intervals guided by serum NTZ concentrations	No recurrence of clinical or radiological disease activity during personalized NTZ dosing
	De Mercanti et al.[32]	Retrospective cohort	316	NTZ 300 mg in a <5 weeks interval or ⩾5 weeks interval	Comparable MRI activity between the two groups
	Riancho et al.[33]	Retrospective cohort	39	NTZ 300 mg in an 8-week interval	Comparable disease activity before start extended interval and after start extended interval

The NOVA study (ClinicalTrials.gov Identifier: NCT03689972) is an international study randomizing patients to either 4- or 6-week natalizumab dosing intervals during 72 weeks of follow-up.

NEXT-MS study (ClinicalTrials.gov Identifier: NCT04225312) which is an investigator-initiated study applying therapeutic drug monitoring of natalizumab with an aim of 10 μg/mL trough concentrations (and in a subgroup an aim of 5 μg/ mL trough concentration) in an open label, nonrandomizedmulticenter study.

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MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

No increase of serum neurofilament light in relapsing-remitting multiple sclerosis patients switching from standard to extended-interval dosing of natalizumab

Magnus Johnsson, Helen H Farman, Kaj Blennow, Henrik Zetterberg, Clas Malmeström, Markus Axelsson and Jan Lycke

Multiple Sclerosis Journal
2022, Vol. 28(13) 2070–2080
DOI: 10.1177/13524585221108080

MSJ Experimental Translational Clinical

Original Research Article

Extended Interval Dosing Natalizumab and impact on neuropsychological deficits in Relapsing-Remitting Multiple Sclerosis

Eileen J. McManus and Karen M. ClarkChristopher FramptonJamie A.B. Macniven and Jan Schepel

Multiple Sclerosis Journal—Experimental, Translational and Clinical
January–March 2022, 1–7
DOI: 10.1177/20552173211070752

Short Communication

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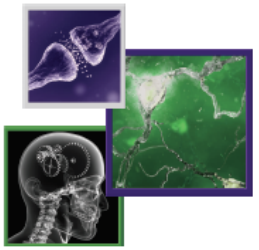
Neurodegenerative Disease Management



Healthcare resource utilization and costs for extended interval dosing of natalizumab in multiple sclerosis

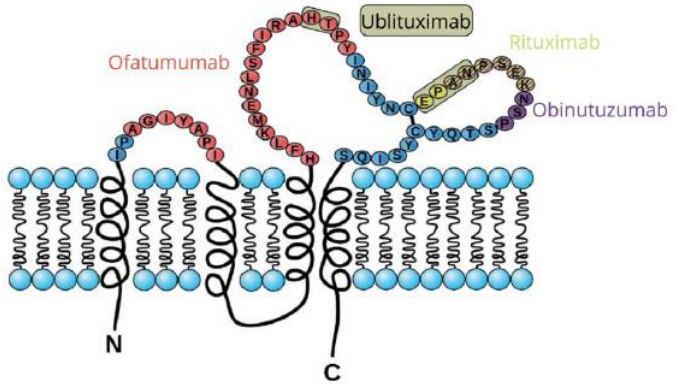
Marcello Moccia*,[1], Ilaria Loperto[2], Laura Santoni[3], Silvia Masera[3], Giuseppina Affinito[2], Antonio Carotenuto[1], Roberta Lanzillo[1], Maria Triassi[2], Vincenzo Brescia Morra[1] & Raffaele Palladino[2,4]

Anti CD20 in MS

DMT	Mechanism of action	Dose, administration and interval of application
Rituximab	Anti-CD20 mAb depleting lymphocytes B	Dose: 500–1000 mg iv Every 6–12 months (some protocols initiate the treatment with two applications 2 weeks apart)
Ocrelizumab	Anti-CD20 mAb depleting lymphocytes B	Dose: 600 mg iv Every 6 months (apart from the first two cycles with 300 mg two weeks apart)
Ofatumumab	Anti-CD20 mAb depleting lymphocytes B	Dose: 20 mg sc Every 28 days (apart from first applications on 1st, 8th, and 15th day)
Ublituximab	Anti-CD20 mAb depleting lymphocytes B	Dose: 450 mg iv Every 24 weeks (apart from 150 mg on day 1 and 450 mg on day 15)

Neurotherapeutics (2022) 19:753–773
https://doi.org/10.1007/s13311-022-01224-9

Figure 2 Epitopes on CD20 recognized by anti-CD20 monoclonal antibodies



CD20-targeted monoclonal antibodies recognize epitopes either identical or spatially in close neighborhood. Only ublituximab binds to a unique epitope on the CD20 domain. From ref. 31 with permission by SAGE Publishers.

