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Inquadramento infettivologico dei pazienti con Sclerosi Multipla

Disclosures

- Dr. Agostino Riva received speaker's honorarium from the following companies:
  - Novartis
  - Sanofi
  - VIIV
  - BMS
  - Gilead

Multiple Sclerosis and Risk of Infection-Related Hospitalization and Death in US Veterans

Richard E. Nelson, PhD; Yan Xie, PhD; Scott L. DuVall, PhD; Jorie Butler, PhD;

Table 2. **Infection rates in non-MS patients and patients with MS and by MS subtype**

	Non-MS			MS			Relapsing-remitting MS		
Infection type	No.	Rate	95% CI	No.	Rate	95% CI	No.	Rate	95% CI
Serious	N = 30,972			n = 7743			n = 1740		
Overall	1314	10.3	9.8-10.9	572	19.2	17.6-20.8	90	11.6	9.3-14.2
OI	35	0.3	0.2-0.4	8	0.3	0.1-0.5	1	0.1	0.0-0.6
Non-OI	1279	10.1	9.5-10.6	564	18.9	17.4-20.5	89	11.5	9.2-14.0
Resp	406	3.2	2.9-3.5	155	5.1	4.3-6.0	18	2.3	1.3-3.5
UTI	175	1.4	1.2-1.6	231	7.6	6.7-8.7	39	5.0	3.5-6.7
SSTI	18	0.1	0.1-0.2	5	0.2	0.1-0.4	2	0.3	0.0-0.8
Sepsis	60	0.5	0.4-0.6	44	1.4	1.0-1.9	9	1.1	0.5-2.1
Fatal	N = 27,292			n = 6,826			n = 1,554		
Overall	42	0.5	0.3-0.6	26	1.2	0.8-1.7	0	0.0	0.0-0.7
OI	1	0.0	0.0-0.1	1	0.0	0.0-0.2	0	0.0	0.0-0.7
Non-OI	41	0.4	0.3-0.6	25	1.2	0.7-1.7	0	0.0	0.0-0.7
Resp	12	0.1	0.1-0.2	6	0.3	0.1-0.6	0	0.0	0.0-0.7
UTI	3	0.0	0.0-0.1	7	0.3	0.1-0.6	0	0.0	0.0-0.7
SSTI	0	0.0	0.0-0.0	1	0.0	0.0-0.2	0	0.0	0.0-0.7
Sepsis	15	0.2	0.1-0.3	10	0.5	0.2-0.8	0	0.0	0.0-0.7

Abbreviations: CI, confidence interval; MS, multiple sclerosis; OI, opportunistic infection; Resp, respiratory infection; SSTI, skin and soft-tissue infection; UTI, urinary tract infection.
Note: Infections measured as the number of patients with at least one such infection; infection rate = per 1000 patient-years.

Int J MS Care. 2015;17:221–230.

Multiple Sclerosis and Risk of Infection-Related Hospitalization and Death in US Veterans

Richard E. Nelson, PhD; Yan Xie, PhD; Scott L. DuVall, PhD; Jorie Butler, PhD;

The purpose of this study was to determine the rates of serious and fatal infections in US veterans with and without MS and to estimate the association between MS and the risk of infections. We found that, overall, veterans with MS were more than 50% more likely to have a serious infection than veterans without MS. In addition, patients with MS were significantly more likely than those without MS to have respiratory, urinary tract, and sepsis infections resulting in hospitalization, as well as fatal infections of all types. Although we found that veterans with each of the MS subtypes were at a significantly elevated risk for serious infection compared with those without MS, the magnitude of this increased risk was greatest in veterans with PRMS.

Int J MS Care. 2015;17:221–230.

Possibili ragioni

- Processo disimmune???
- Disabilità
- Uso di DMDs soprattutto IS e biologici

Terapie della SM

OLD INJECTABLE DMTs	INTERFERONE
	GLATIRAMER ACETATO
OLD IMMUNOSUPPRESSANT	MITOXANTRONE
	CICLOFOSFAMIDE
NEW ORAL DRUGs	DIMETILFUMARATO
	TERIFLUNOMIDE
	FINGOLIMOD
MONOCLONAL ANTIBODIES	NATALIZUMAB
	ALEMTUZUMAB
	OCRELIZUMAB
	RITUXIMAB

NON BIOLOGICI

BIOLOGICI

Natalizumab

2006-2007→ approvato 1° mAb e.v.

Meccanismo d'azione: Anti- VLA-4 (α4β1 integrina) Impedisce adesione agli endoteli e diapedesi dei linfociti nel SNC attraverso la barriera emato-encefalica

Eventi avversi a breve termine:

- ***Infezioni***
  - IVU
  - Polmoniti
  - Faringiti, sinusiti
  - Riattivazione erpetica (HSV/VZV)

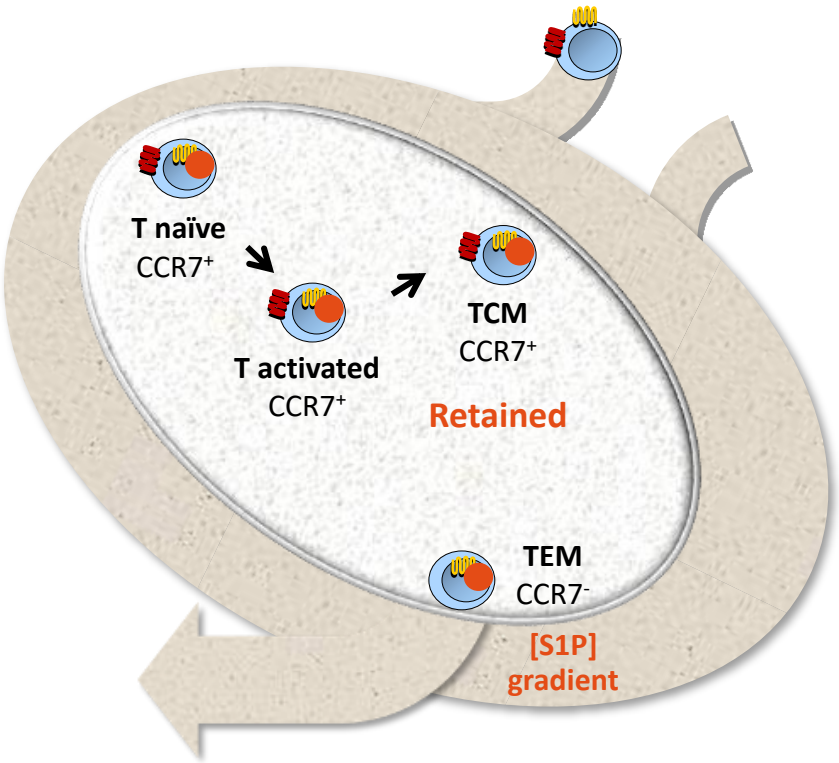
Eventi avversi a lungo termine:

- ***Leucoencefalopatia (PML) correlata a sieropositività per JCV, durata trattamento, pregresso uso IS →stratificazione del rischio in base ai vari fattori***

Fingolimod

Meccanismo d'azione: trattiene selettivamente diverse sottopopolazioni linfocitarie T negli organi linfoidi

- CCR7: mediates retention in the lymph node
- S1P: favours egress and overrides CCR7
- Fingolimod



- Fingolimod results in selective retention of CCR7+ T cells (T naïve and TCM)

TEM hanno un ruolo fondamentale nella sorveglianza immunitaria

Safety and efficacy of fingolimod in relapsing-remitting multiple sclerosis (FREEDOMS II)

	Fingolimod		Placebo (N=355)
	1·25 mg (N=370)	0·5 mg (N=358)	
All events			
At least one adverse event	359 (97%)	350 (98%)	343 (97%)
Any adverse event leading to discontinuation of study drug*	72 (20%)	66 (18%)	37 (10%)
Any serious adverse event	53 (14%)	53 (15%)	45 (13%)
Deaths†	0	0	0
Frequent or special-interest adverse events‡			
Infections	269 (73%)	263 (74%)	255 (72%)
Total upper respiratory tract infection	188 (51%)	187 (52%)	185 (52%)
Upper respiratory tract infection	92 (25%)	87 (24%)	86 (24%)
Nasopharyngitis	88 (24%)	84 (24%)	85 (24%)
Sinusitis	45 (12%)	57 (16%)	45 (13%)
Influenza viral infections	27 (7%)	35 (10%)	24 (7%)
Lower respiratory tract and lung infection	43 (12%)	38 (11%)	30 (9%)
Bronchitis	34 (9%)	30 (8%)	20 (6%)
Pneumonia	5 (1%)	5 (1%)	0
Herpes viral infections	35 (10%)	30 (8%)	19 (5%)
Urinary tract infection	48 (13%)	53 (15%)	59 (17%)

Lancet Neurol 2014; 13: 545–56

Long-term effects of fingolimod in multiple sclerosis

The randomized FREEDOMS extension trial

Adverse event, n (%)	Placebo-fingolimod 0.5 mg (n = 155)	Placebo-fingolimod 1.25 mg[a] (n = 145)	Continuous fingolimod 0.5 mg (n = 331)	Continuous fingolimod 1.25 mg[a] (n = 289)
Any AE	148 (95.5)	133 (91.7)	314 (94.9)	272 (94.1)
Infection	109 (70.3)	100 (69.0)	240 (72.5)	204 (70.6)
Cardiac disorder	10 (6.5)	6 (4.1)	19 (5.7)	19 (6.6)
Abnormally elevated hepatic enzymes	20 (12.9)	28 (19.3)	24 (7.3)	24 (8.3)
AE leading to study drug discontinuation	14 (9.0)	14 (9.7)	15 (4.5)	16 (5.5)
Most commonly reported AEs[b]				
Nasopharyngitis	44 (28.4)	39 (26.9)	84 (25.4)	82 (28.4)
URT infection	24 (15.5)	23 (15.9)	58 (17.5)	39 (13.5)
Lymphopenia	17 (11.0)	19 (13.1)	52 (15.7)	52 (18.0)
Headache	26 (16.8)	18 (12.4)	41 (12.4)	27 (9.3)
Influenza	12 (7.7)	9 (6.2)	33 (10.0)	30 (10.4)
Lymphocyte count decrease	14 (9.0)	12 (8.3)	16 (4.8)	29 (10.0)
ALT increase	9 (5.8)	16 (11.0)	11 (3.3)	10 (3.5)
Herpesvirus infection	14 (9.0)	14 (9.7)	40 (12.1)	31 (10.7)

Kappos et al. Neurology, 2015

Alemtuzumab

Meccanismo d'azione: deplezione delle cellule immunitarie circolanti CD52-positive

Linfociti T CD4⁺

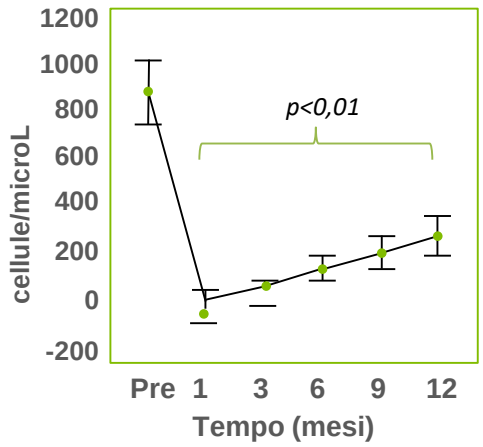


Figura 1A da Rif. 1

Linfociti T CD8⁺

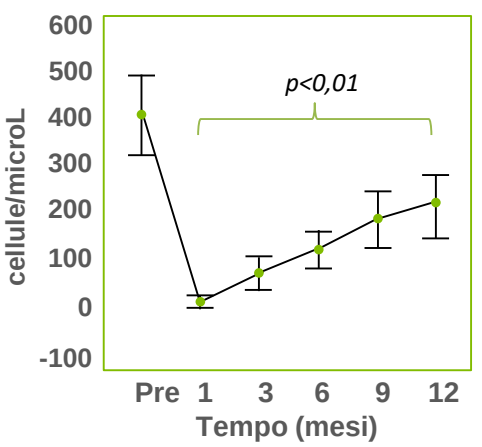


Figura 1B da Rif. 1

Linfociti B CD19⁺

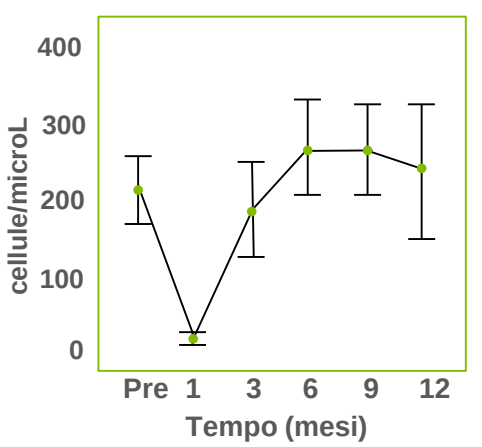


Figura 1D da Rif. 1

Effetto sulle sottopopolazioni linfocitarie nell'uomo

Alemtuzumab: incidenza di infezioni

Le infezioni, più frequenti nei pazienti trattati con alemtuzumab rispetto ai pazienti con IFNB-1a, erano soprattutto di gravità lieve-moderata[1,2]

INCIDENZA DI INFEZIONI RIPORTATA NEGLI STUDI CARE-MS I e CARE-MS II

	CARE-MS I[1]	
	Alemtuzumab 12 mg (n=376)	IFNβ-1a 44 µg SC (n=187)
Qualsiasi evento, n (%)	253 (67%)	85 (45%)
Eventi riportati in >10% dei pazienti, n (%)		
Nasofaringite	74 (20%)	25 (13%)
Infezione del tratto urinario	64 (17%)	8 (4%)
Infezioni erpetiche	62 (16%)	3 (2%)
Infezioni delle vie aeree superiori	57 (15%)	25 (13%)
Eventi avversi seri, n (%)	7 (2%)	2 (1%)

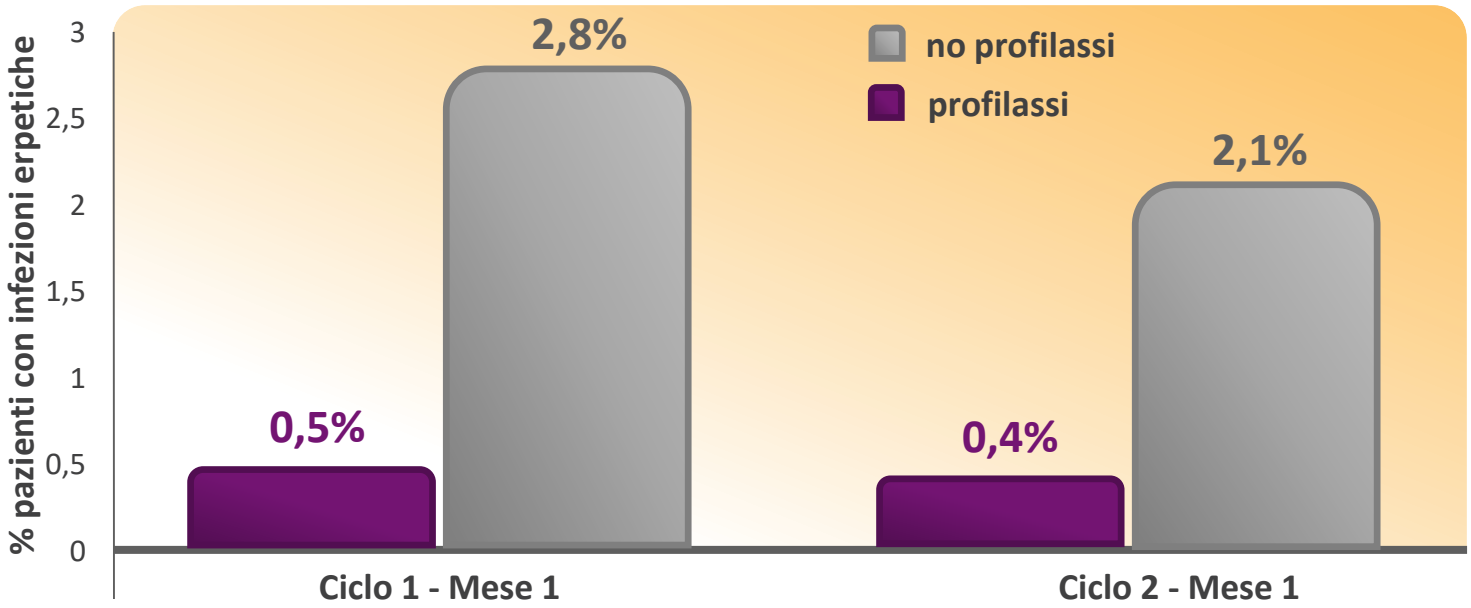
	CARE-MS II[2]	
	Alemtuzumab 12 mg (n=435)	IFNβ-1a 44 µg SC (n=202)
Qualsiasi evento, n (%)	334 (77%)	134 (66%)
Eventi riportati in >10% dei pazienti, n (%)		
Nasofaringite	128 (29%)	48 (24%)
Infezione del tratto urinario	93 (21%)	23 (11%)
Infezioni erpetiche	68 (16%)	8 (4%)
Infezioni delle vie aeree superiori	71 (16%)	25 (12%)
Sinusite	58 (13%)	20 (10%)
Influenza	41 (9%)	11 (5%)
Eventi avversi seri, n (%)	16 (4%)	3 (1%)

