High risk of KL-6 elevation when DPP-4 inhibitors and amiodarone are prescribed simultaneously

Sir, Amiodarone-caused pulmonary toxicity, including interstitial lung diseases, is a well-known side effect and its incidence has been reported as approximately 5.7%. In addition, dipeptidyl peptidase-4 (DPP-4) inhibitors, which are oral hypoglycaemic agents to treat patients with type 2 diabetes mellitus, recently attracted physicians’ attention as a cause of drug-induced interstitial lung diseases. Notwithstanding, there must be patients who are prescribed both DPP-4 inhibitors and amiodarone simultaneously. In such cases, patients might have an increased risk for interstitial lung disease.

Recent study undertaken
Given the lack of clarity regarding the risk for drug-induced interstitial lung disease under the combination therapy of DPP-4 inhibitors and amiodarone, we estimated serum Krebs von den Lungen-6 (KL-6) levels in patients who were prescribed: amiodarone without DPP-4 inhibitors; DPP-4 inhibitors without amiodarone; and both DPP-4 inhibitors and amiodarone simultaneously. This was done because KL-6 has been reported as a useful biomarker for the diagnosis of interstitial pneumonia, the evaluation of disease activity, and the assessment of the response to treatment.

The study protocol was reviewed and approved by our hospital review board and was conducted in accordance with the Declaration of Helsinki. Written, informed consent to participate in this clinical study was obtained.

Study results
Forty-seven patients were prescribed amiodarone without DPP-4 inhibitors (designated as the ‘amiodarone group’); 44 patients were prescribed DPP-4 inhibitors without amiodarone (designated as the ‘DPP-4 inhibitors group’); 15 patients were prescribed both amiodarone and DPP-4 inhibitors (designated as the ‘DPP-4 inhibitors and amiodarone group’).

Elevation in KL-6 levels beyond the upper limit of normal range (reference range <500 U/ml) was observed in three patients in the amiodarone group, in three patients in the DPP-4 inhibitors group, and in three patients in the DPP-4 inhibitors and amiodarone group.

The frequency of KL-6 levels beyond the upper limit of normal range in the amiodarone group was 6.4%, and it was 6.8% in the DPP-4 inhibitors group, while it was 20% in the DPP-4 inhibitors and amiodarone group.

Discussion
Although the sample size was small, this clinical study provides important information. We confirmed that KL-6 levels were in the normal range before initiating DPP-4 inhibitors and/or amiodarone administration. Moreover, KL-6 levels were transiently elevated and normalised within one year after DPP-4 inhibitors and/or amiodarone termination. All of the participating patients showed normal results on chest X-ray examination throughout the observation period.

Under these conditions, the incidence of KL-6 levels beyond the upper limit of normal range in the DPP-4 inhibitors and amiodarone group seemed to be significantly higher than those of either the amiodarone group or of the DPP-4 inhibitors group.

Thus, when prescribing DPP-4 inhibitors, physicians should probably be concerned about whether their patients have been prescribed amiodarone as well. KL-6 measurement might be one of the useful screening methods to detect interstitial lung diseases in the stage of recovery fully without any specific medication.

References

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Declaration of interests
There are no conflicts of interest declared. No funding was received for this study.

Practice points
• When prescribing DPP-4 inhibitors physicians should probably be concerned about whether patients have been prescribed amiodarone as well – this is in view of a potential for drug-induced interstitial lung disease
• Although Krebs von den Lungen-6 (KL-6) has some limitations, KL-6 measurement might be one of the useful screening methods to detect interstitial lung diseases in the stage of recovery fully without any specific medication

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