Registre Lorrain des Scléroses en Plaques

ReLSEP

Rapport d'activité 2020

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Introduction

a. Environnement du registre

Le Registre Lorrain des SEP a été qualifié par le Comité National des Registres le 24 novembre 2009. Sa qualification a été renouvelée le 10 novembre 2016 pour une durée de 5 ans par le Comité d'Evaluation des Registres. Il s'agit du seul registre national pour cette maladie et du seul registre avec des données médicales de suivi, à l'exception des registres scandinaves.
Le registre est situé au Centre d'Epidémiologie Clinique (INSERM CIC-EC CIC 1433) du CHRU de Nancy qui assure l'hébergement de la base de données, sa gestion, son exploitation scientifique, la formation et le recrutement des Infirmières de Recherche Clinique et des Techniciens d'Etudes Cliniques (IRC/TEC) qui s'engagent à respecter les principes de confidentialité tels que définis en conformité avec l'autorisation de la CNIL (avis n° 913001) et du CCTIRS (dossier 10.258).

b. Objectifs du registre

Les objectifs du registre se déclinent en objectifs de surveillance, notamment de mesure de l'incidence et de la prévalence de la maladie sur le territoire lorrain et d'objectifs de recherche, s'appuyant sur les données de la cohorte.

Objectifs de Santé publique

- Estimer l'incidence de la SEP en Lorraine
- Surveiller l'évolution de l'incidence de la SEP en Lorraine
- Confirmer ou infirmer une possible augmentation différentielle de l'incidence selon le sexe (notamment chez les femmes)
- Donner aux autorités médico-administratives les moyens de planifier les futurs besoins en soins
- Donner aux autorités médico-administratives les moyens de planifier les futurs besoins sociaux utiles à la prise en charge de cette pathologie, notamment en ce qui concerne les conséquences des incapacités fonctionnelles.

Objectifs de Recherche

- Proposer des explications à ce changement d'incidence
- Estimer la prévalence de la SEP en Lorraine
- Suivre le changement des niveaux d'invalidité avec l'émergence des nouvelles thérapeutiques spécifiques à la SEP
- Etudier les facteurs pronostiques de l'invalidité, de la prise en charge
- Déterminer les facteurs prédictifs de symptômes spécifiques comme la fatigue et de la santé perçue (qualité de vie)

L'intérêt du registre et du suivi des cas incidents (exhaustif ou sur échantillon représentatif) est de permettre de développer à la fois des travaux d'épidémiologie générale et d'épidémiologie clinique.

c. Système d'information

Le Logiciel EDMUS (European Database of Multiple Sclerosis : Confavreux et al. J Neurol.Neurosurg.Psychiatry 1992 ; 55 : 671-676.) est l'outil de recueil des informations cliniques des patients atteints de Scléroses en Plaques notifiés.

Ce logiciel est largement utilisé dans la communauté neurologique dans de nombreux centres français et européens. L'adoption d'un langage commun pour la description médicale des patients atteints de SEP est d'une grande utilité.
En mettant en exergue les informations décisives et pertinentes, elle facilite le suivi médical et l'échange des informations entre médecins. EDMUS a déjà largement contribué à la réalisation d'études internationales largement reconnues et publiées dans les meilleures revues neurologiques et généralistes. EDMUS a permis d'aboutir à un consensus sur le langage commun à adopter (définitions, dénominations, classifications), la nature des données à incorporer et les caractéristiques techniques de base du programme à développer.

Chapitre I. Etat d'avancement du recueil et validation des cas

I.1. Sources d'identification des cas

La démarche d'identification des cas a été mise en place à l'occasion de l'étude EPISEP (avis favorable du CCTIRS le 12 février 2009, dossier 08.575bis, autorisation CNIL du 29 juin 2009, dossier 909089), étude de capture-recapture, organisée pour estimer l'exhaustivité du registre. L'autorisation CNIL a été mise à jour en 2014 (autorisation du 6 janvier 2014, avis n° 913001) permettant notamment d'inclure la caisse nationale militaire de sécurité sociale comme source pour l'année 2015.

Table I.2.1Bis. Sources sollicitées

Strucure « source »	Nombre de sources	Sollicitations	Mode de consultation	Rythme de consultation	1ère année de consultation
Neurologues	15 services hospitaliers	15	Visite sur place	Selon les critères tous les 1,5 ans (jusqu'à une fois par semaine)	1996
	28 neurologues libéraux	28			2003
Etablissements de soins	909 Hôpitaux publics	888	Demande de liste	Annuel	2011
	91 Cliniques privées	90			2011
	37 MPR	34			2011
Caisse d'Assurance Maladie	2 régimes généraux + spéciaux	Nord-Est	Demande de liste	Annuel	2012
		Alsace-Moselle			2012
		RSI			2011
		MSA			2014
		CNMSS			2014
ATIH	1	1	Demande de liste	Annuel	2013
Laboratoires de biologie médicale spécialisés	Nancy	1	Demande de liste	Annuel	2015
	Metz Thionville	1			2013
Réseau LORSEP	1	1	CODRI, Consentement, ETP, Liste, Nouveaux patients, Nouvelles adresses, e-mail	Echanges réguliers	2003
Réseau alSacEP	1	1	Demande de liste	Annuel	2013

Source = ReLSEP
Date d'extraction = 01/01/2021

I.2. Qualité de l'information recueillie – Exhaustivité

Tous les neurologues de la région, qui sont par ailleurs impliqués dans le réseau LORSEP (Réseau Lorrain pour la prise en charge de la Sclérose en plaques), participent au registre Lorrain des SEP et s'engagent à prendre part et respecter une procédure de démarche qualité. L'identification de cas résidents en Lorraine et suivi et/ou diagnostiqués est étendue aux départements limitrophes.
En pratique, des IRC/TEC ont pour mission d'intégrer les données médicales et démographiques dans la base du registre à partir des dossiers des neurologues de la région et de faire valider les données par ceux-ci.

Ils se déplacent chez les neurologues qui mettent systématiquement de côté tous les dossiers de cas porteurs de SEP. Une feuille de consentement validée par le CCTIRS est signée par chaque cas en vue de la notification au registre.
Lorsque cela est nécessaire les dossiers dont le diagnostic de SEP n'est pas clairement défini sont revus par un neurologue responsable de la qualité des données, le Dr Guillaume Mathey.
La cohérence globale du dossier, la qualité des données est revue et discutée avec les IRC/TEC et, si nécessaire, directement avec le neurologue.

Concernant les sources médico-administratives, les laboratoires, et le réseau LORSEP, tout cas potentiel retrouvé fait l'objet d'une procédure de dédoublonnage par rapport à la base EDMUS, et pour les suspicions de cas identifiés par ces sources, un retour au dossier source est réalisé.

Le ReLSEP, hébergé au CIC-EC, en suit les procédures qualité : contrôle de qualité, bonnes pratiques épidémiologiques, intégrées dans une démarche qualité (manuel qualité général, et procédures spécifiques par projet).

I.3. Résultats

I.3.i. Incidence

Les résultats d'incidence sont présentés pour les années n-5, soit 2015 et antérieures, délai jugé nécessaire pour obtenir des estimations fiables en raison de délai diagnostique parfois long après les tout premiers symptômes. Les données ont été extraites au 01/01/2021.

Table I.3.2. Nombre de nouveaux cas et population résidente par an en Lorraine

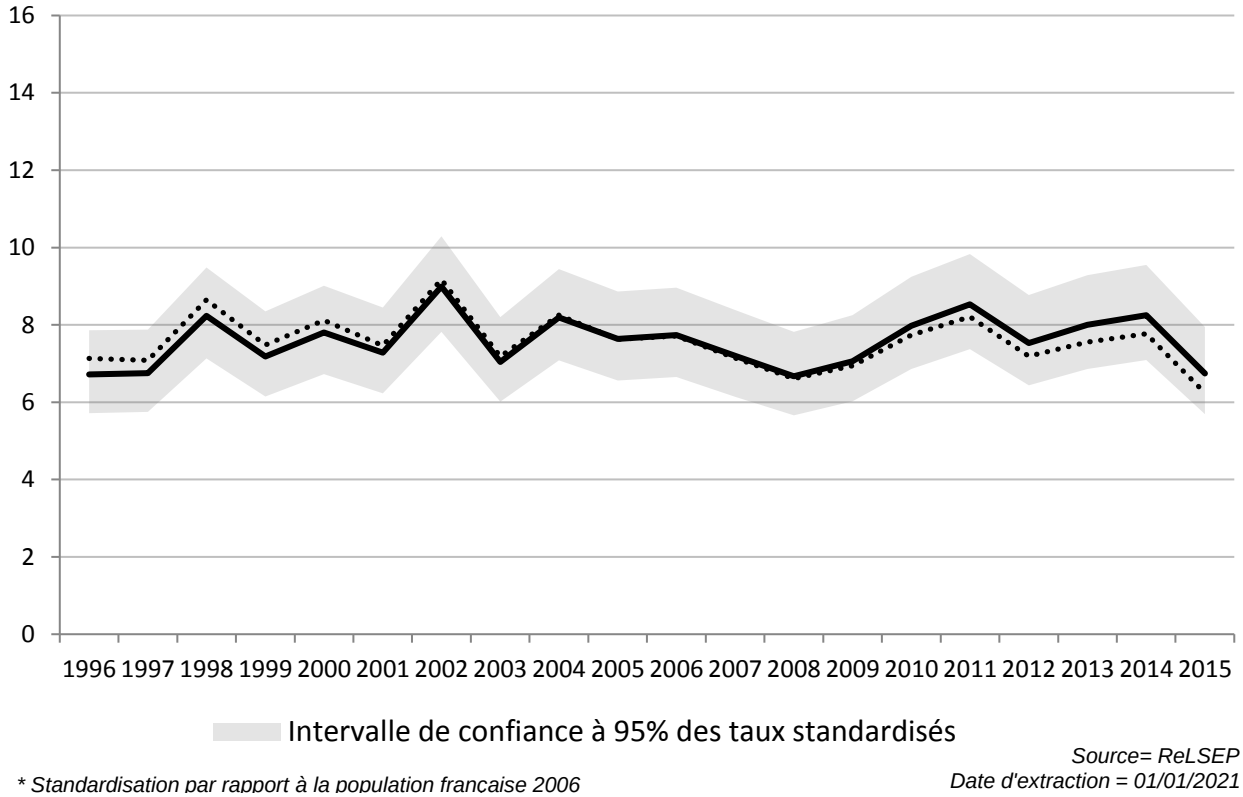
	Cas incidents	Population résidente
1996	165	2 315 782
1997	164	2 316 244
1998	200	2 312 566
1999	173	2 311 655
2000	188	2 314 909
2001	173	2 318 791
2002	213	2 323 026
2003	167	2 326 019
2004	192	2 328 136
2005	178	2 332 468
2006	180	2 335 749
2007	167	2 339 881
2008	155	2 346 361
2009	163	2 350 112
2010	182	2 350 920
2011	193	2 350 657
2012	169	2 349 816
2013	177	2 345 197
2014	182	2 342 397
2015	146	2 341 531

