Development of AIMIX® Combination Tablets LD&HD, a Novel Fixed-Dose Combination Medicine of Irbesartan and Amlodipine Besilate

Dainippon Sumitomo Pharma Co., Ltd.
Pharmacology Research Laboratories
Masaya MORI*
Hiroshi KATO*

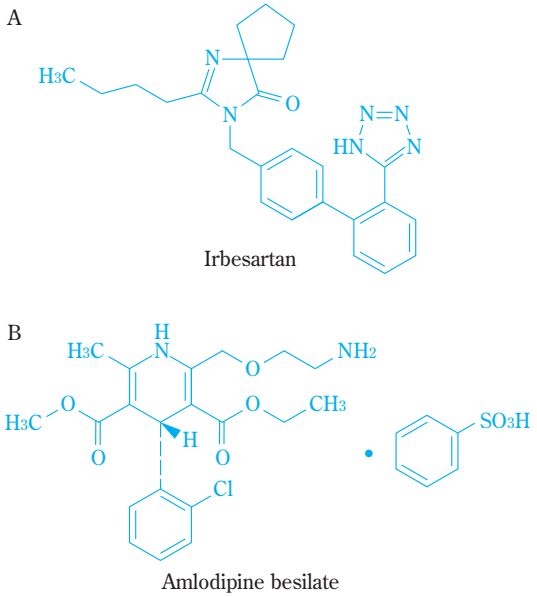
AIMIX® combination tablets LD&HD is a novel fixed-dose combination medicine of irbesartan, an angiotensin receptor blocker (ARB), and amlodipine besilate, a calcium channel blocker (CCB). This product was launched for the treatment of hypertension in Japan on Dec 19, 2012. In this review, we firstly outline the trends in antihypertensive drugs in the past decades and the current situation for combination tablets. We secondly review the development concept, pharmacological effects, and results of clinical trials of AIMIX® combination tablets LD&HD.

This paper is translated from R&D Report, "SUMITOMO KAGAKU", vol. 2013.

Introduction

Hypertension is a major risk factor for the circulatory diseases such as ischemic heart disease and cerebral vascular disease, and its effects are known to be greater than other risk factors.[1)–3)] According to the Japanese Society of Hypertension "Guidelines for the Management of Hypertension JSH 2009," the number of patients with hypertension in Japan is estimated to be about 40 million, and it is estimated that half or more of those patients are not receiving sufficient treatment.[4)] Therapeutic drugs with various mechanisms of action have been approved for the treatment of hypertension in Japan since the launch of vasodilators in the 1950s. Generally, combination therapy is standard to treat patients with moderate to severe hypertension, because monotherapy is difficult to use for controlling blood pressure in such patients. However, the blood pressure levels are not adequately controlled in approximately 50% of the hypertensive patients, when evaluated based on the guidelines.[5)] The insufficient control of blood pressure is mainly due to medication noncompliance by patients themselves.[6)] Therefore, combination medicines have been developed and launched in order to improve drug compliance in recent years.

AIMIX® combination tablets LD&HD are a combination medicine of irbesartan (an angiotensin II receptor blocker (ARB)), and amlodipine besilate (a calcium channel blocker (CCB)) (**Fig. 1**). This product was launched for the treatment of hypertension in Japan on December 19, 2012. In this article, we firstly outline the trend in antihypertensive drugs in past decades and the current situation for combination tablets. We secondly review the development concept, pharmacological effects, and results of clinical trials of AIMIX® combination tablets LD&HD.



Chemical structures of irbesartan (A), amlodipine besilate (B).

Fig. 1 Chemical structures

* Currently: Development Research Laboratories

Trends in Antihypertensive Drugs in Past Decades

The history of antihypertensive drugs in Japan starts with the advent of vasodilators and peripheral sympathetic blocking agents in 1954. Thereafter, thiazide diuretics were launched in the latter half of the 1950s, potassium-sparing diuretics, loop diuretics, and beta-receptor blockers in the 1960s, CCBs (first-generation) in the 1970s, and alpha-receptor blockers and angiotensin converting enzyme inhibitors (ACEI) in the 1980s. Though the first-generation CCBs were short-acting, the second-generation CCBs were comparatively long-acting. Then amlodipine, a third-generation CCB with an extremely long-acting, was launched in the first half of the 1990s, and ARBs in the latter half of the 1990s. In this manner, antihypertensive drugs with different mechanisms of action have appeared during a period of approximately 50 years. Currently, five different classes of drug are recommended as first-line drugs for the treatment of hypertension in Japan (**Table 1**). These antihypertensive agents are carefully selected for patients in consideration of their pathology, complications, and contraindications.