1. Cohen JA et al. Lancet. 2012;380(9856):1819-28. **2.** Coles AJ et al. Lancet. 2012;380(9856):1829-39.

Incidenza di infezioni da Herpes Virus

La profilassi con aciclovir riduce il numero di pazienti con infezione erpetica nei mesi successivi al trattamento con alemtuzumab[1]

EFFETTO DELLA PROFILASSI CON ACICLOVIR SULLE INFEZIONI ERPETICHE – STUDIO CARE-MS II[1,2]



Elaborazione grafica di dati da testo, Rif. 1

- Negli studi clinici ai pazienti è stato somministrato **200 mg di aciclovir per due volte al giorno** o un trattamento equivalente[1,2]
- **La profilassi orale per le infezioni erpetiche deve essere somministrata a tutti i pazienti** a partire dal primo giorno di ogni ciclo di trattamento e per almeno 1 mese dopo il trattamento con alemtuzumab[2]

1. Coles AJ et al. Lancet. 2012;380(9856):1829-39. **2.** RCP

Alemtuzumab CARE-MS II 5-year follow-up

Efficacy and safety findings

A. J. Coles et al. Neurology, 2017

	Incidence, core and extension studies (5 y), n (%)[a]					EAIR per 100 patient-years (no. of events)[b]		
						Core study (2 y)	Extension study (3 y)	Core and extension studies (5 y)
	Year 1 (n = 435)	Year 2 (n = 434)	Year 3 (n = 412[c])	Year 4 (n = 387)	Year 5 (n = 367)	Years 0-2 (n = 435)	Years 3-5 (n = 412)	Years 0-5 (n = 435)
Any AE	412 (94.7)	402 (92.6)	343 (83.3)	316 (81.7)	284 (77.4)	871.3	201.3	703.6
Any AE excluding IARs[d]	373 (85.7)	379 (87.3)	341 (82.8)	312 (80.6)	284 (77.4)	255.8	195.0	213.8
AE leading to study drug discontinuation	9 (2.1)	5 (1.2)	1 (0.2)	3 (0.8)	2 (0.5)	1.6	0.4 (5)	1.0
Any serious AE	55 (12.6)	43 (9.9)	39 (9.5)	53 (13.7)	36 (9.8)	11.1	10.5	9.9
Any serious AE excluding IARs	48 (11.0)	41 (9.4)	39 (9.5)	53 (13.7)	34 (9.3)	10.0	10.4	9.2
Deaths	0	2 (0.5)	0	0	0	0.2 (2)	0	0.1 (2)
Any infection event	275 (63.2)	268 (61.8)	206 (50.0)	195 (50.4)	162 (44.1)	89.0	54.1	65.2
Serious infections	9 (2.1)	8 (1.8)	5 (1.2)	9 (2.3)	7 (1.9)	1.9	1.6	1.7
Any thyroid disorder[e,f]	31 (7.1)	40 (9.2)	68 (16.5)	23 (5.9)	12 (3.3)	8.8	14.1	11.3
Serious thyroid AEs	0	2 (0.5)	10 (2.4)	2 (0.5)	2 (0.5)	0.2 (2)	1.3	0.8 (16)
ITP[e]	1 (0.2)	3 (0.7)	2 (0.5)	7 (1.8)	1 (0.3)	0.5 (4)	0.9 (10)	0.7 (14)
Nephropathy[e]	0	1 (0.2)	0	0	0	0.1 (1)	0	0.1 (1)
Malignant disease	0	2 (0.5)	2 (0.5)	0	0	0.2 (2)	0.2 (2)	0.2 (4)

AEs through year 5 of the extension in patients treated with alemtuzumab 12 mg

Ocrelizumab

2017→ approvato da FDA il 4° mAb e.v.

Meccanismo d'azione: Anti-CD20 umanizzato, deplezione prolungata dei B linfociti

Eventi avversi a breve termine:

- Reazioni infusionali (34-40%)
- *Infezioni*
  - Infezioni alte (40-49%) e basse (8-10%) vie respiratorie
  - Riattivazioni infezioni herpetiche (5-6%)
  - Infezioni della cute (14%)
  - No infezioni opportunistiche

Eventi avversi a medio termine (mancano a lungo termine):

- *Infezioni: lieve aumento del rischio*
- No casi di PML
- Neoplasie: non aumento del rischio (0,7-2,3%)
- Ipogammaglobulinemia, neutropenia
- Ab Anti-OCRE (0,9%)

Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis

S.L. Hauser, A. Bar-Or, G. Comi, G. Giovannoni, H.-P. Hartung, B. Hemmer, F. Lublin, X. Montalban, K.W. Rammohan, K. Selmaj, A. Traboulsee, J.S. Wolinsky, D.L. Arnold, G. Klingelschmitt, D. Masterman, P. Fontoura, S. Belachew, P. Chin, N. Mairon, H. Garren, and L. Kappos, for the OPERA I and OPERA II Clinical Investigators*

Variable	OPERA I Trial		OPERA II Trial	
	Ocrelizumab (N=408)	Interferon Beta-1a (N=409)	Ocrelizumab (N=417)	Interferon Beta-1 (N=417)
	no. of patients (%)			
Any adverse event	327 (80.1)	331 (80.9)	360 (86.3)	357 (85.6)
Adverse event leading to treatment discontinuation	13 (3.2)	26 (6.4)	16 (3.8)	25 (6.0)
At least 1 infusion-related reaction	126 (30.9)	30 (7.3)	157 (37.6)	50 (12.0)
Infection†	232 (56.9)	222 (54.3)	251 (60.2)	219 (52.5)
System organ class infection or infestation	231 (56.6)	216 (52.8)	251 (60.2)	217 (52.0)
Herpes infection				
Herpes zoster	9 (2.2)	4 (1.0)	8 (1.9)	4 (1.0)
Oral herpes	9 (2.2)	8 (2.0)	15 (3.6)	9 (2.2)
Neoplasm‡	3 (0.7)	1 (0.2)	1 (0.2)	1 (0.2)
Death§	0	1 (0.2)	1 (0.2)	1 (0.2)
Any serious adverse event	28 (6.9)	32 (7.8)	29 (7.0)	40 (9.6)
Serious infection or infestation¶	5 (1.2)	12 (2.9)	6 (1.4)	12 (2.9)

Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis

X. Montalban, S.L. Hauser, L. Kappos, D.L. Arnold, A. Bar-Or, G. Comi, J. de Seze, G. Giovannoni, H.-P. Hartung, B. Hemmer, F. Lublin, K.W. Rammohan, K. Selmaj, A. Traboulsee, A. Sauter, D. Masterman, P. Fontoura, S. Belachew, H. Garren, N. Mairon, P. Chin, and J.S. Wolinsky, for the ORATORIO Clinical Investigators*

Event	Ocrelizumab (N=486)	Placebo (N=239)
Any adverse event — no. of patients (%)†	462 (95.1)	215 (90.0)
Adverse event leading to discontinuation of trial agent — no. of patients (%)	20 (4.1)	8 (3.3)
Death — no. of patients (%)‡	4 (0.8)	1 (0.4)
Infusion-related reactions		
≥1 Reaction — no. of patients (%)	194 (39.9)	61 (25.5)
Total no. of reactions	485	145
Grade of reaction — no. of patients (%)		
1: mild	129 (26.5)	38 (15.9)
2: moderate	59 (12.1)	19 (7.9)
3: severe	6 (1.2)	4 (1.7)
4: life-threatening	0	0
5: death	0	0
Any serious adverse event — no. of patients (%)	99 (20.4)	53 (22.2)
Serious infections — no. of patients (%)	30 (6.2)	14 (5.9)
Neoplasms — no. of patients (%)§	11 (2.3)	2 (0.8)

Rituximab

Farmaco noto ma **off label** usato dai centri per NMO e meno per SM→ Parere favorevole CTS-AIFA febbraio 2017 per inserimento nell'elenco **Legge 648/96 di RTX** per la SM-PP, prescrivibile dopo uscita in gazzetta ufficiale.

Eventi avversi a breve termine:

- Reazioni infusionali (7,8%)
- Reazioni allergiche
- **Infezioni**

Eventi avversi a lungo termine :

- **Maggior rischio di infezioni** per livelli costantemente bassi di IgG
- Scarsa risposta ai vaccini e richiami vaccinali

Incidence rates for serious infections with biologic DMARDs across RCTs and LTE studies.

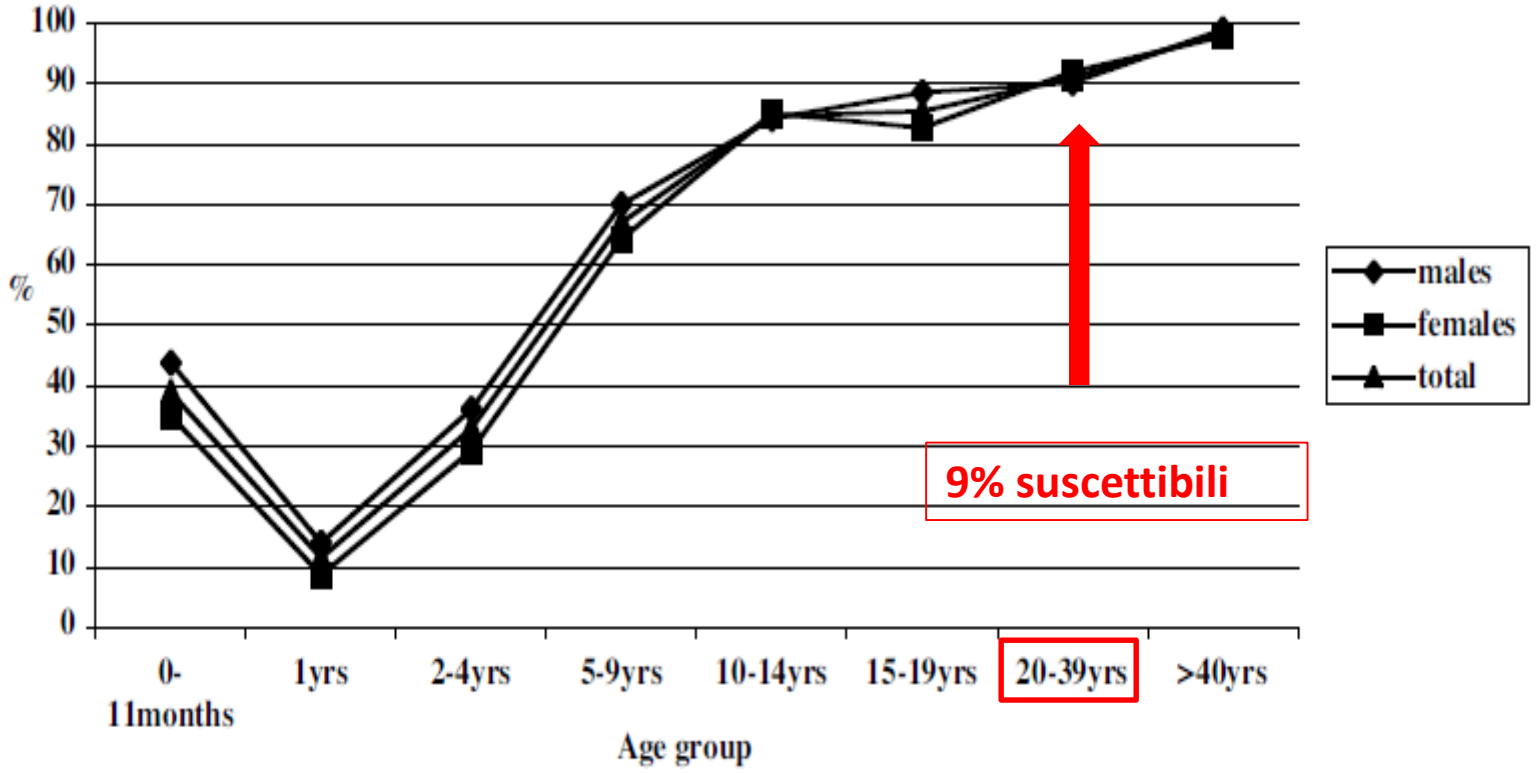
Drug	No. trials	Serious infection incidence rate, patients with events per 100 pt-yrs (95% CI)	Patients (N)	Cumulative exposure (pt-yrs)
Abatacept	11	3.04	5953	6070
Rituximab	8	3.72	2926	2687
Tocilizumab	13	5.45	5547	4522
Infliximab	11	6.11	4592	3555
Etanercept	17	4.06	7141	13037
Certolizumab pegol	5	7.59	3212	1339
Golimumab	6	5.31	2820	1648
Adalimumab	18	5.04	6570	7095
TNFi	57	4.90	26492	29429
Tofacitinib, Phase 3, 5 mg BID	6	3.02	1587	1464
Tofacitinib, Phase 3, 10 mg BID	6	3.00	1609	1501
Tofacitinib, LTE, 5 mg BID	1	2.50	1452	4005
Tofacitinib, LTE, 10 mg BID	1	3.19	3375	5191
Tofacitinib, Phase 2, Phase 3, LTE (all doses)	14	2.93	5671	12664
Adalimumab (tofacitinib, Phase 3, ORAL Standard)	1	1.68	204	179

Strand et al. Arthritis Research & Therapy 2015

Prevalenza di anticorpi anti-VZV

nella popolazione italiana

Soggetti esaminati= 3569



Gabutti et al, BMC Public Health 2008; 8:372

The humanistic, economic and societal burden of Herpes Zoster in Europe: a critical review

Adam Gater[1*], Mathieu Uhart[2], Rachael McCool[1] and Emmanuelle Préaud[2]

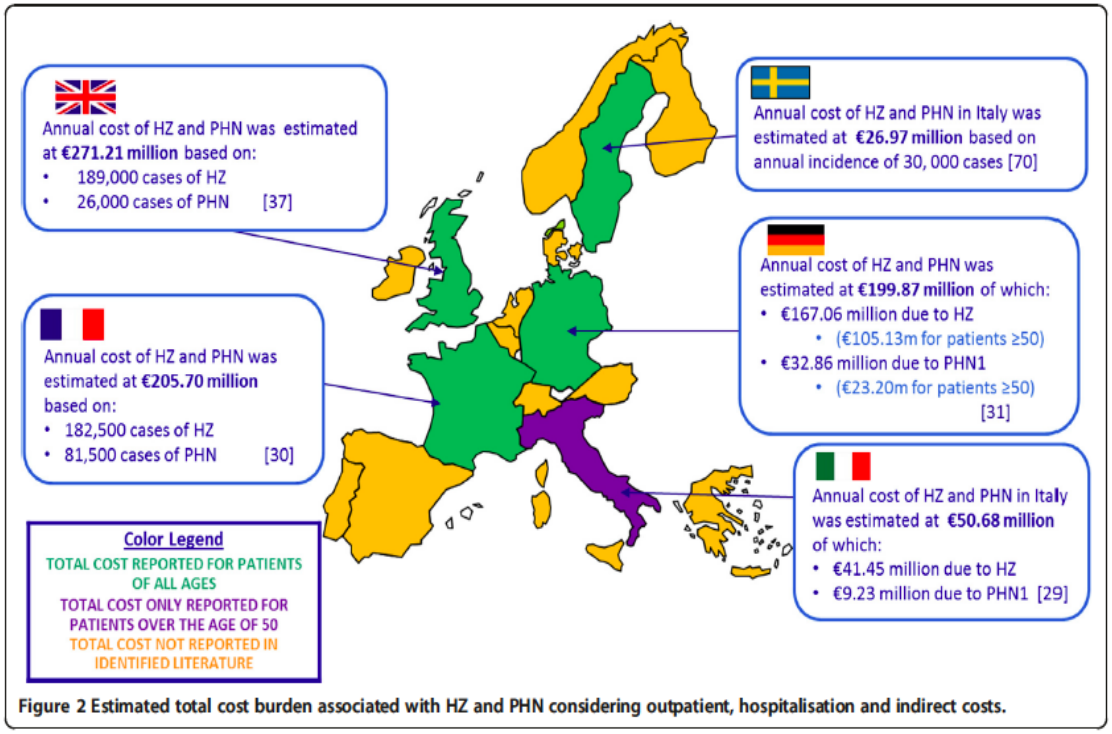


Figure 2 Estimated total cost burden associated with HZ and PHN considering outpatient, hospitalisation and indirect costs.