Source = ReLSEP
Date d'extraction = 01/01/2021

➢ Evolution de l'incidence

- **Incidence globale standardisée sur la population française 2006**

Fig 1. Evolution du taux d'incidence standardisée*(10^{-5} habitants) par année

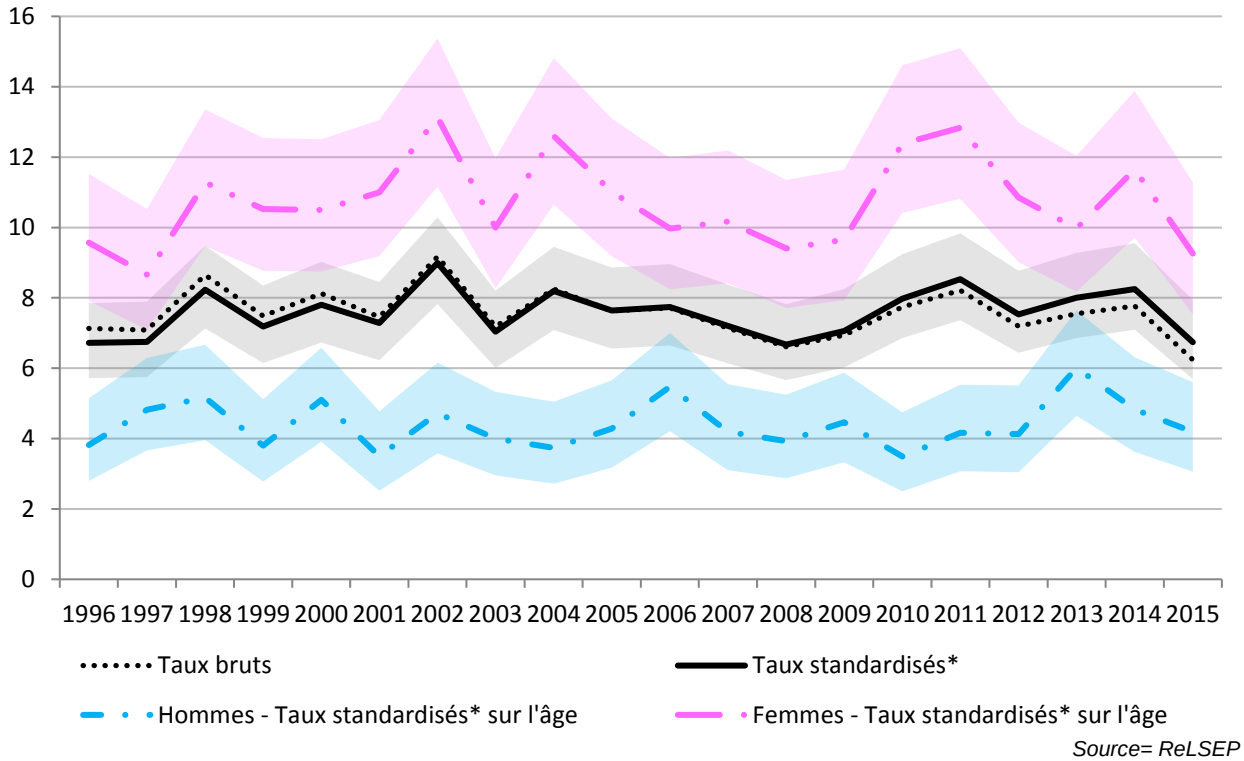


Source= ReLSEP
Date d'extraction = 01/01/2021

** Standardisation par rapport à la population française 2006*

- **Incidence spécifique**

Fig 2. Evolution du taux d'incidence standardisée*(10-5 habitants) sur l'âge et le sexe par année

