Review Article

Fimasartan: A new armament to fight hypertension

Akshyaya Pradhan[1], Vikas Gupta[1], Rishi Sethi[1]

[1]*Department of Cardiology, King George Medical University, Lucknow, Uttar Pradesh, India*

Abstract

Hypertension is a major public health problem of modern era. Fimasartan is a new Angiotensin Receptor Blocker approved for treatment of hypertension. It is more potent and longer acting angiotensin receptor blocker with effects lasting over 24 hours. Many clinical studies have affirmed its role in pharmacotherapy of hypertension. Further, it is renoprotective and has proven beneficial in diabetes also. This article briefly discusses the pharmacology and clinical evidence with fimasartan with a short summary of previous angiotensin receptor blockers.

Keywords: Angiotensin receptor blocker, clinical studies, fimasartan, hypertension, pharmacokinetics

Introduction

Hypertension is a major public health problem of modern era. Up to 28% of the world's adult population had uncontrolled hypertension in a study published in 2011.[1] Anchala *et al.* reported an overall hypertension prevalence of 29.8% in India in their meta-analysis.[2] The prevalence of hypertension in this study was significantly higher in urban Indians than in rural Indians (33.8% vs. 27.6%, respectively).[2]

Hypertension if left untreated can lead to end organ damage, such as retinopathy, chronic kidney disease, cerebrovascular disease, heart failure, coronary artery disease, and atrial fibrillation. Various classes of drugs are available for treatment of hypertension. Among these angiotensin receptor blockers (ARBs) are most widely used antihypertensive drugs and have maximal patient acceptability profile. ARBs hold class I recommendation for pharmacological management of hypertension in various guidelines including European and American guidelines.[3-5]

Address for correspondence: Dr. Akshyaya Pradhan, Department of Cardiology, King George's Medical University, Lucknow - 226 003, Uttar Pradesh, India.
E-mail: akshyaya33@gmail.com

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Mechanism of Action of ARBs

The ARBs selectively inhibit angiotensin II by competitive antagonism of the angiotensin receptors [Figure 1]. Thereby, they antagonize angiotensin II-induced vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, and water retention. These mechanisms reduce adverse effects and possibly improve clinical efficacy in comparison to angiotensin convertase enzyme inhibitors (ACEIs). The currently available ARBs are summarized briefly in Table 1.

Fimasartan - the Latest "Sartan"

Fimasartan is a latest[9] angiotensin II receptor antagonist with selectivity for the AT(1) receptor subtype, developed by a korean company Boryung Pharmaceutical as an oral antihypertensive drug. Figure 2 demonstrates journey of ARBs from first marketed ARB molecule to recently introduced fimasartan. Fimasartan has been approved for use in patients with hypertension by FDA of Korea. Boryung has also got approval for this molecule in many other countries such as China, Singapore, and Russia. Fimasartan has also been approved in India by CDSCO (Central Drugs Standard Control Organization) recently.

Fimasartan is a biochemical derivative of losartan in which the imidazole ring has been replaced. This change provides higher potency and longer duration of action to this molecule.

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Table 1: Brief description of currently available ARBs ("Sartans")[6-9]

Drug	Active Metabolite	Half Life (hours)	Starting Dose (mg)	Major Trials
Candesartan	Yes	3.5-4 (3-11 of metabolite)	16	SCOPE, DIRECT-PREVENT
Eprosartan	No	5-7	600	MOSES, OSCAR
Irbesartan	No	11-15	150	IRMA-2, IDNT
Losartan	Yes	2 (6-9 of metabolite)	50	RENAAL, LIFE
Olmesartan	Yes	13	20	ORIENT, ROADMAP,
Telmisartan	No	24	40	PROFESS, TRANSCEND
Azilsartan	No	11	50	Bakris *et al.*, Sica *et al.*
Valsartan	No	9	80	NAVIGATOR
Fimasartan	No	5-16	30	Safe-KanArb

