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Cost-benefit effectiveness of angiotensin-II receptor blockers in patients with uncomplicated hypertension: A comparative analysis

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Abstract

Objective—The treatment of hypertensive patients (HTs) requires a long-term commitment of compliance for the patient and resources by the healthcare system. This poses an economic dilemma in countries where universal healthcare is standard. The aim of this study was to evaluate the costs/health benefit and effectiveness of treatment with angiotensin-II receptor blockers (ARBs) in uncomplicated essential hypertension.

Design and methods—The daily and annual economic commitment for treating patients with ARBs was estimated using pharmacy dispensing records and the BP-lowering effects of candesartan, irbesartan, losartan, olmesartan, telmisartan and valsartan was evaluated retrospectively. In 114 HTs (mean age 59.4 ± 13.5 year, 57.5% men), the BP-lowering effect of ARBs as in monotherapy and in fixed-dose combination (FDC) with hydrochlorothiazide at the doses commonly used in the market to reach BP control (i.e. BP <140/90 mmHg) was analyzed. The BP lowering-effect was evaluated after an average of 6-month follow-up consulting medical professionals. Analysis of variance for repeated measures was provided.

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Results—Treatment with candesartan (14.1%) and olmesartan (32.4%) versus other ARBs resulted in a significant decrease in BP as for mono- than for FDC therapy. Our studies suggest that daily (data not shown) and annual costs of olmesartan were higher than candesartan as in mono- (4577.71 ± 1120.55 vs. 894.25 ± 127.75 €) than for FDC therapy (5715.90 ± 459.90 vs. 1580.45 ± 113.15 €).

Conclusions—Treatment of BP with candesartan appears to be the most favorable option in terms of cost-effectiveness coupled with favorable health outcomes. These data have some limitations, but open the question if candesartan should be preferred to olmesartan in BP management. Further prospective studies comparing ARBs based on their effect on BP control in uncomplicated HTs are needed for validation

Keywords

Angiotensin II receptor blockers; Cost-effectiveness; Hypertension; Outpatients; Sartans

1. Introduction

Hypertension (HT) has been reported to be the most impactful modifiable global risk factor for cardiovascular and cerebrovascular events [1,2]. Fortunately, antihypertensive pharmacotherapy effectively reduces hypertension-related morbidity and mortality [3]. However, given the increasing prevalence of HT and the cost burden that it poses to society if left untreated or uncontrolled, the main HT guidelines debates the question of the cost-effectiveness of the antihypertensive treatment [4]. Cost-effectiveness analysis of a drug treatment provides information on the associated outcomes including costs and the gained clinical benefits of the treatment [5]. This information can be useful in decision-making processes, particularly in cases where limited resources need to be allocated among a variety of different drug treatments [6]. Despite the wide suggestions of the main hypertension guidelines, prescribing practices of antihypertensive drugs, particularly of angiotensin-II receptor blockers (ARBs), remained discrepant with recommendations [7]. Pharmaceutical costs can lead to a barrier in effective treatment. The increasing prevalence of HT and the rising expense of its treatment influence the prescribing patterns among physicians and compliance to the treatment by the patients [4,5]. In this respect, in order to contain the costs of the antihypertensive treatment, the health polices of the Veneto region (northeast of Italy), promoted regulations and legislations for the prescription of ARBs [8]. The aim of this study was to analyze in retrospective manner, the prescription pattern of ARBs as well as the cost incurred to achieve blood pressure control in uncomplicated hypertensive subjects.

2. Materials and methods

A retrospective cross-sectional study was conducted on hypertensive patients (HTs) without a history of cardiovascular events attending to the Hypertension Centre for uncontrolled HT (i.e., office systolic blood pressure [SBP] and diastolic blood pressure [DBP] values of <140 and <90 mmHg, respectively). In details, 114 HTs (mean age 59.4 ± 13.5 , 57.5% men) taking anti-hypertensive therapy with angiotensin-II receptor blockers (ARBs) and inserted in the database of our Hypertension Centre has been evaluated. The local Ethics Committee and Institutional Review Board approved the study protocol, and procedures were followed

in accordance with ICH Harmonized Tripartite Guidelines for Good Clinical Practice and with the Helsinki Declaration of 1964, as revised in 2013.