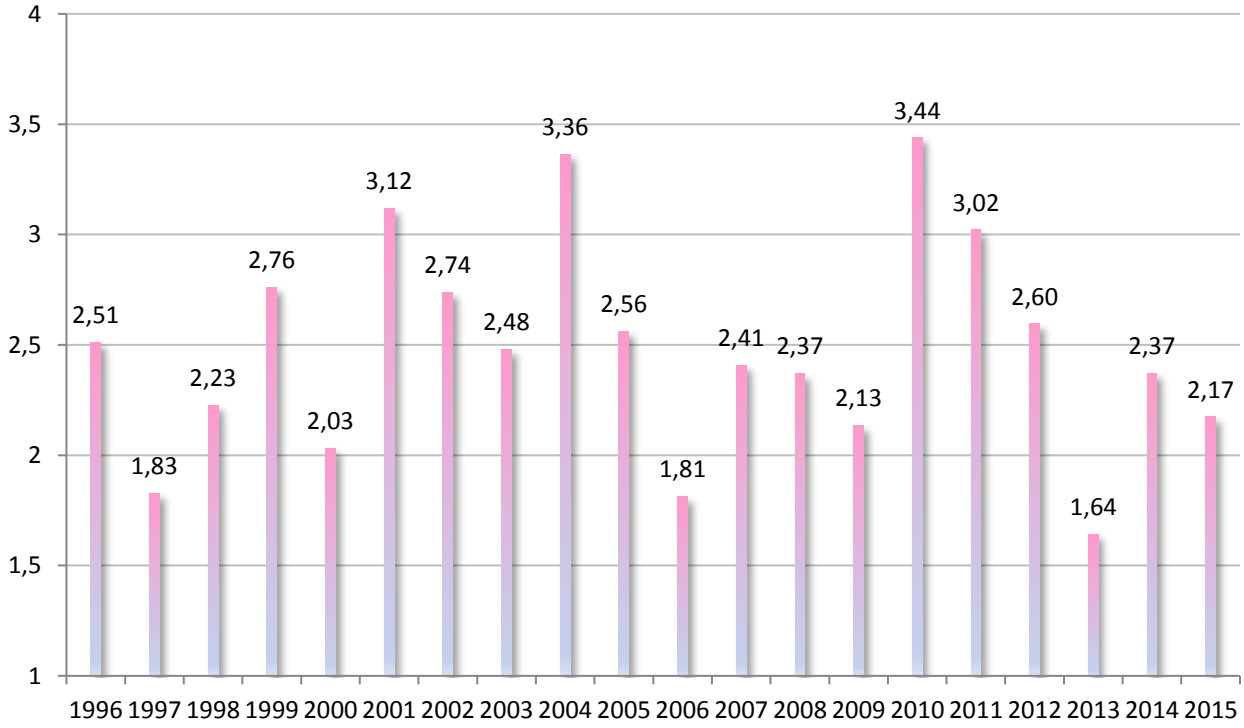


Source= ReLSEP
Date d'extraction = 01/01/2021

** Standardisation par rapport à la population française 2006*

- **Caractéristiques des cas**
- **Sex ratio - cas incidents**

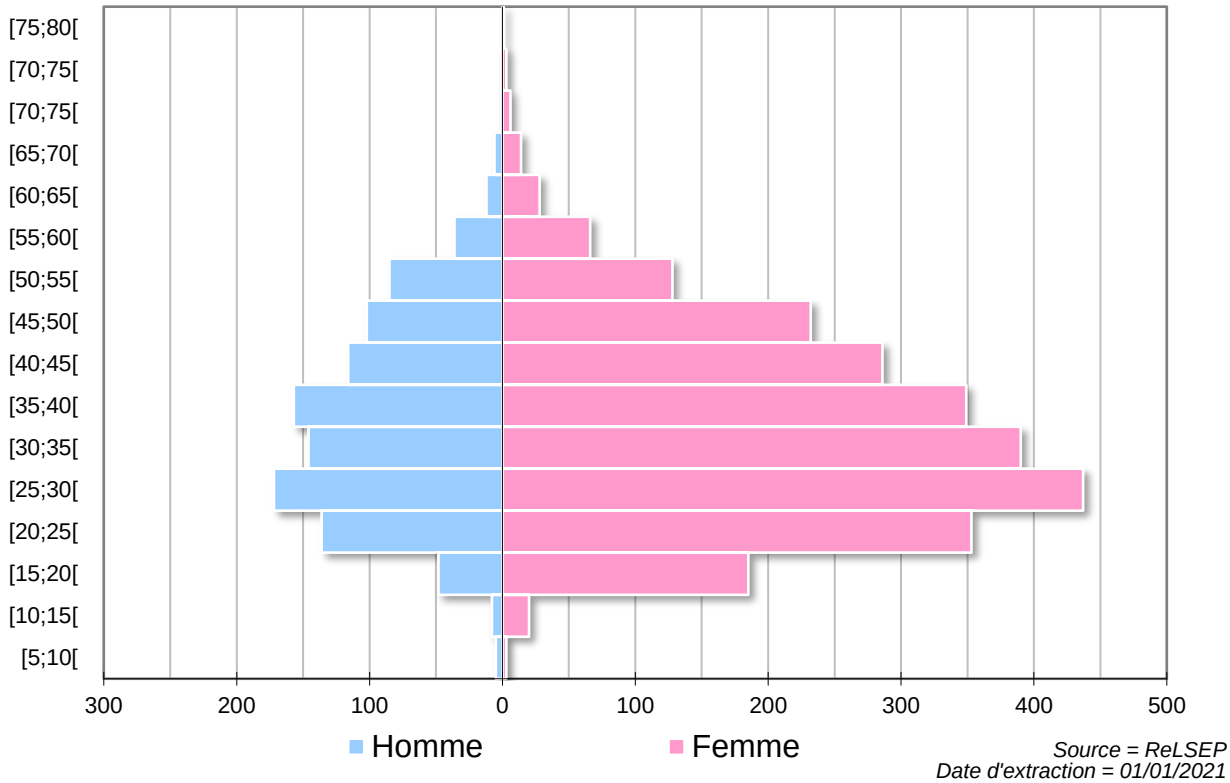
Fig 3. Sexe ratio Femme/Homme



Source = ReLSEP
Date d'extraction = 01/01/2021

- **Pyramide des âges - cas incidents**

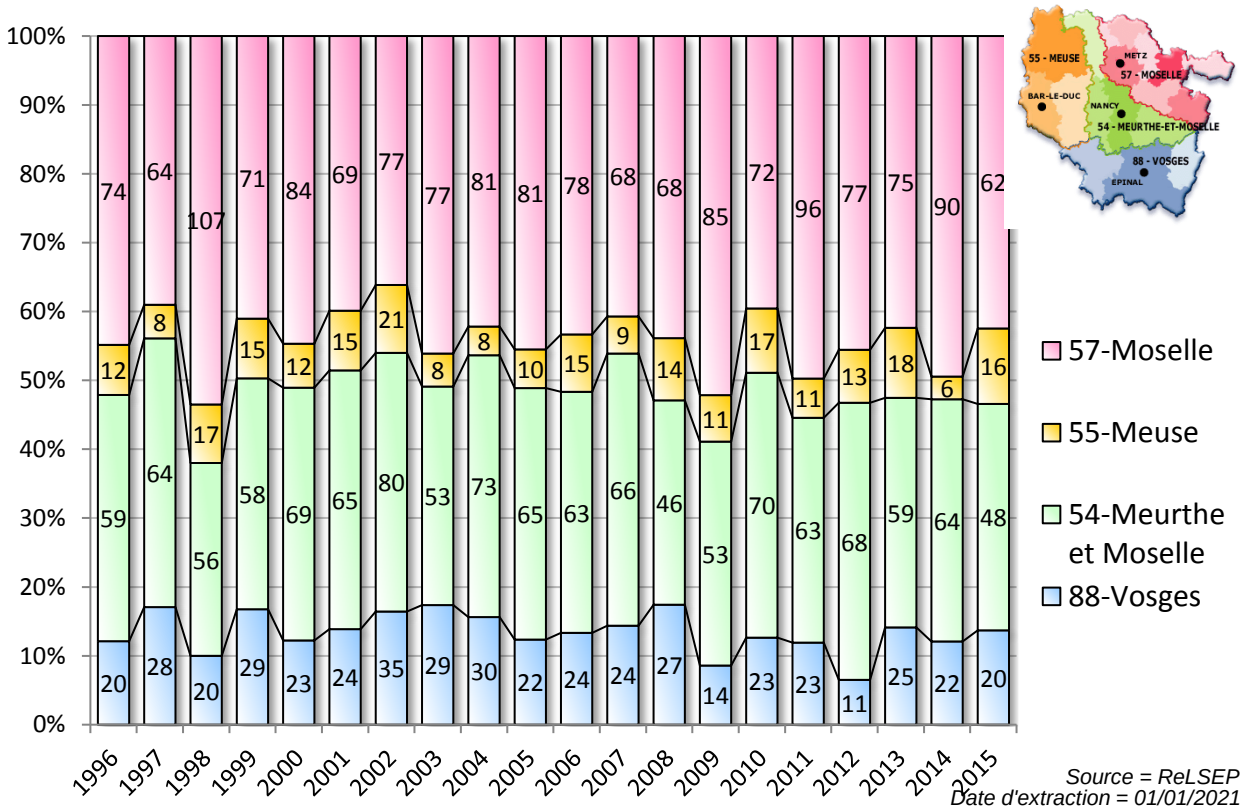
Fig 4. Pyramide des âges à l'incidence



Source = ReLSEP
Date d'extraction = 01/01/2021

- **Répartition du département de résidence au moment de l'incidence**

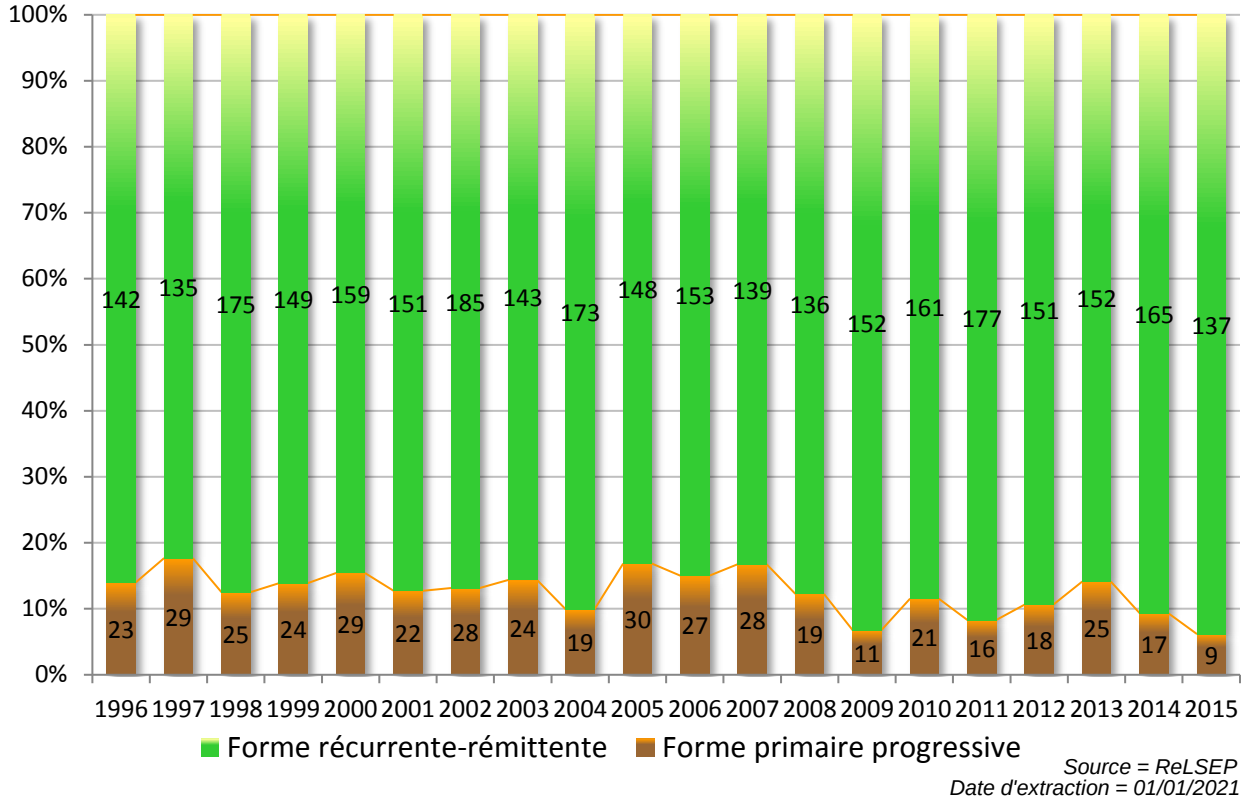
Fig 5. Cas incidents par département



Source = ReLSEP
Date d'extraction = 01/01/2021

- **Caractéristiques de la maladie**
- **Forme de la SEP au moment de l'incidence**

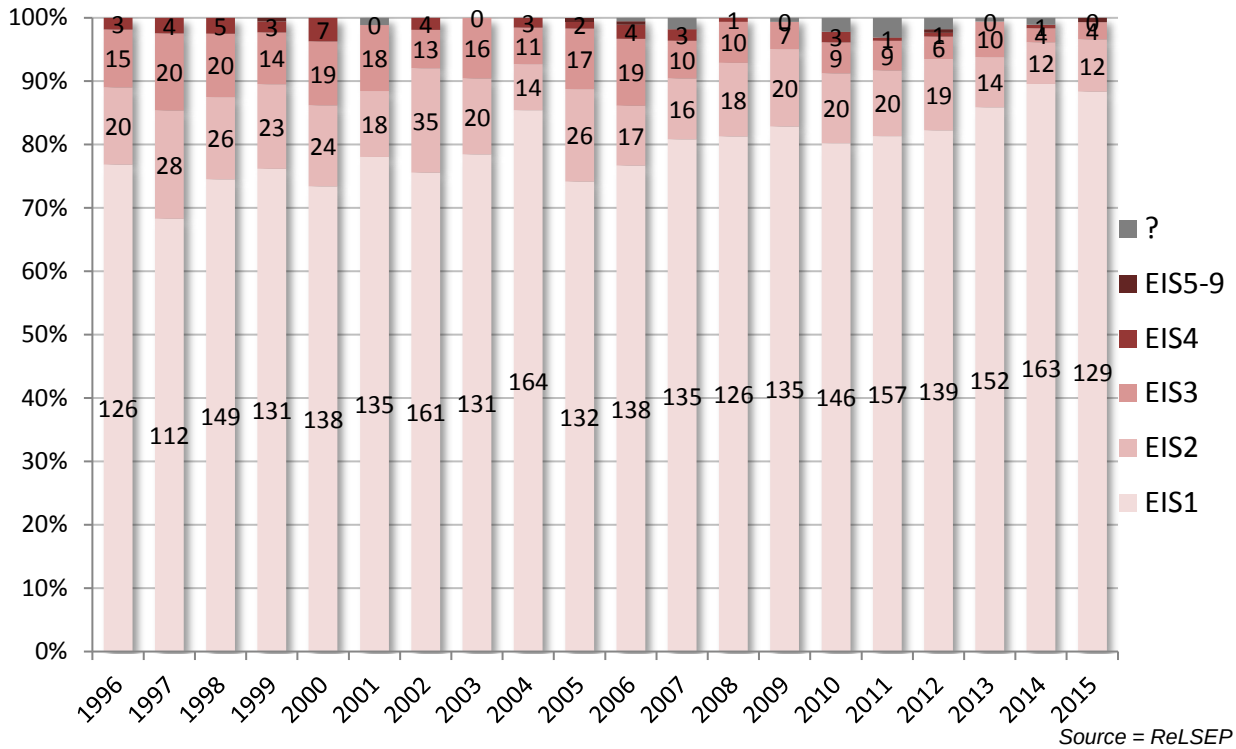
Fig 6. Forme à l'incidence



Source = ReLSEP
Date d'extraction = 01/01/2021

- **Niveau d'invalidité au 1er épisode, mesuré par l'EIS (European database for multiple sclerosis Impairment Scale)**

Fig 7. Niveau d'invalidité après la première poussée



I.3.ii. **Prévalence :**

Les résultats de prévalence sont présentés pour l'année 2015.

Nous ne présentons pas d'évolution de la prévalence, les sorties de la cohorte n'étant pas toutes identifiées (déménagements, décès, cas n'ayant pas bénéficié d'une prise en charge par un neurologue depuis plus de 5 ans).

- **Prévalence**

Au 1er janvier 2015, il y avait 5 041 cas prévalents de SEP pour 2 341 531 habitants, soit 1 415 hommes pour 1 143 149 hommes et 3 626 femmes pour 1 198 382 femmes.
La prévalence chez les hommes, standardisée sur la structure d'âge des hommes dans la population française en 2006 était de 123,27 / 100 000 hommes.
La prévalence chez les femmes, standardisée sur la structure d'âge des femmes dans la population française en 2006 était de 300,85 / 100 000 femmes.

- **Caractéristiques des cas**

Le ratio femmes / hommes était de 2,56.

La classe d'âge la plus représentée au moment des dernières nouvelles était la classe 60 ans ou +.

- **Caractéristiques de la maladie**

Au 1er janvier 2015, les formes cliniques des cas prévalents se répartissaient ainsi :

- Syndromes cliniquement isolés : 14,3%
- SEP récurrente-rémittente : 45,2%
- SEP primaires progressives : 12,8%
- SEP secondairement progressives : 27,7%.

