EPIDEMIOLOGIA, CLINICA E PREVENZIONE DELLE INFEZIONI NEI PAZIENTI CON SCLEROSI MULTIPLA TRATTATI CON FARMACI BIOLOGICI

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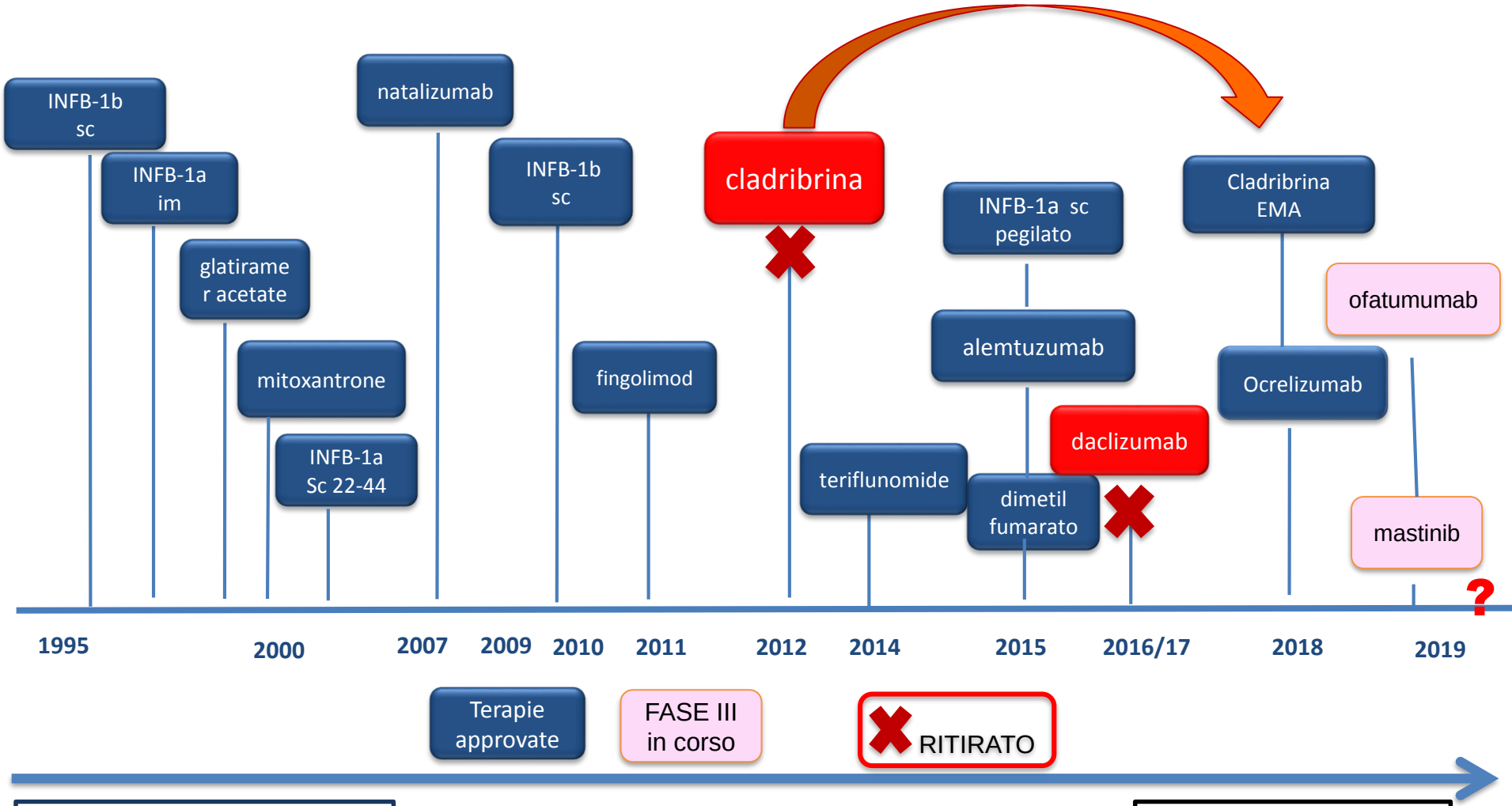
ASST Fatebenefratelli Sacco

Disclosures

- Dr. Agostino Riva received speaker's honorarium from the following companies:

  - Novartis
  - Sanofi
  - VIIV
  - BMS
  - Gilead
  - Roche
  - Biogen
  - MSD

Timeline of DMDs in MS



Prima aa 90:
Assenza di famaci

Attualmente:
> di 13 farmaci

DMDs for MS

• DMTs have been shown to reduce the risk of relapses and have a beneficial impact on imaging outcomes

•Because of the importance of humoral and cell-mediated immunity in the pathophysiology of MS, nearly all therapies involve modulation of the immune system with interferons, glatiramer acetate, and immunosuppressive medications

• These drugs target the inflammatory process in MS by modulating the immune system or by immunosuppression

• 8 immunosuppressive medications:
  - •monoclonal antibodies (natalizumab, alemtuzumab, and ocrelizumab)
  - •a chemotherapeutic agent (mitoxantrone)
  - •small-molecule oral agents (fingolimod, dimethyl fumarate, and teriflunomide, cladribine)

DMDs: mechanisms of action

The drugs have diverse mechanisms of action

- alteration of lymphocyte trafficking (natalizumab and fingolimod)
- lymphocyte depletion (alemtuzumab, cladribine and ocrelizumab)
- disruption of lymphocyte replication (mitoxantrone and teriflunomide)
- dimethyl fumarate acts via unknown mechanisms, though it clearly causes lymphocytopenia.

Assessing infectious risk of multiple sclerosis therapies

- Patients with MS undergoing immunosuppression may be at risk of
  - reactivation of latent pathogens,
  - worsening of asymptomatic chronic infections,
  - contracting *de novo* infections.

– Prevention is preferable to treatment, reducing both infectious morbidity and mortality, as well as interruptions of MS therapy.

– Simultaneously, unnecessary screening, particularly using tests with poor sensitivity and specificity, risks false-negative and false-positive results, which can result in either unfounded reassurance or delayed treatment for MS

MS therapies and IDs

- Overall, all the molecules for MS show a low incidence of infectious complications, mostly mild and easily managed
- Each single drug moderately increases the risk of specific opportunistic infections
- No or very little and unreliable predictions can be deduced for single patients

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

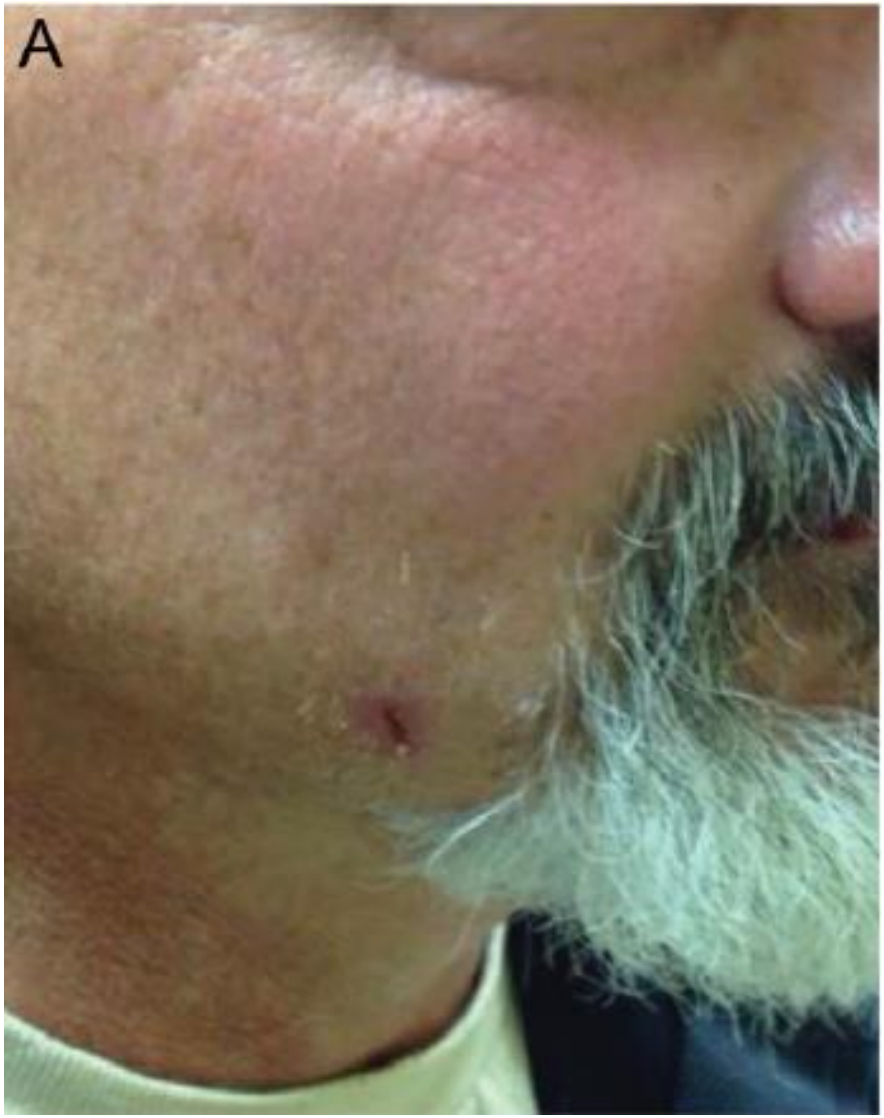
	Fingolimod		Placebo (N=355)
	1·25 mg (N=370)	0·5 mg (N=358)	
All events			
At least one adverse event	359 (97%)	350 (98%)	343 (97%)
Any adverse event leading to discontinuation of study drug*	72 (20%)	66 (18%)	37 (10%)
Any serious adverse event	53 (14%)	53 (15%)	45 (13%)
Deaths†	0	0	0
Frequent or special-interest 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

