ABOUT SACUBITRIL/ VALSARTAN: A CLINICALLY-ORIENTED PRIMER FOR INTERNISTS

Mihnea Casian, Alice Elena Munteanu

"Dr. Carol Davila" Central University Emergency Military Hospital, Bucharest, Romania

Corresponding author:

Casian Mihnea: mihnea.casian@gmail.com

Abstract

The medical therapy of heart failure (HF) has been traditionally based on inhibiting the main pathophysiologic mechanisms: the adrenergic and renin-angiotensin-aldosterone systems. Introducing the therapeutical triad of beta-blockers, angiotensin converting enzyme inhibitors and mineralocorticoid receptor antagonists in the treatment of HF patients almost 40 years ago marked an important step since they were not only addressing the symptoms of HF, but also the prognosis and life- expectancy of these patients. Although many discoveries have been made in the past years, no other therapeutic class was able to increase survival among HF patients, until recently, when the SA e benefits of modulating the natriuretic peptide system were brought to the attention of the scientific community. Increasing the levels of natriuretic peptides with Sacubitril/Valsartan (SV) led to several benefits for the reduced ejection fraction HF population, including less long and short term complications, increased survival and a reduced symptom burden. As this article is being written, it is estimated that more than 2.8 million patients are being treated with SV⁽¹⁾. Therefore, SV is an important and validated therapy for HF patients and internists should be aware of its indications, benefits and management in clinical practice.

Keywords: sacubitril, valsartan, natriuretic peptide, heart failure, reduced ejection fraction, neprilysin.

Rezumat

Terapia medicamentoasă a insuficienței cardiace (IC) a fost bazată pe inhibarea principalelor mecanisme fiziopatologice implicate, anume: sistemul adrenergic și sistemul renină-angiotensină- aldosteron. Introducerea terapiei etiopatogenice, compusă din beta-blocante, inhibitori ai enzimei de conversie a angiotensinei și antagoniști ai receptorilor mineralocorticoizi a marcat începutul unei noi ere în tratamentul insuficienței cardiace, întrucât folosind acest arsenal terapeutic a fost obținut atât controlul simptomelor, cât și ameliorarea prognosticului. Deși au fost adăgate noi opțiuni terapeutice, tratamentul insuficienței cardiace a fost bazat pe aceleași principii terapeutice, nefiind introduse noi clase.

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Beneficiile observate în contextul modulării activității sistemului peptidelor natriuretice prin inhibarea neprilizinei, cum ar fi ameliorarea prognosticului și scăderea incidenței complicațiilor pe termen lung și scurt, au constituit premisele promovării sacubitril/ valsartanului (SV) în tratamentul pacienților cu IC cu fracție de ejeție redusă. La ora actuală, aproximativ 2.8 milioane de pacienți se află deja în tratament cu SV, ceea ce atestă eficiența și importanța SV în tratamentul IC⁽¹⁾. Tocmai de aceea, medicii interniști ar trebui să fie informați despre indicațiile, beneficiile și principiile clinice ale tratamentului cu SV.

Cuvinte cheie: sacubitril, valsartan, neprilizină, insuficiență cardiacă, fracție de ejeție redusă, peptide natriuretice.

Introduction

Sacubitril/ Valsartan (SV) was one of the last decade's major break-throughs in the treatment of heart failure (HF), as proven by the PARADIGM-HF1 and PIONEER-HF studies. It marked a paradigm shift in the treatment of HF since it is not only a symptomatic therapy, but also a prognostic-changing therapy, having the ability to increase the survival of patients with reduced ejection fraction heart failure (HFrEF). Dubbed a miracle for highly symptomatic HFrEF patients, SV is now a valid and more importantly, available therapeutical option. These promising results prompted the European Society of Cardiology (ESC) to include ARNI (angiotensin receptor blocker and neprilysin inhibitor) in the therapeutical algorithm for symptomatic

patients with HFrEF as a class I recommendation. As a consequence, since May 2020, the monthly costs for the treatment are entirely supported by the National Insurance House, with more and more patients benefiting from this new therapy.