Table 1 First-line drugs for hypertension in Japan

Class	Common name
ACEIs	captopril, enalapril, imidapril, etc.
ARBs	losartan, candesartan, valsartan,telmisartan, olmesartan, irbesartan, etc.
Beta-blockers	carvedilol, propranolol, atenolol, etc.
CCBs	amlodipine, nifedipine, benidipine, cilnidipine, etc.
Diuretics	hydrochlorothiazide, frosemide, indapamide, etc.

ACEI: angiotensin converting enzyme inhibitor;
ARB: angiotensin receptor blocker;
CCB: calcium channel blocker

Current Situation of Combination Tablets

The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH2009) clearly describe that antihypertensive drug therapy for grade I hypertension (140–159/90–99 mmHg) without complications should be started using a single drug at the minimum dose, and that for grade I hypertension with high risk or grade II hypertension (160–179/100–109 mmHg), therapy should be started using a single drug at the normal dose or combined drugs at each minimum dose.[4] For combination therapy, the use of renin-angiotensin system (RAS) inhibitors such as ACEI and ARB with a diuretic or a CCB, and that of a CCB with a diuretic or a beta blocker are recommended.[4]

Among these combinations, the RAS inhibitors, for which there are reports of superior cardiac and renal protective action in large-scale clinical trials,[7)–9)] and the CCBs, which have significantly reduced stroke incidence in a meta-analysis[10)] by J. A. Staessen et al., can be considered as the optimal combination from the standpoint of efficacy and safety. In overseas large-scale clinical trials, the combination therapy of ACEI

Table 2 Combination tablets for hypertension in Japan

Class	Launch	Brand name	Fixed-dose combination
ARB+HCTZ	December 2006	PREMINENT tablets	losartan 50mg + HCTZ 12.5mg
	March 2009	Co-DIO combination tablets MD&EX	valsartan 80mg + HCTZ 6.25mg
			valsartan 80mg + HCTZ 12.5mg
	March 2009	ECARD combination tablets LD&HD	candesartan 4mg + HCTZ 6.25mg
			candesartan 8mg + HCTZ 6.25mg
	June 2009	Micombi combination tablets AP&BP	telmisartan 40mg + HCTZ 12.5mg
			telmisartan 80mg + HCTZ 12.5mg
ARB+CCB	April 2010	EXFORGE combination tablets	valsartan 80mg + amlodipine 5mg
	April 2010	REZALTAS combination tablets LD&HD	olmesartan 10mg + azelnidipine 8mg
			olmesartan 20mg + azelnidipine 16mg
	June 2010	UNISIA combination tablets LD&HD	candesartan 8mg + amlodipine 2.5mg
			candesartan 8mg + amlodipine 5mg
	October 2010	Micamlo combination tablets AP&BP	telmisartan 40mg + amlodipine 5mg
			telmisartan 80mg + amlodipine 5mg
	December 2012	AIMIX combination tablets LD&HD	irbesartan 100mg + amlodipine 5mg
			irbesartan 100mg + amlodipine 10mg

ARB: angiotensin receptor blocker; HCTZ: hydrochlorothiazide; CCB: calcium channel blocker

perindopril and CCB AML has significantly reduced all-cause mortality including cardiac death compared to the combination therapy of a beta blocker and a thiazide diuretic at the similar blood pressure-lowering effects. The combination therapy of ACEI and CCB has been highly effective for the primary prevention of cardiovascular events.[11)]

The prescription rate for the combination use of RAS inhibitors such as ACEI and ARB with a CCB has also been increasing year by year in Japan. Under these conditions, a fixed-dose combination drug with an ARB and a diuretic, and that with an ARB and a CCB have been launched in Japan since 2006 and 2010 respectively (**Table 2**). The fixed-dose combination drugs in a single tablet were expected to have better drug compliance than the use of separate corresponding drug tablets. In fact, it has been reported that compared with free-drug combinations, fixed-dose combination drugs are associated with a significant improvement in drug compliance in meta-analysis.[12)]

Development Concept for AIMIX® Combination Tablets LD&HD

AIMIX® combination tablets LD&HD are combination drugs for the treatment of hypertension. "AIMIX® combination tablet LD" is a combination of 100 mg IRB and 5 mg AML, and "AIMIX® combination tablet HD" is a combination of 100 mg IRB and 10 mg AML.

