Placebo response and remission rates in ulcerative colitis clinical trials: Systematic review and meta-analysis

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Background: Defining the magnitude and modifiers of placebo rates in randomized controlled trials (RCTs) of ulcerative colitis (UC) are essential for the design and conduct of efficient trials and to optimize the detection of true drug-placebo differences. We conducted a contemporary meta-analysis of placebo response and remission rates in induction and maintenance phases of RCTs for active UC and assessed factors influencing these rates. We report the results of our analysis of the induction trials here.
Methods: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and the Cochrane IBG group specialized trials register were searched from inception to April 2014, without language restriction. Conference proceedings were hand searched between 2002-2014. Eligible studies were placebo-controlled trials of UC in adult patients which: (1) contained an induction and/or maintenance phase; (2) used the UCDAI (Mayo/Sutherland/Partial equivalent) as criteria for enrolment and assessment of response/remission; and (3) evaluated the efficacy of four major drug classes (steroids, aminosalicylates, immunosuppressives, biologics). Data were extracted independently in pairs and disagreements resolved with a third reviewer. Placebo rates for each outcome were pooled using a binomial-normal model for meta-analysis of proportions. Random-effects meta-regression was conducted to assess the effects of study-level characteristics on placebo response and remission rates.
Results: We identified 7,587 citations and 58 studies eligible for inclusion (48 induction, 10 maintenance). For induction trials, the pooled placebo remission (n=40) and response (n=43) rates were 10% (95% CI 7% to 13%; range 1% to 49%) and 33% (95% CI 28% to 38%; range 6% to 92%) respectively, both with highly significant heterogeneity ($P < 0.001$). Features associated with a lower placebo response in induction trials were greater disease duration prior to enrolment (33% for >5 yrs vs. 47% for ≤ 5 yrs), endoscopy subscore ≥2 at study entry (34% for score ≥2 vs. 46% for score ≥1) and requirement for improvements in endoscopy and bleeding subscores as outcome measures. Features associated with lower placebo remission rates were longer disease duration prior to enrolment (10% for >5 yrs vs. 19% for ≤ 5 yrs), endoscopy subscore ≥2 at study entry (11% for score ≥2 vs. 24% for score ≥1), the requirement for improvement in the endoscopy subscore from baseline as an outcome measure and publication date after 2005 (12% for ≤2005 vs. 9% > 2005). No difference in

placebo response or remission rates was observed when disease was classified as mild-moderate vs. moderate-severe at study entry, for a UCDAI cut-point ≥6 vs. <6, or duration of follow-up.
Conclusion: Lower placebo response and remission rates were observed in UC induction trials enrolling patients with more active disease defined by endoscopic subscore, rather than a higher composite UCDAI. This reinforces the importance of enrolling patients and assessing outcomes using objective markers of active disease.