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RESEARCH LETTER

Starting sacubitril-valsartan is safe in patients with transthyretin cardiac amyloidosis and impaired ejection fraction

O início do tratamento com sacubitril-valsartan é seguro em doentes com amiloidose cardíaca transtirretina e fração de ejeção reduzida

Transthyretin amyloid cardiomyopathy (ATTR-CM) is the most common type of cardiac amyloidosis, and is significantly underdiagnosed.[1] Disease management is focused on support therapy for heart failure (HF).

Although ATTR-CM usually presents as HF with preserved left ventricular ejection fraction (LVEF), nearly one third of patients have reduced LVEF at diagnosis.[2] Optimal management of HF is challenging in this scenario and euvolemia becomes the cornerstone of HF management.

Despite their benefits in HF with reduced and mildly reduced LVEF,[3] evidence supporting the use of angiotensin receptor-neprilysin inhibitors (ARNI) in ACTTR-CM is lacking. Moreover, they are usually described as poorly tolerated, mainly because of hypotension and renal impairment.[1]

We present our initial experience with patients with ACTTR-CM and HF with impaired LVEF who received ARNI. Our aim was to analyze the tolerance and safety of starting ARNI in this population.

We conducted a prospective observational study including consecutive patients referred to the Cardiomyopathy Unit between 2018 and 2021 with ACTTR-CM and impaired ejection fraction (LVEF <50%). ACTTR-CM was diagnosed using current recommendations.[4] ARNI was started at a dose of 12/13 mg twice daily and titrated to maximum tolerated dose in all cases. Laboratory and clinical examinations were carried out before starting ARNI and at one, three and six months, as per the Unit's protocol. The study was approved by the local ethics committee and informed consent was obtained.

Six patients were included. All had been non-invasively diagnosed with wild-type ATTR-CM. The main characteristics of the study population are shown in Table 1. Patients were male (100%), aged 84.2±6.5 years, and had other comorbidities (five out of six had chronic kidney disease).

Clinical status at baseline suggested advanced HF. All patients had presented at least one decompensation in the last year. Functional class was usually poor (83.3% in New York Heart Association [NYHA] class III/IV). Mean baseline LVEF was 39.0±5.3% and severe diastolic dysfunction was present in all cases (E/e′ 20.0±3.3). Natriuretic peptides were highly elevated (mean N-terminal B-type natriuretic peptide [NT-proBNP] 7728.8±5458.1 pg/ml). As shown, patients were under medium to high doses of loop diuretics and most of them were receiving more than one diuretic.

ARNI was promptly started in most patients (4/6 within six months of ATTR-CM diagnosis). Maximum dose was not achieved in any case, but medium dose (49/51 mg twice daily) was tolerated in three out of six patients. Therapy onset was generally well tolerated. One patient (#1) needed a temporary withdrawal for one week due to symptoms of hypotension. Blood pressure measurements showed no clinically significant hypotension and renal function remained similar in all cases (estimated glomerular filtration rate improved in 50% of patients). Moderate hyperkalemia was observed in one case (#2) but was successfully controlled with dietary recommendations and medical therapy. No hospitalizations due to acute HF were observed within six months of starting ARNI.

The main result of our work was that, when carefully titrated, ARNI was well tolerated, with only mild deleterious effects on blood pressure or renal function. We also observed a general improvement in clinical status after ARNI onset as assessed by NYHA class, relief of edema, weight loss and decreased natriuretic peptides (Table 1).

Several factors could explain the results observed. Biologically, improvement in systolic and diastolic function with ARNI is based on its dual mechanism through angiotensin receptor and neprilysin inhibition. Both effects seem to be the main mechanisms leading to an increase in natriuresis and diuresis, vasodilation, reduction in sympathetic tone and antiremodeling effects.[5] On the other hand, autonomic impairment is more important in light-chain and variant ATTR-CM, in which amyloid deposits occur in the nerves.[6] In wild-type ATTR-CM, patients usually experience age-related autonomic dysfunction, which can be more easily managed.

In addition, ARNI have shown fewer side effects than angiotensin-converting enzyme inhibitors in outpatient management. This is especially important when dealing with aged patients.

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Table 1 Clinical characteristics of the study population.

