NHS Greater Glasgow and Clyde

Scottish Biologic Therapeutic Drug Monitoring Service –Gastroenterology Guidance

The purpose of this document is to provide advice and information for users of the Scottish Biologic Therapeutic Drug Monitoring Service.

1. INTRODUCTION

Anti-tumour necrosis factor α (anti- TNFα) biologic drugs have proven efficacy in the treatment of inflammatory bowel disease (IBD). Examples of drugs in this class include infliximab, adalimumab and golimumab. Newer classes of non anti-TNFα biologic drugs such as vedolizumab (α4β7-integrin inhibitor) and ustekinumab (anti-interleukin 12/23) have penetrated the market recently increasing the treatment options available to clinicians.

These agents have greatly improved clinical care for individuals with IBD but treatment outcomes are not universally favourable. Among infliximab and adalimumab treated cohorts primary non-response occurs in up to 30% and secondary loss of response in up to 46% (1,2). In addition the prescribing costs associated with biologic drug use have risen sharply. In 2016 almost £50 million was spent in NHS Scotland on infliximab and adalimumab alone (3). Ensuring safe and effective biologic prescribing is a key priority within NHS Scotland and the Effective Prescribing Programme (EPP) Biologics group was created to develop strategies to optimise use of these drugs. Patent expiry of originator infliximab in 2015 saw the introduction of less expensive biosimilar infliximab preparations and managed switching programmes were successfully implemented in many health boards (4,5). In 2018 biosimilar adalimumab will launch in NHS Scotland and it is anticipated that further opportunities for biosimilar switching may arise.

Therapeutic Drug Monitoring (TDM) of the most commonly used anti-TNF biologic medicines, infliximab and adalimumab, has emerged as a helpful tool for optimising the use and effectiveness of these drugs and can identify selected patients in whom it may be possible to reduce or even withdraw anti-TNF biologic treatment without adversely affecting clinical outcomes (6). Biologic TDM involves the measurement of serum drug and anti-drug antibody levels. In 2016 the EPP Biologics group submitted a successful business case to the Board Chief Executives seeking funding for a Scottish Biologic TDM service to measure infliximab and adalimumab drug and anti-drug antibody levels for gastroenterology and rheumatology.

2. SCOTTISH BIOLOGIC THERAPEUTIC DRUG MONITORING SERVICE

The Scottish TDM service launched in January 2018, located at the Clinical Biochemistry Department, Queen Elizabeth University Hospital, Glasgow. It offers IBD services across Scotland the opportunity to perform drug and anti-drug antibody levels for all infliximab and adalimumab formulations. The service has been commissioned by the National Services Division of NHS Scotland and is centrally funded. Importantly this means there is no direct cost for clinician or clinical service for TDM testing.

3. TDM TESTING GUIDANCE

There are a growing number of circumstances in which TDM testing can aid clinical decision making. It is important to consider what clinical question the test is intended to answer before the test is performed.

3.1 WHEN TO PERFORM TDM TESTING - TIMING

DRUG	WHEN TO TEST
Infliximab	**Immediately prior to next infusion**
Adalimumab	**As close to next dose as possible**

TDM testing is intended to measure trough drug levels and therefore is usually performed immediately prior to the next scheduled biologic treatment. In some circumstances non-trough testing may be appropriate. Drug levels and anti-drug antibody levels are routinely performed for all samples sent for TDM testing. A single blood sample in a yellow-top tube is required for TDM testing.

Local clinical biochemistry and immunology labs should automatically send all TDM test requests from within NHS Scotland to the clinical biochemistry laboratory at QEUH. Results will return to the requester in the usual way according to local lab policies. The target turnaround time for sample results is 2 weeks. In the near future it is hoped that host Health Boards which run Trakcare based lab requesting will offer an automated requesting process via Trakcare. **In the interim paper TDM requests should be completed and sent with specimens.**

3.1.1 INFLIXIMAB TDM REQUEST FORM

3.1.2 ADALIMUMAB TDM REQUEST FORM

3.2 WHEN TO PERFORM TDM TESTING - SETTING

TDM testing has an established role in several clinical scenarios. Additional benefits in other clinical situations continue to be identified.

