Drug Information Response Center Questions

Is there an increased risk of cancer with angiotensin receptor blockers?
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Angiotensin receptor blockers (ARBs) are commonly prescribed to treat hypertension and congestive heart failure. ARBs compete with angiotensin II for the angiotensin II type 1 receptor to prevent activation of the renin-angiotensin-aldosterone system, which contributes to an increase in blood pressure.[1] In addition to benefits to the cardiovascular system, ARBs also have a protective effect on the kidneys and have proven to be beneficial in patients with diabetes. Currently the Joint National Commission (JNC), American Heart Association (AHA) and American Diabetes Association (ADA) recommend the use of ARBs as an alternative to angiotensin converting enzyme inhibitors (ACEIs) to adequately control blood pressure in patients with hypertension, heart failure, and diabetes.[2,3]

ARBs are generally regarded by clinicians as safe and well-tolerated. However, there have been concerns about their long term use.[4] In 2010, Sipahi et al conducted a meta-analysis of 9 clinical trials and found that ARBs were associated with an increase in incidence of new malignancy, particularly lung and prostate cancer.[5] Following this, the Food and Drug Administration (FDA) performed a drug safety review and reported that there was no clear evidence showing an increased cancer risk with long term use of ARBs.[4,6] Dr. Thomas Marciniak, a senior FDA official, investigated this issue further, examining individual patient data from clinical trials.[7] In May 2013, Marciniak reported a 24% increase in lung cancer risk associated with ARB use and concluded that stronger warnings for ARB use are necessary, contrary to the 2010 FDA report. Despite this, the FDA issued a statement urging patients NOT to discontinue ARB usage.[8]

A search of the literature revealed several studies in which investigators sought to determine an association between ARB use and cancer.[5,9-12] As mentioned previously, Sipahi et al conducted a meta-analysis, collecting data from prospective trials.[5] All trials included patients taking ARBs and/or ACEIs for ≥1 year. Reviews and other meta-analyses, trials with duration less than 1 year, or of small sample size (<100 subjects), or with no information about cancer were excluded. The primary objective was to determine the effect of ARBs on occurrence of new cancer at any site; the secondary objective was to determine the effect of ARBs on occurrence of specific types of cancer and cancer death.

Data from the following 9 trials were extracted and analyzed: LIFE and OPTIMAAL which studied losartan; ONTARGET, TRANSCEND and PROFESS for telmisartan; CHARM-Overall program for candesartan; TROPHY, VAL-HEFT and VALIANT trials for valsartan.5 Among the trials, only LIFE, ONTARGET, and TRANSCEND included cancer occurrence as an endpoint. The average age of patients in most of the trials was 67 years, except the TROPHY trial, in which the average age was 48.6 years. Regarding the primary endpoint, ARB use was associated with an increased risk of new cancer occurrence (relative risk [RR] = 1.08, 95% confidence intervals [95% CI]: 1.01-1.15, p = 0.016). ARBs were also associated with a higher risk of cancer compared to ACEIs (RR = 1.08, 95% CI: 1.00-1.16, p = 0.041). Regarding secondary endpoints, specifically in

patients with no background ACEI use, there was no statistically significant association between ARBs and development of lung cancer (RR = 1.50, 95% CI: 0.93-2.41, p = 0.097), prostate cancer (RR = 1.17, 95% CI: 0.97-1.41, p = 0.10), or breast cancer (RR = 0.99, 95% CI: 0.74-1.32, p = 0.93). The association between ARBs and cancer death was also not significant (RR = 1.07, 0.97-1.18, p = 0.183).

There were limitations to this study.[5] Some of the cancer data were not peer-reviewed and some of the trials did not measure cancer occurrence as an endpoint. Such publication and analytic bias may confound the results. Also, while trials of duration ≤1 year were excluded, the investigators did not report on the effect of duration of ARB use on new onset cancer.

Pasternak et al conducted a retrospective study in response to Sipahi et al's meta-analysis.[9] In this study, data were collected from a registry in Denmark to analyze the correlation between ARBs and new onset cancer. Patients aged ≥35 years with ≥1 prescription for an ARB between January 1, 1998 and December 31, 2006 were included. Patients who took ARBs during a 2-year washout phase prior to cohort entry were excluded. In addition, in order to minimize the error of counting patients with incipient cancer a 180-day lag period from the first ARB fill was instituted. Any patient who was diagnosed with cancer during that period was excluded from the study. Pertinent information of each prescription (fill date, ARB type, and days' supply) was retrieved for further analysis. The primary endpoint of the study was defined as the risk of new onset cancer in all new ARBs users compared to ACEI users. The investigators also assessed risk of different types of cancer categorized by anatomical site.

