A randomized, double-blind study comparing the efficacy and safety of a combination of formoterol and ciclesonide with ciclesonide alone in asthma subjects with moderate-to-severe airflow limitation

Sir,

We read with interest the article[1] entitled, "A randomized, double-blind study comparing the efficacy and safety of a combination of formoterol and ciclesonide with ciclesonide alone in asthma subjects with moderate-to-severe airflow limitation." We would like to offer following comments:

It has been conclusively proved by various studies that in moderate-to-severe asthma, use of inhaled corticosteroids (ICSs) in moderate doses and above in combination with long-acting beta2-agonist (LABA) is superior to ICS alone.[2,3] The same has been recommended by the joint Indian Chest Society/National College of Chest Physicians Guidelines.[4] As a corollary, this should also stand good for ciclesonide (C) alone and in combination with formoterol, which has also been agreed upon by authors in discussion. The present study would have been more relevant if the combination of formoterol with ciclesonide (FC) had been compared with other ICS and LABA combinations, which would have also justified authors suggesting FC combination as a new option to currently available ICS and LABA combination. Moreover, in discussion, authors have compared the present study with a study by Korn and Buhl, which is not relevant since the quoted study refers to comparison between FC and salmeterol with fluticasone.

In discussion, double-dose of ciclesonide during treatment has been compared with single dose of ciclesonide during run-in period which revealed significant improvement in symptoms and rescued medication use without showing improvement in forced expiratory volume in 1 s, morning and evening peak expiratory flow rates. The results have been compared with the study regarding dose–response relationship of ICS in adolescents and adults with mild-to-moderate persistent asthma, which showed dose–response relationship only with budesonide. The interpretation of this observation in the present study seems to be related to author's suggestion that patients uncontrolled on low-dose steroids may benefit more by addition of LABA than doubling the dose of inhaled steroids. If it is true, then this is out of context of the present study, which is not about comparison between low-dose steroids with LABA versus double-dose of steroids but comparison of the same dose (160 mcg/day) of ciclesonide in both arms with additional formoterol in one arm. This requires clarification from authors.

Authors have self-criticized the comparison of ciclesonide with additional formoterol and an equivalent dose of ciclesonide which has been explained by stating that efficacy of adding LABA to ciclesonide over conventional dose of ciclesonide has not been demonstrated. First, this self-criticism is not understood since the inhaled steroid has been compared with an equivalent dose of steroid in chronic asthma earlier also.[5] Second, the conventional dose of ciclesonide needs to be elaborated by authors.

Authors have quoted low systemic absorption, smaller particle size of ciclesonide, resulting in better deposition and minimal side effects compared to other ICS. However, superiority comparisons of ciclesonide with budesonide and fluticasone are lacking as shown in a systematic review,[6] and therefore, it would not be prudent to suggest FC as a better option than other ICS and LABA combinations. Although this systematic review included studies done in children, the age group varied from 4 to 17 years.

When it has been conclusively proved by various studies that in moderate-to-severe asthma, use of ICS in moderate doses and above in combination with LABA is superior to ICS alone[2,3] and authors in discussion have also stated the same; then, is it not an ethical issue to deprive one arm of moderate-to-severe asthma patients the advantage of additional LABA?

There was no significant improvement in symptoms between two arms, but significant improvement has been mentioned in conclusion part of abstract and beginning of discussion although this has been corrected in the later part of discussion.

FC combination in single inhaler and inhalation capsules was introduced in Indian market by Cipla about 15 years back and was withdrawn after a few years. It will be of interest to know if the formulation and device used in the present study are different, apart from the study device being hydrofluoroalkane based, from the previous one.

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Conflicts of interest
There are no conflicts of interest.

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