Le dernier niveau d'invalidité était égal ou supérieur à 6 (nécessité d'une aide à la marche) chez 24,5% des cas prévalents.

I.3.iii. **Nombre moyen de sources par cas :**

Il y avait en moyenne 2,65 sources par cas incidents en Lorraine sur la période 1996-2015 au 01/01/2021.

Chapitre II. Etat d'avancement du suivi des cas

Le suivi des cas est systématique. La SEP est caractérisée par sa morbidité. Le suivi est réalisé à partir du dossier médical /hospitalier, en cabinet libéral ou en service hospitalier. Chaque dossier est consulté au moins tous les deux ans. Du fait du mode évolutif de la SEP, un cas peut ne pas avoir revu son médecin pendant un an, voire plusieurs années.
Malgré la crise sanitaire liée au Covid-19 et les complications auxquelles ont dû faire face l'équipe du registre, le nombre de cas sans consultation du dossier depuis plus de 2 ans a diminué, il est de 19.7% en 2020 alors qu'il était de 25% en 2019.

La mise en place d'accès à distance dans certains centres hospitaliers a permis aux IRC/TEC de continuer les suivis des patients et de poursuivre ainsi l'activité du registre.

Chapitre III. Publications et travaux scientifiques

Les travaux réalisés à partir des données du registre ont permis d'explorer des questions concernant :

- le diagnostic de la maladie, son optimisation, ou sa prédiction à partir de formes préliminaires isolées (1-3)
- le pronostic de la maladie en fonction de diverses caractéristiques des patients (4-7)
- la mesure de l'état de santé des patients (8)
- les effets de différentes thérapeutiques observées dans la cohorte constituée ou dans des essais dans lesquels des patients identifiés dans le registre ont pu être inclus (9-22)
- les conséquences médico-économiques de la maladie (23)

Diagnostic de la maladie, son optimisation, ou sa prédiction à partir de formes préliminaires isolées

1. Radiologically Isolated Syndrome: 10-Year Risk Estimate of a Clinical Event
Christine Lebrun-Frenay, Orhun Kantarci, Aksel Siva, Maria P Sormani, Daniel Pelletier, Darin T Okuda, 10-year RISC study group on behalf of SFSEP, OFSEP
Ann Neurol. 2020 Aug;88(2):407-417. doi: 10.1002/ana.25799.

Abstract

Objective: We have previously identified male sex, younger age, and the presence of spinal cord lesions as independent factors that increase the 5-year risk for evolution from radiologically isolated syndrome (RIS) to multiple sclerosis. Here, we investigate risk factors for the development of a clinical event using a 10-year, multinational, retrospectively identified RIS dataset.

Methods: RIS subjects were identified according to 2009 RIS criteria and followed longitudinally as part of a worldwide cohort study. We analyzed data from 21 individual databases from 5 different countries. Associations between clinical and magnetic resonance imaging (MRI) characteristics and the risk of developing a first clinical event were determined using multivariate Cox regression models.

Results: Additional follow-up data were available in 277 of 451 RIS subjects (86% female). The mean age at RIS diagnosis was 37.2 years (range, 11-74 years), with a median clinical follow-up of 6.7 years. The cumulative probability of a first clinical event at 10 years was 51.2%. Age, positive cerebrospinal fluid for oligoclonal bands, infratentorial lesions on MRI, and spinal cord lesions, were baseline independent predictors associated with a subsequent clinical event.

The presence of gadolinium-enhanced lesions during follow-up was also associated with the risk of a seminal event. The reason for MRI and gadolinium-enhancing lesions at baseline did not influence the risk of a subsequent clinical event.

Interpretation: Approximately half of all individuals with RIS experience a first clinical event within 10 years of the index MRI. The identification of independent predictors of risk for symptom onset may guide education and clinical management of individuals with RIS. ANN NEUROL 2020;88:407-417.

2. High performance of cerebrospinal fluid immunoglobulin G analysis for diagnosis of multiple sclerosis.

Gamraoui S, Mathey G, Debouverie M, Malaplate C, Anxionnat R, Guillemin F, Epstein J
J Neurol. 2019 Apr;266(4):902-909. doi: 10.1007/s00415-019-09212-4.

Abstract

BACKGROUND: The 2017 revision of the McDonald criteria highlights the usefulness of cerebrospinal fluid (CSF) immunoglobulin G (IgG) analysis to diagnose multiple sclerosis (MS). The objective of this study was to assess the diagnostic performances of CSF IgG analysis in the absence of a gold standard.

METHODS: All patients who underwent CSF IgG analysis for events suggestive of MS in Nancy University Hospital (France) from 2008 to 2011 were retrospectively included. A latent class analysis with Bayesian approach was used to infer MS prevalence (latent variable) as well as the diagnostic properties of the 2005 and 2010 McDonald criteria and CSF IgG analysis (observed variables).

RESULTS: Data from 673 patients were analysed. For CSF IgG analysis, the Bayesian latent class analysis estimated sensitivity of 0.93 (95% CrI 0.89-0.96) and specificity of 0.81 (95% CrI 0.77-0.85). The true prevalence estimate was 36% (95% CrI 0.33-0.40). Sensitivity and specificity estimates for patients with events suggestive of remitting-onset MS were similar to those for the whole sample-0.92 (95% CrI 0.85-0.96) and 0.80 (95% CrI 0.76-0.84), respectively-but higher for patients with signs of progressive-onset MS-0.95 (95% CrI 0.84-0.99) and 0.88 (95% CrI 0.78-0.94), respectively.

CONCLUSIONS: In the absence of a gold standard, latent class analysis indicates good diagnostic properties of CSF IgG analysis for MS. This test could thus be useful, especially for patients who tested negative for the 2005 and 2010 McDonald criteria. These findings deserve to be confirmed prospectively.

3. Oligoclonal bands increase the specificity of MRI criteria to predict multiple sclerosis in children with radiologically isolated syndrome

Naila Makhani, Christine Lebrun, Aksel Siva, Sona Narula, Evangeline Wassmer, David Brassat, J Nicholas Brenton, Philippe Cabre, Clarisse Carra Dallière, Jérôme de Seze, Francoise Durand Dubief, Matilde Inglese, Megan Langille, Guillaume Mathey, Rinze F Neuteboom, Jean Pelletier, Daniela Pohl, Daniel S Reich, Juan Ignacio Rojas, Veronika Shabanova, Eugene D Shapiro, Robert T Stone, Silvia Tenembaum, Mar Tintoré, Ugur Uygunoglu, Wendy Vargas, Sunita Venkateswaren, Patrick Vermersch, Orhun Kantarci, Darin T Okuda, Daniel Pelletier.
Mult Scler J Exp Transl Clin. 2019 Mar 20;5(1):2055217319836664. doi: 10.1177/2055217319836664.

Abstract

Background: Steps towards the development of diagnostic criteria are needed for children with the radiologically isolated syndrome to identify children at risk of clinical demyelination.

Objectives: To evaluate the 2005 and 2016 MAGNIMS magnetic resonance imaging criteria for dissemination in space for multiple sclerosis, both alone and with oligoclonal bands in cerebrospinal fluid added, as predictors of a first clinical event consistent with central nervous system demyelination in children with radiologically isolated syndrome.

Methods: We analysed an international historical cohort of 61 children with radiologically isolated syndrome (≤18 years), defined using the 2010 magnetic resonance imaging dissemination in space criteria (Ped-RIS) who were followed longitudinally (mean 4.2 ± 4.7 years). All index scans also met the 2017 magnetic resonance imaging dissemination in space criteria.

Results: Diagnostic indices (95% confidence intervals) for the 2005 dissemination in space criteria, with and without oligoclonal bands, were: sensitivity 66.7% (38.4-88.2%) versus 72.7% (49.8-89.3%); specificity 83.3% (58.6-96.4%) versus 53.9% (37.2-69.9%). For the 2016 MAGNIMS dissemination in space criteria diagnostic indices were: sensitivity 76.5% (50.1-93.2%) versus 100% (84.6-100%); specificity 72.7% (49.8-89.3%) versus 25.6% (13.0-42.1%).

Conclusions: Oligoclonal bands increased the specificity of magnetic resonance imaging criteria in children with Ped-RIS. Clinicians should consider testing cerebrospinal fluid to improve diagnostic certainty. There is rationale to include cerebrospinal fluid analysis for biomarkers including oligoclonal bands in planned prospective studies to develop optimal diagnostic criteria for radiologically isolated syndrome in children.

Pronostic de la maladie en fonction de diverses caractéristiques des patients

4. Sunlight exposure exerts immunomodulatory effects to reduce multiple sclerosis severity

Ostkamp P, Salmen A, Pignolet B, Görlich D, Andlauer TFM, Schulte-Mecklenbeck A, Gonzalez-Escamilla G, Bucciarelli F, Gennero I, Breuer J, Antony G, Schneider-Hohendorf T, Mykicki N, Bayas A, Then Bergh F, Bittner S, Hartung HP, Friese MA, Linker RA, Luessi F, Lehmann-Horn K, Mühlau M, Paul F, Stangel M, Tackenberg B, Tumani H, Warnke C, Weber F, Wildemann B, Zettl UK, Ziemann U, Müller-Myhsok B, Kümpfel T, Klotz L, Meuth SG, Zipp F, Hemmer B, Hohlfeld R, Brassat D, Gold R, Gross CC, Lukas C, Groppa S, Loser K, Wiendl H, Schwab N; German Competence Network Multiple Sclerosis (KKNMS) and the BIONAT Network.

Proc Natl Acad Sci U S A. 2021 Jan 5;118(1):e2018457118. doi: 10.1073/pnas.2018457118.

Abstract

Multiple sclerosis (MS) disease risk is associated with reduced sun-exposure. This study assessed the relationship between measures of sun exposure (vitamin D [vitD], latitude) and MS severity in the setting of two multicenter cohort studies (n_{NationMS} = 946, n_{BIONAT} = 990). Additionally, effect-modification by medication and photosensitivity-associated *MC1R* variants was assessed. High serum vitD was associated with a reduced MS severity score (MSSS), reduced risk for relapses, and lower disability accumulation over time. Low latitude was associated with higher vitD, lower MSSS, fewer gadolinium-enhancing lesions, and lower disability accumulation. The association of latitude with disability was lacking in IFN-β-treated patients. In carriers of *MC1R*:rs1805008(T), who reported increased sensitivity toward sunlight, lower latitude was associated with higher MRI activity, whereas for noncarriers there was less MRI activity at lower latitudes. In a further exploratory approach, the effect of ultraviolet (UV)-phototherapy on the transcriptome of immune cells of MS patients was assessed using samples from an earlier study.