From a review of 1619 abstracts, 53 eligible articles

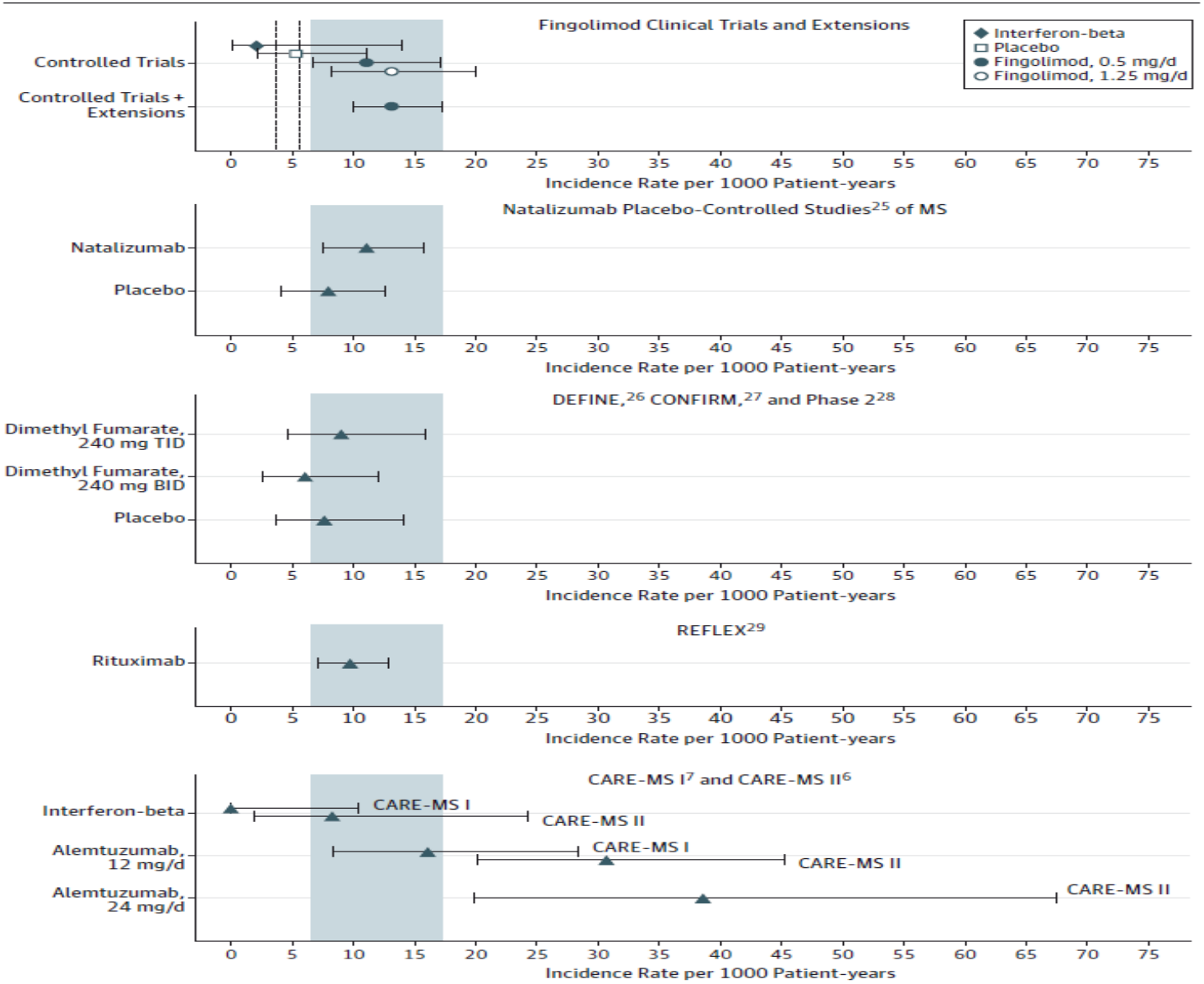
Table 6 Level of pain interference across seven health state domains as assessed by the ZBPI (or similar instrument)

Health state domains	HZ (mean scores)	PHN (mean scores)
General activity	3.8-4.4	3.1-5.7
Mood	3.4-4.5	3.4-5.9
Walking ability	1.7-4.0	1.7-5.8
Normal work	3.3-4.4	2.9-6.1
Social relations	2.1-3.5	2.1-5.4
Sleep	4.5-4.9	6.3-6.5
Enjoyment of life	3.6-4.0	3.8-5.2

Data from Bouhassira 2012 [15], Gater 2014 [50], Lukas 2012 [58], Serpell 2014 [14], Weinke 2010 [77].

Gater et al. BMC Public Health (2015) 15:193

Incidence of VZV Infections in Fingolimod Trials and Comparison With Other MS DMTs



Risk of stroke after HZ and HZO compared to control periods

	All HZ		HZO	
	No. of strokes in risk period	IRR (95% CI)	No. of strokes in risk period	IRR (95% CI)
Risk period 3 months				
Stroke (any type)	352	1.29 (1.16–1.44)	31	1.59 (1.10–2.32)
Ischemic and unspecified stroke	310	1.27 (1.13–1.42)	27	1.57 (1.05–2.35)
Hemorrhagic stroke	42	1.53 (1.11–2.11)	4	1.82 (0.62–5.37)
Subdivided risk periods (secondary analysis)				
<2 weeks	59	1.30 (1.00–1.68)	2	0.63 (0.16–2.53)
week 3–4	73	1.52 (1.20–1.91)	12	3.56 (1.99–6.38)
month 2–3	219	1.24 (1.08–1.42)	17	1.37 (0.84–2.25)
month 4–6	274	1.09 (0.97–1.24)	25	1.44 (0.96–2.17)
month 7–12	444	0.96 (0.87–1.06)	29	0.63 (0.87–1.35)

Schink T, et al.. PLoS ONE 2016

Age-adjusted incidence ratios for ischemic stroke and myocardial infarction in risk periods after zoster diagnosis

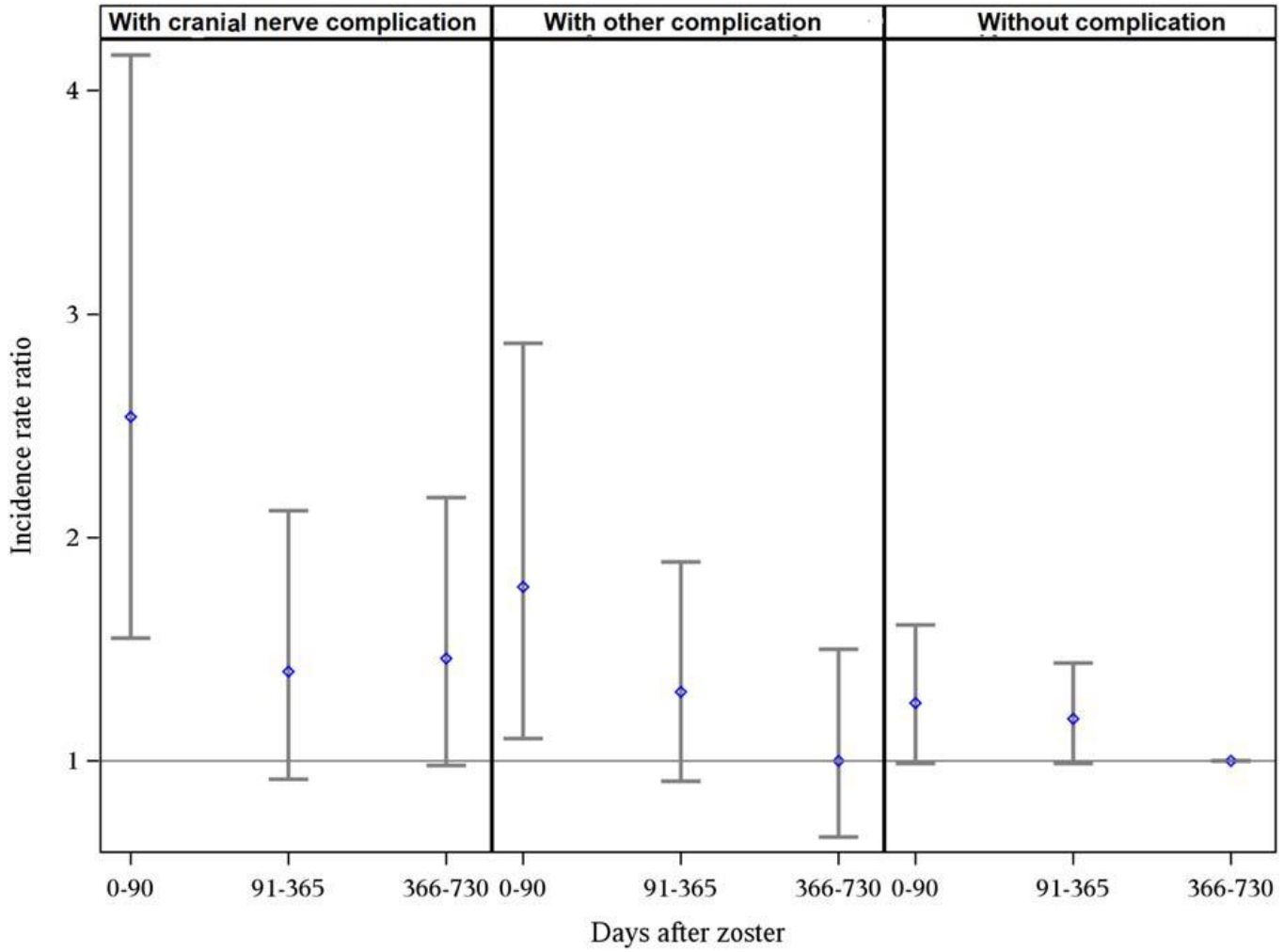
Risk Period	Number of Ischemic Stroke Cases (n = 42,954)	Ischemic Stroke IR[a] (95% CI)	Number of MI Cases (n = 24,237)	MI IR[a] (95% CI)
Baseline	32,179	1	18,071	1
Risk period after zoster				
1 wk	499	2.37 (2.17–2.59)[b]	213	1.68 (1.47–1.92)[b]
2–4 wk	967	1.55 (1.46–1.66)[b]	470	1.25 (1.14–1.37)[b]
5–12 wk	1,841	1.17 (1.11–1.22)[b]	1,019	1.07 (1.00–1.14)[c]
13–26 wk	2,588	1.03 (0.99–1.07)	1,537	1.02 (0.96–1.07)
27–52 wk	3,981	1.00 (0.96–1.03)	2,459	1.02 (0.98–1.07)

Zoster ophtalmicus

Risk Period	Number of Ischemic Stroke Cases (n = 6,971)	Ischemic Stroke IR[a] (95% CI)	Number of MI Cases (n = 3,946)	MI IR[a] (95% CI)
Baseline	5,125	1	2,891	1
Risk period after HZO				
1 wk	93	2.73 (2.22–3.35)[b]	43	2.06 (1.52–2.79)[b]
2–4 wk	177	1.77 (1.52–2.05)[b]	85	1.38 (1.11–1.72)[b]
5–12 wk	326	1.29 (1.15–1.44)[b]	160	1.02 (0.87–1.20)
13–26 wk	428	1.06 (0.96–1.17)	282	1.15 (1.01–1.30)[c]
27–52 wk	651	1.02 (0.94–1.11)	421	1.07 (0.97–1.19)

Minassian C, et al.PLoS Med 2015

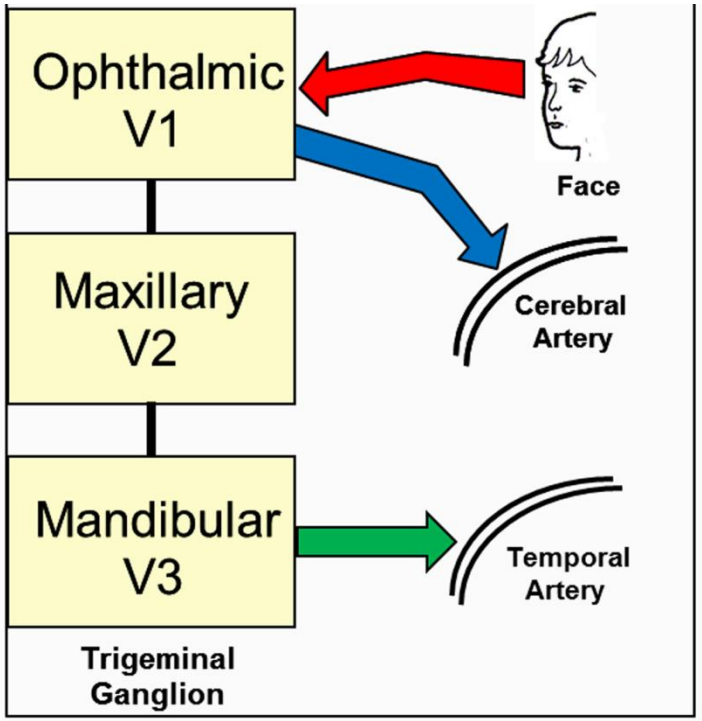
Herpes Zoster and the Risk for Stroke in Patients with Autoimmune Diseases

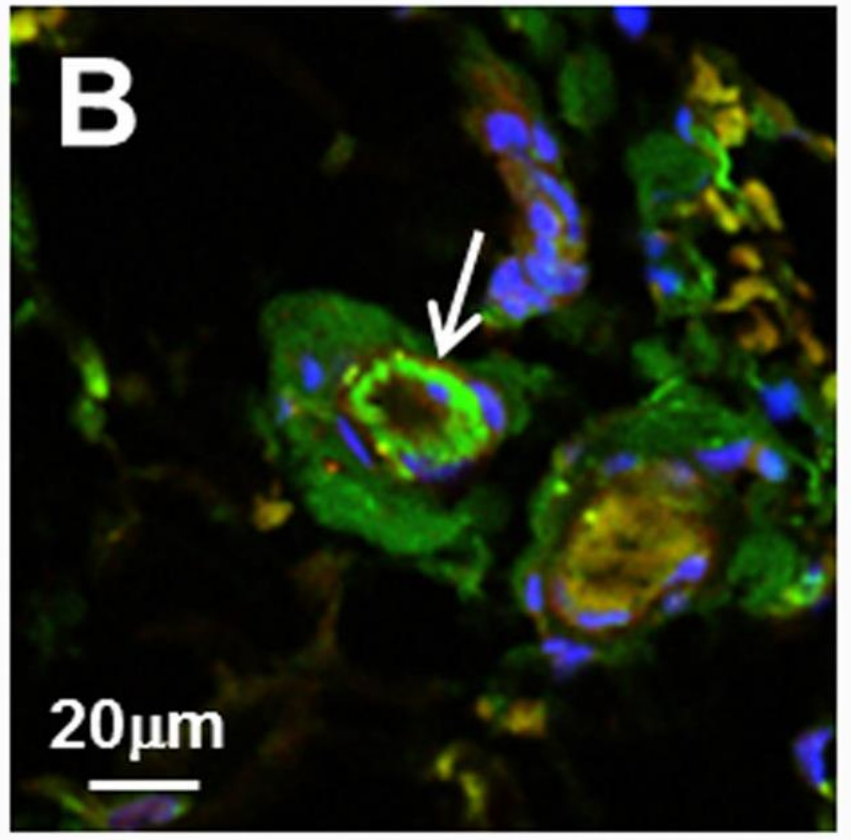


Incidence Rate Ratios of Hospitalized Stroke by time since Herpes Zoster and zoster phenotype

