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Review

A review of clinical studies on angiotensin II receptor blockers and risk of cancer

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ABSTRACT

Angiotensin II receptor blockers (ARBs) are one of the most frequently used antihypertensive drugs with good tolerability and are indicated for treatment of many cardiovascular morbidity. Findings from clinical studies conducted in the past decade, suggest a possible relationship between some ARB-active substances, and certain malignancies cannot be excluded. Despite a lack of agreement, clinical results do not rule out the possibility that type 2 angiotensin II receptor stimulation during ARB therapy may also have unfavorable consequences, such as the development of certain malignancies. However, according to the current official position of FDA, the cardiovascular benefits of ARB therapy far outweigh the risks. Based on the limited information available, this review aims to provide medical practitioners with a clearer view on the balance of the benefits and risks of ARBs.

1. Introduction

Products blocking type 1 angiotensin II receptor (AT_1R), known as angiotensin II receptor blockers (ARBs), represent a group of medicines used for a wide range of indications. ARBs are successful primarily in the therapy of hypertension, but may also be beneficial in patients with intolerance to angiotensin-converting enzyme (ACE) inhibitors for the treatment of several cardiovascular diseases, such as stable coronary heart disease, the state after acute myocardial infarction, and heart failure [1–4]. ARBs are used widely in everyday clinical practice because of their well-known effectiveness and proven good tolerability [5]. Approximately 25% of hypertensive patients worldwide are taking ARBs. The number of patients treated with products belonging to this group of medicines is approximately 200 million worldwide [6].

In addition to losartan, introduced nearly 20 years ago, there are seven other active substances (valsartan, candesartan, irbesartan, telmisartan, olmesartan, eprosartan, and azilsartan), which have been used in several major clinical studies in recent years. Based on safety data obtained in these trials, a favorable image has been formed on the tolerability of ARBs, confirmed also by the results of long-term adherence studies.

However, experimental studies in the recent decade have shown yet unmapped areas of the renin–angiotensin–aldosterone system (RAAS) with certain effects and clinical consequences, which cannot be disregarded in the use of ARBs. The RAAS, as well as AT_1R and type II angiotensin II receptor (AT_2R), play a role in the regulation of cell proliferation and neoplastic progression. Therefore, evaluating these effects might be desirable for medicines, which exert their effect directly on these receptors [7]. Clinical studies evaluating ARB-active substances primarily examined the cardiovascular endpoints, and usually did not report on the incidence of various cancers.

The first data on cancers were shown by the Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity (CHARM) study. The CHARM study showed that the incidence of neoplastic diseases was increased by candesartan to a significant extent compared with the placebo group in patients with heart failure [8]. This study was also the first to show an increased incidence of myocardial infarction (57%) during the use of ARBs, which caused concern, and has been debated since this study.

Abbreviations: ACE, angiotensin-converting enzyme; ACTIVE, the advanced cognitive training for independent and vital elderly; AR, absolute risk; ARB, angiotensin II receptor blocker; AT_1R, type 1 angiotensin II receptor; AT_2R, type II angiotensin II receptor; CHARM, Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity; CI, confidence interval; ESH, European Society of Hypertension; FDA, Food and Drug Administration; Fig., figure; HOPE, Heart Outcomes Prevention Evaluation; LIFE, Losartan Intervention For Endpoint reduction in Hypertension; I-PRESERVE, Irbesartan in Heart Failure With Preserved Systolic Function; n, number; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; OR, odds ratio; p, probability; PRoFESS, Prevention Regimen For Effectively avoiding Second Strokes; RAAS, renin–angiotensin–aldosterone system; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; RR, relative risk; SIIA, Italian Hypertension Society; TRANSCEND, Telmisartan Randomised Assessment Study in Ace Intolerant Subjects with Cardiovascular Disease; TROPHY, Trial of Preventing Hypertension; VALIANT, Valsartan in Acute Myocardial Infarction; VALUE, Valsartan Antihypertensive Long-term Use Evaluation.

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In this review, results are discussed that may help clarify this issue for the practicing physician and may dispel some misconceptions. Mainly the results of clinical studies with a large number of subjects and a long follow-up period are discussed, including studies that recorded the incidence of neoplastic diseases.

2. Incidence of cancerous diseases in clinical studies during the use of ARBs

2.1. CHARM-Overall study

An increased incidence of some neoplastic diseases during the use of ARBs was first shown by the CHARM study (n = 7,601), which compared candesartan with placebo in patient with chronic heart failure (CHARM-Overall program) in 2003 [8,9]. Although the candesartan significantly reduced cardiovascular deaths and hospital admissions for heart failure during the follow-up of 37.7 months, this study showed a significant increase (42%) in the risk of developing a fatal cancer in patients treated with candesartan upon randomization compared with the placebo group (absolute risk [AR] 2.3% vs. 1.6%; relative risk [RR] 1.42; n = 86 vs. 59; p = 0.038). At the time of this study, the investigators considered this imbalance as accidental, and then explained it with differences in risks between the groups.

