Assessment of No Evidence of Disease Activity (NEDA-3) in alemtuzumab-treated patients with aggressive MS who failed multiple disease-modifying drugs

Sin
XLVII CONGRESSO
Venezia, 22-25 Ottobre 2016
Polo Congressuale - Lido di Venezia

L. Prosperini[1], P. Annovazzi[2], L. Boffa[3], M. C. Buscarinu[4], A. Gallo[5], M. Matta[6], L. Moiola[7], L. Musu[8], P. Perini[9], C. Avolio[10], M.R. Rottoli[11], A. Bianco[12], D. Farina[13], E. Ferraro[14], A. Francia[1], F. Granella[15], L. Grimaldi[16], A. Laroni[17], G. Lus[5], F. Patti[18], E. Pucci[19], A.M. Repice[20], P. Sarchielli[21]; Italian Alemtuzumab Study Group

(1) Dept. of Neurology and Psychiatry, Sapienza University, Rome; (2) S. Antonio Abate Hospital, Gallarate (VA); (3) MS Centre, Tor Vergata University; (4) Centre for Experimental Neurological Therapies (CENTERS), S. Andrea Hospital, Rome; (5) Dept. of Medical, Surgical, Neurological, Metabolic and Aging Sciences, Second University of Naples; (6) Regional MS Centre, S. Luigi Gonzaga Hospital, Orbassano (TO); (7) S. Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan; (8) ASL-8 Cagliari University, Cagliari; (9) Dept. of Neurosciences, MS Centre, University Hospital, Padova; (10) Dept. of Medical and Surgical Sciences, University Hospital, Foggia; (11) Papa Giovanni XXIII Hospital, Bergamo (MI); (12) Institute of Neurology, School of Medicine 'A. Gemelli', Rome; (13) Dept. of Neuroscience and Imaging, University 'G. d'Annunzio', Chieti; (14) S. Filippo Neri Hospital, Rome; (15) Dept. of Neurosciences, University of Parma, Parma, (16) Fondazione Istituto San Raffaele "G.Giglio', Cefalù (PA); (17) Dept. of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Genova; (18) Dept. of Medical and Surgical Sciences and Advanced Technologies, Neuroscience Section, University of Catania, Catania; (19) Neurology Unit, ASUR Marche AV3, Macerata; (20) Neurology Unit, Careggi Hospital, Firenze; (21) Neurology Unit, Perugia University, Perugia.

INTRODUCTION

- The anti-CD52 humanized monoclonal antibody alemtuzumab was recently approved for the treatment of active relapsing-remitting multiple sclerosis (MS) based on phase-2 (CAMMS223) and phase-3 clinical trials (CARE-MS I and CARE-MS II), where high-dose interferon beta-1a was used as active comparator.[1-3]
- Both CAMMS223 and CARE-MS I recruited treatment-naive patients with MS duration ≤3 and 5 years (respectively) and Expanded Disability Status Scale (EDSS) score ≤3.0.
- By contrast, CARE-MS II recruited patients with MS duration ≤10 years, EDSS score ≤5.0, and prior exposure to disease-modifying drugs (DMDs); to note, however, almost 3/4 of them had just a single therapeutic course with a DMD.
- Therefore, the potential use of alemtuzumab in aggressive, longer-lasting and multiple DMD-refractory MS deserves further investigation.

OBJECTIVE

- To assess the proportion of alemtuzumab-treated patients who had no evidence of disease activity (NEDA-3) after discontinuation of multiple DMDs because of lack of response or safety concerns.
- NEDA-3 was defined as no relapses, no disability worsening, and no magnetic resonance imaging (MRI) activity over a maximum follow-up time of 2 years.