IRB is a non-peptidic ARB originally created by Sanofi (France). The antihypertensive effect of IRB is exerted by selectively blocking AT_1 receptors abundantly present in vascular smooth muscle and inhibiting the strong vasoconstrictor action of angiotensin II. Furthermore, since IRB inhibits binding of angiotensin II to AT_1 receptors present in the adrenal cortex, it inhibits the excretion of aldosterone which is a sodium retention hormone. The elimination half-life of IRB is approximately 10–15 hours in humans, and the antihypertensive effect can be maintained for up to 24 hours with once-daily dosing. In addition, because there is no difference in types and frequency of adverse events between IRB and the placebo and there are few drug-drug interactions, it is now sold in more than 80 countries. Furthermore, IRB has been reported to reduce the risk for progression of advanced diabetic nephropathy and the risk of progression from microalbuminuria to overt nephropathy in large-scale clinical trials such as IDNT[9)] and IRMA2[13)]. In Europe and the United States, IRB has also been indicated for the treatment of diabetic nephropathy in patients with hypertension. In the domestic Japanese market, IRB was approved for the treatment of hypertension in April 2008, and it is used with a dosage regimen of 50–100 mg (maximum 200 mg) once daily administered orally.

AML is a third-generation dihydropyridine type CCB manufactured by Pfizer (United States). CCBs exert antihypertensive effects based on the inhibition of L-type calcium channels in vascular smooth muscle. It has been reported that short-acting CCBs (the first-generation) induce an activation of the sympathetic nervous system through the baroreceptor reflex due to a rapid vasodilation,[14)] resulting in tachycardia along with an increase in angiotensin II production by RAS activation. Conversely, since the vasodilatory action of AML is slow in onset, there is the characteristic that AML does not induce tachycardia via the baroreceptor reflex.[15)] In addition, the elimination half-life of AML is 35–38 hours in humans, and a stable antihypertensive effect and antianginal effect are sustained for up to 24 hours with once daily dosing. For the above reasons, AML has been approved in more than 100 countries in indications for the treatment of hypertension and angina pectoris as a superior CCB. Furthermore, it has been reported that AML can prevent cardiovascular diseases in many clinical trials including CAMELOT[16)] and CAPARES.[17)] In the domestic Japanese market, AML was approved for the treatment of hypertension and angina pectoris in 1993 and its dosage regimen is 2.5–5 mg (maximum 10 mg) once daily administered orally for hypertension and 5 mg once daily administered for angina pectoris.

Since AIMIX® combination tablets LD&HD is a combination of an ARB and a CCB which have different mechanisms of action, it can be a reasonable combination in terms of efficacy and safety. In other words, in terms of efficacy, a potent antihypertensive effect is expected. In addition, in terms of safety, the appearance of peripheral edema, which is raised by increased hydrostatic pressure and the shift of peripheral body fluids into the interstitial compartment accompanying the arterial dilating action of the CCB, is thought to be corrected and reduced by the venodilating action of the ARB. Furthermore, the most important feature of AIMIX® combination tablets LD&HD is that AIMIX® combination tablets HD is the only combination drug in Japan containing 10 mg AML, and it is expected to exert a potent antihypertensive effect while reducing occurrences of peripheral edema.

Pharmacological Effect

1. Pharmacological effect of IRB

Using human and rat aortic smooth muscle cell membranes, a concentration required to displace 50% of ^{125}I-angiotensin II binding (IC_{50} value) by IRB and losartan (LOS), which exhibits a selective antagonist for AT_1 receptors, was compared. The IC_{50} values for IRB and LOS were 0.79 nmol/L and 12.23 nmol/L, respectively, in human cell membranes and 1.58 nmol/L and 13.98 nmol/L, respectively, in rat cell membranes. IRB had more potent inhibitory activity for angiotensin II receptor than LOS in human and rat cell membranes. In addition, the inhibitory activity of IRB for angiotensin II receptors in rat liver cell membranes was approximately 10-fold more potent than that of LOS, and the Scatchard plot analysis revealed that IRB was the competitive inhibitor. Furthermore, the IC_{50} values for IRB and LOS for the AT_2 receptors were both 10 μmol/L or greater by using rat adrenocortical cell membranes in which the AT_1 receptors were inactivated by dithiothreitol treatment. These results show that IRB is a more potent selective AT_1 receptor antagonist than LOS.

