Tolerability and Clinical Experience with Sacubitril/Valsartan (Entresto™) at a Veterans Affairs Medical Center

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Abstract

Background: Sacubitril/valsartan has been shown to significantly reduce cardiovascular mortality and heart failure (HF) hospitalizations when compared to target doses of an angiotensin converting enzyme inhibitor (ACEI). We reviewed our clinical experience with sacubitril/valsartan in our HF clinic to assess the tolerability of the medication and to identify any opportunities for improvement with the prescribing and management of sacubitril/valsartan.

Methods: Retrospective chart reviews were conducted on 14 patients. Data collected included sacubitril/valsartan doses, pertinent labs, adverse reactions, other concomitant HF therapies, the ACEI or ARB they were converted from and if a washout period appropriately took place.

Results: A majority of patients (71.4%) were unable to be titrated to the maximum/target dose of sacubitril/valsartan; 50% of patients were only able to tolerate low dose (50mg twice daily), 21.4% tolerated moderate dose (100mg twice daily), and 28.6% tolerated maximum/target dose (200mg twice daily). Symptomatic hypotension (42.8%) was the most common cause that prevented dose titration of sacubitril/valsartan. Patients who were only able to tolerate low dose sacubitril/valsartan averaged enalapril-equivalent dose of 6.8mg daily prior to conversion.

Conclusions: Prior to conversion to sacubitril/valsartan, many of the patients in our HF clinic were taking a lower dose of ACEI or ARB than studied in the PARADIGM-HF trial. This contributed to the inability to titrate the majority of the patients to the maximum/target dose of sacubitril/valsartan. Our sacubitril/valsartan approval and prescribing process will be modified, reserving sacubitril/valsartan for patients tolerating a stable dose of an ACEI or ARB equivalent to at least enalapril 10mg daily.

Heart failure (HF) is a major health problem associated with significant morbidity and mortality. In the United States, it is estimated that 5.7 million adults have heart failure.[1] The prevalence is projected to increase by 46% from 2012-2030. It is estimated that about half of the people who are diagnosed with heart failure will die within five years. Heart failure also carries a substantial economic burden with an estimated total cost of $30.7 billion in the United States in 2012, of which 68% was directly attributable to medical costs.

Medications play a large role in the management of HF, particularly HF with reduced ejection fraction (HFrEF). One of the newest medications and drug classes approved by the FDA for patients with HFrEF is the angiotensin receptor-neprilysin inhibitor (ARNI), sacubitril/valsartan (Entresto™). Sacubitril/valsartan, when compared to enalapril in the landmark PARADIGM-HF trial in symptomatic patients with HFrEF, showed a significant reduction (20%) in cardiovascular mortality and HF hospitalization.[2] This finding is groundbreaking given that the ARNI was compared to a target dose of enalapril that has been known to improve outcomes in previous landmark clinical trials.[3] Based on the data from this trial, the recently updated 2017 ACC/AHA/HFSA HF guidelines provide a class I recommendation for patients with New York Heart Association (NYHA) II or III chronic symptomatic HFrEF tolerating an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) to replace the ACEI or ARB with an ARNI to further reduce morbidity and mortality.[4]

The PARADIGM-HF trial was a multicenter, prospective, randomized, comparative trial of 8,399 patients at 1,043 centers in 47 countries conducted from 2009 to 2012.[2] Patients needed to be on a stable dose of ACEI or ARB for at least four weeks, at a dose equivalent to or greater than enalapril 10mg/day. Prior to randomization, patients underwent a single blind run-in period starting with enalapril 10mg twice daily for two weeks. After a washout period of 36 hours, sacubitril/valsartan was initiated at 100mg twice daily for 4 to 6 weeks then increased to 200mg twice daily (maximum/target dose). If patients had no unacceptable side

TABLE 1. Characteristics of the Milwaukee VAMC Sacubitril/Valsartan Patients at Baseline

Characteristic	*Milwaukee VAMC (n=14)*
Mean age, years	70.3 ± 7.0
Systolic Blood Pressure, mmHg	122 ± 21.4
Serum Creatinine, mg/dl	1.23 ± 0.35
NYHA functional class – no. (%)	
II	4 (28.6)
II-III	5 (35.7)
III	5 (35.7)
Treatment prior to conversion – no. (%)	
ACEI	7 (50)
ARB	7 (50)
Beta blocker	14 (100)
Aldosterone Antagonist	6 (42.8)
Diuretic	14 (100)

effects at the target doses of the two study medications during the run-in period, they were randomized to receive either enalapril 10mg twice daily or sacubitril/valsartan 200mg twice daily. The study drug dose was reduced or discontinued if the patient was unable to tolerate the medication or experienced significant side effects. However, the study drug could be re-challenged at a previous higher dose or reintroduced based on the clinical judgment and discretion of the investigator.

