Evidence for de-escalating (or continuing) infliximab or adalimumab in patients with Crohn’s Disease who are currently responding to escalated doses

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Background
NICE (TA 187 and CG152) guidance recommends infliximab or adalimumab as options for management of adults with severe active Crohn’s Disease (CD), whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments) or who are intolerant of or have contraindications to conventional therapy. NICE recommend that infliximab or adalimumab should be given as a ‘planned course of treatment’ until treatment failure occurs (this includes the need for surgery) or until 12 months after the start of treatment, whichever is shorter. NICE suggest that CD be re-assessed on a case-by-case basis to determine whether ongoing treatment remains clinically appropriate.

A significant proportion of patients (40-60%) who initially responded to infliximab or adalimumab will lose response or experience attenuated response. Reasons for this are unclear but it may be due to the development of neutralising antibodies and increased disease activity. (1-3) In this difficult to treat population of patients with refractory CD, dose escalation of infliximab or adalimumab is a useful, and often successful, therapeutic strategy. (4-9) NICE recommendations allow for dose escalation for patients in whom there has been a loss of response to maintenance therapy. However, guidance is not clear on the optimal method and duration of dose escalation, nor on which patients are most likely to benefit from it or which patients will maintain response or remission following de-escalation once a secondary response has been established. (10-13) Long term use of escalated doses of infliximab or adalimumab may be associated with potential safety risks, such as infection, and increased risk of malignancy as well as having a significant cost burden. (14)

Therefore it is important to appraise the current evidence which may offer insight into the optimal duration of escalated regimens of these drugs in patients with refractory CD. It is also important to evaluate attempts at de-escalation (from escalated dosing regimens) and to try and identify patient groups in whom de-escalation (or stopping) of treatment is likely to be successful.

Problem and questions to be addressed
Commissioning groups are being asked to fund requests for adalimumab escalated from 40mg every other week to 40mg every week or for infliximab from 5mg/kg every 8 weeks to 10mg/kg every 8 weeks or 5mg/kg every 4 or 6 weeks. Funding decisions in this area are problematic due to considerable uncertainty about the clinical and cost effectiveness of escalated doses of both drugs over periods longer than 1 year. There is also uncertainty about the strength of the evidence for the use of infliximab/adalimumab at escalated doses for CD. Questions remain regarding optimal treatment strategies that are not covered by the NICE recommendations. This review summarises the available evidence to address these following questions:

Summary: when and how should de-escalation occur (following sustained good response to an escalated dose of infliximab or adalimumab) in patients with refractory CD?
There is little guidance or reliable evidence on when and how to de-escalate doses of adalimumab or infliximab safely and successfully whilst maintaining symptom control. Further studies are still needed to evaluate this. Where attempts at de-escalation have been described, they generally involve a change in regimen directly from the escalated regimen back to the maintenance regimen. The British Society of Gastroenterology Guidelines recommend that if response is regained, it may then be possible to decrease back to the previous maintenance dose but they do not detail when this can be done.(10)

The largest relevant study was a retrospective cohort study in 720 patients with CD who were using escalated doses of adalimumab. De-escalation was attempted in 54% of patients after a median duration of 3 months and was successful in 63% of these patients. (4) Other smaller studies (n=100) reported similar findings and overall, the data suggest that around half (51-64%) of all patients may de-escalate safely and successfully after several months (between 3 and 12 months) of using escalated dosing regimens. (2;4;6;15) Follow up of patients after de-escalation was usually limited, or not fully reported, but there is some evidence of durable response post de-escalation. One study (n=55) suggested that response may last for over a year after de-escalation, but the number of patients followed up to a year was very small (n=15). (2) A very small prospective study (n=14) found that at 322 days (10.7 months), around half (57%) of patients in whom de-escalation of adalimumab after 3 months was successful, remained in response. (16) A further two retrospective cohort studies were specifically designed to characterise the median duration of response from infliximab or adalimumab dose escalation. This was reported as...
The commissioning policy on de-escalation should be worked up in conjunction with expert gastroenterologists, but from the data in the literature, it is theoretically possible to have a reasonably standardised approach to time points for reviewing patients on de-escalated dosing regimens. Though these data are limited and subject to wide interpatient variability, it may be pragmatic to review continued use of escalated dosing regimens at, or within, the timeframes reported in the studies (the largest study reviewed escalated dosing regimens at 3 months post escalation). It is not appropriate to apply a standard indiscriminate de-escalation policy and ultimately all decisions would need to be made on a case by case basis. When the decision is made to de-escalate therapy, the evidence and the British Society of Gastroenterology Guidelines suggest decreasing back to the previous maintenance dose.

**Summary: what is the evidence for continuing escalated doses for longer than a year, particularly where there has been a response?**

A high proportion of patients with CD regain response when their doses of their infliximab or adalimumab are escalated. For some patients who have regained response, clinicians would consider subsequent de-escalation as described above. However, there may be other patients using escalated doses of infliximab or adalimumab whom clinicians may be reluctant to de-escalate, perhaps because their condition is less stable. Of these patients, some will maintain response for a year or even longer on escalated dosing regimens of infliximab or adalimumab. However, the risk of relapse needs to be carefully balanced with potential long term safety risks as well as cost-effectiveness and there are no guidelines to inform clinicians or commissioners on the optimal duration of using these escalated dosing regimens. An interrogation of the published literature found little reliable data upon which to inform these difficult decisions.