The effects of IRB and LOS on contractile response induced by angiotensin II was investigated with isolated rabbit aortas. The IC_{50} values for IRB and LOS were 4.05 nmol/L and 26.4 nmol/L, respectively.[18] In addition, the pA_2 value for IRB calculated from the antagonistic action on angiotensin II concentration dependent contractile response was 8.64 (slope 1.29), and an insurmountable type of antagonistic action with decrease of the maximal response was exhibited. On the other hand, the pA_2 value for LOS was 7.96 (slope 1.12), and a competitive type of antagonism was exhibited.

The antihypertensive effect of IRB was examined using various animal models. High renin and normal blood pressure Rhesus monkey models were generated by giving intramuscular injections of furosemide and a sodium-depleted diet. The effect on blood pressure and heart rate of a single oral administration of IRB (0.3–3 mg/kg) was investigated in this model. IRB produced a dose-dependent decrease in mean blood pressure without affecting heart rate.[19] In addition, a single oral administration of IRB (3–100 mg/kg) decreased systolic blood pressure in a dose-dependent manner, and that effect continued for up to 24 hours with 30–100 mg/kg in spontaneously hypertensive stroke prone rats (SHRSP) in which vascular wall RAS activity was enhanced.[20] On the other hand, a single oral administration of IRB (30 mg/kg) did not produce any effect on blood pressure or heart rate in deoxycorticosterone acetate/salt (DOCA/salt) hypertensive rats (low renin model).[21] These results indicate that the antihypertensive effect of IRB can be attributed to antagonistic action for angiotensin II receptors.

Renoprotective effect of IRB is reported in streptozotocin -treated spontaneously hypertensive rats (SHR) as a model of diabetes and hypertension.[22] IRB treatment, at 15 mg/kg per day by gavage for 32 weeks, prevented the development of albuminuria and completely abrogated the down regulation of nephrin. Nephrin is a transmembrane protein and a main structural component of the slit-diaphragm in renal glomerular epithelial cells. These results suggest that the antiproteinuric effect of IRB accompanies the recovery of nephrin expression contributing to normalization of the slit diaphragm function.

2. Pharmacological effect of AML

Using various isolated aortas, the Ca antagonistic action of AML and nifedipine (NIF), which is a first-generation CCB, was examined.[23] The IC_{50} value against 50 mmol/L KCl-induced contraction in the isolated dog femoral artery, which is an indicator of the blocking action for the voltage-dependent Ca channel, was compared with the IC_{50} value against norepinephrine-induced contraction in the isolated dog femoral artery, which is an indicator of the blocking action for the receptor-operated Ca channel. AML operated with approximately 850-fold selectivity for the voltage-dependent Ca channel, and the selectivity of AML for the voltage-dependent Ca channel was approximately 17-fold higher than that of NIF. In addition, an isolated dog coronary artery was precontracted with 150 mmol/L KCl and the effect of AML on that contraction was examined. AML exerted a concentration-dependent relaxation in a range of 10^{-9}–10^{-7} mol/L. The relaxation induced by AML was gradual in onset, and it took approximately 40–120 minutes to reach the maximum reaction at each concentration. NIF also exerted a concentration-dependent relaxation in a range of 10^{-9}–10^{-7} mol/L, but the relaxation induced by NIF was rapid in onset, and the maximum reaction at each concentration was reached within 30 minutes. Furthermore, the effect of pretreatment of AML and NIF at 10^{-7} mol/L was

examined with an isolated rat aorta in which contraction was induced by 50 mmol/L KCl. The maximum inhibition of NIF for the contraction was reached within 1 hour after the pretreatment, but the maximum inhibition of AML was reached at 2 hours after the pretreatment. The KCl-induced contraction returned almost completely at 2 hours after the washout of NIF, but approximately 50% inhibition for the contraction was found at 4 hours after the washout of AML. These results indicate that the selectivity of AML for voltage-dependent Ca channels is higher than that of NIF, and AML exerts more gradual onset and extinction of the action than NIF, that is, AML provides more persistent pharmacological effects than NIF.