Graf J et al 2020

Table 3 Overview of anti-CD20 mAb for the treatment of MS

	Rituximab	Ocrelizumab	Ofatumumab	Ublituximab
				
Molecular structure	Chimeric murine/human IgG1 kappa	Recombinant humanized glycosylated IgG1	Fully human IgG1 kappa	Chimeric IgG1 with glycoengineered Fc segment
Human sequence	65%	> 90%	100%	65%
Molecular weight	~ 145 kDa	~ 145 kDa	~ 146 kDa	~ 144.5 kDa
Immunogenicity	+++	++	+	++
Mechanism of B-cell depletion				
ADCC	++	+++	++	++++
CDC	++	+	+++	+

ADCC antibody-dependent cell cytotoxicity, *CDC* complement-dependent cytotoxicity, *IgG* immunoglobulin G

Neurotherapeutics (2022) 19:753–773
https://doi.org/10.1007/s13311-022-01224-9

Overview of pivotal trials and studies researching dosing and infusion intervals (1)

Rituximab

	Authors	Trial design	*N*	Dosing regimen	Outcome
Rituximab	Bar-Or et al.[7]	Phase I	26	RTX 1000 mg at day 1 and 15 and week 24 and 26	Fewer clinical and radiological disease activity was seen during RTX in comparison with prior to the study
	Hauser et al.[8]	Phase II	104	RTX 1000 mg at day 1 and 15 or placebo	Significant reduction of radiological disease activity compared with placebo at 24 and 48 weeks after infusion
	Naismith et al.[9]	Phase II	30	RTX 375 mg/m² in weekly, four consecutive doses in combination with injectable therapies (interferons or glatiramer acetate)	Reduction of radiological activity after RTX treatment in comparison with prior to RTX treatment
	De Flon et al. (2016)[49]	Phase II	75	RTX 1000 mg at day 1 and 15	Reduction of radiological activity after RTX treatment in comparison with prior to RTX treatment on injectables (interferons or glatiramer acetate)
	Salzer et al.[11]	Retrospective cohort study	822	RTX 500 or 1000 mg every 6–12 months, initial dose ranging from 500 to 2000 mg divided over two infusions	Low rates of clinical and radiological disease activity comparable in the low- and high-dose groups
	Zecca et al.[36]	Retrospective cohort study	472	RTX 1000 mg every 6 months and reinfusion when CD19 > 1% of lymphocytes or CD27 > 0.05% of lymphocytes	Comparable ARR, EDSS progression, and time to first relapse between the fixed dose group and personalized group
	Disanto et al.[37]	Prospective cohort study	57	RTX dose de-escalation from 1000 to 500 mg every 6 months	No relapses occurred, three new T2 lesions appeared on MRI (follow-up of 12 months)
	Novi et al.[38]	Prospective cohort study	102	RTX dosing based on memory B-cell count after a loading dose of 2× 1000 mg	Very low ARR and radiological disease activity, annual infusion rate of 0.78 in second and third year
	Maarouf et al. (2020)[50]	Prospective observational study	33	Interim analysis of RTX 1000 mg dosed every 24 months	No disease activity or progression over a median follow-up of 11 months

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Overview of pivotal trials and studies researching dosing and infusion intervals

