Good example of telmisartan role in prevent recurrent vascular events in patients...

Health & Medicine, Stress

who have had an ischemic stroke

BACKGROUND

Prolonged lowering of a patient’s blood pressure after a stroke occurs has been observed to reduce the risk of recurrent stroke. Additionally, the inhibition of the renin-angiotensin system in with regard to high-risk patients has also managed to reduce the rate of subsequent cardio vascular events, which includes stroke related complications. However, the effect of lowering a patient’s blood pressure using a renin-angiotestin system inhibitor such as Telmisartan, soon after an ischemic stroke has occurred has not yet been clearly established.

According to previous research studies and statistics retrieved from WHO, stroke has been ranked second as the most frequent cause of death in the world and is responsible for the death of more than 5 million people annually. In addition, more than 15 million people have been reported to have experienced non-fatal strokes, with a third of this population ending up with disabling consequences. The largest risk factor for patients with stroke and lowering of blood pressure is the issue of elevated blood pressure, especially if they record substantially elevated levels such as systolic pressure of beyond 160mm Hg. After a stroke has occurred, lowering blood pressure using a combination of a diuretic and an angiotensin-converting-enzyme (ACE) inhibitor reduced the rate of recurrent stroke in the study Perindopril Protection Against Recurrent Stroke Study (PROGRESS Trial) (Yusuf et al, 2008)

DRUG OVERVIEW

Angiotensin receptor blockers (ARB) are broadly effective in lowering blood pressure and also have relatively few side effects, notably the absence of angioedema and cough, which largely represents their key advantage over the ACE inhibitors. In regard to Telmisartan, this is an ARB that was approved back in the year 1998 and has since then provided lasting blood pressure control as compared to other agents. It is an angiotension II receptor antagonist used in the management of hypertension. Telmisartan has demonstrated a reduction of mortality and the general hospital admissions. Telmisartan is an effective drug that is normally administered at a dose of 40-80mg once daily. Some patients are also known to benefit at a daily dose of 20mg, however in the case that the targeted patient's blood pressure has not yet been achieved, this medication can be increased to a dosage of a maximum of 80mg once daily.

STANDARD OF CARE/KNOWN EFFECTIVE TREATMENTS

- Literature Evaluation

In previous research studies and clinical trials, there have been raised the possibility of an extra mechanism, which is independent of blood-pressure lowering, and by which the blockers of renin-angiotensin system may result to being beneficial in patients with stroke. In one of the Trials, The Heart Outcomes Prevention Evaluation (HOPE) trial showed that the ACE-Inhibitor therapy greatly reduced the rate of stroke in patients especially who have previously experienced cardiovascular and high risk diabetics events despite a causing a significant reduction in blood pressure. In another recent trial, it

was further demonstrated that, an angiotensin receptor blocker (ARB), which was started soon after a stroke occurred, reduced the rates of deaths and other cardiovascular events while recording no pressure reduction.

In most of the studies available with regard to ARBs role in preventing recurrent vascular event in ischemic stroke patients, these patients were enrolled many months or years after stroke occurred, and also putting into consideration the benefits of the use of Renin-Angiotensin system blockers especially after a stroke was not clearly established (Yusuf et al, 2008). In light of these findings we initiated an evaluation on whether therapy with telmisartan, given at a dose of 80mg per day, could end up reducing the risk of stroke when evaluated within 4 months after the occurrence of a stroke and also continued for 2. 5years.

STUDY METHODS

The information on the trial protocol in regard to this study have been published previously. In this trial, patients from 698 centers in a total of 35 countries who had recently experienced an ischemic stroke were included in the clinical trial. A two-by-two factorial design was adopted so as to compare four regimens: an arrangement of both acetylsalicylic acid (Aspirin) and the extended release dipyridamole as compared with other ARs such as clopidogrel, and also telmisartan when compared with placebo. In addition, all the patients that were included in this trial received medications for blood-pressure control at their investigator’s discretion. This trial was approved by the Ethics board, and institutional review committee at both the

local and national site. The method for this trial focuses on the comparison between telmisartan with the placebo.

STUDY DESIGN

In this multicenter trial, it involved 20, 332 patients who had recently suffered ischemic stroke. From this figure, 10, 146 patients were randomly assigned to receive telmisartan (80 mg daily) while 10, 186 were to receive placebo. Therefore this was a placebo –controlled clinical trial design. The primary outcome of this study was recurrent stroke while the secondary outcome was expected to be the major cardiovascular events which includes deaths from recurrent stroke, cardiovascular causes, worsening heart failure and myocardial infarction.

Data for this clinical trial were collected by the designated investigators at each site. The analysis of the final statistics were conducted simultaneously by the Independent statisticians at the Medical university of S. Carolina, who also went further to provide data and interim analysis reports and also safety monitoring. For the study to take place as expected and without numerous hiccups, it was agreed that minor discrepancies would be resolved through mutual agreements. Additionally, the three main investigators to this trial had full access to the data, wrote manuscripts and vouched for completeness and accuracy of the data that was analyzed all along the clinical trial period.