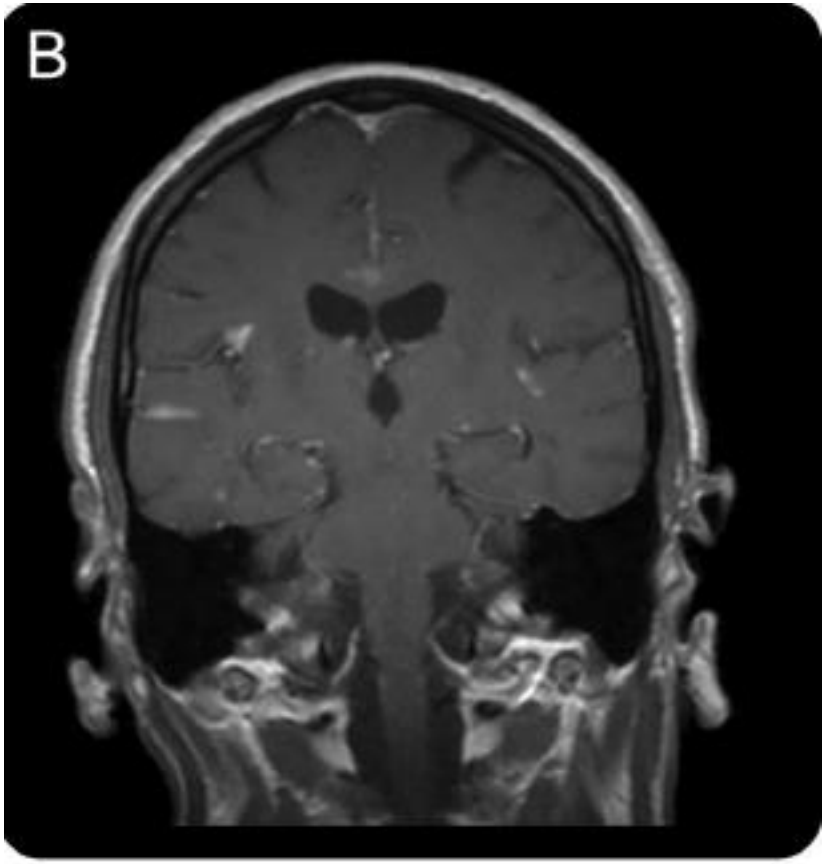
Case report

- 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

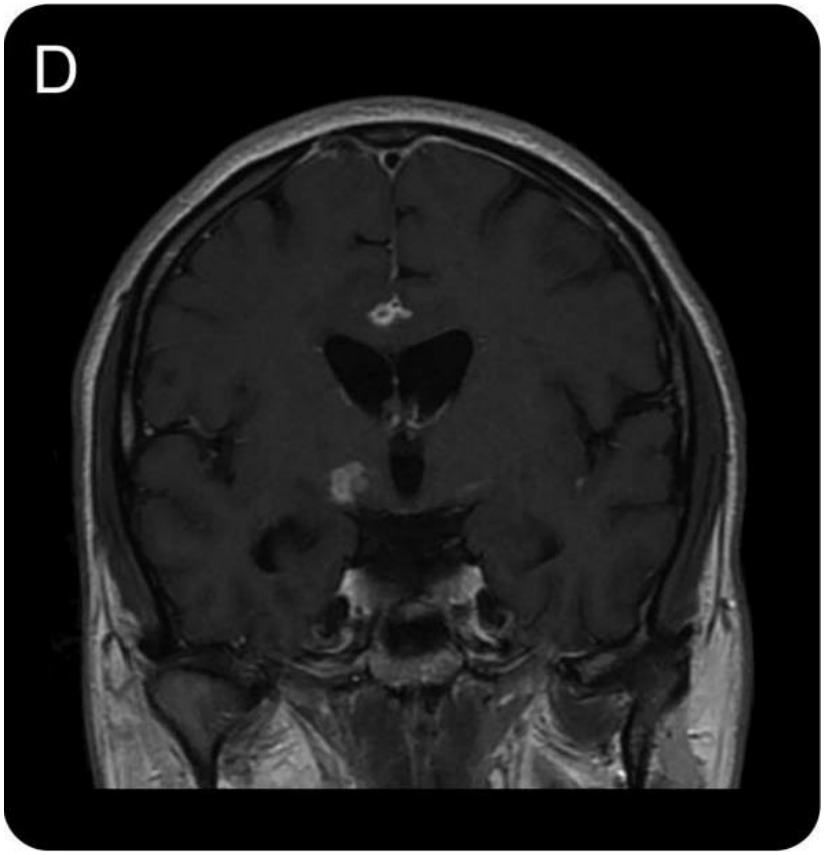
Facial skin lesion



Brain MRI



Diffuse meningeal enhancement



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

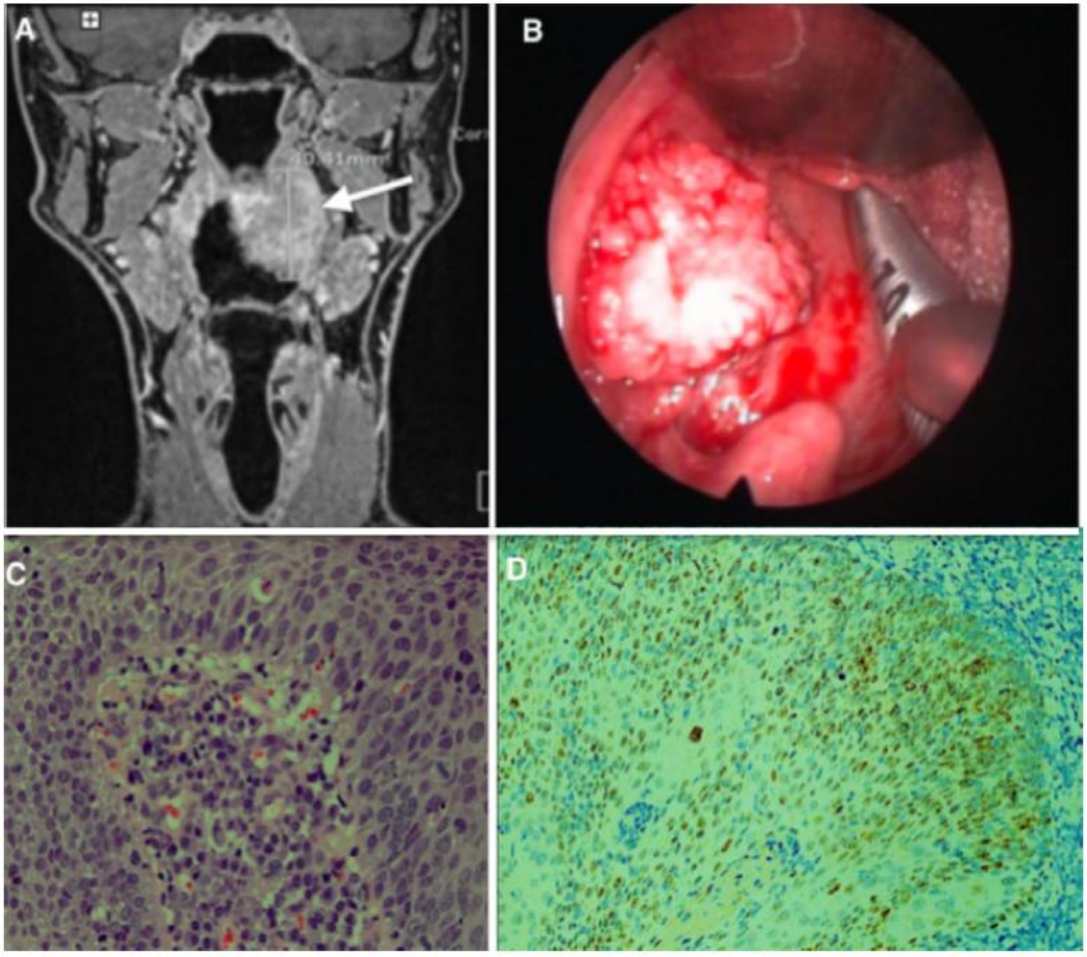
Cryptococcal meningitis: 28 cases

Duration of Fingolimod treatment (months)	Outcome	Notes
27	Complete resolution	
37	Lethal	Steroids just before event
> 36	Recovering	
36	Recovering	Steroids just before event
21	Recovering	
36	Recovering	Steroids just before event
28	Recovering	Disseminated infection
48	Recovering	Steroids 2 months earlier
37	Recovering	Disseminated infection
40	Lethal	
36	Unknown	Previous cryptococcosis
42	Recovery with sequelae	
43	Unknown	
33	Lethal	
58	Unknown	
37	Recovering	
60	Recovering	
57	Lethal	
> 36		DM, melanoma, carotic sheath tumor,
16	Unknown	
24	Lethal	
>24	Lethal	Steroids just before event

Case report

HPV-related papillary squamous cell carcinoma of the tonsil during treatment with fingolimod

Maria Donata Benedetti[a], Antonio Marangi[a,*], Silvia Bozzetti[a], Francesca Gobbin[a], Marco Turatti[a], Maurizio Pea[b], Alberto Gajofatto[a], Stelio Mocella[c]