Reactive TDM - performed when treatment failure is developing e.g. in secondary loss of response, drug intolerance or insfusion reaction. Can be undertaken during induction if primary non response (PNR) is suspected.

Proactive TDM - performed in patients who have achieved a satisfactory clinical response with the aim of optimising therapy to prevent future flares and loss of response.

Conventionally a reactive approach to TDM has been adopted. Recent publications have demonstrated potential benefits for proactive TDM testing, coupled to a "treat-to-target" approach to disease management (7-10).

The Scottish TDM service can be used for reactive and/or proactive testing.

The clinical settings in which TDM should be considered appropriate include, but are not limited to, the following situations:-

- **Infliximab**
  - **REACTIVE**
    - Primary non response
    - Loss of response/flare
  - **PROACTIVE**
    - End of induction (usually week 14)
    - Maintenance treatment -every 24 weeks (usually every 3 doses)
    - After dose adjustment

- **Adalimumab**
  - **REACTIVE**
    - Primary non response
    - Loss of response/flare
  - **PROACTIVE**
    - End of induction
    - Maintenance treatment– every 24 weeks (usually every 12 doses)
    - After dose adjustment

There is no clear evidence demonstrating optimal timing of reactive TDM in a patient failing to respond to therapy during induction. For responders to infliximab, end of induction proactive testing

at week 14 is recommended (11,12,13). For adalimumab the optimum timing for proactive end of induction testing has not been established. TDM testing as early as week 4 has been shown to predict persistence of response at week 12 and 52 (14,15). A recent study prospectively measuring adalimumab drug and anti-drug antibodies at week 10-12 found a positive association between end of induction trough levels and clinical response (16).

