Systemic corticosteroids in COVID-19 related smell dysfunction: an international view.

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Summary

The frequent association between COVID-19 and olfactory dysfunction is creating an unprecedented demand for a treatment of the olfactory loss. Systemic corticosteroids have been considered as a therapeutic option. However, based on current literature, we call for caution using these treatments in early COVID-19 related olfactory dysfunction since (1) evidence supporting their usefulness is weak; (2) the rate of spontaneous recovery of COVID-19 related olfactory dysfunction is high and (3) corticosteroids have well-known potential adverse effects. We encourage randomized placebo-controlled trials investigating the efficacy of systemic steroids in this indication. Based on current knowledge, we strongly emphasize to initially consider smell training, which has no known side effects, is low cost and is supported by a robust evidence base.

Text

The high rate of patients experiencing COVID-19 related olfactory dysfunction (C19OD) (approximately 20% of COVID-19 patients are reported to have OD at 8 weeks after the onset of the disease[1]) and mental and physical burden induced by losing the sense of smell is creating an unprecedented demand for a treatment of the olfactory loss.

In contrast to previously known, non-COVID-19 associated, postinfectious olfactory dysfunction where patients usually present for medical consultation months after the infectious event, C19OD patients are being seen earlier in the course of the disease at specialised smell and taste centers. The heightened attention to smell disorders and the pronounced fear that of COVID-19 associations, paired with the worries about recovery, may biases our approach to very early changes after postinfectious smell disorders. This presents a unique opportunity for an early intervention, but also raises the question whether such intervention is needed to increase the likelihood for olfactory recovery.

C19OD likely results from two separate pathological processes. First, an obstructive inflammatory process blocking odorant access[2] at an early stage of the disease; and second, a neurosensory post-infectious smell loss [3,4].

Systemic corticosteroids (CS) are part of the ENT armamentarium in several inflammatory (i.e. chronic rhinosinusitis (CRS)) and sensorineural conditions (i.e. sudden sensorineural hearing loss (SSNHL) and idiopathic facial palsy). CS are also considered as neuroprotective agents in acute neurological conditions such as spinal cord injury. Consequently, systemic CS therapy has been considered as an option to treat C19OD[5]. However, it is important to consider the balance of risks and benefits of systemic CS. In the absence of data supporting the lack of major side effects of systemic CS in COVID-19 patients, several professional groups such as

EAACI[6] have called for caution and recommended against the use of systemic CS in CRS during COVID-19. Moreover, the efficacy of CS in their classical neurological indications, such as SSNHL and acute spinal cord injury remains questionable[7,8], and it is well know that their use is associated to potentially serious adverse effects[8]. Therefore, when considering whether such treatment should be used for C19OD, natural history and potential added benefit versus treatment risk must be carefully considered.

As an expert group in clinical olfaction, we aim to briefly review and summarize evidence for and against CS treatment in C19OD based on current literature on COVID-19 and post-infectious olfactory loss in general.

Rate of COVID-19 related olfactory dysfunction and spontaneous recovery

Recent meta-analyses have determined that the pooled frequency of OD in COVID-19 patients (either based on questionnaire or smell psychophysical tests) was 56%[9]-61%[10]. However, there is extremely high variability in the reported prevalence of this symptom, ranging from 5%[11] to 98%[12].

Similarly, documented rates of olfactory recovery amongst COVID-19 patients vary, most likely due to methodological discrepancies and sampling bias both between and within studies. However, in general there appears to be a high rate of recovery. At one month, authors found resolution rates of OD in 33%-96% of patients[13-17]. At 2 months, return to normal olfactory function was reported by 54% of patients[18]. Figure 1 details reported rates of OD as a function of time, based on self-assessment[13-21]. When assessing olfactory function based on psychophysical testing (Figure2), follow-up studies found a 63% rate of normosmia at 5 weeks[22], 54%-79% at 2 months [1,23,24]; 86% at 3 months[25] and 95% at 6 months[21]. Of note, the

rate of hyposmia in the general population is approximately 20%[26,27]. Although it is probable that a majority of patients reporting C19OD had normal olfaction at baseline, it cannot be ruled out that some were hyposmic at baseline and became alerted to it through COVID-related public attention.