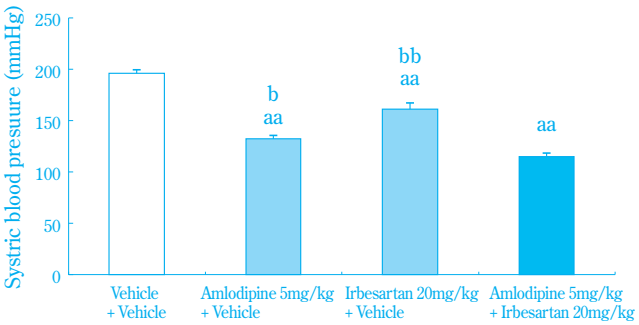
The antihypertensive effect of AML was examined in comparison with NIF using various animal models.[24] Oral administration of AML (3–10 mg/kg) produced a dose-dependent reduction of blood pressure in SHRs. The antihypertensive effect reached a maximum at 4–6 hours after administration, and the antihypertensive effect was sustained for up to 24 hours after administration of AML (10 mg/kg). On the other hand, oral administration of NIF (3–10 mg/kg) produced a dose-dependent reduction of blood pressure, but this effect reached a maximum at 1 hour after administration, and the blood pressure recovered to initial level prior to 8 hours after administration. The dose of AML and NIF required to decrease blood pressure by 30 mmHg (ED_{30} value) was 2.3 and 2.7 mg/kg, respectively.

In renal hypertensive rats with high plasma renin activity and DCOA/salt hypertensive rats with low plasma renin activity, the ED_{30} values of AML and NIF were 2.4 and 2.2 mg/kg respectively for AML and 2.4 and 2.1 mg/kg respectively for NIF. These results indicate that AML produces an antihypertensive effect with a similar potency to NIF *in vivo* regardless of the cause of hypertension, but with a profile of slow onset and long duration.

3. Pharmacological effect of combination of IRB and AML

To clarify the antihypertensive effect of the combination of AML and IRB, SHRs were orally administrated once daily for 7 days, and the antihypertensive effect was examined with systolic blood pressure as an indicator.[25] The experimental groups consisted of 4 groups, a vehicle (0.5% methylcellulose solution) group, AML 5 mg/kg group, IRB 20 mg/kg group, and AML 5 mg/kg + IRB 20 mg/kg combined administration group. Measurements of systolic blood pressure and heart rate were carried out before administration (0 hours) and 5 hours and 24 hours after administration on the first day, third day, and seventh day of administration in unanesthetized rats by a tail-cuff method using a noninvasive blood pressure measurement with an automated device. A test for statistical significance was carried out for systolic blood pressure at 5 hours after administration on the seventh day.

There was no difference in the systolic blood pressure on the first day before administration among the groups for the vehicle group, AML group, IRB group and combined group (**Table 3**). Five hours after administration on the seventh day, the AML group, IRB group, and combined group showed a significant lowering of systolic blood pressure compared with the systolic pressure of the vehicle group, and furthermore, the combined group showed a significant reduction in systolic blood pressure over the AML group and IRB group (**Fig. 2**). At this time, the AML group and combined group showed a rising tendency in heart rate compared with the vehicle group, but no intensification due to the combined administration was found (**Table 4**). These results indicate that combined administration of IRB and AML exerts more potent antihypertensive effects than administration of IRB or AML alone while keeping the effects on heart rate small.



Systolic blood puressure was measured at 5 hours after last administration. Each value shows the mean ± S.E. of 8 rats. $^{aa}P<0.01$: significantly different from the Vehicle + Vehicle group (Dunnett's test). $^{b}P<0.05$, $^{bb}P<0.01$: significantly different from the Amlodipine 5mg/kg + Irbesartan 20mg/kg group (Dunnett's test). Adapted from REF. 25.

Fig. 2 Effects of amlodipine besilate, irbesartan, and their combination on systolic blood pressure at 5 hours after last administration in spontaneously hypertensive rats

Table 3 Effects of amlodipine besilate, irbesartan, and their combination on systolic blood pressure in spontaneously hypertensive rats

