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LETTER

Systemic isotretinoin therapy in the era of COVID-19

Dear Editor,

Oral isotretinoin (13-*cis*-retinoic acid), a synthetic analog of vitamin A, is a first-generation retinoid approved for the treatment of severe cases of acne vulgaris. Isotretinoin can only be used as second-line treatment for acne when appropriate response to systemic antibiotics, such as doxycycline, and topical therapy could not be achieved within a 3-month course of therapy. Practically, isotretinoin benefit is not limited to severe forms of acne, but also for mild-to-moderate acne in addition to a wide range of "off-label" uses.[1] Although acne is principally a disorder of adolescence (12-18 years), adult patients may be also affected.[2] Interestingly, there are 965 reported cases in China with COVID-19 in patients younger than age of 19.[3] Transmission of COVID-19 infection from an asymptomatic carrier (silent infection), including adolescents, has been reported. Asymptomatic carrier is usually prone to have various nonspecific atypical manifestations and be mildly ill during hospitalization.[4]

The recommended daily dose of isotretinoin ranges from 0.3 to 0.5 mg/kg for a duration of at least 6 months in the European guidelines. In case of insufficient response, the course of treatment period can be extended. Two or three courses of isotretinoin may be required for relapsed cases, that is, acne retrial. Relapse rate may be correlated directly with decreased total systemic exposure to isotretinoin.[5] Lidose-isotretinoin was hence suggested by experts to improve drug bioavailability.[6]

Most of the side effects of isotretinoin are skin related and associated with xerosis.[5] Drylip/cheilitis was the most known side effect reported by 241 patients on isotretinoin studied by Tugrul et al.[7] In another study, dry nasal membrane has also been reported in two-thirds of patients during isotretinoin treatment,[2] which can lead to epistaxis. Nasal complications are generally not serious, especially with low-dose isotretinoin.[8]

Nasal mucosa is a vulnerable area for virus or bacteria to colonize owing to its abundant blood vessels, mucinous glands, and serous glands which create a humid environment. Angiotensin-converting enzyme-2 (ACE2) receptor expression was found in the basal layer of the nonkeratinizing squamous epithelium in nasal mucosa. Breakdown of nasal mucosal, exposing the basal layer, would increase of likelihood nasal mucosa invasion by coronaviruse.[9]

Isotretinoin treatment disturbs nasal mucociliary clearance significantly, which reduces normal and regenerated mucosal thickness, causing severe inflammation, increasing the reactive changes in the respiratory epithelium, and higher recruitment of neutrophils in the nasal surface mucosa.[10,11] A theoretical increased risk of COVID-19 viral load is hence thought by the British Association of Dermatologists (https://www.bad.org.uk/shared/get-file.ashx?itemtype=document&id=6661).

Chinese experts recommended to clean nasal vestibule with normal saline, tap water or suds, or to wipe the nasal vestibule using gentle cotton swab dipped with water/mucosa disinfectants for three to five rounds to ensure entire cleansing, which could be applied for both health care worker dealing with COVID-19 patients and those on isotretinoin.[12] Nasal moisturizers (D-panthenol, vaseline, glycerin, hypertonic solutions, and hyaluronic acid) are also recommended for these patients before starting isotretinoin, during the treatment, and for few months after the end of the treatment, as recommended by otorhinolaryngologist.[13]

Coronavirus may be also detected in the nasal discharge of patients with olfactory dysfunction. Nasal cavity olfactory epithelium is the likely site of enhanced binding of SARS-CoV-2. Olfactory epithelium non-neural cell types express two host receptors, ACE2 and type 2 transmembrane serine protease (TMPRSS2), that facilitate SARS-CoV-2 replication and accumulation, and subsequently central nervous system invasion which may lead to respiratory failure of COVID-19 patients.[14] Lechien et al noted that 85.6% of their patients had olfactory dysfunction (79.6% were anosmic and 20.4% were hyposmic) related to COVID-19 infection, with no significant associated rhinorrhea or nasal obstruction. Olfactory dysfunction signs may appear before, during, or after the general symptoms of COVID-19.[15] Olfactory dysfunction can be a possible phenotypic marker of folate deficiency in treatment-resistant depression.[16] Isotretinoin has an enhancing effect on olfactory function in acne patients.[17]

As transcription of TMPRSS2 gene requires androgen receptor hyperactivity. Patients with hyperandrogenic phenotype, such as polycystic ovaries (PCO), might have a risk of COVID-19 increased viral load, increased viral dissemination and severity of lung involvement.[18] Feily et al noted that low-dose isotretinoin (0.5 mg/kg/day for 15-20 weeks) in PCO patients with moderate-to-severe nodulocystic acne resulted in significant decreases in levels of serum total testosterone, prolactin, and dihydrotestosterone but increased dehydroepiandrosterone levels.[19]

In nutshell, till further studies on the multifaceted pathogenesis of COVID-19 infection, we suggest low, lid-dose of isotretinoin with folic acid supplement, together with proper nasal mucosal care for isotretinoin patients. Isotretinoin treatment should be questioned in all COVID-19 suspected patients presented with nasal/olfactory dysfunction symptoms.

