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Research Article

Review of angiotensin II receptor blockers (ARBs) in migraine prophylaxis

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ABSTRACT

Migraine is a one of the neurological conditions to cause disability and affect patient's daily activities. The use of prophylactic agent is preferred over acute therapy in patients with frequent attacks of migraine. However, tolerability issues associated with first line agents in migraine prophylaxis may limit their use. There is always a need to study other agents that is effective in migraine prevention with good tolerability profile. This article compared available data on the clinical use of Angiotensin II Receptor Blockers (ARBs) in migraine prophylaxis to answer the following question: For adult patients, were ARBs proven effective for migraine prevention as measured by the number of migraine days. This review addresses both efficacy and safety of ARBs use for migraine prophylaxis. The review included three randomized controlled studies and one open label study. Only candesartan, olmesartan, and telmisartan among ARBs were for this indication. Candesartan was proven to be superior to placebo and not inferior to propranolol while telmisartan failed to show any significant differences from placebo. The quality of data presented in olmesartan study was not good enough to generalize the results. There is no evidence supporting the use of other ARBs for migraine prophylaxis. More studies are required to determine the efficacy of candesartan in migraine prophylaxis and whether its effect is drug specific or class general. It seems reasonable for clinicians to individualize the prophylactic therapy for migraine based on safety profile, contraindication and comorbid conditions.

Key words: *Migraine; Angiotensin II Receptor Blockers (ARBs); Candesartan; Telmisartan, Olmesartan*

INTRODUCTION

Migraine is a lifelong neurological condition that has a negative impact on patients' quality of life and healthcare cost, and societies' productivity.[1,2,3,4]Migraine is ranked globally as the most leading cause of disability among all neurological disorders and the seventh among all diseases.[5]The estimated proportion of world population with migraine is 2%.[6] Female suffer from migraine three time as often as male.[1] In patients with frequent attacks of migraine, prophylactic management is preferred over acute management because of medication-overuse headache.[7,8]

Prophylactic therapy of migraine is recommended for patients with more than two migraine attacks per month, failure or intolerability of acute treatment, or severely impaired quality of life.[8]The goals of prophylactic therapy for patients with migraine are to reduce migraine frequency and migraine intensity, decrease/eliminate the need for acute therapy, and improve the quality of patients' life.

There are many pharmacological options that can be used for the prophylactic treatment of migraine such as Beta-blockers, antiepileptics, and antidepressants.[9-12].

However, the side effects associated with these pharmacological classes may limit compliance and their long-term use. For example, fatigue with propranolol, hepatotoxicity with valproate, cognitive impairment with topiramate, and anticholinergic effect with amitriptyline may not be tolerable with some patients especially if no comorbid condition exists.[13-16]

The 2012 AHS/AAN (American Headache Society/ American Academy of Neurology) guideline assign medications to 1 of 5 levels (A to U) based on the strength of evidence supporting their use for migraine prevention. Level A list medications with established efficacy and level U list medications with conflicting or inadequate evidence.[10]Some antihypertensive medications have been shown to have either established efficacy or probable efficacy for migraine prophylaxis but propranolol and timolol are the only antihypertensive medications approved by the FDA for this indication. Although angiotensin receptor blockers (ARB) have been studied for migraine prophylaxis, they are not approved by the FDA for this indication. Candesartan was categorized as level C drugs (possibly effective) by the 2012 AHS/AAN evidence-based treatment guideline for prevention of episodic migraine based on a single study.

The objective of this review is to evaluate the available data on the prophylactic effect of ARBs in migraine as measured by reduction in the number of migraine days compared to placebo and/or active comparator drug.

METHODOLOGY

A literature search was conducted using Medline/Ovid (1946-present, Dec 3 2017) and Embase (1980-2017).

The following key words were used: (candesartan or telmisartan or losartan or irbesartan orolmesartan or valsartan or angiotensin receptor blocker$) and (migraine$ or migraine disorder$ or headache$). The search was limited to human study, adult age group, and English language. After excluding non-relevant studies and repetitive studies, four out of seven studies were identified (3 randomized controlled trials, 1 open label study).

