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Inhaled corticosteroids in early COVID-19—A tale of many facets

To the Editor,

Following our early report in Allergy,[1] there was several studies published in the same direction showing the benefit of continuation of inhaled steroids in COVID-19. Inhaled budesonide represents a standard of care for patients with asthma, allergic rhinitis, and chronic rhinosinusitis.[1-3] It is recommended that in COVID-19, patients with chronic inflammatory airway diseases should continue guideline-based pharmacological treatment, including ICS and/or biological therapies.[1,2] New data indicate that patients with various asthma endotypes may show a different risk profile for SARS-CoV-2 infection and a different course of COVID-19. Patients suffering from allergic asthma (type 2 inflammation) seem to have a lower risk of developing COVID-19 than patients with non-type 2 asthma.[4]

Ramakrishnan et al. performed an open-label, parallel-group, randomized controlled trial to compare standard of care with the additive use of inhaled budesonide (Figure 1).[5] The authors claim that this is an easily accessible and effective intervention in early COVID-19. Their data also suggest a potential benefit in the prevention of long COVID-19.

However, these statements may not be sufficiently proven. This was an open study, in which patients and staff were aware of the therapy used. *Placebo* effects, for example, for inhalant asthma drugs, can be observed in 21 to 46% of cases, especially for subjective outcomes.[6] Effects assessed during this study, including the primary endpoint (COVID-19-related urgent care visit, including emergency department visits or hospitalization), may all be influenced by the subjective perception of the patients and their treating physicians. Secondary endpoints, including objective measures like blood oxygen saturation and SARS-CoV-2 load, were not different between the groups. The study population was small, including 146 participants of which 73 were randomized to usual care and 73 to the budesonide group. A cautious interpretation of these data is warranted, since an updated interim analysis from a larger phase-III study, including 2,617 people with risk factors for adverse outcomes with COVID-19, did not show such favorable results.[7] Inhaled budesonide reduced the time to self-reported recovery by a median of 3 days. However, it did not meet the primary outcome parameter (COVID-19 hospitalizations/deaths) even though these rates were

