Escalated Anti-TNF Dosing in Crohn's disease - Criteria for use

There is local agreement that anti-TNF therapy (intravenous infliximab/adalimumab) can be escalated above standard escalated doses within the agreed criteria for use below to achieve therapeutic levels if this is thought more clinically appropriate than switching to other agents.

The agreed escalated dosing's are:

- Intravenous infliximab: 10mg/kg every four/six weeks
- Adalimumab 80mg weekly

The chosen dose will depend on results of therapeutic drug monitoring.

The IBD specialist teams recognise that off-label use of licensed biologics may be used before switching to licensed biologics for this select patient cohort as there is strong evidence to support targeting therapeutic drugs levels with improved patient outcomes.

Criteria for use

All of the following criteria must be met for use of off-label dosing of IV infliximab or s/c adalimumab:

- Ongoing active disease despite escalated infliximab/adalimumab dosing within current recommendations (standard escalated doses are currently infliximab 10mg/kg every 8 weeks or adalimumab 40mg weekly)
- More evidence to support use of anti-TNF over other agents due to disease behaviour/location (e.g. perianal Crohn's disease, extensive stricturing small bowel disease and/or upper GI disease)
- On concomitant oral immunomodulation unless medical contraindications to such therapies
- A consensus decision to treat the patient with escalated dosing of IV infliximab or s/c adalimumab is made and documented at the biologics multidisciplinary team meeting
- Drug levels that demonstrate there are no antibody developments (GSTfT assay does not show presence of antibodies if drug level detectable)
- Patients will be escalated to this higher dosing regimen if there is evidence of active disease with infliximab or adalimumab levels of less than 10 micrograms/ml with no anti-drug antibodies present
- Patients will be assessed at 3 months and if there is no evidence of response (as defined on the next page under stopping criteria) to this higher regimen they will be switched to another agent
- Patients who show response at 3 months will continue on this higher regimen to 6 months. At this point if they are in remission they will be de-escalated to a standard dosing regimen if drug levels allow
- Target drug levels according to table 1.

Table 1. Adalimumab and infliximab concentrations to target[1]

Drug concentration and time	Target level (micrograms/ml)
Infliximab concentration to target with active disease	>10
Infliximab concentration to target during maintenance therapy with disease in remission	>5
Adalimumab concentration to target with active disease	>10
Adalimumab concentration to target during maintenance with disease in remission	>5

Response

- A 6 month assessment of disease activity after initiation will be reviewed to determine if continuation of treatment is appropriate after escalation taking into account disease activity score, biochemistry (including C-reactive protein and faecal calprotectin) and endoscopic assessment or cross sectional imaging
- Improvement in grading from severe to moderate disease is an acceptable response. If there is no improvement after six months discontinuation of therapy should be considered.
- Failure of response to treatment defined as lack of improvement in these parameters (as defined by physician's global assessment grading) despite escalated dose and/or achievement of target drug levels.

Stopping Criteria

- If there is no improvement after six months discontinuation of therapy should be considered

Safety considerations

- Current evidence suggests that higher levels are not associated with additional adverse effects.

Suggested approach to monitoring implementation and outcomes

- A database of these patients will be maintained to track patient outcomes, safety and adherence to include criteria
- Patients will be monitored closely at fixed intervals, as outlined above
- Data and usage will be presented at the IBD group

References

1. Cheifetz, Adam S.; Abreu, Maria T.; Afif, Waqqas ; Cross, Raymond K. MD, ; Dubinsky, Marla C. ; Loftus, Edward V. Jr; Osterman, Mark T. MD, ; Saroufim, Ariana; Siegel, Corey A. MD,; Yarur, Andres J.; Melmed, Gil Y.; Papamichael, Konstantinos DM. A Comprehensive Literature Review and Expert Consensus Statement on Therapeutic Drug Monitoring of Biologics in Inflammatory Bowel Disease, The American Journal of Gastroenterology: August 13, 2021 - Volume - Issue - 10.14309/ajg.0000000000001396