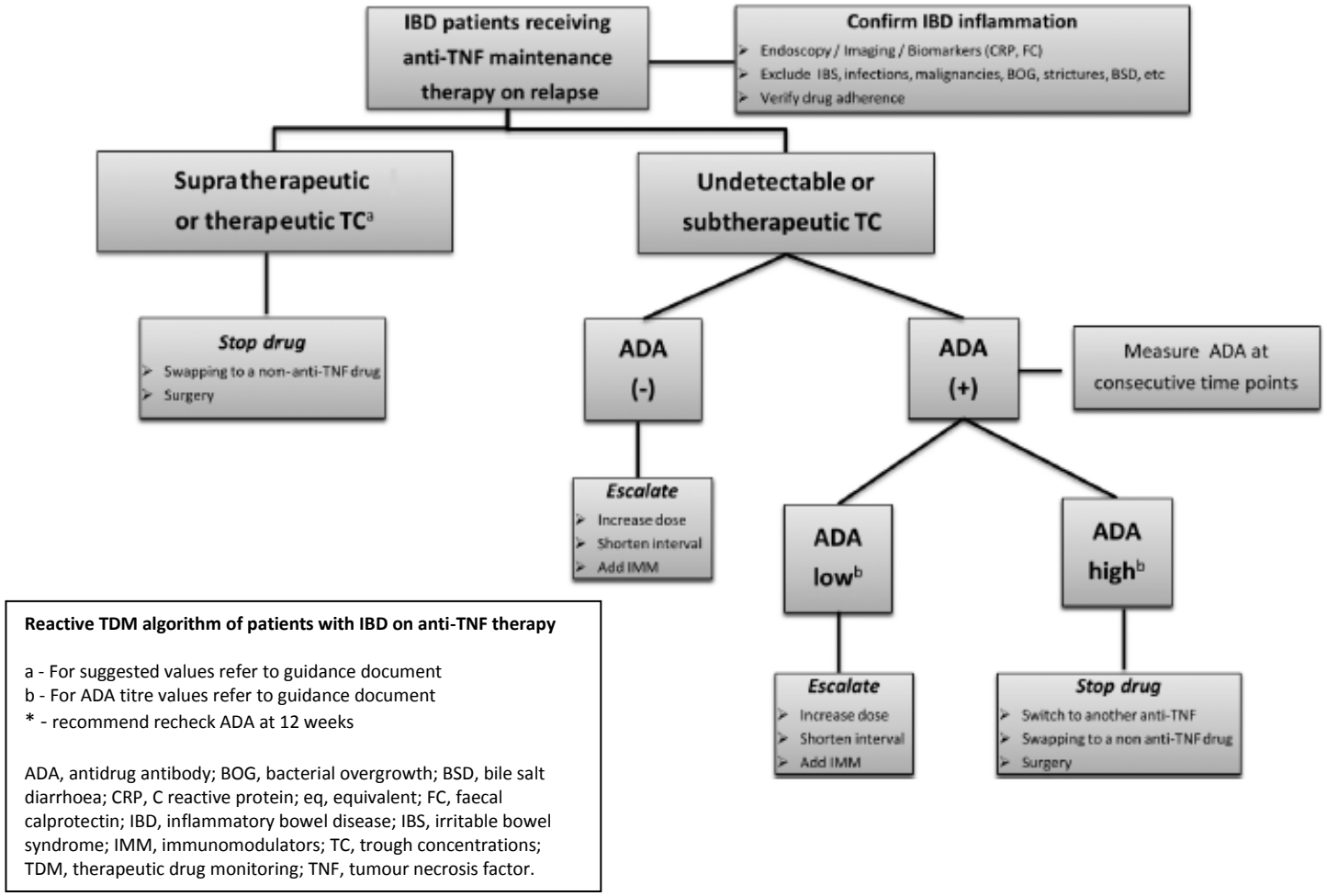
Other clinical situations which may merit TDM testing include:-

- **Prior to a planned drug holiday**
- **After a drug holiday before recommencing therapy (anti-drug antibody levels only)**
- **Following withdrawal of concomitant immunosuppressive therapy**
- **Early primary non-response**
- **Presence of low or moderate levels of anti-drug antibody**
- **Possible non-compliance**

TDM results should be interpreted alongside other relevant clinical findings and assessments to aid clinical decision making. Evidence for changing clinical management based on TDM results alone has not been established. Several algorithms for interpreting TDM results have been published.

The following algorithms published in Frontline Gastroenterology are provided as guidance to help interpret TDM results for both REactive and PROactive based testing strategies (17).

