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Disease-modifying therapies use in relapsing-onset MS patients in real-life settings in France: data from the OFSEP database over the period 1996-2017

E. Leray[1,2], F. Rollot[3], R. Casey[3], J. de Sèze[4], D.A. Laplaud[5], S. Vukusic[3,6,7], for the OFSEP investigators

[1]Département METIS, EHESP School of Public Health, [2]EA 7449 REPERES, EHESP / Rennes 1 University, Rennes, [3]Observatoire Français de la Sclérose en Plaques, OFSEP ; Université Claude Bernard Lyon I ; Hospices Civils de Lyon, Lyon, [4]CHU Strasbourg, [5]CHU Nantes, [6]Fondation Eugène Devic EDMUS contre la Sclérose en Plaques, Hospices Civils de Lyon, [7]INSERM 1028 et CNRS UMR5292, Centre des Neurosciences de Lyon, Lyon, France

Background: **Beta interferon, first disease-modifying therapy (DMT) for multiple sclerosis (MS), was approved in France in 1996.** Twenty years later, **12 medications are available**, improving the therapeutic arsenal regarding acceptance and tolerability (injectable, oral and infused medications) but first of all efficacy, despite potential adverse effects. **Approval of natalizumab in 2007 and oral first-line treatments in 2014 were major steps in the therapeutic strategy**. Increased availability of DMTs associated with better knowledge of their efficacy and their risks had consequences on therapeutic decisions made by neurologists in daily practice among relapsing-remitting (RR) MS patients.

Objective: **To describe use of DMTs in relapsing-remitting MS patients in France over the last 20 years, the therapeutic sequences and switches; to assess impact of the arrival of new drugs on the practices; to search for a period effect in DMTs use.**

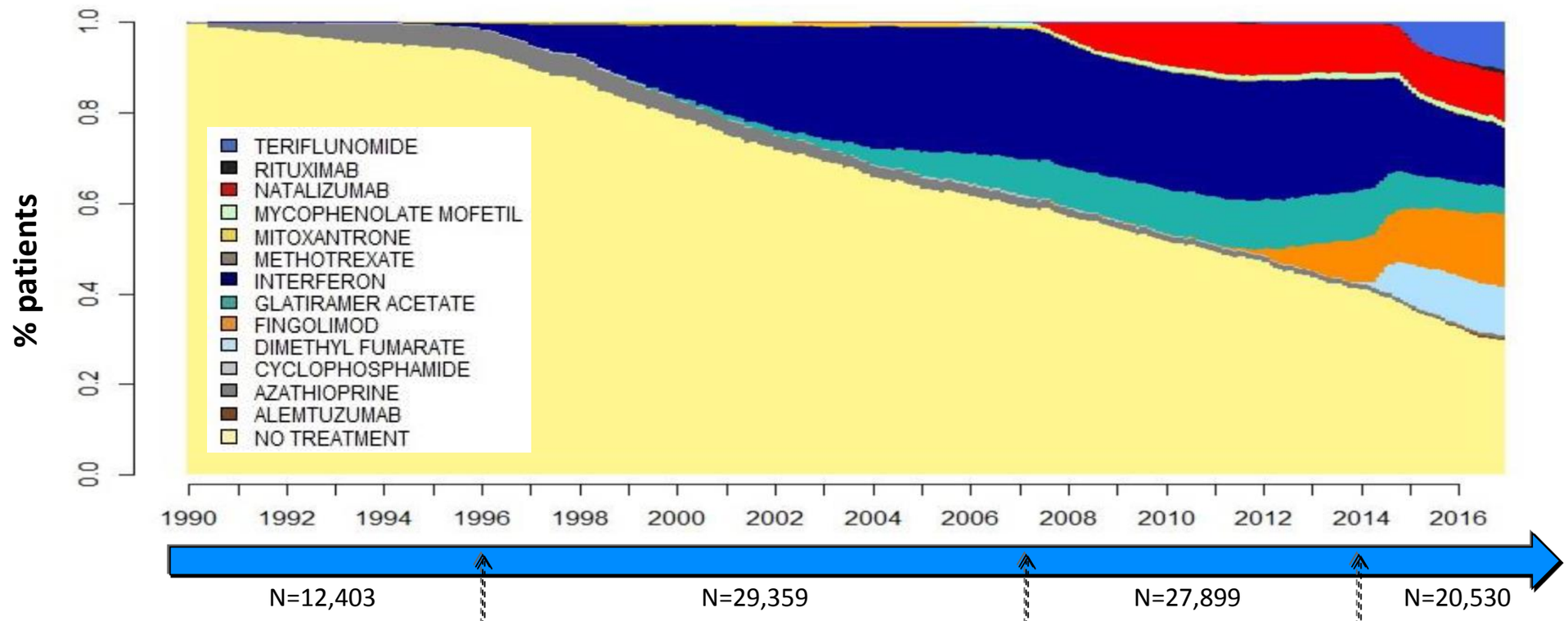
Methods: All OFSEP patients with **relapsing-onset MS, not converted into SPMS and alive on 1996, Jan 1st** (to get a chance to be treated with a DMT approved in MS) were included, i.e. **41,305 patients**. Follow-up duration for every patient starts at MS clinical onset, and stops at the date of progression onset or at last clinical information if still RR. All DMT were considered, without any minimal duration. DMT were considered specifically and grouped according to their place in therapeutic strategy and ways of administrations into four categories: **first-line injectable drugs** (glatiramer acetate, interferon), **first-line oral drugs** (dimethyl fumarate, teriflunomide), **second-line drugs** (alemtuzumab, fingolimod, mitoxantrone, natalizumab) and **off-label drugs** (azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, rituximab). Periods were defined according to specific therapeutic milestones in France: **<1st Jan 1996** (approval of interferon), **1st Jan 1996 to 1st Apr 2007** (approval of natalizumab), **1st Apr 2007 to 1st Jan 2014** (approval of dimethyl fumarate), and **>=1.1.2014**. In each period was considered the cohort of MS incident cases in the period, as well as the follow-up of MS cases whose disease has started in the previous period(s). A **therapeutic switch** was defined as a drug change with a **maximum of 6 months between the end of DMT N°X and the initiation of DMT N° X+1**.

