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Rolla, Simona; De Mercanti, Stefania Federica; Bardina, Valentina; Horakova, Dana; Habek, Mario; Adamec, Ivan; Cocco, Eleonora; Annovazzi, Pietro; Vladić, Anton; Novelli, Francesco; ...

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Short Communication

Lack of CD4 + T cell percent decrease in alemtuzumab-treated multiple sclerosis patients with persistent relapses

Simona Rolla[a], Stefania Federica De Mercanti[a], Valentina Bardina[a], Dana Horakova[b], Mario Habek[c], Ivan Adamec[c], Eleonora Cocco[d], Pietro Annovazzi[e], Anton Vladic[f], Francesco Novelli[g], Luca Durelli[a], Marinella Clerico[a,*]

[a] Clinical and Biological Sciences Department, University of Torino, San Luigi Gonzaga Hospital, Orbassano (TO), Italy
[b] Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University, General University Hospital, Czech Republic
[c] Department of Neurology, Referral Center for Autonomic Nervous System, University Hospital Center, University of Zagreb, School of Medicine, Zagreb, Croatia
[d] Multiple Sclerosis Center, Department of Medical Science and Public Health, University of Cagliari, Italy
[e] Multiple Sclerosis Study Center, AO S. Antonio Abate, Gallarate (VA), Italy
[f] Department of Neurology, Clinical Hospital Sveti Duh Zagreb, Medical Faculty University, J.J. Strossmayer, Osijek, Croatia
[g] Center for Experimental Research and Medical Studies (CERMS), Azienda Ospedaliera Città della Salute e della Scienza di Torino, Italy

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ABSTRACT

Alemtuzumab, a highly effective treatment for relapsing remitting multiple sclerosis (RRMS), induces lymphopenia especially of CD4 + T cells. Here, we report the atypical CD4 + T population behaviour of two patients with persistent disease activity despite repeated alemtuzumab treatments. Whereas lymphocytes count decreased and fluctuated accordingly to alemtuzumab administration, their CD4 + cell percentage was not or just mildly affected and was slightly below the lowest normal limit already before alemtuzumab. These cases anticipate further studies aimed to investigate whether the evaluation of the CD4 + cell percentage could represent a helpful tool to address the individual clinical response to alemtuzumab.

1. Introduction

Alemtuzumab (Lemtrada™) is a humanized monoclonal antibody that selectively targets the CD52 antigen, expressed mainly on T and B lymphocytes and, at lower levels, on natural killer, monocytes and dendritic cells (Turner et al., 2013; Hartung et al., 2015). In two phase 3 clinical trials (Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis - CARE-MS I and CARE-MS II) (Cohen et al., 2012; Coles et al., 2012) in relapsing remitting multiple sclerosis (RRMS) patients, alemtuzumab resulted more effective than interferon beta-1a (IFN beta-1a) in reducing relapses and brain volume loss. Alemtuzumab induces a profound and prolonged lymphopenia especially of the CD4 + population (Cossburn et al., 2013). The depletion of CD4 + cells usually lasts for years, but an accelerated CD4 + recovery was associated with an early return of disease activity (Cossburn et al., 2013).

2. Cases

Here we report the atypical immunological features of two RRMS patients who presented a sustained disease activity despite alemtuzumab treatment. These patients belong to the cohort of 29 alemtuzumab treated patients from CARE-MS I and CARE-MS II trials of our previous (De Mercanti et al., 2016) and ongoing studies (Durelli et al., 2016). Patients were neurologically evaluated at baseline and then every 6 months or in case of relapses. Immunological studies were performed at baseline and every 6 months during the first 24 months and every 12 months thereafter.

Patient number 1 (P#1) is a 36 years old woman, diagnosed with RRMS in 2000, initially treated with IFN beta-1a, who developed a sustained disease activity with 4 relapses in the two years preceding alemtuzumab administration. The first alemtuzumab course (5 days) was given in July 2009; before alemtuzumab treatment the patient had an EDSS (Expanded Disability Status Scale) (Kurtzke, 1983) score of 2.0. After 12 months the second alemtuzumab course (3 days) was administered and patient EDSS was 1. In June 2012 and in February 2013 the patient had two relapses, with an increase of EDSS score to 2.5 and 3, respectively, both treated with intravenous (iv) methylprednisolone 1000 mg/day for 3 days and a subsequent return to the pre-relapses condition of EDSS 1. After the second relapse, on February 2013, a further 3-day alemtuzumab course was given. In August 2015, the

* Corresponding author.
E-mail address: marinella.clerico@unito.it (M. Clerico).