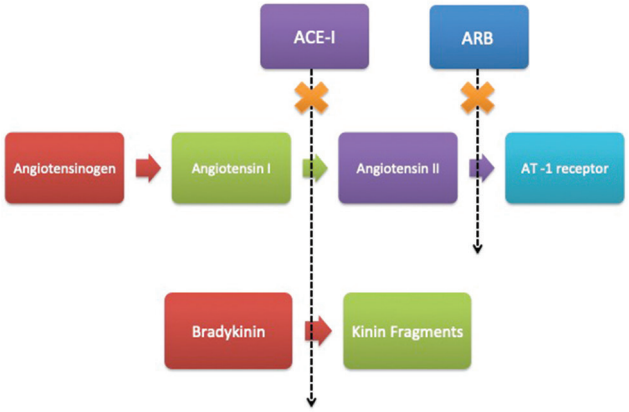

Figure 1: Mechanism of action of angiotensin convertase enzyme inhibitors and angiotensin receptor blockers

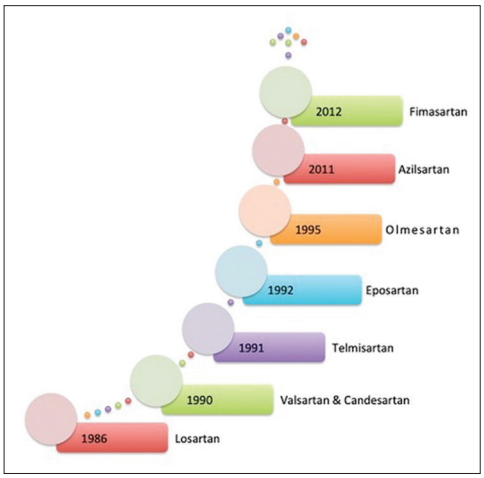

Figure 2: Development journey of angiotensin receptor blockers

Fimasartan is selective angiotensin II type 1 (AT_1) receptor antagonist.[10] In contrast to other ARBs, it did not show agonistic action to AT_2 receptor in animal models.[11]

Pharmacokinetics and Dynamics

The pharmacokinetics and pharmacodynamics of fimasartan are highlighted in Table 2. It is a long acting drug, requiring once daily dosing. It is usually given in dosage of 60–120 mg OD. The onset of action of fimasartan is faster that it's congeners. It is usually well tolerated in mild to moderate renal dysfunction, but dose reduction is required in severe renal dysfunction (<30 mL/min creatinine clearance starting dose is 30 mg OD). It is safe in mild hepatic dysfunction. Fimasartan should be avoided in severe hepatic dysfunction, patients on hemodialysis, pregnant or nursing mothers, and patients with hypersensitivity reaction.

The drug has been well tolerated in clinical studies. Most adverse reactions were transient and not dose related. Headache and dizziness were the most common ones reported. Other reported side effects include nausea, pain abdomen, cough, pruritus, hot flushes, increased liver enzymes, etc.

Clinical Evidence for Use in Hypertension

We have now accumulated data for fimasartan use in close to 20,000 patients. Fimasartan was found to have an excellent efficacy and tolerability profile in a large-scale observational population study - Safe-KanArb. In this study, a total of 14,151 patients with mean age of 59 ± 12 years were evaluated. This study established the safety, efficacy, and compliance of this molecule. The Systolic blood pressure (SBP) fell by an average of -18.65 mm of Hg and Diastolic blood pressure by - 9.73 mm of Hg with drug therapy at 2 months. Interestingly, the pulse rate declined from 74.4 to 71.9 beats per min in the treatment arm. The benefits were attained irrespective of age, sex, comorbidities and background antihypertensive therapy. It should be noted that more than half of the study population (63%) was on background anti-hypertensive therapy underscoring the potency and efficacy of the drug. The drug was found to be excellent in patients potentially at higher risk for adverse events.[12]

The K-MetS study of 10601 patients was planned to evaluate long-term effects of fimasartan on major adverse cardiovascular outcomes. The study also evaluated long-term metabolic effects of fimasartan. Three-year follow-up was planned in this study. At 1-year follow-up, in a sub group analysis published in 2017, fimasaratn significantly decreased the albumin/creatinine ratio. The systolic blood pressure fell from 143.7 ± 17.2 mm of Hg to 126.7 ± 12.6 mm of Hg at 1 year (a fall of around 17 mm of Hg). On a similar note, the diastolic BP decreased from 88.4 ± 11.48 at baseline to 78.6 ± 8 mm of Hg. Waist circumference and triglyceride levels were also diminished simultaneously.[13]