	Authors	Trial design	*N*	Dosing regimen	Outcome
Ocrelizumab	Kappos et al.[12]	Phase II	218	OCR 600 mg (first dose divided) every 24 weeks, OCR 1000 mg on day 1 and 15 and after 24 weeks, placebo, interferon β-1a	Comparable reduction of contrast-enhancing lesions and relapses in the OCR groups compared with placebo
	Hauser et al.[14]	Phase III	1656	OCR 600 mg (first dose divided) every 24 weeks, interferon β-1a	Significant reduction of disease activity and progression of the OCR treated group compared with the interferon β-1a group
	Barun et al.[39]	Retrospective cohort study	33	OCR delay of next infusion (median interval of 7.7 months) due to COVID-19	No relapses were reported during interval extension
	Tazza et al.[40]	Retrospective cohort study	56	OCR redosing based on disease activity and CD19 B-cell count (cutoff 1% of total lymphocyte count)	No relapses of MRI activity was reported during personalized treatment
	Van Lierop et al.[41]	Retrospective cohort study	159	OCR redosing when B cells repopulated >10 cells/μL	No relapses and minimal radiological disease activity was reported
	Rolfes et al.[42]	Retrospective cohort study	116	Extended infusion interval of ⩾4 weeks than regular OCR interval	Disease activity was comparable between standard intervals and extended intervals
Ofatumumab	Sorensen et al.[15]	Phase II	38	OFA 2 iv doses of 100 or 300 or 700 mg dose 2 weeks apart of placebo	Decrease of clinical and radiological disease activity compared with placebo
	Bar-Or et al.[16]	Phase II	231	OFA sc 3 or 30 or 60 mg every 12 weeks or 60 mg every 4 weeks or placebo	Decrease of gadolinium-enhancing lesions compared with placebo
	Hauser et al.[17]	Phase III	1882	OFA sc 20 mg every 4 weeks with a loading dose of 20 mg at day 1, 7, and 14 or teriflunomide	Decrease of clinical and radiological disease activity compared with teriflunomide

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ARTICLE OPEN ACCESS

Ocrelizumab Extended Interval Dosing in Multiple Sclerosis in Times of COVID-19

Leoni Rolfes, MD,* Marc Pawlitzki, MD,* Steffen Pfeuffer, MD, Christopher Nelke, MD, Anke Lux, Refik Pul, MD, Christoph Kleinschnitz, MD, Konstanze Kleinschnitz, PhD, Rebeca Rogall, MD, Katrin Pape, MD, Stefan Bittner, MD, Frauke Zipp, MD, Clemens Warnke, MD, Yasemin Goereci, MD, Michael Schroeter, MD, Jens Ingwersen, MD, Orhan Aktas, MD, Luisa Klotz, MD, Tobias Ruck, MD, Heinz Wiendl, MD, and Sven G. Meuth, MD

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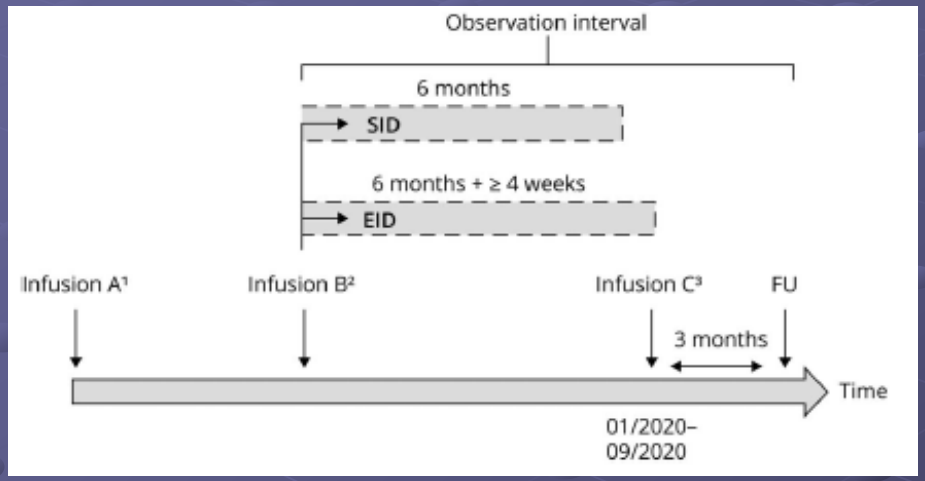
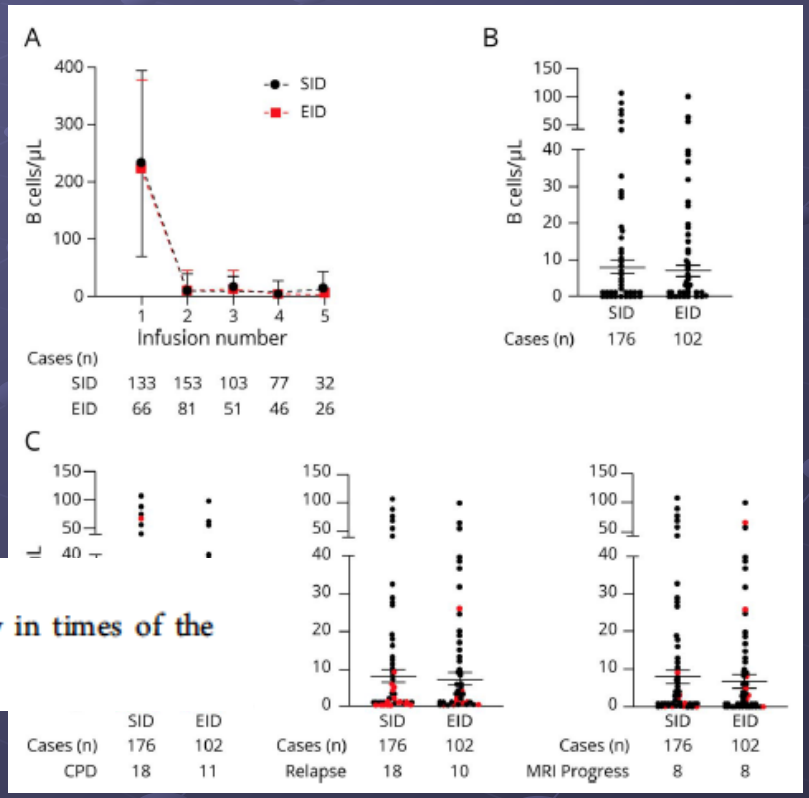
Neurol Neuroimmunol Neuroinflamm 2021;8:e1035. doi:10.1212/NXI.0000000000001035