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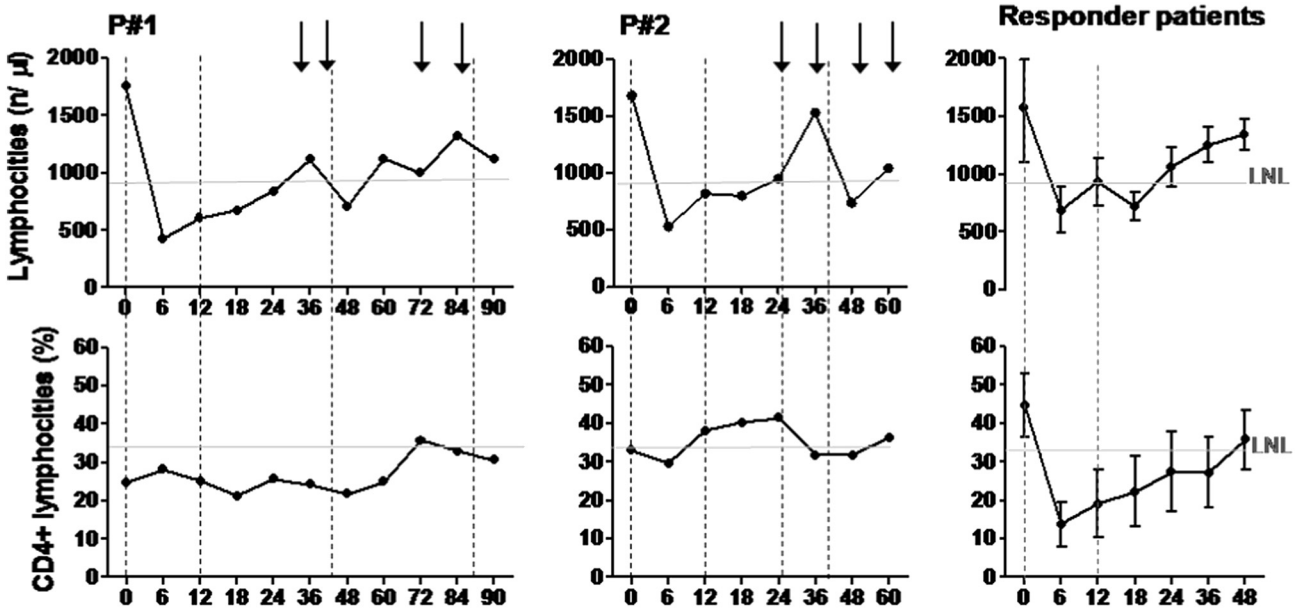

Fig. 1. Effect of alemtuzumab on lymphocyte count (upper panels) and CD4 + T cell percentage (lower panels) in two non-responder (P#1 and P#2) and in 27 responder patients (mean ± SD). Dotted vertical lines indicate alemtuzumab courses, black arrows indicate the clinical and/or radiological relapses during the follow-up. The horizontal lines are the lowest normal limit (LNL).

patient had unique MRI activity without clinical signs of relapse and EDSS 1. In August 2016 the patient presented both new enhancing lesions at MRI as well as clinical manifestation of relapse with EDSS 3. The patient did not recover from the relapse as the EDSS was still 3 and in October 2016 she received a further 3-day alemtuzumab course (Fig. 1).

Patient number 2(P#2) is a 27 years old female, diagnosed with RRMS in 2008; she was treated with IFN beta-1a from 2008 to 2009 and had 2 relapses on January and April 2009; in July 2009 she was randomised in the IFN beta-1a branch and was clinically stable for two years with an EDSS score of 1.5. She was then switched to alemtuzumab in the extension phase of the CARE-MS II study and received the first alemtuzumab course (5 days) in August 2011. In August 2012 she received the second alemtuzumab course (3 days). The patient had a relapse in August 2013 with an EDSS increase to 2.0; she received a further 3-day alemtuzumab course and in January 2014 her EDSS went down to 1.5. In October 2013 she became unexpectedly pregnant and had delivered in July 2014. In the post-partum period (October 2014) she had a clinical relapse, treated with iv methylprednisolone 1000 mg/day for 3 days. In January 2015 she received a further 3-day alemtuzumab course. In October 2015 and August 2016 the patient had two more clinical relapses, associated with evidence of new enhancing lesions at MRI and with an EDSS increase to 3.5. In December 2016 the patient EDSS was 1.5 and she started fingolimod therapy. Both patients did not developed any autoimmune side effects.

These patients display a peculiar behaviour of CD4 + population associated with sustained clinical and radiological disease activity despite repeated alemtuzumab courses. Fig. 1 reports the immunological reconstitution in terms of lymphocytes count and CD4 + T cell percentage in both patients and in the other 27 patients of our cohort that responded to alemtuzumab treatment (responder patients). Six months after the first alemtuzumab course the lymphocytes count was still strongly decreased in both patients: from 1752/µl to 427/µl in P#1 and from 1682/µl to 530/µl inP#2. By contrast the percentage of CD4 + T cells was marginally affected or showed a mild increase in P#1 (from 24.8% to 28.2%). Lymphocyte count then recovered to normal values around Month 24, as in the responder patients, and fluctuated accordingly to alemtuzumab administration, thereafter. In P#1, the percentage of CD4 + T cells, starting below the lowest normal limit (LNL) at baseline, did not change significantly and remained always below LNL with the exception of Month 72 when showed a slight increase during an MRI relapse. In P#2 the percentage of CD4 + T cells, starting just below LNL at baseline, increased at month 24 in concomitance with a relapse, decreased a little after the third alemtuzumab course, and then remained unchanged.