PATIENT ENROLMENT

The inclusion criterion for this study required that the any patient that would participate must be 55 years of age and less than 90 years old, and must

have had Ischemic stroke in the less than 3months before randomisation. Additionally, their general health condition was expected to be stable for one to be eligible for the study. Ischemic stroke was defined by the investigators as a new focal neurologic deficit for cardiovascular origin which was persisting for more than 24hour, therefore, the patients whose symptoms lasted for less than 24 hours could not be eligible to participate in the study. However, there were some modifications in the inclusion criteria for this study as it progressed. After 6000 patients had been accepted as fit for the study, the age limit was modified so as to allow for younger patients of age 50-54 years to be included in the study and also to enrol the patients who had had fewer counts of strokes for the past 90-120days. Most of the patients who had experienced primary haemorrhagic stroke, complications to the various study on antiplatelet agents, severe disability mostly after the qualifying stroke, or other factors that would make the patient unsuitable for randomization were excluded from the study (Yusuf et al, 2008).

EXPOSURE VARIABLES

The eligible patients who were willing to participate in the study underwent randomization via the use of a central telephone system so as to receive either a twice-daily fixed dose which was a combination of aspirin 25mg and dipyridamole of 200mg. the other option was to take a once-daily clopidogrel (75mg) or a once daily dose of telmisartan (80mg) or placebo. These patients would be evaluated at the time of discharge from the hospital the n after 1, 3 and 6 months during clinical visits.

OUTCOME MEASURES

In the primary outcome for this clinical trial was recurrent stroke of any type. On the other hand, the secondary outcome were the major cardiovascular events (myocardial infarction, death from cardiovascular causes, recurrent stroke or new or worsening heart failure) and also new-onset diabetes.

STATISTICAL ANALYSIS

This clinical trial was initially designed to enroll 15, 500 patients, with a sample size that was considered enough to accrue 2170 patients over a 4 year trial period. With this assumption, this study had the power of more than 99% of detecting the relative risk of 25% with regard to the telmisartan group. Nonetheless, due to the high turn-out in the sample size up to 20, 000 and also due to the 6 month extension of the trial, only a total of 175 patients experiencing recurrent stroke were projected.

RESULTS

In the findings from this study, about 42% of the participants were of ethnic backgrounds other than white European. 19% of them had atherosclerosis while 25% had had instances of transient ischemic attacks (TIA) or before qualifying stroke. The median interval from ischemic to randomization was 15 days. In the mean follow-up that was of 2. 5years was composed of a blood pressure of 3. 8/2. 0 mmHg lower in the telmisartan group than in the placebo group (Yusuf et al, 2008). 880 patients in the telmisartarn group and 934 patients in the placebo group recorded a subsequent stroke (hazard ratio in the telmisartan group, 0. 95; 95% confidence interval [CI], 0. 86 to 1. 04; P = 0. 23). Major CVD events occurred in (13. 5%) 1367 patients in the

telmisartan group and (14. 4%) 1463 patients in the placebo group (hazard ratio, 0. 94; 95% CI, 0. 87 to 1. 01; P = 0. 11). The new onset diabetes was observed to have occurred in 1. 7% of the telmisartan group while 2. 1% of in the placebo group (hazard ratio, 0. 82; 95% CI, 0. 65 to 1. 04; P = 0. 10). By the end of this clinical trial, the use of diuretics, calcium-channel blockers, ACE inhibitors and beta-blockers was observed to be more frequent in the placebo group as compared to the telmisartan group.

STRENGTHS AND LIMITATIONS OF THE STUDY

However, this study also experienced its fair share of shortcomings, one of the limitations that this trial faced was with regard to the adherence to the telmisartan reginment, it was observed to be lower than that in other clinical trials of telmisartan. This can be attributed to the absence of a run-in period in this study and also due to the fact that most patients experienced headaches caused by aspirin and the extended release dipyridamole ultimately stopping both sets of blinded medications in the factorial design. It major strength was the central adjudication of all the MRI scans by 2 experienced and blinded neuroradiologists.

CRITIQUE/EVALUATION

With a patient follow up of an average of 2. 5 years, telmisartan was compared with placebo that was initiated soon after an ischemic stroke attack. In this trial, it was shown that telmisartan did not significantly reduce the risk of undergoing a subsequent stroke, new onset diabetes and also of the composite outcome of the major CVDs. This is because, increased blood pressure especially after a stroke was associated with recurrent events and

also a long-term lowering of the blood pressure was concluded to be reducing strokes in the PROGRESS study. However, there exist numerous differences between this study and the PROGRESS study, s. In the PROGRESS, the BP was higher (147/86mm Hg) as compared to this study which has (144/84mm Hg). Secondly, most of the patients in the PROGRESS study had been set to receive a combination of perindopril and indamide unlike in the case in this study. In general, the results of this study analysis were unaltered and conformed to all the set requirements for carrying out ethical researches.

CONCLUSION

References

Yusuf, S., Diener, H. C., Sacco, R. L., Cotton, D., Ôunpuu, S., Lawton, W. A., & Yoon, B.

W. (2008). Telmisartan to prevent recurrent stroke and cardiovascular events. New England Journal of Medicine, 359(12), 1225-1237.