Dialing Back M for Monoclonal: Successful De-escalation of Dose-Intensified Anti-tumor Necrosis Factor Therapy in Inflammatory Bowel Disease

Wei Ting Soo^{1,2} · Samuel P. Costello^{1,2} · Robert V. Bryant^{1,2}

Accepted: 4 March 2021 / Published online: 25 March 2021

© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2021

Anti-tumor necrosis factor (TNF) therapy helps to achieve disease remission and improve long-term outcomes in patients with inflammatory bowel disease (IBD) [1]. With an expanding therapeutic armamentarium, modern management of IBD incorporates a treat-to-target approach, aiming for resolution of clinical symptoms and amelioration of objective inflammation [2]. In order to achieve these ambitious targets, the use of therapeutic drug monitoring (TDM) to guide proactive and rational escalation of anti-TNF therapy has become a cornerstone of IBD care [1, 3]. Among patients who experience secondary loss of response to anti-TNF therapy, dose intensification recaptures response in a proportion of patients [4]. Nevertheless, once remission has been achieved, appropriate strategies for de-escalation of dose-intensified anti-TNF therapy are less well established. Dose de-escalation is important, both from a patient safety standpoint in order to avoid risks associated with potentially unnecessary immunosuppression and from a health economic and administrative burden perspective.

In a single-center retrospective study, Little et al. [5] report on outcomes of de-escalation of 25 patients (20 Crohn's disease and 5 ulcerative colitis) treated with dose-intensified anti-TNF therapy (infliximab 5 mg/kg 6 weekly or adalimumab 40 mg weekly) for 7–27 months. Prior to de-escalation, cases were discussed at a virtual IBD multidisciplinary meeting including IBD specialists, IBD nurse practitioners, and a pharmacist. Remission was confirmed objectively using biomarkers (fecal calprotectin and C-reactive protein), gastrointestinal ultrasound (GIUS), and/

or endoscopy. At 12 months following de-escalation, 64% (16/25) were successfully maintained on the de-escalated dose. At a median of 6 months, 36% (9/25) of patients experienced a disease flare requiring either re-escalation of anti-TNF therapy (6 patients) or enrolment into a clinical trial (3 patients). Remission was recaptured in all patients who required dose re-intensification. There was no difference in baseline biomarker activity between successes and failures, nor any significance differences among anti-TNF levels at the time of de-escalation or failure. While a small study, these findings suggest that anti-TNF de-escalation among a group having undergone dose intensification maintained clinical effectiveness in majority of the patients after 12 months, with no new safety concerns.

To date, there are few studies demonstrating success of anti-TNF therapy de-escalation following dose intensification. Similar to the study by Little et al., prior small studies have shown similar rates of successful de-escalation of dose-intensified anti-TNF therapy (63–68%) [6, 7]. Chaparro et al. [6] recorded that 16/24 (68%) patients with Crohn's disease maintained remission at 12 months after de-intensification of anti-TNF therapy. The authors did not identify any factor predictive of disease relapse but noted that perianal Crohn's disease was associated with a higher risk of relapse ($p=0.06$). Baert et al. [7] assessed the durability of dose de-escalation in an adalimumab-intensified cohort with Crohn's disease ($n=75$) after 3 months of remission. The success rate of de-escalation of dose-intensified therapy was 63% and again no predictive factor was identified, likely due to small study numbers. While lack of power also precluded Little et al. from identifying baseline predictors of successful de-escalation, a prior study published in abstract form was able to identify risk factors for failure, including the absence of concurrent immunomodulator therapy, a structuring or fistulizing Crohn's disease phenotype, previous IBD surgery, and extra-intestinal manifestations [8]. Of note, all of the

✉ Robert V. Bryant
Robert.bryant@sa.gov.au

¹ IBD Service, Department of Gastroenterology, The Queen Elizabeth Hospital, 28 Woodville Rd., Woodville South, SA 5011, Australia

² School of Medicine, Faculty of Health Sciences, University of Adelaide, North Terrace, Adelaide, SA 5000, Australia

patients in the study by Little et al. received concomitant immunomodulator therapy.

While Little et al. report on de-escalation of intensified anti-TNF therapy, it is prudent to learn from prior studies evaluating anti-TNF withdrawal in IBD [6, 7]. One important factor is the objective confirmation of remission of inflammation prior to considering therapy de-escalation [9]. Endoscopic mucosal healing is associated with lower rates of disease complications (hospitalization, surgery), as well as more durable disease remission during anti-TNF therapy and lower rates of relapse when anti-TNF therapy is withdrawn [2]. The STORI trial identified lack of mucosal healing as a primary risk factor for disease relapse following infliximab withdrawal in patients receiving combination therapy [10, 11]. Moreover, surrogates for active inflammatory disease including white blood cell count $> 5 \cdot 10^9/L$ and hemoglobin < 12.5 g/dL at the time of IFX withdrawal are predictive of relapse [4, 10, 11]. Demographic and lifestyle factors, along with disease course and chronology, also need to be taken into account, including young age at diagnosis, active smoking, extensive disease, perianal and structuring Crohn's disease, previous need for surgery, unsuccessful immunomodulator therapy, or frequent relapses [4, 10].