3.3 REACTIVE TDM TESTING ALGORITHM



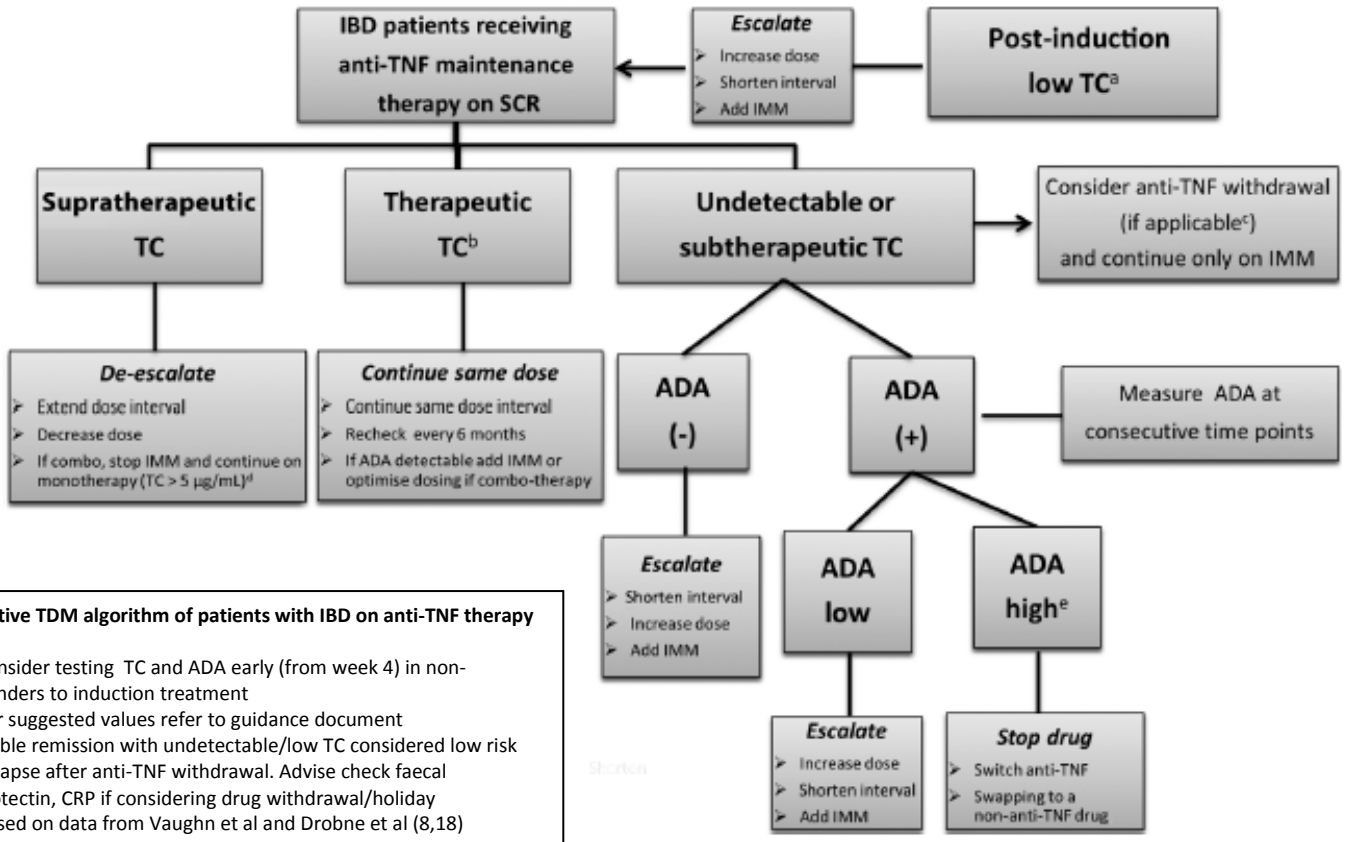
Reactive TDM algorithm of patients with IBD on anti-TNF therapy

a - For suggested values refer to guidance document
b - For ADA titre values refer to guidance document
* - recommend recheck ADA at 12 weeks

ADA, antidrug antibody; BOG, bacterial overgrowth; BSD, bile salt diarrhoea; CRP, C reactive protein; eq, equivalent; FC, faecal calprotectin; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IMM, immunomodulators; TC, trough concentrations; TDM, therapeutic drug monitoring; TNF, tumour necrosis factor.

Figure 1 – (with modification) from Papamichael K, Cheifetz AS. Frontline Gastroenterology 2016;0:1–12. doi:10.1136/flgastro-2016-100685

3.4 PROACTIVE TDM TESTING ALGORTITHM



Proactive TDM algorithm of patients with IBD on anti-TNF therapy

a - Consider testing TC and ADA early (from week 4) in non-responders to induction treatment
b - For suggested values refer to guidance document
c - Stable remission with undetectable/low TC considered low risk for relapse after anti-TNF withdrawal. Advise check faecal calprotectin, CRP if considering drug withdrawal/holiday
d - Based on data from Vaughn et al and Drobne et al (8,18)
e - For ADA titre values refer to guidance document

ADA, antidrug antibody; IBD, inflammatory bowel disease; IMM, immunomodulators; SCR, sustained clinical remission; TC, trough concentration; TDM, therapeutic drug monitoring; TNF, tumour necrosis factor.

