

Commentary: IBD combination therapy - adalimumab plus immunosuppressants

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I read with interest the study by Reenaers *et al.*,¹ on adalimumab (ADA) in Crohn's disease, and whether co-therapy with immunosuppressants (IS) enhances the outcomes. The authors have mirrored the methodology of Sokol *et al.*² in an attempt to determine whether a benefit can be shown in using IS with ADA. This is a widely debated area, with only poorly controlled retrospective and post hoc data to guide us. Yet, it is of great clinical concern, as we wish to get the most out of biologics, but without unnecessary excess risk to patients.

As always, with retrospective observational studies, the devil is in the detail. Their data appear to show some benefit with combination (ADA + IS) therapy, but only for certain outcomes or in subsets of patients. Fewer semesters with flare were seen in those receiving both drugs at initiation of ADA, although only in those in whom combination therapy was continued; yet, the overall ADA failure rate was lower in those with combination therapy in the first trimester (regardless of whether IS was continued or ceased). Thus, we get intriguing hints, but not clear-cut proof, that combination therapy does give better efficacy when using ADA as appears to be the case for infliximab.²

However, what we do not know is how much the results were influenced by unreported factors. In particular, we do not know how many patients were IS-naïve at ADA onset, whether this was a selected group in some way (as weight is generally low considering the ~40% proportion of male subjects), whether any compliance/adherence assessment was made (as noncompliance would lead to convergence between groups) and what the power of the study was to detect various (negative) potential outcomes. In addition, we do not know much

about methotrexate use (route, dose), nor are we told whether there was a standard approach taken at each centre thus potentially confounding interpretation.

Allowing for these provisos, the data are interesting, and appear to suggest that in those in whom there are compelling reasons to use ADA, greatest efficacy, and smallest failure rate, results from early combination therapy. In addition, this approach may save money (with a lower rate of ADA weekly dosing), which is important as all healthcare funding is under pressure and therefore a costs analysis would be of interest using their data. What is not yet clear is whether ongoing combination is justified. As discussed by the authors, there is a small extra risk (infectious, malignant) of this approach, and until more robust data emerge, the choice between gaining the benefit or avoiding the risk must be taken after consideration of each case and discussion with the patient. It is doubtful whether we will ever get an RCT evaluating this issue; however, a discontinuation study as done for Infliximab³ may help clarify things further.

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Commentary: adherence and detection rates in colorectal cancer screening

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SIRS, I read with interest the meta-analysis comparing immunochemical faecal occult blood test (FIT), guaiac-based faecal occult blood test (g-FOBT) and endoscopy

in the detection rate for advanced neoplasia as well as the uptake to screening.¹ Certainly CRC screening remains a very much debated issue at the moment, not just in the more established countries but also in the developing world where it is just a matter of time before CRC screening takes off on a large scale.

The study addressed two very relevant questions comparing the two main methods of population screening at present. Hassan *et al.* found that perhaps not surprisingly, faecal occult blood tests have a higher rate of adherence compared with endoscopy; [optical colonoscopy(OC) and flexible sigmoidoscopy(FS)]. It would certainly be ideal to have more data comparing FS and OC, particularly if FS becomes more available in an outpatient setting. The most interesting finding was that endoscopy was superior in detecting advanced neoplasia even in an intention-to-treat (ITT) basis, i.e. taking into account the whole targeted population. This is presumably due to the false-negative rate of faecal occult blood tests and the low uptake of follow-up endoscopy in positive cases.

Despite these findings, many other considerations are to be taken into account when considering a large population-based screening program. The cost effectiveness of each strategy remains difficult to determine.² As the

studies in the meta-analysis were mainly in Western countries, the findings may not necessarily apply to other populations. Availability of endoscopy is a significant problem in the developing world. A study is underway comparing the Asia-Pacific Colorectal Screening score³ and FIT in the detection of advanced neoplasia. It would certainly be ideal if we could identify and target at risk individuals without an excessive endoscopic burden or the large scale use of FIT.

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Commentary: adherence and detection rates in colorectal cancer screening – author's reply

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We read with interest the letter by Hilmi *et al.* suggesting the integration of a patient-orientated score able to stratify asymptomatic subjects according to the risk of advanced neoplasia in colorectal cancer (CRC) screening policies.^{1, 2} In detail, the Asia-Pacific score is based on simple risk factors, such as age, sex, smoke and family history, and it is able to select a subgroup of asymptomatic ≥ 50 years subjects at higher risk of advanced neoplasia.²

This suggestion fits-in well-integrated with our observation of a higher efficacy of endoscopy over faecal tests in detecting advanced neoplasia in a primary screening set-

ting.³ It would appear reasonable, from a population perspective, to recommend a primary endoscopic approach to those ≥ 50 years subjects at higher risk of advanced neoplasia, such as those with a positive family history for CRC, whereas reserving the less effective, but also less costly, faecal tests to those at lower risk. Alternatively, in the case of limited economic/medical resources, CRC screening could be limited to those at higher risk, who may gain more benefit from the affordable investment.

However, there may be some uncertainty on the validity of such approach. First, despite the logistic regression score has been externally validated in Asian countries, it may be less effective when adopted in Western countries, requiring a country-specific validation prior to its application. Secondly, it would select a population at reduced prevalence of advanced neoplasia for faecal tests, potentially affecting their positive predictive values, when the same cut-off presently recommended would be maintained. As pointed out by the same authors,¹ only a comparative study between a score-based screening policy and a nonstratified approach may unveil the eventual superiority in terms of either efficacy or cost-effectiveness of the former option.