PROMISING NEW DRUG FOR ARTHRITIS PAIN – OR SAME OLD STORY?

Use this commentary as an example for how you are expected to respond to questions critiquing the article. Side notes from the instructor to you, which are simply informational, are in [* ].

Q: What were the study’s rationale/hypothesis and objectives?

This study aimed to test the safety, efficacy, and possible side effects of a new drug for treatment of osteoarthritis of the knee. Given the limited existing treatment options for the condition, and a small Phase 1 trial which suggested possible benefits of tanezumab, the investigators aimed to compare treatment of arthritis pain with different injected doses of the drug to treatment with a placebo injection.

Q: What were the assigned treatment and control groups, and how were they defined?

Individuals were randomly allocated to treatment with either 10, 25, 50, 100 or 200 ug of tanezumab via injection, or a placebo (control group), also injected.

Q: Was there any way that the blinding of treatment status could have been compromised (in other words, if the investigator somehow figures out treatment status)? If so, what might have been its potential impact?

The pharmacist preparing the dosage (either the drug or placebo) was aware of the subject’s randomization to treatment or placebo. It is unlikely the pharmacist would have (accidentally or purposefully) changed someone’s treatment from their randomly assigned one, and since the pharmacist presumably played no part in the analysis of study data, their awareness of treatment status did not likely affect the study’s findings. Similarly, the statistician’s knowledge would not be expected to have an impact, barring unethical research practices from this individual. An opportunity for un-blinding may have been presented if individuals assigned to placebo experienced significantly more knee pain, or if individuals assigned to tanezumab experienced many side effects – but this is really only likely to occur when the investigator ascertains the outcome directly (such as by interviewing or examining the patient). Because participants self-reported all of their outcome information (i.e., instead of being directly assessed by a physician) throughout the study, and this information was summarized later by the investigators, compromise of the investigator’s blinding to subject treatment status was unlikely and probably did not constitute a major source of bias in this study.
Q: What was the outcome of interest for this study? How was it measured? Do you see any problems with the way the outcome of interest was measured? If so, suggest some alternatives.

Pain while walking and overall knee pain was recorded by the patient in a daily diary. The patient’s overall assessment of their pain during the trial (called “global assessment” by the authors) was recorded at the time of 7 study visits (on days 14, 28, 70, 84, 112, 136, and 182). Adverse events were evaluated by telephone at week 6. Since the outcome data was provided directly by the participant (i.e., self-reported discomfort), and categorized afterward by the investigator based on previously established clinical guidelines (OMERACT-OARSI), we should not be overly concerned about possible investigator influence on the way outcome was measured. The way participant’s report pain scales on a daily basis may change over time, as participants tolerance for pain may change over time, regardless of treatment status. However, it is hard to imagine a more objective way to measure pain, as pain is a rather subjective endpoint. [Side note: one reason that scores and scales are used to evaluate subjective outcomes like pain is because they can better deal with the variation in pain tolerance and other differences in how individuals might characterize pain.]

Q: Are there any possible concerns about patient compliance with their assigned treatment? What impact might non-compliance have on study findings?

Data were analyzed using a modified intent-to-treat approach, despite some individuals being lost to follow-up. We can see from Figure 1 that many patients chose to enter the open-label extension of the study (offered at day 112), [*this is just a continuation of the existing study that examines long-term safety of the drug], and that some had an adverse event, did not respond to contact, or discontinued the study for some other reason. However, the modified intent-to-treat analysis still included the majority of the individuals randomized to treatment or placebo [*it is called a “modified” intent-to-treat because it doesn’t include everyone regardless of compliance, as we would do in a “true” intent-to-treat analysis].

Since we know there were quite a few people who discontinued the study for some reason, we have to be concerned about the potential impact of non-compliance on study findings. Non-compliance reduces the benefit of randomization – making our treated and placebo groups similar with respect to confounding factors. Table 1 shows that randomization was initially (i.e., at the start of the study) effective at distributing those factors equally between treatment groups. If we compare the proportion of participants having no response or no contact (i.e., lost to follow-up) to the numbers analyzed in the intent-to-treat approach, the major concern is the loss of this benefit from randomization. [For example, Figure 1: of the 75 individuals assigned to placebo,
41 (54.6%) were lost by the study’s end.) We also don’t know to what extent people who remained in the study actually complied with their assigned treatment regimen.

The authors collected data on “rescue” treatments in order to determine if use of rescue medication also declined over time. However, we might also consider the possibility that taking acetaminophen or tramadol may have impacted the efficacy of the tanezumab treatment. The authors do not discuss this possible influence of rescue medications on the study findings.

Q: Why do you think there was an entire paragraph dedicated to disclosure of who conducted, oversaw, and analyzed the study’s findings? What implications does this information have on the study?

In order for research to be ethical, the persons funding research needs to be fully disclosed, or else there is the possibility for a conflict of interest. The pharmaceutical industry is a multi-billion dollar industry. Knowing the Pfizer conducted the study does not imply there was anything wrong with regard to the study’s conduct, but it does demonstrate the likelihood of a financial interest in the study’s findings. To avoid conflicts of interest, safety and operations were monitored by an external (i.e., not Pfizer) monitoring board.

Q: To what population(s) do you think this study’s findings may or may not be generalizable, and why?

Since this study was conducted among individuals aged 40 to 75 years old with existing knee pain, this same population is the group to which study findings are most easily applied. [*In other words, we may have some confidence that the findings would apply on average to other people of the same age with the same problem.] Notably, the drug is intended for arthritis pain, specifically. The findings of this study don’t necessarily apply to individuals with other types of pain, since the mechanism for how these drugs work may differ in various parts of the body. Therefore we also cannot know for sure if the drug would show the same benefit among younger people with knee pain (i.e., younger than 40 years), perhaps pain that is not associated with arthritis.

Q. This trial may have some relevance to clinical practice, but there were adverse events associated with some of the treatment levels. Based on the frequency and type of adverse events described in the article, what advice might you want to provide physicians regarding the use of tanezumab for osteoarthritis pain?

At the very end of the paper we learn that there were enough severe adverse events in a separate study to at least temporarily put a hold on further examination of tanezumab, specifically the development of arthritis in other joints. This is obviously of some concern. The concept of equipoise states that in order for us to
experimentally test a new drug on a human population, we must be certain that it is no less effective than the current standard of care (normal treatments), and we have a reason to believe it might be of benefit. Certainly the earlier, smaller trials suggested some benefit, so conducting the trial was appropriate. However, at least one other study suggested that there may be more than the acceptable level of harm coming from treatment with this drug. The adverse events occurring in the current study appear to have been concentrated among the higher dose treatment groups, but the authors admit they were unable to fully evaluate that possibility. Additionally, the adverse events were mild in most cases, but since this was a short-term study, the risk and severity of adverse events with long-term treatment remain unknown. My advice to physicians at this point might be to continue to prescribe standard treatments but to be aware that additional, more long-term studies of tanezumab proving benefit with minimal risks may make it a possible future treatment option.