Calabrese LH et al. Arthritis & Rheumatology 2016

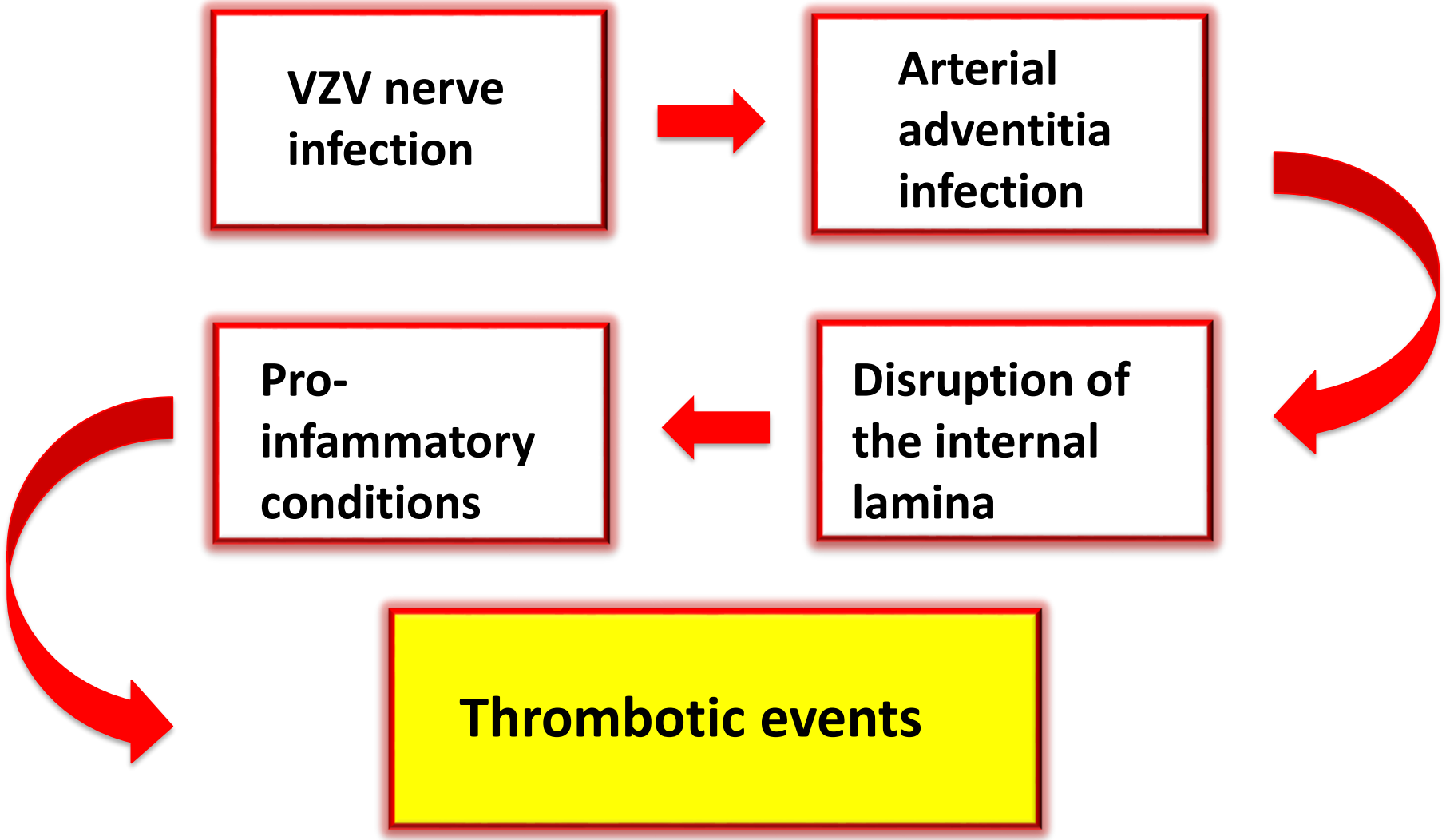
Varicella-zoster virus infection, the trigeminal ganglion and arteritis



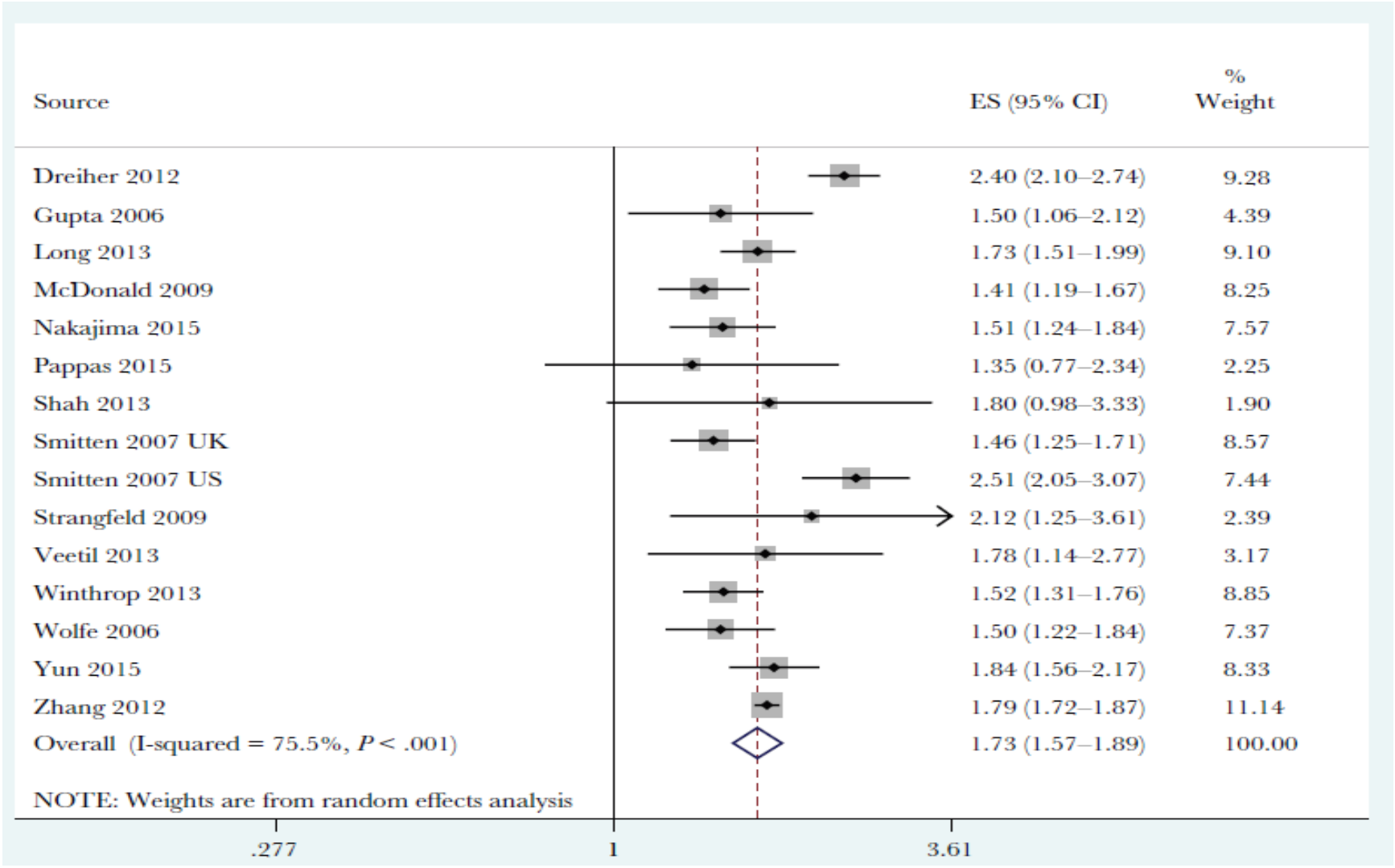


Grose C Circulation. 2016

Physiopathology of herpes zoster ophthalmicus and vasculopathy



Risk of herpes zoster with corticosteroids compared with control, pooled analysis of observational studies

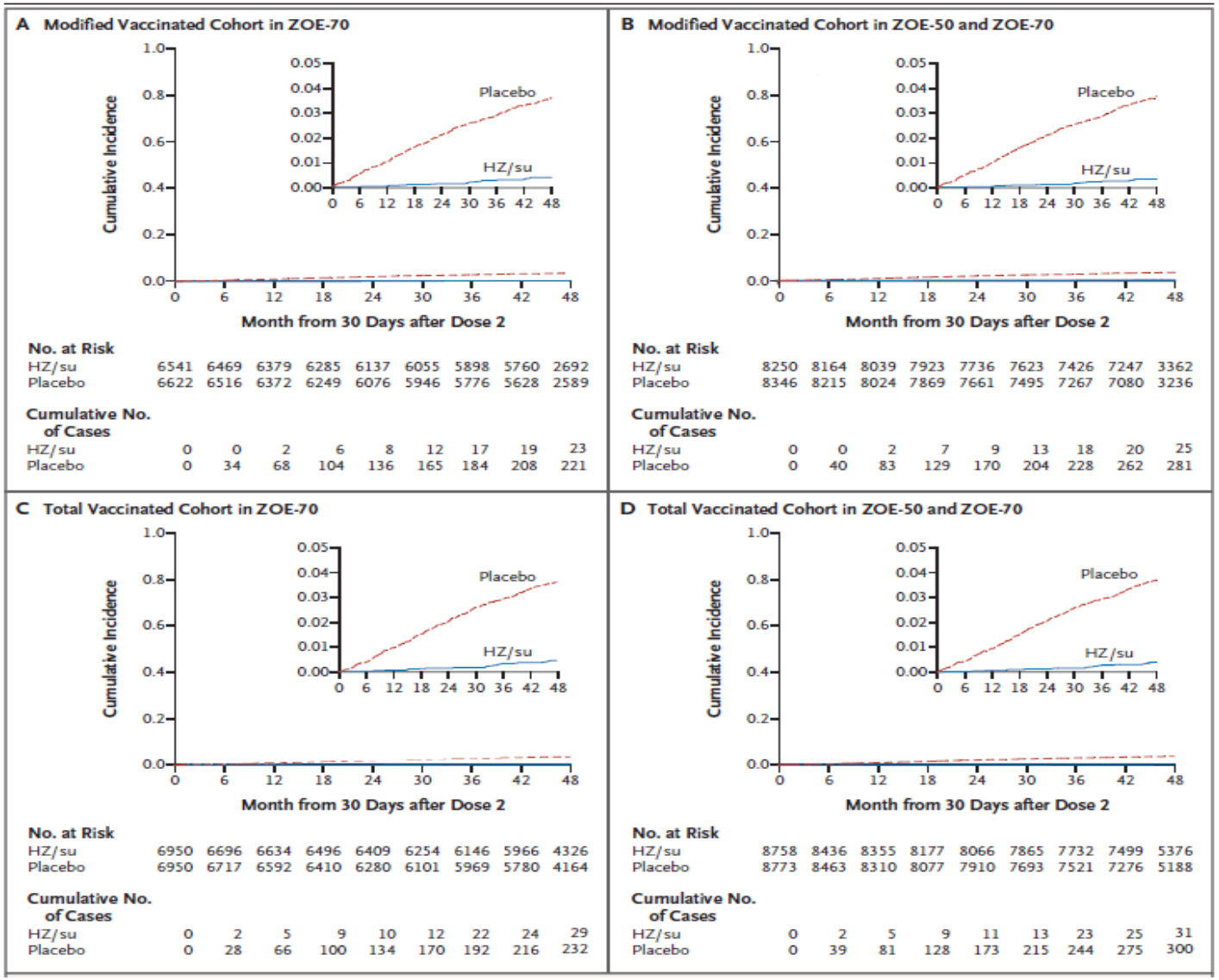


Efficacy of herpes zoster vaccines in different populations

Authors	Populations	Sample size	Design	Reduction	Efficacy (%)	95%CI
Live attenuated vaccine						
Oxman et al., 2005 [33]	Immunocompetent >60 years	38,546 19,270 (active) 19,276 (placebo)	Randomized Double-blind vs. placebo	Incidence of HZ Severity PHN	51.30 61.10 66.50	(44.2–57.6) (51.1–69.1) (47.5–79.2)
Schmader et al., 2012 [45]	Immunocompetent 50–59 years	22,439 11,211 (active) 11,228 (placebo)	Randomized Double-blind vs. placebo	Incidence Z Severity	69.80 73.00	(54.1–80.6) (52.7–84.6)
Morrison et al., 2015 [34]	Immunocompetent >60 years 7–11 years post-vaccination	6867	Models based on the placebo groups in the SPS and STPS trials	Incidence of HZ Severity PHN	21.10 37.30 35.40	(10.9–30.4) (26.7–46.4) (8.8–55.8)
Tseng et al., 2014 [42]	Before starting cancer chemotherapy	4710 vaccinated vs. 16,766 not vaccinated	Prospective cohort	Incidence of HZ	42	(27–53)
Langan et al., 2013 [11]	>65 years General population (including immune-compromised individuals)	4469 immuno-compromised vaccinated vs. 140,925 not vaccinated	Retrospective cohort	Incidence of HZ (immunocompromised) Incidence of HZ (immunocompetent) PHN (total)	37 51 59	(6–58) (41–59) (21–79)
Zhang et al., 2012 [43]	RA, CIBD, Pso, PsA, SPA (>60 years)	633 vaccinated during biotherapy (within 42 days after vaccination)	Retrospective cohort	Incidence of HZ (biologics) Incidence of HZ (total)	47 42	
Subunit vaccine						
Lal et al., 2015 [56]	Immunocompetent >50 years	15,411 7698 (active) 7713 (placebo)	Multicenter Randomized Double-blind vs. placebo	Incidence of HZ	97.20	(93.7–99.0)

C.T. Tran et al. Joint Bone Spine 2016

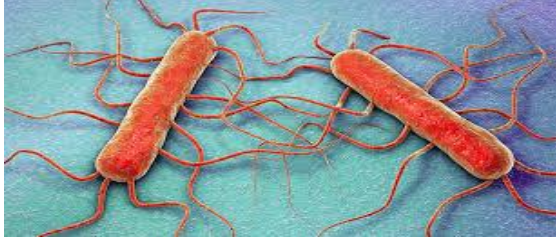
Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older



Risk of Development of Herpes Zoster after Vaccination

A.L. Cunningham et al.
N Engl J Med 2016

Listeriosis



Listeria monocytogenes, which causes listeriosis, is an important pathogen in pregnant patients, neonates, elderly individuals, and immunocompromised individuals, although it is an uncommon cause of illness in the general population.

It is typically a food-borne organism. The most common clinical manifestation is diarrhea.

Bacteremia and meningitis are more serious manifestations of disease that can affect individuals at high risk.

Since marketing authorisation, Genzyme Sanofi pharmacovigilance has been informed of 32 cases of Listeria meningitis/septicaemia. During this time, roughly 13,000 people have received alemtuzumab.