Two retrospective cohort studies (n<100) reported the median duration of regained response from infliximab or adalimumab dose escalation as being approximately 9 to 16 months respectively with broad interpatient variability. (3;17) Five published retrospective studies and two prospective studies were not specifically designed to evaluate durability of response, but included subgroups of patients who continued (or likely to have continued) use of escalated doses for more than a year. The largest study included 720 patients but the others were small (n=33 to 108). (1;4;6;18-20) There was no detail in the papers on whether patients who responded (or were in remission) after their doses of infliximab or adalimumab were escalated were still responding, in remission and/or tolerating the escalated dosing regimens at follow up. Therefore, we can only assume that there may have been some patients using (and probably responding to and tolerating) escalated doses of adalimumab to the end of follow up. The longest follow up period was 5 years in one of the small studies (n=55) but only 20% of patients were still using (or potentially using) escalated dosing regimens at 5 years (2).

Further long term safety and cost-effectiveness data for use of escalated dosing regimens of infliximab or adalimumab are needed. Limitations of the studies include their inherent lack of detail in, heterogeneity between them and their retrospective design with inherent risk of recall bias. Most of the studies were not designed to assess durability of escalated dosing regimens and were limited further by their small sample sizes (typically <100 patients) and relatively short follow up periods. Therefore estimates of durability are imprecise and not sufficient to inform the optimal duration of using escalated dosing regimens of infliximab or adalimumab.

As suggested, the commissioning policy on de-escalation should be worked up in conjunction with expert gastroenterologists but there are some, albeit limited, data to support extended use of escalated dosing regimens of infliximab or adalimumab for up to 5 years. However, the average time to loss of response to escalated dosing is not well characterised and varies considerably, so decisions about how long to continue with escalated dosing must be made on a case by case basis.

**Summary: whether there are any criteria (such as therapeutic drug monitoring parameters) that could be used to inform decision making about which patients with CD can successfully be de-escalated?**

The British Society of Gastroenterology Guidelines recommend that if response is regained, it may then be possible to decrease back to the previous maintenance dose (de-escalate) but they do not suggest which patients would remain in response and which ones can then be successfully de-escalated. (10)

There were no published studies designed specifically to identify predictors of successful de-escalation. Hence we cannot suggest any robust predictors of response to successful de-escalation. There were several published studies in which the identification of predictors to successful dose escalation was considered as a secondary outcome measure. (2;17;21-28) From these we were able to tentatively suggest some factors which may be helpful to consider when trying to predict response to dose escalation. However, these factors are derived from studies which are not designed for this purpose and they are not fully applicable to the problem because they relate to the likelihood of regaining response to anti-TNF agents via dose escalation rather than the likelihood of sustaining already re-captured response. Furthermore, these speculations are based on our analysis of the available...
The factors which may be helpful to consider when trying to predict response to dose escalation (which may potentially be useful to help identify patients who might de-escalate successfully) are:

- **CRP levels**: Elevated CRP levels at the time of dose escalation may predict a poor response to dose escalation according to one study. (17) In another study, however, CRP levels at the time of relapse was not predictive of response to dose escalation.(26) Because these data are conflicting, use of CRP levels to predict response to dose escalation should be undertaken with caution and not in isolation.

- **Corticosteroid use**: One study reported that prolonged and continuous use of corticosteroids (>6 months) in the 5 years prior to dose escalation predicted those patients less likely to achieve durable remission following dose escalation. (2) This may reflect that patients with very refractory, steroid dependant, CD are less likely to respond to medical therapy (including escalated dosing regimens of infliximab or adalimumab) and will eventually need to be managed surgically. Not all other studies which looked at corticosteroid use identify it as a predictor though.

- **Serum drug trough levels**: Several studies suggest that having adequate serum trough levels of infliximab or adalimumab at the time of dose escalation predicts poor response to dose escalation. (23;24;26-29) Data are somewhat conflicting on this; one study reported that clinical response to dose escalation was not accurately predicted by infliximab trough serum concentrations at the time of escalation(25) whilst two studies suggest that in patients with adequate serum trough drug levels, switching to a different drug class is more likely to achieve a durable response over dose escalation, particularly if anti-drug antibodies are detected.(26;28) Data from analyses in Europe and the USA suggest that monitoring serum trough levels of infliximab or adalimumab to help decide whether to dose-escalate or not is a potentially cost effective strategy with similar clinical outcomes as a conventional approach. (33-35)

However there are no published cost-effective analyses based on the UK healthcare system specifically. Overall, it seems that if serum drug trough levels are low at the time of dose escalation, patients may benefit from dose escalation. In patients who have adequate serum drug trough levels when dose escalation is being considered, dose escalation is unlikely to lead to a clinical response and switching to an alternative drug or drug class (e.g. to vedolizumab – for details on switching to vedolizumab see the main body of the document) should be considered instead. It stands to reason that patients with adequate serum drug trough levels, who are not clinically responding to the escalated dose, are unlikely to develop a response with prolonged use of escalating dosing. For patients who are clinically responding to escalated dosing regimens and whose levels serum drug trough levels are adequate, the decision to decide if and when to de-escalate or stop therapy would need to be based on clinical parameters.

