Background

Management strategies and clinical outcomes vary substantially in patients newly diagnosed with Crohn's disease. We evaluated the clinical utility of a biomarker in patients randomised to either "top-down" or "accelerated step-up" therapy for newly-diagnosed, active Crohn's disease. Here we focus on endoscopic outcomes.

Methods

PROFILE (PRedicting Outcomes For Crohn's dIsease using a moLecular biomarker, ISRCTN 11808228) was an open-label, biomarker-stratified, randomised controlled trial. It enrolled adults with newly-diagnosed active Crohn's disease (Harvey Bradshaw Index ≥7 and elevated CRP or faecal calprotectin ≥200 ug/g, with active inflammation at endoscopy). Following biomarker testing patients were randomised to "top-down" (infliximab/immunomodulator) or "accelerated step-up" treatment stratified by: biomarker subgroup (termed IBDhi/IBDlo), endoscopic severity (mild/mod/severe) and extent (colonic/other). Ileo-colonoscopies were undertaken at baseline and week 48. Where possible they were video recorded, uploaded to Endoread® and centrally-read. The remainder were scored locally. The primary endpoint was sustained steroid and surgery-free remission to week 48 and the key secondary endpoint was endoscopic remission (absence of ulcers / SES-CD ulcer subscore=0) at week 48. Tertiary endoscopic endpoints included: endoscopic remission at week 48 using centrally-read videos only, endoscopic response at week 48 (≥50% improvement in SES-CD vs baseline), and deep endoscopic remission at week 48 (total SES-CD=0). The full analysis ('intention-to-treat') population was analysed.

Results

386 patients were randomised from Dec 2017 to Jan 2022. Median time from diagnosis to trial enrollment was 12 days (0-191). Primary outcome data were available for 379 eligible participants, with sustained steroid and surgery-free remission being more frequent in "top-down" compared to "accelerated step-up" (79% vs 15%, absolute difference 64%, 95% CI=57-72%, p<0.001). No biomarker-treatment interaction was observed. By week 48, of the 190 patients on "accelerated step-up" 85% were on immunomodulators and 41% had escalated to infliximab. Endoscopic remission at week 48 was assessed in 253 patients and was significantly greater in "top-down" compared to "accelerated step-up" (67% vs 44%, absolute difference 23%,

95% CI=11-36%, p<0.001). Respective proportions in endoscopic remission were 60% vs 45% where only the 166 centrally-read colonoscopies were considered. Endoscopic response at week 48 was more frequent in “top-down” compared to “accelerated step-up” (82% vs 63%), as was deep endoscopic remission (52% vs 37%).

Conclusion

“Top-down” treatment with combination infliximab and immunomodulator achieved substantially better clinical and endoscopic outcomes at week 48 compared to “accelerated step-up” therapy. The biomarker lacked clinical utility. “Top-down” should now be considered standard-of-care for patients with newly-diagnosed active Crohn’s disease.