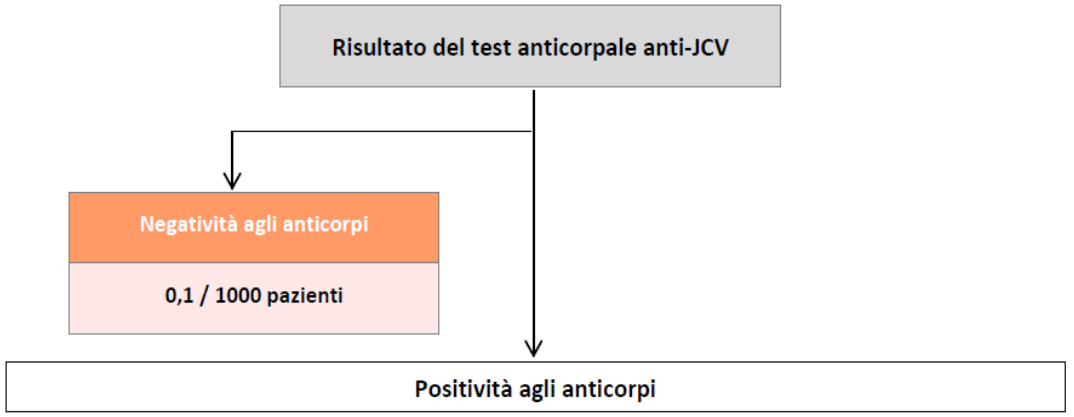


Neck MRI image revealed
a voluminous left tonsillar mass
indicated by the white arrow
Exophytic and ulcerated
(intraoperative image)
Hematoxylin eosin staining: high
grade atypia associated with
numerous mitoses
in the context of papillary
squamous carcinoma.
By in situ hybridization diffuse HPV-
16 hybridization signal

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

Stime aggiornate del rischio di PML nei pazienti in terapia con natalizumab



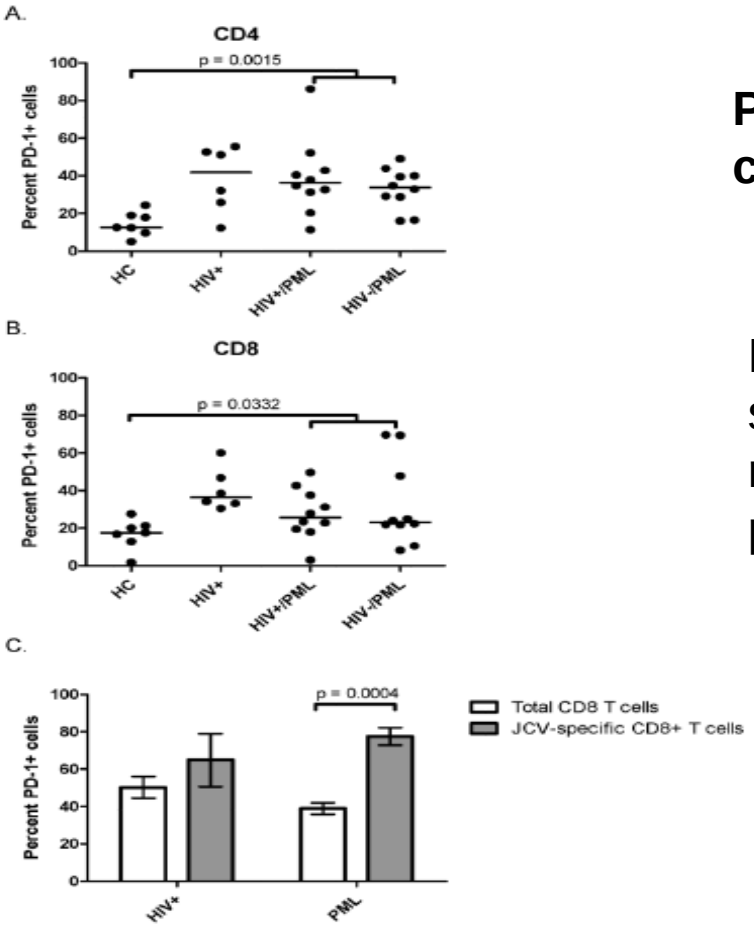
Durata del Trattamento con natalizumab	Valori stimati del rischio di PML su 1.000 pazienti				
	Pazienti senza precedente uso di immunosoppressori				Pazienti con precedente uso di immunosoppressori
	Nessun valore di Index	Index anticorpale ≤ 0,9	Index anticorpale >0,9 ≤ 1,5	Index anticorpale >1,5	
1-12 mesi	0,1	0,1	0,1	0,2	0,3
13-24 mesi	0,6	0,1	0,3	0,9	0,4
25-36 mesi	2	0,2	0,8	3	4
37-48 mesi	4	0,4	2	7	8
49-60 mesi	5	0,5	2	8	8
61-72 mesi	6	0,6	3	10	6

Ho et al Risk of natalizumab associated progressive multifocal leukoencephalopathy in multiple sclerosis patients: analysis from four large clinical studies. Lancet Neurology 2017

J Acquir Immune Defic Syndr. 2012 July 1; 60(3): 244–248. doi:10.1097/QAI.0b013e31825a313c.

Increased Program Cell Death - 1 (PD-1) Expression on T Lymphocytes of Patients with Progressive Multifocal Leukoencephalopathy (PML)

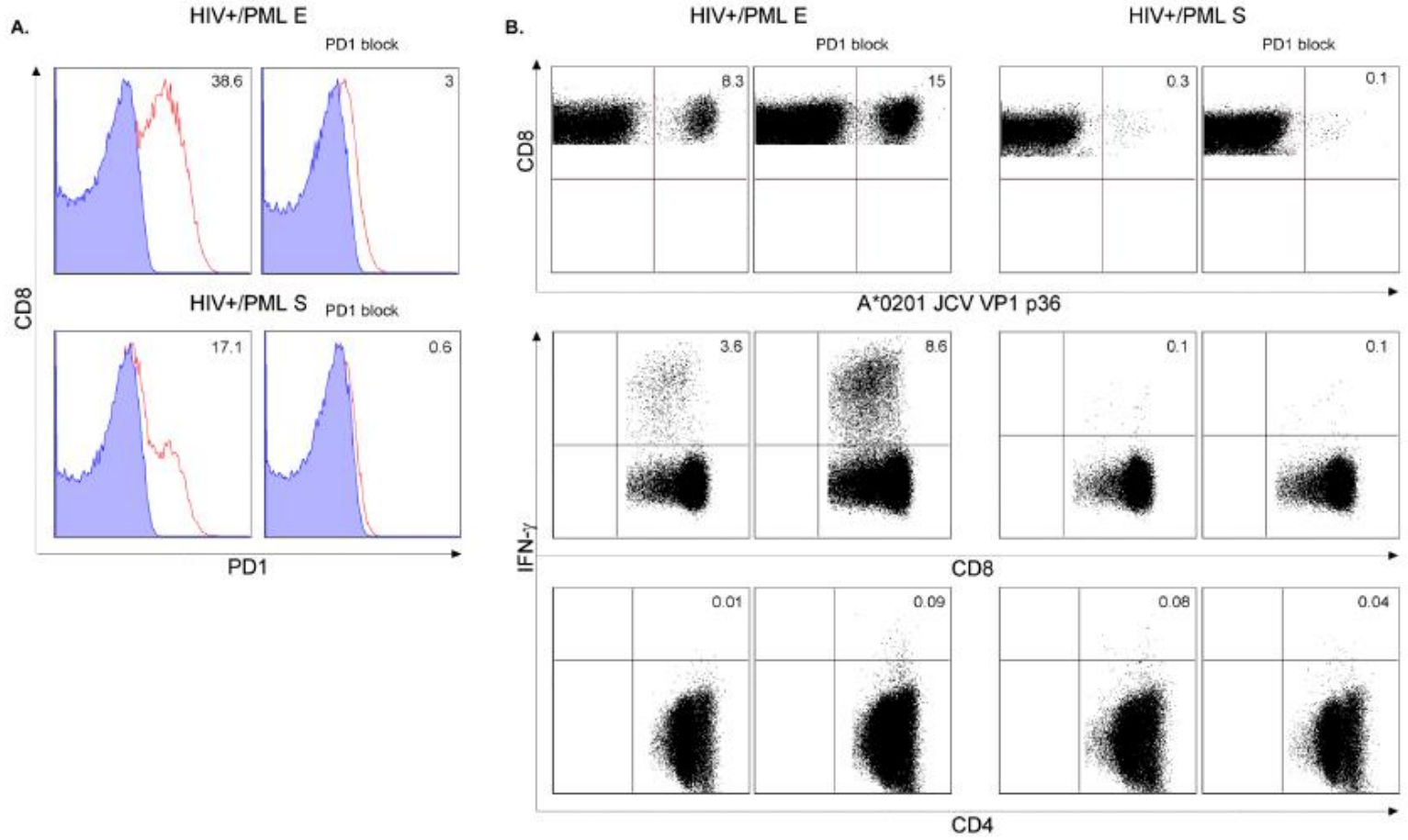
Chen Sabrina Tan[1,2,3], Evelyn Bord[2,3], Thomas A Broge Jr[2,3], Brett Glotzbecker[4,5], Heidi Mills[4,5], Sarah Gheuens[2,3], Jacalyn Rosenblatt[4,5], David Avigan[4,5], and Igor J Koralnik[2,3]



Percentage of PD-1+ CD4+ and CD8+ T-cells in PML patients and controls

Blocking PD-1 receptors increased JCV-specific CTL response to JCV VP1-p36 restricted by HLA A*0201 in a PML early patient but not in a PML survivor

JCV-specific T-cell response can be augmented by blocking PD-1 in some patients



PML patients with and without HIV have significantly elevated median PD-1 expression on CD4+ T-cells (A) and CD8+ T-cells (B) compared to healthy controls