In another study, the drug was associated with reduction in day to day BP variability independent of absolute BP reduction.[14] Fimasartan was similarly effective in reducing Systolic as well as diastolic BP in hypertensive elderly patients compared with nonelderly patients in a sub group analysis of K-MetS study. It also resulted in better pulse pressure reduction with similar home blood pressure reduction efficacy and safety in hypertensive elderly patients.[22]

One recent study evaluated the effects of fimasartan and amlodipine therapy on carotid atherosclerotic plaque inflammation using 18F-fluorodeoxyglucose positron emission tomography imaging. Both drugs were found to decrease carotid atherosclerotic plaque inflammation similarly in patients with acute coronary syndrome.[23] The major studies done with fimasartan so far are depicted in Table 3.

Table 2: Pharmacokinetics and pharmacodynamics of fimasartan[9-11]

Half life	5-16 h
Protein binding	95%
Bioavailability	18.6%
Metabolism	>90% stable
Excretion	Predominantly fecal and biliary, only 2% renal
Dosage	60-120 mg OD orally with or without food
Renal impairment	No dose adjustment required in mild to moderate renal impairment, but <30 mL/min creatinine clearance starting dose is 30 mg OD
Hepatic impairment	The drug is not recommended in moderate to severe hepatic impairment
In pregnancy and lactation	Not recommended
Adverse reactions	Headache, dizziness Syncope, dyspepsia, asthenia, Muscular twitching, pruritus, cough, erectile dysfunction
Common	
Uncommon	

Implications for Clinical Practice

The prevalence of hypertension is continuously rising, yet the proportion of patient's with their blood pressures under target remains low. The ACC/AHA 2017 hypertension guidelines suggest that most of the hypertensive patients will need combination therapy for attaining BP goals. In real world, primary care physician (not the cardiologist) is usually the first contact of a patient for hypertension consultation. So longer acting, potent antihypertensive drugs with least side effect profile are needed to make the task of hypertension control easy. ARBs have proven their efficacy in treatment of hypertension for past two decades. They have most favorable side effect profile among current antihypertensive portfolio. Fimasartan is newer longer acting and potent ARB. So, it can be safely used by primary care physician in an efficient manner for management of hypertension.

Future Directions

FANTASTIC study will assess renoprotective effect of fimasartan and the target blood pressure to reduce adverse outcomes in hypertensive diabetic chronic kidney disease patients with overt proteinuria.[24] The safety and efficacy of drug in elderly patients (>70 years) against perindopril is being evaluated in FITNESS study (NCT 03246555). The FRESH (FimasaRtan-basEd BP Targets After Drug SwitcHing) study aimed to find proportion of patients achieving BP goals after switching to fimasartan-based regimens in patients with uncontrolled hypertension (NCT 03649646).

Conclusion

A good number of clinical evidences support the use of this newer, potent, longer acting ARB- Fimasartan [See Figure 3].

Table 3: Major studies establishing the clinical role of fimasartan in hypertension.[12-21][BP-Blood Pressure; FMS- Fimasartan; HCTZ-Hydrochlorthiazide]

