European Journal of Clinical Pharmacology
https://doi.org/10.1007/s00228-020-02959-0

LETTER TO THE EDITOR

Durvalumab and multiple sclerosis: a causal link or simple unmasking?

Francesca Caputo[1] · Alessia Manni[1] · Pietro Iaffaldano[1] · Maria Trojano[1] · Damiano Paolicelli[1]

Received: 8 May 2020 / Accepted: 9 July 2020

Dear Sirs,

Immune checkpoint inhibitors (ICIs) became the new milestone of the immune-oncology therapy. This family includes three drug classes: anti-cytotoxic T lymphocyte–associated protein4 (CTLA4), anti-programmed cell death 1 (PD-1), and anti-programmed death-ligand 1 (PD-L1). Durvalumab is a monoclonal antibody that prevents the binding of PD-L1 with PD-1 and CD80, stimulating immune response against tumors [1, 2]. The phase III clinical trial PACIFIC showed that durvalumab improved the overall survival in patients with non-small cell lung cancer (NSCLC) treated with definitive chemoradiotherapy (CRT) [3]. Therefore, it was recently approved, both by the US Food and Drug Administration and the European Medicines Agency, for patients with unresectable stage III NSCLC and unprogressed disease following CRT. However, its toxicity on central nervous system (CNS) is not well established. To date, cases of exacerbations or new diagnosis of multiple sclerosis (MS) during durvalumab are not reported in literature, nor in the main databases of pharmacovigilance (https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard; http://www.adrreports.eu/it/search.html). According to our knowledge, we hereby describe the first case of a patient who develops brain magnetic resonance imaging (MRI) demyelinating lesions during durvalumab therapy.

In 2018, a Caucasian 46-year-old man was diagnosed with locally advanced pulmonary adenocarcinoma EGFR and KRAS wild type. The PD-L1 expression was >1%. After CRT, he started durvalumab 120 mg endovenously. After ten infusions, restaging whole-body computed tomography showed a reduction of the lung neoformation but a right peritrigonal contrast enhancing (CE+) lesion. A brain MRI revealed other multiple T2 white matter hyperintensities, with subcortical and periventricular localization diagnosed as demyelinating lesions (Fig. 1). The spinal cord MRI was normal. Durvalumab was discontinued, and the patient received a course of methylprednisolone 1 g/die ev for 4 days, with a reduction of CE+. He was admitted to our Neurology Department to rule out a demyelinating disorder, and he reported fluctuating episodes of paraesthesia of right limbs since 2013. The neurological examination was unremarkable. All clinical and laboratory tests were normal, but the cerebrospinal fluid analysis showed twenty-three oligoclonal bands.

He was diagnosed with MS according to 2017 McDonald criteria. Considering the clinical features and his comorbidity, he started treatment with glatiramer acetate 40 mg three times per week subcutaneously. From the beginning of this therapy, MS remained stable. Since his malignancy did not show radiological signs of progression, durvalumab was not restarted.

Our case suggests that PDL-1 is an immunological checkpoint that may trigger active demyelinating lesions in CNS. Although it is unknown if ICIs anti-PD1 and anti-PDL1 can determinate de novo demyelinating diseases, they can exacerbate or unmask them, since the PD-1/PD-L1 pathway modulates immune functions in MS patients [4]. Moreover, in experimental autoimmune encephalomyelitis (EAE), mice with aberrant T cell regulation for PD-1 deficiency show increased T lymphocytes expansion with an earlier onset or worsening of EAE compared with wild-type mice [5]. Furthermore, it is hypothesized that PDL-1 is overexpressed on astrocytes and microglia in inflammatory environments; therefore, the anti-PD-1/PD-L1 antibodies could increase preexisting inflammatory conditions [6].

Considering the wide use of anti-PDL1 in cancer therapy and how other ICI agents can cause a rapid worsening of neurological status and deaths in MS patients [7], it is crucial to be aware of durvalumab's role in neurological inflammatory disease, even if no demyelinating events has been reported during PACIFIC study. Nowadays, we are aware how post-