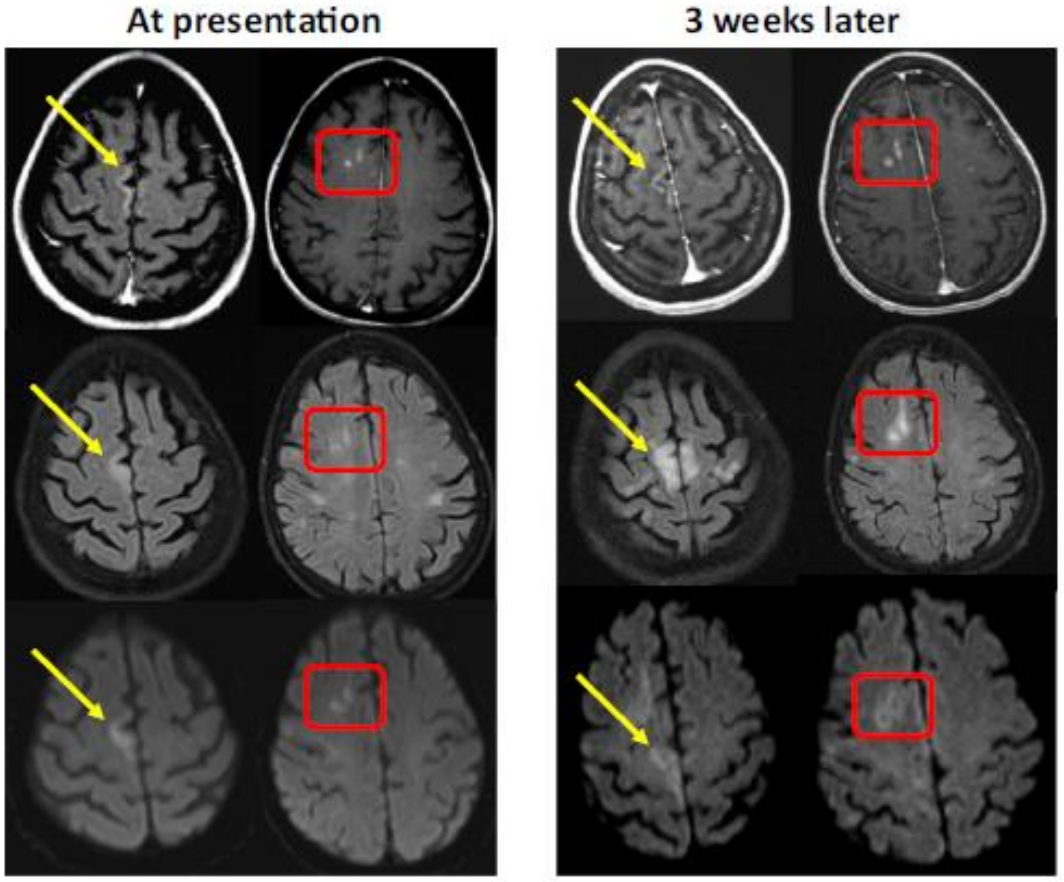
Journal of NeuroVirology (2019) 25:284–287
https://doi.org/10.1007/s13365-019-00738-x

CASE REPORT

Progressive multifocal leukoencephalopathy treated with nivolumab

Ethan Hoang[1] · Nancy L. Bartlett[2] · Manu S. Goyal[1,3] · Robert E. Schmidt[4] · David B. Clifford[1]

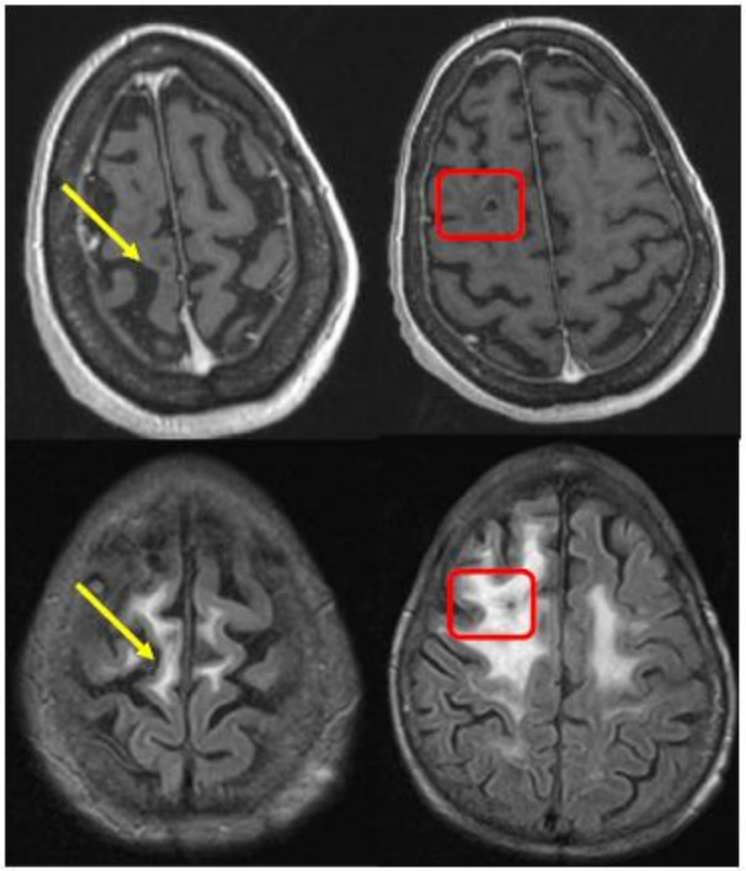
Routine brain MRI including pre- and post-contrast T1 , T2, FLAIR with fat suppression, and DWI sequences



At presentation, several enhancing lesions associated with FLAIR hyperintensity and diffusion restriction

Expansion of all of the lesions

Brain MRI findings 1 year after diagnosis



The previously noted lesions had all evolved such that there was no residual enhancement or diffusion restriction (yellow arrow and red square). In its place were areas of FLAIR hyperintensity (bottom row) and T1 hypointensity (top row), likely reflecting regions of gliosis.

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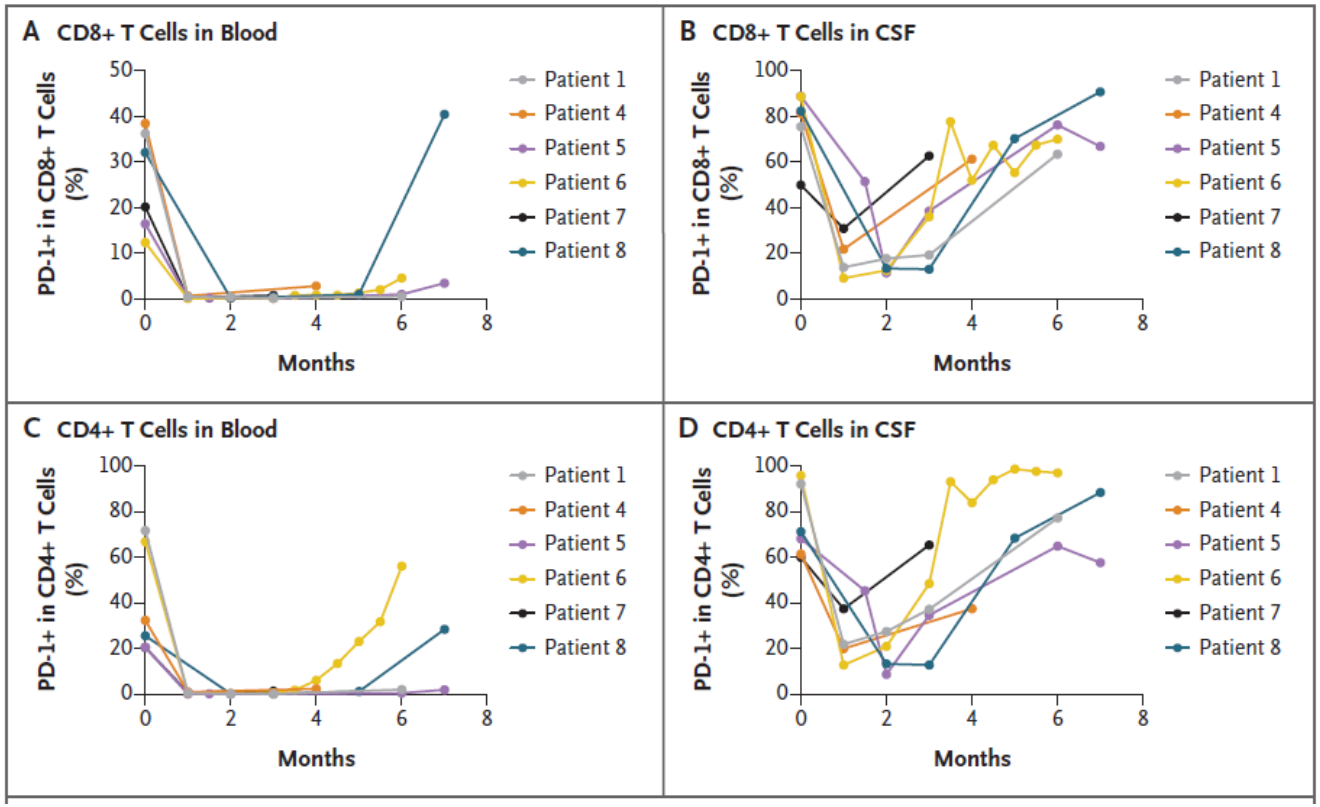
Pembrolizumab Treatment for Progressive Multifocal Leukoencephalopathy