- **Antibody titres**: Two papers provided evidence that patients with detectable antibody titres (regardless of drug serum trough levels) are less likely to respond to dose escalation. They suggested that having detectable antibody titres is predictive of failure of anti-TNF agents as a class and switching to another drug class should be considered. (26;28) In contrast, another paper suggested that clinical response to dose escalation can occur in patients with detectable drug antibody titres. (29) Overall, the relationship between the presence of antidrug antibodies and clinical response to dose escalation is not completely understood and so the reliability of this as a predictor of response is limited.

- **Clinical parameters**: It has been suggested that de-escalation of treatment should be considered in patients with high risk of severe adverse events and low relapse risk (patients in deep remission) on a case by case basis. (14)

Though these tentative data may be helpful to consider when predicting response to dose escalation, any commissioning policy on de-escalation should be worked up in conjunction with expert gastroenterologists, who may consider the above factors (and possibly other factors) when providing advice.

The involvement of patients in decision making, particularly where they have concerns regarding relapse where doses are to be de-escalated or treatment discontinuation considered.

We found no papers which focussed on the involvement of patients in decision making regarding de-escalation of their infliximab or adalimumab dosing. The NICE guidance recommends discussing with patients (and/or their parents or carers if appropriate), options for managing their disease when they are in remission, including both no treatment and continued treatment. The discussion should include the risk of inflammatory exacerbations (with and without drug treatment) and the potential side effects of long term drug treatment. The person's views should be documented within their notes.(13)
Methodology

A. Search of relevant guidance (2015)
NICE, British Society of Gastroenterologists Guidelines, European Crohn's and Colitis Organisation (ECCO), Cochrane, SMC, SIGN, AWMSG, NICE Evidence, NETAG, Google.

B. Literature search of Medline and Embase (2015)

- EMTREE terms (CROHN DISEASE/dm, dr, dt, th) and (DRUG DOSE ESCALATION/ OR DRUG DOSE INCREASE/ OR DRUG DOSE INTENSIFICATION/ or DRUG DOSE EFFECT RELATIONSHIP/ or DRUG DOSE REDUCTION/) and (*INFliximAb/ or *AdalimumAb/) and (DRUG TREATMENT FAILURE/ or TREATMENT FAILURE/ or MAINTENANCE DOSAGE/ or MAINTENANCE DOSE/ or MAINTENANCE DRUG DOSE/ or MAINTENANCE THERAPY/ or FOLLOW UP/ or LONG TERM CARE/ or FOLLOW UP STUDY/ or FOLLOW-UP STUDIES/)
  - EMTREE terms: (*INFliximAb/ or *AdalimumAb/) and ([DRUG DOSE ESCALATION/ or DRUG DOSE/ OR DRUG DOSE INCREASE/ or DRUG DOSE INTENSIFICATION/ or DRUG DOSE REDUCTION/] or [DRUG MONITORING/ or MONITORING/ or DRUG BLOOD LEVEL/ or BLOOD LEVEL/ or DRUG CONCENTRATION/]) and CROHN DISEASE/).
  - EMTREE terms: (*DRUG MONITORING/ or *DRUG BLOOD LEVEL/ or *DRUG CONCENTRATION/) and (*CROHN DISEASE/) and (INFliximAB/ or ADalimumAB/)
  - MeSH terms (DRUG MONITORING/) and (CROHN DISEASE/) ad (ANTIBODIES, MONOCLONAL, HUMANIZED/ or exp ANTIBODIES, MONOCLONAL/ or infliximab.ti,ab or adalimumab.ti,ab)
  - MeSH terms (Dose-Response Relationship, Drug) and (Crohn Disease OR Crohn's disease) and (adalimumab or infliximab)
  - MeSH terms: (inflxiHam.ab or adipalimumab.ab) and (*CROHN DISEASE/dt) and (TREATMENT FAILURE/ or TREATMENT OUTCOME or DOSE-RESPONSE RELATIONSHIP, DRUG/ or TIME FACTORS)

Abstracts were used to identify relevant studies

Rationale

When and how de-escalation should occur (following a sustained good response to an escalated dose to infliximab or adalimumab) in patients with refractory CD?

Very few published studies report on de-escalation of therapy (following a good response). Patients in large registration studies (CHARM, CLASSIC II, ACCENT I and II) who needed dose escalation continued on escalated doses for the duration (usually to the 12 month endpoint) or they would drop out of the study due to relapse. The high dropout rates in the ACCENT studies suggest that that even response to escalated doses lacks durability and wanes within a year in around 50% of patients. (5,9) Some patients, however, do have a durable response to dose escalation but we do not know exactly how durable this response is likely to be.

Our systematic search of the published literature found no studies which prospectively sought to determine the optimal duration of escalated regimens. Attempts at dose de-escalation have been studied retrospectively with findings published by a few centres where de-escalation was attempted. Overall, however, there remains a paucity of reliable data with respect to the optimal duration of dose escalation following recaptured response. Therefore a standard indiscriminate policy cannot be applied to all patients as to when to de-escalate and various other patient specific factors must be considered (see later) on a case by case basis before a decision regarding de-escalation of treatment is made.

