Asthma management made too SIMPLE

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McIvor AR, Kaplan A, Koch C, Sampalis JS. Montelukast as an alternative to low-dose inhaled corticosteroids in the management of mild asthma (the SIMPLE trial): an open-label effectiveness trial. *Can Respir J* 2009;16(Suppl A):11A-21A.

Research question

Is montelukast an effective alternative to low-dose inhaled corticosteroids (ICSs) in the management of mild asthma?

Type of article and design

This study—referred to as the Singulair in Mild Asthma: Compliance and Effectiveness (SIMPLE) trial—was a multicentre, Canadian, phase IV open-label study with 2 phases: a survey phase and a treatment phase. The survey phase was designed to estimate the proportion of patients who had uncontrolled symptoms or who were dissatisfied with their current ICS treatment (250 µg/day or less of fluticasone or equivalent). The treatment phase was a 6-week, prospective open-label study during which ICS treatment was discontinued and montelukast therapy was initiated. Patients 15 years of age or older (60.1% of participants in the treatment phase) received 10 mg of montelukast tablets to be taken once daily at bedtime. Patients between the ages of 6 and 14 years (39.9%) were treated with 5 mg of montelukast once daily at bedtime during the treatment phase. Study subjects were allowed to use short-acting β_2-agonists for rescue therapy during the study. During the open-label treatment phase, there was no ICS group with which the montelukast arm was compared. The authors assumed that the baseline state, obtained from data from the survey phase, represented the effects of previous treatment and could therefore serve as a measure of control.

Relevance to family physicians

Asthma represents one of the most common chronic conditions encountered in primary care, and numerous reports suggest that asthma control in Canada is suboptimal.[1,2] The factors that contribute to these observations are complex and multifactorial, and might include issues related to medication compliance. At present, ICSs are indicated as first-line therapy in patients with persistent symptoms, as they have been shown (in randomized controlled trials) to be more effective than leukotriene receptor antagonists (LTRAs).[3] For some individuals who cannot tolerate ICSs or for those who do not want to use ICSs for asthma control, leukotriene modifying agents have been described as a reasonable alternative.[4]

For adults whose asthma is not controlled on low to medium doses of ICSs, the addition of a long-acting β_2-agonist (LABA) is recommended.[4] As family physicians are usually the first caregivers to initiate or modify therapy in patients with asthma, information relating to selection of the most appropriate first-line and add-on therapies must be clear and based on the best available evidence.

Overview of study and outcomes

The primary effectiveness outcome measure of this study was the proportion of patients in whom asthma control was achieved or maintained after 6 weeks of treatment with montelukast compared with their baseline state. The absence of all symptoms of asthma as outlined in the Canadian Asthma Consensus Guidelines[4] was used to define asthma control. The absolute change in the Asthma Control Questionnaire score between the baseline and the 6-week assessments was included as a secondary measure of effectiveness. The very short duration of the study did not permit a meaningful evaluation of health outcomes, such as exacerbations and hospitalization—end points that might be more clinically relevant than asthma control.

Results

A total of 1817 patients were screened by 113 physician-investigators, all of whom were included in the survey phase of the study. Among them, 534 eligible patients (29.4%) from 85 sites agreed to participate in the treatment phase. Among the survey phase patients, there were 1397 patients (76.9%) with uncontrolled asthma symptoms, 1379 patients (75.9%) who were not adherent to their ICS regimens, and 439 patients (24.2%) who reported that they were dissatisfied or very dissatisfied with their ICS treatment. Data for pediatric and adult patients were not presented separately. Compliance with ICS therapy at baseline was 41%, according to data presented in the abstract. In the results section, however, compliance with ICS therapy at baseline was reported to be 58.1%; this difference was not explained. Most patients in the treatment phase (n=375, 70.2%) were taking fluticasone as their low-dose ICS at baseline; budesonide was the second most common ICS (n=77, 14.4%). At baseline, "daytime symptoms ≥4 days/week" were most commonly reported. At baseline, 455 treatment-phase patients (85.2%) had uncontrolled asthma symptoms, while 79 (14.8%) had controlled asthma symptoms but were not satisfied with or were reluctant to use their current ICS medications.

After 6 weeks of treatment with montelukast, the proportion of patients with controlled asthma increased from 14.8% to 57.5% ($P<.001$). Among all patients the mean (SD) Asthma Control Questionnaire score decreased from 1.44 (0.82) at baseline to 0.61 (0.62) at week 6 ($P<.001$).

Analysis of methodology

Of all the eligible patients identified during the survey phase, only 29.4% agreed to participate in the treatment phase. An explanation as to why less than half the eligible patients agreed to participate in the treatment phase was not provided, but this finding introduces the possibility of selection bias. Further, inclusion of a high number of patients (42% to 59%) who were not adherent to ICS therapy introduces an additional bias related to patient factors and inhaler medication use, as improper inhaler technique can lead to lack of perceived benefit and patient dissatisfaction. Further, the fact that the SIMPLE trial was funded by the manufacturer of Singulair might introduce additional bias.