2.2. LIFE study

In the LIFE (Losartan Intervention For Endpoint reduction in Hypertension) study the losartan and atenolol therapies were compared in 9193 hypertensive patients with LVH. During the mean follow-up of 4.8 years losartan prevents more cardiovascular morbidity and death than atenolol for a similar reduction in blood pressure and is better tolerated. This study also reported data on losartan related to cancer [9,10]. The risk of neoplastic diseases was increased by 12% compared with the control group, but this difference was not significant (AR 7.8% vs. 7.0%; RR 1.12; n = 358 vs. 320; p = 0.143). When the risk of the most commonly occurring lung cancer was analyzed, the use of losartan represented a significantly higher risk (AR 0.6% vs. 0.3%; RR 2.41; n = 29 vs. 12; p = 0.01). Pulmonary carcinoma also occurred at a high rate in ARB groups in other studies, but this was below the level of significance in most of the studies [8]. Prostate cancer, another type of tumor correlated with the use of ARBs [8], showed a 38% increase in its incidence in the losartan group. However, because of the low number of subjects, this was proven to be non-significant (AR 2.7% vs. 2.0%; RR 1.38; n = 58 vs. 42; p = 0.11).

2.3. ONTARGET and TRANSCEND studies

Five years after the LIFE study, the results of the ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) and TRANSCEND (Telmisartan Randomised Assessment Study in Ace Intolerant Subjects with Cardiovascular Disease) studies, were published [11,12]. In the ONTARGET study the ACE inhibitor ramipril, the ARB telmisartan, and the combination of the two drugs were compared in patients with vascular disease or high-risk diabetes (n = 25,620). Based on the results of primary endpoint (composite of death from cardiovascular causes, myocardial infarction, stroke and hospitalization for heart failure), telmisartan was equivalent to ramipril, and the combination of the two drugs was associated with more adverse events without an increase in benefit. In the TRANSCEND study telmisartan did not show any additional cardiovascular benefit over the placebo in patients unable to tolerate ACE inhibitors (HR 0.92, p = 00.216). A report on the increased incidence of malignant tumors observed among patients treated with telmisartan in these studies was presented to the advisory board of the Food and Drug Administration (FDA) on cardiovascular and renal medicines in July 2009 [13].

In the ONTARGET study, the incidence of neoplastic diseases was increased by 9% in patients taking ARBs compared with the control treatment arm (9.3% vs. 8.6%; RR 1.09; p = 0.054), but this difference was not significant [9]. However, for malignant tumors, there was a significantly higher risk of development of cancer in patients treated with the combination of telmisartan + ramipril compared with ramipril monotherapy; either a malignancy was present or not present at baseline (AR 9.7% vs. 8.6%; RR 1.14; n = 824 vs. 735; p = 0.011).

In the TRANSCEND study, the incidence of cancerous diseases was increased by 16% in the telmisartan group compared to placebo, but this was not significant (AR 8.0% vs. 6.9%; RR 1.16; n = 236 vs. 204; p = 0.099). However, the risk of developing malignancies in patients who were free of cancer at baseline (95% of all participants) was significantly increased by 24% in patients treated with telmisartan compared with those who received placebo (AR 7.3% vs. 6.0%; RR 1.24; n = 206 vs. 169; 95% confidence interval [CI] 1.01–1.52) [9].

2.4. PRoFESS study

In the PRoFESS (Prevention Regimen For Effectively avoiding Second Strokes) study telmisartan did not significantly lower the rate of recurrent stroke, major cardiovascular events, or diabetes in patients with previous ischemic stroke compared to placebo (n = 20,332, mean follow-up 2.5 years). The study of the most common malignancies, including lung cancer, prostate cancer, and breast cancer, showed a non-significant increase of 24, 12% and 36% in the ARB (telmisartan) group compared to placebo, a non-significant 4% decrease in the total number of cancers was reported by the investigators (AR 3.3% vs. 3.4%; RR 0.96; n = 326 vs. 340; p = 0.610). Unfortunately, no data showing the background of this contradiction can be found in publications [9,14].

2.5. VALUE and VALIANT studies

With regard to valsartan, inconsistent data are available as shown in the VALUE study. The VALUE (Valsartan Antihypertensive Long-term Use Evaluation) study compared valsartan- and amlodipine-based therapies in 15,245 hypertensive patients at high cardiovascular risk, and the primary endpoint (time to first cardiac event) did not differ between the treatment groups during the mean follow-up of 4.2 years. The study showed a significant 15% decrease in neoplastic diseases in the ARB group (AR 0.7% vs. 0.8%; odds ratio [OR] 0.85; n = 510 vs. 591; 95% CI 0.75–0.96) [15,16]. The VALIANT (Valsartan in Acute Myocardial Infarction Trial) study did not find any significant differences in the effects of captopril, valsartan, and their combination on atherosclerotic events (fatal and non-fatal AMI) in patients who had acute myocardial infarction (n = 14,703). This study showed a non-significant increase of 22% for cancer-related mortality in the valsartan group compared with the captopril group (AR 1.1% vs. 1.4%; OR 1.22; n = 67 vs. 55; 95% CI 0.85–1.74) [16,17].

3. Pooled analysis of the various studies

The results from the above-mentioned studies, except for the PRoFESS and VALUE trials, show that a newly developed cancer occurs in a higher number of patients treated with ARBs than those not treated with ARBs in all surveyed studies (Fig. 1). However this result was non-significant in most of the studies because of the low number of cases. In this regard the various, correctly compiled analyses especially useful, because they make powerfull tendencies and observations experienced in single studies less ambiguous.

The first prominent analysis which drew attention to a potential correlation between ARB therapy and neoplastic diseases was published by Coleman in 2008 [18]. They processed the data of 126,137 patients from 27 studies (subjects with hypertension, cardiac failure, coronary heart disease, or renal disease). Although the analysis has come to the basic conclusion that neither of the five large groups of antihypertensive