A novel aspect to the study by Little et al. is the contribution of a virtual multidisciplinary team (MDT) clinic toward facilitating clinical decision-making. As previously published by the authors, this conference, conducted on a monthly basis [12], facilitates integration of TDM with objective evaluation of disease activity in order to better inform therapeutic decisions. Non-invasive markers of disease activity, both fecal calprotectin and gastrointestinal ultrasound, were used to closely monitor disease and tailor therapy, reducing the cost, risk, and unpleasantness associated with frequent endoscopy. A similar proactive approach to 'tight' disease control improved rates of mucosal healing and prevented long-term major complications such as hospitalization or surgery in real-world studies [13, 14]. Despite close monitoring of drug levels, anti-TNF levels prior to de-escalation were not predictive of failure in the study by Little et al., which may be reflective of lack of power. Previous studies have shown that TDM may help to identify suitable patients for drug de-escalation, as patients with low or undetectable drug level appear to have lower risk of disease relapse after drug de-escalation [4], likely to reflect that remission has been achieved in the absence of therapeutic drug level [4].

Any consideration for de-escalation of therapy in IBD must be tailored, taking into account a patient's particular beliefs and wishes and timing of the decision relative to major life-events as well as work and personal life. A detailed discussion of the risks of de-escalation and likely success of retreatment is pertinent to inform decision-making. De-escalation in patients who have undergone multiple

prior surgeries must be viewed with caution, given the risk of short bowel syndrome if further surgery is required due to relapse. Optimum surveillance intervals post-de-escalation have not been well defined in prospective studies. Since subclinical disease recurrence may occur as a harbinger of a clinical flare, monitoring clinical symptoms alone is inadequate [9]. Proactive and intensive monitoring within the 12 months post-withdrawal is imperative given that risk of relapse is the highest within the first year [9]. Little et al. demonstrate the success of this approach, showing that with close monitoring and early detection of recurrent inflammation, appropriate action led to 100% success with dose re-intensification.

There is a clear appetite to identify de-escalation strategies in IBD so as to maintain remission while using rational and appropriate medication regimens. Clinician fear and inertia can hamper appropriate de-escalation in the setting of sustained deep remission. Though the study by Little et al. provides hope that de-escalation of dose-intensified anti-TNF therapy can be undertaken successfully and safely in IBD with close monitoring and dose re-intensification as necessary, further high-quality prospective studies with large cohorts and protracted follow-up are required to better characterize outcomes of de-escalation strategies as well as to inform selection of optimal candidates for dose de-escalation.

References

1. Mitrev N, Vande Casteele N, Seow CH et al. Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases. *Aliment Pharmacol Ther* 2017;46:1037–1053
2. Peyrin-Biroulet L, Sandborn W, Sands BE et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol* 2015;110:1324–1338
3. Ricciuto A, Dhaliwal J, Walters TD, Griffiths AM, Church PC. Clinical outcomes with therapeutic drug monitoring in inflammatory bowel disease: a systematic review with meta-analysis. *J Crohns Colitis* 2018;12:1302–1315
4. Chapman TP, Gomes CF, Louis E, Colombel JF, Satsangi J. De-escalation of immunomodulator and biological therapy in inflammatory bowel disease. *Lancet Gastroenterol Hepatol* 2020;5:63–79
5. Little RDC, IE; Ward MG; Sparrow MP. De-escalation from dose-intensified anti-TNF therapy is successful in the majority of IBD patients at 12 months. *Dig Dis Sci*. (Epub ahead of print). <https://doi.org/10.1007/s10620-021-06937-z>.
6. Chaparro M, Barreiro-de Acosta M, García-Planella E et al. Outcome after a dose "de-intensification" strategy with anti-TNF drugs in patients with Crohn's disease. *Gastroenterol Hepatol* 2016;39:255–260
7. Baert F, Glorieux E, Reenaers C et al. Adalimumab dose escalation and dose de-escalation success rate and predictors in

- a large national cohort of Crohn's patients. *J Crohns Colitis* 2013;7:154–160
8. Benítez JM, Barreiro-de Acosta M, Chaparro M et al. P327 Evolution after a “de-intensification” strategy with anti-TNF therapy in patients with inflammatory bowel disease in clinical remission: multicenter study. *J Crohns Colitis* 2017;11:S243–S243
 9. Doherty G, Katsanos KH, Burisch J et al. European Crohn's and colitis organisation topical review on treatment withdrawal ['exit strategies'] in inflammatory bowel disease. *J Crohns Colitis* 2018;12:17–31
 10. Torres J, Boyapati RK, Kennedy NA, Louis E, Colombel JF, Satsangi J. Systematic review of effects of withdrawal of immunomodulators or biologic agents from patients with inflammatory bowel disease. *Gastroenterology* 2015;149:1716–1730
 11. Louis E, Mary JY, Vernier-Massouille G et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology* 2012;142:63–70.e65
 12. Srinivasan A, van Langenberg DR, Little RD, Sparrow MP, De Cruz P, Ward MG. A virtual clinic increases anti-TNF dose intensification success via a treat-to-target approach compared with standard outpatient care in Crohn's disease. *Aliment Pharmacol Ther* 2020;51:1342–1352
 13. Colombel JF, Panaccione R, Bossuyt P et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet* 2018;390:2779–2789
 14. Khanna R, Bressler B, Levesque BG et al. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. *Lancet* 2015;386:1825–1834

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.