Moving Towards a New Era: Algorithms in the Management of Crohn's Disease

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Successful, cost-effective, and efficient management of disease treatment is the driving factor behind many scientific studies, particularly for diseases such as Crohn's disease (CD), a disorder of unknown aetiology characterised by transmural inflammation of the gastrointestinal tract.[1] With no cure available, treatment paradigms have adhered to symptom control and remission; however, within the last 10 years the focus has shifted towards 'mucosal healing': the prevention of structural damage to the intestinal wall. Consequently, to achieve these new treatment goals more aggressive treatment and earlier use of immunosuppressants and biologics are required.[2] Some patients benefit from such early aggressive treatment; others, however, incur the disadvantages of immunosuppression, of which includes the increased risk of severe infections. As a result, a major question today is whether a 'top-down' or a 'step-up' treatment approach is better suited for CD management.

Top-down treatment starts with a combination of biological and immunosuppressant agents and is de-escalated if necessary, whereas step-up treatment commences with weaker topical steroids followed by a step up to systemic steroids and, if necessary, subsequent immunosuppression and biologic use.[2] Patient diversity, however, does not permit an all-encompassing treatment, and as we are gearing towards an era of precision medicine, over and undertreatment must be avoided at all cost, prompting the need of an algorithm delineating the best patient treatment path.

Top-down is proposed as an alternative approach to classical step-up treatment because some studies have shown that immunosuppression therapy is effective in the management of CD; it is, however, seen as overtreatment by several. In a therapy update session on CD at the United European Gastroenterology (UEG) Week 2019, Dr Gerhard Rogler, University of Zurich, Zurich, Switzerland, expressed his views on the algorithm of CD management. The session opened with data from a network meta-analysis on the comparative effectiveness of agents for the induction of remission in CD, demonstrating that high doses of aminosalicylates (5-ASA), budesonide, and corticosteroids are effective, contrary to earlier guidelines which stated that 5-ASA are not effective and should not be considered during therapy, fuelling the notion that step-up is still relevant.[3]

If 5-ASA are as effective as corticosteroids, then why have they been trivialised? This may be attributable to the lack of scientific evidence regarding the efficacy of 5-ASA in CD patients. The Epi-IBD cohort, a prospective European population-based cohort, revealed that the

majority of the patients who received 5-ASA required mild or no treatment during follow-up and experienced a quiescent disease course. This establishes that patient stratification at baseline to prevent not only undertreatment, but, more importantly, overtreatment is pivotal, with Dr Rogler stating: "Top-down for everybody with CD is overtreatment." In support of this, he presented a diagram exemplifying a potential algorithm to support the management of CD. Displaying that in all population cohorts of inflammatory bowel disease, 40% have mild CD and are sufficiently treated with 5-ASA or step-up , 40% have moderate CD requiring accelerated step-up treatment with some requiring biological therapy, while only 20% have severe disease symptoms and should receive top-down targeted treatment.[3] Before proceeding to talk about ways to optimise current treatment paradigms, he emphasised that he personally believes "the slogan T2T (treat-to-target) is M4M (marketing for morons)," expressing his opposing view on everyone receiving a top-down treatment.

Knowing that budesonide is as effective as systemic steroids, despite it only having a 10% bioavailability, is a driving reason to optimise standard therapy and avoid the side effects associated with systemic steroid use. Another class of drugs that require optimisation are immunosuppressants, including thiopurines. Current guidelines recommend 2.0–2.5 mg/kg/day of azathioprine (AZA) or 1.0-1.5 mg/kg/day of mercaptopurine (6-MP) for the management of CD, but these are not efficacious for all patients.[3] Dose-response treatment appears to be the next step forward according to a meta-analysis, showcasing a lower odds-ratio to achieve treatment response. Data also revealed that when AZA treatment is not tolerated, there is a potential to switch to the lower dosage treatment of 6-MP because over half of the patients who did not tolerate AZA tolerated 6-MP. To determine how to best optimise treatment, Dr Rogler presented an algorithm involving measuring 6-thioguanine nucleotide (6-TGN) and metabolite mercaptopurine (MMP). In this model, low or absent 6-TGN and MMP demonstrates non-adhering patients who could benefit from counselling. Low 6-TGN or low to normal MMP may signify underdosing and identify patients who may benefit from a dose increase, and patients that are thiopurine refractory should be recommended another drug.

When biological treatment is necessary, what should our first line biologic be? Dr Rogler revealed that infliximab is the most potent agent to induce clinical remission in moderate-to-severe CD, but it loses efficacy when maintaining clinical remission. Whereas, adalimumab has efficacy in the opposite manner, having a lower rate of inducing remission but is better at maintenance. The European Crohn's and Colitis Organisation (ECCO) e-Guide, a collection of algorithms based on the ECCO guidelines, provides an algorithm for the optimisation of anti-TNF therapy in CD. It emphasises that regular assessment is vital, and that after relapse therapy should be revaluated and optimised, rather than switching the drug.

In summary, Dr Rogler presented the 'Swiss Algorithm', a combination of all algorithms providing a potential new structure to treating CD. He expressed his concerns regarding the therapy target of mucosal healing, which has been shown to not be achievable in most patients; therefore, is this goal suitable? In some instances, mucosal healing has been demonstrated post-surgery, yet the first-line treatment choice after surgery is still unclear. A Cochrane network analysis on interventions for maintenance of surgically induced remission in CD has shown that 5-ASA is the only significantly effective drug in the post operation situation. Combined with the fact that 5-ASA is also a drug that can be used as the first step in mild-to-moderate CD, and is as effective as corticosteroids, we are left questioning whether we have jumped the gun with top-down treatment and should step up our therapy algorithm with step-up treatment.

References

1. BMJ Best Practice. Crohn's disease. 2019. Available at: https://bestpractice.bmj.com/topics/en-gb/42. Last accessed: 19 November 2019.
2. Rogler G. Top-down or Step-Up Treatment in Crohn's Disease? Dig Dis. 2013;31(1):83-90.
3. United European Gastroenterology (UEG). Crohn's disease. 2019. Available at: https://www.ueg.eu/education/document/crohn-s-disease/211464/. Last accessed: 20 November 2019.