Results: **More than 2/3 of RRMS patients received at least one DMT, initiated at a mean age of 35.9 ± 10.4 years, after a mean MS duration of 5.0 ± 6.2 years, and for a cumulative DMT duration accounting for 49% of F/U period (mean number of DMT initiations per patient = 2.2 ± 1.5).**

Table: Initial MS characteristics of the overall population and of incident cases in each period

	Overall N=41,305	<1996 n=12,403	1996-2007 n=16,956	2007-2014 n=9,213	>=2014 n=2,733
Sex ratio F:M	2.8 (30423:10882)	2.9 (9203:3200)	2.8 (12503:4553)	2.8 (6757:2456)	2.5 (1960:773)
Age at MS clinical onset (y)	31.4 ± 10.1	28.7 ± 8.8	32.1 ± 10.0	33.0 ± 10.6	33.7 ± 11.0
Follow-up (F/U) duration from MS clinical onset (y)	11.1 ± 9.0	20.0 ± 9.3	9.7 ± 5.5	4.6 ± 2.6	1.3 ± 0.9
Received at least one DMT over F/U period	27879 (67.5 %)	7512 (60.6%)	12075 (71.2%)	6776 (73.6%)	1516 (55.5%)

Figure: Distribution of DMT use over time in the period 1990-2017, and treatment characteristics in the four incident cohorts



	N=12,403	N=29,359	N=27,899	N=20,530
# incident cases:	12,403	16,956	9,213	2,733
Newly treated:	1646 (**13.3%**)	8376 (**49.4 %**)	5335 (**57.9 %**)	1516 (**55.5 %**)
Age at 1st DMT (y):	33.1 ± 8.9	33.7 ± 9.6	33.6 ± 10.3	33.7 ± 10.5
MS duration* (y):	**3.0 [1.0-7.0]**	**1.5 [0.7-3.1]**	**0.8 [0.4-1.6]**	**0.5 [0.3-0.9]**
# switchs:**	93 (**5.7 %**)	2458 (**29.3 %**)	1705 (**31.9 %**)	352 (**23.2 %**)
P25* before switch:**	--	**1.6 [1.4-1.7]**	**1.1 [1.0-1.2]**	**0.9 [0.8-1.0]**

* Median [Q1-Q3]; ** among treated patients; ***P25: percentile 25 of Kaplan-Meier estimate of the time between DMT initiation and stop for therapeutic switch (years), with 95% confidence interval

Discussion: Our study shows how arrival of new approved drugs had consequences on daily practices of MS neurologists in France. It also shows **how initial therapeutic decision changed over time, with more and more patients treated, patients treated earlier in the disease course** (not at a younger age as older at MS clinical onset)**, with different kind of drugs, and with switches occurring more frequently** (except in the last period: better initial choice? Or too short F/U?) and **earlier in the disease course.** Those changes in practice are probably **linked to a wider range of available drugs, as well as a better knowledge of natural history of disability progression and higher expectations regarding potential treatment benefits**.

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