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Angioedema in the omalizumab chronic idiopathic/spontaneous urticarial pivotal studies: Clinical relevance versus statistical significance

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In virtually all clinical research reports published in modern journals, various tools are used to demonstrate the presence or absence of statistical significance in reporting results. Yet it is clear that statistical significance and clinical significance do not always align. This can pose multiple concerns about the use of a specific modality in the spectrum of available treatment options including therapeutic superiority vs. equivalence, economic and even safety issues.

In this issue of the *Annals*, Zazzali and colleagues¹ report on the impact of omalizumab therapy for chronic idiopathic urticarial on accompanying angioedema. Among numerous other findings, they observed a significantly greater mean proportion (%) of angioedema-free days from weeks 4 to 12 with 300 mg of omalizumab vs placebo in data from participants in three clinical trials: ASTERIA I (96.1% vs 88.2%, $P < 0.001$), ASTERIA II (95.5% vs 89.2%, $P < 0.001$), and GLACIAL (91.0% vs 88.1%, $P < 0.001$). The P-values were calculated from a statistical test used to assess the statistical (null) hypothesis that the mean proportion of angioedema-free days for study participants who received 300 mg of omalizumab is identical to the mean for those who received placebo. Trials that yield comparative data with similar means tend to produce test statistics that are small in magnitude and have large P-values ($0.05 < P < 1.0$) and, conversely, trials that yield dissimilar means tend to produce test statistics that are large in magnitude and have small P-values ($0.0 < P < 0.05$). Thus, if the mean in the study population of omalizumab participants is actually identical to that of the placebo population, and the assumptions underlying the validity of the statistical test employed in producing the P-value are true, then one would expect to only find $P < 0.05$ by chance. Since each individual trial in the report by Zazzali et al produced $P < 0.001$, the observed differences in outcome means in each trial casts serious doubt on the hypothesis that the true means are in fact identical. The consistency of these results across the three studies provides compelling evidence that the mean proportion of angioedema-free days is significantly higher in patients with chronic

Conflicts of Interest

There are no known conflicts of interest with this article.

Trial registration: Not applicable

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idiopathic/spontaneous urticaria when they are treated with 300 mg omalizumab. However, statistically significant findings are not necessarily clinically relevant and, moreover, interpretation of clinical relevance may vary from one study to the next. One view is that a research finding that favors one intervention over another is clinically relevant if it sufficiently impresses a large number of physicians that they modify their use of the intervention in their patients. Although it is unlikely that authors would report in a typical article a large number of physician opinions on the clinical relevance of results for a specific trial, it is not unusual to summarize meaningful assessments of clinical importance that are of interest to practicing physicians. In the article by Zazzali et al., the difference in mean proportion of angioedema-free days with 300 mg omalizumab vs placebo over the 8 week (56 day) accounting period was $(96.1 - 88.2 = 7.9\%)$ realized in the ASTERIA I trial, followed by $(95.5 - 89.2 = 6.3\%)$ in ASTERIA II, and $(91.0 - 88.1 = 3.9\%)$ in GLACIAL. Thus, estimates of the realized gains in mean angioedema-free days in the three groups, respectively, after 56 days are approximately 4.4, 3.5, and 2.2 days. Assessed in this metric, clinical benefit does not seem nearly as relevant as statistical significance.

Clinical trials typically are conducted to determine which if any of two or more interventions is superior for managing a health issue that is of interest to the investigators. A widely used study plan for comparing interventions is the double masked, parallel arms design, where the arms are two independent groups of participants with one group receiving the active intervention and the other receiving the placebo. Because there usually is substantial variability in characteristics of potential study participants, including the way they may respond to intervention, participants are randomly assigned to the study arms. Superiority is commonly assessed as the intervention resulting in a statistically significant favorable mean response for the primary outcome. However, if the active intervention is actually equivalent to the placebo, as might be the case if unbeknownst to the investigators both groups were assigned to placebo, some random treatment assignments by chance may lead to a statistically significant between-group difference in favorable response. If in fact the intervention effects are identical and the analysis employs the 0.05 level of significance, one would expect the probability of a false conclusion to be 0.05. On the other hand, if the active intervention is investigated for its potential to have a beneficial effect, the ability of a statistical test to detect a specified minimum effect as statistically significant, depends on the magnitude of this effect where the probability of detection is usually higher with larger sample sizes. Irrespective of whether the active intervention is ultimately deemed statistically significant, the difference between outcome means may or may not be clinically relevant.

During the planning of a well-designed two arm controlled clinical trial, as an example, it is the statistician's role to estimate the minimum sample size required to provide sufficiently high power (probability) for detecting a specified minimum intervention effect on the primary outcome. It is the clinical investigator's responsibility to provide the statistician with an informed estimate of the minimum difference in response means between the intervention and control participants that should be observed in order to be clinically relevant. It is this minimum clinically relevant difference that is used as the specified intervention effect to be employed in estimating the minimum required sample size. Using this approach, the recommended sample size should be sufficiently large to provide a well-

powered study for detecting statistical significance for any study outcome that is equal to or greater than the investigator-defined clinically relevant threshold. Hence, once clinical relevance is realized, there should be an excellent chance the finding will also be statistically significant.

Results of clinical studies that compare the efficacious merits of two or more inventions in terms of meaningful outcomes often are reported as summary statistics such as means and standard deviations coupled with P-values that indicate statistical significance of comparative differences. All too often, however, an analytical presentation that includes a discussion of the clinical relevance of findings is not reported even though a stimulating dialog may substantially elevate the level of reader interest.

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