2.1. Data collection

Patients aged 18 years and diagnosed with essential hypertension were included in this study. Office blood pressure (diastolic Korotkoff phase 5) was measured in triplicate in the lying position using a mercury sphygmomanometer at 10-min intervals, taking care to avoid any terminal digit preference [4]. To minimize white-coat effects, if any, the average of the last two-clinostatic measurements was taken as blood pressure. Heart rate was also taken at the same time. Exclusion criteria were severe hypertension (office SBP 180 mmHg or DBP 110 mmHg), secondary hypertension, neoplastic or hepatic diseases, chronic heart or renal failure, positive history or clinical signs of ischemic heart disease, severe obesity (body weight >150% of the ideal), disabling diseases such as dementia or inability to cooperate, pregnancy or breast-feeding. HTs who were on antihypertensive medication with only one active ingredient were defined as receiving monotherapy; those taking two active ingredients in a combination pill were defined as receiving fixed dose combination (FDC) therapy.

The information collected from each prescription included the name of drugs (generic as well as brand name), dosage, frequency, type of therapy (monotherapy and FDC) and cost of the drugs. Costs of the ARBs were estimated based on pharmacy dispensing records and the BP-lowering effects of candesartan, irbesartan, losartan, olmesartan, telmisartan and valsartan were evaluated.

Total daily and annual therapy costs, the latter was defined as the average cost for doses of antihypertensives prescribed for a year, was calculated.

Study design—Following the initial medical examination performed between November 2015 and April 2016, the dose of ARBs was increased to the maximum recommended (i.e. office SBP/DBP <140/90 mmHg). the BP-lowering effect of ARBs was evaluated after an average of a 6-month follow-up.

2.2. Statistical analysis

Continuous variables were expressed as mean and standard deviation, and compared with analysis of variance followed by a Bonferroni's post-hoc test. The Chi-square test was used for comparisons between categorical variables. Analysis of variance for repeated measures compared changes of different blood pressure components at baseline and at follow-up visits; differences between continuous variables were evaluated in the two groups with Tukey's post-hoc test. All statistical analyses were performed using the SPSS package version 17.0 for Windows (SPSS, Chicago, IL, USA). The null hypothesis was always rejected for $P < 0.05$.

3. Results

The general characteristics of HTs at baseline and divided by specified therapeutics are shown in Table 1. Olmesartan (32.4%) was the most prescribed drug followed by valsartan (18.4%) with no statistical differences between genders in each group. The mean daily dose

of ARBs at baseline was significant higher for irbesartan (192.0 ± 68.0 , $p < 0.001$) and valsartan (128.0 ± 75.1 , $p < 0.001$) due to their respective dose indications. In contrast, the mean daily dose of hydrochlorothiazide was not different between treatments. At baseline the BP values and history of hypertension were not different among ARBs (Fig. 1). Treatment with candesartan (14.1% of HTs) and olmesartan (32.4% of HTs) versus other ARBs resulted in a significantly decrease in BP as for mono- than for combination therapy (Fig. 2). Antihypertensive treatment with olmesartan was the most cost-effective monotherapy (12.54 ± 3.07 and 4577.71 ± 1120.55 daily and per year respectively) than FDC with hydrochlorothiazide (15.66 ± 1.26 and 5715.90 ± 459.90 daily and per year respectively) comparing to the other antihypertensive prescribed. One-way ANOVA analysis on daily expenditure showed a significant difference in cost ($F: 96.2$, $p < 0.0001$); specifically olmesartan was higher than other ARBs. The summary of drug utilization and costs of different antihypertensive drugs used per day as well as per year are shown in Table 2.

