# 2-year follow-up of 19 patients treated with alemtuzumab for active relapsing-remitting MS: the Lyon's experience

**F. Durand-Dubief[1,2], R. Marignier[1,3,4], I. Ionescu[1], J. Pique[1], C. Lavie[1], S. Vukusic[1,3,4]**

*1-Service de Neurologie, sclérose en plaques, pathologies de la myéline et neuro-inflammation, Hôpital Neurologique, Hospices Civils de Lyon, Bron Lyon Cedex, 2-CREATIS (CNRS UMR5220 & INSERM U1206), Bâtiment Blaise Pascal, 7 Avenue Jean Capelle, Université de Lyon, Villeurbanne Cedex, 3-Centre des Neurosciences de Lyon, INSERM 1028 et CNRS UMR5292, Lyon, 4-Université Claude Bernard Lyon 1, Faculté de Médecine Lyon-Est, Villeurbanne, France*

**Introduction** Alemtuzumab has been approved by the European Medicines Agency as a treatment of relapsing-remitting MS (RRMS). However, with regards to its safety profile, French regulators have limited its use to radiologically and clinically active and severe cases only.

**Objectives** To describe the efficacy and safety profile of alemtuzumab in a monocentric cohort of patients.

**Methods** We prospectively collected clinical and radiological data of RRMS patients treated with alemtuzumab since January 2015.

**Results** 19 RRMS patients (16 women/3 men) received alemtuzumab (mean age at treatment: 34.3 years). Mean disease duration was 11.4 years (range: 2.5-20) and mean EDSS was 4.8 (range 0-8) at treatment onset. Mean number of previous disease modifying treatments (DMT) before alemtuzumab was 4 (2-7) (*Table 1*). In the year before, mean number of relapses was 1.6 (range 1-5). Pre-treatment MRI showed new T2 lesions in 91% and Gadolinium-enhancing lesions in 82% of patients (from 1 to 30 G+ lesions/patient). After one year of follow up, 16 patients did not relapse and mean EDSS decreased by 0.4. New T2 lesions and new Gadolinium-enhancing lesions were found in 42 % (from 1 to 11 G + lesions / patient). At two years, 10/14 patients had no relapse and mean EDSS decreased by 0.7. New T2 lesions and new Gadolinium-enhancing lesions were found in respectively 30 % and 15 % of the patients (from 8 to 14 G + lesions/patient) (*Table 2*, *Figure 1*). Infusion-related reactions were found in 85% of the patients (mainly rash and headache/pyrexia). Noteworthy, 8 patients presented short-term moderate to severe adverse events: 4 episodes of bradycardia (25-45 pulses/mn), 1 pleural and pericardial effusion associated to hepatic cytolysis, 1 pericarditis, 1 spontaneous multiple cervical artery dissection complicated by ischemic stroke and 1 intra alveolar haemorrhage. After 2 years, 1 patient had severe immune thrombocytopenia and neutropenia and 2 patients developed thyroid disorders (*Table 3*).

**Table 1 : Patients Characteristics**

| 19 Patients | Number |
|---|---|
| Gender F/M | 16/3 |
| Age (Mean, Years) | 34.3 (23- 46) |
| Disease Duration (Mean, Years) | 11.4 (2.5 – 20) |
| EDSS (Mean, Range) | 4.8 (0 – 8) |
| Number of previous DMT | 3.8 (2 – 7) |

**Figure 1 : MRI of the patient number 9 at one year (10 Gd + Lesions) and two years (8 Gd+ Lesions).**

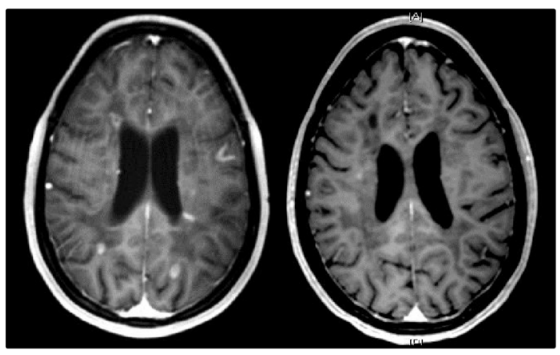

**Table 2 : Evolution of each patient in terms of EDSS, number of relapse, MRI with new T2 lesions, new Gadolinium enhanced lesion, and their number, at the baseline, at one year and two years**

