Response to Lazarus

Dr Lazarus is correct. In our article,1 instead of black box warning the text should say warning. The main message from this point, however, does not change.

After the approval of ambrisentan, and after postmarketing reports of adverse effects, the Food and Drug Administration issued an updated report, where under the warnings and precautions and adverse reactions section, fluid retention was added.2 In section 5.3 of the update, the Food and Drug Administration explained: “...In addition, there have been post-marketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting LETAIRIS. Patients required intervention with a diuretic, fluid management, or, in some cases, hospitalization for de-compensating heart failure.” Which is exactly the point our article was making.

We appreciate the article by Shapiro et al,3 provided by Dr Lazarus. In this article that was published after our original submission to Circulation Research, the authors grouped the 2 ambrisentan randomized trials (ARIES 1 and 2) and further analyzed the profile of the patients reporting edema as opposed to the ones that did not. The need for such a report confirms the fact that peripheral edema is an important problem in patients treated with ambrisentan. We think that the findings of this work (which was sponsored by Gilead Sciences Inc) actually support the points we were making. The authors found that edema was experienced in almost a quarter (23%) of patients on ambrisentan compared with placebo (14%). Within the ambrisentan group, patients who did not develop edema improved their 6-minute walk by 38.9 meters. In contrast, patients who developed edema on ambrisentan improved their walk by half (ie, only 19.4 meters). Although the ambrisentan patients that did not develop edema improved their brain natriuretic peptide (BNP) levels (P<0.001), patients with edema did not improve BNP levels compared with placebo in a statistically significant manner (P<0.058). There were no differences in renal function between the 2 groups to suggest that it was a predisposing factor for edema.

We think that these data are compatible with an adverse effect of this drug on the right ventricle of a subgroup of patients who may have the most hypertrophied right ventricular myocardium as we had speculated in our article. In such a group, the potentially beneficial effects of the drug on the pulmonary vessels (ie, the afterload of the right ventricle) may be limited by simultaneous negative effects on right ventricular contractility. As our ex vivo experiments showed, these effects are acute, compatible with the postmarketing reports of edema shortly after initiation of ambrisentan therapy. This is perhaps why these patients improve much less in terms of 6-minute walk performance and BNP levels. It is arguable whether an improvement of 19.4 meters in the 6-minute walk is clinically meaningful, particularly if to gain this small improvement in walking distance, the patients need to be exposed in new or additional diuretics. We think that whether it is best to continue the drug and add diuretics in such patients, versus discontinuing the drug, should be subject to appropriately designed blinded trials in the future.

As discussed in our article, we do think that this is a class effect of endothelin receptor antagonists and not specific to ambrisentan. We think that new mechanistic knowledge on the action of drugs should be considered in the design of clinical trials toward a more personalized approach in complex diseases like pulmonary arterial hypertension.

Disclosures

None.

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References
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