

## Tolerability and Quality of Life in ARB-treated Patients

### **Abstract**

Side effects associated with some antihypertensive agents can adversely affect patient adherence to a treatment regimen. Controlled clinical trials involving >11 000 patients have consistently shown that the angiotensin receptor blockers (ARBs) are generally well tolerated. Adverse effects, such as headache, lightheadedness, dizziness, nausea, and diarrhea, have been described as mild to moderate. The frequency of cough is significantly lower in patients treated with ARBs than in those receiving angiotensin-converting enzyme inhibitors (ACEIs). Angioedema, a less common but more serious side effect, also appears to be seen less frequent with ARBs than with ACEIs, although cross-reactivity is possible. Quality of life (QOL) is another important factor affecting treatment adherence. Recent studies have shown improvements in QOL measures in patients switched from other classes of antihypertensive agents to ARBs.

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Since the approval of the first angiotensin receptor blocker (ARB) in 1994, >11 000 patients have participated in randomized, double-blind, placebo-controlled trials of the various agents that are now in this class.<sup>1</sup> These studies have consistently demonstrated the tolerability of these agents. Tolerability is an important consideration in prescribing decisions in general, but especially so with antihypertensive therapy. Approximately half of all antihypertensive treatment failures are the result of poor adherence.<sup>2</sup> Many factors contribute to this problem, including side effects associated with some antihypertensives, such as cough, fatigue, dizziness, edema, cough, and headache.<sup>3</sup>

### **Safety and Tolerability of ARBs**

Overall, the ARBs are well tolerated. Adverse effects reported in clinical trials

have been described as mild to moderate and include headache, lightheadedness, dizziness, nausea, and diarrhea.<sup>4</sup> Because cough is a common problem associated with angiotensin-converting enzyme inhibitors (ACEIs), many of the ARB studies have addressed this symptom. Overall, the frequency of cough in ARB-treated patients is significantly lower than in those taking ACEIs or diuretics, and comparable to that with placebo.<sup>5-9</sup>

Angioedema is a more serious side effect of antihypertensives and typically involves the face, lips, tongue, larynx, as well as other locations. It may occur with the use of ACEIs, vasoepitidase inhibitors, and, less frequently, ARBs.<sup>10,11</sup> Estimates of the incidence of angioedema in ACEI-treated patients vary, ranging from 0.1% to 2%.<sup>12</sup> Although incidence is relatively low, considering that more than 30 million patients are treated with ACEIs, angioedema could still account for a large number of fatalities per year.

Although the exact mechanism responsible for angioedema is unknown, it is believed to result at least in part from increasing availability of bradykinin.<sup>13-15</sup> For this reason, it is sometimes assumed that drugs that do not affect bradykinin metabolism should not present a risk of angioedema for patients who had this complication while taking ACEIs.<sup>16</sup> Because ARBs selectively block the angiotensin type I receptor and are not known to affect bradykinin, they may be associated with a lower incidence of angioedema than that observed with ACEIs.<sup>17-19</sup> However, some animal data suggest that there may be a relationship between ARB use and increased tissue bradykinin levels secondary to stimulation of the type 2 receptors for angiotensin II.<sup>15</sup>

The possibility for cross-sensitivity anaphylactic reactions between ACEIs and ARBs cannot be ruled out. Sica and Black<sup>11</sup> recommended that in patients who have experienced ACEI-related angioedema, ARBs should be used cautiously, if at all. Warner and coworkers<sup>20</sup> conducted a MEDLINE literature search for publications regarding angioedema and ARBs between January 1966 and August 1999 and identified 19 case reports of angioedema with ARBs. One patient was treated with valsartan, whereas the other 18 patients received losartan. Among these 19 patients, 6 (32%) had previously experienced an episode of angioedema attributed to ACEI therapy.