3. Discussion

One of the main challenges in the research on MS is the identification of biomarkers detectable in the biological fluids, especially blood, that could easily identify the response to therapy and guide patient management reliably. In this context, lymphocytes count and their immunological profile seems to act as response predictors to second line drugs in which risks and benefits should be carefully balanced: recently, it was observed that lymphocytes subpopulation evaluation might predict the risk of clinical and radiological activities in fingolimod treated patients (Paolicelli et al., 2017) and that lymphocytosis could be a biomarker of therapeutic efficacy in natalizumab treated patients (Signoriello et al., 2016). Cossburn et al. (Cossburn et al., 2013) reported, in 56 RRMS alemtuzumab treated patients followed for a median of 39.5 months, that relapse-free patients had a significant lower CD4 + lymphocyte count from 6 months after treatment until the end of the study period compared to patients with one or more relapses. Similarly, our case report on the long lasting behaviour of the CD4 + T cells subset in alemtuzumab treated patients shows two patients (followed for 5 and 7.5 years from starting alemtuzumab) with almost unchanged T CD4 + percentage from baseline despite the repeated alemtuzumab administrations needed for clinical and radiological relapses. In our study cohort (De Mercanti et al., 2016; Durelli et al., 2016) alemtuzumab administration strongly affected the percentage of CD4 + cells: it was reduced by 66% at Month 6 and by 51% at Month 12 and then slowly increased returning to baseline around Month 48 (Fig. 1). By contrast, the CD4 + population of these 2 patients seems not affected by alemtuzumab. The CD52 different expression in CD4 + T cell (Bandala-Sanchez et al., 2013) might explain why some patients do not show a CD4 + T cell decrease after alemtuzumab. In addition, the CD4 + T cell percentage was below LNL already before alemtuzumab in those two patients. It could be possible that they had

CD4 + T cells already suppressed by preceding treatment with IFN beta-1a; one of the effects of IFNβ is indeed the impairment of lymphocytes egression from the lymphnodes (Shiow et al., 2006); CD4 + T cells could remain concealed from the usual therapeutic effects of alemtuzuamb as it was hypothesized in patients who developed unexpected disease activity during alemtuzuamb treatment after fingolimod discontinuation (Willis et al., 2017). These patients might so require a treatment with a drug that preferentially affects B rather than T cells, or a better strategy for the therapeutic switch. Based on the small sample size, definitive conclusions cannot be drawn and further analyses are needed. If our results will be confirmed in a higher number of patients, the evaluation of the CD4 + T cells percentage, before and after alemtuzumab treatment, could become a helpful tool to predict clinical response to the drug, in order to better address the therapeutic choice.

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Competing interests statement

Dr. Simona Rolla had travel expenses for congresses paid by Sanofi-Genzyme; Dr. Stefania Federica De Mercanti had travel expenses for congresses paid by Merck, Biogen, Novartis and Sanofi-Genzyme; Dr. Valentina Bardina has not conflict of interest; Dr. Dana Horakova was supported by the Czech Ministry of Education project Progress Q27/LF1 and received compensation for travel, speakerhonoraria and consultant fees from Biogen Idec, Novartis, Merck, Bayer, Sanofi Genzyme, Roche, and Teva, as well as support for research activities from Biogen Idec; Dr. Mario Habek participated as clinical investigator and/or speaker for Biogen, Sanofi Genzyme, Merck, Bayer, Novartis, Pliva/Teva, Roche, Alvogen, Actelion, Alexion Pharmaceuticals; Dr. Ivan Adamec reports no disclosures; Dr. Eleonora Cocco received support for participating to advisory boards from Biogen, Bayer, Genzyme- Sanofi, Serono, Novartis and Teva and for lectures from Almirall, Biogen, Bayer, Serono, Novartis, Genzyme- Sanofi and Teva; Dr. Pietro Annovazzi received support for consultancy from Sanofi-Genzyme, Novartis, Teva, Biogen, Serono and Roche, for lectures from Biogen, Teva and Novartis, for travel accommodation from Sanofi-Genzyme, Biogen and Teva; Dr. Anton Vladic reports no disclosures; Dr. Francesco Novelli reports no disclosures; Prof. Luca Durelli received personal compensation by Sanofi-Genzyme for participating to advisory boards; by Merck for editorial collaborations and had travel expenses for congresses paid by Merck, Biogen, Novartis and Sanofi-Genzyme; Dr. Marinella Clerico received personal compensation by Merck and Biogen for participating to advisory boards; by Merck for editorial collaborations and had travel expenses for congresses paid by Merck, Biogen, Novartis and Sanofi-Genzyme.

Contributorship statement

SR, VB, FN: analysis and interpretation of immunological data; SFDM, MC: analysis and evaluation of clinical data; DH, MH, IA, EC, PA, AV: clinical follow-up and recording of clinical data; SR, SFDM, LD and MC: drafting/revising the manuscript for content, including medical writing for content; LD: study concept and design.

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