Indications

SV is formally indicated in HF patients with a NYHA class of III or IV, in whom the EF is less than 40% and who are still symptomatic despite optimal treatment with angiotensin converting enzyme inhibitors (ACEIs)/ angiotensin receptor blockers (ARBs), beta-blockers (BBs) and mineralocorticoid receptor antagonists (MRAs). The treatment is to be maintained in all patients, regardless the NYHA class. Furthermore, SV can be

Figure 1. The interplay between the renin- angiotensin- aldosterone system and natriuretic peptide system. ACEI- angiotensin converting enzyme inhibitor, NI- neprilysin inhibitor, ARB- angiotensin receptor blocker, AT1- angiotensin receptor type 1, AT2- angiotensin receptor type 2. Notice the involvement of neprilysin in both systems

Figure 2. The crucial step when initiating SV in HFrEF patients

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initiated in patients with acute heart failure or decompensated chronic heart failure, provided the EF is less than 40% and hemodynamically stable. Currently, SV is not indicated for HF patients with preserved (>50%) or mid-range (40-49%) EF, although some data suggest potential benefits even in these patients (PARAGON-HF trial).

Mechanism of action

In the pathophysiology of HF, three major systems play a significant role in the maladaptive response: the adrenergic system, the renin-angiotensin-aldosterone system (RAAS) and the natriuretic peptide system.

Blocking the detrimental effects by using the adequate therapy (beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers and more recently, neprilysin inhibitors: sacubitril) reduces the mortality and morbidity in HF. RAAS activation leads to vasoconstriction, increased aldosterone levels, increased sympathetic tone and cardiac remodeling, all of which perpetuate the progression of the disease⁽¹⁾.

On the other hand, the natriuretic peptide system works antagonistically to the RAAS and has favorable effects on the pathogenesis of heart failure, such as increased diuresis with natriuresis,

decreased sympathetic tone, aldosterone levels and antifibrotic effect⁽¹⁾.

The natriuretic peptides are broken down by an enzyme called neprilysin. Inhibiting neprilysin will increase the levels of the natriuretic peptides (BNP, ANP, CNP, DNP), with beneficial effects on the pathogenesis of HF. However, neprilysin is also involved in breaking down angiotensin II in order to antagonize the effects of the activated RAAS. Therefore, inhibiting neprilysin will increase the levels of angiotensin II, along with amplifying its undesired effects. In addition, neprilysin is also responsible for breaking down bradykinin into inactive components. The main outcomes of inhibiting neprilysin will be: increased levels of natriuretic peptides, increased levels of angiotensin II and increased levels of bradykinin. As a consequence, in order for sacubitril to be beneficial in the therapy of HF patients, another drug is needed to counteract the undesired effects of angiotensin II and bradykinin.

Therefore, sacubitril must be administered concomitantly with valsartan (type 1 angiotensin receptor blocker). Angiotensin converting enzyme inhibitors are not a solution for reducing the high levels of angiotensin II in this case, since they will increase even more the already higher than normal circulating levels of bradykinin, leading to angioedema.

Dose	Systolic BP	Current ACEI/ ARB dose
24/26mg BID	100-110mmHg	Low dose: <10mg enalapril daily or <160mg valsartan daily or equivalents
49/51mg BID	> 110mmHg	High dose: >10mg enalapril daily or >160mg valsartan daily or equivalents

Table 1. Criteria for choosing the adequate initial dose of SV. The 49/51mg starting dose should not be considered for patients with a systolic BP of less than 110mmHg(2, 3)