Consequently, it appears from the current literature that C19OD is largely reversible for most affected patients in the short- to medium-term, while a significant minority progress to a persistent olfactory dysfunction characterized by hyposmia and, in many cases, parosmia, typical of a neural post-infectious OD[28].

Usefulness of CS in post-infectious olfactory dysfunction

Although several studies have investigated the usefulness of CS administered through different formulations, routes and doses in patients with post-infectious olfactory dysfunction (PIOD), their general efficacy remains controversial[29,30].

A recent systematic evidence-based review investigated the use of CS in non-sinonasal OD[30], and reported very weak evidence to support the use of systemic CS therapy (Level 4). Of note, it appears that topical CS sprays are not effective in non-sinonasal OD. The only evidence suggested that, in conjunction with olfactory training, nasal irrigation with budesonide has more favourable outcome than saline irrigation alone among patients with non-sinonasal OD[31] (Level 1b). However, for this last study, results have not been interpreted as a function of the aetiology and it is difficult to generalise these results to the PIOD population. Another recent evidence-based review of treatment options for PIOD concluded that olfactory training is a recommendation for the treatment of PIOD; while systemic or topical steroids remain "optional" due to the lack of high-quality studies[29].

It has been suggested that the favourable effect of CS in PIOD could be attributed to their effects on any underlying sinonasal inflammation[30,32], theoretically resulting from mucosal effects of an upper respiratory tract infection. Thus, standard rhinological examination remains mandatory in patients with persistent olfactory loss and rhinosinusitis must be treated appropriately[32,33].

Importantly, although CS are often reported as having the potential to improve olfactory function, an animal study found that they may impair the neuronal regeneration at the level of the olfactory epithelium[34].

Therefore, there is low level evidence supporting the usefulness of CS in PIOD. Although level 4 studies suggest that systemic CS could improve olfactory loss in PIOD (Level 4), there is a lack of high-quality studies, and no consensus can be reached at this time. On the other hand, there is also low evidence that CS are not effective or would impair olfactory function. Currently, CS are thus considered as a therapeutic option in selected patients and after personalised consideration of the potential risk[5,29].

In contrast, a currently accepted recommendation for the treatment of non-COVID-19 PIOD is smell training[29,32], which has been shown with solid data[29,32] to improve the recovery of PIOD.

Systemic CS in COVID-19 patients

At the onset of the pandemic, caution was recommended regarding the use of systemic CS due to the uncertainty regarding their immunosuppressive effect in COVID-19. However, they have turned out to constitute an important weapon against COVID-19[35], and are recommended by the WHO in patients with severe and critical COVID-19 since they appear to reduce 28-day mortality[36]. Conversely, their use is not recommended in patients with mild

COVID-19 because it may increase the risk of death when administrated in non-severe COVID-19 patients[35,36] although this was a conditional recommendation based on low certainty evidence. Of note, it has been suggested that OD mainly affects patients with mild COVID-19[37] although this is still debated.

A recent case report suggested that systemic CS could be effective for the treatment of C19OD[38]. In this case report, a patient with anosmia received oral prednisolone, after failure of topical steroids, and was found to improve 6 days later. However, due to the rate of spontaneous recovery of C19OD, it cannot be ruled out that this is the natural evolution of the disease. Recently, a prospective study aimed to compare the efficacy of systemic CS associated with olfactory training (9 patients) to olfactory training alone (18 patients). The study found that only patients with combined therapy significantly improved olfactory function at 10 weeks follow-up. However, this has to be tempered by the fact that groups were not exactly similar. There was a higher number, and hence a higher variance, of patients in OT group. Also, patients receiving systemic CS were mainly anosmic and had therefore a higher chance to spontaneously improve their olfactory function. Moreover, there were no data regarding endoscopic examination and signs of nasal inflammation[39]. Another prospective study evaluating the rate of recovery of OD among COVID-19 patients found that neither topical (administrated in 71 patients) nor systemic CS (administrated in 58 patients) influenced the prognosis of olfactory recovery[40]. Therefore, there is currently no robust evidence supporting a potential effect of systemic CS in COVID-19 patients.