The HF clinic at the Milwaukee Veterans Affairs Medical Center (VAMC) is a multidisciplinary service comprised of one cardiologist, one nurse practitioner, one nurse, one part-time dietitian, and two part-time clinical pharmacists. A social worker and psychiatrist are also readily available for consultation. Specially trained pharmacists meet with patients one-on-one during scheduled appointments to manage and optimize heart failure therapies, including sacubitril/valsartan. This involves ordering and assessing pertinent laboratory work, evaluating dietary sodium and fluid intake, providing HF education, medication reconciliation, and adjusting and titrating HF medications based on the patients' clinical presentation, interview and pharmacist evaluation.

The National VA Pharmacy Benefits Management (PBM) Service criteria for use (CFU) restricts the prescribing of sacubitril/valsartan to VAMC cardiology services.[5] At the Milwaukee VAMC, the process was modified further to restrict sacubitril/valsartan prescribing to the HF service. This is to ensure that HF patients deemed appropriate for this medication are receiving appropriate and consistent HF care, including medication and disease state education, monitoring, titration and close follow up.

Unlike the PARADIGM-HF trial, the VAMC CFU for sacubitril/valsartan does not require a run-in period with enalapril 10mg twice daily. Our CFU recommends that patients be taking a stable dose of an ACEI or ARB equivalent to at least enalapril 10mg daily prior to consideration for sacubitril/valsartan. However, patients taking less than enalapril 10mg daily may also be considered for sacubitril/valsartan on a case-by-case basis.

Objectives

The primary objective of this project was to assess the utilization and tolerability of sacubitril/valsartan in veteran patients at the Milwaukee VAMC HF clinic. A secondary objective was to identify any opportunities for improvement with prescribing and management of this medication.

Methods

A report was generated to identify all patients at the Milwaukee VAMC who had active prescriptions for sacubitril/valsartan. As of March 2017, there were 14 patients on sacubitril/valsartan. Patient data were collected through retrospective chart review of the patients' electronic medical record. Baseline characteristics collected included age, most recent blood pressure, NYHA functional class, concomitant HF medications, baseline serum creatinine and potassium. Additional data collected included sacubitril/valsartan doses utilized, changes in serum creatinine, potassium, and blood pressures, adverse reactions, the dose of ACEI or ARB they were converted from, and if an appropriate washout period occurred when switching from an ACEI.

Consistent with package labeling, a 36-hour washout period from an ACEI was required when converting patients from an ACEI to sacubitril/valsartan.[6] A washout period was not necessary when converting from an ARB to sacubitril/valsartan. Patients were then started on low dose sacubitril/valsartan 50mg twice daily, unless they were taking more than 10mg/day of enalapril or equivalent dose of another ACEI or ARB. If patients were taking more than 10mg/day of enalapril or equivalent, they were started on a moderate dose of sacubitril/valsartan, 100mg twice daily.

TABLE 2. Maximally Tolerated Sacubitril/Valsartan Doses at Milwaukee VAMC Compared to Enalapril-Equivalent Dose Prior to Conversion

Maximally tolerated sacubitril/valsartan dose	*Milwaukee VAMC (n=14), no. (%)*	*Average enalapril-equivalent dose prior to conversion*
Low Dose = 50mg twice daily	7 (50)	6.8mg
Moderate Dose = 100mg twice daily	3 (21.4)	15mg
Maximum/Target Dose = 200mg twice daily	4 (28.6)	15mg

Once sacubitril/valsartan was initiated, the goal was to titrate the dose if tolerated no faster than every two to four weeks to the maximum/target dose of 200mg twice daily. A basic chemistry panel was drawn and evaluated prior to any dose adjustment.

Results

Baseline characteristics of the Milwaukee VAMC sacubitril/valsartan patients are listed in Table 1. The 36-hour washout period was completed and documented appropriately in 6 of the 7 patients who were converted from an ACEI. One patient did not receive a washout period due to inability of HF clinic staff to reach the patient by telephone despite repeated attempts. All patients were on stable, maximally tolerated beta blockers prior to conversion. Of the 14 patients on sacubitril/valsartan, 12 (85.7%), were started on low-dose sacubitril/valsartan 50mg twice daily. Two patients (14.3%) were started on moderate-dose sacubitril/valsartan 100mg twice daily. During the time of chart review, all 14 patients had reached their maximally tolerated doses of sacubitril/valsartan and were no longer being actively titrated; 50% of patients were at low dose, 21.4% at moderate dose, and 28.6% at maximum/target dose. A patient was at the maximally tolerated dose if the prescriber felt it was unsafe to further titrate up the dose or they had reach the maximum/target dose of 200mg twice daily.

