

Pathophysiological mechanisms and management of patients with long-time anosmia related to COVID-19

Dear Editor,

We carefully read the letter of Locatello *et Oreste* regarding our paper entitled 'Prevalence and 6-month recovery of olfactory dysfunction: a multi-centre study of 1363 COVID-19 patients' [1]. The authors [2] highlighted an important unresolved issue: the pathophysiological mechanisms and the management of patients with long-term anosmia. As stated by authors, the development of anosmia is related to the infection of the sustentacular and basal cells, which highly express ACE2 [3,4]. We know that the ACE2 expression may substantially vary between individuals regarding ethnicity, genetic pattern, etc [3]. In that way and because the regeneration of sustentacular cells is usually more rapid, the persistence of long-term anosmia is still mysterious. According to a recent systematic review, it seems conceivable that some patients may express ACE2 in their olfactory neurons [4], which may therefore be injured during the inflammatory reaction. Considering the longer regenerate time of olfactory neurons, the recovery of olfactory function in these patients could be longer than those of patients who express ACE2 only on sustentacular and basal cells. Interestingly, recent studies reported that SARS-CoV-2 may persist in the host body through anatomical sanctuaries [5], leading to potential re-activation [6]. Another theoretical explanation of long-term anosmia consists of the persistence of virus into the olfactory bulb (sanctuary) and the repeated reinfections of sustentacular and basal cells leading to chronic immune response and inflammatory cell destruction. This hypothesis is less probable but has to be investigated in future functional imaging and basic science studies.

As proposed by authors, the management of COVID-19 patients with olfactory dysfunction has to be based on olfactory training [7], whilst additional molecules could be proposed, such as alpha-lipoic acid, vitamin A or zinc [7,8]. All patients in our study followed olfactory training over the follow-up. We did not give nasal or oral corticosteroids because they were carefully contraindicated in the onset of the pandemic [9]. However, nowadays, we believe that the use of oral

corticosteroids may particularly sense regarding two previous studies reporting safety and better olfactory outcomes in COVID-19 anosmic patients taking oral corticosteroids compared with those only following olfactory training [10,11]. Although these studies did not include a large number of patients, authors did not report a worsening of the disease after the intake of oral corticosteroids. The interest of nasal corticosteroids was not yet demonstrated in patients with COVID-19. The use of nasal corticosteroids may be consistent in patients with olfactory cleft oedema, which seems to be a transient mechanism of olfactory loss in COVID-19 [12]. Future studies are needed to demonstrate the potential interest of nasal corticosteroids and to compare their efficacy with the other drugs.

Conflict of interest

The authors have no conflicts of interest.

Author contribution

Jerome R Lechien: Conceptualization (equal); Investigation (equal); Methodology (equal); Writing-original draft (equal). **Carlos M Chiesa-Estomba:** Supervision (equal); Validation (equal). **Stephane Hans:** Supervision (equal); Validation (equal). **Sven Saussez:** Supervision (equal); Validation (equal); Writing-review & editing (equal).

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