Group		Vehicle + Vehicle	Aml 5 + Vehicle	Vehicle + Irb 20	Aml 5 + Irb 20
Dose (mg/kg)		0	5	20	5 + 20
Number of animals		8	8	8	8
	Pre	192 ± 3.8	194 ± 3.0	192 ± 3.8	196 ± 2.5
1day	0hr	192 ± 3.7	199 ± 2.9	193 ± 3.5	200 ± 4.2
	5hr	193 ± 1.6	142 ± 5.1	167 ± 6.3	129 ± 5.5
	24hr	197 ± 3.5	191 ± 2.3	174 ± 4.7	176 ± 6.1
3day	0hr	200 ± 2.8	196 ± 5.1	170 ± 4.3	174 ± 4.6
	5hr	193 ± 3.3	136 ± 5.3	156 ± 5.3	120 ± 6.1
	24hr	195 ± 3.7	186 ± 2.0	170 ± 3.8	171 ± 3.9
7day	0hr	198 ± 3.2	197 ± 5.0	182 ± 3.7	175 ± 3.4
	5hr	196 ± 3.3	132 ± 3.4 aa b	161 ± 6.1 aa bb	115 ± 3.5 aa
	24hr	200 ± 2.7	192 ± 5.5	173 ± 6.1	168 ± 7.1

Each value shows the mean (mmHg) ± S.E. $^{aa}P<0.01$: significantly different from the Vehicle + Vehicle group (Dunnett's test). $^{b}P<0.05$, $^{bb}P<0.01$: significantly different from the Aml 5 + Irb 20 group (Dunnett's test). Aml: amlodipine besilate; Irb: irbesartan

Table 4 Effects of amlodipine besilate, irbesartan, and their combination on heart rate in spontaneously hypertensive rats

Group		Vehicle + Vehicle	Aml 5 + Vehicle	Vehicle + Irb 20	Aml 5 + Irb 20
Dose (mg/kg)		0	5	20	5 + 20
Number of animals		8	8	8	8
	Pre	345 ± 10.3	357 ± 10.5	355 ± 9.2	351 ± 11.7
1day	0hr	345 ± 8.9	354 ± 7.6	362 ± 14.7	350 ± 5.9
	5hr	361 ± 11.3	426 ± 17.7	379 ± 13.9	413 ± 14.7
	24hr	355 ± 9.1	345 ± 9.0	353 ± 12.7	351 ± 12.1
3day	0hr	337 ± 11.2	348 ± 12.1	344 ± 12.1	351 ± 11.9
	5hr	362 ± 15.9	435 ± 15.2	349 ± 13.3	425 ± 8.3
	24hr	347 ± 8.1	350 ± 10.5	360 ± 13.3	356 ± 11.3
7day	0hr	345 ± 9.2	342 ± 10.9	362 ± 14.3	327 ± 7.8
	5hr	347 ± 11.3	414 ± 15.0 (0.0114)	357 ± 17.9 (0.9337)	394 ± 15.3 (0.0928)
	24hr	334 ± 8.4	335 ± 8.8	334 ± 13.6	330 ± 10.3

Each value shows the mean (mmHg) ± S.E. Values in parentheses show p-value (Dunnett's test). Aml: amlodipine besilate; Irb: irbesartan

Results of Clinical Trials

The aim of the clinical trials was to evaluate the clinical efficacy of the combination therapy of IRB and AML for 8 weeks compared with monotherapy in an essential hypertensive patient population whose blood pressure was not controlled by 100 mg IRB or 5 mg AML alone. An IRB based trial (I trial) and an AML based trial (A trial) were carried out as a late phase 2 trials.[26] The primary end point for efficacy was changed from baseline in seated trough systolic blood pressure to the final time of evaluation. The changes in systolic blood pressure for the combination therapy group were significantly greater than the monotherapy groups in both the I trial and A trial. In the I trial, combination therapy of 100 mg IRB and 10 mg AML exerted a reduction in systolic blood pressure of approximately 20 mmHg compared with 100 mg IRB monotherapy. On the other hand, in the A trial, combination therapy of 5 mg AML and IRB exerted a reduction in systolic blood pressure of 5–10 mmHg compared with 5 mg AML monotherapy regardless of the differences in the dose of IRB. The proportion for incidence of adverse events was almost the same between the combination therapy and the monotherapy in both tests. The findings of this study show that in patients who do not achieve target blood pressure with 100 mg IRB or 5 mg AML monotherapy, combination therapy of IRB and AML provide superior antihypertensive effects than monotherapy, and the safety is considered within the range of monotherapy.

