application of the FTRD, even if, unlike the technique proposed by Meier and colleagues [10], the volume of the lesion is bigger than the cap, which increases the risk of incomplete resection. Prospective studies are needed to further evaluate the efficacy, safety, rate of recurrence and long-term outcomes of this novel resection technique.

Conflict of interest

None declared.

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Low-dose biologics to treat inflammatory bowel disease. Ready for prime time?

Dear Editor

I read with interest the paper by Pouillon et al. on adalimumab dose de-scalation in patients with inflammatory bowel disease (IBD) [1]. The authors show that in approximately 2/3 of patients with both ulcerative colitis (UC) and Crohn's disease (CD) adalimumab dose can be successfully de-escalated from the typical every 2 week schedule to every 3 week schedule. They report that inactive disease at magnetic resonance imaging and/or endoscopy in the year before adalimumab dose de-escalation significantly decreased the risk of failure.

This is an excellent study — with results consistent with those previously published by Van Steenbergen et al. [2] and with those of our own earlier dose titration study in patients with post-operative relapse of CD [3]. In the latter study patients were treated prophylactically with infliximab 5 mg/Kg after surgery to prevent disease relapse. After three years of treatment – with patients in complete clinical, endoscopic and biochemical remission – infliximab was stopped and a colonoscopy performed immediately before the next scheduled infusion. In patients showing endoscopic recurrence infliximab was immediately re-started at a dose of 1 mg/Kg. After six months the patients underwent colonoscopy which showed persistence of inflammation in all. The infliximab dose was then escalated to 2 mg/Kg which was insufficient to re-induce endoscopic remission in most patients at six months. Therefore, the dose was increased to 3 mg/Kg — which restored and maintained mucosal integrity in all patients in the long term (1 year). A subgroup of these patients was later tested for infliximab trough levels (TL) and antibodies to infliximab (ATI) [4]. Although most patients had infliximab TL lower than recommended therapeutic values [5] and a number of them had low-titer ATI they all continued to remain in full endoscopic and clinical remission after 3 years on 3 mg/Kg infliximab — i.e. on a dose 40% less than standard, a reduction similar to that reported by Pouillon et al. [1]. Adalimumab TL were measured in a minority of patients in the Pouillon study so it is unclear whether they impacted on the risk of failure. Per authors' discussion, absent TL in patients in remission have been reported to be associated with low risk of relapse in those stopping therapy. However it is worth noting that patients successfully managed with adalimumab every three weeks were those with minimal or no inflammation at time of dose de-escalation. Hence those patients had a low disease burden just like patients with initial post-operative relapse after surgery. Taken together these observations do suggest that disease burden is a more rationale and practical target of disease management than TL [6]. As such it is possible that some patients (bearing a very low disease burden) can be managed with an even greater dose de-escalation. In our own study, mucosal integrity in a few patients could be reestablished with infliximab 2 mg/Kg — a reduction of 60% of the standard dose [3]. However that study was small and it is unclear whether such dose reduction could be used to manage CD patients who have never undergone surgery. Another interesting issue raised by this study is whether patients who were maintained in remission on adalimumab every 3 weeks could have been managed with a lower dose/longer interval from the outset. Clearly this can only be speculated upon. It is indeed possible that low disease burden patients (including those in the Pouillon study) might respond well to low initial medication doses. Early dose finding studies with anti-TNF agents in IBD patients were conducted in long standing disease [7] — when any medical therapy may be only marginally effective. Hence, it is possible that only "high" doses – which became the standard recommended doses – might have shown efficacy in those early studies. Later, we learned to treat IBD (especially CD) with anti-TNF agents at an earlier time — when patients are more responsive [8]. Hence, doses lower than those currently recommended might indeed be effective in a number of patients even at disease presentation. By contrast, if only standard doses are effective at presentation the persistence of remission after dose de-escalation must find different explanations. One possible explanation is that induction of remission with biologics might reset the immune system and re-establish partial immunological tolerance. This has