| | EDSS | | | Relapses | | | IRM pre-ttt | | | IRM 1 years | | | IRM 2 years | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | Y0 | Y+1 | Y+2 | Y-1 | Y+1 | Y+2 | Nx T2 | Gd+ | Nb Gd+ | Nx T2 | Gd+ | Nb Gd+ | Nx T2 | Gd+ | Nb Gd+ |
| 1 | 3 | 3 | 3 | 2 | 0 | 0 | 1 | 1 | 3 | 1 | 1 | 2 | 1 | 0 | 0 |
| 2 | 7 | 4 | 5,5 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | 5,5 | 2 | 0 | 3 | 0 | 0 | 1 | 1 | 7 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | 8 | 8 | 8 | 2 | 3 | 0 | 1 | 1 | 2 | 1 | 1 | 5 | 0 | 0 | 0 |
| 5 | 6 | 6 | 6 | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 6 | 6 | 6 | 6 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| 7 | 6,5 | 7 | 7 | 1 | 0 | 0 | 1 | 1 | 4 | 1 | 1 | 10 | 1 | 1 | 14 |
| 8 | 6,5 | 6,5 | 6,5 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 9 | 0 | 0 | 0 | 4 | 3 | 2 | 1 | 1 | 30 | 1 | 1 | 10 | 1 | 1 | 8 |
| 10 | 6,5 | 6 | NA | 1 | 0 | NA | 1 | 1 | 4 | 0 | 0 | 0 | NA | NA | NA |
| 11 | 5,5 | 4,5 | 4,5 | 2 | 0 | 0 | 1 | 1 | 8 | 0 | 0 | 0 | 0 | 0 | 0 |
| 12 | 6 | 6 | 6,5 | 1 | 1 | 0 | 1 | 1 | 7 | 1 | 1 | 1 | 0 | 0 | 0 |
| 13 | 0 | 2 | 1 | 1 | 0 | 0 | 1 | 1 | 10 | 0 | 0 | 0 | NA | NA | NA |
| 14 | 6 | 4 | 4 | 1 | 0 | 0 | 1 | 1 | 3 | 1 | 1 | 1 | 0 | 0 | 0 |
| 15 | 6,5 | 7,5 | NA | 2 | 0 | NA | 1 | 1 | 5 | 0 | 0 | 0 | NA | NA | NA |
| 16 | 2 | 2 | NA | 1 | 0 | NA | 1 | 0 | 0 | 1 | 1 | 5 | NA | NA | NA |
| 17 | 3 | 2 | NA | 1 | 0 | NA | 1 | 1 | 10 | 0 | 0 | 0 | NA | NA | NA |
| 18 | 6 | 6 | NA | 1 | 0 | NA | 1 | 1 | 1 | 0 | 0 | 0 | NA | NA | NA |
| 19 | 1,5 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 11 | 0 | 0 | 0 |
| Average | 4,8 | 4,4 | 4,1 | 1,6 | 0,4 | 0,3 | 91% | 82% | 6,3 | 42% | 42% | 2,4 | 30% | 15% | 1,7 |

**Table 3 : Side effects of the treatment, from moderate to severe.**

| Patients | Cycle 1 tolerance | Cycle 2 tolerance | Long term tolerance |
|---|---|---|---|
| 1 | Bradycardia 47 bpm; skin rash | Bradycardia 45 bpm | |
| 2 | Bradycardia 25 bpm; thoracic pain, hypotension | Bradycardia 40 bpm | |
| 3 | Bradycardia 39 bpm | | Dysthyroidism, anti-TRAK Ab + |
| 4 | | | Dysthyroidism, anti-thyroglobulines Ab + |
| 5 | Bradycardia 40 bpm; skin rash | | Dysthyroidism, hypo puis hyperthyroidism |
| 6 | Hyperthermia 38,5°C; skin rash | | Anti-TPO Ab + |
| 7 | Skin rash | | Anti-TPO Ab +, anti-thyroglobuline Ab + |
| 8 | Hyperthermia 39°C | Hyperthermia 39°C | Anti-récepteurs de TSH Ab + |
| 9 | Bradycardia 45 bpm; skin rash | Bradycardia 45 bpm; skin rash | |
| 10 | **Pericardial and pleural effusion, liver cytolysis** | NA | |
| 11 | Headache; skin rash | | **Auto-immune thrombocytopenia + neutropenia** |
| 12 | | | |
| 13 | Hyperthermia 38°C; skin rash | Prurirtis, œdema | |
| 14 | Skin rash | Skin rash | |
| 15 | **Cervical artery dissections + stroke** | NA | |
| 16 | Headache; skin rash | **Pericarditis** | Anti-thyroglobuline Ab + |
| 17 | skin rash | NA | |
| 18 | skin rash | NA | **Recurrence of a nephrotic syndrome** |
| 19 | Pruritis | **Moderate alveolar haemorrhage** | |

**Discussion** Alemtuzumab is an efficient treatment in MS. Among the 19 patients treated in our department, most had a dramatic improvement of clinical and radiological disease activity. However five patients failed to respond, displaying MRI activity with up to 14 Gadolinium enhancing lesions, contrasting with low or absent clinical activity. This discrepancy questions the underlying pathophysiological processes of this phenomenon. Moreover our patients encountered a unexpectedly high number of immediate or long term adverse events, moderate to severe. One potential explanation could be the restriction of its indications in France, that makes the use of alemtuzumab probably too late in the disease history, in terms of age, disease duration, disability, accumulation of previous DMT.

**Conclusion** Our experience emphasizes the possible modified efficacy and safety profile of alemtuzumab when used as a rescue therapy, rather than in its original early indication, in patients previously exposed to many other DMTs. Further evaluations are warranted to support this assumption.

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