Conclusion

Our data support EID of ocrelizumab as potential risk mitigation strategy in times of the COVID-19 pandemic.

No differences were observed and ED has been proposed as a potential mitigation strategy in time of the COVID pandemic

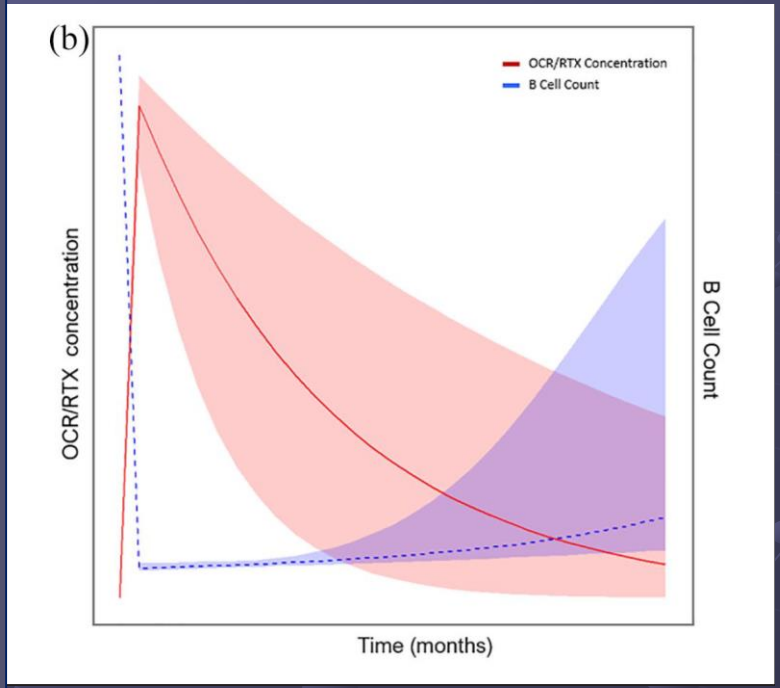
RTX/OCRE

Repopulation of B cells after the last RTX/OCRE dose takes far longer than 24 weeks at which redosing is now mostly scheduled.

In a phase II study of OCRE, median time to B-cell repopulation (defined as the lower limit of normal; ⩾80 CD19 cells/μL) after the last 600 mg infusion was 72 (range = 27–175) weeks.

In a phase II study studying different doses of OFAT (two doses given 2 weeks apart), only a few patients reached B-cell repopulation (defined as ⩾100 CD19 cells/μL) during the 48-week follow-up.

In a recent study exposing earlier data of the phase II OCRE study, clinical and MRI disease activity stayed low long after ocrelizumab cessation.