Phototherapy induced a vitD and type I IFN signature that was most apparent in monocytes but that could also be detected in B and T cells. In summary, our study suggests beneficial effects of sun exposure on established MS, as demonstrated by a correlative network between the three factors: Latitude, vitD, and disease severity.

However, sun exposure might be detrimental for photosensitive patients. Furthermore, a direct induction of type I IFNs through sun exposure could be another mechanism of UV-mediated immune-modulation in MS.

5. New OFSEP recommendations for MRI assessment of multiple sclerosis patients: Special consideration for gadolinium deposition and frequent acquisition

Brisset JC, Kremer S, Hannoun S, Bonneville F, Durand-Dubief F, Tourdias T, Barillot C, Guttmann C, Vukusic S, Dousset V, Cotton F; Collaborators.
J Neuroradiol. 2020 Jun;47(4):250-258

Abstract

Purpose: New multiple sclerosis (MS) disease-modifying therapies (DMTs), which exert beneficial effects through prevention of relapse, limitation of disability progression, and improvement of patients' quality of life, have recently emerged. Nonetheless, these DMTs are not without associated complications (severe adverse events like. progressive multifocal leukoencephalopathy). Patient follow-up requires regular clinical evaluations and close monitoring with magnetic resonance imaging (MRI). Detection of new T2 lesions and potential brain atrophy measurements contribute to the evaluation of treatment effectiveness. Current MRI protocols for MS recommend the acquisition of an annual gadolinium (Gd) enhanced MRI, resulting in administration of high volume of contrast agents over time and Gd accumulation in the brain.

Methods: A consensus report was established by neuroradiologists and neurologists from the French Observatory of MS, which aimed at reducing the number of Gd injections required during MS patient follow-up.

Recommendations: The French Observatory of MS recommends the use of macrocyclic Gd enhancement at time of diagnosis, when a new DMT is introduced, at 6-month re-baseline, and when previous scans are unavailable for comparison. Gd administration can be performed as an option in case of relapse or suspicion of intercurrent disease such as progressive multifocal leukoencephalopathy. Other follow-up MRIs do not require contrast enhancement, provided current and previous MRI acquisitions follow the same standardized protocol including 3D FLAIR sequences.

6. Economic burden of multiple sclerosis in France estimated from a regional medical registry and national sick fund claims.

Detournay Bruno, Debouverie Marc, Pereira Ouarda, Seyer Dominique, Soudant Marc, Courouve Laurène, Jomaa Khalil, Epstein Jonathan, Guillemin Francis.
Mult Scler Relat Disord. 2019 Nov;36:101396. doi: 10.1016/j.msard.2019.101396.

Abstract

Background: Estimating direct healthcare costs of patients with multiple sclerosis (MS) and identifying risk factors of high costs including relapse are important drivers of public health decision making in France.

Methods: This is a longitudinal retrospective study based on patient charts (qualified registry of MS in Lorraine (ReLSEP)) and claims data (from the main compulsory health insurance and national hospital database estimated monthly. All patients with MS not deceased or lost to follow-up reported in the registry in 2013-2014 were included. Outpatient costs were those paid to the healthcare provider and inpatient costs were those related to national cost estimates. Mean total

costs per patient by disease severity were estimated monthly, accounting for MS evolution over the study period. Costs of MS relapse were estimated using a general linear model.

Results: A total of 4373 patients were identified in the ReLSEP registry, and 2166 of these patients were included in the study. Among those, outpatient claims were available for 1366 and 627 were hospitalized at least once. The average annual direct costs for patients with MS were estimated to be €12,296 in 2014. Furthermore, ambulatory costs represented 87.8% out of those costs and were mainly driven by medications (60.6%) and paramedic visits (11.2%). Monthly direct costs were higher in patients with severe disease (€1249 for EDSS 7-9) compared to those with mild or moderate disease (€992 for EDSS 0-3; €953 for EDSS 4-6) ($p < 0,006$). Interestingly, drug costs were higher in patients with mild disease, whereas costs related to paramedical care, medical devices, and transportation were higher in those with severe MS. The unit cost of relapse was estimated between €1681 and €2193.

Conclusion: Costs were mainly driven by medications and highly related to disease severity. Relapse cost was the main contributor to total cost.

7. Neuraxial analgesia is not associated with an increased risk of post-partum relapses in MS

Lavie C, Rollot F, Durand-Dubief F, Marignier R, Ionescu I, Casey R, Moreau T, Tourniaire P, Hutchinson M, D'Hooghe MB, Laplaud DA, Clavelou P, De Sèze J, Debouverie M, Brassat D, Pelletier J, Lebrun-Frenay C, Le Page E, Castelnovo G, Berger E, Hautecoeur P, Heinzlef O, Durelli L, Clerico M, Trojano M, Patti F, Vukusic S; PRIMS and POPARTMUS investigators
Mult Scler. 2019 Apr;25(4):591-600.

Abstract

Background: Obstetrical analgesia remains a matter of controversy because of the fear of neurotoxicity of local anesthetics on demyelinated fibers or their potential relationship with subsequent relapses.

Objective: To assess the impact of neuraxial analgesia on the risk of relapse during the first 3 months post-partum, with a focus on women who experienced relapses during pregnancy.

Methods: We analyzed data of women followed-up prospectively during their pregnancies and at least 3 months post-partum, collected in the Pregnancy in Multiple Sclerosis (PRIMS) and Prevention of Post-Partum Relapses with Progestin and Estradiol in Multiple Sclerosis (POPARTMUS) studies between 1992-1995 and 2005-2012, respectively. The association of neuraxial analgesia with the occurrence of a post-partum relapse was estimated by logistic regression analysis.

Results: A total of 389 women were included, 215 from PRIMS and 174 from POPARTMUS. In total, 156 women (40%) had neuraxial analgesia. Overall, 24% experienced a relapse during pregnancy and 25% in the 3 months post-partum. Women with a pregnancy relapse were more likely to have a post-partum relapse (odds ratio (OR) = 1.83, $p = 0.02$), independently of the use of neuraxial analgesia. There was no association between neuraxial analgesia and post-partum relapse (OR = 1.08, $p = 0.78$).

Conclusion: Neuraxial analgesia was not associated with an increased risk of post-partum relapses, whatever multiple sclerosis (MS) activity during pregnancy.

Mesure de l'état de santé des patients

8. Assessing the experience of the quality of care of patients living with multiple sclerosis and their caregivers: The MusiCare questionnaire

Veillard D, Baumstarck K, Edan G, Debouverie M, Wiertlewski S, De Sèze J, Clavelou P, Pelletier J, Verny C, Chauvin K, Cosson ME, Loundou A, Auquier P.

Eur J Neurol. 2020 Dec 16. doi: 10.1111/ene.14685. Online ahead of print. PMID: 33326668

Abstract

Background and purpose: Patients with a chronic illness, such as multiple sclerosis (MS), and their natural caregivers have a specific experience of healthcare and health services. These experiences need to be assessed to evaluate the quality of care. Our objective was to develop a French-language questionnaire to evaluate the quality of care as experienced by MS patients and their natural caregivers.

Methods: Eligible patients had been diagnosed with MS according to the McDonald criteria. Eligible caregivers were individuals designated by the patients. The MusiCare questionnaire was developed in two standard phases: (i) item generation, based on interviews with patients and caregivers; and (ii) validation, consisting of validity, reliability, external validity, reproducibility, and responsiveness measures.

Results: In total, 1088 patients (n = 660) and caregivers (n = 488) were recruited. The initial 64-item version of MusiCare was administered to a random subsample (n = 748). The validation process generated a 35-item questionnaire. Internal consistency and scalability were satisfactory. Testing of the external validity revealed expected associations between MusiCare scores and sociodemographic and clinical data. The questionnaire showed good reproducibility and responsiveness.

Conclusions: The availability of a reliable and validated French-language self-report questionnaire probing the experience of the quality of care for MS will allow the feedback of patients and caregivers to be incorporated into a continuous healthcare quality-improvement strategy.

Effets de différentes thérapeutiques observes dans la cohort constituée ou dans des essais dans lesquels des patients identifiés dans le registre ont pu être inclus

9. The long-term outcome of MOGAD: an observational national cohort study of 61 patients

Romain Deschamps, Julie Pique, Xavier Ayrignac, Nicolas Collongues, Bertrand Audoin, Hélène Zéphir, Jonathan Ciron, Mikael Cohen, Jennifer Aboab, Guillaume Mathey, Nathalie Derache , David Laplaud, Eric Thouvenot, Bertrand Bourre, Aurélie Ruet, Françoise Durand-Dubief, Valérie Touitou, Catherine Vignal-Clermont, Caroline Papeix , Olivier Gout, Romain Marignier, Elisabeth Maillart, NOMADMUS study group

Eur J Neurol. 2021 Feb 2. doi: 10.1111/ene.14746

Abstract

Background: The prognosis in Myelin oligodendrocyte glycoprotein antibody (MOG-IgG) associated disease (MOGAD) is a matter of debate. Our aim was to assess long-term outcomes of patients with MOGAD.

Methods: We retrospectively analysed clinical and paraclinical data of patients who tested positive for MOG-IgG and had clinical follow-up of at least 8 years from their first episode, from the French nationwide observatory study NOMADMUS.

Results: Sixty-one patients (median age at onset 27, range 3-69) with median follow-up of 177 months (mean 212.8, range 98-657) were included. Among 58 patients with a relapsing course, 26.3% relapsed in the first year from onset. Of the 61 patients, 90.2% experienced at least one episode of optic neuritis. At last visit, the median EDSS was 1 (mean 2.12; range 0-7.5), 12.5% had an EDSS ≥6 and 37.5% had an EDSS ≥3. Of 51 patients with final visual acuity available, 15.7% had visual acuity ≤0.1 in at least one eye and 25.5% had visual acuity ≤0.5 in at least one eye. Bilateral blindness (visual acuity ≤0.1) was present in 5.9% of patients. Finally, 12.5% of patients presented bladder dysfunction requiring long-term urinary catheterization. No factor associated significantly with a final EDSS ≥3 or with final visual acuity ≤0.1 was found.

Conclusion: Overall long-term favourable outcomes were achieved in a majority of our patients, but severe impairment, in particular visual damage, was not uncommon.

