Evaluating the Safety and Tolerability of Sacubitril/Valsartan

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Introduction

Sacubitril/valsartan is recommended in clinical practice to reduce morbidity and mortality in patients with chronic symptomatic heart failure with reduced ejection fraction (HFrEF).[1] The PARADIGM-HF trial showed that sacubitril/valsartan was superior to enalapril in reducing the risk of death and hospitalisation in patients with chronic heart failure secondary to left ventricular systolic dysfunction.[2] Findings from further trials showed improvement in cardiac remodeling with sacubitril/valsartan in patients with HFrEF.[3,4] The TITRATION study tested the tolerability of initiation and up-titration of sacubitril/valsartan and demonstrated that hypotension and hyperkalaemia were the most common adverse events recorded, but were most often not severe enough to require treatment discontinuation.[5] Due to safety concerns, development of a protocol is required for patients on sacubitril/valsartan to reach the target dose with gradual dose titration and with appropriate follow-up to improve tolerability and allowing patients to attain expected treatment benefits. [6]

Setting

This medicine use evaluation was undertaken at the outpatient Heart Failure Clinic, Department of Cardiology, Mater Dei Hospital, acute general public hospital, Malta. Sacubitril/valsartan is not yet included on the national health system (NHS) in Malta and patients requiring this combination medicine are paying out-of-pocket to access this medicine.

Aim

To demonstrate the safety and tolerability of sacubitril/valsartan and provide a basis for inclusion of the medicine on the NHS

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Method

- Patients prescribed sacubitril/valsartan between 2015 and 2019 and who are taking the medication were identified from hospital records.
- A data collection form was developed to record patient demographics and medical history, sacubitril/valsartan start date and final daily dose, relevant investigations for safety and tolerability (blood pressure, renal function, potassium levels), adverse effects (such as angioedema and cough) and related dose titrations/discontinuations.
- The data collection form was completed for each patient by extracting data from software held within the hospital system, namely the Cardiovascular Information Management System and iSoft Clinical Manager. The patient records were reviewed to capture data for three months to three years. Descriptive statistics were computed using Microsoft Excel.

Results

- Thirty-five patients (27 male, mean age 58, median age 61, range 29-77 years) were evaluated.
- The year of starting sacubitril/valsartan therapy was as follows: 2015 (n=15), 2016 (n=5), 2017 (n=3), 2018 (n=6), 2019 (n=6).
- Twenty-two patients had a cardiac resynchronization therapy device insertion and 20 patients had dilated cardiomyopathy.
- Twenty-five patients were on previous angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) therapy, 1 patient was not on previous ACEI/ARB treatment, while this information was not found in the patient records for 9 patients.
- Starting dose of sacubitril/valsartan was 49/51mg twice daily (n=20) and 24/26mg twice daily (n=15). The final daily dose after up-titration was: 100mg (n=1), 200mg (n=5), 300mg (n=1), 400mg (n=28).
- The impact on treatment due to symptomatic hypotension, renal impairment and hyperkalaemia is shown in Table 1. No cases of angioedema were reported and 3 patients complained of a persistent cough, however none of them discontinued treatment.

Table 1: Impact of adverse effects on sacubitril/valsartan treatment (N=35)

Adverse effect	Impact on treatment
Symptomatic hypotension (systolic blood pressure ≤95 mmHg)	**Dose down-titration (n=3)**
Renal impairment (eGFR <30 mL/min/1.73 m^2; creatinine ≥115 µmol/L)	**Dose down-titration (n=2)** **Temporary therapy discontinuation (n=1)**
Hyperkalaemia (K^+ >5.4 mmol/L)	**Complete therapy discontinuation (n=1)**

Conclusion

This therapy review highlighted the requirement to emphasise in the clinical protocol the importance of ensuring regular patient monitoring, focusing on blood pressure measurement, renal function and serum potassium level monitoring. This data establishes the protocol to prepare for incorporation of the medicine on the Maltese NHS.

References

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