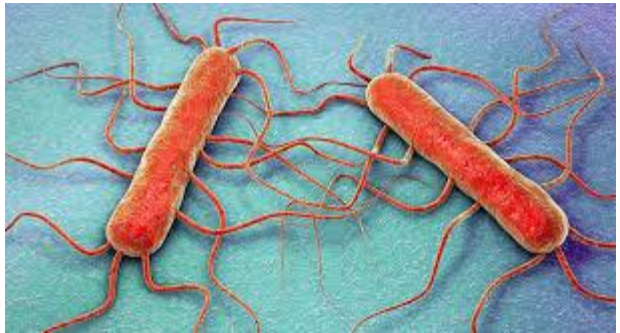
The risk of Listeria meningitis/septicaemia is about 0.25% in the first month after each cycle of alemtuzumab treatment.

Characteristics of reported cases of listeriosis associated with alemtuzumab reported

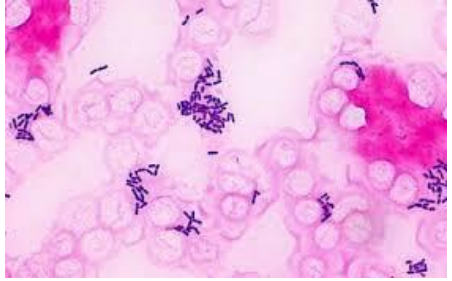
Source (reference)	Type of listeriosis	Gender	Indication	Number of infusions	Days from first infusion to onset	Outcome
VigiBase 2017 (3)	Meningitis	Female	Multiple sclerosis	5	Unknown	Unknown
VigiBase 2016 (3)	Meningitis	Female	Multiple sclerosis	5	8	Recovering
VigiBase 2016 (3)[a]	Listeriosis	Male	Not reported	Unknown	Unknown	Died
VigiBase 2016 (3)	Meningitis	Female	Multiple sclerosis	3	5	Recovered
VigiBase 2016 (3)	Unknown	Female	Multiple sclerosis	5	17	Unknown
VigiBase 2016 (3)	Unknown	Female	Multiple sclerosis	5	23	Unknown
Sanofi Genzyme, data on file VigiBase 2016 (3)	Meningoencephalitis	Female	Multiple sclerosis	5	7	Died
VigiBase 2016 (3)	Meningitis	Female	Multiple sclerosis	5	17	Recovered
VigiBase 2016 (3)	Unknown	Female	Multiple sclerosis	3	8	Recovered
VigiBase 2016 (3)	Unknown	Unknown	Multiple sclerosis	5	9	Unknown
VigiBase 2016 (3)	Septicaemia	Female	Multiple sclerosis	Unknown	Unknown	Unknown
VigiBase 2015 (3)	Unknown	Male	Multiple sclerosis	5	9	Recovered
VigiBase 20 14 (3)	Meningitis	Female	Multiple sclerosis	5	1	Not recovered
Rau 2015 (4)	Meningitis	Female	Multiple sclerosis	5	6	Recovered
Rau 2015 (4)	Meningitis	Female	Multiple sclerosis	5	8	Recovered
Wray 2009 (5)	Meningitis	Female	Multiple sclerosis	3	19	Recovered
Ohm 2009 (6)	Sepsis	Female	Multiple sclerosis	3	13	Not recovered
VigiBase 2010	Meningitis	Male	Unknown	NA	Unknown	Not recovered
VigiBase 2009 (3)	Unknown	Female	B cell lymphoma	NA	Unknown	Died
VigiBase 2010 (3)	Sepsis	Male	Chronic lymphocytic leukemia	NA	Unknown	Unknown
VigiBase 2011	Unknown	Unknown	Chronic lymphocytic leukemia	NA	Unknown	Unknown

Listeria infections Complicating Alemtuzumab Treatment in MS

- Since infections occurred briefly after the first infusions, immunosuppression induced by alemtuzumab has to be assumed as causative
- Listeria meningitis induced by alemtuzumab may be facilitated by immune cell depletion in the adaptive as well as the innate immune system, possibly by an outburst of a pre-existing, clinically silent and CD8 T-cell controlled infection with Listeria monocytogenes.
- In most of these cases, a latent Listeria infection must be presumed, since clinical symptoms occurred briefly after the first infusions.



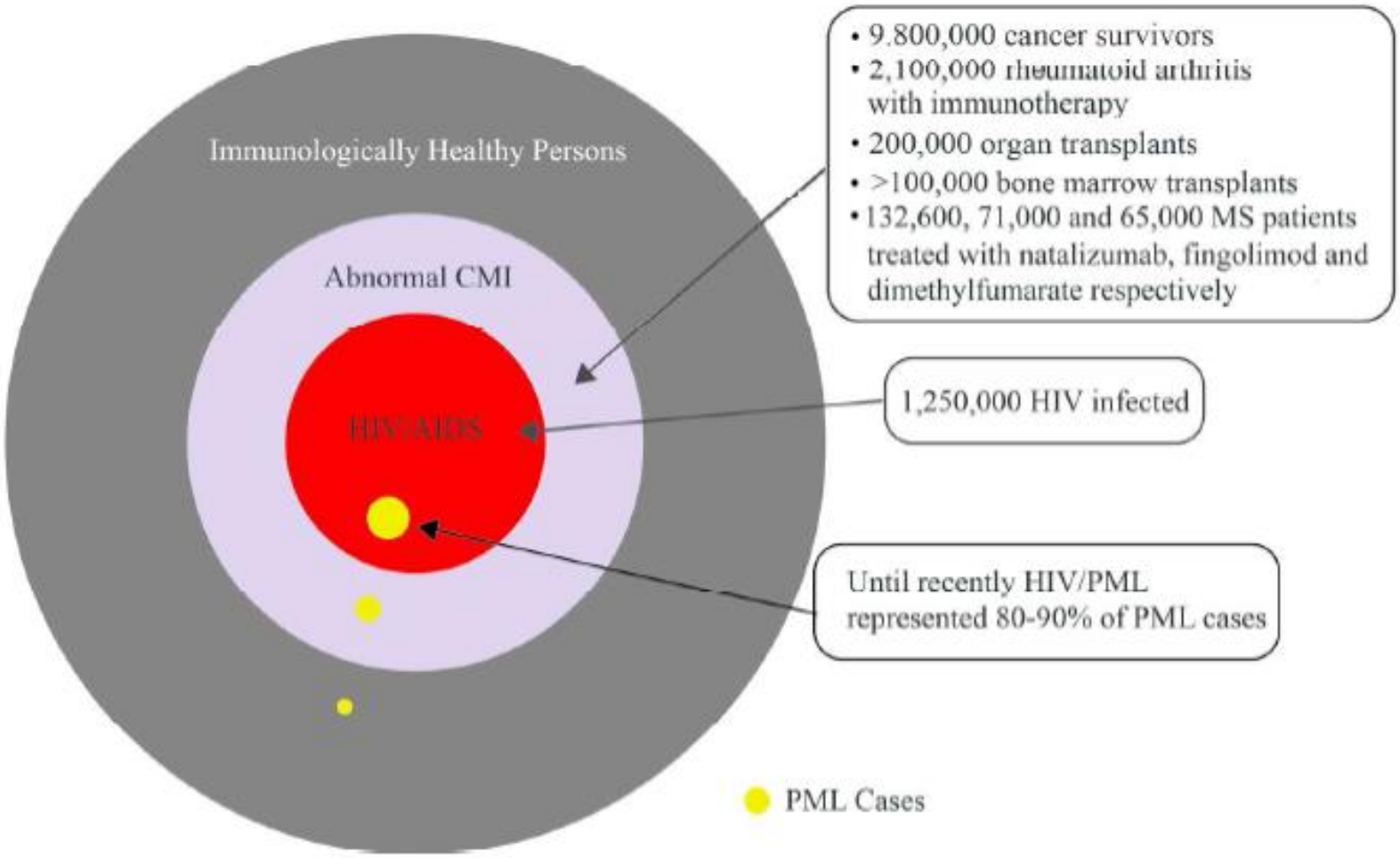
Rau D. et al. Int. J. Mol. Sci.2015



Norme alimentari e comportamentali per limitare il rischio di contagio con Listeria da adottarsi un mese prima ed un mese dopo il ciclo infusionale con alemtuzumab

Alimento o strumento a rischio	Comportamento
Latte non pastorizzato	• Non bere latte non pastorizzato • Non mangiare formaggi freschi fatti con latte non pasteurizzato
Verdure crude e frutti raccolti a terra	• Lavare abbondantemente prima di utilizzarli
Contaminazione e proliferazione in frigorifero	• Mantenere sempre la temperatura del frigorifero <4°C • Evitare la conservazione di cibi preconfezionati o precotti per più giorni in frigorifero
Carne cruda	• Evitare assunzione di carni crude • Evitare assunzione di hot dog • Non mangiare carni avanzate, se non riscaldate ad alte temperature • Evitare la conservazione di cibi preconfezionati o precotti per più giorni in frigorifero • Non mangiare insalate pronte contenenti pollo, tacchino, uova, prosciutto • Non cucinare o riscaldare la carne nel forno a microonde
Pesce	• Evitare assunzione di pesce crudo • Non mangiare insalate pronte contenenti tonno e frutti di mare • Non mangiare salmone affumicato
Pesce e carne	• Mantenere la carne cruda e il pesce separato dai cibi che verranno mangiati crudi
Utensili e taglieri	• Lavarli abbondantemente se sono stati utilizzati per carni crude, pesce e frutti di mare
Mani	• Lavarsi adeguatamente le mani dopo avere maneggiato carni crude, pesce e frutti di mare

Schematic diagram of the occurrence of PML in the US

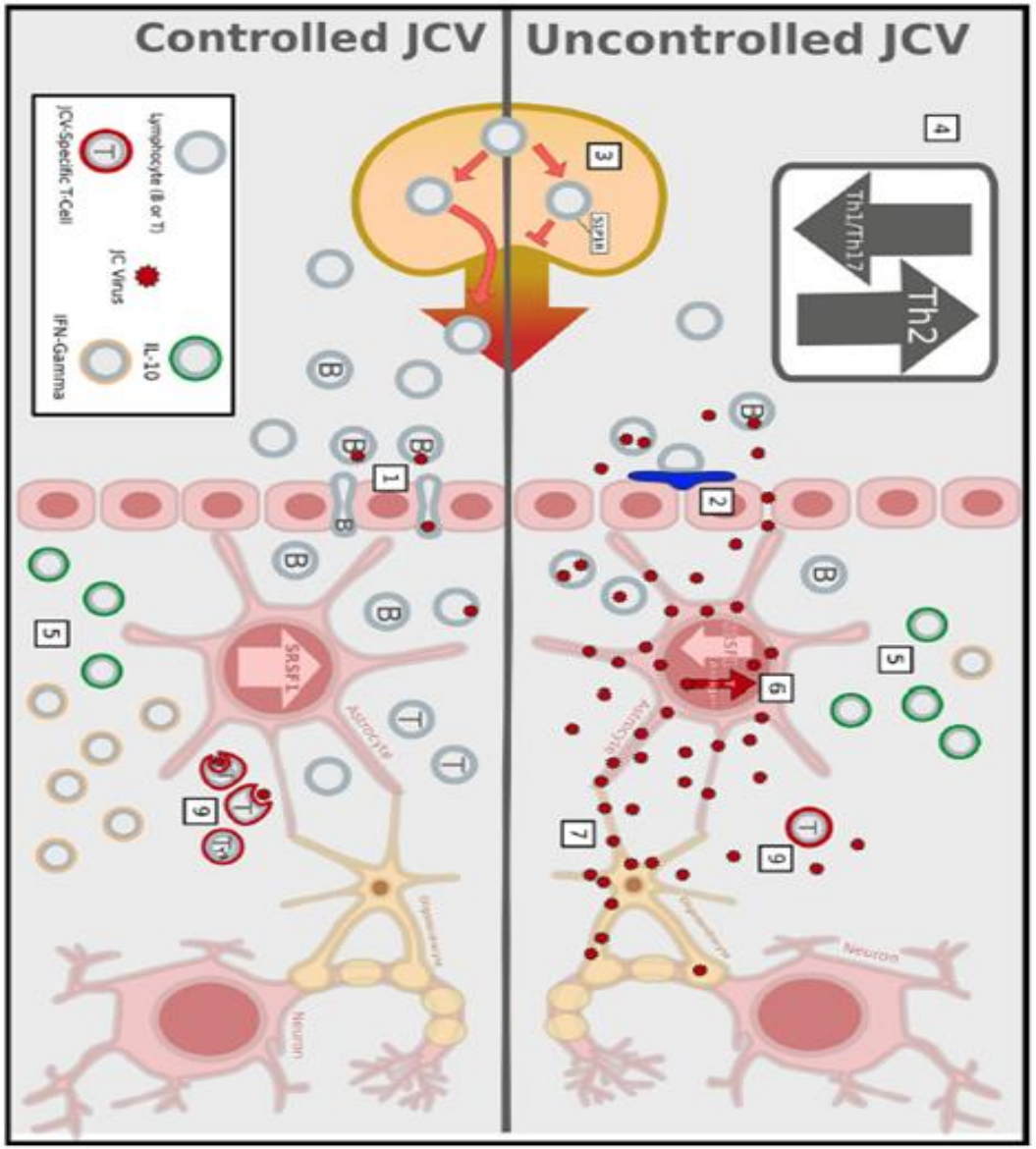


Classes of agents with known or possible risk for PML

Therapeutic Agent	Treated condition predisposes to PML?	Latency from time of drug initiation to PML	Frequency/ Incidence of PML	Year drug introduced into U.S. and European markets	Patients/patient-year (PY) exposure#
Class I – high potential risk of PML	**No**	**Yes**	**High**		
Natalizumab	MS and Crohn's disease	None < 8 months; > 85% of cases > 24 months	1/100–1/1000	U.S.- approved 2004; withdrawn Feb 2005; reintroduced Jun 2006 EUR – Apr 2006	161,300 patients ~527,159 PY (September 30, 2016)
Class II – low potential risk of PML	**No**	**Yes**	**Low/infrequent**		
Dimethyl fumarate	MS and psoriasis	18–54 months	~1/50,000	U.S. – Mar 2013 Europe – Feb 2014	224,542 patients 308,732 PY
Fingolimod	MS	18–54 months*	~1/18,000	U.S.- Sep 2010 EUR-Mar 2011	160,000 patients 368,000 PY
Class III – no or very low potential risk of PML	**Yes**	**No**	**Very low or evident only with related drug**		
Alemtuzumab	Hematological malignancies, transplantation		Unknown; no cases with MS	U.S. – Nov 2014 EUR – Sep 2013	~11,000 patients ~6000 PY
Rituximab	Lymphoproliferative disorders, rheumatoid arthritis, ANCA-associated vasculitis, SLE		1/30,000	MS – unapproved indication	No data
Mitoxantrone	Non-Hodgkins lymphoma and leukemia			U.S.-Oct 2000 EUR-divergent dates	No data
Teriflunomide	No PML observed with teriflunomide but with related leflunomide			U.S.-Sep 2012 EUR-Aug 2013	68,952 patients 96,909 PY
Daclizumab	No PML observed with MS or as prophylaxis for renal transplant			U.S.-May 2016 EUR-Jul 2016	1516 patients 3744 PY

Immunosuppressive activities of MS therapies facilitate JCV infection and replication in the CNS

MS immunomodulatory therapies associated with progressive multifocal leukoencephalopathy have different mechanisms of action, but ultimately lead to an immunosuppressed state within the CNS that increases the likelihood of a productive infection of glial cells by JCV.