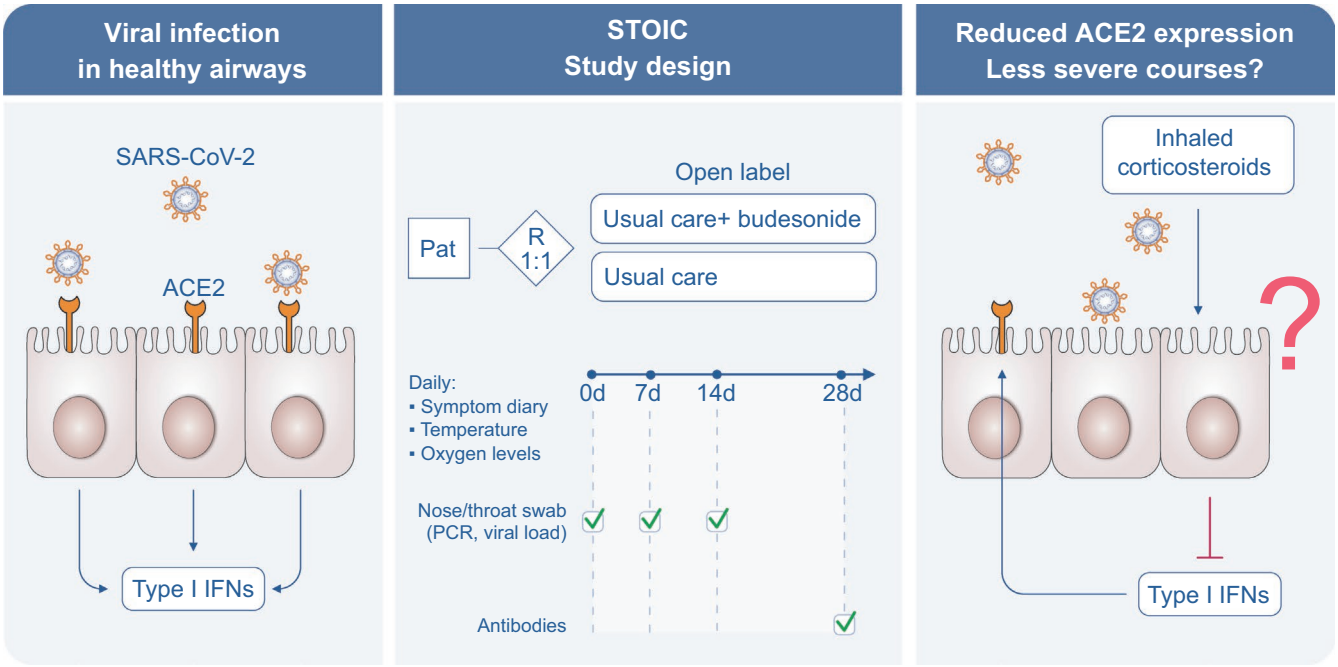

FIGURE 1 SARS-CoV-2 is entering the airways epithelial cells via ACE2-receptors. The study aims to proof protection in respond to SARS-CoV-2 infection using topical Budesonide. In general, this study does not allow to generate sufficient information to answer the question, whether early treatment with Budesonide is protecting against severe courses of COVID-19

lower in the budesonide versus the usual care group (59/692 (8.5%) and 100/968 (10.3%), respectively).[7]

Ramakrishnan et al. hypothesized that an early administration of inhaled budesonide is beneficial at the early stage of COVID-19 (Figure 1). Importantly, this would suggest a low-cost and safe therapy. However, based on the evidence from this and other studies, more research is still necessary to support this recommendation.

KEYWORDS

COVID 19, inhalant steroids, SARS-CoV-2, treatment

CONFLICT OF INTEREST

Dr. Klimek reports grants and personal fees from Allergopharma, grants and personal fees from MEDA/Mylan, personal fees from HAL Allergie, grants from ALK Abelló, grants and personal fees from LETI Pharma, grants from Stallergenes, grants from Quintiles, grants and personal fees from Sanofi, grants from ASIT biotech, grants from Lofarma, personal fees from Allergy Therapeut., grants from AstraZeneca, grants from GSK, grants from Inmunotk, personal fees from Cassella med, outside the submitted work; and Membership: AeDA, DGHNO, Deutsche Akademie für Allergologie und klinische Immunologie, HNO-BV, GPA, EAACI.

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Dr. Bousquet has nothing to disclose.

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AUTHOR CONTRIBUTIONS

LK and JB analyzed the primary data and made the literature search on the topic in question. LK, JB and TZ provided a first draft of this report, that all coauthors reviewed, improved and amended. All co-authors gave final approval for submission.

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N−3 fatty acid supplementation in asthma management: A systematic review and meta-analysis

To the Editor,

Laboratory and epidemiological evidence suggests that n−3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are beneficial in asthma prevention and possibly treatment through their anti-inflammatory effect.[1] The mechanisms underlying the anti-inflammatory actions of n−3 fatty acids include activation of transcription factor peroxisome proliferator-activated receptor γ, binding to the G protein-coupled receptor, altered cell membrane phospholipid composition, inhibition of activation of the pro-inflammatory transcription factor nuclear factor kappa B, and inflammation resolving mediators called resolvins, protectins, and maresins.[2] However, evidence from randomized controlled trials remains inconsistent.[3] Therefore, we aimed to examine the summarized effect of n−3 fatty acids on asthma control and management.

We conducted a systematic review and meta-analysis including randomized controlled trials on the effect of n−3 fatty acid supplementation in patients with asthma on lung function, fractional exhaled nitric oxide (FeNO), symptom score, bronchodilator use, and postexercise decline in forced expiratory volume in 1 s (FEV_1) (see Figure S1, Tables S1–S4 for detailed information). The scales used to evaluate symptoms varied across studies, but all of them reported their symptom scores as a number, with higher scores indicating severer asthma symptoms. In the subgroup analysis, participants aged >18 years were classified as adults; intervention ≥3 weeks was considered long duration. High dosage was defined as >4 g since it was the median number of dosages for all the included studies.

In the 16 trials included, four studies that compared n−3 fatty acid supplementation with placebo found that the decline in FeNO