Study	Outcome
PARAGON-HF	Increased survival with less major cardiovascular events A 16% risk reduction has been observed for all-cause mortality in patients treated with SV Reduced risk of hospital re-admission due to HF related events A significant reduction in HF hospitalizations in women
PROVE-HF	An average increase of 9.4% in EF after 12 months of therapy Beneficial effect on cardiac remodelling Reduced risk of hospital re-admission due to heart failure related events
PARADIGM-HF	A reduction in sudden cardiac death risk, regardless of the use of implantable cardiac defibrillators ⁽⁴⁾ Reduction in ventricular volumes and increase in LVEF after 6 months.
PARADIGM/ PARAGON	Pointing to an extended benefit in reducing HF related hospitalizations for patients with an EF of up to 55% Reduction in serum uric acid was associated with improved outcomes in patients with preserved EF ⁽⁵⁾

Table 2. The main clinical trials which included patients treated with SV and their outcomes

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Initiation and administration

SV should be initiated in the hospital under the surveillance of the cardiologist. For initiation, patients should have stopped the administration of ACEIs or ARBs for at least 36 hours prior to the first dose of SV (see Figure 2). MRAs can be continued. Furthermore, the patient must be hemodynamically stable, with a systolic blood pressure of at least 100mmHg and have normal blood levels of potassium ($<5,5$ mmol/L). SV must not be given to patients receiving ACEIs or renin inhibitors (aliskiren) or to those who have a history of angioedema with prior use of ACEIs or ARBs.

The initial dose is chosen based on the current systolic blood pressure (BP) and dose of ACEI/ ARB (see Table 1), with the possibility of choosing a starting dose of 24mg of sacubitril with 26mg of valsartan (24/26mg) BID or 49/51mg BID. For patients starting with the lower dose (24/26mg BID), the dose can be doubled in 2-4 weeks.

The target dose for patients is the one which showed the most benefits in the clinical trials, 97/103mg BID. In order to achieve this target, the dose can be doubled every 2 or 4 weeks, as long as the patient tolerates. However, in clinical practice, few patients will achieve this target dose in the first months. In some cases, doubling the dose can be difficult, as patients will develop hypotension.

In these cases, administering intermediate doses, such as 49/51mg with 24/26mg daily, can be considered if the patient does not tolerate the double dose (49/51mg BID) and will also increase the chances of tolerating a double dose in the future.

Side effects and monitoring of the treatment

The most common, undesired and sometimes troubling side effect of SV is hypotension (systolic BP < 90 mmHg), which can be clinically manifested as dizziness, fatigue, or even syncope. Patients who develop hypotension will have a lower adherence to treatment and smaller chances of reaching their target dose.

In order to decrease the chances of patients developing hypotension while receiving SV, clinicians should consider administering SV apart from other hypotensive drugs, such as diuretics or MRAs. If hypotension occurs when switching to a higher dose, intermediate doses may be considered as demonstrated earlier.

Other side effects include bradykinin induced angioedema (manifesting as persistent coughing), hyperkalemia and decreased renal function, defined as a drop in the estimated glomerular filtration rate of 35% or more. Therefore, patients should have their BP, renal function and serum potassium

periodically monitored after initiation or when switching to a different dose. SV should be stopped in patients who develop angioedema. Allergic reactions are very rare⁽²⁾.

Main benefits

The treatment with SV marks an important reduction in the symptom burden for most HFrEF patients. As observed in the daily clinical practice, after initiating the treatment, patients will be less symptomatic, upgrading their NYHA class, with some even becoming asymptomatic. The ejection fraction may improve significantly with SV (PROVE-HF trial). Interestingly enough, in some patients, the EF may stay the same, or improve only by a minimal amount, while the NYHA class will be significantly upgraded. Other important benefits are mentioned below in Table 2.

In conclusion, SV is a game-changing therapy for patients and clinicians as well. Every clinician should understand the potential of this novel therapy and encourage their patients to talk about SV with a cardiologist, if they are eligible for treatment. Last but not least, its future is even more exciting, since new benefits and even indications may be

proven by on-going and prospective trials.

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