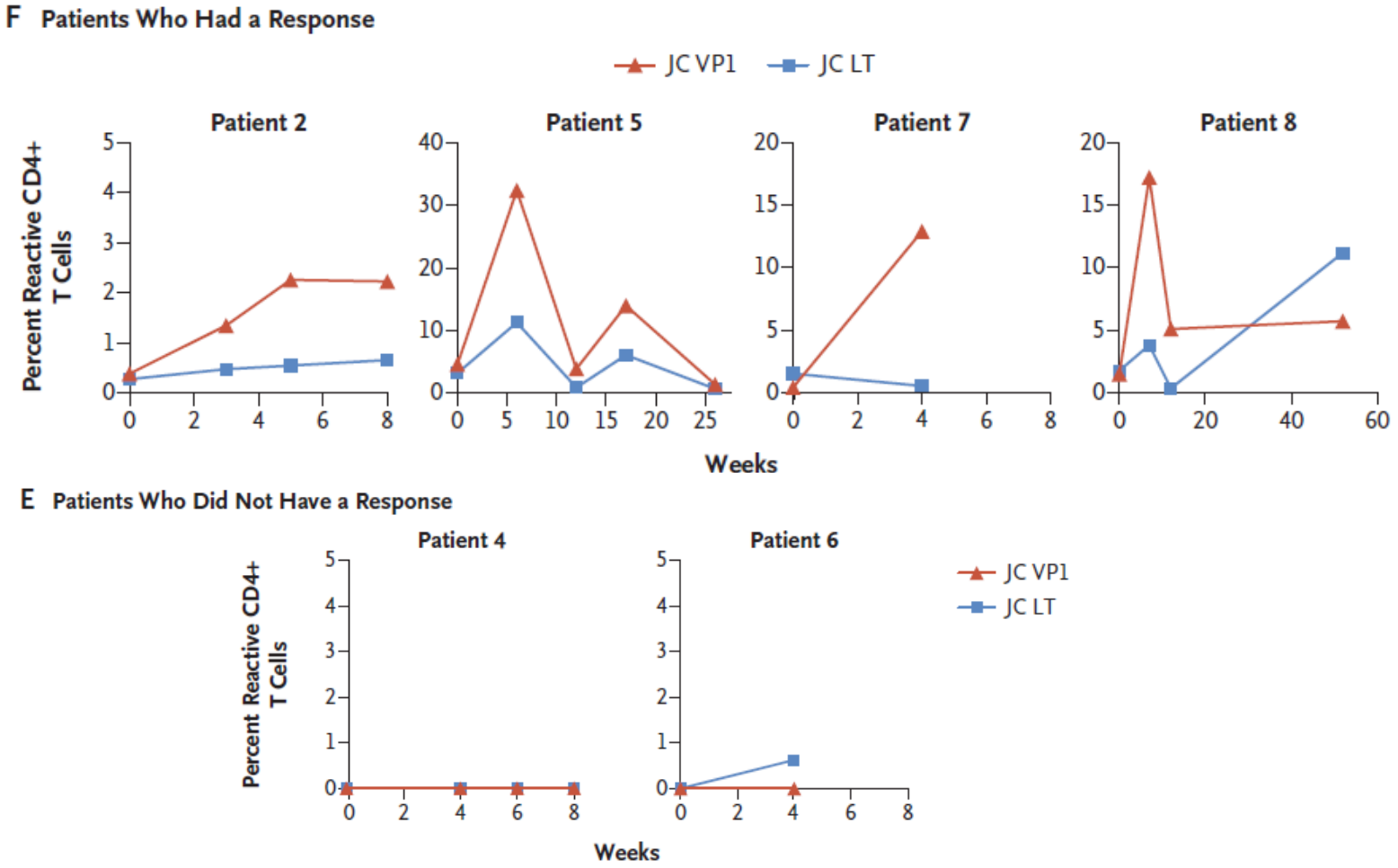
Irene Cortese, M.D., Pawel Muranski, M.D., Yoshimi Enose-Akahata, Ph.D., Seung-Kwon Ha, D.V.M., Ph.D., Bryan Smith, M.D., MariaChiara Monaco, Ph.D., Caroline Ryschkewitsch, B.S., Eugene O. Major, Ph.D., Joan Ohayon, M.S.N., Matthew K. Schindler, M.D., Ph.D., Erin Beck, M.D., Ph.D., Lauren B. Reoma, M.D., Steve Jacobson, Ph.D., Daniel S. Reich, M.D., Ph.D., and Avindra Nath, M.D.

PD-1 Expression and Antiviral Immune Responses after Treatment with Pembrolizumab



Percentage of PD-1+ in CD8+ T cells in blood and in CSF and percentage of PD-1+ in CD4+ T cells in blood and in CSF after treatment with pembrolizumab (month 0).

Percentage of CD4+ T cells reactive to JC viral peptides VP1 and LT according to patient



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%)

Dati da Tabella 3, Rif. 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%)

Dati da Tabella 3, Rif. 2

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

Dati sulle displasie/patologie invasive HPV correlate negli studi analizzati per farmaco vs placebo

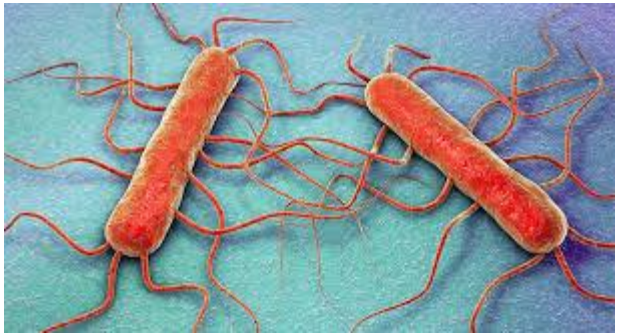
Farmaco	N pazienti	Displasie/ carcinomi	%	IC al 95%	p	OR (95%CI)
Alemtuzumab	1292 pts	7 casi	0.54%	0.2-1.2	**0.039**	**4.01 (1.17-13.73)**
Natalizumab	627	1 caso	0.16%	0.0-1.0	0.66	1.18 (0.13-10.55)
Teriflunomide	1230	2 casi	0.16%	0.0-0.7	0.81	1.2 (0.22-6.56)
Glatiramer	351	1 caso	0.28%	0.0-1.8	0.96	2.1(0.23-18.89)
DMF	1525	1 caso	0.07%	0.0-0.4	0.57	1.22 (0.08-19.51)
DAC	1336	1 caso	0.07%	0.0-0.5	0.85	0.48 (0.05-4.33)
IFN beta 1a	1422	1 caso	0.07%	0.1-0.5	0.9	0.52 (0.06-4.64)
Cladribina	884	1 caso	0.11%	0.0-0.7	0.71	0.83 (0.09-7.48)
Fingolimod	3130	1 caso	0.03%	0.0-0.0	0.34	0.23 (0.03-2.11)
Ocrelizumab	486	0 casi	0	0.0-1.0	0.92	0.67 (0.04-12.53)
Placebo	2950	4 casi	0.14%	0.0-0.4	reference	

HPV

- No data on the association between MS and the natural history of HPV infection and progression to pre-invasive and invasive forms are available.
- Referral to a gynecologist for cervical screening according to guidelines and adherence to the HPV vaccine proposal are recommended for all women at the diagnosis of MS.
- In patients with MS, data are insufficient to state that the use of the following DMDs exposes the patient to a higher risk of pre-invasive and invasive HPV-related diseases compared with placebo or alternative DMD: natalizumab, teriflunomide, glatiramer acetate, dimetilfumarate, IFN beta, cladribine, fingolimod, ocrelizumab. Therefore, a standard, age adjusted, HPV screening program, should be followed
- The reported higher prevalence of HPV related diseases in MS patients treated with alemtuzumab, despite lacks of evidence, suggests the recommendation of a specific HPV screening program

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.

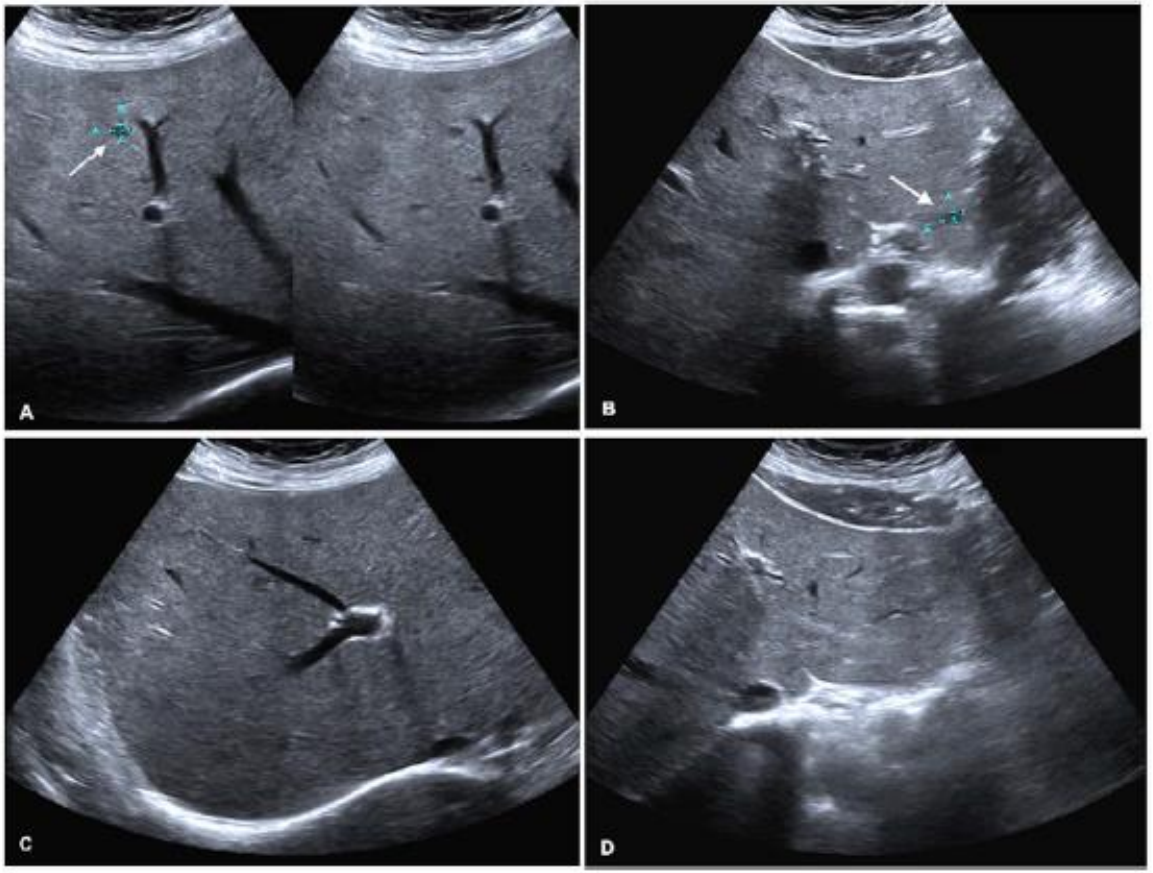


Rau D. et al. Int. J. Mol. Sci.2015

Characteristics of reported cases of listeriosis associated with alemtuzumab reported until February March 3, 2017

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

Hepatic microabscesses during CMV reactivation in a multiple sclerosis patient after alemtuzumab treatment



(A, B) small hypoechoic lesions in the liver, suggestive of multiple microabscesses
(C, D) no evidence of residual hypoechoic lesions after treatment with valganciclovir.