RESULTS AND DISCUSSION

Four studies were included in this review; three randomized controlled trials and one open label study. Table-1 list the study characteristics of included trials of prophylactic treatment of episodic migraine headaches. Table2 summarizes the efficacy outcomes of angiotensin II receptor blockers in migraine prophylaxis.

Charles et al conducted an open label study to investigate both efficacy and safety of olmesartan for migraine prophylaxis.[19] The study evaluated 24 patients aged 27 to 76 years with comorbid hypertension or prehypertension treated with olmesartan at a dose of 10-40 mg daily. The patients were followed-up for at least 3 months and up to 12 months to record headache frequency and intensity. Results showed 82.5% reduction in headache frequency and 45% reduction in headache intensity compared.. There were no incidents of serious adverse events and none requiring discontinuation of therapy. From baseline, olmesartan decreased systolic blood pressure by 21 mmHg and diastolic blood pressure by 15 mmHg. The study is subject to limitations. The most important limitation is the fact that it is not randomized controlled trial and the results in headache frequency and headache intensity was compared to baseline rather than placebo or comparator drug. It is also limited by the small sample size and short space of time. Only patients with comorbid hypertension or prehypertension were studied therefore, the results need to be interpreted with caution. Minimal study data were presented and no statistical data was provided.

A randomized, double-blind, placebo-controlled Phase II study by Diener et al investigates the safety and prophylactic efficacy of telmisartan in patients with 3-7 migraine attacks in 3 months.[20]

The primary outcome was reduction in the migraine frequency during the last 4 weeks of 12-week treatment period compared to baseline. Ninty-five patients were included and randomly assigned on 1:1 ratio to receive either telmisartan 80 mg or placebo. Out of 95 patients, 84 patients completed the study and were included in the efficacy analysis.

At baseline, there was a difference in the mean number of migraine days between telmisartan group (6.2) and placebo group (7.6), P= 0.09. The numerical values of primary and secondary endpoints were higher in telmisartan group compared to placebo group but failed to achieve statistical significance.

Two randomized trials investigate the effect of candesartan in migraine prevention.[21,22] The first trial that was carried out in a Norwegian neurologic outpatient clinic, by Trovnik et al, investigated the prophylactic effect of candesartan in reducing the number of headache days.[21] It is randomized, double-blind, placebo-controlled crossover study. A total of 60 patients aged 18 to 65 years with 2-6 migraine attacks per month were included. Thirty patients were randomly assigned to receive 16 mg candesartan in the first 12-week period and placebo in the second

12-week period. Treatment periods were separated by 4-week washout period.

The remaining 30 patients received placebo followed by candesartan. Out of 60 patients, 3 patients dropped out in the first treatment period and 57 patients were included in efficacy analysis. Headache frequency were reduced by 26% in candesartan group (13.6 days) compared to placebo group (18.5 days), P= 0.001. Compared to baseline, the use of candesartan resulted in 47% reduction in migraine days. Twenty-three patients in candesartan group achieved ≥ 50% reduction in migraine days compared to 2, in placebo group. Treatment with candesartan resulted in reduction in systolic blood pressure by 11 mmHg and diastolic blood pressure by 7 mmHg. Adverse drug events rate in candesartan and placebo periods were similar. Limitations of the study include crossover design, small sample size, high non-compliance rate, short treatment duration.

The second trial was conducted by Stovner et al that believe to be the first to compare ARB to an active comparator agent.[22] It is randomized triple-blind, placebo controlled, double crossover study. The study was conducted to test whether candesartan is superior to placebo and non-inferior to propranolol. Propranolol is one of the migraine prophylactic agent that has level A evidence per AHS/AAN guideline. A total of 72 patients were treated in six possible treatment sequences with candesartan 16 mg, propranolol slow-release 160 mg, and placebo. The treatment duration for each agent was 12 weeks. The primary endpoint was the frequency of migraine days in 4 weeks. In a modified intention-to-treat analysis, patients treated with candesartan experienced a statistical significant reduction in the number of migraine days compared to those received placebo (2.95 days versus 3.53 days, p=0.02). There was no significant difference in the number of migraine days between candesartan group and propranolol group (2.95 days versus 2.91). The adverse events rate was similar with candesartan and propranolol (133 versus 143) however the adverse events profile was different. The most frequently reported adverse events of candesartan were dizziness and paraesthesia.The most frequently reported adverse events of propranolol were bodily pain and low pulse at exercise.

