OPINION ARTICLE

Migraine Prophylaxis: Comparable Effects or Unadjusted Effects That Could Be Misleading? A Review of a Study by Maizels et al. Published in *Headache: Journal of Head and Face Pain*

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Based on the findings from a randomized, double-blind, placebo-controlled trial (RCT) published in Headache: *Journal of Head and Face Pain* that evaluated the efficacy for migraine prophylaxis, Morris Maizels et al. concluded that Riboflavin 25 mg used in the trial as the placebo treatment showed an effect comparable to a combination of 400 mg Riboflavin, 300 mg Magnesium and 100 mg Feverfew.[1] Of the 49 patients who completed the 3-month trial, there was no significant difference noted between the combination drug group (n=24) and "placebo" group (n=25) for the primary efficacy measure, a 50% or greater reduction from baseline in monthly migraine frequencies, which was achieved by 10 (42%) and 11 (44%) patients, respectively. With reference to the published data, Morris Maizels et al. concluded that the placebo response observed in this trial exceeded that of the placebo response found in any other trials of migraine prophylaxis, which was approximately 24% (95% CI: 18.3% to 28.8%), reported in a meta-analysis by Van der Kuy and Lohman.[2]

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Were these really comparable effects or were there some contributing factors Morris Maizels et al. did not consider? To the general public and research community, the conclusion provides very confusing information.[3]

This trial was originally designed to randomize 48 patients per group for a statistical power of 80% to detect a difference of 30% in response rate at the significance level of 0.05 (2-sided), based on an anticipated response rate of 60% for the combination drug and 30% for the placebo. However, it did not employ a washout period prior to randomization for patients who might have been on migraine prophylaxis. Furthermore, the trial allowed patients to use Triptan medications, which are indicated for migraine headache, throughout the study; and, patients could have changed their Triptan doses over the course of the 3-month treatment. Considering the fact that Triptan medications reduce the migraine frequencies at a response rate ranging from 55% to 77%,[4,5] the anticipated response rate of 60% was clearly a long shot for the combination drug in this trial that actually had an add-on design; and consequently, the trial was lacking adequate power.

As reported, patients in this trial used Triptan medications on average 4.72 and 3.09 doses per month during the third treatment month, respectively, for the "placebo" and combination groups, whereas it was 4.2 and 3.3 doses per month prior to randomization, respectively.[1] In reference to the baseline use, placebo-treated patients apparently increased the monthly Triptan doses during the blinded

treatment period, while patients on the combination treatment decreased the monthly Triptan doses. Relative to the patients in the combination treatment, the use of Triptan medications was approximately 53% more [i.e., (4.72-3.09)/3.09=0.53] at the third treatment month in the placebo-treated patients, which was obviously too large of a percentage to be ignored.

In order to make a fair comparison, we calculated the adjusted response rate of the primary efficacy for the placebo group, relative to the combination group, for the use of Triptan medications in the third treatment month. The calculation was done in accordance with the following: subtract from the original response rate of the placebo group a portion defined as the original response rate multiplied by the factor of 0.53, which was attributable to the Triptan use. As a result, the adjusted response rate was 21% [i.e., (44%-44%∑0.53)=21%] for the placebo treatment, which fell well within the range of 18.3% to 28.8% for the placebo response in the published data reported by Van der Kuy and Lohman.[2] For this trial, the primary efficacy response rate was therefore 42% for the combination of 400 mg Riboflavin, 300 mg Magnesium and 100 mg Feverfew; and, 21% for the "placebo" (or Riboflavin 25 mg) after adjusting the monthly use of Triptan medications. Consequently, the p value (2-sided) associated with the difference in response rate after adjustment was 0.113 and 0.027, respectively, for both the actual sample size and the planned sample size had the trial been completed as originally designed. Although the adjustment to the response rate and p value calculation was performed ad hoc and from a non-model-based approach, it was unlikely that anyone who assessed the confounding factor of Triptan use would have reached the same conclusions as the authors for this trial.

As mentioned before, this trial also allowed the ongoing use of prophylactic drugs. However, it did not report the changes in the use of these prophylactic drugs in the placebo and combination groups during the randomized treatment period, which could have impacted the efficacy findings as well.

For researchers and healthcare professionals in a clinical practice, it is important to understand the limitations and weaknesses of a trial design and its conduct, to utilize appropriate statistical methodologies and take into consideration any possible factors that may confound the results.

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REFERENCES

1. Maizels M, Blumenfled A, Burchette R. A combination of riboflavin, magnesium, and feverfew for migraine prophylaxis; a randomized trial. *Headache: Journal of Head and Face Pain*. 2004;44:885-890.
2. Van der Kuy P-HM, Lohman JJHM. A quantification of placebo response in migraine prophylaxis. *Cephalalgia*. 2002;22:265-270.
3. Awang D VC. Combination of feverfew, magnesium, and riboflavin for migraine prevention. *HerbalGram*. 2005;65:36-37.
4. Merck & Co. Inc. Maxalt" package insert accessed online, http://www.maxalt.com/rizatriptan_benzoate/maxalt/hcp/index.jsp, 2006 (June).
5. Ortho-McNeil Pharmaceuticals Inc. Axert" package insert, accessed online, http://www.axert.com/content/Documents/AxertPI.pdf#zoom=100, 2006 (June).