Stefania Barone et al. Multiple Sclerosis and Related Disorders 2018

Contents lists available at ScienceDirect

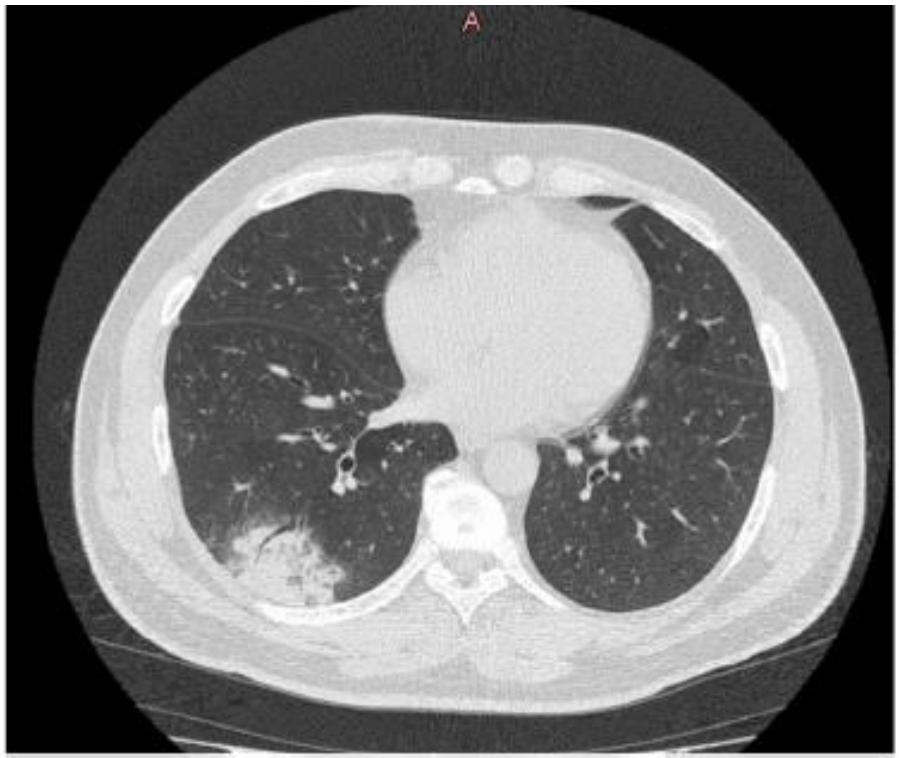
Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Case report

Bacterial and CMV pneumonia in a patient treated with alemtuzumab for multiple sclerosis

Antonio Riccardo Buonomo[a,*], Francesco Saccà[b], Emanuela Zappulo[a], Federico De Zottis[a], Roberta Lanzillo[b], Ivan Gentile[a], Antonio Carotenuto[b], Guglielmo Borgia[a], Cinzia Valeria Russo[b]



Further studies are needed to assess:

- the incidence of CMV reactivation in real-life setting
- the effective need of a close monitoring of serum CMV-DNA
- the indication and duration of maintenance therapy.

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)

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.

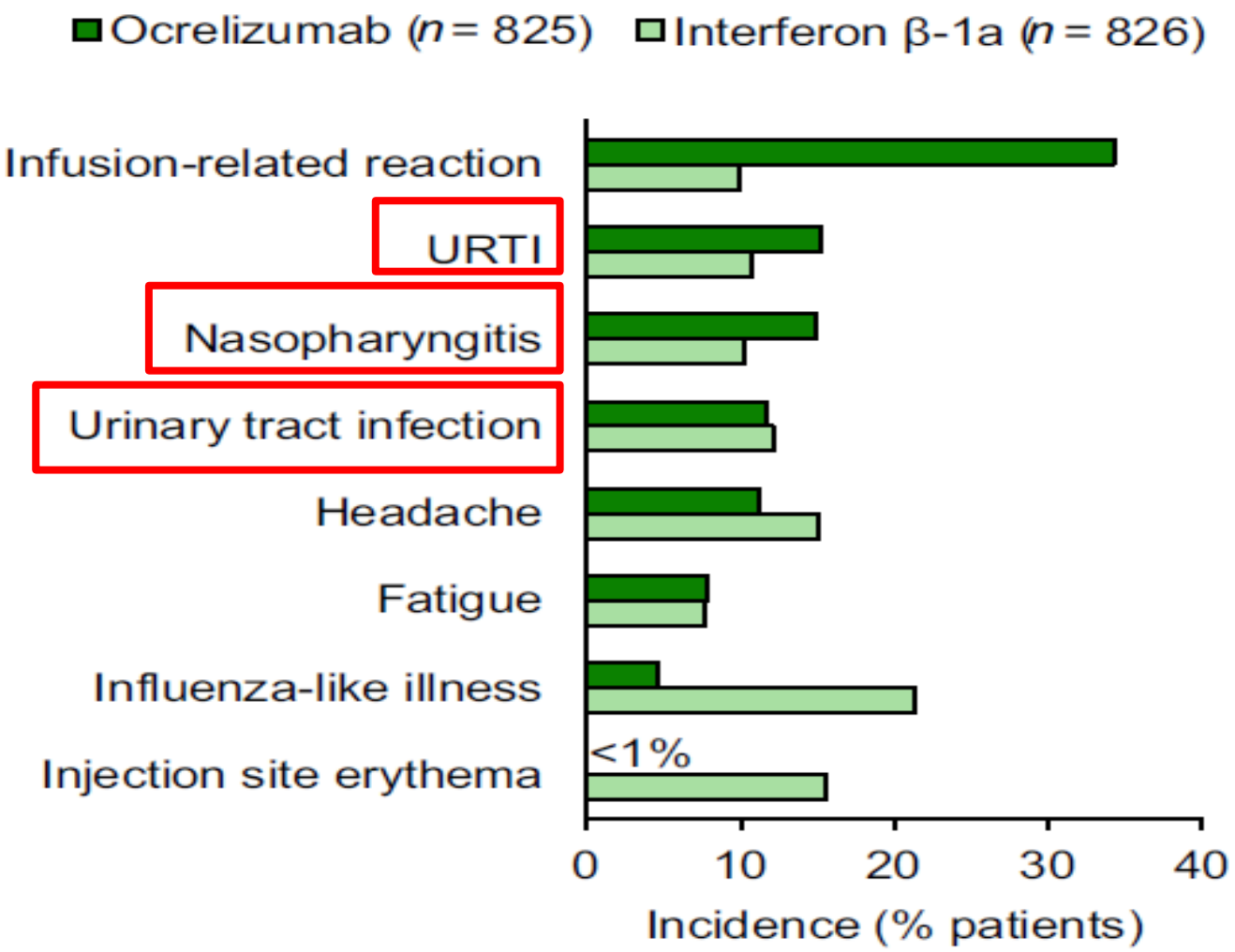
Eventi avversi a breve termine:

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

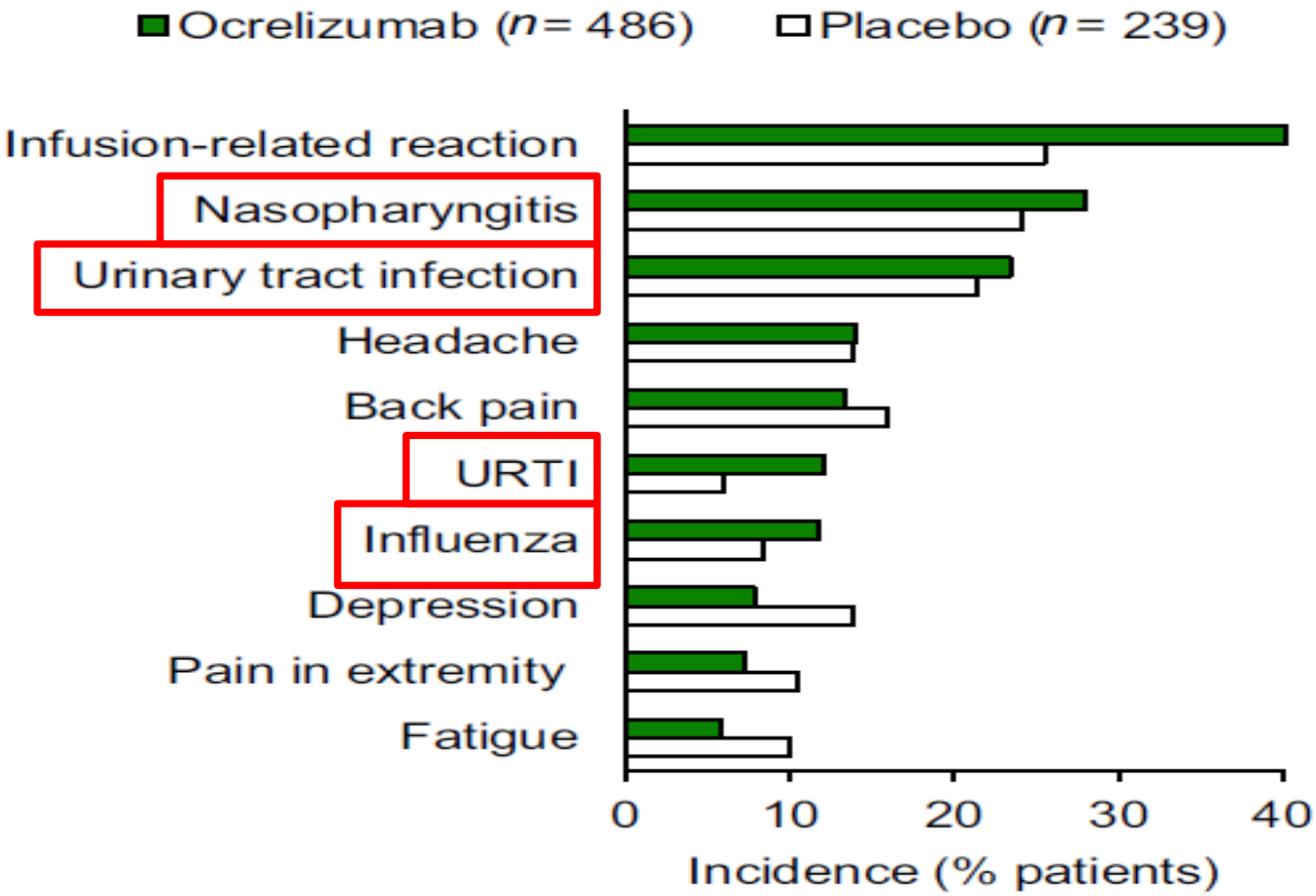
Eventi avversi a lungo termine :