We found seven retrospective observational cohort studies and two small prospective analyses in which de-escalation of infliximab or adalimumab was attempted (following successful escalation) in patients with refractory CD. These studies, including patient characteristics, are detailed in Table 1 and key findings are summarised below. Where de-escalation attempts were described, they usually involved a change in regimen directly from the escalated regimen back to the maintenance regimen. However most of these studies were fairly small (n<100) and heterogeneous in design with respect to the specific intervention and populations studied. Some studies were open label to investigators, many involved subjective reporting of ‘success’ related to treatment and they often lacked the use of standardised measures of CD activity such as the Harvey Bradshaw Index, all of which could confound the findings. The studies were not designed to inform the optimal duration of escalated regimens or on how to de-escalate successfully which makes the conclusions somewhat speculative in nature. Follow up periods were, however, reasonably long and the cohorts were representative of ‘real-life’ situations.
De-escalation was attempted in two retrospective studies and was successful in some patients. These studies support the concept of successful de-escalation but they do not provide sufficient detail so as to allow us to comment on the optimal time to attempt de-escalation nor on the best method. (3;17)

- In a small retrospective cohort study, 80% (24 of 30) of patients with CD who had lost response to infliximab regained response following dose escalation. Ten patients (33%) were reported to be in clinical remission at the median follow up period of 41 months (3.4 years), either whilst remaining on escalated doses of infliximab or following de-escalation. The proportion of those who successfully de-escalated was not reported. (3)

- In a small retrospective cohort study, 74 of 92 patients with uncontrolled CD regained response after adalimumab dose escalation (from fortnightly to weekly 40mg or 80mg fortnightly). The mean duration of follow up was 3.27 years (range 0.7 to 5.7 years) and de-escalation was attempted in 13 of these 74 patients after a median time of 343 weeks (around 6.5 years) and was successful in 11 of the patients in whom it was attempted. The lack of detail available makes it difficult to identify exactly how long patients remained on escalated regimens or why de-escalation was attempted after such a long time after response was regained and why the time to de-escalation seems to be longer than median follow up. The incidence of tertiary loss of response was 56.8% (n=42) and the median time to tertiary loss of response was around 11 months (range 5.7 to 18.5 months). (17)

Three retrospective studies also supported the concept of de-escalation and they provided some detail as to when de-escalation was attempted or carried out successfully. In these studies, de-escalation was attempted or carried out between 3-6 months, on average, after sustained response to escalated doses had been achieved. (2;4;6) However, there was significant interpatient variability and the actual time to attempted or actual de-escalation ranged broadly from 1 month to around 6 years after sustained response to escalated doses had been achieved. In many of the studies, around half (51-63%) of all patients whose doses had been escalated after 3-6 months of using escalated dosing regimens were then able to de-escalate safely and successfully whilst maintaining remission. (2;4;6;17) However, the retrospective nature of these studies and interpatient variability precludes accurate reporting on the typical durability of a successful response to de-escalation. One small study showed that many patients remain in response/remission (as defined by lack of steroid use) a year following de-escalation, but the number of patients is too small to form a definite conclusion regarding durability of response post de-escalation. (2)

(2) A very small prospective study (n=14) found that at 322 days (10.7 months), around half (57%) of patients in whom de-escalation of adalimumab after 3 months was successful remained in response. (16)

- Dose de-escalation of infliximab was attempted in a small (n=94) retrospective observational cohort study in patients with CD. The study was not specifically designed to investigate the success of dose de-escalation. De-escalation after a median duration of 6 (range 3-9) months was successful in 5 patients with CD following sustained response to escalated doses. Details on the number of patients in whom de-escalation was attempted or on the criteria for deciding to de-escalate were not reported. (6)

- A large retrospective cohort study in 720 patients with CD reported that de-escalation was attempted in 54% of patients after a median duration of 3 months of using escalated dosing of adalimumab. De-escalation was successful in 63% of patients in whom it was attempted at this time but it was not clear exactly how often this success lasted or how durable it was. (4)

- In another small retrospective study, doses of anti-TNFα therapy (infliximab or adalimumab) were escalated for a median duration of 5 months (range 1-47 months) in 55 patients with CD. In 51% of patients, de-escalation was considered to be successful after a median of 4 months (range 1-15) of using escalated regimens. Follow up was available for more than 12 months after de-escalation in 17 patients and 15 of the 17 (88%) had data for steroid use available. Of these 15 patients, 12 (80%) did not require steroids 1 year after de-escalation. However, at the last follow up period at 46 months (3.8 years), 25% of patients remained on escalated regimens. (2)

Data from a prospective study suggests that a response to 322 days (10.7 months) will be achieved in around half (57%) of those in whom de-escalation of adalimumab after 3 months was successful. (16) In another small prospective analysis, 64% of patients with CD or Ulcerative Colitis (UC) who responded to dose escalation with infliximab or adalimumab were successfully de-escalated to standard regimens, after 1 year of escalated anti-TNF administration. (15) In one large study, dose escalation was required in around 20% of the 614 patients involved and most (60-70%) successfully de-escalated, though details on when de-escalation was attempted or carried out are lacking. (36)

- The only prospective study designed to assess the success of de-escalation was a small (n=14)
uncontrolled, open label pilot study which involved temporary dose escalation of adalimumab in patients with CD with secondary non response. In this study, dose escalation with adalimumab was planned to last for only 3 months with fortnightly adalimumab re instituted thereafter. At the time of publication of the abstract (at a median follow up time of 322 days) 57% were still in response or remission following de escalation. (16)