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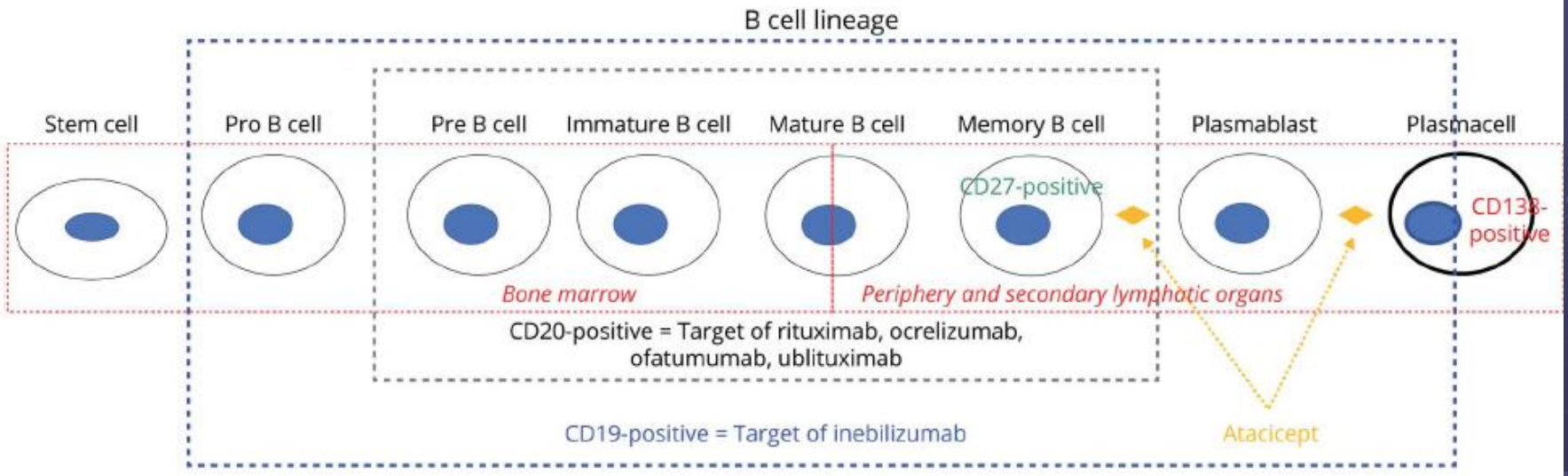
For B-cell depleting therapies, **monitoring of B cells** is likely an easy biomarker for treatment effect.
As anti-CD20 therapies interfere with the flow cytometry of CD20 cells, the CD19 B-cell marker is used as a surrogate measure to quantify B cells.

Figure 3 Cellular targets of CD19 and CD20 cell depletion therapies



Neurol Neuroimmunol Neuroinflamm 2021;8:e918. doi:10.1212/NXI.0000000000000918

As anti- CD20 therapies deplete pre-B cells to late plasmablasts (including memory B cells), using **CD19 counts** as a sole biomarker might be **oversimplistic** as we are still uncertain which lineage of cells is mostly responsible for disease activity and progression in MS.

The Wearing off effect with mAbs in MS

ARTICLE

The natalizumab wearing-off effect

End of natalizumab cycle, recurrence of MS symptoms

Zoé L.E. van Kempen, MD, Djoeke Doesburg, MD, Iris Dekker, MD, Birgit I. Lissenberg-Witte, PhD, Annick de Vries, PhD, Iris A. Claessen, MSc, Anja ten Brinke, PhD, Theo Rispens, PhD, and Joep Killestein, MD, PhD