QUESTIONS:

Please answer to these questions:

Fully agreeing / partly agreeing / partly disagreeing / fully disagreeing

- Systemic CS should be prescribed within 3 first weeks after the onset of COVID-19 OD

(fully disagree)

- Systemic CS should be considered as a first line treatment in COVID-19 OD

(fully disagree)

- There is no place for systemic CS in the treatment of COVID-19 OD

(partly disagree)

- In the lack of evidence, caution should prevail, and systemic CS should not be considered as a standard treatment in patients with COVID-19 OD

-(fully agree)

- Olfactory training should be prescribed as soon as possible in the course of COVID19 OD

-(fully agree)

Discussion

Acute C19OD and classical PIOD may exhibit some differences. For example, the high number of young and even adolescent patients experiencing impaired smell differentiates this condition from PIOD. However, C19OD and classical PIOD share many similarities including the temporary and more permanent form of OD, the frequent presence of parosmia, or the higher frequency of women affected. Extrapolation from classical PIOD may be tempting, but there is considerable bias in terms of the attention C19OD has received compared to previous

PIOD which was often disregarded by the medical community and perhaps unnoticed by patients.

Current evidence supporting the usefulness of systemic CS in PIOD, and in particular for C19OD, is weak; while the rate of spontaneous recovery of C19OD is high. Considering the potential acute and possibly long-term adverse effects of CS, we suggest that caution must prevail, and systemic CS should not be considered as standard of care treatment intended for all patients having C19OD, in the early phase of the disease.

To adequately stratify the risks and benefits related to systemic CS treatment, randomized placebo-controlled trials should be considered, and the question of the dose and duration of the treatment must be investigated. Moreover, it is notable, from our cumulative experience, that many C19OD patients complain of parosmia, frequently appearing several months after the acute infectious event[28]. Therefore, long-term follow-up studies are needed to evaluate whether CS treatment has the potential to decrease the risk of developing qualitative olfactory disorders. Given that many patients appear to recover without intervention, it will likely take large numbers of patients in such trials to demonstrate enhanced recovery with corticosteroid treatment, although given the recent increases in COVID19, recruitment may not be difficult, sadly.

Considering the full spectrum of CS route of administration, an alternative is the use of topical CS. The option of nasal lavage with CS should also be investigated because it has been suggested that it could constitute an efficient and potentially less harmful alternative compared to systemic CS. However, their efficacy has not been specifically studied in PIOD patients and more data are needed to confirm their usefulness. Although we mentioned that

topical CS are typically not useful to treat PIOD, this may also be related to the fact that classical nasal spray administration does not reach the olfactory cleft. It has been suggested that the use of specific nasal cannulas for administration of sprays[41] or application of nasal drops in the Kaiteki position[42] could be effective for delivering medications into the olfactory cleft. Therefore, studies considering the effectiveness of different routes of administration of CS will be useful to define the most efficient option, if there is one.

Conclusion

Currently there is no evidence that any kind of CS treatment may substantially change the outcome of C19OD. In contrast there is sufficient evidence that even limited unjustified systemic CS treatment has harmful side effects such as long term increased risk for hip fractures or decompensating glaucoma[43]. In light of the huge number of patients possibly receiving steroids for C19OD, based on poor evidence, we call for caution using these treatments. At the same time, we encourage controlled studies investigating this issue.

As an expert group we strongly emphasize to initially consider smell training[44]. Smell training has no known side effects and is low cost. Moreover, it is the only available treatment for PIOD supported by a robust evidence base[29,32].

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Figure legends

Figure 1

Rates of self-reported olfactory loss (absent or incomplete recovery) among COVID-19 patients over time, based on available literature. References are mentioned at the top of the bars. Time is expressed as the average delay between the onset of the COVID-19 and rating of olfactory function. The dashed horizontal line represents the rate of hyposmia among the general population[26].

Figure 2

Distribution of the rates of normosmia, hyposmia and anosmia among patients infected by SARS-CoV-2, at 4 weeks, 5 weeks, 2 months, 3 months and 6 months after the onset of the disease. Olfactory function was assessed using diverse psychophysical methods (SST: Sniffin' Sticks Test; SAOT: Self-administrated olfactory Test; CCCRC: Connecticut Chemosensory Clinical Research Center; B-SIT: Brief Smell Identification Test). References are reported at the top of the bar. The dashed horizontal line represents the rate of hyposmia among the general population[26].