- A prospective analysis aimed to evaluate how often patients with CD or UC who required escalated dosing of infliximab or adalimumab can successfully de-escalate. Of the 161 patients, 31 required dose escalation (n=30 with CD) and this maintained remission to 1 year in 25 patients. After 1 year of using escalated dosing, their dose was de-escalated and this was successful in 16 of 25 (64%) of patients. Durability of response thereafter was not reported. (15)

- A large observational 5 year cohort study assessed the long term clinical benefit of infliximab in 614 patients with CD. Data showed that an increase of the dose to 10mg/kg was required in 16.3% of patients or an increase of the dose plus a reduction of the interval in 3.8% of patients. It was reported that 62-72% of patients whose dose had been escalated were able to go back to the standard dose. However, there is no detail on when de-escalation was carried out. (36)

What is the evidence for continuing escalated doses for longer than a year, particularly where there has been a response?

Infliximab and adalimumab are known to be safe and efficacious for up to a year; this includes use of escalated dosing regimens. However, long term (> 1 year) response, durability and safety of dose escalation in patients with CD has not been well evaluated. The pivotal studies (CHARM, CLASSIC II, ACCENT I and II) were of relatively short duration (<1 year) and they did not evaluate long term response to dose escalation in those patients who did continue to respond beyond the duration of these studies. (5;7;8;37) A review article suggests that stopping immunomodulator monotherapy after a period of remission is associated with high rates of relapse in patients with CD or UC (around 75% relapse by 5 years after therapy was stopped). (38) The risk of relapse needs to be carefully considered alongside the potential long term safety risks as well as cost-effectiveness. It is therefore important to evaluate the data with regards to the optimal duration of using escalated dosing regimens of infliximab or adalimumab.

We carried out a systematic search of the published literature for studies in which escalated regimens were in use for longer than a year. The literature evaluating the durability of dose escalation is limited, largely retrospective and predominantly presented as subgroup analyses. Overall, studies were limited by the lack of detail and heterogeneity between them; specifically with respect to the population characteristics, context and setting and variability regarding definition of response or remission. Clinical decision making about dose escalation, de-escalation or discontinuation of medication within the studies may have also been subject to variability. Some studies lacked use of objective tests and/or validated and standardised measure of disease activity such as the Harvey Bradshaw index. Almost all of the studies were retrospective evaluations with inherent risk of recall bias. Most of the studies were not designed to assess durability of escalated dosing regimens and were limited further by their small sample sizes (typically fewer than 100 patients) and relatively short follow up periods. Therefore estimates of durability are imprecise and not sufficient to inform the optimal duration of using escalated dosing regimens of infliximab or adalimumab. There was often no detail in the papers on whether patients who responded (or were in remission) after their doses of infliximab or adalimumab were escalated were still responding, in remission and/or tolerating the escalated dosing regimens at follow up.

We found two retrospective cohort studies specifically designed to characterise the duration of recaptured response from infliximab or adalimumab dose escalation. (3;17) These studies are detailed in Table 1 and key findings are summarised below.

- A small retrospective observational single centre cohort study, mentioned previously, aimed to investigate durability and predictors of response to dose escalation with infliximab over a median follow up period of 41 months (3.4 years). Investigators extracted data from local healthcare records and response or lack thereof was judged by physicians and based on disease related symptoms and inflammatory markers or imaging. In this study, 24 of 30 patients with CD who had lost response to infliximab regained response following dose escalation. Of these 24 patients, 23 were followed for longer than 12 months. Of these 23 patients, 8 lost response within 12 months and 15 (65%) remained as responders for longer than 12 months (they were classed as long term responders). Investigators suggested that overall; dose escalation had extended infliximab therapy by a median duration of 9 months (range 6 to 17 months) which was determined using the Kaplan-Meier statistical method. Ten patients were reported to be in clinical remission at the median follow
up time of 41 months (range 22 to 64 months), either whilst remaining on escalated doses of infliximab or following de-escalation. Fourteen patients had adverse effects which led to eventual discontinuation but the nature of these was not documented. The proportion of those who successfully de-escalated was not reported. (3)

- A small retrospective longitudinal cohort study, also mentioned previously, was designed to characterise the duration of recaptured response from adalimumab dose escalation (from fortnightly to weekly 40mg) and to define the incidence of subsequent tertiary loss of response in 92 patients with CD. The median duration of follow up was 3.27 years (range 0.7 to 5.7 years) and investigators extracted data from local and regional healthcare records. Investigators found that 74 of 92 (80%) patients regained response following dose escalation with adalimumab. Responders experienced subsequent loss of response (as assessed by a gastroenterologist using a standardised measure of disease activity and markers of inflammation or endoscopy/CT scan results) at a median time of around 16 months (range 6.8 to 24.7 months), which was determined using the Kaplan-Meier statistical method. The incidence of tertiary loss of response was 56.8% (n=42) and the median time to tertiary loss of response was around 11 months (range 5.7 to 18.5 months). Further dose escalation or re-induction was tried in those experiencing tertiary loss of response but of these many ended up discontinuing due to loss or lack of response (N=18) and some needed surgery. As mentioned above, de-escalation was successful in some of the patients after some time.(17)

We also found a further five retrospective studies and two prospective studies which included relevant subgroup analyses evaluating durability of response to escalated dosing regimens of infliximab or adalimumab for longer than 12 months. (1;2;4;6;18-20) These studies are detailed in Table 1 and key findings are summarised below. However, lack of available detail from the papers makes it difficult to draw relevant conclusions other than to assume that there may have been some patients included within the studies who were using (and probably responding to) escalated doses of adalimumab for up to the end of the follow up period in the studies; 5 years was the longest follow up period. As mentioned, these speculations regarding durability also depend on a variety of factors including local variations in clinical practice, definition of and method of evaluating loss of response, the population studied and concomitant medicines used.

