Articles in Response to Previously Published Articles

Letter in response to "Effectiveness and safety of levocetirizine 10 mg versus a combination of levocetirizine 5 mg and montelukast 10 mg in chronic urticaria resistant to levocetirizine 5 mg: A double-blind, randomized, controlled trial" by Sarkar *et al*.

Sir,

Current international guidelines on managing chronic urticaria are based on evidence from published literature where available. However, there is a scarcity of clinical trials even among well-established therapeutic options. We thank the authors for addressing an important evidence gap by conducting a randomized controlled trial to test the comparability of a standard dose of levocetirizine 5 mg plus montelukast 10 mg and doubling the dose of levocetirizine to 10 mg. We wish to share a number of observations that would benefit from some clarification from the authors.

Although the study was relatively well reported in terms of CONSORT (CONsolidated Standards of Reporting Trials),[1] we thought blinding was not sufficiently described. The authors report in the methods section that "one treatment group was given tablet levocetitizine 10 mg." Do they mean a single levocetirizine 10 mg tablet or two 5 mg tablets? Then they describe the other group as having "a combination of tablet levocetirizine 5 mg plus montelukast 10 mg." Does this mean a levocetirizine 5 mg tablet plus another tablet of montelukast 10 mg or was it a preparation that combined the two? This ambiguity leaves the reader in some doubt whether any actual blinding could have occurred. If one pack contained two tablets and the other contained one tablet, then it would have been easy to feel through the sealed opaque envelope.

We also have some concerns regarding potential selective reporting of outcomes. We note that the authors registered the trial retrospectively as recruitment commenced in March 2014 whereas the trial was registered on 26th November 2014. Trial registration should occur before any patients are recruited.[2] Moreover, although the authors report on most of the outcomes as per the registered protocol, we wonder why planned cost outcomes have not been reported in the study results.

We also wish to ask the authors about their choice of Urticaria Total Severity Score as one of the primary outcome measures. We agree the Total Severity Score includes more parameters of disease severity than the Urticaria Activity Score, but we are not aware that Total Severity Score has been validated (construct or criterion) or tested for repeatability or sensitivity to change to render it suitable as an assessment tool for chronic urticaria.

Finally, we would like to highlight an important issue in the study design. We note the study aims to demonstrate that the efficacy of levocetirizine 5 mg combined with montelukast 10 mg is "comparable" to levocetirizine 10 mg in the treatment of chronic urticaria, implying an equivalence or noninferiority trial design. However, the sample size calculation was powered to detect a two-point difference in the Total Severity Score between the two study groups, which implies a superiority rather than equivalence study design. In addition, the authors have focused on reporting and emphasizing inappropriate within-group rather than between-groups differences that address the study question. Equivalence cannot be inferred simply by the absence of a significant difference between treatments in a superiority trial design.[3]

Despite the above concerns, we recognize the importance and clinical relevance of the study objective and acknowledge the authors' efforts at comprehensively reporting the methodology and findings of the trial.

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Conflicts of interest
There are no conflicts of interest.

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