Figure 2 - (with modification) from Papamichael K, Cheifetz AS. Frontline Gastroenterology 2016;0:1–12. doi:10.1136/flgastro-2016-100685

4. LABORATORY SERVICE

The laboratory at QEUH uses ELISA based assays manufactured to measure drug and anti-drug antibodies.

The following analytes can be tested:

Infliximab	Drug Levels
	Total and free anti-drug antibody levels
Adalimumab	Drug levels
	Total and free anti-drug antibody levels

4.1 DRUG LEVEL TESTING

The working ranges of the assays for drug levels are:

Analyte	Lower limit of measurement	Upper limit of measurement	Units
Adalimumab	<0.4	>12	ug/mL
Infliximab	<0.3	>14	ug/mL

The recommended target trough concentrations for drug levels in luminal IBD are:

Analyte	Lower end of target range*	Upper end of target range*	Units
Adalimumab	5	10	ug/mL
Infliximab	3	8	ug/mL

* In some clinical scenarios, e.g. active Perianal Crohn's disease, trough drug levels higher than the specified upper end of target range may be desirable.

The evidence base for these therapeutic ranges is reviewed in the recently published article by Mitrev at al - Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases (19).

4.2 ANTI-DRUG ANTIBODY LEVEL TESTING

The interpretation of anti-drug antibody results is complex. Quantitative evaluation of anti-drug antibodies is considered to be more beneficial than qualitative evaluation (19). Some assays measure total anti-drug antibody levels whilst others measure only free anti-drug antibody titres therefore anti-drug antibody result interpretation is assay specific.

From September 2018 the service will **no longer perform an anti-drug antibody assay when the drug level is supratherapeutic . Where the drug levels is above the therapeutic range, the report will state that a "Total ADA test is not required".**

The Scottish TDM service will continue to provide a total anti-drug antibody titre for all specimens with an undetectable drug level, subtherapeutic drug level or therapeutic drug level. Reflex free antibody testing will be performed as an additional test when the total anti-drug antibody result is positive. The working range of the anti-drug antibody assays are:

Analyte	Lower limit of measurement	Upper limit of measurement	Units
TOTAL anti-adalimumab drug antibodies	<10	>200	AU/mL
FREE anti-adalimumab drug antibodies	<10	>400	AU/mL
TOTAL anti-infliximab drug antibodies	<10	>400	AU/mL
FREE anti-infliximab drug antibodies	<5	>288	AU/mL

AU/ml = arbitrary units per millilitre

Low titre TOTAL anti-drug antibodies may be transient and can disappear with repeat testing. Furthermore low-titre TOTAL anti-drug antibodies can sometimes be reversed with dose intensification and do not appear to reduce the probability of clinical response compared to patients with undetectable antibodies (19,20)

The following table provides advice on interpretation of total anti-drug antibody results from the Scottish TDM service lab:

TOTAL Anti-drug antibody Titre (AU/ml)	Interpretation of Result
<10	NEGATIVE
>10 <40	Low titre positive
>40 <200	Moderate titre positive
>200	High titre positive

5. SERVICE OUTCOMES AND EVALUATIONS

The Scottish TDM service is subject to continuous cycles of audit and evaluation as part of the terms and conditions of the service contract. Clinical advice is subject to change in light of these evaluations. It is anticipated that further drug assays (e.g. Vedolizumab, Ustekinumab) will be added to the service and there may be an opportunity to undertake TDM research on newer biologic drugs and assays. Contributions to service audit, evaluation and research from clinicians, IBD nurses and trainees across the country is welcome as is any feedback or comments on the published guidance.

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