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

Most common adverse events in patients with relapsing multiple sclerosis in a pooled analysis of the OPERA trials



Most common adverse events in patients with primary progressive multiple sclerosis in the ORATORIO trial



Herpes

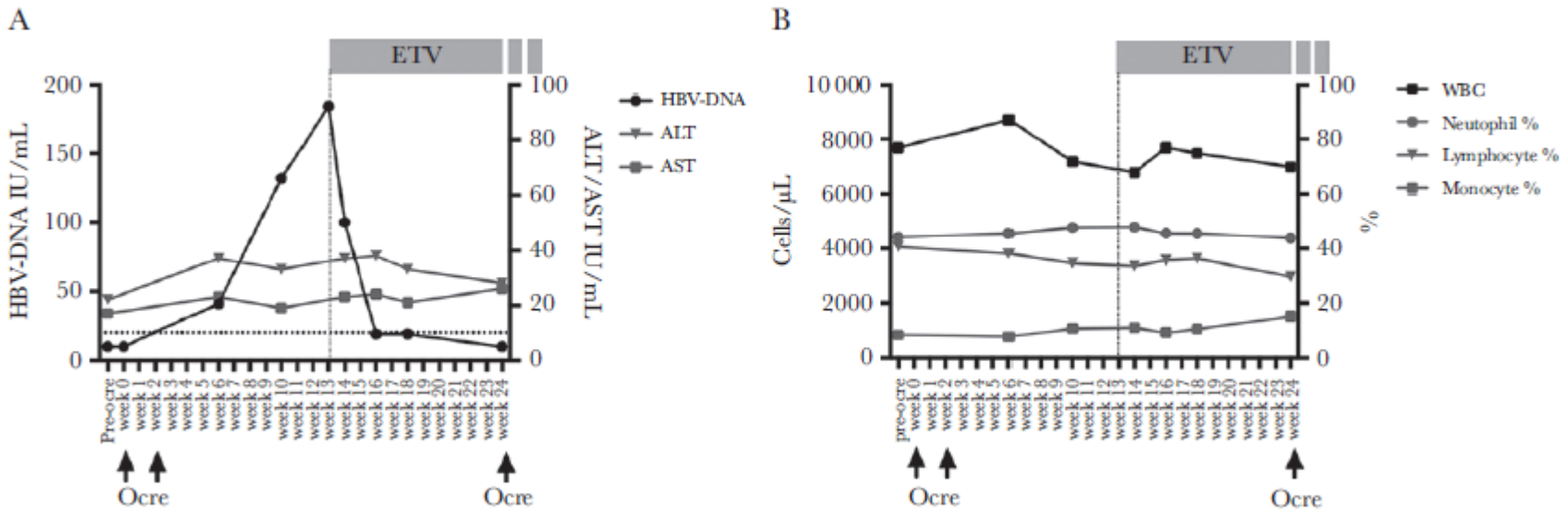
- In the OPERA I–II trials, the proportion of patients reporting herpesvirus-associated infections was 5.9% in the ocrelizumab group and 3.4% in the interferon beta-1a group.
- In the ORATORIO trial, herpesvirus infections (4.7% with ocrelizumab and 3.3% with placebo) and oral herpes were more common among patients who had received ocrelizumab than among those who had received placebo (2.3% *versus 0.4%); all* cases were mild to moderate.
- No opportunistic infections were reported in any study over the controlled treatment period.

Open Forum Infectious Diseases

ID CASE

Reactivation of Hepatitis B Virus With Immune-Escape Mutations After Ocrelizumab Treatment for Multiple Sclerosis

Maria R. Ciardi,[1] Marco Iannetta,[1] Maria A. Zingaropoli,[1] Romina Salpini[2] Marianna Aragri,[2] Rosanna Annecca,[3] Simona Pontecorvo,[3] Marta Altieri,[3] Gianluca Russo,[1] Valentina Svicher,[2] Claudio M. Mastroianni,[1] and Vincenzo Vullo[1]



Longitudinal evaluation of hepatitis B virus (HBV)–DNA, liver enzymes, and white blood cell counts before and after ocrelizumab treatment.

HBV-HCV

- No data are available regarding the intake of DMDs drugs for MS and the reactivation of HBV or HCV, as patients with evidence of HBV/HCV infections were excluded from clinical trials.

HBV-HCV

- All patients with MS should be screened for HBV/HCV infection at diagnosis and before any DMD is started. Screening should include: HBsAg, HBcAb, HBsAb and HCVAb. All patients positive for any of these markers should be referred to a specialist, with the exception of HBV vaccinated patient with isolated HBsAb reactivity.

HBV-HCV

- MS patients with acute or chronic HBV or HCV infections should be managed according to international guidelines (EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017; EASL 2018 Recommendations for the management of Hepatitis C J Hepatol 2018 in press)

Recommendations for Approach to Patients With Serologic Markers of HBV Infection by Drug

Drug	Risk of HBV Reactivation or Flare	HBsAg (+)	HBsAg (-) Anti-HBc (+)	Duration of Preemptive or Prophylactic Management
Natalizumab	Moderate	Prophylaxis	Prophylaxis or preemptive	During and for 6 mo after therapy
Alemtuzumab	High			
Ocrelizumab	Very high	Prophylaxis		During and for 12 mo after therapy
Mitoxantrone	Moderate	Prophylaxis	Prophylaxis or preemptive	During and for 6 mo after therapy
Fingolimod	Low	Prophylaxis or preemptive	Preemptive or periodic LFT monitoring	During and for 6 mo after therapy
Dimethyl fumarate	Low			
Teriflunomide	Low			

Abbreviations: anti-HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LFT, liver function test.

Cladribine: overview of infections occurring during treatment period *(all-exposed cohort)*

Pooled data cohort comprised 1976 patients treated with cladribine and 802 treated with placebo

Total infections and infestations[1]	**Cladribine** 27.12 per 100 patient-years **Placebo** 31.44 per 100 patient-years	**No increase in risk**
Serious or severe infections1	**Cladribine** 1.25 per 100 patient-years **Placebo** 1.08 per 100 patient-years	**0.17 additional infections per 100 patient-years**
Localized herpetic infections[b,1]	**Cladribine** 1.14 per 100 patient-years **Placebo** 0.25 per 100 patient-years	**90%** of pts (86/95) who had herpes zoster events → **non-severe episodes**

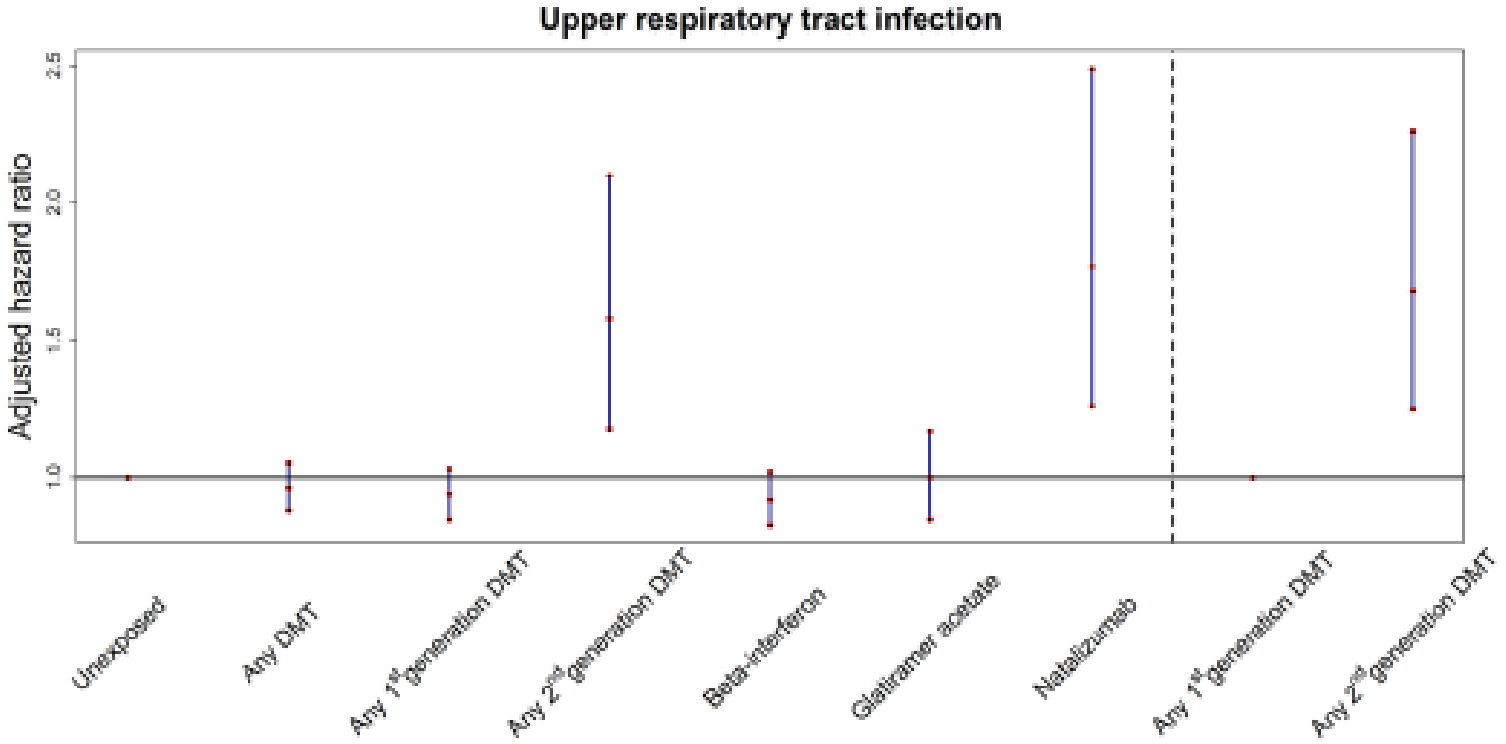
[a]All-exposed cohort: cladribine 8650 patient-years; placebo 2361 patient-years; maximum follow-up; oral, intravenous and subcutaneous routes of administration are included; [b]Values presented are those for system organ class infections and infestations for the preferred term herpes zoster in the all-exposed cohort. All values quoted are adjusted adverse event rates. [c]In clinical studies, events of malignancies were observed more frequently in cladribine-treated patients compared to patients who received placebo[2]