Because such a large number of patients were not adherent to ICS therapy at baseline, it is not appropriate to use the baseline state as both "representing the effect of previous treatment" and the control against which montelukast is compared, as it is not known how many of these nonadherent patients were using any ICSs. It is possible that for many patients ICSs were not used at all or were used at doses that were inadequate to achieve control. Consequently, the title of the paper is misleading—it is not clear what montelukast was actually compared with. The fact that in the real world there are some patients who do not adhere to or do not prefer to use ICSs does not justify a comparison (as with the SIMPLE trial) between retrospective data (which might be seriously biased by selection and suboptimal use of ICSs) and prospective data obtained in a formal clinical trial setting among patients whose response to treatment might be heavily influenced by a high level of dissatisfaction at baseline. In fact, the finding that 58.1% of patients reported not missing their scheduled doses of ICSs during the previous 2 weeks suggests that compliance was adequate among most patients. Therefore, the implication that poor asthma control is related to medication compliance does not appear valid. The approach of switching patients who are compliant but uncontrolled from low-dose ICSs to montelukast is not consistent with current guideline recommendations. Such patients should be considered for add-on therapy with LABAs. Without a placebo arm, an ICS arm, or an ICS and LABA arm, the results of the SIMPLE trial cannot be interpreted in a clinically meaningful fashion in keeping with current guidelines. Given these limitations, it cannot be concluded that montelukast is an effective alternative to low-dose ICSs in the management of mild asthma. Further, it could be argued that the comparison between treatments was not driven by a relevant clinical question.

BOTTOM LINE

- The title of the trial is misleading, as the study design did not include a direct, prospective comparison between montelukast and inhaled corticosteroids (ICSs).
- Important study design limitations make the results of the trial virtually impossible to interpret in a clinically meaningful way.
- Inhaled corticosteroids remain first-line therapy in asthma management.
- Switching adult patients (ie, those who are compliant but uncontrolled with ICSs) to montelukast runs contrary to current guidelines on asthma management. Such patients should be offered ICSs in combination with long-acting β_2-agonists, preferably as a single inhaler.

POINTS SAILLANTS

- Le titre de l'étude porte à confusion, parce que la conception de l'étude n'incluait pas de comparaison prospective directe entre le montélukast et les corticostéroïdes par aérosol (CSA).
- D'importantes limites dans la conception rendent l'étude presque impossible à interpréter de manière cliniquement significative.
- Les corticostéroïdes par aérosol demeurent la thérapie de première intention dans la prise en charge de l'asthme.
- Changer la thérapie de patients adultes (p. ex. ceux qui se conforment au traitement par CSA mais dont l'asthme n'est pas contrôlé) pour un traitement au montélukast est contraire aux guides de pratique clinique actuels sur la prise en charge de l'asthme. Il faudrait plutôt offrir à de tels patients des CSA combinés à des β_2-agonistes à longue durée d'action, préférablement sous forme d'un seul inhalateur.

Competing interests. Both the SIMPLE trial and the supplement in which the SIMPLE trial was published were supported by the manufacturer of Singulair (ie, Merck Frosst Canada Ltd). Koch is a clinical researcher at Merck Frosst Canada Ltd and Sampalis is an employee of JSS Medical Research Inc, a clinical research organization. McIvor and Kaplan were consultants for the SIMPLE study; both have received honoraria for continuing medical education and have attended advisory board meetings for various pharmaceutical organizations, including Merck Frosst.

Application to clinical practice

Although the benefits of montelukast and other LTRAs have been clearly highlighted in the literature,[4,5] the

results of the SIMPLE trial do not provide a valid assessment of how montelukast compares with low-dose ICSs in the management of mild asthma, owing to fundamental study design flaws outlined above. The directive for using ICSs as first-line therapy for asthma management is clearly stated in national and international guidelines,[4,6] which are based on numerous studies now dating back several decades. The challenges of real-world asthma management, clearly highlighted by the authors of the SIMPLE trial, should be addressed by prospective trials with designs that are consistent with guideline recommendations. Given the benefits of ICSs in asthma management, family physicians are encouraged to identify barriers to ICSs use among patients and remind them of the importance of medication compliance. Furthermore, adult patients taking low to medium doses of ICS who remain uncontrolled, despite good compliance, should be offered a trial of ICS and LABA combination therapy. Switching adult patients who are compliant but uncontrolled from ICS therapy to montelukast runs contrary to current guideline recommendations and sends a conflicting message to family physicians. Current evidence clearly indicates that add-on therapy to ICSs with LABAs is more effective than LTRAs.[4]

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Competing interests

Dr D'Urzo has participated in many clinical trials studying the use of long-acting β_2-agonists and inhaled corticosteroids in asthma management that were funded by various pharmaceutical organizations.

References

1. McIvor RA, Boulet LP, FitzGerald JM, Zimmerman S, Chapman KR. Asthma control in Canada. No improvement since we last looked in 1999. *Can Fam Physician* 2007;53:672-7.
2. FitzGerald JM, Boulet LP, McIvor RA, Zimmerman S, Chapman KR. Asthma control in Canada remains suboptimal: the Reality of Asthma Control (TRAC) study. *Can Respir J* 2006;13(5):253-9.
3. Ng D, Salvio F, Hicks G. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database Syst Rev* 2004;(3):CD002314.
4. Becker A, Lemière C, Bérubé D, Boulet LP, Ducharme FM, FitzGerald M, et al. Summary of recommendations from the Canadian Asthma Consensus guidelines, 2003. *CMAJ* 2005;173(6 Suppl):S3-11.
5. McIvor RA, Kaplan A, Koch C, Sampalis S. Montelukast as an alternative to low-dose inhaled corticosteroids in the management of mild asthma (the SIMPLE trial): an open-label effectiveness trial. *Can Respir J* 2009;16(Suppl A):11A-21A.
6. Global Initiative for Asthma. *Global strategy for asthma management and prevention.* Bethesda, MA: Medical Communications Resources Inc; 2008. Available from: **www.ginasthma.org/GuidelineItem.asp?intId=60.** Accessed 2010 Aug 30.