Study	Number of Patients	Study Drugs	Key Findings
Cardona *et al.*[15]	272	60 and 120 mg FMS alone or combined with HCTZ	FMS safe and effective in grade 1-2 essential hypertension
Shin *et al.*[14]	1,396	30-120 mg FMS for 3 months	3 months of FMS reduces day-to-day BP variability independent of BP reduction
Safe-KanArb Study[12]	14,151	60 or 120 mg OD	Established efficacy, safety, and tolerability of FMS
K-Mets study[13]	3,250	FMS for 3 months	FMS reduced the albumin/creatinine ratio in hypertensive patients
Duran *et al.*[16]	40	60-120 mg FMS	FMS reduced SBP, DBP adequately with decrease in albuminuria at 24 weeks
Lee *et al.*[17]	75	Low-dose FMS (30 mg) or valsartan 80 mg daily	Low dose FMS lowers 24 hrs BP comparable to valsartan in mild to moderate hypertension
Lee *et al.*[18]	92	FMS 60-120 mg or valsartan 80 mg daily for 8 weeks	Once daily FMS effectively maintained BP maintained over 24 h dosing interval comparable to slightly better than valsartan
Rhee *et al.*[19]	263	60-120 mg once daily FMS alone or with 12.5 mg HCTZ	Combination therapy achieved better BP control than FMS monotherapy and had comparable safety and tolerance to FMS monotherapy
Kim *et al.*[20]	143	FMS 60 mg monotherapy or FMS 60 mg + amlodipine 10 mg	Combination therapy produced superior BP reductions and low levels of adverse effects compared with monotherapy.
Yang *et al.*[21]	41	FMS 60-120 mg or amlodipine 5-10 mg for 16 weeks	Compared with amlodipine FMS increased late phase insulin release in patients with type 2 diabetes mellitus and hypertension

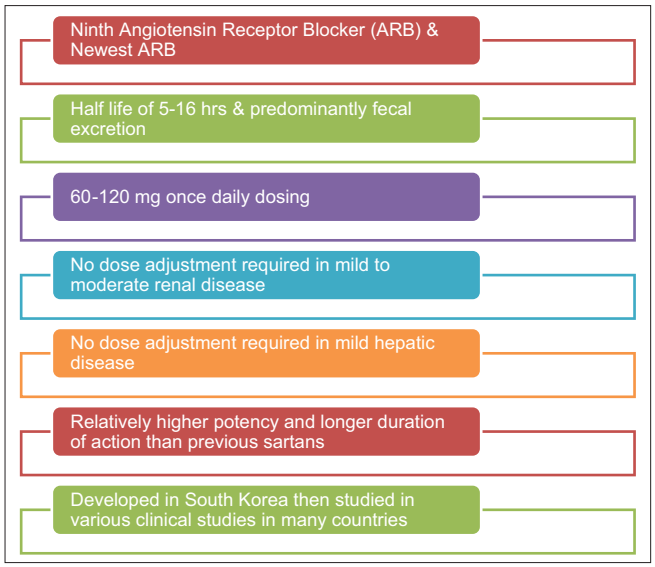

Figure 3: Key points for the clinician regarding Fimasartan

Fimasartan achieved clinically significant blood pressure reduction in various studies with effect persisting over 24 h dosing interval. It was also shown to be renoprotective too. Apart from being efficacious, it has also demonstrated safety in elderly and high risk populations. So, this newer ARB has shown promising results in terms of efficacy, safety, and tolerability in clinical studies. The molecule is currently being used in number of countries in treatment of hypertension. In India, it has been launched recently. Fimasartan appears as a promising drug for management of hypertension for future in our country.

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Conflicts of interest

There are no conflicts of interest.