been the subject of intense studies in other disciplines but it is an hypothesis that has never been definitely proven. Another possible explanation is that remission in these patients might depend on the specific timing of dose reduction relatively to the individual natural course of IBD. Landmark studies dating back more than 20 years have shown that in the majority (two thirds) of IBD patients – independently of treatment – the disease course fluctuate between years in relapse and years in remission with waves of at least 2 years duration [9]. Hence, in most patients the disease appears to proceed with a course a poussées. When such patients are treated with anti-TNF agents during a phase of flare this will result, in most cases, in improvement of inflammation and clinical symptoms and induction of remission. If remission is deep and maintained for a long enough time it is possible that – at dose de-escalation – the disease might remain in remission since timing may now coincide with the naturally occurring phase of quiescence [10].

Ideally – as also suggested by the study of Pouillon et al. – patients subjected to dose de-escalation should be carefully monitored for disease relapse, well before symptoms take place. In our own study we showed that stool markers of inflammation such as lactoferrin and calprotectin could be used for the purpose [2]. A prospective, dedicated study should confirm those initial observations.

In conclusion, prospective and larger studies should confirm the current preliminary findings including those by Pouillon et al. However, biologic dose de-escalation or therapeutic interval extension – a concept well known in rheumatoid arthritis and other immune mediated diseases and already empirically adopted by many gastroenterologists – is slowly finding its way into mainstream clinical practice. An additional, important option for the long term management of IBD patients.

Conflict of interest

D. Sorrentino has been a consultant for AbbVie, Centocor, Ferring, Giuliani, Hoffmann-LaRoche Janssen, LabTech, MSD, Schering-Plough, Medtronic. This manuscript was not supported by the pharmaceutical industry.

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The crucial need of internal control validation in the normalization of circulating microRNAs

To the Editor

We read with great interest the results indicating that miR-125b-5p levels became elevated with disease progression in the serum of patients with chronic hepatitis B and that its high expression may serve as a predictor for poor outcomes in this disease, as reported by Tao et al. [1]. MicroRNA expressions were normalized to U6 as a reference control in this study, but its reliability needs to be verified.

Reference-control selection crucially affect the biological interpretation of data, and, due to the divergent expression of reference controls in various diseases, they cannot simply be transposed from one study to another without validation. First, it is noteworthy that the authors did not validate U6 as a reference control with a constant expression in their experimental cohort. In addition, several studies have shown that U6 is not an appropriate reference control for hepatitis B and other liver disorders. For example, Zhu et al. evaluated five microRNAs and U6 to identify suitable reference genes for RT-qPCR analysis of circulating microRNAs in patients with hepatitis B. They found that U6 had the largest variation in expression (10 cycles) between patients with hepatitis B and healthy controls and that U6 was differently expressed between the two groups (p-value < 0.05). The results of geNorm and NormFinder analysis indicated that U6 was the least stable reference control among the candidates [2].

Other studies have shown that U6 is not a reliable reference control in liver disorders. Li et al. investigated the potential reliability of U6 in liver carcinoma and found that the Ct values for U6 were significantly different in the serum of pre- and post-operative patients (p-value < 0.001). Using four algorithms (geNorm, NormFinder, BestKeeper, and the comparative ΔCt method), they demonstrated that U6 has the highest stability value and thus is the least stable reference control among the 10 candidates [3]. Similarly, Tang et al. demonstrated that U6 is not a suitable reference control for normalizing the expression of circulating microRNAs in various hepatic disorders. They also showed that using U6 as a reference control produced significant analysis bias and led to erroneous results [4]. By analyzing U6 levels in the serum of 64 patients with liver fibrosis and 44 healthy controls, Benz et al. found that the serum levels of U6 had a high interindividual variability in patients with liver fibrosis compared to a spiked-in RNA (p-value < 0.001), and they also reported that U6 levels are downregulated in the sera of patients

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