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Title: Therapeutic drug monitoring of inhaled corticosteroids in exhaled breath for adherence assessment

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To the Editor:

We have read with great interest the article by Alahmadi et al, which demonstrated the relationship of serum inhaled corticosteroid (ICS) levels and exacerbation rates in severe asthma[1]. As indicated in the article, therapeutic drug monitoring of serum ICS level after inhalation may be a marker of treatment adherence. However, we have concerns about the weakness of the relationship between the serum ICS level and therapeutic efficacy. Therefore, we suggest paying attention to the difference between serum and lung concentrations. In the article, marked variability in serum pharmacokinetics was shown between patients, and the authors suggested that the main sources of variation are deposition, oral bioavailability, lipophilicity, and volume of distribution. Most ICS are metabolized by CYP3As in the liver. The systemic pharmacokinetics of CYP3A substrates varies widely by genetic variation in CYP3As and concomitant CYP3As inhibitors. CYP3As are mainly expressed in the liver and intestine but rarely in the lungs[2,3]. Therefore, there may be a difference between the concentration in the lung and systemic circulation. Recently, Sadiq et al have reported that the lung fluticasone concentration after inhalation was higher than plasma concentration[4]. The gap between the lung and plasma concentrations could be a reason for the weak correlation between serum concentration and therapeutic effects in

Alahmadi's study[1].

Since it is difficult to routinely perform lung biopsy for the assessment of inhalation therapy adherence, a noninvasive method for estimating lung concentration should be developed to evaluate the therapeutic effect in the lung. Our previous report has demonstrated that ICS in exhaled breath could be detected immediately after inhalation of dry-powder inhaler (DPI), and the exhaled drug amount increased, depending on the participants' inhalation flow rate[5]. Other *in vitro* studies have indicated that the deagglomeration rate and pulmonary deposition rate of DPI increase depending on the inhalation flow rate[6]. In general, a high inhalation flow rate is required for the deagglomeration of DPI. Then, submicron particles, which are likely to be exhaled, are also generated by high inhalation flow rate. Therefore, the exhaled drug amount after inhalation should correlate with the deagglomeration rate and pulmonary deposition rate of DPIs. We propose a novel therapeutic drug monitoring method of ICS in exhaled breath for monitoring treatment adherence. The drug amount in exhaled breath is unlikely to be affected by individual variability of metabolic enzymes and depends on inhalation techniques such as inhalation flow rate. In addition, since the drug concentrations in exhaled breath immediately after inhalation are larger than the reported serum concentrations, it can be quantified not only by liquid chromatography

with tandem mass spectrometry but also by high performance liquid chromatography with ultraviolet detection, which is a more clinically available method. Although further clinical studies should be conducted, the exhaled ICS monitoring may also be a good biomarker for the assessment of adherence to inhalation therapy.

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