- A large (N=720) industry sponsored retrospective study aimed to study the incidence and success rate of dose escalation (and de-escalation) in a large, real life, cohort of patients with moderate to severe CD. Success was assessed by clinicians using the standardised Harvey-Bradshaw index and CRP values. Dose escalation rates were 24% over 1 year and 55% over 2 years. The study had a median follow up time of 14 months (range 3-75 months) and some patients, though it is not clear how many, would have remained on the escalated dosing regimen of weekly 40mg of adalimumab for this duration (3 months to 6 years). Furthermore, the definition used for response in this study was continued use at 6 months post escalation, which may not have captured efficacy accurately.(8)

- In a prospective cohort study, 54 patients with CD underwent dose escalation following loss of response to infliximab therapy. The majority of patients (75.9%) who required dose escalation remained on infliximab at the conclusion of the study which lasted 30 months. As explained earlier, there is a lack of detail which makes it difficult to derive reliable evidence from this study. (19)

- A smaller retrospective study (n=33) collected data on CD patients in a community based gastroenterology practice whose dose of infliximab was escalated (to 10mg/kg and/or 5mg/kg every 4-7 weeks) at median time of 12 months due to loss of response. Patients were followed up for 4-39 months and 83%, 69%, 47%, and 29% of patients who had an initial response to dose escalation maintained response at 6, 12, 18, and 36 months. The loss of efficacy after escalation was estimated as being 43% per patient-year of follow-up. In terms of safety, one patient had an infusion reaction after 36 doses and one patient developed a herpes zoster infection although it is not clear how many were on escalated dosing. (1)

- In a small (n=94) retrospective observational cohort study, not designed to investigate the success of dose de-escalation of infliximab, de-escalation was attempted in 5 patients with CD following sustained response to escalated doses after a median duration of 6 (range 3-9) months. The median duration of response to escalated infliximab regimens was 16 +/- 10.7 months for patients whose dosing interval was shortened and 17 +/- 16.4 months in those whose dose was doubled. (6)

- An observational, multicentre, retrospective cohort study carried out at six Australian hospitals investigated the impact of dose escalation of either adalimumab or infliximab on outcomes of CD (corticosteroid use, need for surgery and physicians perception). The study involved 55 patients with CD who required dose escalation due to secondary loss of response. The infliximab dose interval was either shortened to 6 weeks, 4 weeks and/or the dose was increased to 10mg/kg whilst the adalimumab dose was escalated to 40mg every week. Doses of anti-TNFα therapy were escalated for a median duration of 5 months (range 1-47 months) with a median duration of 20 months following successful re-induction of response in 65% of
patients. Reasons for discontinuing escalated regimens were included inability to access further treatment (12%) as well as lack of response (19%). At the last follow up period at 46 months, 25% of patients remained on escalated regimens and 21% of patients were still on escalated regimens at 60 months (5 years). Details on the durability and safety of using escalated doses for long periods of time were not reported as part of this study. (2)

- A prospective 52 week placebo controlled randomised controlled trial with a 96 week open label extension was carried out in order to assess long term safety and efficacy of adalimumab in Japanese patients with moderate to severe CD. The study included a small cohort of patients (n=40) who required dose escalation of their adalimumab to 80mg every other week. In the dose-escalation sub cohort, 75% achieved clinical remission 48 weeks after dose escalation. Patients were followed up for up to 148 weeks (~ 3 years) and it is possible that some patient's dose escalation cohort would have remained on the escalated dosing regimen for this duration. However, lack of detail makes it difficult to report more precisely on this. The incidence of adverse effects, including serious adverse effects, increased after the dose was escalated but the incidence or type of adverse effects occurring with use of escalated dosing over the long term (more than 1 year) was not reported. It was reported, however, that adalimumab was tolerated and no deaths were reported to follow up.(20)

- A prospective multicentre cohort study included 42 adults with active CD with the aim of assessing long term (to 14.5 months) safety and efficacy of 80mg weekly of adalimumab. Within the 14 weeks of dose escalation, 33.3% of patients had achieved clinical remission and 54.8% had responded. Most patients maintained a clinical benefit at month 6 and at this time point, 12% required major abdominal surgery. Nine patients were reported to remain on adalimumab 80mg weekly at the end of the study. Adverse events were reported in 13 patients (31%) and included infections which were treated successfully (genital herpes, dental abscess, vulvar furuncle, bacterial overgrowth, and intra-abdominal abscess). Five patients developed skin lesions, including neutrophilic dermatosis, psoriasiform skin lesions, eczema, and injection site reactions, leading to a decrease in the dose for 2 patients and adalimumab withdrawal for one patient. One patient developed a mood disorder that improved after adalimumab withdrawal.(18)

**Whether there are any criteria (such as therapeutic drug monitoring parameters) that could be used to inform decision making about which patients with CD can successfully be de-escalated?**

Once patients CD is stable following dose escalation, it is then difficult discern which patients will successfully be able to de-escalate and which ones are likely to relapse if de-escalation is attempted. We systematically searched the published literature for relevant data to try and identify predictors to facilitate decision making about this. We found no studies designed specifically to identify predictors of successful de-escalation. However, we did identify several pooled analyses/review articles that involved identification of predictors of response to dose escalation. We were unable to identify any robust predictors of response to dose escalation or to successful de-escalation but we can draw some potentially relevant inferences from the data.