10. Determinants of therapeutic lag in multiple sclerosis

Roos I, Leray E, Frascoli F, Casey R, Brown JWL, Horakova D, Havrdova EK, Debouverie M, Trojano M, Patti F, Izquierdo G, Eichau S, Edan G, Prat A, Girard M, Duquette P, Onofrj M, Lugaresi A, Grammond P, Ciron J, Ruet A, Ozakbas S, De Seze J, Louapre C, Zephir H, Sá MJ, Sola P, Ferraro D, Labauge P, Defer G, Bergamaschi R, Lebrun-Frenay C, Boz C, Cartechini E, Moreau T, Laplaud D, Lechner-Scott J, Grand'Maison F, Gerlach O, Terzi M, Granella F, Alroughani R, Iuliano G, Van Pesch V, Van Wijmeersch B, Spitaleri D, Soysal A, Berger E, Prevost J, Aguera-Morales E, McCombe P, Castillo Triviño T, Clavelou P, Pelletier J, Turkoglu R, Stankoff B, Gout O, Thouvenot E, Heinzlef O, Sidhom Y, Gouider R, Csepany T, Bourre B, Al Khedr A, Casez O, Cabre P, Montcuquet A, Wahab A, Camdessanche JP, Maurousset A, Patry I, Hankiewicz K, Pottier C, Maubeuge N, Labeyrie C, Nifle C, Coles A, Malpas CB, Vukusic S, Butzkueven H, Kalincik T

Mult Scler. 2021 Jan 11:1352458520981300. doi: 10.1177/1352458520981300.

Abstract

Background: A delayed onset of treatment effect, termed therapeutic lag, may influence the assessment of treatment response in some patient subgroups.

Objectives: The objective of this study is to explore the associations of patient and disease characteristics with therapeutic lag on relapses and disability accumulation.

Methods**:** Data from MSBase, a multinational multiple sclerosis (MS) registry, and OFSEP, the French MS registry, were used. Patients diagnosed with MS, minimum 1 year of exposure to MS treatment and 3 years of pre-treatment follow-up, were included in the analysis. Studied outcomes were incidence of relapses and disability accumulation. Therapeutic lag was calculated using an objective, validated method in subgroups stratified by patient and disease characteristics. Therapeutic lag under specific circumstances was then estimated in subgroups defined by combinations of clinical and demographic determinants.

Results: High baseline disability scores, annualised relapse rate (ARR) $\geqslant$ 1 and male sex were associated with longer therapeutic lag on disability progression in sufficiently populated groups: females with expanded disability status scale (EDSS) < 6 and ARR < 1 had mean lag of 26.6 weeks (95% CI = 18.2-34.9), males with EDSS < 6 and ARR < 1 31.0 weeks (95% CI = 25.3-36.8), females with EDSS < 6 and ARR $\geqslant$ 1 44.8 weeks (95% CI = 24.5-65.1), and females with EDSS $\geqslant$ 6 and ARR < 1 54.3 weeks (95% CI = 47.2-61.5).

Conclusions: Pre-treatment EDSS and ARR are the most important determinants of therapeutic lag.

11. Cumulative effects of therapies on disability in relapsing multiple sclerosis

Rollot F, Casey R, Leray E, Debouverie M, Edan G, Wiertlewski S, Vukusic S, Laplaud DA

Mult Scler. 2021 Jan 6:1352458520980366. doi: 10.1177/1352458520980366.

Abstract

Background: Long-term effectiveness of treatment remains a key question in multiple sclerosis (MS) and the cumulative effects of past treatment have not been investigated so far.

Objective: Explore the relationship between treatment exposure and disability risk in patients with relapsing-remitting multiple sclerosis (RRMS).

Methods: A total of 2285 adult patients from the French nationwide cohort were included. Outcomes were irreversible EDSS4, and conversion to secondary progression of multiple sclerosis (SPMS). Associations between treatments and risk of disability were assessed using a novel weighted cumulative exposure model, assuming a 3-year lag to account for reverse causality. This flexible approach accounts for past exposure in a multivariate Cox proportional hazards model by computing a weight function.

Results: At baseline, mean ± standard deviation age of patients was 33.4 ± 8.9 years and 75.0% were women. A 15-year continuous treatment starting 20 years ago was associated with a decrease in risk of 26% for irreversible EDSS4, and 34% for SPMS compared to a 5-year treatment starting 10 years ago. The risk of disability decreased with increasing duration of exposure to disease-modifying treatment (DMT).

Conclusion: Long-term use of treatments in RRMS has a stronger beneficial cumulative impact than only early uses and delays the occurrence of moderate disability and conversion to SPMS.

12. Discontinuation of disease-modifying treatments for multiple sclerosis in patients aged over 50 with disease Inactivity

Kaminsky AL, Omorou AY, Soudant M, Pittion-Vouyovitch S, Michaud M, Anxionnat R, Guillemin F, Debouverie M, Mathey G.

J Neurol. 2020 Dec;267(12):3518-3527. doi: 10.1007/s00415-020-10029-9. Epub 2020 Jul 2. PMID: 32617659.

Abstract

Background: Treatments may become redundant in older patients with multiple sclerosis (MS). Our aim was to explore whether stopping treatments might be possible in patients aged over 50 with disease inactivity.

Methods: Patients over 50 were included from the population-based MS Lorraine registry if they had a relapsing-remitting course at onset and had experienced no relapse for ≥ 3 years. Patients who stopped treatments were defined as "stoppers", and the others as "stayers". The outcomes were the time to first relapse, to first disability progression, and to the occurrence of EDSS score of 6, assessed by multivariate analysis using a propensity score.

Results: 132 stoppers and 366 stayers had a median follow-up of 7 years. There was no difference in Log-rank tests for the times to first relapse ($p = 0.61$) and to first disability progression ($p = 0.22$).

In Cox models, stopping treatments was not associated with an increased risk of relapse (adjusted Hazard ratio (aHR) = 0.92 [0.72-1.16; p = 0.47]) or of an increase in EDSS score (aHR = 0.89 [0.71-1.13; p = 0.34]). However, stopping was associated with a higher risk of occurrence of EDSS score of 6 (aHR = 3.29 [2.22-4.86; p < 0.0001]), with a significant difference for the time to occurrence of EDSS score of 6 (p = 0.003).

Conclusion: Our study suggests that stopping injectable disease-modifying treatments, in patients over 50 with disease inactivity, is not associated with an increased risk of relapse or EDSS progression, but there might be a higher risk of reaching EDSS 6. These results have to be confirmed by interventional studies.

13. BEST – MS : A prospective head-to-head comparative study of natalizumab and fingolimod in active relapsing MS

Cohen M, Mondot L, Bucciarelli F, Pignolet B, Laplaud DA, Wiertlewski S, Brochet B, Ruet A, Defer G, Derache N, Vermersch P, Zephir H, Debouverie M, Mathey G, Berger E, Cappé C, Labauge P, Carra C, De Seze J, Bigaut K, Brassat D, Lebrun-Frenay.

Mult Scler. 2020 Oct 30:1352458520969145. doi: 10.1177/1352458520969145.

Abstract

Background: There are few head-to-head studies to compare highly active treatments in multiple sclerosis (MS).

Objective: The aim of this study was to compare the effectiveness between natalizumab (NTZ) and fingolimod (FTY) in active relapsing-remitting MS.

Method: Best Escalation STrategy in Multiple Sclerosis (BEST-MS) is a multicentric, prospective study with a 12-month follow-up including patients with active MS. Treatment choice was at the discretion of physician. Clinical and magnetic resonance imaging (MRI) data were collected at baseline and at 12 months. The primary outcome was the proportion of patients reaching no evidence of disease activity (NEDA) at 12 months. Secondary outcomes included annualized relapse rate and MRI activity.

Results: A total of 223 patients were included (NTZ: 109 and FTY: 114). Treatment groups were well balanced at baseline. Proportion of NEDA patients was 47.8% in NTZ group versus 30.4% in FTY group (p = 0.015). This superiority was driven by annualized relapse rate and MRI activity. In the multivariate analysis, treatment group was the only factor associated with NEDA at 12 months with a lower probability in FTY group (odds ratio (OR) = 0.49, p = 0.029).

Conclusion: BEST-MS is a prospective study that compared head-to-head the effectiveness of NTZ and FTY in active relapsing-remitting MS. Our results suggest a superiority of NTZ over FTY.

Keywords: Multiple sclerosis; fingolimod; magnetic resonance imaging; natalizumab; therapeutics.

14. Delay from treatment start to full effect of immunotherapies for multiple sclerosis

Roos I, Leray E, Frascoli F, Casey R, Brown JWL, Horakova D, Havrdova EK, Trojano M, Patti F, Izquierdo G, Eichau S, Onofrj M, Lugaresi A, Prat A, Girard M, Grammond P, Sola P, Ferraro D, Ozakbas S, Bergamaschi R, Sá MJ, Cartechini E, Boz C, Granella F, Hupperts R, Terzi M, Lechner-Scott J, Spitaleri D, Van Pesch V, Soysal A, Olascoaga J, Prevost J, Aguera-Morales E, Slee M, Csepany T, Turkoglu R, Sidhom Y, Gouider R, Van Wijmeersch B, McCombe P, Macdonell R, Coles A, Malpas CB, Butzkueven H, Vukusic S, Kalincik T; MSBase; OFSEP investigators.

Delay from treatment start to full effect of immunotherapies for multiple sclerosis.
Brain. 2020 Sep 1;143(9):2742-2756.

Abstract
In multiple sclerosis, treatment start or switch is prompted by evidence of disease activity. Whilst immunomodulatory therapies reduce disease activity, the time required to attain maximal effect is unclear. In this study we aimed to develop a method that allows identification of the time to manifest fully and clinically the effect of multiple sclerosis treatments ('therapeutic lag') on clinical disease activity represented by relapses and progression-of-disability events. Data from two multiple sclerosis registries, MSBase (multinational) and OFSEP (French), were used. Patients diagnosed with multiple sclerosis, minimum 1-year exposure to treatment, minimum 3-year pretreatment follow-up and yearly review were included in the analysis. For analysis of disability progression, all events in the subsequent 5-year period were included. Density curves, representing incidence of relapses and 6-month confirmed progression events, were separately constructed for each sufficiently represented therapy. Monte Carlo simulations were performed to identify the first local minimum of the first derivative after treatment start; this point represented the point of stabilization of treatment effect, after the maximum treatment effect was observed. The method was developed in a discovery cohort (MSBase), and externally validated in a separate, non-overlapping cohort (OFSEP). A merged MSBase-OFSEP cohort was used for all subsequent analyses. Annualized relapse rates were compared in the time before treatment start and after the stabilization of treatment effect following commencement of each therapy. We identified 11 180 eligible treatment epochs for analysis of relapses and 4088 treatment epochs for disability progression. External validation was performed in four therapies, with no significant difference in the bootstrapped mean differences in therapeutic lag duration between registries. The duration of therapeutic lag for relapses was calculated for 10 therapies and ranged between 12 and 30 weeks. The duration of therapeutic lag for disability progression was calculated for seven therapies and ranged between 30 and 70 weeks. Significant differences in the pre- versus post-treatment annualized relapse rate were present for all therapies apart from intramuscular interferon beta-1a. In conclusion we have developed, and externally validated, a method to objectively quantify the duration of therapeutic lag on relapses and disability progression in different therapies in patients more than 3 years from multiple sclerosis onset. Objectively defined periods of expected therapeutic lag allows insights into the evaluation of treatment response in randomized clinical trials and may guide clinical decision-making in patients who experience early on-treatment disease activity. This method will subsequently be applied in studies that evaluate the effect of patient and disease characteristics on therapeutic lag.