Mechanisms involved in natalizumab-induced PML

- First, natalizumab administration was demonstrated to result in the release of premature B cells from bone marrow stores.
- These B cells might be sites of viral latency, and transcription factors associated with their maturation might result in an increase of JC virus replication;
- B cells have the appropriate genetic machinery to facilitate generation of mutations in the noncoding control region of the virus, and perhaps elsewhere, potentially resulting in the conversion to the pathogenic prototype strain of JC virus

Mechanisms involved in natalizumab-induced PML

- Natalizumab, an α4β1 integrin and α4β7 integrin inhibitor, prevents lymphocytes and other inflammatory cells from binding to vascular cell adhesion protein 1 (VCAM-1) and crossing the blood brain barrier, as this type of immune cell migration is dependent on α4β1 integrin.
- Elimination of the monoclonal antibody by plasmapheresis in natalizumab-associated PML permits entry of JC virus-specific CD8+ T cells into the brain, which almost invariably results in PML immune reconstitution inflammatory syndrome

Estimated incidence of PML stratified by the three known risk factors

	RISK OF PML		
	Anti-JC negative	Anti-JC positive	Anti-JC positive
Natalizumab treatment duration		No prior immunosuppressive use	Prior immunosuppressive use
1-24 months	< 1/1000	< 1/1000	1/1000
25-48 months		3/1000	13/1000
49-72 months		7/1000	9/1000

Chaliin S et al. J. Neurovirol. 2014

PML cases reported under fingolimod treatment after natalizumab treatment

- According to Berger criteria, 12 cases[1] of definite or probable PML plus 3 cases that occurred prior to start of fingolimod therapy, account for a total of 15 cases reported after prior exposure to NTZ[2]
- The incidence of PML in fingolimod treated patients who have switched from NTZ is therefore 0.507 (95% CI: 0.277, 0.850) per 1000 patients who are assumed to have previously taken NTZ (15% of fingolimod patients).[2]
  - Of the 12 cases after start of fingolimod therapy, the duration of prior NTZ exposure ranged between 1 year 10 months to 6 years 8 months with a washout period between NTZ and fingolimod therapy between 1 to 4 months
  - 3 cases occurred prior to start of fingolimod therapy
- For natalizumab, the risk of PML is 4.18 per 1,000 patients[3]

NTZ, natalizumab; PML, progressive multifocal leukoencephalopathy

1. Berger JR et al. Neurology. 2013 Apr 9;80(15):1430-8.
2. Novartis data on file. Data cut-off 31st August 2016.
3. Tysabri safety update.

Estimated Risk of reported PML cases in MS patients exposed to fingolimod not attributed to natalizumab

The overall rate of PML under fingolimod therapy not attributed to previous natalizumab treatment is very rare and estimated to be less than 1:10,000 patients

Treatment duration	MS patient exposure to fingolimod[1-2]	Number of PML cases in treated MS patients	Estimated Risk	Estimated Risk
Overall	~184,000 patients	10 cases in ~184,000 treated patients	0.054 / 1,000 patients 95% CI: (0.026, 0.100)	~1: 18,000
More than 2 years	~74,000 patients	9 cases In ~74,000 treated patients	0.121 / 1,000 patients (95%CI: 0.055 , 0.23)	~1: 8,000

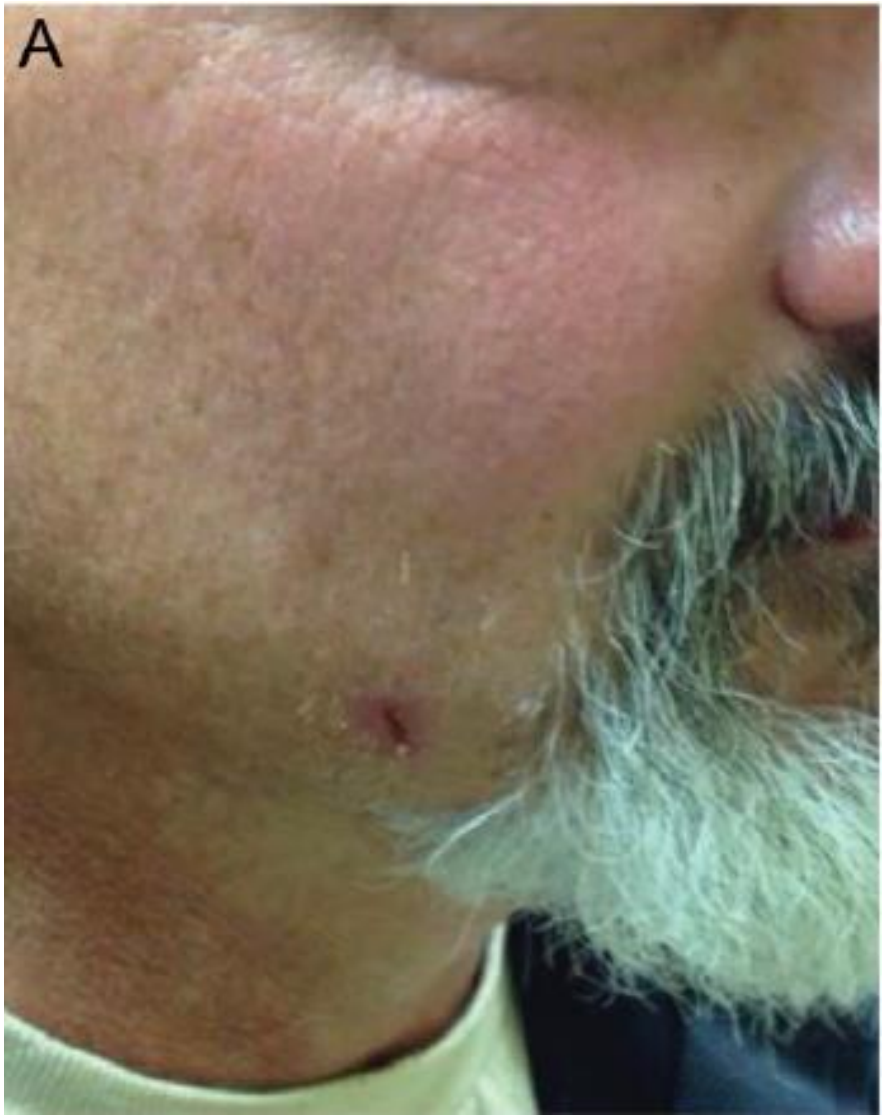
Current issues related to the management of drug-induced progressive multifocal leukoencephalopathy in multiple sclerosis

- PML cases have been reported with several MS therapies (natalizumab, fingolimod, and DMF)
- Limited information available on PML related to fingolimod and DMF
- Prediction of PML at the individual patient level remains challenging
- Limited number of available biomarkers in routine practice
- Incomplete knowledge on JCV and PML pathogenesis
- Immune reconstitution remains the only treatment with demonstrated efficacy

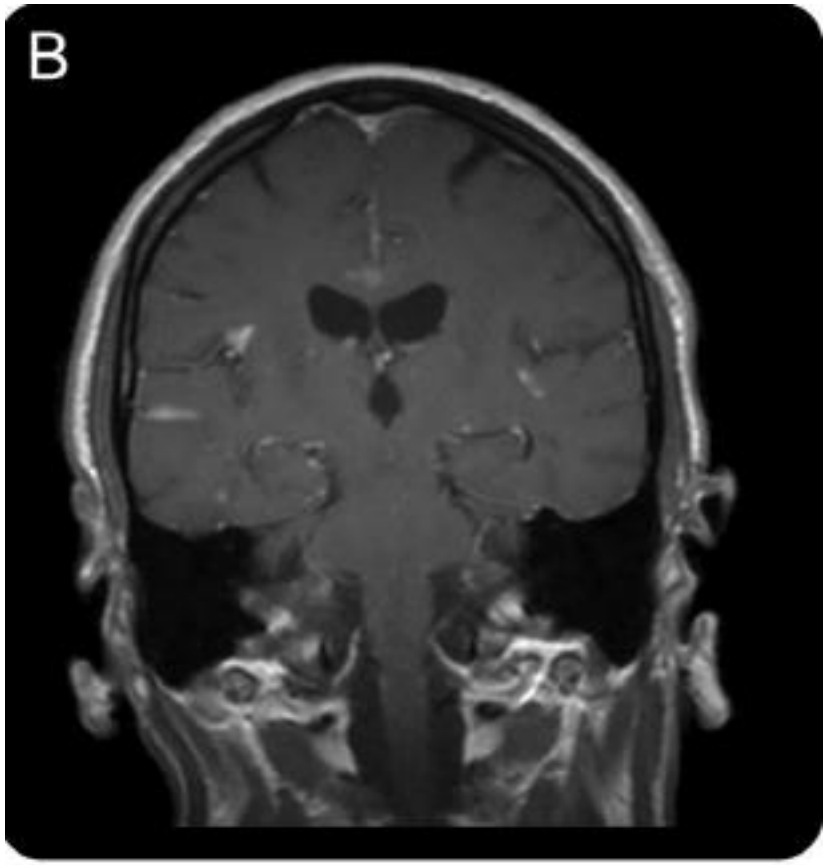
Case report

- A 50-year-old man with a history of MS and migraine
- Fingolimod therapy for 3.5 years
- He presented with 2 weeks of headache
- Lymphocyte count was $0.5x10^3/mm^3$
- Afebrile, no nuchal rigidity
- Brain MRI: no evidence of acute intracranial pathologies
- Divalproex sodium for presumed diagnosis of migraine headache
- Headache worsened in 1 week and he developed sleepiness, nausea, vomiting, imbalance

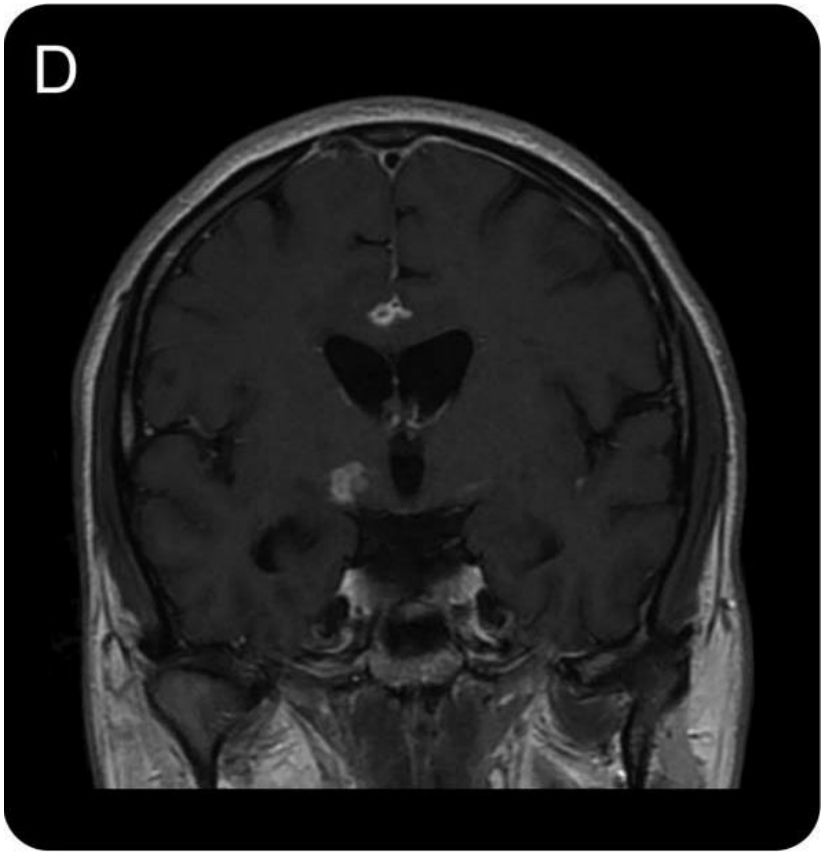
Facial skin lesion



Brain MRI



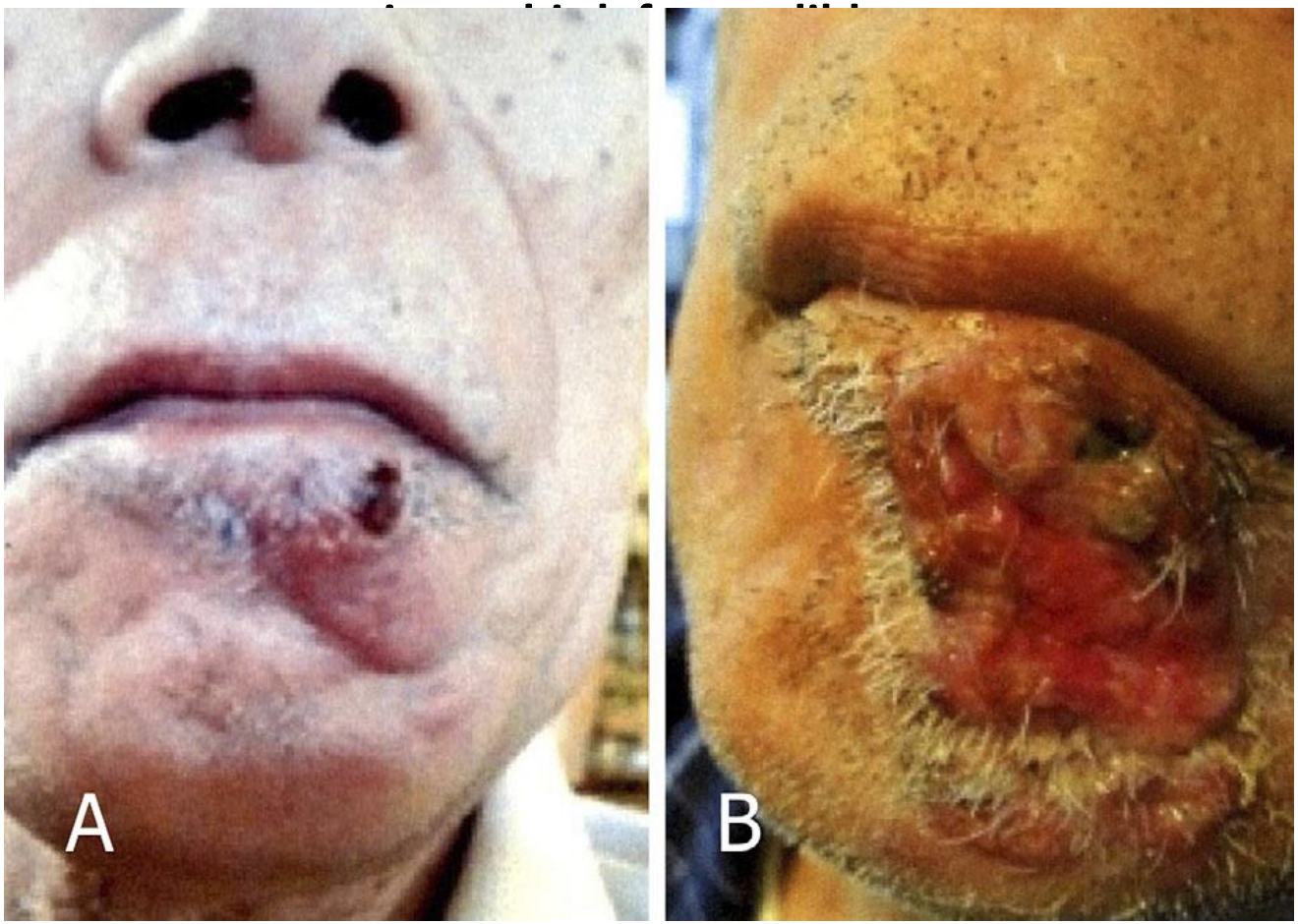
Diffuse meningeal enhancement



Formation of ring-like structure with enhancement in the corpus callosum and left thalamus