As displayed in Table 2, patients who were only able to tolerate low dose sacubitril/valsartan averaged enalapril-equivalent dose of 6.8mg daily prior to conversion, patients who tolerated moderate dose averaged 15mg enalapril-equivalent daily, and patients who tolerated maximum/target dose sacubitril/valsartan averaged 15mg enalapril-equivalent daily prior to conversion.

Adverse effects noted were symptomatic hypotension (n=6), hypotension, defined as systolic blood pressure < 100mmHg, (n=4), elevated serum potassium (n=2), chest pain (n=2), elevated serum creatinine (n=1), abdominal pain (n=1), face numbness (n=1), and increased urination (n=1). Discontinuation occurred in 21% of the patients at the Milwaukee VAMC due to symptomatic hypotension, hyperkalemia, increase in serum creatinine, and abdominal pain. All patients were eventually restarted at low dose sacubitril/valsartan. The average maximally tolerated total daily dose of sacubitril/valsartan was 207mg. The most common cause that prevented patients from titrating up to a higher dose of sacubitril/valsartan was symptomatic hypotension (n=6, 42.8%).

TABLE 3. Total Daily Dose Equivalence Chart for ACEIs and ARBs in Heart Failure Commonly Prescribed at the Milwaukee VAMC Compared to Sacubitril/Valsartan[2,8]

*Enalapril**	ACEI	5mg	10mg	20mg
Lisinopril	ACEI	5mg	10mg	20mg
Losartan	ARB	25mg	50mg	100mg
*Valsartan**	ARB	80mg	160mg	320mg
*Sacubitril/valsartan**	ARNI	100mg	200mg	400mg

**Enalapril, valsartan, and sacubitril/valsartan are typically dosed twice daily in HF, total daily dose is listed for comparative purposes*

Discussion

The design of the PARADIGM-HF trial included a run-in period, prior to randomization, during which patients were titrated to the target dose of enalapril 10mg twice daily then converted and titrated to the maximum/target dose of sacubitril/valsartan 200mg twice daily to ensure that a higher proportion of patients would tolerate the study medication.[2] In fact, the PARADIGM-HF trial attained the highest average dose of enalapril of any large clinical trial.[7] Out of 8,399 participants in the PARADIGM-HF trial, >99.9% in both arms achieved the maximum/target dose after randomization. In an intent to treat analysis, 43% of patients in the enalapril arm and 42% of patients in the sacubitril/valsartan arm reduced their dose at any time after randomization with 35.3% and 39.8% subsequently returning to maximum/target study medication doses respectively. This resulted in a final mean total daily dose of 375mg daily of sacubitril/valsartan and 18.9mg daily of enalapril.

In contrast, the 14 patients at the Milwaukee VAMC only achieved a final mean total daily dose of 207mg sacubitril/valsartan. This likely stems from a much lower enalapril-equivalent ACEI or ARB dose at the time of conversion and the lack of a run-in period at an enalapril-equivalent target dose of 10mg BID to assess tolerability. Table 3 provides a comparison chart of the equivalent daily doses used in heart failure of some common ACEIs and ARBs relative to the sacubitril/valsartan dose.[8] Of note, the dose conversions used for the heart failure indication may not directly align with the dose conversions when used for hypertension. Our patients averaged an enalapril-equivalent total daily dose of 10.9mg prior to conversion which is almost half of the 20mg achieved in the PARADIGM-HF trial prior to randomization. This could explain the higher incidence of symptomatic hypotension seen at our site when compared to the rate from the PARADIGM-HF trial (Table 4).