15. Efficacité en vie réelle de diméthylfumarate dans la sclérose en plaques (SEP) : cohorte à partir des données du Système National des Données de Santé (SNDS)

Bosco-Levy P, Lignot S, Abdelilah A, Debouverie M, Brochet B, Guillemin F, Blin P.
Rev Neurol (Paris). 2020 Sep;176S:S76.

Résumé

Introduction : Dans le cadre de la réinscription à 5 ans du diméthylfumarate (Tecfidera®) par la Haute Autorité de Santé en 2020, une étude de cohorte a été menée dans le SNDS.

Objectifs : Evaluer l'efficacité en vie réelle de diméthylfumarate dans la sclérose en plaque (SEP) comparativement aux autres traitements oraux (tériflunomide, fingolimod), et aux traitements immunomodulateurs injectables (IID).

Patients et méthodes : Cohorte de patients identifiés dans le SNDS avec un premier traitement de SEP (patients naïfs) entre le 01/07/15 et le 31/12/16, un historique de 4,5 années, et suivis jusqu'au 31/12/17. Le nombre annuel de poussées a été comparé entre deux traitements durant la période d'exposition pour des patients appariés 1 :1 sur un score de propension à haute dimension, avec un modèle de régression binomiale négative et un résultat exprimé en risque relatif (RR [IC95 %]).

Résultats : Sur 1,5 ans, 5812 patients naïfs ont été identifiés en France, 1930 initiant le tériflunomide (33,2 %), 1800 un IID (31,0 %), 1775 le diméthylfumarate (30,6 %) et 307 le fingolimod (5,3 %). Pour les 940 patients diméthylfumarate appariés à 940 patients tériflunomide, le nombre moyen annuel de poussées était de 0,14 versus 0,17 (RR=0,79 [0,63–1,00], *p*=0,0457), et pour les 1019 patients diméthylfumarate appariés à 1019 patients IID, de 0,14 versus 0,18 (RR=0,71 [0,56–0,90], *p*=0,0051).

Discussion : Les poussées ont été identifiées avec un algorithme complexe basé sur des épisodes de soins (hospitalisation et forte dose de corticothérapie) qui a fait l'objet d'une validation par des cliniciens en aveugle de l'algorithme, avec une valeur prédictive négative de 100 % et positive de 95,2 %. Le faible nombre de patients fingolimod et leurs caractéristiques n'ont pas permis d'effectuer de comparaison.

Conclusion : Cette étude en pratique courante a montré un risque de poussées significativement plus faible avec le diméthylfumarate que le tériflunomide et les IID pour des patients partageant les mêmes caractéristiques.

16. Relapses in Patients Treated with High-Dose Biotin for Progressive Multiple Sclerosis

Sophie Mathais, Xavier Moisset, Bruno Pereira, Frédéric Taithe, Jonathan Ciron, Pierre Labauge, Cécile Dulau, David Laplaud, Jérôme De Seze, Jean Pelletier, Eric Berger, Christine Lebrun-Frenay, Giovanni Castelnovo, Gilles Edan, Gilles Defer, Patrick Vermersch, Bertrand Bourre, Jean-Philippe Camdessanche, Laurent Magy, Anne-Marie Guennoc, Guillaume Mathey, Thibault Moreau, Olivier Gout, Olivier Heinzlef, Elisabeth Maillart, Sandra Vukusic, Pierre Clavelou, SFSEP and OFSEP investigators

Neurotherapeutics. 2020 Sep 22. doi: 10.1007/s13311-020-00926-2.

Abstract

High-dose biotin (HDB) is a therapy used in non-active progressive multiple sclerosis (PMS). Several reports have suggested that HDB treatment may be associated with an increased risk of relapse. We aimed to determine whether HDB increases the risk of clinical relapse in PMS and describe the characteristics of the patients who experience it. We conducted a French, multicenter, retrospective study, comparing a group of PMS patients treated with HDB to a matched control group. Poisson regression was applied to model the specific statistical distribution of the annualized relapse rate (ARR). A propensity score (PS), based on the inverse probability of treatment weighting (IPTW), was used to adjust for indication bias and included the following variables: gender, primary PMS or not, age, EDSS, time since the last relapse, and co-prescription of a DMT. Two thousand six hundred twenty-eight patients treated with HDB and 654 controls were analyzed with a follow-up of 17 ± 8 months. Among them, 148 validated relapses were observed in the group treated with biotin and 38 in the control group (p = 0.62). After adjustment based on the PS, the ARR was 0.044 ± 0.23 for the biotin-treated group and 0.028 ± 0.16 for the control group (p = 0.18). The more relapses there were before biotin, the higher the risk of relapse during treatment, independently from the use of HDB. While the number of relapses reported for patients with no previous inflammatory activity receiving biotin has gradually increased, the present retrospective study is adequately powered to exclude an elevated risk of relapse for patients with PMS treated with HDB.

17. Treatment of MOG-IgG-associated disorder with rituximab: An international study of 121 patients

Daniel H Whittam, Alvaro Cobo-Calvo, A Sebastian Lopez-Chiriboga, Santiago Pardo, Matthew Gornall, Silvia Cicconi, Alexander Brandt, Klaus Berek, Thomas Berger, Ilijas Jelcic, Grace Gombolay, Luana Micheli Oliveira, Dagoberto Callegaro, Kimihiko Kaneko, Tatsuro Misu, Marco Capobianco, Emily Gibbons, Venkatraman Karthikeayan, Bruno Brochet, Bertrand Audoin, Guillaume Mathey, David Laplaud, Eric Thouvenot, Mikaël Cohen, Ayman Tourbah, Elisabeth Maillart, Jonathan Ciron, Romain Deschamps, Damien Biotti, Kevin Rostasy, Rinze Neuteboom, Cheryl Hemingway, Rob Forsyth, Marcelo Matiello, Stewart Webb, David Hunt, Katy Murray, Yael Hacohen, Ming Lim, M Isabel Leite, Jacqueline Palace, Tom Solomon, Andreas Lutterotti, Kazuo Fujihara, Ichiro Nakashima, Jeffrey L Bennett, Lekha Pandit, Tanuja Chitnis, Brian G Weinshenker, Brigitte Wildemann, Douglas Kazutoshi Sato, Su-Hyun Kim, Saif Huda, Ho Jin Kim, Markus Reindl, Michael Levy, Sven Jarius, Silvia Tenembaum, Friedemann Paul, Sean Pittock, Romain Marignier, Anu Jacob
Mult Scler Relat Disord. 2020 Sep;44:102251. doi: 10.1016/j.msard.2020.102251.

Abstract

Objective: To assess the effect of anti-CD20 B-cell depletion with rituximab (RTX) on relapse rates in myelin oligodendrocyte glycoprotein antibody-associated disorder (MOGAD).

Methods: Retrospective review of RTX-treated MOGAD patients from 29 centres in 13 countries. The primary outcome measure was change in relapse rate after starting rituximab (Poisson regression model).

Results: Data on 121 patients were analysed, including 30 (24.8%) children. Twenty/121 (16.5%) were treated after one attack, of whom 14/20 (70.0%) remained relapse-free after median (IQR) 11.2 (6.3-14.1) months. The remainder (101/121, 83.5%) were treated after two or more attacks, of whom 53/101 (52.5%) remained relapse-free after median 12.1 (6.3-24.9) months. In this 'relapsing group', relapse rate declined by 37% (95%CI=19-52%, p<0.001) overall, 63% (95%CI=35-79%, p = 0.001) when RTX was used first line (n = 47), and 26% (95%CI=2-44%, p = 0.038) when used after other steroid-sparing immunotherapies (n = 54). Predicted 1-year and 2-year relapse-free survival was 79% and 55% for first-line RTX therapy, and 38% and 18% for second-/third-line therapy. Circulating $CD19^{+}$B-cells were suppressed to <1% of total circulating lymphocyte population at the time of 45/57 (78.9%) relapses.

Conclusion: RTX reduced relapse rates in MOGAD. However, many patients continued to relapse despite apparent B-cell depletion. Prospective controlled studies are needed to validate these results.

18. Frequency and characteristics of short versus longitudinally extensive myelitis in adults with MOG antibodies: A retrospective multicentric study.

Jonathan Ciron, Alvaro Cobo-Calvo, Bertrand Audoin, Bertrand Bourre, David Brassat, Mikael Cohen, Nicolas Collongues, Romain Deschamps, Françoise Durand-Dubief, David Laplaud, Elisabeth Maillart, Caroline Papeix, Hélène Zephir, Matthieu Bereau, Bruno Brochet , Clarisse Carra-Dallière, Nathalie Derache, Clarisse Gagou-Scherer, Carole Henry, Philippe Kerschen, Guillaume Mathey, Nicolas Maubeuge, Aude Maurousset , Alexis Montcuquet, Thibault Moreau, Christophe Prat , Frédéric Taithe , Eric Thouvenot, Ayman Tourbah , Fabien Rollot, Sandra Vukusic, Romain Marignier
Mult Scler. 2020 Jul;26(8):936-944. doi: 10.1177/1352458519849511.

Abstract

Objectives: We aim to (1) determine the frequency and distinctive features of short myelitis (SM) and longitudinally extensive transverse myelitis (LETM) in a cohort of adults with myelin oligodendrocyte glycoprotein (MOG)-antibody (Ab)-associated myelitis and (2) determine baseline prognostic factors among MOG-Ab-positive patients whose disease started with myelitis.

Material and methods: We retrospectively analyzed clinical and paraclinical variables from a multicentric French cohort of adults with MOG-Ab-associated myelitis. At last follow-up, patients were classified into two groups according to the severity of the Expanded Disability Status Scale (EDSS) as $\leqslant$2.5 or $\geqslant$3.0.

Results: Seventy-three patients with at least one episode of myelitis over disease course were included; among them, 28 (38.4%) presented with SM at the time of the first myelitis. Motor and sphincter involvement was less frequently observed in SM (51.9% and 48.2%, respectively) than in LETM patients (83.3% and 78.6%, respectively), p = 0.007 and p = 0.017; 61% of LETM patients displayed brain lesions compared to 28.6% in the SM group, p = 0.008, and the thoracic segment was more frequently involved in the LETM (82.2%) than in the SM group (39.3%), p < 0.001. EDSS at last follow-up was higher in LETM (median 3.0 (interquartile range: 2.0-4.0)) compared to SM patients (2.0, (1.0-3.0)), p = 0.042. Finally, a higher EDSS at onset was identified as the only independent risk factor for EDSS $\geqslant$3.0 (odds ratio, 1.40, 95% confidence interval (CI): 1.01-1.95, p = 0.046).