1. Cook S et al. ECTRIMS 2016 [Poster P635; Abstract 552]; 2. MAVENCLAD® EU SmPC, 2017

RESEARCH PAPER

Disease-modifying drugs for multiple sclerosis and infection risk: a cohort study

José Maria Andreas Wijnands,[1] Feng Zhu,[1] Elaine Kingwell,[1] John David Fisk,[2] Charity Evans,[3] Ruth Ann Marrie,[4,5] Yinshan Zhao,[1] Helen Tremlett[1]

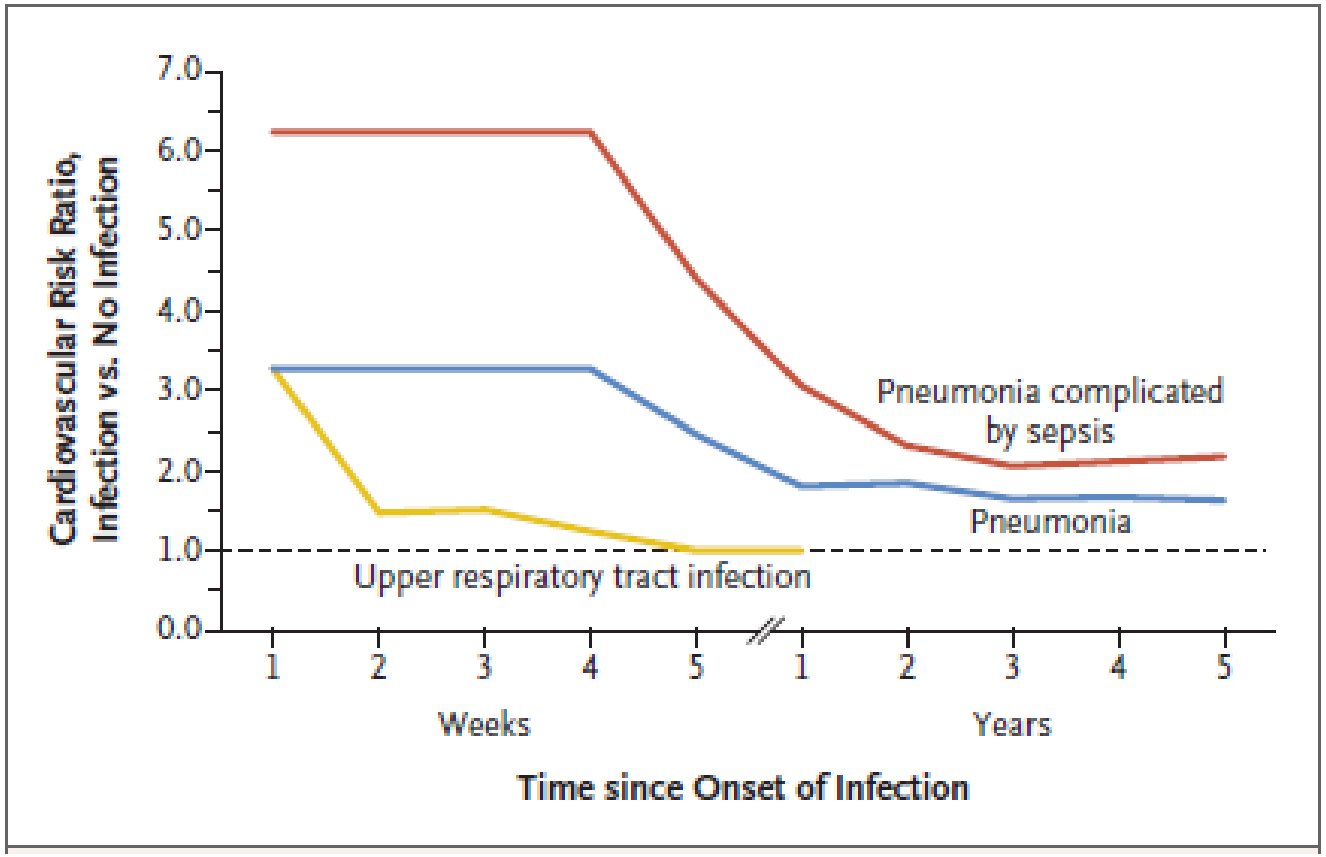


Adjusted HRs and 95% CIs for physician claims for specific infections by multiple sclerosis disease-modifying treatment

Dan L. Longo, M.D., *Editor* The NEW ENGLAND JOURNAL of MEDICINE

Acute Infection and Myocardial Infarction

Daniel M. Musher, M.D., Michael S. Abers, M.D.,
and Vicente F. Corrales-Medina, M.D.



Temporal Pattern of Cardiovascular Risk after the Onset of Acute Infection

Cardiovascular Risk and vaccination

- A meta-analysis of five randomized trials showed a 36% lower risk of a composite of cardiovascular events among adults who had received influenza vaccine than among those who had not.
- The benefit was even greater when the analysis was limited to persons with known coronary artery disease.
- In contrast, there are limited data from randomized trials regarding the effect of pneumococcal vaccination on cardiovascular risk.
- A meta-analysis of eight observational studies showed a 17% lower risk of myocardial infarction among patients 65 years of age or older who had received pneumococcal polysaccharide vaccine than among those who had not.

Recommendations for infectious disease screening in migrants to Western Europe with inflammatory arthropathies before starting biologic agents. Results from a multidisciplinary task force of four European societies (SIR, SER, SIMET, SEMTSI) facing the largest impact of the flow of migrants today

F. Bartalesi[1], C.A. Scirè[2], A. Requena-Méndez[3], M.A. Abad[4], D. Buonfrate[5], R. Caporali[6], F. Conti[7], F. Diaz-Gonzalez[8], C. Fernández-Espartero[9], C. Martinez-Fernandez[10], M. Mascarello[11], E. Generali[12], G. Minisola[12], A. Morrone[13], J. Muñoz[3], P. Richi[14], G. Sakellariou[6], J. Salas Coronas[14], M. Spinicci[1], F. Castelli[15], A. Bartoloni[1], Z. Bisoffi[5], F. Gimenez-Sanchez[16], S. Muñoz-Fernández[14], M. Matucci-Cerinic[17]

Clinical and Experimental Rheumatology 2017; **35**: 752-765.

List of latent infection considered by the panel of expert for recommendation

Disease	Screening	Candidates for screening	Available tests
Mycobacterial diseases			
Hansen's diseases	No		None
Non-TB mycobacteria	No		None
MDR-TB	Yes	All patients[§]	TST/IGRAs
Bacterials diseases			
Brucellosis	No		Serology
Salmonellosis (typhi/paratyphi)	Yes	Patients from highly endemic areas with cholelithiasis/urinary tract defect	Stool and urine cultures
Parasitic diseases			
Leishmaniasis	No		Serology, PCR
Babesiosis	No		Blood smears, serology, PCR
Strongyloidiasis	Yes	Migrants from endemic areas and autochthonous patients with eosinophilia	Serology and stool test if available
Cysticercosis	No		Serology
Chagas disease	Yes	Patients from/whose mother was born in/blood transfused in endemic area	Serology
Viral diseases			
HEV	No		Serology, PCR
HTLV-1	No		Serology, PCR
Fungal diseases			
Histoplasmosis	Yes	Patients from endemic areas with suggestive history/radiological signs	Serology
Coccidioidomycosis	Yes	Patients from endemic areas and compatible clinical symptoms/history	Serology
Paracoccidioidomycosis	No		Serology

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, consider 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
- Zoster
- Measles

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

STATEMENT 4

We infer that interferon beta (IFNB) does not affect the response to influenza vaccination, with limitations due to the observational nature of studies and small sample sizes.

STATEMENT 5

Conclusions are difficult to be drawn on glatiramer acetate, ocrelizumab, dimethyl fumarate, teriflunomide, natalizumab, fingolimod, alemtuzumab, daclizumab, and cladribine.

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