One clinic reported their experience over 3 years with 10 cases in which patients with confirmed angioedema attributed to ACEI use were safely switched to an ARB without incident.<sup>14</sup> Six of the affected patients had been receiving ACEIs for more than 1 year before developing angioedema. In all cases, the ARB was well tolerated. A larger clinical study reported on the outcome of 64 patients with ACEI-related angioedema, 24 of whom switched to ARBs.<sup>16</sup> As reported in the smaller clinical study,<sup>14</sup> the use of ARBs as substitutive therapy in the larger study was largely favorable. The study found that an ARB may have caused angioedema in only 2 of the 26 patients who switched to this class of drugs, a number the authors indicated was too small to be of clinical concern.<sup>16</sup>

Adding to insights of such case reports in the medical literature is the considerable knowledge gleaned from postmarketing surveillance, which can be valuable in determining the incidence of angioedema and other adverse events associated with drug therapy. The US Food and Drug Administration (FDA)'s Adverse Event Reporting System (AERS) database is a resource for identifying areas of concern. Researchers conducted a search of the 2.5 million adverse event reports in the FDA's AERS database to identify differences in the reporting of angioedema among patients receiving ACEIs and ARBs and presented their findings in a poster presentation at the 2005 American Society of Hypertension scientific meeting.<sup>21</sup> Adverse events reported

through the first quarter of 2004 were included in the analysis, regardless of whether the drug was considered suspect or concomitant with respect to adverse events. The total number of adverse event reports with angioedema were 851 and 6642 for the ARBs and ACEIs, respectively. The corresponding reporting proportions of angioedema were 3.0% (851 of 28 624) for ARBs and 5.6% (6642 of 119 556) for ACEIs. The reporting proportion of angioedema for individual agents within each drug class ranged between 2.2% and 3.4% and 3.5% and 6.5% for agents within the ARB and ACEI classes, respectively.

Because the AERS database relies on voluntary reports, it is not representative of community practice and requires further confirmation through properly designed epidemiological studies. Characteristics such as the high level of underreporting and the possibility of reporting bias of this system require that these results be interpreted with caution. However, this analysis is consistent with reports in the clinical trial literature showing that angioedema occurs more frequently with ACEIs than ARBs.

#### Quality-of-life Considerations

Beyond safety and tolerability, experiences with quality of life (QOL) also contribute to patient adherence. Two recent studies have evaluated the effects on QOL of switching from other classes of antihypertensives to ARBs. An open study evaluated a change in regimen from dihydropyridine calcium channel blockers (CCBs), the most frequently used antihypertensive agents in Japan, to candesartan cilexetil.<sup>22</sup> CCB side effects, such as nocturia, flushing, and palpitations, are reported to be a problem in this population.<sup>22</sup> One hundred patients with mild-to-moderate hypertension being treated with dihydropyridine CCBs were randomly selected to receive candesartan (8-12 mg once daily), then followed for 3 months.

Blood pressure (BP) was equally well controlled with both medications. Candesartan patients, however, showed improvements in several aspects of QOL, including general symptoms, physical symptoms and well-being, work and satisfaction, sleep scale, emotional state, and cognitive

function. Those aged  $\leq 65$  years reported a significant improvement in sexual function.

The second trial evaluated the effects of a change in medication on symptoms and QOL in 550 patients who reported bothersome side effects from antihypertensives.<sup>23</sup> Patients were taking a variety of BP medications, but the most common were ACEIs and CCBs. Physicians changed the patients' BP medications to either valsartan (70% of patients) or valsartan + hydrochlorothiazide (HCTZ) (30% of patients), then monitored patients for 7 weeks. After the change, the severity of cough, headache, and edema were reduced in 93%, 86%, and 87% of patients, respectively. QOL data were collected for 420 patients, who reported significant improvements in mean physical and mental scores after changing to valsartan or valsartan + HCTZ.

**Conclusion**

As a class, ARBs are generally well tolerated. Adverse effects reported in clinical trials, such as headache and dizziness, have been described as mild to moderate. Overall, the frequency of cough in ARB-treated patients is significantly lower than in those taking ACEIs and comparable to that with placebo. Angioedema is a rare but potentially fatal side effect of ACEI therapy that is reported less frequently in patients using ARBs. QOL assessments of patients switching from other BP medications to ARBs showed improvements in both physical and mental status after the change in medication.

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