

DEFINING AND ANALYZING MEANINGFUL RELIEF IN CLINICAL TRIALS OF ACUTE MIGRAINE HEADACHE

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BACKGROUND

International Headache Society (IHS) 1991 guidelines recommended pain free at 2 hr as the primary measure of efficacy for treatment of acute migraine headaches. Equally important were the measurements of relapse and use of rescue medications. Most pivotal trials submitted for approval of acute migraine therapy in the US use pain response at 2 hrs as the primary measure of efficacy. Seemingly less important has been the rate of recurrence after 2 hrs or the subsequent use of rescue medication within 24 hrs. In recently revised guidelines (Cephalgia, 2000), the IHS further stressed that 2 hr sustained pain free was the measure that best reflects the patients' expectations and identified sustained pain free as the ideal response to a drug for treatment of migraine headache because it accounted for relapse and use of rescue medication.

OBJECTIVES

- To compare various measures of efficacy using data from a double-blind, randomized, placebo-controlled clinical trial in subjects with severe migraine headaches
- To identify the commonalities and departures of various migraine pain endpoints, their relevance in clinical settings, and their statistical robustness using data from subjects with severe pain at baseline.
- To recommend clinically meaningful endpoints and appropriate statistical methods.

METHODS

Efficacy data were obtained from 295 subjects who treated severe migraine headaches with an oral triptan, a combination of triptan plus NSAID, or placebo. All subjects were to self medicate for their migraine headaches when the pain was either moderate or severe

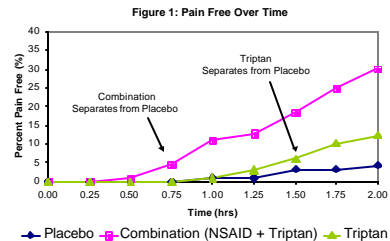
METHODS (cont'd)

and were allowed to rescue 2 hrs after taking study medication as deemed necessary. Subjects completed diary cards every 15 minutes for the first 2hrs after dosing, at 30 minute intervals from 2 through 4 hrs, and then hourly through 24 hrs. Data collected included pain scores (0-4 scale) and use of rescue medication. Various measures of pain response were analyzed for treatment differences using SAS v8.02.

RESULTS

Both the triptan and combination treatments were better than placebo for the 2 hr pain-free response (reduction to no pain).

As illustrated in Figure 1, the pain free response for the combination treatment is significantly better than the placebo or the triptan by 45 minutes. The triptan treatment is significantly better than placebo by 1.5 hrs.



The 2 hour pain-free response rate deteriorates over time as subjects begin to relapse in pain and take rescue medication. Less than 5% of the placebo subjects sustained pain-free response for the 24 hour

RESULTS (cont'd)

period. While both the triptan and combination treatments showed significantly better 2 hour pain free rates than placebo (see Figure 1), 50% of the triptan only treatment responders relapsed, resulting in a similar sustained pain free rate as the placebo group. Only 12% of the combination treatment responders relapsed resulting in a wider margin of difference between the treatment groups.

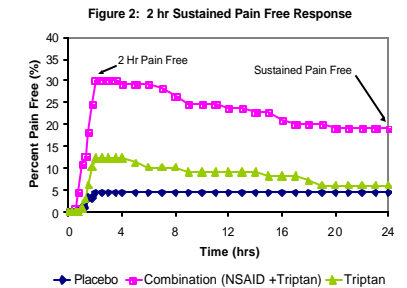
Table 1: Pain Free by 2 hrs and Relapse Between 2 - 24 hrs

Severe Migraine at Baseline	Placebo	Triptan	Combination (NSAID + Triptan)
Total Treated	89	97	109
Pain free by 2 hrs	4 (4.49%)	12 (12.37%)	33 (30.27%)
Responders who relapsed between 2 and 24 hrs	0 (0.00%)	6 (6.18%)	12 (11.01%)
Sustained pain-free	4 (4.49%)	6 (6.19%)	21 (19.27%)

Table 1 summarizes the pain-free responses and relapse rates for each treatment.

Figure 2 shows the rates of pain-free response from 2 to 24 hours. This figure assumes that a lack of response by 2 hours is a failure for the subsequent 22 hours, therefore subjects can only maintain their pain-free status or relapse. The end result is sustained pain free response.

RESULTS (cont'd)



CONCLUSIONS

Measures of pain response (or pain free) at 2 hrs may allow some treatments to appear effective at a single point in time. However, measures of sustained response incorporate not only pain response at 2 hrs but also relapse and use of rescue medication in the subsequent hours. Sustained pain-free is a measure that more closely matches the vision of IHS as an ideal endpoint. Analysis of the endpoint is straightforward, robust and insensitive to time-dependent fluctuations in pain response.

REFERENCES

International Headache Society Committee on Clinical Trials in Migraine. Guidelines for controlled trials of drugs in migraine. 1st Edition, Cephalgia, 1991; 11:1-12.

International Headache Society Clinical Trials Subcommittee. Guidelines for controlled trials of drugs in migraine: 2nd Edition, Cephalgia, 2000; 20:765-786.