Drug-Induced Gout with Neprilysin Inhibitors

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INTRODUCTION
A number of pharmacological drugs can induce hyperuricemia, and sometimes gout, usually by interfering with the renal tubular excretion of urate but also by increasing the formation of uric acid. We report the case of a 74-year-old patient hospitalized for refractory gout-related polyarthritis despite treatment by allopurinol at maximum dose concomitant with the introduction of Entresto®, which is an association of the neprilysin inhibitor Sacubitril [1] and the angiotensin receptor blocker (ARB, not known to influence hyperuricemia)[2].

This neprilysin inhibitor is part of a new class of therapies used in the third line of chronic heart failure with compromised left ventricular ejection fraction (<35%) [3,4]. The patient was being monitored for arrhythmic cardiomyopathy which led to severe heart failure and was taking Furosemide and spironolactone for five years, without history of hyperuricemia or gout. The patient reported that the gout flare-ups were concomitant with the initiation of Entresto®, associated with a progressive increase in serum uric acid level until 470 micromole/l despite initiation of urate-lowering therapy by allopurinol up to the maximum dose, in association with colchicine. Corticosteroid treatment (per os + injections) was used to control the flare-up during hospitalization, and the patient was then given febuxostat knowing that treatment with the neprilysin inhibitor could not be stopped. A partial response to febuxostat was observed, with decrease of uric acid level and frequency of acute gout attacks.

Entresto® was retained as the source of hyperuricemia in this patient in view of the sequence of events, and the case was documented in the French national pharmacovigilance bank. The risk of gout is not mentioned in the product characteristics for the combination of Neprilysin inhibitor and fixed-dose ARB, nor are there any published cases [4,5]. However, 6 other cases involving neprilysin inhibitors have already been reported in the French national pharmacovigilance bank since these drugs arrived on the market in 2016. The most detailed case was that of an 80-year-old patient, with no gout, who was under long term treatment with bisoprolol, amiodarone, spironolactone and furosemide. Three days after the introduction of Entresto®, the patient had a gout flare-up that persisted despite the discontinuation of furosemide and the introduction of colchicine. The gout did not respond to treatment with febuxostat.
Though the exact mechanism has not yet been established, this hyperuricemic effect of Sacubitril may potentially be a result of its diuretic effects, similar to the effects of thiazide or furosemide, by reducing urate excretion by both directly and indirectly increasing urate reabsorption and decreasing urate secretion. Moreover, caution should be exercised when these drugs are used in combination with NSAIDs and colchicine in the elderly and/or patients with impaired renal function, since there is a risk of further deterioration in renal function [3,6]. The potential risk of drug interaction between urate-lowering therapy (allopurinol, febuxostat) and sacubitril via cytochrome CYP450 appears limited [1,7] but cannot be excluded. Going forward, physicians should be familiar with this new heart failure drug given its potential side-effect on hyperuricemia and gout.

DISCLOSURE
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REFERENCES