A majority of patients (71.4%) at our facility were unable to be titrated to the maximum/target dose of sacubitril/valsartan. In fact, half of the patients were unable to be titrated beyond the low dose of sacubitril/valsartan of 50mg twice daily. Of note, the low dose of sacubitril/valsartan, 50mg twice daily, was not studied in the PARADIGM-HF trial, but has been developed by the manufacturer for treatment naïve patients or those on low doses of ACEI or ARB to allow for dose titration. This raised the question of whether sacubitril/valsartan would confer any benefit at lower than target doses when compared to lower than target doses of enalapril. Vardeny, et al conducted a post-hoc analysis of the PARADIGM-HF trial evaluating the efficacy of low (50mg twice daily) and moderate (100mg twice daily) doses of sacubitril/valsartan compared

TABLE 4. Adverse Events Reported with Sacubitril/Valsartan at the Milwaukee VAMC vs PARADIGM-HF

Event	Milwaukee VAMC (n=14), No. (%)	PARADIGM-HF (n=4187)[2] No. (%)
Symptomatic Hypotension	6 (42.8)	588 (14.0)
Hypotension (SBP < 100mmHg)	4 (28.6)	Not reported
Elevated Serum Potassium	2 (14.3)	674 (16.1)
Elevated Serum Creatinine	1 (7.1)	139 (3.3)
Cough	0 (0)	474 (11.3)
Angioedema	0 (0)	19 (0.4)

to equivalent low and moderate doses of enalapril.[7] The analysis found that although dose reduction was associated with a higher risk of the primary event, overall the treatment benefit of sacubitril/valsartan over enalapril was similar at lower doses (HR 0.80, 95% CI 0.70-0.93, P<0.001) to patients who did not experience any dose reduction (HR 0.79,95% CI 0.71-0.88, P<0.001). However, when the low and moderate doses were analyzed separately, the benefit was not statistically significant with low dose of sacubitril/valsartan compared to the low dose of enalapril (HR 0.79, 95% CI 0.58-1.07). Further studies on low dose sacubitril/valsartan compared to equivalent dose of ACEI or ARB are needed to determine the best course of action for patient unable to be titrated to moderate or maximum doses of sacubitril/valsartan.

Efficacy, safety, and cost should all be taken into consideration when evaluating the option of converting a patient from an ACEI or ARB to sacubitril/valsartan if other inclusion criteria have been met. The post hoc analysis did not find a statistically significant benefit of low dose sacubitril/valsartan over an equivalent low dose of enalapril.[7] Fifty percent of our patients could not tolerate a dose higher than the low dose and symptomatic hypotension was the most common reason for discontinuation of sacubitril/valsartan which poses a safety concern. Lastly, at this time, sacubitril/valsartan is more costly than most ACEIs or ARBs available on the market. When weighing these three factors, and until further studies are performed with low dose sacubitril/valsartan, our heart failure clinic will be more strict with adhering to our PBM's guidance. Specifically, that patients are tolerating a stable dose of an ACEI or ARB equivalent to at least enalapril 10mg daily prior to consideration for sacubitril/valsartan. For patients who are on a low dose ACEI or ARB, titration to at least an enalapril-equivalent dose of 10mg daily will be recommended prior to conversion to ensure tolerability. If unacceptable adverse effects occur, such as symptomatic hypotension or significant elevations in serum creatinine or potassium, with dose titration of ACEI or ARB, then sacubitril/valsartan would not be recommended. This is to ensure that the sacubitril/valsartan doses found to provide a statistically significant benefit in patients are utilized. Once a patient is started on low or moderate dose sacubitril/valsartan, it is important to consider reserving dose titration only for patients that have blood pressure room to do so. Lastly, for patients who have been approved for sacubitril/valsartan therapy, the prescription will be placed on hold until HF clinic staff has reached the patient to provide education on the medication and instructions for completing an appropriate washout period.

Future direction for management of sacubitril/valsartan therapy at the Milwaukee VAMC include evaluating changes to ejection fraction (EF) after reaching the maximally tolerated dose of sacubitril/valsartan, changes in quality of life, and assessing the total number of HF related hospitalizations and mortality.

Limitations

The small sample size decreases the ability to interpret the results and therefore a statistical evaluation of the data and the comparative analysis with the PARADIGM-HF trial was not conducted.

Conclusion

Prior to conversion to sacubitril/valsartan, many of the patients in our HF clinic were taking a lower dose of ACEI or ARB than studied in the PARADIGM-HF trial. This contributed to the inability to titrate the majority of the patients to the maximum/target dose of sacubitril/valsartan, which was most commonly limited by symptomatic hypotension. Our sacubitril/valsartan approval and prescribing process will be modified, reserving sacubitril/valsartan for patients tolerating a stable dose of an ACEI or ARB equivalent to at least enalapril 10mg daily.

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PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

Acknowledgments: Steven Kennedy, PharmD, BCPS, Clinical Pharmacy Specialist - Cardiology.

Disclosures: The authors declare no real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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