To the Editor

We agree with Danese et al that prospective studies to evaluate the disease modifying action of anti-TNF drugs are overdue.1 As a counterpoint to this informative review, we would like to highlight some additional evidence for the role of thiopurines as disease modifying agents in Crohn’s disease. A cohort study by Magro et al supports a role for thiopurines in delaying phenotype progression from an inflammatory (B1) to a stricturing/penetrating (B2/B3) disease (Hazard Ratio 0.15, 95% CI 0.11-0.19).2 A meta-analysis of 10 population based, multicentre, and referral centre studies comprising 12,586 patients found thiopurine use was associated with a 40% reduction in risk of first intestinal surgery (Hazard Ratio 0.59, 95 % CI 0.48 – 0.73).3 Furthermore several studies also support a role for early thiopurine use particularly in young patients who are at greater risk of disease progression.4,5,6 RAPID was not powered to evaluate surgical endpoints but despite this found early thiopurine use reduced the need for perianal surgery.7 Whilst there was also a numerical reduction in the need for intestinal surgery with early treatment this did not reach significance, likely due to small numbers and the relatively short duration of the study, underscoring the need for studies conducted over several years. The evidence that anti-TNFs have a disease modifying action based on requirement for surgery or indices of bowel damage is actually quite limited. As yet, we do not have a trial to confirm mucosal healing reduces the long term risk of surgery and bowel damage. The quoted meta-analysis by Mao et al. comprised data on anti-TNFs from only the ACCENT and CHARM studies, which demonstrates the paucity of research in this area.8 A recent paediatric multicentre study showed a benefit of early anti-TNF use in reducing progression from inflammatory (B1) to penetrating (B3) phenotype but disappointingly failed to demonstrate any reduction in progression to stricturing disease (B2).9 There has been a concern that sustained thiopurine monotherapy may have an adverse safety profile compared to anti-TNFs with respect to risk of lymphoma, however recent evidence suggests the risks are in fact comparable.10 Thiopurines should not therefore be ruled out as disease modifying agents and should be integral to the design of future prospective studies of disease modification in Crohn’s disease.

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