4. Discussion

Appropriate antihypertensive drug therapy is mandatory, as the prevalence of hypertension has risen dramatically in last three decades [9]. In this respect, any deviation from the recommendations of hypertension guidelines contributes to the high cost of drugs and creates difficulties in clinical and health-care policy decision-making processes [10]. The angiotensin II type I receptor blockers (ARBs), are the most selective antagonists of the renin-angiotensin system [11] available in the treatment of HT (Fig. 3). Introduced in the market about 20 years ago, during this period ARBs has been accompanied by the clinical evidence of their ability to lower BP in both monotherapy and combination therapy, to protect against hypertension-related organ damage [12] and to prevent cardiovascular disease [13,14]. The efficacy of ARBs is similar of the other antihypertensive drugs classes, but the wide use in clinical practice is in part due to a fewer side effects than other classes of drugs [4]. In addition, the higher tolerability of ARBs leads to a more favorable health outcome, as the inadequate patient compliance with therapy has been recognized as a frequent cause of treatment failure. These studies support that all classes of ARBs showed a significant BP-lowering effect, but the treatment with candesartan and olmesartan resulted in a more favorable clinical response in BP as for mono- than for FDC therapy. These results raise important questions that will be addressed in the following sections.

4.1. Do all ARBs have the same beneficial BP-lowering effects?

In clinical practice, eight ARBs are available as azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan. Based on their chemical structures, ARBs use different binding pockets of the angiotensin II receptors, which are associated with differences in dissociation times and with insurmountable antagonism of the AT1 receptor. Clinical studies showed a degree affinity for the AT1 receptor for different ARBs in the following descending order: candesartan > olmesartan > azilsartan > telmisartan > valsartan > irbesartan > eprosartan > losartan [15]. The insurmountable antagonism of the AT1 receptor which characterizes certain ARBs as well as candesartan and olmesartan, makes reason of a prolonged and irreversible inhibition of the AT1 receptor, in contrast to is observed with losartan that induces a transient and readily reversible

inhibition [15]. This pharmacodynamic difference leads to important repercussions on antihypertensive activity of ARBs and comparative clinical studies confirmed that the BP-lowering effects of candesartan and olmesartan – as observed in our experience – are higher than that of the other ARBs [16,17].

Does cost-effectiveness analysis to be performed before to start anti-hypertensive treatment?—There is no doubt that a cost/benefit analysis is a useful tool to reduce the long-term economic impact of drugs treatment of hypertension. However, the continuous increases of the economic burden for the hypertension management are largely related to unfortunate impact of not treating this disease at early stages. In addition, some negative impacts on the hypertension management are the result of the failure to achieve blood pressure control with some antihypertensive drugs. As a consequence, the elimination of costs in the absence of effective benefits represents the most effective method for reducing the wastage of money in hypertension treatment. In agreement with the data of a recent review, olmesartan resulted the more cost/benefit-effective therapy than other ARBs [18]. On the contrary, in this study, candesartan, was estimated to be the most favorable treatment option of the ARBs tested. Our studies were monocentric, retrospective and limited by its short treatment period and relatively small-sized treatment groups. Office BP and not using 24-h ambulatory BP monitoring evaluated the BP-lowering effect of ARBs. We could not assess the adherence of the treatment of the HTs.

In conclusions, these data open the question if candesartan should be preferred to olmesartan in the treatment of uncomplicated hypertension, and even in to switch to candesartan when BP is uncontrolled with olmesartan. However, for definite conclusions, further prospective multi-center studies comparing ARBs based on their effect on BP control in this setting of HTs are needed. Furthermore, optimization of available resources to maximize health outcomes will be the key challenge to health care systems in the next decade. Several countries like the Veneto Region in Italy, recently introduced guidelines or legislation to mandate cost-effectiveness assessment, particularly for the prescription and reimbursement of ARBs, and we hope that these thresholds of cost-effectiveness may be considered to improve the management of hypertension.

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Fig. 1.

Differences for office blood pressure values from baseline among different antihypertensives. SBP: systolic blood pressure; DBP: diastolic blood pressure; ARBs: angiotensin-II receptor blockers (ARBs).

Fig. 2. Correlation between the degree of insurmountability and the half-lives of sartans dissociation from the human AT1 receptor. Adapted from Van Liefde and Vaquelin [14].

Fig. 3. Mechanism of action of the angiotensin-II receptor blockers (ARBs). ACE: angiotensin converting enzyme. AT₁: angiotensin-II type 1 receptor; AT₂: angiotensin-II type 2 receptor.