References

1. Danaei G, Finucane MM, Lin JK, Singh GM, Paciorek CJ, Cowan MJ, *et al.* National, regional, and global trends in systolic blood pressure since 1980: Systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. Lancet 2011;377:568-77.
2. Anchala R, Kannuri NK, Pant H, Khan H, Franco OH, Di Angelantonio E, *et al.* Hypertension in India: A systematic review and meta-analysis of prevalence, awareness, and control of hypertension. J Hypertension 2014;32:1170-7.
3. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;71:1269-324.
4. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, *et al.* 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021-104.
5. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, *et al.* 2014 evidence-based guideline for the management of high blood pressure in adults: Report From the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507-20.
6. Olin BR. Drug Facts and Comparisons. St. Louis: JB Lippincott Co; 2002. p. 514-8.
7. Bumier M. Angiotensin II type 1 receptor blockers. Circulation 2001;103:904-12.
8. Jones JD, Jackson SH, Agboton C, Martin TS. Azilsartan medoxomil (Edarbi): The eighth angiotensin II receptor blocker. *P* T 2011;36:634-40.
9. Fimasartan. Am J Cardiovasc Drugs 2011;11:249-52.
10. Kim TH, Shin S, Bashir M, Chi YH, Paik SH, Lee JH, *et al.* Pharmacokinetics and metabolite profiling of fimasartan, a novel antihypertensive agent, in rats. Xenobiotica 2014;44:913-25.
11. Chi YH, Lee H, Paik SH, Lee JH, Yoo BW, Kim JH, *et al.* Safety, tolerability, pharmacokinetics, and pharmacodynamics of fimasartan following single and repeated oral administration in the fasted and fed states in healthy subjects. Am J Cardiovasc Drugs 2011;11:335-46
12. Park JB, Sung K-C, Kang SM, Cho EJ. Safety and efficacy of fimasar-tan in patients with arterial hypertension (Safe-KanArb Study) Am J Cardiovasc Drugs 2013;13:47-56.
13. Park JB, Kim S-A, Sung K-C, Kim JY. Gender-specific differences in the incidence of microalbuminuria in metabolic syndrome patients after treatment with fimasartan: The K-MetS study. PLoS One 2017;12:e0189342.
14. Shin MS, Kang DR, Kim C, Cho EJ, Sung KC, Kang SM, *et al.* Fimasartan for independent reduction of blood pressure variability in mild-to-moderate hypertension. Drug Des Devel Ther 2016;10:1573-80.
15. Cardona-Munoz EG, Lopez-Alvarado A, Conde-Carmona I, Sánchez-Mejorada G, Pascoe-González S, Banda-Elizondo RG, *et al.* Safety and efficacy of fimasartan in Mexican patients with grade 1–2 essential hypertension. Arch Cardiol Mex 2017;87:316-25.
16. Durán AM, Corcuera JO. Antihypertensive efficacy of fimasartan and additional benefits in patients with renal dysfunction. Ann Clin Exp Hypertension 2017;5:1046.
17. Lee HY, Kim CH, Song JK, Chae SC, Jeong MH, Kim DS, *et al.* 24-Hour blood pressure response to lower dose (30 mg) fimasartan in Korean patients with mild to moderate essential hypertension. Korean J Intern Med 2017;32:1025-36.
18. Lee H, Kim KS, Chae SC, Jeong MH, Kim DS, Oh BH. Ambulatory blood pressure response to once-daily fimasartan: An 8-week, multicenter, randomized, double-blind, active-comparator, parallel-group study in Korean patients with mild to moderate essential hypertension. Clin Ther 2013;35:1337-49.
19. Rhee MY, Baek SH, Kim W, Park CG, Park SW, Oh BH, *et al.* Efficacy of fimasartan/hydrochlorothiazide combination in hypertensive patients inadequately controlled by fimasartan monotherapy. Drug Des Devel Ther 2015;9:2847-54.
20. Kim K, Shin MS, Ihm SH, Youn HJ, Sung KC, Chae SC, *et al.* A randomized, double-blind, multicenter, phase III study to evaluate the efficacy and safety of fimasartan/amlodipine combined therapy versus fimasartan monotherapy in patients with essential hypertension unresponsive to

fimasartan monotherapy. Clin Ther 2016;38:2159-70.

21. Yang YS, Lim MH, Lee SO, Roh E, Ahn CH, Kwak SH, *et al.* Fimasartan increases glucose-stimulated insulin secretion inpatients with type 2 diabetes and hypertension comparedwith amlodipine. Diabetes Obes Metab 2018;20:16707.
22. Cho EJ, Sung KC, Kang SM, Shin M-S, Joo SJ, Park JB. Fimasartan reduces clinic and home pulse pressure in elderly hypertensive patients: A K-MetS study. PLoS One 2019;14:e0214293.
23. Oh M, Lee CW, Ahn JM, Park DW, Kang SJ, Lee SW, *et al.* Comparison of fimasartan and amlodipine therapy on carotid atherosclerotic plaque inflammation. Clin Cardiol 2019;42:241-6.
24. Kim JY, Son JW, Park S, Yoo TH, Kim YJ, Ryu DR, *et al.* FimAsartaN proTeinuriA SusTaIned reduCtion in comparison with losartan in diabetic chronic kidney disease (FANTASTIC): Study protocol for randomized controlled trial. Trials 2017;18:632.