Editorial / Editöryal Yorum

Sacubitril/valsartan in real-life clinical practice

Gerçek yaşamdaki klinik uygulamada sacubitril/valsartan

Yüksel Çavuşoğlu, M.D.

Department of Cardiology, Eskişehir Osmangazi University School of Medicine, Eskişehir, Turkey

Sacubitril/valsartan (sac/val), an angiotensin receptor-neprilysin inhibitor (ARNi), has been introduced into clinical practice in the treatment of heart failure with reduced ejection fraction (HFrEF) based on the results of the PARADIGM HF trial.[1] PARADIGM-HF demonstrated that compared with enalapril treatment, sac/val was associated with significant reductions in cardiovascular (CV) mortality, hospitalizations for heart failure (HF), all-cause mortality and also significant improvements in symptoms and health-related quality of life. Accordingly, the 2016 European Society of Cardiology[2] and 2016 American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA)[3] and Turkish Society of Cardiology guidelines[4] recommended the use of sac/val with a class IB indication as a replacement for angiotensin-converting-enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) treatment in ambulatory patients with HFrEF who remain symptomatic despite treatment with a beta blocker (BB) and/or a mineralocorticoid receptor antagonist (MRA). In addition, the real-life experiences of sac/val have been reported in several studies, showing effectiveness and safety of sac/val in clinical practice.

Data from recently published TRANSITION,[5] PIONEER HF,[6] PROVE HF[7] and EVAULATE HF[8] trials expanded the usage of sac/val to the ACEi/ARB-naïve patients and to the patients hospitalized for acute decompensated HF who are clinically and hemodynamically stabilized in hospital period before discharge. Recent PARADISE MI trial[9] demonstrated that compared with ramipril, sac/val showed similar or even numerically better clinical benefit in post-myocardial infarction patients in terms of CV death, hospitalization for HF and outpatient HF requiring treatment. In the light of these advances, sac/val is now referred as the first choice treatment option over ACEi/ARB in 2021 Update of the ACC Expert Consensus Document on Optimization HFrEF Therapy[10] and in a national expert consensus HFrEF treatment algorithm,[11] sac/val is recommended as the preferred drug over ACEi/ARB at the first step of the therapy. ACEi/ARB are now recommended to be considered only in patients with contraindications, intolerance and inaccessibility to sac/val.

Abbreviations:

ACC	*American College of Cardiology*
ACEi	*Angiotensin-converting-enzyme inhibitor*
AHA	*American Heart Association*
ARB	*Angiotensin receptor blocker*
ARNi	*Angiotensin receptor-neprilysin inhibitor*
BB	*Beta blocker*
BP	*Blood pressure*
CV	*Cardiovascular*
DM	*Diabetes mellitus*
EF	*Ejection fraction*
HF	*Heart failure*
HFrEF	*Heart failure with reduced ejection fraction*
HFSA	*Heart Failure Society of America*
MRA	*Mineralocorticoid receptor antagonist*
NT-proBNP	*N-terminal pro-brain natriuretic peptide*
NYHA	*New York Heart Association*
sac/val	*sacubitril/valsartan*

Although there have been a number of prospective, randomized, controlled, landmark clinical trials establishing the efficacy of sac/val,[1,5-8] the effectiveness and particularly safety and tolerability of the drug need to be evaluated in real-life clinical practice. Patients who meet with selection criteria are

Correspondence: Yüksel Çavuşoğlu, M.D. Department of Cardiology, Eskişehir Osmangazi University School of Medicine, Eskişehir, Turkey
Tel: +90 222 - 239 29 79 e-mail: yukselc@ogu.edu.tr

included in clinical trials and some subgroup of patients with severe comorbid conditions or worse clinical picture are usually excluded from the studies and therefore this kind of population in randomized, controlled trials does not fully reflect real-world patient population. One of the typical examples is the run-in phase of PARADIGM HF trial.[1] Patients tolerating maximal doses of both enalapril and sac/val with potassium ≤5.4 mmol/L; eGFR ≥30 mL/min 1.73 m^2 and no decrease in eGFR of >25% (later amended to >35%) from the screening visit; no symptomatic hypotension, no postural symptoms and systolic blood pressure (BP) ≥95 mmHg; no other adverse events precluding continuation of the study drug during run-in period were included in the study.[1] In other words, patients who completed 'stress test' were able to be included in the randomized phase. Thus, effectiveness of the sac/val was favorably tested in a population in which over 75% of patients received target doses of the study drugs. However, run-in phase selection or elimination makes it difficult to interpret data on safety and tolerability. Therefore, run-in selection bias should always be kept in mind when interpreting data on safety and tolerability. In this respect, real-world observational studies provide important insights not only on effectiveness but also safety, tolerability, compliance, adherence, persistence and implementation.