METHODS

- This is a longitudinal, observational study collecting clinical and MRI data of a real-world cohort of patients treated with alemtuzumab between May 2014 and June 2015 in 21 tertiary Italian MS Centres according to a "free-of-charge" protocol available before its approval by the Italian Medicines Agency.
- Patients will be followed for at least 2 years after their first infusion (the end of study is planned in June 2017).
- The study sample consists of 40 patients with MS (33 women, 7 men); see **Table 1** for their demographic, clinical and MRI data.
- The median number of previous DMDs taken by patients was 4 (interferons: n=36; natalizumab: n=32; fingolimod: n=29; glatiramer acetate: n=19; mitoxantrone: n=12; cyclophosphamide: n=7; dimethylfumarate :n=3; rituximab: n=1; autologous hematopoietic stem cells transplantation: n=1) [**Table 2**].
- The main characteristics of study sample in comparison to previous studies are shown in **Table 1 & 2** (the blue arrow indicates the present study).

Table 1.

	Italy	CARE-MS II[3] (12 mg group)	France[4]	United Kingdom[5]
Sample size	40	426	16	87
Female sex, %	82%	66%	68%	70%
Age, years mean (SD)	34.0 (8.0)	34.8 (8.4)	35.1 (7.0)	33.0 (8.0)
Time since first symptom, years mean (SD) median [range]	11.7 (5.9) 10.6 [1.2-28.6]	4.5 (2.7) 3.8 [0.2-14.4]	11.5 (4.3) 10.2 [3.1-20.1]	N/A 3 [0.5-12]
EDSS score mean (SD) median [range]	4.0 (1.8) 4.0 [1.0-7.0]	2.7 (1.3) 2.5 [0-6.5]	5.9 (1.8) 6.0 [2.5-9.0]	3.8 (1.94) 3.5 [0-8.0]
Relapses in previous year mean (SD) median [range]	1.95 (1.13) 2 [0-4]	1.7 (0.9) 1 [0-5]	1.8 (1.5) 2 [0-5]	1.78 (0.82)* N/A
Number of GD+ lesions mean (SD) median [range] Patients with GD+ enhancement, %	3.5 (4.0) 2.5 [0-17] 72%	2.3 (6.0) 0 [0-72] 42%	10.3 (8.6) 8 [1-25] 100%	N/A N/A N/A

*ARR over 2 years pre-treatment; N/A: not available

Table 2.

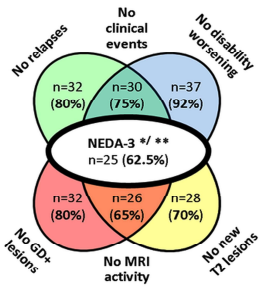
	Italy	CARE-MS II[3] (12 mg group)	France[4]
Sample size	40	426	16
No. of previous MS treatments, n (%) 0 1 2 3 ≥4	 1 (2.5%) 1 (2.5%) 3 (7.5%) 13 (32.5%) 22 (55%)	 - 299 (70%) 92 (22%) 24 (6%) 11 (3%)	 - - 4 (25%) 6 (37.5%) 6 (37.5%)
mean (SD) median [range]	4.1 (1.8) 4 [0-8]	1.0 (0.7) 1 [1-4]	3.6 (1.5) 3 [2-7]
Last MS treatment, n (%) Fingolimod Natalizumab Cyclophosphamide Dimethyl Fumarate Glatiramer Acetate Interferon Beta Mitoxantrone Others**	 15 (37.5%) 13 (32.5%) 4 (10%) 3 (7.5%) 1 (2.5%) 1 (2.5%) 0 (0%) 2 (5%)	 N/A 	 1 (6.25%) 1 (6.25%) 2 (12.5%) 0 (0%) 4 (25%) 1 (6.25%) 5 (31.25%) 2 (12.5%)
Time (months) from last MS treatment mean (SD) median [range]	5.5 (8.5) 3 [0-48]	N/A	N/A