✉ Damiano Paolicelli
damiano.paolicelli@uniba.it

[1] Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari, Bari, Italy

Published online: 13 July 2020

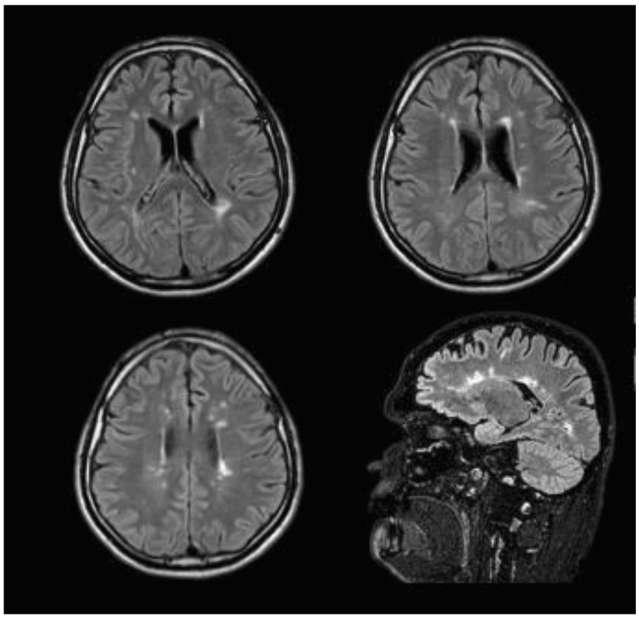

Fig. 1 Periventricular and subcortical demyelinating lesions in the brain and in the corpus callosum shown by MRI scans (T2-weighted fluid-attenuated inversion recovery) after ten infusions of durvalumab

authorization safety studies are needed to assess the complex performance of new drugs in the real world and to discover uncommon or rare adverse events. Therefore, a multidisciplinary approach is mandatory for the management of these new biodrugs especially in patients with a diagnosis of MS or with red flags for preexisting neurological pathologies.

Compliance with ethical standards

Conflict of interest F. Caputo and A. Manni report no disclosures relevant to the manuscript.

P. Iaffaldano received advisory board membership, speaker honoraria, travel support, research grants, consulting fees, or clinical trial support from Almirall, Bayer Schering, Biogen, Celgene, Excemed, Genzyme, Merck, Mylan, Novartis, Sanofi, Roche, and Teva.

M. Trojano received advisory board membership, speaker honoraria, travel support, research grants, consulting fees, or clinical trial support from Actelion, Allergan, Almirall, Bayer Schering, Biogen, Celgene, Excemed, Genzyme, Merck, Mylan, Novartis, Sanofi, Roche, and Teva.

D. Paolicelli received advisory board membership, speaker honoraria, travel support, research grants, consulting fees, or clinical trial support from Almirall, Bayer Schering, Biogen, Celgene, Excemed, Genzyme, Merck, Mylan, Novartis, Sanofi, Roche, and Teva.

References

1. Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E, Watkins A, Mullins S, Chodorge M, Andrews J, Bannister D, Dick E, Crawford N, Parmentier J, Alimzhanov M, Babcook JS, Foltz IN, Buchanan A, Bedian V, Wilkinson RW, McCourt M (2015) Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Res 3: 1052–1062
2. Postow MA, Callahan MK, Wolchok JD (2015) Immune checkpoint blockade in cancer therapy. J Clin Oncol 33:1974–1982
3. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Yokoi T, Chiappori A, Lee KH, de Wit M, Cho BC, Bourhaba M, Quantin X, Tokito T, Mekhail T, Planchard D, Kim YC, Karapetis CS, Hiret S, Ostoros G, Kubota K, Gray JE, Paz-Ares L, de Castro Carpeño J, Wadsworth C, Melillo G, Jiang H, Huang Y, Dennis PA, Özgüroğlu M, PACIFIC Investigators (2017) Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 377:1919–1929
4. Trabattoni D, Saresella M, Pacei M, Marventano I, Mendozzi L, Rovaris M, Caputo D, Borelli M, Clerici M (2009) Costimulatory pathways in multiple sclerosis: distinctive expression of PD-1 and PD-L1 in patients with different patterns of disease. J Immunol 183: 4984–4993
5. Kroner A, Schwab N, Ip CW, Ortler S, Göbel K, Nave KA, Mäurer M, Martini R, Wiendl H (2009) Accelerated course of experimental autoimmune encephalomyelitis in PD-1-deficient central nervous system myelin mutants. Am J Pathol 174:2290–2299
6. Yshii LM, Hohlfeld R, Liblau RS (2017) Inflammatory CNS disease caused by immune checkpoint inhibitors: status and perspectives. Nat Rev Neurol 13(12):755–763
7. Garcia CR, Jayswal R, Adams V, Anthony LB, Villano JL (2019) Multiple sclerosis outcomes after cancer immunotherapy. Clin Transl Oncol 21:1336–1342