The aim of the next clinical trials was to evaluate the

clinical efficacy of AIMIX® combination tablets LD (IRB/AML at 100 mg/5 mg) and AIMIX® combination tablets HD (IRB/AML at 100 mg/10 mg) for 52 weeks compared with IRB or AML monotherapy in an essential hypertensive patient population whose blood pressure was not controlled by 100 mg IRB, 5 mg AML, or 10 mg AML.[27] Two periods, a screening period (SC period, 5–8 weeks) and a therapy period (52 weeks), were established, and only subjects for which the blood pressure values in the SC period satisfied inclusion criteria moved on to the therapy period. For 8 weeks from the start of the therapy period, subjects who had been administered 100 mg IRB or 5 mg AML during the SC period were administered the LD tablets, and subjects who had been administered 10 mg AML during the SC period were administered HD tablets. In consideration of antihypertensive effects and safety, it was possible to change to the LD tablets or HD tablets after 9 weeks from the start of the therapy period. Regardless of the drug administered during the SC period, a quick reduction in blood pressure was exhibited in the starting 2 weeks of the therapy period, and controlled blood pressure continued up to 52 weeks after the start of administration. The proportion for incidence of adverse events was 16.9%. The main adverse events were peripheral edema, dizziness and abnormalities in liver function, all of which are known with IRB or AML monotherapy, and novel adverse events were not found. These results indicate that AIMIX® combination tablets LD and HD maintained superior antihypertensive effects in long-term administration over 52 weeks for patients who do not achieve target blood pressure with 100 mg IRB, 5 mg AML, or 10 mg AML. In addition, there were no important problems with safety; therefore, the usefulness of the AIMIX® combination tablets LD and HD was confirmed.

Conclusion

Blood pressure levels are not adequately controlled in approximately 50% of hypertensive patients, when evaluated based on the guidelines.[5] The insufficient control of blood pressure is mainly due to medication noncompliance by patients themselves.[6] Therefore, a large number of combination medicines have been launched in order to improve drug compliance in recent years. Currently five combination tablets of ARBs and CCBs, including AIMIX® combination tablets LD&HD, have been launched in Japan, but AIMIX® combination tablets HD is the first combination tablet that includes the maximum dosage of 10 mg of AML. The incidence rate of peripheral edema associated with the administration of AIMIX® combination tablets HD was lower than the incidence rate of that in long-term administration trials of 10 mg AML that have already been reported.[28] In other words, it can be assumed that the incidence rate of peripheral edema, which is a concern with high dosage AML, is reduced by the combination with IRB. Therefore, AIMIX® combination tablets HD can be a very useful drug not only for hypertensive patients who do not achieve target blood pressure with 100 mg IRB or 5 mg AML, but also for severe hypertensive patients who do not achieve target blood pressure with AIMIX® combination tablets LD or 10 mg AML alone. AIMIX® combination tablets LD&HD are expected to make a large contribution to the treatment of hypertensive patients.

References

1) A. Hozawa, T. Okamura, Y. Murakami, T. Kadowaki, K. Nakamura, T. Hayakawa, Y. Kita, Y. Nakamura, R.D. Abbott, A. Okayama and H. Ueshima; NIPPON DATA80 Research Group, *Hypertens Res.*, **30**, 1169 (2007).
2) A. Ikeda, H. Iso, K. Yamagishi, M. Inoue and S. Tsugane, *Am J Hypertens.*, **22**, 273 (2009).
3) T. Yamamoto, Y. Nakamura, A. Hozawa, T. Okamura, T. Kadowaki, T. Hayakawa, Y. Murakami, Y. Kita, A. Okayama, R.D. Abbott and H. Ueshima; NIPPON DATA80 Research Group, *Circ J.*, **72**, 545 (2008).
4) Writing committee on Guidelines for the Management of Hypertension in the Japanese Society of Hypertension, "Guidelines for the Management of Hypertension JSH2009", Life Science Publishing Co., Ltd. (2009).
5) T. Ohkubo, T. Obara, J. Funahashi, M. Kikuya, K. Asayama, H. Metoki, T. Oikawa, H. Takahashi, J. Hashimoto, K. Totsune and Y. Imai; J-HOME Study Group, *Hypertens Res.*, **27**, 755 (2004).
6) T. Ashida, Nihon Rinsho, **64**, 29 (2006).
7) S. Yusuf, P. Sleight, J. Pogue, J. Bosch, R. Davies and G. Dagenais, *N Engl J Med.*, **342**, 145 (2000).
8) B.M. Brenner, M.E. Cooper, D. de Zeeuw, W.F. Keane, W.E. Mitch, H.H. Parving, G. Remuzzi, S.M. Snapinn, Z. Zhang and S. Shahinfar; RENAAL Study Investigators, *N Engl J Med.*, **345**, 861 (2001).

