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Subgroups

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Clinical research has greatly expanded within the field of gastroenterology and, by nature, I am most familiar with those trials related to IBD. In many clinical trials the overall differences between active therapy and comparator (be it placebo or a different dose of the active therapy) are what many would consider to be rather modest. For example, in one trial, of which I was an investigator (*Am J Gastroenterol* [2005] 100: 2478–2485), the difference between the primary outcomes for patients with moderate ulcerative colitis who received mesalazine 2.4 g per day compared with mesalazine 4.8 g per day was 13% (59% versus 72%, $P = 0.036$). As a clinician, other factors, besides overall efficacy, need to be considered when making 'individualized' therapeutic decisions. These factors include potential risks, costs and optimizing adherence to and persistence with therapy. Given that 59% of patients will respond to the lower dose of mesalazine, I want to know who the 13% of patients are who will benefit from the increased dose.

Understanding that within the range of entry criteria for any given trial there are attempts to randomly allocate patients according to the factors predicted most likely to impact on outcomes (usually Table 1, baseline characteristics, in any trial), it is usually not possible to stratify patients according to all potential biases. Furthermore, most trials in patients with rare or chronic conditions are not able to enroll enough patients to generate sample sizes sufficient to provide statistical power for subgroup analyses. Hence, according to Kent and Hayward, "averaging effects across such different patients can give misleading results to physicians who care for individual, not average patients" (*JAMA* [2007] 298: 1209–1212). There are individuals within each treatment group that can benefit (or be harmed) to a greater or lesser degree than suggested by the average patient outcome in a trial.

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Take the example of the mesalazine trial: the entry criteria differed from many other clinical trials in patients with ulcerative colitis, by separating patients with 'mild' from those with 'moderate' disease. In two previous trials (*Aliment Pharmacol Ther* [2007] 26: 205–215), one with the same mesalazine formulation and the other with a similar formulation, the lower dose was actually found to be more efficacious in patients with mild disease. Thus, separating mild from moderate disease did make an overall difference, and helped form the hypothesis that a higher dose would be more effective in patients with moderate ulcerative colitis. However, other differences were found in the subgroups receiving the different formulations that were helpful for the selection of those patients who were more likely to benefit from the higher dose. These factors included having more 'refractory' disease (according to the duration of the flare-ups), prior use of corticosteroids and, of most relevance, lack of response to lower doses of mesalazine.

Kent and Hayward illustrate the use of risk-based analysis for trials where there may be substantial individual variation of the baseline risk as well as the absolute treatment benefits. They point out that when subgroup analyses are based on common and important risk variables, there is likely to be low statistical power to identify one variable at a time in subgroup analyses. In these situations with diseases such as IBD, in which clinical trial populations are an order of magnitude smaller than they are for common conditions, I look between trials for consistent effects in subgroups to try to elucidate commonalities that are lost because of insufficient patient numbers in individual trials.

SB Hanauer is Editor-in-Chief of Nature Clinical Practice Gastroenterology & Hepatology.

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