A total of 438,728 patients were included in the analysis as new ARB users.[9] The average age was 63 years and 55% were female. The average duration for 1 ARB prescription was 97 days and the average interval between the end of the last prescription and the next fill was 74 days. Overall, the mean duration of ARB use was 2.9 years. Compared to the ACEI group, the crude relative risk of new onset cancer after long term ARB use was 0.89 (95% CI: 0.85-0.92) and the adjusted relative risk (accounting for factors such as age and gender) was 0.99 (95% CI: 0.95-1.03). Similarly, past exposure and long-term use (5 years or above) of ARBs were not found to significantly increase the risk of cancer (RR = 1.03, 95% CI: 0.96-1.11, and RR = 1.01, 95% CI: 0.94-1.08, respectively). The investigators did find that ARB use was associated with an increase in risk of development of male genital cancer (RR = 1.15, 95% CI: 1.02-1.28, p = 0.02) but not in other types of cancer, including lung cancer (RR = 0.92, 95% CI: 0.82-1.02, p = not significant [NS]). Of note, this study had several limitations, including a retrospective design and use of claims data; multiple factors such as adherence and lifestyle could confound the results and were not evaluated.

Rao et al conducted a retrospective cohort study to investigate the correlation between ARBs and risk of prostate cancer among veterans.[10] The investigators identified new ARB users between 2003 and 2009; these were patients who had not previously received ARBs or patients who had not received ARBs since 1999. For comparison, Rao et al selected patients who were seen by a Veterans Affairs (VA)-affiliated clinician who did not receive any ARB treatment during the analysis period. The investigators selected patients in a 1:15 case:control ratio. The study endpoints were defined as the occurrence of prostate cancer or death.

Rao et al identified 34,275 cases and 509,222 controls.[10] The mean age for the entire cohort was 63.2 years. The hazard ratio (HR) for prostate cancer was found to be 0.91 (95% CI: 0.84-1.00, p = 0.49). Tobacco users were found to have a higher risk compared to non-tobacco users (HR = 1.69, 95% CI: 1.38-2.06, p<0.001). The investigators concluded that ARBs may have a protective effect against prostate cancer. Like the previous study,[9] this retrospective cohort had several limitations.[10] Though efforts had been made to minimize confounding factors, the study may not have addressed all known, possible risk factors for prostate cancer, thus affecting the accuracy of the results.

Rao et al conducted an additional retrospective cohort study to investigate the association between ARBs and lung cancer.[11] The study design, target population for the cohort, inclusion, exclusion criteria, analysis and study endpoints were almost identical to those of their study mentioned above.[10,11] However, the age range for inclusion in the lung cancer study was 40 to 80 years.[11] Additionally, Rao et al performed an analysis on the effect of individual ARBs (losartan, candesartan, irbesartan and valsartan).

Rao et al identified 78,075 cases and 1,151,826 controls.[11] The mean age for the entire cohort was 62.9 years. The rate of new onset of lung cancer was 346 cases/year and 6,577 cases/year for the ARB arm and comparator arm, respectively. The hazard ratio of lung cancer for ARBs was found to be 0.74 (95% CI: 0.67-0.83, p<0.001). For tobacco users, the hazard ratio of lung cancer for ARBs was 0.72 (95% CI: 0.64-0.82, p<0.001). When ARBs were stratified by drug for further analysis, none were found to increase the risk of lung cancer (p value not significant). Rao et al concluded that there was no evidence to support an association between ARB use and lung cancer.

Bhaskaran et al also conducted a cohort study to elucidate any correlation between ARB use and cancer incidence.[12] The investigators pooled data from the UK General Practice Research Database, including data from patients aged 18 years or above with first documented ACEI or ARB use between 1995 and 2010. Similar to Pasternak et al's study,[9] a 1-year lag period was applied to selected patients after receiving the first prescription for an ARB. Exclusion criteria were development of cancer during the lag period and treatment breaks for more than 90 days during the initial treatment period. Patients must have switched from an ACEI to an ARB during the 1-year lag period to be included in the risk analysis. The primary endpoint was new onset cancer.

A total of 377,649 patients were identified as new ARB users.[12] At baseline, 37,060 patients (10%) had initiated ARBs while the remainder had switched from ACEIs. During the study, 19% of the total population switched from an ACEI to an ARB. The mean follow-up duration was 4.6 years. The hazard ratio for cancer with ARB use was 1.03 (95% CI: 0.99-1.06, p = 0.1). In an analysis of specific types of cancer (breast and prostate), ARB use was associated with a statistically significant increase in cancer risk (HR = 1.11, 95% CI: 1.01-1.21, p=0.02, and HR = 1.10, 95% CI: 1.00-1.20, p=0.04, respectively). Clinically, this was reported as 0.5 to 1.1 new cases in 1000-person years. Interestingly, ARB use was associated with a risk reduction in lung cancer (HR = 0.84, 95% CI: 0.75-0.94, p = 0.003). The authors concluded that ARB use was not associated with an increased risk of cancer.

Of note, this study included patients who switched from ACEIs to ARBs, suggesting that the results may be confounded by ACEI use.[12] Additionally, like the studies by Rao et al and Pasternak et al,[9-11] the study is limited by its retrospective design.[12]

In summary, based on the available data, there is a lack of evidence demonstrating a significant association between ARBs and cancer. However, Marciniak's findings suggest that further investigation is necessary. Per the FDA, discontinuation of ARBs is not advised at this time.8 However, clinicians should be aware of the possible increase in cancer risk with ARB use and assess patients for other potential risk factors.

References:

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