- A pooled analysis of 39 studies (including studies with follow up of less than 1 year) evaluated loss of efficacy and/or need for adalimumab dose escalation. It also identified predictors of response to dose escalation. These were; male gender, current/former smoker status, family history of IBD, isolated colonic disease, extra-intestinal manifestations, use of 80/40 mg induction therapy, having a longer disease duration, greater baseline CDAI score, concomitant corticosteroid use, no deep remission at week 12, low serum trough concentrations of adalimumab, previous infliximab non-response and previous treatment with anti-TNF agent. (21)

- The authors of a review article recommend measurement of adalimumab trough levels and antidrug antibodies, prior to dose escalation, as the benefit from dose escalation is likely to be limited if trough levels are already in therapeutic range or if high titres of antibodies to adalimumab are present at the time of dose escalation. In the case of low or undetectable adalimumab trough levels, dose escalation to 40 mg weekly is recommended, whereas high antibody titres or adverse events frequently require switching to an alternative anti-TNF agent. They discuss that active inflammation despite therapeutic adalimumab trough levels requires alternative strategies such as switching to drugs with a different mode of action or surgical intervention. It should be noted however these findings are largely from retrospective studies and therefore can only be used to identify trends and not be used to accurately select patients in practice. (22)

- Another review article suggests that de-escalation should be considered in those patients with high risk of severe adverse events and low relapse risk (patients in deep remission) after drug withdrawal. They suggest that selection of patients for de-escalation should be on a case by case basis. Authors of this review suggested that de-escalation of anti-TNFα agents should occur by decreasing dosage or increasing the interval in patients who are in clinical remission and who have therapeutic trough levels of their anti-TNFα. (14)
We identified nine studies in which the identification of predictors was considered as a secondary outcome measure. Potential predictors of poor response to escalated dosing are elevated CRP levels and requirement for corticosteroids for prolonged periods (>6 months continuous) to maintain disease stability. The well-defined dose-response relationship for infliximab and adalimumab in CD and several studies suggest that patients with low serum drug trough levels at the time of escalation may benefit from escalated dosing; which should then result in adequate serum trough levels of the drug and clinical response. In patients who have adequate serum drug trough levels at the time of treatment failure, when dose escalation is being considered, dose escalation is unlikely to lead to a clinical response and switching to an alternative drug or drug class should be considered. It stands to reason that patients with adequate serum drug trough levels, who are not clinically responding to the escalated dose, are unlikely to develop a response with prolonged use of escalating dosing. For patients who are clinically responding and whose levels serum drug trough levels are adequate, the decision to decide if and when to de...

Patients with adequate serum drug trough levels, who are not clinically responding to the escalated dose, are unlikely to develop a response with prolonged use of escalating dosing. For patients who are clinically responding and whose levels serum drug trough levels are adequate, the decision to decide if and when to de-escalate or stop therapy would be based on clinical parameters. Note that the definition of low serum anti-TNF drug levels varies considerably, however. Overall, the studies suggest that if anti-TNF antibodies are present, response to dose escalation is likely to be limited. However, in some published papers clinical response to dose escalation occurred even in patients with positive drug antibody titres. So the clinical implications of having positive anti-TNF antibody titres are not completely understood. Relevant papers are detailed in Table 2 and key findings are summarised below:

- A small retrospective longitudinal cohort study (n=92) was designed to characterise the duration of recaptured response from adalimumab dose escalation to weekly 40mg. This study is mentioned previous section where methodology and patient characteristics are described. One of the secondary outcome measures was to examine risk factors predicting response to dose escalation to tertiary loss of response. It was reported that need for concurrent steroids at the time of escalation predicted non-response to dose escalation. Elevated CRP levels (>10.0 mg/L) at the time of dose escalation was associated with a 3-fold increased risk of tertiary loss of response. Time to loss of response was also shorter among patients with a high CRP at escalation. No other risk factors (including disease classification, behaviour, phenotype, activity or concurrent medications at the time of escalation) were found to predict response to adalimumab dose escalation. Authors suggested that patients with a high inflammatory disease burden are less likely to respond to dose escalation because of the refractory nature of their CD. It was suggested that elevated CRP (interpreted in light of the clinical context) can be an adjunct in the assessment of secondary loss of response and in deciding between adalimumab dose optimisation or switching out of class. (17)

- A small observational, multicentre, retrospective cohort study (n=55) described above investigated the impact of dose escalation of either adalimumab or infliximab on outcomes of CD. The only predictor of durable, and steroid free remission, over 12 months following dose escalation was the absence of prolonged, continuous use of corticosteroids for >6 months in the 5 years prior to dose escalation (OR 3.5, 95% CI 1.05 to 12.05, p<0.042). (2)