63-year-old man with MS and 2 years of treatment with fingolimod

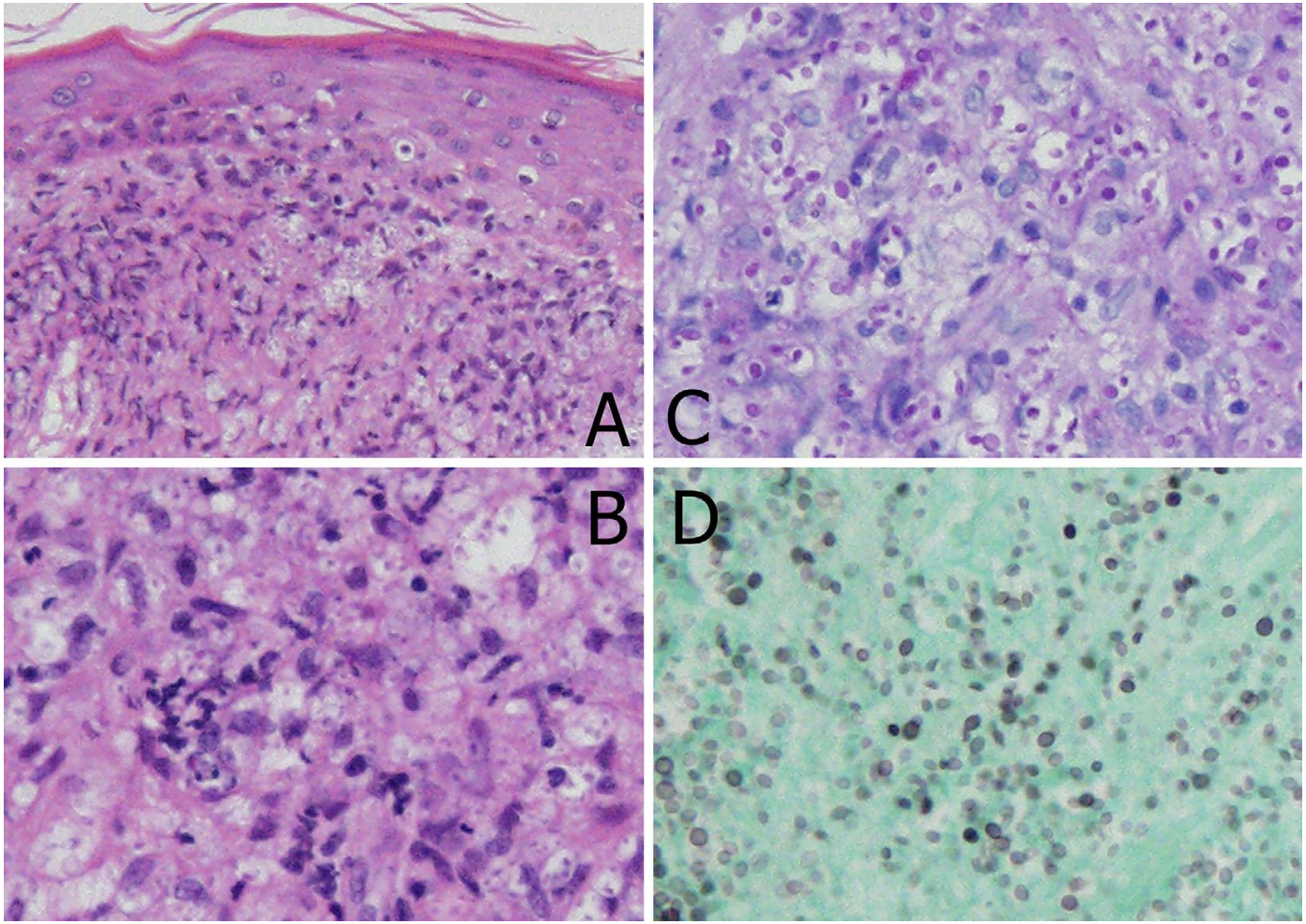
3-month history of a cutaneous nodular lesion of his jaw, low grade fever, lethargy and progressive cognitive impairment **5×3 cm in**



Three months prior to admission an erythematous nodule beneath the lower lip

On admission, there was an erythematous multilocular lesion with ulcer

Disseminated cryptococcosis



Mucicarmine histochemistry staining shows numerous multinucleated giant cells containing carmininophilic yeasts with clear halo around each yeast.

DeRen Huang, Neurology, 2015

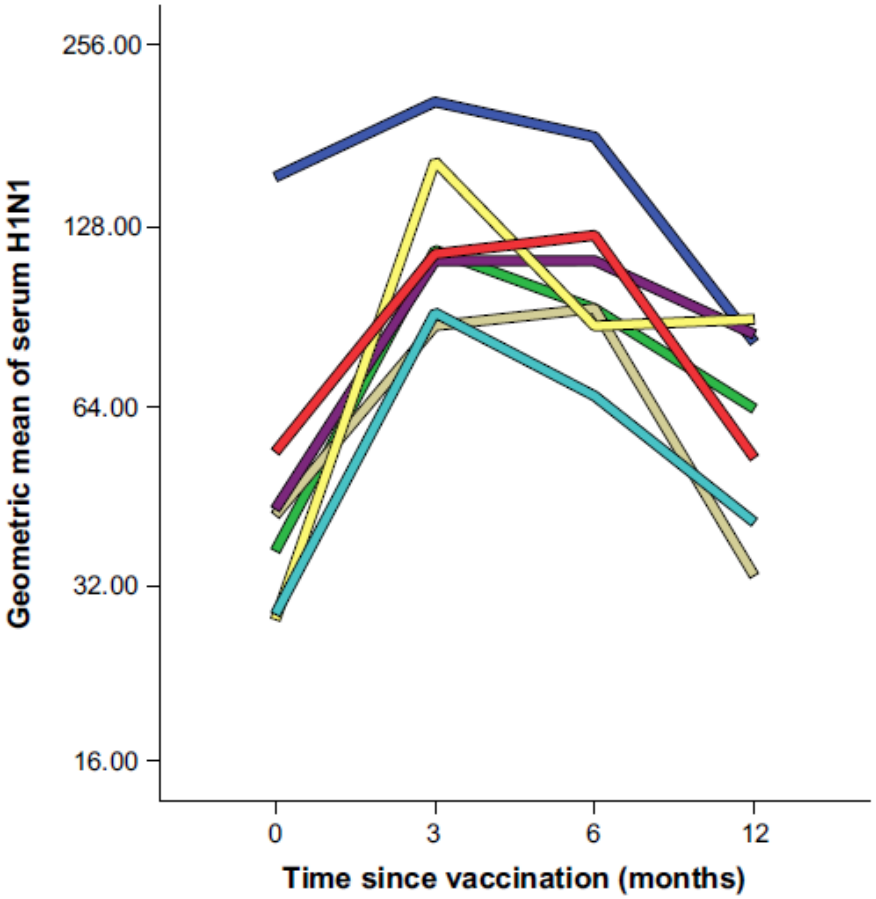
Age distribution and duration of treatment of patients treated with Fingolimod who developed cryptococcal infections.

Patient age/ gender	Site of Infection	Duration of Fingolimod treatment
62/ (M)	CNS	36 months
62/(F)	Cutaneous	36 months
52/ (M)	Disseminated	42 months
40/(M)	CNS	24 months
67/ (F)	CNS	41 months (symptom onset after 6–8 weeks after discontinuation)

Response to influenza vaccinations in patients on various treatments for multiple sclerosis

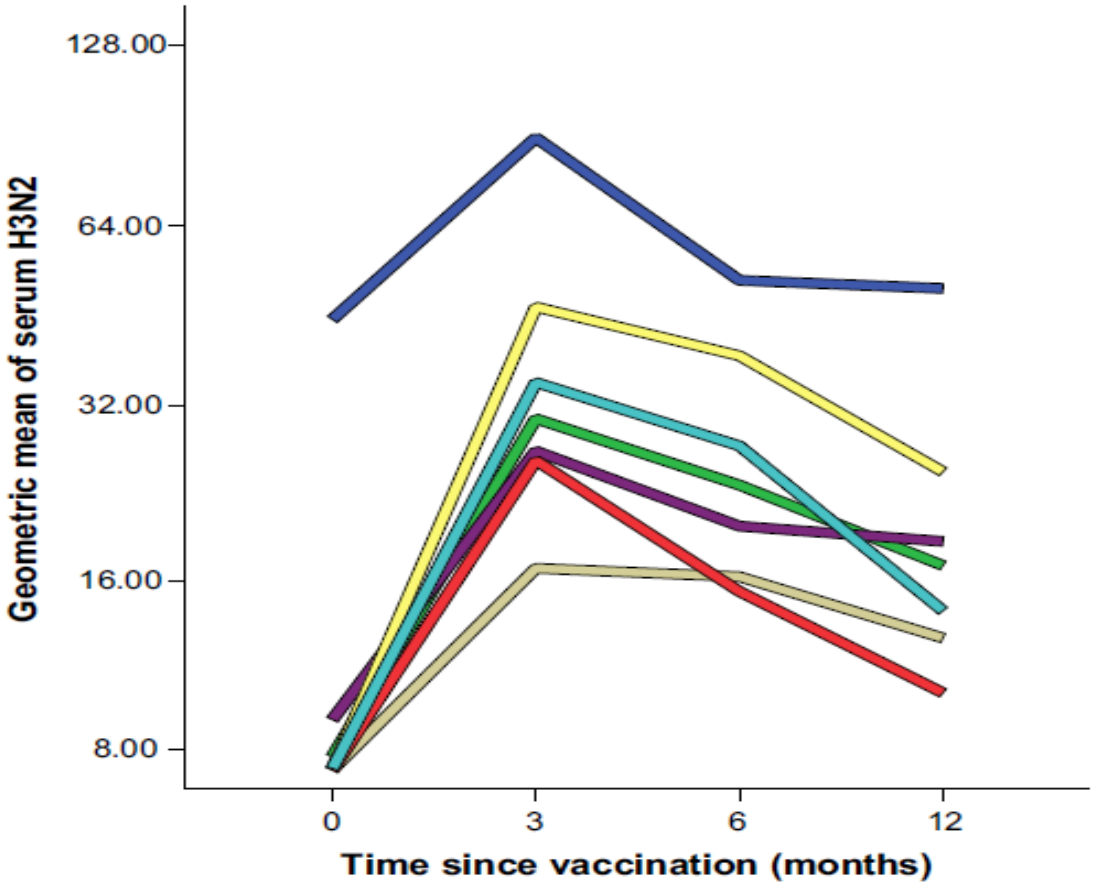
Tretment	Response to influenza vaccination
Interferons	Unchanged vaccination response (23)
Glatiramer acetate	H3N3 2010: 41.7% (GA) versus 79.5% (untreated HC) (23)
Teriflunomide	Slightly reduced response (24)
Dimethyl-fumarate	No studies in MS
Fingolimod	43% (fingolimod) compared with 75% (placebo) (25)
Mitoxantrone	H1N1 2009: 0% (mitoxantrone) versus 43.5% (untreated HC) (23)
Natalizumab	Inconsistent results: reduction of vaccination response (23.5% [natalizumab] versus 43.5% [untreated HC]) or unchanged response (23)
Alemtuzumab	Debatably no reduction in vaccination response; vaccination against influenza is expressly recommended, possibly with repeat vaccination if the titer is too low: all vaccinations in patients on alemtuzumab should be given at least 6 months after the most recent infusion (26)
Daclizumab	No studies in MS

Geometric mean hemagglutination inhibition serum antibody titers to H1N1 plotted on log2 scale according to time since vaccination



Blue, controls;
green, MS;
brown, fingolimod;
purple, glatiramer acetate;
yellow, interferon beta-1a/1b;
red, natalizumab;
pale blue, none

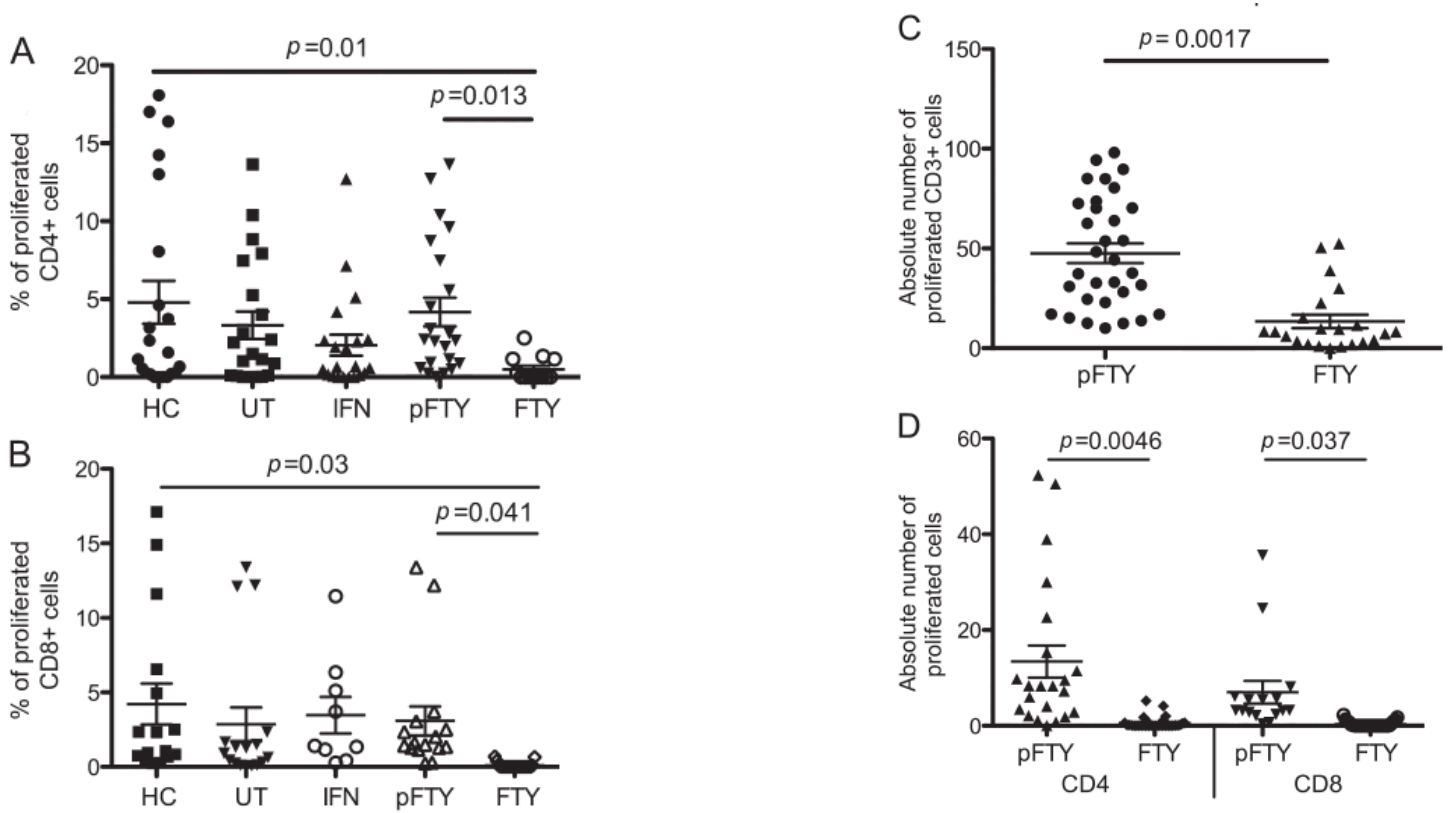
Geometric mean hemagglutination inhibition serum antibody titers to H3N2 plotted on log2 scale according to timesince vaccination



Blue, controls;
green, MS;
brown, fingolimod;
purple, glatiramer acetate;
yellow, interferon beta-1a/1b;
red, natalizumab;
pale blue, none

T-cell response against varicella-zoster virus in fingolimod-treated MS patients

FTY induced a prominent decrease of proliferating CD4 T cells, as well as of CD8 T cells, compared with pFTY and HC



Meret E. Ricklin, et al. *Neurology 2013;81;174-181*

Vaccine responses after alemtuzumab treatment

Diphtheria, tetanus, and poliomyelitis vaccine (n = 22)				
	No. (%) seroprotected prevaccine	No. (%) seroprotected postvaccine	GMTR (±90% CI)	GMTR from literature controls
Diphtheria	22 (100)	22 (100)	2.6 (±1.2)	2.2[a] (2.0-2.5)
Tetanus	22 (100)	22 (100)	Not done[b]	
Polio 1	21 (95)	22 (100)	3.5 (±22)	7.3[a] (5.9-9.0)
Polio 2	21 (95)	21 (95)	5.0 (±7.5)	10.0[a] (8.4-11.9)
Polio 3	17 (77)	21 (95)	16.5 (±15.6)	17.1[a] (13.6-21.4)
Hib and Men C conjugate vaccine (n = 23)				
	No. (%) seroprotected prevaccine	No. (%) seroprotected postvaccine	No. (%) seroconversion 4-fold antibody increase	% Seroconversion from literature controls
Men C	3 (13)	21 (91)	19 (83)	97.6-100[c]
Hib	17 (74)	23 (100)	18/19 (95)[d]	82-90[e]

Infectious diseases assessment

In MS patients at diagnosis, a **baseline "infectious disease" evaluation** is recommended*

This should include, at a minimum, the following:

- Personal history (childhood diseases, present or past tuberculosis contacts, travel history, personal or familiar potential sources of infection, search for possible immune deficiencies (e.g. asplenia, diabetes, etc.)
- Life style

Baseline ID assessment

- Baseline serologic assessment
  - Toxoplasma IgG,
  - Hepatitis B and C virus
  - Herpes simplex virus IgG
  - Varicella zoster virus IgG
  - Cytomegalovirus IgG,
  - Epstein–Barr virus IgG
  - Human immunodeficiency virus
  - JCV Screening with Stratify
- Baseline screening for human papillomavirus (Pap smear for females) Men? If MSM anoscopy and HPV PCR

Baseline ID assessment

- TB-IGRA or PPD-IDR
  - If positive
    - Lung x-rays
    - Verify previous therapy
    - If no therap or prophylaxis, conider prophylaxis regimen before initiating immunesuppressive treatment

- Personal and familiar counseling in order to avoid future contagion, if appropriate, and travel medicine counseling (for patients intending to travel)

Baseline ID assessment

All MS patients should be evaluated for immunization status with the recommended vaccines at the time of diagnosis.

