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Summary

Shaping immunity: Innovation trials in IBD

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The speaker outlined methodological innovations to improve IBD trial efficiency and inclusivity, emphasizing asymmetric randomization, Bayesian designs with historical controls, head-to-head comparisons, subtype-specific studies, and master protocols as strategies to address worsening recruitment challenges and reduce placebo exposure.

KEY POINTS

- Trial recruitment has become increasingly difficult, with centers now typically recruiting only one patient per year, a problem expected to worsen as more therapies become available.
- Asymmetric randomization (e.g., 1 in 5 chance of placebo) and Bayesian designs that incorporate historical placebo data can substantially reduce patient exposure to placebo while maintaining regulatory acceptability, as demonstrated in pediatric trials where such approaches enable drug approval.
- A secukinumab study in Crohn's disease used historical data from 670 placebo patients down-weighted to 20 subjects, requiring only 40 drug-treated and 20 placebo patients to demonstrate harm from IL-17 inhibition.
- Head-to-head trials remain rare in IBD but are the only definitive way to determine drug positioning; a recent IL-23 versus IL-12/23 inhibitor non-inferiority trial showed non-inferiority at week 24 and superiority at week 48, though the speaker cautioned that non-inferiority designs are vulnerable to bias from poor study conduct.
- Important disease subtypes—including pouchitis, perianal Crohn's disease, proctitis, and stoma-related complications—are systematically excluded from trials, leaving one-third or more of patients without evidence-based treatment options beyond TNF inhibitors.

– Master protocols that test multiple drugs across disease subtypes with shared control arms and outcome measures, already standard in oncology and pediatric IBD development, represent an efficient path forward, as does biologically rational combination therapy following the example of a study showing near-doubling of efficacy when combining IL-23 and TNF inhibition.

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