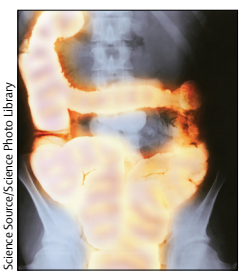
Infliximab or ciclosporin for acute severe ulcerative colitis?



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Acute severe ulcerative colitis remains one of the most challenging patient populations to treat. Despite significant therapeutic advances that have resulted in higher rates of remission and lower rates of surgery in patients with Crohn's disease and ulcerative colitis,[1] this improvement in outcomes is modest in those with severe disease requiring hospitalization, and rates of treatment response remain inadequate.[2] There exist two effective options for treating steroid refractory acute severe ulcerative colitis—ciclosporin and infliximab—both of which have individually established efficacy in the short and medium terms in rigorously conducted randomised controlled trials.[3,4] However until recently, there was little data on the comparative efficacy of both agents and choice was informed primarily by individual and institutional experience. In 2012, Laharie and colleagues[5] published the CYSIF trial, the first open-label randomised trial including 115 patients with steroid refractory acute severe ulcerative colitis, randomised to ciclosporin or infliximab. Rates of treatment failure and need for colectomy were similar in both groups at the end of 98 days. In *The Lancet Gastroenterology & Hepatology*, Williams and colleagues[6] present the results of a second trial—CONSTRUCT—similarly comparing infliximab and ciclosporin for acute steroid refractory colitis. Adopting a pragmatic design, the authors select a primary outcome of quality-adjusted survival, defined as the area under the curve described by the score from the Crohn's and Ulcerative Colitis Questionnaire till year 3. Secondary outcomes included changes in general quality of life (using EQ-5D and SF-12 scales), need for surgery, length of stay, and cost-effectiveness. 270 patients were recruited from 52 hospitals over the 3 years of the study (135 in each group) with the primary outcome being analysable in 242 patients. Over a median follow-up of 765 days, there was no difference in quality-adjusted survival between the two groups (p=0.63). For secondary outcomes, there was no difference in the proportion requiring colectomy (41% with infliximab *vs* 48% with cyclosporine, p=0.223) or in time to colectomy, and no differences were noted in adverse effects between both groups. The cost-effectiveness analysis showed significantly higher health-care costs with infliximab.

The novel pragmatic trial design and quality-adjusted survival as outcomes are directly relevant to real-world practice, where restoration of normal quality of life is an important goal of therapy in inflammatory bowel diseases, and cost-effectiveness of treatment strategies is an important determinant of position of various therapies in the treatment pyramid. However, a few aspects of the trial design leave some important key questions unanswered. Many of the endpoints we now recognize as important in inflammatory bowel diseases, such as mucosal healing and quantification of disease activity (through clinical or proxy measures such as calprotectin or C-reactive protein), are not included as outcomes in this trial.[7] Time to symptom response, an important outcome in the ill, hospitalised patient, is also not presented. The use of a quality-of-life measure as a primary outcome also raises questions about the accuracy of a measure to inform comparative efficacy that is affected not just by disease activity (the main treatment effect) but also substantially by co-morbidity (eg, depression or functional bowel disease), with the potential for both under and over-estimating treatment effects without an accompanying objective endpoint.

Both the CONSTRUCT trial[6] and the CYSIF trial[5] are landmark publications in a challenging patient population where there is dearth of high-quality comparative data. The equivalence of both treatments in the two studies provide reassurance to the treating clinician about comparability of ciclosporin and standard-dose infliximab, and that choice can continue to be determined by provider and institutional experience. However, factors in the trial design in both trials (inclusion of previously thiopurine-exposed patients in the CYSIF trial and lack of a defined post-hospitalisation treatment plan in the CONSTRUCT trial) preclude both from being the final answers to this question. It is possible that response rates may be higher with aggressive optimisation of care. With the recognition of substantial fecal loss of infliximab in acute severe ulcerative colitis,[8] it is possible that a more aggressive upfront infliximab strategy,[9] perhaps in conjunction with an immunomodulator, may improve the outcomes in infliximab-treated patients with acute severe ulcerative colitis. Furthermore,

whether the efficacy of ciclosporin can be amplified by maintenance treatment with agents such as vedolizumab remains to be established, having demonstrated promise in small cohorts.[10] Examination of personalised strategies guided by therapeutic drug monitoring is essential to further inform our practice and improve outcomes in this ill group of patients. In parallel, there is the need for clinical, genetic, and other -omics based tools that can a priori predict an individual patient's likelihood of response to either therapy, allowing the treating physician to precisely match the patient to the treatment with highest likelihood of benefit.

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I declare no competing interests.

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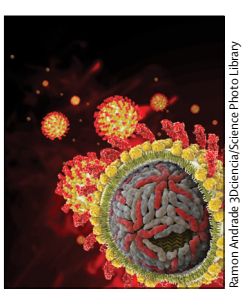
Genotype 4 and the global challenge of hepatitis C treatment

The therapeutic revolution in therapy for hepatitis C virus (HCV) seen in recent years has left some crucial gaps, with genotypes other than genotype 1 having either less evidence of efficacy or proven lower efficacy. Even with the potential availability of drugs with cure rates approaching 100%, it is uncertain how many populations across the world will have the finance and the health system organisation to access these therapies.[1]

Genotype 4 HCV accounts for an estimated 8% of HCV infections worldwide, most of which are in Egypt (where genotype 4a predominates) and surrounding countries of north, central, and east Africa.[2] Although fairly uncommon in the USA and northern Europe, genotype 4 is seen increasingly as a result of migration from high-burden regions.

The Articles in *The Lancet Gastroenterology & Hepatology* by Tarik Asselah and colleagues[3] and Imam Waked and colleagues[4] provide data to help treat patients with genotype 4. Previous studies have shown that ombitasvir, paritaprevir, and ritonavir plus ribavirin achieves high cure rates in HCV genotype 4 infection, but doubts about the optimum regimen have persisted, mainly because of the small number of patients with HCV genotype 4 infection treated in the registration trials. One area of uncertainty was the duration of treatment needed in patients with advanced fibrotic liver disease, in whom a longer regimen than the standard 12 weeks has been suggested to improve response rates. In AGATE-I, Asselah and colleagues[3] studied patients with HCV genotype 4 infection and cirrhosis who had not previously been treated with direct-acting antivirals, comparing 12 weeks with 16 weeks of ombitasvir, paritaprevir, and ritonavir once daily with weight-based ribavirin. AGATE-I was done in 120 participants in North America and Europe (64 [53%] with genotype 4a infection; 60 [50%] with treatment experience). Cure rates were very high and equivalent in both groups (57 [97%] of 59 in the 12-week treatment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