Vaccinations to be considered for adult MS patients should include the ones recommended by local regulations, except in cases of additional risk factors (travel, sexual habits, etc.)

Vaccinations

- Seasonal influenza every year for all patients
- Tetanus/diphtheria/pertussis acellular if never received (TD recall if needed)
- Hib if never received
- Pneumococcal conjugate vaccine (PCV13) followed by PPV23 after >2 months
- Inactivated polio vaccine if never received and planning to travel in endemic countries

Vaccinations

- Hepatitis B vaccine if HBcAb negative and HBsAb negative
- Hepatitis A vaccine if hepatitis A virus IgG negative and traveler, men who have sex with men, raw seafood eater, etc.
- MCV4 and MenB
- HPV9 for those <26 years
- Varicella (VAR) vaccine for those VZV IgG negative

Vaccination

Timing and schedule of vaccinations should be tailored to:

- The timing of DMD administration (past or planned)
- The time elapsed since last acute exacerbation
- The time elapsed since last corticosteroid pulse

Vaccination

TIMING OF DMD ADMINISTRATION (past or planned)

- Inactivated vaccines (either first or recall dose) should be administered at least 2 weeks before the introduction of immunosuppressive disease modifying drugs, due to efficacy concerns.
- Similarly, even though inactivated vaccines will never pose a risk of "vaccine disease" in immunosuppressed patients, their efficacy is not guaranteed until a certain time after drug interruption: this interval is not uniformly defined In any case, such vaccines should be re-administered when initially given during a period of intense immunosuppression*.
- Nonetheless, seasonal influenza vaccine is always indicated, irrespective of concomitant MS DMDs, on the assumption that even a reduced response might be at least partially efficacious

Vaccination

TIMING OF DMD ADMINISTRATION (past or planned)

- Live attenuated vaccines should be administered at least 4–6 weeks before initiation of treatment with ~~i~~immunosuppressive DMDs.
- They should never be administered to a patient on immunosuppressive drugs, or before a certain time since their interruption, the duration of which is based on expert opinion

- <u>Specific recommendations on live vaccines</u>
  - HCDS 2014 considered 3 months to be a safe interval for live-attenuated vaccination after an immunosuppressive steroid dosage is given.
  - For B-depleting therapy and both B- and T-depleting treatment, it is suggested to wait until B-cells have returned to normal levels, and no earlier than 6 months for rituximab.
  - Daclizumab prescribing information recommends to start treatment no earlier than 4 months.
  - Fingolimod prescribing information recommends avoiding live vaccines for 2 months after discontinuation.
  - For teriflunomide, it is recommended to wait for 6 months, while it is less clear for alemtuzumab (“after recent treatment”, in the SmPC).

Vaccination

TIMING SINCE LAST ACUTE EXACERBATION

- Based on expert opinion, without any study data:
  - Wait for at least 4–6 weeks after the onset of an acute MS exacerbation before vaccination (for either first or recall dose): the situation has to be stabilized.
  - In case of an infected wound for which the TT is indicated, this can be administered even if the exacerbation is not resolved.

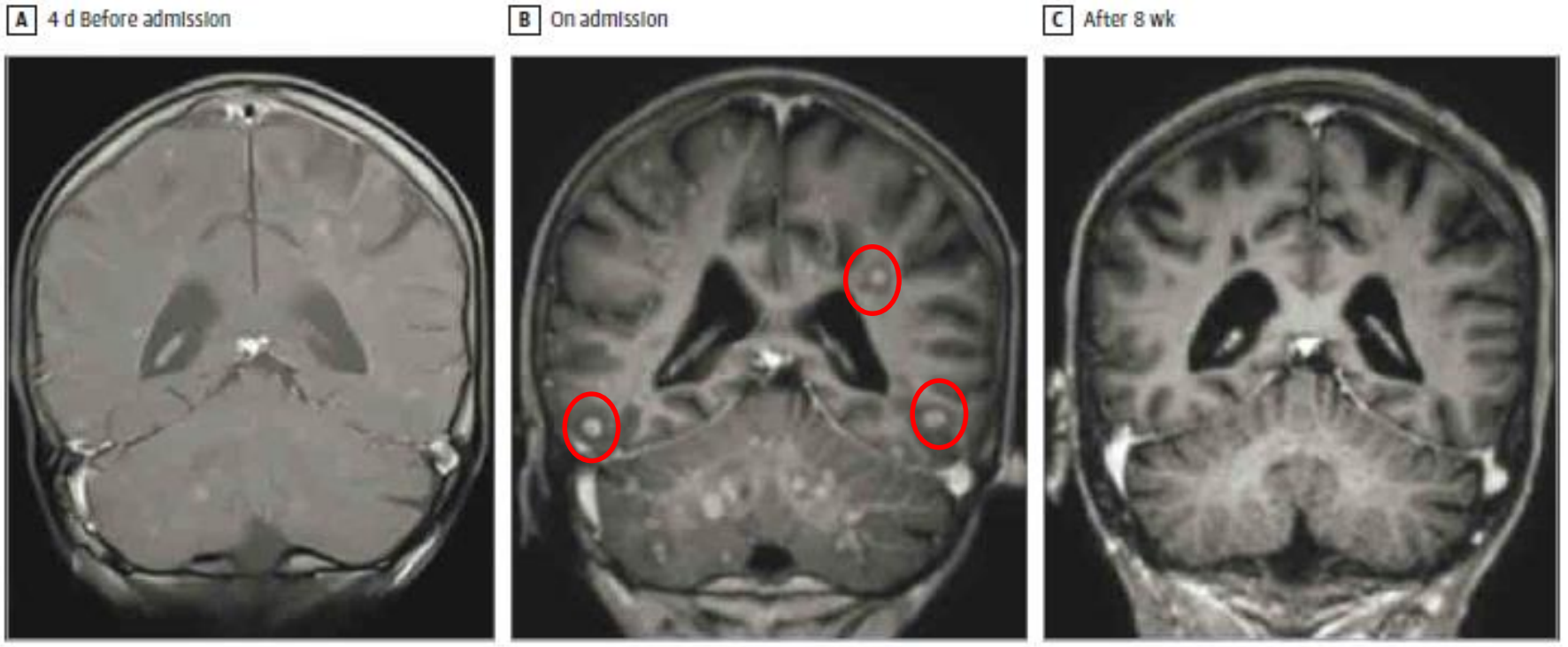
Neurologists treating multiple sclerosis with potent agents should actively prepare to avoid infectious diseases and keep calm but anyway ready to expect the unexpected

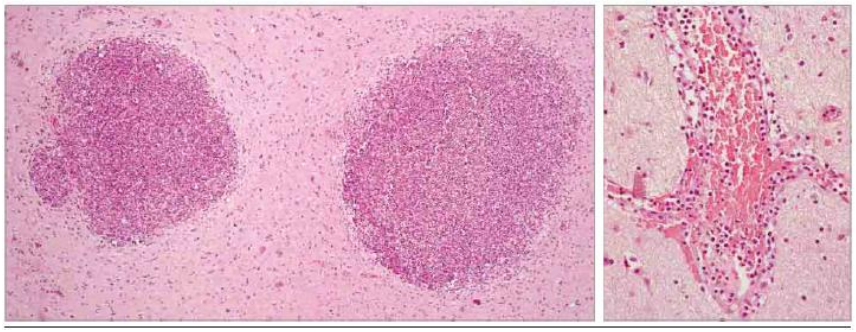
Case report

- Woman in her late 40s
- MS in 2007
- Hypothyroidism, recurrent infection, anorexia (BMI: 14)
- Previous natalizumab treatment
- 18 weeks after NTZ cessation she received Alemtuzumab infusion
- 4 months later reduced ambulation and personality change

Penkert et al. JAMA Neurology 2016

Brain MRI and brain biopsy





Depleted mononuclear fraction

Absolute Number of Leukocytes per Microliter of Patient's Blood

Cells per μL (Normal Range)	Before Alemtuzumab (January 15)	On Admission (June 15)	On Follow-up (August 15)
Leukocytes (4000-9000)	4070	9120	10 810
Granulocytes	2446	8664	9289
Monocytes	224	365	757
CD4+ T cells (450-1400)	568	5	90
CD8+ T cells (250-850)	392	3	70
CD19+ B cells (65-550)	185	4	40
Natural killer cells (70-530)	207	37	200

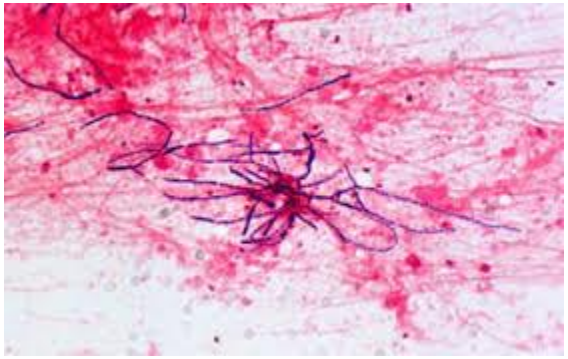
Penkert et al. JAMA Neurology 2016

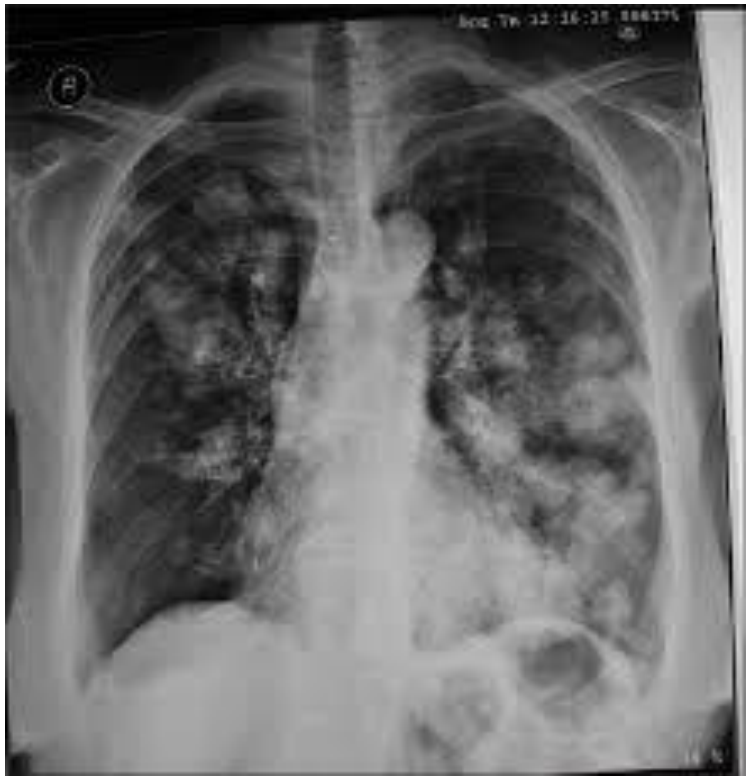
MULTIPLE SCLEROSIS JOURNAL | MSJ

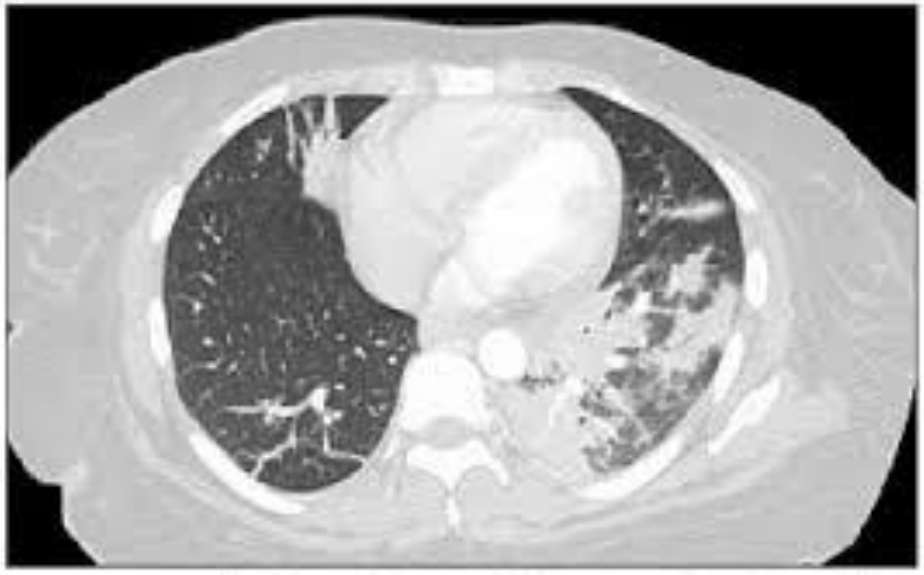
Case Report

Pulmonary *Nocardia beijingensis* infection associated with the use of alemtuzumab in a patient with multiple sclerosis

Marwan Sheikh-Taha and Lourdes C Corman







Active CMV infection in two patients with multiple sclerosis treated with alemtuzumab

Marinella Clerico, Stefania De Mercanti, Carlo Alberto Artusi, Luca Durelli and Robert T Naismith

- A 29-year-old Caucasian woman with MS
- In September 2015, she began alemtuzumab
- After 7 days of last alemtuzumab infusion, the patient was hospitalized for fever, abdominal pain, and emesis
- The CMV viral DNA PCR was positive for 9800 copies/ mL, while it was negative before treatment.
- The patient was treated with ganciclovir 900 mg i.v. twice daily for 5 days, followed by oral valganciclovir 900 mg a day for 4 weeks.
- Viral load was re-tested weekly, peaking 2 weeks later with 21,900 copies/mL before becoming undetectable (January 2016).
- Patient's fever and gastrointestinal symptoms resolved soon after initiating ganciclovir.

Multiple Sclerosis Journal

2017, Vol. 23(6) 874–876

Active CMV infection in two patients with multiple sclerosis treated with alemtuzumab

Marinella Clerico, Stefania De Mercanti, Carlo Alberto Artusi, Luca Durelli and Robert T Naismith

- 32-year-old African American woman with MS
- In February 2016 she started alemtuzumab
- After 21 days,, she experienced weakness, fever, chills, hyporexia, nausea, vomiting, abdominal pain, headaches, diarrhea, and dizziness
- Laboratory tests showed a transaminitis with ALT 352 U/L, AST 130 U/L, and ALP of 58 U/L
- CMV viral DNA PCR was positive at 1940 IU/ml
- She was discharged on oral valganciclovir 900 mg twice a day induction for 14 days, followed by oral valganciclovir 900 mg daily for 2 weeks.
- After 2 weeks of initiating treatment, her symptoms and transaminitis had resolved.

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