8.4 Fremanezumab to prevent migraine headaches

Dr. David Dodick (whose conflict of interest disclosures for this paper run 4.75 column inches in JAMA) and colleagues recently reported results of a randomized, double-blind trial of fremanezumab, a new monoclonal antibody[1] used to prevent migraine headache (1) The investigators compared monthly and quarterly doses of fremanezumab with placebo; for simplicity we will focus only on comparisons of the (more effective) monthly dosing with placebo.

a.) The proportion of patients who achieved at least a 50% reduction in the number of headache days per month was 47.7% in the monthly fremanezumab group compared with 27.9% in the placebo group. What was the number needed to treat with fremanezumab to get one additional patient with a ≥ 50% reduction in headache days?

**Although in this case the outcome is phrased as the probability of something good rather than something bad, we can still just take the risk difference to get the number needed to treat 1= 1/(47.7% – 27.9%) = 1/19.8% = ~5.**

**Following the convention of calculating the risk of a bad outcome is a bit awkward. The bad outcome is < 50% reduction in number of headache days. The risk of that bad outcome was 52.3% in the treatment group and 72.1% in the control group. The ARR is (still) 72.1% - 52.3% = 19.8%, and the NNT is still ~5.**

b.) Fremanezumab costs about $600/monthly dose.[2] It was well tolerated in the trial. If we ignore possible late adverse effects and focus only on the medication cost, what is the approximate cost per month per patient who achieved a 50% reduction in headache days?

**Since the NNT is 5, it will be about 5 times the monthly cost, of ~$3,000. It may help in (c) to note that this is also $600 / (72.1% - 52.3%) .**

c.) Per the abstract, "From baseline to 12 weeks, mean migraine days per month decreased from 8.9 days to 4.9 days in the fremanezumab monthly dosing group, and from 9.1 days to 6.5 days in the placebo group. This resulted in a difference with monthly dosing vs placebo of -1.5 days/month (95% CI, -2.01 to -0.93 days; P < .001)." If we consider a migraine day a bad outcome, what would be the CBOP, i.e., the approximate cost to prevent one migraine day?

**It costs about $600 to treat for a month, which will prevent 1.5 migraine days, so the cost to prevent 1 migraine day would be about $600/1.5 = $400.**

[1] It targets calcitonin gene-related peptide.

[2] Price for Ajovy® 225mg/1.5 ml injection with a free coupon at www.GoodRx.com, accessed 10/24/18.

**This is a continuous or at least a count outcome, but the parallel with (b) is clear. In (b), the expected bad outcomes in the control group was 0.721 and in the treatment group was 0.523, so the difference in expected outcomes is 0.721 – 0.523 = 0.198. This costs $600, so we got $600 / 0.198 = ~$3000 per bad outcome (<50% reduction) prevented. Here, the expected decrease in headache days in the control group was 2.6 and in the treatment group was 4. So the difference in the expected number of headache days is 4 – 2.6 = 1.4 (or 1.5 before rounding). This coses $600, so we get $600/1.5 = $400 per headache day prevented.**

d.) Let's suppose that this medication only works for true migraines and that everyone in the trial was sufficiently screened that all of them had true migraines. But out in the "real world" we are considering treating someone with headaches that we think might be migraines, but we are unsure. If we believe it is worth $500 to prevent one headache day, and if there were no other therapeutic options available, at what probability of migraine would the headache reduction benefit of fremanezumab justify the cost?

**The problem gives you the benefit per bad outcome prevented = BBOP = $500. So the treatment threshold = CBOP/BBOP = $400/$500 = 80%. So if we believe the probability that the headaches our patient is suffering are migraines is at least 80%, then the expected cost of preventing a headache day will be justified by the expected benefit.**

e.) The investigators excluded patients who had previously failed 2 classes of migraine-preventive medicine from the study and compared fremanezumab with placebo. What effect do these study design decisions have on the clinical usefulness of the study results?

**These design decisions reduce the clinical usefulness of the study because it now answers a question different from what most patients and clinicians want to know. This is an expensive new medication with uncertain long-term safety, so it would not be my first choice medication unless it had been shown to be substantially safer or more effective than existing treatments. So I would either want to see the subjects eligible for the study restricted to those who had failed or could not tolerate existing treatments or have the comparison group be a standard treatment in order to know whether to consider prescribing this medication.**

1. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine: A Randomized Clinical Trial. JAMA. 2018;319(19):1999-2008.