Conclusion: SM in MOG-Ab-associated disease is not rare. The severity at onset was the only independent factor related to the final prognosis in MOG-Ab-associated myelitis.

19. Memory improvement in multiple sclerosis after an extensive cognitive rehabilitation program in groups with a multicenter double-blind randomized trial

Brissart H, Omorou AY, Forthoffer N, Berger E, Moreau T, De Seze J, Morele E, Debouverie M.
Clin Rehabil. 2020 Jun;34(6):754-763

Abstract

Objective: The aim of this study is to determine the effectiveness of an extended cognitive rehabilitation program in group's sessions in multiple sclerosis.

Design: Double-blind multicenter randomized trial.

Participants: People with multiple sclerosis of 18 to 60 years, Expanded Disability Status Scale $\leqslant$6.0, mild to moderate cognitive impairment.

Interventions: They were randomized into cognitive rehabilitation program (ProCog-SEP) or in a placebo program. ProCog-SEP comprises 13 group's sessions over 6 months and includes psychoeducational advices and cognitive exercises. Placebo program included non-cognitive exercises. No strategy and no cognitive advice were provided.

Main measures: The primary endpoint was the percentage of verbal memory learning measured by the Selective Reminding Test. A comprehensive neuropsychological assessment is carried out before and after interventions by a neuropsychologist blinded to intervention. Effectiveness of the ProCog-SEP versus Placebo has been verified using linear regression models.

Results: In total, 128 participants were randomized and 110 were included in the study after planning session in groups; 101 completed this trial (77.2% females); mean age: 46.1 years (±9.6); disease duration: 11.8 years (±7.5). ProCog-SEP was more effective in increasing in learning index (9.21 (95% confidence interval (CI): 1.43, 16.99); $p = 0.02$) and in working memory on manipulation (0.63 (95% CI: 0.17, 1.09); $p = 0.01$), and updating capacities (-1.1 (95% CI: -2.13, -0.06); $p = 0.04$). No difference was observed for other neuropsychological outcomes. Regarding quality of life outcomes, no change was observed between the two groups.

Conclusion: These findings suggest that ProCog-SEP could improve verbal learning abilities and working memory in people with multiple sclerosis. These improvements were observed with 13 group sessions over 6 months.

20. Progressive Multifocal Leukoencephalopathy Incidence and Risk Stratification Among Natalizumab Users in France

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Abstract

Importance: Risk of developing progressive multifocal leukoencephalopathy (PML) is the major barrier to using natalizumab for patients with multiple sclerosis (MS). To date, the association of risk stratification with PML incidence has not been evaluated.

Objective: To describe the temporal evolution of PML incidence in France before and after introduction of risk minimization recommendations in 2013.

Design, setting, and participants**:** This observational study used data in the MS registry OFSEP (Observatoire Français de la Sclérose en Plaques) collected between April 15, 2007, and December 31, 2016, by participating MS expert centers and MS-dedicated networks of neurologists in France. Patients with an MS diagnosis according to current criteria, regardless of age, were eligible, and those exposed to at least 1 natalizumab infusion (n = 6318) were included in the at-risk population. A questionnaire was sent to all centers, asking for a description of their practice regarding PML risk stratification. Data were analyzed in July 2018.

Exposures: Time from the first natalizumab infusion to the occurrence of PML, natalizumab discontinuation plus 6 months, or the last clinical evaluation.

Main outcomes and measures: Incidence was the number of PML cases reported relative to the person-years exposed to natalizumab. A Poisson regression model for the 2007 to 2016 period estimated the annual variation in incidence and incidence rate ratio (IRR), adjusted for sex and age at treatment initiation and stratified by period (2007-2013 and 2013-2016).

Results: In total, 6318 patients were exposed to natalizumab during the study period, of whom 4682 (74.1%) were female, with a mean (SD [range]) age at MS onset of 28.5 (9.1 [1.1-72.4]) years; 45 confirmed incident cases of PML were diagnosed in 22 414 person-years of exposure.

The crude incidence rate for the whole 2007 to 2016 period was 2.00 (95% CI, 1.46-2.69) per 1000 patient-years. Incidence significantly increased by 45.3% (IRR, 1.45; 95% CI, 1.15-1.83; P = .001) each year before 2013 and decreased by 23.0% (IRR, 0.77; 95% CI, 0.61-0.97; P = .03) each year from 2013 to 2016.

Conclusions and relevance: The results of this study suggest, for the first time, a decrease in natalizumab-associated PML incidence since 2013 in France that may be associated with a generalized use of John Cunningham virus serologic test results; this finding appears to support the continuation and reinforcement of educational activities and risk-minimization strategies in the management of disease-modifying therapies for multiple sclerosis.

21. Comparative effectiveness of teriflunomide vs dimethyl fumarate in multiple sclerosis

Laplaud DA, Casey R, Barbin L, Debouverie M, De Sèze J, Brassat D, Wiertlewski S, Brochet B, Pelletier J, Vermersch P, Edan G, Lebrun-Frenay C, Clavelou P, Thouvenot E, Camdessanché JP, Tourbah A, Stankoff B, Al Khedr A, Cabre P, Lubetzki C, Papeix C, Berger E, Heinzlef O, Debroucker T, Moreau T, Gout O, Bourre B, Wahab A, Labauge P, Magy L, Defer G, Guennoc AM, Maubeuge N, Labeyrie C, Patry I, Nifle C, Casez O, Michel L, Rollot F, Leray E, Vukusic S, Foucher Y; SFSEP and OFSEP groups.
Neurology. 2019 Aug 13;93(7):e635-e646.

Abstract

Objective: In this study, we compared the effectiveness of teriflunomide (TRF) and dimethyl fumarate (DMF) on both clinical and MRI outcomes in patients followed prospectively in the Observatoire Français de la Sclérose en Plaques.

Methods: A total of 1,770 patients with relapsing-remitting multiple sclerosis (RRMS) (713 on TRF and 1,057 on DMF) with an available baseline brain MRI were included in intention to treat. The 1- and 2-year postinitiation outcomes were relapses, increase of T2 lesions, increase in Expanded Disability Status Scale score, and reason for treatment discontinuation. Propensity scores (inverse probability weighting) and logistic regressions were estimated.

Results: The confounder-adjusted proportions of patients were similar in TRF- compared to DMF-treated patients for relapses and disability progression after 1 and 2 years. However, the adjusted proportion of patients with at least one new T2 lesion after 2 years was lower in DMF compared to TRF (60.8% vs 72.2%, odds ratio [OR] 0.60, $p < 0.001$).

Analyses of reasons for treatment withdrawal showed that lack of effectiveness was reported for 8.5% of DMF-treated patients vs 14.5% of TRF-treated patients (OR 0.54, $p < 0.001$), while adverse events accounted for 16% of TRF-treated patients and 21% of DMF-treated patients after 2 years (OR 1.39, $p < 0.001$).

Conclusions: After 2 years of treatment, we found similar effectiveness of DMF and TRF in terms of clinical outcomes, but with better MRI-based outcomes for DMF-treated patients, resulting in a lower rate of treatment discontinuation due to lack of effectiveness.

Classification of evidence: This study provides Class III evidence that for patients with RRMS, TRF and DMF have similar clinical effectiveness after 2 years of treatment

22. Five-year outcome in the copaxone observatory: a nationwide cohort of patients with multiple sclerosis starting treatment with glatiramer acetate in France

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Abstract

The benefits provided by disease-modifying treatments in multiple sclerosis have been demonstrated in clinical trials, but the extent to which they can be extrapolated to everyday care is less clear, as are the long-term benefits of treatment. The objective of this prospective observational cohort study performed in France was to evaluate the effectiveness and safety of glatiramer acetate in patients with relapsing-remitting multiple sclerosis over a 5-year period. All neurologists in France were invited to participate and enroll adult patients starting a first treatment with brand glatiramer acetate 20 mg.

Given the observational nature of the study, no fixed study visits were imposed; consultations took place according to the investigator's normal practice. Occurrence of disease exacerbations and adverse events was documented and neurological disability evaluated with the EDSS at each consultation. Overall, 852 patients were analysable and 269 took glatiramer acetate continuously for 5 years. Median treatment duration was 3.4 years. Principal reasons for discontinuation were inadequate efficacy (38.9%), local tolerability (22.6%) and personal convenience (21.3%). Age, employment status, baseline EDSS score and number of previous exacerbations were variables associated with treatment persistence. The annualised exacerbation rate (5 years) was 0.41 [95% CI 0.39-0.44]; 316 patients (37.2%) remained exacerbation-free throughout. The risk of confirmed disability worsening (5 years) was 43.8% [95% CI 39.9-47.9%]. The most frequent adverse drug reactions were local injection site reactions (584 patients; 68.5%) and systemic immediate post-injection reactions (168 patients; 19.7%). Overall, these findings are consistent with those of previous clinical trials.

Conséquences medico-économiques de la maladie

23. Economic burden of multiple sclerosis in France estimated from a regional medical registry and national sick fund claims.

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Mult Scler Relat Disord. 2019 Nov;36:101396. doi: 10.1016/j.msard.2019.101396.

Abstract

Background: Estimating direct healthcare costs of patients with multiple sclerosis (MS) and identifying risk factors of high costs including relapse are important drivers of public health decision making in France.

Methods: This is a longitudinal retrospective study based on patient charts (qualified registry of MS in Lorraine (ReLSEP)) and claims data (from the main compulsory health insurance and national hospital database estimated monthly. All patients with MS not deceased or lost to follow-up reported in the registry in 2013-2014 were included. Outpatient costs were those paid to the healthcare provider and inpatient costs were those related to national cost estimates. Mean total costs per patient by disease severity were estimated monthly, accounting for MS evolution over the study period. Costs of MS relapse were estimated using a general linear model.

Results: A total of 4373 patients were identified in the ReLSEP registry, and 2166 of these patients were included in the study. Among those, outpatient claims were available for 1366 and 627 were hospitalized at least once. The average annual direct costs for patients with MS were estimated to be €12,296 in 2014. Furthermore, ambulatory costs represented 87.8% out of those costs and were mainly driven by medications (60.6%) and paramedic visits (11.2%). Monthly direct costs were higher in patients with severe disease (€1249 for EDSS 7-9) compared to those with mild or moderate disease (€992 for EDSS 0-3; €953 for EDSS 4-6) ($p < 0,006$). Interestingly, drug costs were higher in patients with mild disease, whereas costs related to paramedical care, medical devices, and transportation were higher in those with severe MS. The unit cost of relapse was estimated between €1681 and €2193.

Conclusion: Costs were mainly driven by medications and highly related to disease severity. Relapse cost was the main contributor to total cost.