Several real-world studies reported that overall, treatment persistence and tolerability of sac/val was high, implementation was slow and variable between different countries, up-titration to target dose was low and use of sac/val was associated with improved quality of life.[12-15] In this context, ARNi TR, a multicenter, retrospective, observational registry published in the Archives of the Turkish Society of Cardiology[16] seems to be a nice addition to the literature on the use of sac/val in real-life clinical practice, reporting significant improvements in New York Heart Association (NYHA) functional class, N-terminal pro-brain natriuretic peptide (NT-proBNP), ejection fraction (EF) and HbA1c levels in diabetic patients and also significant reductions in daily furosemide doses and hospitalizations for HF. However, lack of control group and retrospective design of the study are important limitations. Also, changes in other HF-related medications during study period are not clear, which preclude the interpretation of the findings whether beneficial effects resulted from sac/val itself or not. Moreover, it would be very interesting to see a comprehensive analysis of ACEi/ARB naïve patients.

ARNi-TR showed that almost 80% of patients were initiated with the lowest sac/val dose of 50 mg twice daily (bid) and at 1-year, only 25% of patients reached the target dose of 200 mg bid and 25% remained in the lowest dose of 50 mg bid. Given the fact that 50 mg bid does not provide statistically significant mortality/morbidity advantages over ACEi in the PARADIGM HF subgroup analysis,[17] every effort should be made to reach to target dose of 200 mg bid or at least 100 mg bid. Also, in ARNi-TR,[16] the rate of discontinuation of sac/val has been reported as 4%, which is really less than that of PARADIGM HF,[1] in which discontinuation rate was 10% despite the highly selected criteria for tolerability in the run-in period.

In large-scale clinical trials, NT-proBNP, an important prognostic biomarker for HF, has been reported to decrease very early and significantly after initiation of sac/val.[1,5-8] Lowering in NT-proBNP levels is consistent in almost all sac/val clinical trials including ARNi-TR registry. The reduction is much more prominent with sac/val as compared with enalapril. In PIONEER HF trial,[6] a significant reduction was observed at 7-days of sac/val treatment. Data from PARADIGM HF showed that risk of the primary endpoint of CV mortality or HF hospitalization was 59% lower in patients with a fall in NT-proBNP to ≤1,000 pg/mL than in those without such a fall, and it fell to ≤1,000 pg/mL in 31% versus 17% of patients treated with sac/val and enalapril, respectively.[18] So, NT-proBNP may be used as a biomarker in guiding therapy and estimation of response to sac/val treatment.

Improvement in NYHA functional capacity in ARNi-TR is not a surprising finding, however, an increase in EF at the end of 1-year of sac/val treatment is consistent with the findings of PROVE-HF[7] and EVALUATE HF[8] trials on reverse cardiac remodeling. Furthermore, reduction in rehospitalization in ARNi-TR seems to be favorable as the number of annual hospitalizations was reported to reduce from 1.9±1.8 to 0.5±0.8 during follow-up of outpatients. Moreover, significant reduction in diuretic doses complies with the results of PARADIGM HF.[19] Similar to the PARADIGM HF findings,[20] HbA1c levels

in ARNi-TR were found to be significantly decreased in patients with diabetes mellitus (DM).[16] This important finding supports the use of sac/val in DM patients as the preferred renin angiotensin aldosterone system inhibitor.

In terms of safety, the rate of hypotension (16.9%), hyperkalemia (potassium level >6 mEq/L in 0.7%) and worsening renal function (2.1%) in ARNi-TR[16] are almost similar to those of previously published randomized controlled clinical trials.[1,5-8] Given the prevalent use of MRA in ARNi-TR (>70%), the rate of hyperkalemia and worsening renal function would have been expected to be higher. A tendency of lowest (50 mg bid) or modest doses (100 mg bid) usage of sac/val in ARNi-TR may partly explain this situation. Furthermore, in ACEi/ARB naive patients, the rate of hypotension was reported to be reasonable as compared to those who used these drugs previously (19.5% vs 16%).

In conclusion, data from landmark randomized-controlled clinical trials supported that sac/val is a safe and effective treatment option and should be used as preferred drug over ACEi or ARB in HFrEF therapy. However, real-life observational studies showed that implementation was slow and up-titration to target dose was very low. Therefore, clinicians should make every effort for implementation, adherence, persistence and up-titration of sac/val treatment in order to provide optimal clinical benefit.

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