Neurology® 2019;93:e1579-e1586. doi:10.1212/WNL.0000000000008357

Multiple Sclerosis and Related Disorders 57 (2022) 103364

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

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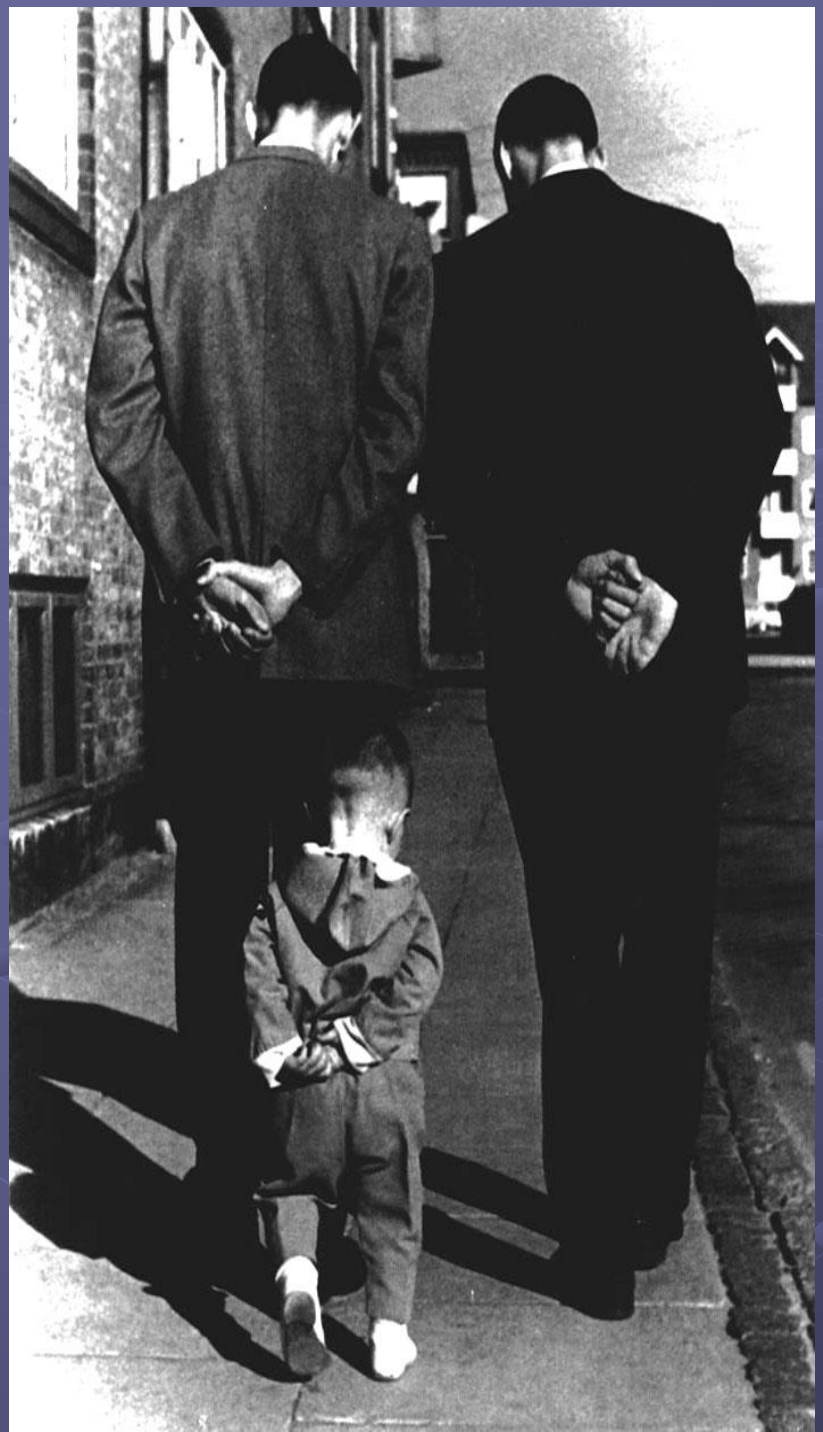
Original article

The wearing-off phenomenon of ocrelizumab in patients with multiple sclerosis

A.A. Toorop [a,*], Z.Y.G.J. van Lierop [a], E.M.M. Strijbis [a], C.E. Teunissen [b], F. Barkhof [c,d,e], B.M. J. Uitdehaag [a], Z.L.E. van Kempen [a], J. Killestein [a]



CONCLUSIONS

- ED of mAbs could lead to potential benefits:
  - Contain increase medication costs.
  - Reduction of side effects and complications (as natalizumab-associated PML).
  - Decrease in Hospital eccess
  - More insight in pathological processes and specific therapeutic targets.
- Need to define the right ED scheme for each mAb
- Definition of markers able to personalize the right interval for every single patient.
- Wearing off effect in some pwMS
- pwMS could also be fearful
- Long term effects

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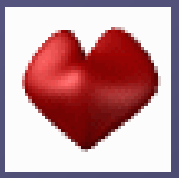

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