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REFERENCES

1. Abdelmaksoud A, Lotti T, Anadolu R, et al. Low dose of isotretinoin: a comprehensive review. *Dermatol Ther*. 2020;33(2):e13251.
2. Skroza N, Tolino E, Mambrin A, et al. Adult acne versus adolescent acne: a retrospective study of 1,167 patients. *J Clin Aesthet Dermatol*. 2018;11:21-25.
3. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *Jama*. 2020;323(13):1239–1242. https://doi.org/10.1001/jama.2020.2648.
4. Huang L, Zhang X, Zhang X, et al. Rapid asymptomatic transmission of COVID-19 during the incubation period demonstrating strong infectivity in a cluster of youngsters aged 16-23years outside Wuhan and characteristics of young patients with COVID-19: a prospective contact-tracing study. *J Infect*. 2020. https://doi.org/10.1016/j.jinf.2020.03.006.
5. Dessinioti C, Zouboulis CC, Bettoli V, Rigopoulos D. Comparison of guidelines and consensus articles on the management of patients with acne with oral isotretinoin. *J Eur Acad Dermatol Venereol*. 2020. https://doi.org/10.1111/jdv.16430.
6. Del Rosso JQ, Stein Gold L, Segal J, Zaenglein AL. An open-label, phase IV study evaluating lidose-isotretinoin administered without food in patients with severe recalcitrant nodular acne: low relapse rates observed over the 104-week post-treatment period. *J Clin Aesthet Dermatol*. 2019;12(11):13-18.
7. Tugrul Ayanoglu B, Demirdag HG, Yalici Armagan B, Bezirgan O. Perceptions about oral isotretinoin treatment. *Dermatol Ther*. 2019;32(3):e12873.
8. Gorpelioglu C, Ozol D, Sarifakioglu E. Influence of isotretinoin on nasal mucociliary clearance and lung function in patients with acne vulgaris. *Int J Dermatol*. 2010;49(1):87-90.
9. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 2004;203:631-637.
10. Cengiz AB, Ozyilmaz C, Tabaru A, et al. Effects of oral ısotretinoin on normal and wounded nasal mucosa: an experimental study. *Eur Arch Otorhinolaryngol*. 2018;275(12):3025-3031.
11. Takci Z, Simsek GG, Karabulut H, Buran Y, Karadag AS. Effect of systemic isotretinoin therapy on mucociliary clearance and nasal surface mucosa in acne patients. *J Drugs Dermatol*. 2013;12(8):e124-e128.
12. Yan Y, Chen H, Chen L, et al. Consensus of Chinese experts on protection of skin and mucous membrane barrier for health-care workers fighting against coronavirus disease 2019. *Dermatol Ther*. 2020;33(4):e13310. https://doi.org/10.1111/dth.13310.
13. İşlek A, Yıldız MG. 2020. Evaluation of nasal Mucociliary clearance, nasal obstruction symptom evaluation, and epistaxis severity score in isotretinoin treatment. *Ear Nose Throat J* 2020 Apr 13:https://doi.org/10.1177/0145561320920425.
14. Butowt R, Bilinska K. SARS-CoV-2: olfaction, brain infection, and the urgent need for clinical samples allowing earlier virus detection. *ACS Chem Neurosci*. 2020;11(9):1200–1203. https://doi.org/10.1021/acschemneuro.0c00172.
15. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol*. 2020. https://doi.org/10.1007/s00405-020-05965-1.
16. Singh J, Ahmad J, Kar SK. Olfactory and gustatory dysfunction in depression: could it be a marker of folate deficiency? *Aust N Z J Psychiatry*. 2016;50(1):99-100.
17. Kartal D, Yaşar M, Kartal L, özcan I, Borlu M. Effects of isotretinoin on the olfactory function in patients with acne. *An Bras Dermatol*. 2017;92(2):191-195.
18. Wambier CG, Goren A. SARS-COV-2 infection is likely to be androgen mediated. *J Am Acad Dermatol*. pii: S0190-9622(20)30608-3. 2020. https://doi.org/10.1016/j.jaad.2020.04.032.
19. Feily A, Taheri T, Meier-Schiesser B, et al. The effect of low-dose isotretinoin therapy on serum androgen levels in women with acne vulgaris. *Int J Womens Dermatol*. 2019;6(2):102-104.