9) E.J. Lewis, L.G. Hunsicker, W.R. Clarke, T. Berl, M.A. Pohl, J.B. Lewis, E. Ritz, R.C. Atkins, R. Rohde and I. Raz; Collaborative Study Group, *N Engl J Med.,* **345**, 851 (2001).
10) J.A. Staessen, J.G. Wang and W.H. Birkenhäger, *Eur Heart J.,* **24**, 504 (2003).
11) B. Dahlöf, P.S. Sever, N.R. Poulter, H. Wedel, D.G. Beevers, M. Caulfield, R. Collins, S.E. Kjeldsen, A. Kristinsson, G.T. McInnes, J. Mehlsen, M. Nieminen, E. O'Brien and J. Ostergren; ASCOT Investigators, *Lancet,* **366**, 895 (2005).
12) A.K. Gupta, S. Arshad and N.R. Poulter, *Hypertension,* **55**, 399 (2010).
13) H.H. Parving, H. Lehnert, J. Bröchner-Mortensen, R. Gomis, S. Andersen and P. Arner; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group, *N Engl J Med.,* **345**, 870 (2001).
14) H. Scholz, *Cardiovasc Drugs Ther.,* **10**, 869 (1997).
15) B. Waeber, E.T. Borges, P. Christeler, M. Guillaume-Gentil, U. Hollenstein and M. Mannhart, *Cardiology,* **80**, 46 (1992).
16) S.E. Nissen, E.M. Tuzcu, P. Libby, P.D. Thompson, M. Ghali, D. Garza, L. Berman, H. Shi, E. Buebendorf and E.J. Topol; CAMELOT Investigators, *JAMA.,* **292**, 2217 (2004).
17) B. Jørgensen, S. Simonsen, K. Endresen, K. Forfang, K. Vatne, J. Hansen, J. Webb, C. Buller, G. Goulet, J. Erikssen and E. Thaulow, *J Am Coll Cardiol.,* **35**, 592 (2000).
18) C. Cazaubon, J. Gougat, F. Bousquet, P. Guiraudou, R. Gayraud, C. Lacour, A. Roccon, G. Galindo, G. Barthelemy, B. Gautret, C. Bernhart, P. Perreaut, J.C. Breliere, G.L. Fur and D. Nisato, *J Pharmacol Exp Ther*, **265**, 826 (1993).
19) C. Lacour, A. Roccon, C. Cazaubon, D. Segondy and D. Nisato, *J Hypertens.*, **11**, 1187 (1993).
20) T. Shimamura, M. Masui, M. Torii and M. Nakajima, *Clin Exp Hypertens.*, **26**, 27 (2004).
21) C. Lacour, F. Canals, G. Galindo, C. Cazaubon, D. Segondy and D. Nisato, *Eur J Pharmacol.*, **264**, 307 (1994).
22) F. Bonnet, M.E. Cooper, H. Kawachi, T.J. Allen, G. Boner and Z. Cao, *Diabetologia.*, **44**, 874 (2001).
23) K. Yamanaka, M. Suzuki, S. Munehasu and J. Ishiko, Nihon Yakurigaku Zasshi, **97**, 167 (1991).
24) K. Yamanaka, M. Suzuki, S. Munehasu and J. Ishiko, Nihon Yakurigaku Zasshi, **97**, 115 (1991).
25) M. Mori and S. Takahashi, Nihon Yakurigaku Zasshi, **142**, 39 (2013).
26) K. Shimada, I. Komuro, H. Matsubara, T. Murata and K. Kochi, J Blood Pressure, **18**, 1231 (2011).
27) K. Shimada, I. Komuro, H. Matsubara, N. Yamamoto and K. Kochi, J Blood Pressure, **19**, 1022 (2012).
28) Amlodin® package insert.

PROFILE

Masaya Mori

Dainippon Sumitomo Pharma Co., Ltd.
Pharmacology Research Laboratories
Research Scientist
(Currently: Drug Development Research Laboratories)

Hiroshi Kato, Ph.D.

Dainippon Sumitomo Pharma Co., Ltd.
Pharmacology Research Laboratories
Group Manager
(Currently: Drug Development Research Laboratories)