	Patient #1		Patient #2		Patient #3		Patient #4		Patient #5		Patient #6	
Medical history												
Age when ARNI was started, years	74		78		87		88		89		89	
Time since ATTR-CM diagnosis, m	24		22		6		3		3		4	
Gender	Male		Male		Male		Male		Male		Male	
Hypertension	Yes		Yes		Yes		Yes		Yes		No	
Diabetes	No		No		No		No		No		No	
CKD	Yes		Yes		Yes		Yes		Yes		No	
Atrial fibrillation	Yes		Yes		Yes		Yes		No		No	
Pacemaker	No		No		Yes		No		No		No	
Previous HF admission	Yes		Yes		Yes		Yes		Yes		Yes	
In previous 6 m	No		No		No		Yes		Yes		Yes	
In previous 12 m	Yes		Yes		Yes		Yes		Yes		Yes	
Medical therapies												
Max. sacubitril/valsartan dose, mg	24/26 once daily		49/51 twice daily		49/51 twice daily		24/26 twice daily		49/51 twice daily		24/ 26 twice daily	
Furosemide, mg	120		80		40		80		40		100	
MRA, mg	No		No		No		No		25		No	
Chlorthalidone, mg	12.5		No		25		No		No		12.5	
Beta-blocker	No		No		No		No		Yes		No	
Clinical status (baseline-6 m)												
NYHA class	IV	III	III	II	III	II	III	III	II	I	III	II
Edemas	+++	++	+++	+	+++	+	++	+	++	+	+++	++
Weight, kg	82	80	90	81	92	82	—	—	61	63	100	98

Table 1 (*Continued*)

	Patient #1			Patient #2			Patient #3			Patient #4			Patient #5			Patient #6		
BP, mmHg (baseline-1 m-6 m)	100/72	81/64	91/66	135/70	120/65	130/70	145/65	115/55	125/60	100/60	105/55	112/65	132/54	137/70	120/65	135/65	115/55	110/50
Echocardiography (baseline-6 m)																		
LVEF, %	40	32		35	47		45	44		43	39		31	30		39	52	
E/e′	24	16		18	9		20	15		16	15.8		24	15		18.1	13	
Biochemical test (baseline-1 m-6 m)																		
Hb, g/dl	17	17.1	17	14.7	13.5	13	13.5	14	15	13.9	13.7	13.5	10.1	12.6	12.4	13.4	13.4	11.7
Cr, mg/dl	1.4	1.7	1.7	2.3	1.9	2	1.6	1.4	1.6	0.9	1.1	1.1	1.3	1.3	1.4	0.8	0.9	0.8
GFR, ml/min/1.73 m²	49	39	38	31	32	40	41	47	39	70	60	62	54	54	53	75	85	63
Sodium, mmol/l	141	145	145	145	140	145	136	138	140	141	144	144	139	143	140	140	141	142
Potassium, mmol/l	3.6	5.3	4.6	5.6	5	5.9	4.2	4.2	4.1	4.6	4.6	4.9	4	5	4.7	4.7	5.1	4
NT-proBNP, pg/ml	11931	10376	9391	14397	12009	5338	11298	10281	9786	1252	857	793	4206	11603	12491	3275	2760	4312

ATTR-CM: transthyretin amyloid cardiomyopathy; BP: blood pressure; CKD: chronic kidney disease; Cr: creatinine; GFR: glomerular filtration rate (MDRD); Hb: hemoglobin; HF: heart failure; LVEF: left ventricular ejection fraction; m: months; MRA: mineralocorticoid receptor antagonist; NT-proBNP: N-terminal B-type natriuretic peptide; NYHA: New York Heart Association.

It is noteworthy that one patient (#6) showed an improvement in LVEF, which is commonly assumed to be rare in patients with cardiac amyloidosis. However, several studies have described an improvement in LVEF after starting treatment with sacubitril-valsartan in patients with reduced LVEF.[7] It is unknown if some of them may have had undiagnosed cardiac amyloidosis.

Finally, observational reports such as ours have major limitations that should be considered. More studies are needed to confirm our findings and support the use of ARNI in wild-type ATTR-CM with impaired ejection fraction.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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