

The great wall of inflammatory bowel disease

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In Ming dynasty China, the emperors built a Great Wall. The essential purpose for this engineering masterpiece was defense against marauders from the Eurasian Steppe. But the flip side of having such a building was that chambers deep within the wall could be used to punish Chinese convicts.

Seven centuries later, we are building a great wall to help protect our patients living with inflammatory bowel disease (IBD). In lieu of quartered troops, we have new therapeutic options; in place of watch towers, we have advanced diagnostic and surveillance modalities. The aim of our wall is to protect patients so that they can live the best quality of life possible, but at the same time, we must be sure to guard against trapping them within this same wall, causing them harm through over-treatment and unnecessary medicalisation.

For keeping a lookout for danger, intestinal ultrasound (IUS) is an attractive option; it is safe, quick, cheap, accurate and shows good patient acceptability. Recent ECCO-ESGAR guidelines recommend IUS to assess disease activity and complications in Crohn's disease (CD),^[1] and we are now seeing IUS outcomes as endpoints in randomized controlled trials (RCTs).^[2] However, concerns remain around reproducibility and reliability of IUS assessment, particularly outside of a small number of centers of global renown, and in patients with higher body mass index (BMI). Additionally, the lack of a validated score to be used in IBD remains a challenge.^[3]

In this issue of SJG, Ahmed and colleagues provide valuable “real world” data regarding the correlation between IUS and magnetic resonance enterography (MRE) when used to assess patients with CD at an expert center in Saudi Arabia. Using a validated scoring system for MRE and a simple definition of ultrasonic evidence of disease activity, the authors demonstrate good correlation between the two modalities.^[4] IUS appeared to have limited utility in the assessment of proximal small bowel disease, in keeping with a previous systematic review of the role of US in CD.^[5] Areas of uncertainty in using IUS in CD remain to be explored, including the role in diagnosis, assessment of complications such as penetrating diseases and presence

of abscess, and predicting postoperative recurrence.^[6] But with this demonstration of the utility of the performance of IUS in Saudi Arabia, attention now turns to challenges of access and training. The availability of courses provided to gastroenterologists can hopefully be of benefit.^[7]

Another area of the wall of IBD still under construction relates to identification of the optimal strategy for postoperative management of patients with CD. Recent years have seen a plethora of well performed studies highlighting the importance of careful patient risk stratification and monitoring in this challenging context, but the question of just which strategy we should be using in our clinics remains unanswered. To address this, it is important to define both risks and the effectiveness of interventions, in the population under treatment. In this issue of the journal, Azzam and colleagues, report the rates of postoperative endoscopic recurrence in patients with CD.^[8] Their cohort was selected for the presence of factors previously reported as associated with moderate to high risk of disease recurrence and importantly, the majority started either an immunomodulator and/or anti-TNF therapy within 3 months of surgery. Encouragingly, three-quarters of the patients were in endoscopic remission at 24 months.

The findings of Azzam and colleagues are of interest within the context of previous RCTs in this area. The PREVENT trial^[9] assessed both clinical and endoscopic recurrence in similar moderate/high risk patients undergoing surgical resection and demonstrated that whilst the use of infliximab did not significantly impact clinical outcomes at the relatively early time point of 1 year, already a significant difference was apparent in the rates of endoscopic recurrence. In the POCER trial,^[10] patients at high risk of disease recurrence were treated with post-operative thiopurines, but thiopurine-intolerant patients received adalimumab therapy. Rates of endoscopic recurrence at 6 months were significantly lower in adalimumab treated patients than those given a thiopurine. In both PREVENT and POCER the presence of penetrating disease was used as a marker of disease risk. Indeed, a previous meta-analysis of 13 studies confirmed that penetrating disease is one of the predictors of recurrence when compared to non-penetrating behavior.^[11] It is remarkable, therefore, that Azzam and colleagues found that in their cohort, patients with penetrating disease were less likely to exhibit

post-operative recurrence. This perhaps reflects clinician preference for early use of anti-TNF therapy in these patients, again underlining that appropriate selection of patients for treatment escalation can improve outcomes even in patients with high-risk phenotypes. However, for patients with a history of intolerance or failure of treatment with anti-TNF therapy, there is a lack of RCT level evidence. Indirect evidence comes from propensity score analyses, suggesting vedolizumab to be inferior to anti-TNF inhibitors agents,^[12] and ustekinumab to be more effective than azathioprine in preventing recurrence.^[13]

Finally, we come to the paper of Abdulla and colleagues from Bahrain, who shed light on which patients are at risk of imprisonment within the wall of treatment failure.^[14] Using a decade of data from a single center, the authors identify 101 patients starting biologic therapy, of whom 14% discontinued treatment within 6 months. On multivariate analysis, the sole predictor of early treatment discontinuation was increasing age. Although the authors of the present study were not able to examine pharmacokinetic predictors of treatment failure, in other cohort studies, low drug levels at the end of the induction period have been associated with treatment failure.^[15] The prediction of response (and non-response) to available biologics can be expected to remain an area of topical research and debate.^[16]

Of course, with aggressive approaches to treatment escalation we should seek to advance understanding of where treatment de-escalation can and should occur, as another means of avoiding harm to our patients. Until very recently, the STORI trial,^[17] was the landmark study in this area, reporting 1 year relapse rates approaching 50% for patients discontinuing infliximab therapy (but remaining on an immunomodulator) for CD in clinical remission. Patients in STORI with biochemical and hematological evidence of disease activity were more likely to relapse, and in recent years the question has arisen as to whether patients in endoscopic remission might be better able to discontinue treatment. A recent RCT presented in abstract form suggests that clinical remission rates for patients with CD remain around only 50% 1 year after discontinuing infliximab, even in patients in combined clinical, endoscopic and biochemical remission.^[18] However, another very recently presented RCT suggested that for patients with CD treated with a combination of infliximab and immunomodulator therapy, discontinuation of the immunomodulator is indeed possible, with equivalent clinical and pharmacokinetic outcomes to those patients continuing combination therapy.^[19] Again, disease relapse occurred within 2 years in approximately 50% of patients

discontinuing anti-TNF therapy. Nevertheless, prompt restart of anti-TNF therapy in those who discontinued the drug could lead to disease recapture in a large majority of patients, resulting in similar periods of time spent in remission between different treatment strategies.

Ultimately, the Ming dynasty collapsed, in part due to a failure to nurture the very people the Great Wall was built to protect. For those contributing to the construction of our contemporary defenses against IBD, the reminder is prescient – we have to continue to develop our arsenal and our systems of surveillance, but we must always do so mindful of the wellbeing and support of those we are seeking to assist.

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Access this article online	
Quick Response Code:	Website:
	www.saudijgastro.com
	DOI:
	10.4103/sjg.sjg_102_22

How to cite this article: Al Sulais E, Raine T. The great wall of inflammatory bowel disease. *Saudi J Gastroenterol* 2022;3:165-7.