* Italy: AHSCT, Rituximab; France: Methotrexate; N/A: not available

RESULTS

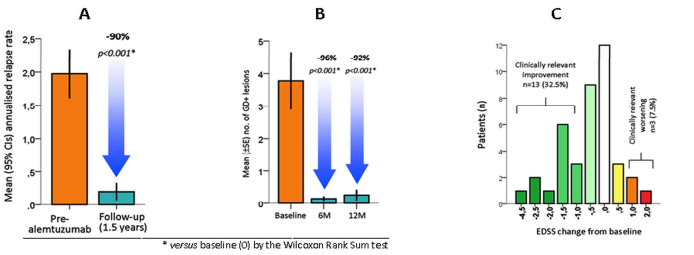
- After a mean follow-up of 1.5 (±0.3) years, 25 (62.5%) patients maintained NEDA-3, 32 (80%) were relapse-free, 37 (92.5%) were disability worsening-free, and 26 (65%) were MRI activity-free **[Fig. 1]**.
- We found a dramatic reduction in relapse rate (–90%; p<0.001) and GD-enhancing lesions (–96% and –92% after 6 and 12 months of follow-up, respectively; p<0.001) with respect to the pre-alemtuzumab year **[Fig. 2/A and B]**.
- About one third of patients (n=13) experienced a clinically relevant disability reduction (estimated as a reduction of ≥1-EDSS point) **[Fig. 2/C]**.
- Infusion-associated reactions (IARs, defined as any adverse event occurring within 24 hours from the last infusion) were observed in 38 (95%) patients during the first alemtuzumab cycle (mild to moderate in most cases).
- We observed a greater incidence of headache during the first days of infusions, while the greater incidence of skin rash were observed at the end of the cycle **[Fig. 3]**.
- Seven (17.5%) patients had infusion-related serious adverse events (SAEs): severe skin rash (n=2), bradycardia with QT interval prolongation (n=1), hyperpyrexia (n=1), hypertension (n=1), haemorrhagic cystitis (n=1), kidney tubulopathy (n=1).
- Out of these 7 SAEs, 3 were most likely related to concomitant medications other than alemtuzumab: bradycardia with QT interval prolongation (antihistamines and steroids); hypertension (steroids); kidney tubulopathy (aciclovir)[6].
- During the follow-up, 5 (12.5%) patients reported cutaneous herpes simplex infections that resolved after aciclovir administration, while autoimmune adverse events were not reported.

Figure 1.



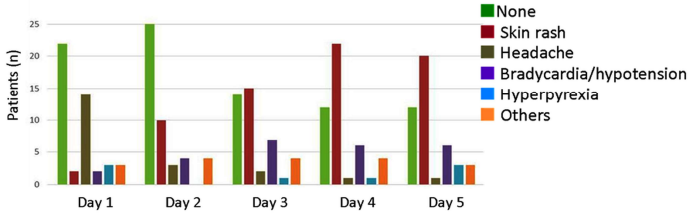
NEDA-3 was defined as absence of either a clinical relapse, or disability worsening, or radiological activity appearance of ≥1 GD-enhancing lesion or new T2-hyperintense lesions (when compared to baseline scan)

Figure 2.



* *versus* baseline (0) by the Wilcoxon Rank Sum test

Figure 3.



CONCLUSION

- Alemtuzumab seems able to promote short-term NEDA-3 in aggressive MS patients, despite previous exposures to multiple DMDs.
- Further data on this population will be collected, elaborated and presented.

References:

1. Coles AJ, Compston DA, Selmaj KW et al. CAMMS223 Trial Investigators. N Engl J Med 2008
2. Cohen JA, Coles AJ, Arnold DL et al; CARE-MS I investigators. Lancet 2012
3. Coles AJ, Twyman CL, Arnold DL et al; CARE-MS II investigators. Lancet 2012
4. Le Page E, Deburghgraeve V, Lester MA et al. J Neurol 2015
5. Tuohy O, Costelloe L, Hill-Cawthorne G et al. J Neurol Neurosurg Psychiatry 2015
6. Bianco A, Gambaro G, Rossini PM, Mirabella M. J Neurol 2015

THIS STUDY WAS SUPPORTED BY GENZYME