Table 1

General characteristics of the hypertensive patients in the six month before the evaluation. HCTZ: hydrochlorothiazide; FDC: fixed-dose combination. SB; systolic blood pressure; DBP: diastolic blood pressure; HT: hypertension.

Items	Candesartan (n = 16)	Irbesartan (n = 16)	Losartan (n = 11)	Olmisertan (n = 37)	Telmisartan (n = 13)	Valsartan (n = 21)	P value
Age (years)	59.8 ± 14.2	62.1 ± 11.6	61.4 ± 16.2	58.2 ± 10.6	58.8 ± 12.2	57.8 ± 17.7	NS
Dose (mg/daily)	19.6 ± 9.8	192.0 ± 68.0	53.1 ± 25.2	19.7 ± 9.9	66.2 ± 22.3	128.0 ± 75.1	<0.001
HCTZ (mg/daily)	15.0 ± 5.3	14.1 ± 4.4	17.5 ± 6.8	16.6 ± 6.1	14.5 ± 5.1	17.0 ± 6.3	NS
Monotherapy (%)	43.8	50.0	45.5	46.0	53.8	57.1	NS
FDC (%)	56.2	50.0	54.5	54.0	46.2	42.9	NS
Gender M/F	9/7	7/9	6/5	20/17	5/8	9/12	NS
SBP (mmHg)	141.4 ± 6.9	143.4 ± 7.8	140.5 ± 9.3	141.0 ± 8.3	139.6 ± 7.3	142.8 ± 10.2	NS
DBP (mmHg)	85.4 ± 6.2	86.2 ± 5.8	84.5 ± 6.3	86.6 ± 6.5	84.9 ± 6.0	87.2 ± 7.1	NS
Hear rate (bpm)	73.6 ± 6.2	72.6 ± 6.0	76.2 ± 8.9	73.9 ± 6.2	73.8 ± 7.8	76.2 ± 8.0	NS
History of HT (years)	10.1 ± 2.3	11.9 ± 2.5	12.4 ± 3.0	11.8 ± 2.4	12.0 ± 2.7	13.3 ± 2.4	NS
Creatinine (mg/dl)	1.02 ± 0.1	0.99 ± 0.2	0.97 ± 0.2	1.00 ± 0.3	1.00 ± 0.2	0.94 ± 0.2	NS
Potassium (mmol/L)	4.4 ± 0.2	4.2 ± 0.3	4.3 ± 0.2	4.1 ± 0.3	4.0 ± 0.1	4.2 ± 0.3	NS

Table 2

Drug acquisition costs of the different antihypertensive drugs prescribed. CPD: Cost per Day; CPY: Cost Per Year. Both CPD and CPY in Euros. FDC: fixed-dose combination.

ARBs	N°	CPD (mean $\pm$ SD)	CPY (mean $\pm$ SD)
Monotherapy			
Candesartan	6	2.45 $\pm$ 0.35	894.25 $\pm$ 127.75
Irbesartan	8	2.64 $\pm$ 0.22	963.60 $\pm$ 80.30
Losartan	5	1.80 $\pm$ 0.13	657.00 $\pm$ 47.45
Olmesartan	19	12.54 $\pm$ 3.07	4577.71 $\pm$ 1120.55
Telmisartan	7	2.24 $\pm$ 0.26	817.60 $\pm$ 94.90
Valsartan	12	2.88 $\pm$ 0.84	1051.20 $\pm$ 306.60
FDC			
Candesartan	10	3.98 $\pm$ 0.31	1580.45 $\pm$ 113.15
Irbesartan	8	2.88 $\pm$ 0.21	1051.20 $\pm$ 73.00
Losartan	6	2.00 $\pm$ 0.12	730.00 $\pm$ 43.80
Olmesartan	18	15.66 $\pm$ 1.26	5715.90 $\pm$ 459.90
Telmisartan	6	2.41 $\pm$ 0.32	879.65 $\pm$ 116.80
Valsartan	9	2.61 $\pm$ 0.45	952.65 $\pm$ 164.25