Table 1: Study characteristics of included trials of prophylactic treatment of episodic migraine headaches

	Charles et al[19]	**Diener et al[20]**	**Trovnik et al[21]**	**Stovner et al[22]**
Study Design	Open-label study	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled, crossover	Randomized, triple-blind, placebo-controlled, double crossover
Study Population	Patients with coexisting hypertension or pre-hypertension	Patients with 3- 7 migraine attacks within the last 3 months	Patients with 2-6 migraine attacks per month	Patients with ≥ 2 migraine attacks per months during the last 3 months and ≥ 2 attacks during the baseline period
Length of Study	3-12 months	4 months	8 months	12 months
Study Drug	10-40 mg olmesartan	80 mg Telmisartan	16 mg Candesartan	16 mg Candesartan
Comparator	Baseline	Placebo	Placebo	Placebo and 160 mg slow-release propranolol
Primary End Point	Reduction in headache frequency and headache intensity	Reduction in the number of migraine days	Number of days with headache	Days with migraine headache per four weeks

Table 2: Analysis of efficacy outcomes of angiotensin II receptor blockers in migraine prophylaxis

	Charles et al[19]	**Diener et al[20]**	**Trovnik et al[21]**	**Stovner et al[22]**
Sample size (patients)	24	TEL: 40 PLA: 44	CAN: 57 PLA: 57	CAN: 56 PLA: 60 PRO: 60
Study drug	Olmesartan	Telmisartan	Candesartan	Candesartan Propranolol
The mean number of migraine days at baseline (days)	Not presented (~ 14.7)	TEL: 6.18 PLA: 7.59	5.7	4.82
The mean number of migraine days per month (days)	Not presented (~ 3.25)	TEL: 4.53 PLA: 6.45 P value= 0.7388	CAN: 3.0 PLA: 4.2 P value< 0.001	CAN: 2.95, 95% CI: 2.35–3.55% PLA: 3.53, 95% CI: 2.98–4.08% (P=0.02 vs. CAN) PRO: 2.91, 95% CI 2.36–3.45 (P= 0.88 vs CAN)
Number of responders (>50% reduction in migraine days compared with baseline)	Not presented (~ 19)	TEL: 16 (40%) PLA: 11 (25%) P value= 0.0686	CAN: 23 (40.4%) PLA: 2 (3.5%) P value< 0.001 **NNT:** 3	CAN: 24 (43%, P= 0.025) **NNT:** 5 PLA: 14 (23%) PRO: 24 (40%, P < 0.050) **NNT**=6

CAN: Candesartan, **PLA:** Placebo, **TEL:**Telmisartan, **PRO:** Propranolol, **NNT:** Number needed to treat

CONCLUSION

There is only one trial comparing an ARB with other active agent for migraine prophylaxis. Clinical trials provide evidence with good data quality showed that candesartan is superior to placebo and not-inferior to the first-line agent, propranolol. As of December 2017, AHS/ AAN guideline has not been updated to reflect the result of this trial. The applicability of evidence from olmesartan trial was limited by poor data quality.

Telmisartan trial failed to show positive prophylactic effect in migraine treatment. No data evaluating the potential clinical use of other ARB agents for migraine prophylaxis were identified. More studies are required to assess the potential role of ARBs in migraine prevention and assess whether the prophylactic effect of candesartan is drug specific or class general.

It is very important to consider the potential teratogenic effect of candesartan before recommend to a female at childbearing age. Pharmacological selection for migraine prevention has to be individualized based on contraindication, safety profile, and comorbid condition.

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