- The sub analysis of a retrospective study, which involved 247 adults and children with IBD (n=205 with CD) with suspected loss of response to infliximab or adalimumab, aimed to identify predictors for loss of response to dose escalation. Investigators examined the correlation between trough levels of anti-TNF agents and antibody titres with clinical outcomes. Trough levels of adalimumab of >4.5 mcg/mL or infliximab >3.8 mcg/mL identified patients who failed to respond to dose escalation or a switch to another anti-TNF agent with 90% specificity hence these were considered to be adequate trough levels. Having adequate trough levels predicted clinical response to dose escalation with more than 75% specificity. Patients with adequate trough levels had a longer duration of response when they switched to a different class of agent than when anti-TNF was dose escalated (p=0.002). Adalimumab antibody levels of >4mcg/mL or infliximab antibody levels of >9 mcg/mL identified patients who did not respond to dose escalation with 90% specificity. Dose escalation was more effective for patients with no or low antibody titres (p=0.02) at the time of escalation. Authors concluded that trough levels of drug and/or antibody titres may be used to guide therapeutic decisions for more than two-thirds of patients with CD with either clinically suspected or definite inflammatory loss of response to therapy. (28)

- A prospective observational study included 82 patients with an active flare of IBD (55% of whom had CD) whilst on adalimumab 40 mg every 2 weeks. The study aimed to determine whether algorithms based on the measurement of infliximab trough levels and antibodies titres could be extrapolated to the pharmacokinetics of adalimumab. All patients adalimumab dosing was escalated to weekly doses of 40 mg weekly and clinical remission rates were assessed against adalimumab trough levels and antibody titres (investigators carrying out measurements were blinded to the clinical data). Patients were categorised into three groups: group A had adalimumab levels >4.9 mcg/mL (n=41), group B had adalimumab levels <4.9 mcg/mL and undetectable antibody titres (n=24) and group C had adalimumab levels <4.9 mcg/mL and...
detectable antibody titres (N=17). Clinical remission was achieved by 29.2%, 67% and 12% in groups A, B and C respectively (p<0.01 between groups A/B and B/C). This suggests that the presence of low serum adalimumab trough levels without antibody titres is strongly predictive of clinical response in 67% of cases after adalimumab dose escalation. Conversely, low adalimumab levels with detectable antibody titres are associated with adalimumab failure and switching to infliximab should be considered. Adalimumab serum trough levels >4.9 mcg/ml are associated with failure of two anti-TNF agents in 90% of CD cases and switching to another drug class should be considered. In this study, CRP level at the time of relapse, disease duration, duration of adalimumab therapy or IBD type were not predictive of remission after dose escalation.(26)

- In a post-hoc analysis of a RCT, 42 patients with CD with treatment failure on standard dosing of infliximab were treated with an escalated dosing regimen of infliximab (5mg/kg every 4 week) for 12 weeks. Trough serum infliximab levels and anti-infliximab antibody levels were measured at treatment failure and the end of the trial. The study aimed to explore the association between changes in serum infliximab levels, antibodies (Abs) and clinical outcomes after infliximab dose escalation. Twenty-one patients (50%) regained clinical response on the escalated infliximab dosing regimen. Increases in infliximab levels following dose escalation were associated with improved clinical outcomes, indicating insufficient drug levels with standard dosing in a subgroup of patients. Anti-infliximab antibodies were detected in 13 patients (32%) and these became undetectable during infliximab dose escalation. This suggests that the relationship between antibodies, dose-escalation and clinical outcomes is complex and not completely understood. (29)

- In contrast, data from a retrospective study of 76 patients with IBD (n=18 with UC, n=55 with CC and n=3 with indeterminate colitis) suggested that clinical response to infliximab dose escalation was not accurately predicted by measurement of infliximab trough serum and antibody concentrations. (25)

- An open-label prospective multicentre study involving 57 patients with active CD evaluated serum trough level measurements of infliximab against clinical response. In patients with loss of response (n=20) after week 14 the dose was escalated to 5mg/kg every 4 weeks. Escalated dosing resulted in clinical response and remission rates of 83.3% (15/18) and 55.6% (10/18), respectively, at week 54. A correlation between clinical efficacy and serum trough level was found (p<0.01). Responders had median serum trough infliximab levels of 1.10mcg/mL whereas non-responders had lower median levels of 0.80mcg/mL. Infliximab trough levels at the time of switching were 0.80mcg/mL in patients in whom the interval was shortened which suggests that the threshold levels for clinical efficacy are 1mcg/mL. (23)

- A Japanese multicentre, open label, dose escalation cohort study involved 39 patients with CD who needed dose escalation of infliximab (to 10mg/kg every 8 weeks from week 0 to week 40) due to lack of efficacy. Serum infliximab levels were measured at week 0 and every 8 weeks and correlations between levels and clinical response were made (though not a primary or secondary endpoint). Remission rate at week 40 (overall) was higher in patients with a trough serum infliximab level of >1mcg/mL (65%) than in those with <1mcg/mL (23%) at week 0. Remission rates were higher in patients with a plasma IL-6 level <2.41 pg/mL versus those with levels of >2.41 pg/mL at week 0. Remission rates were also higher in patients with a serum albumin level of >3.8 g/dL versus those with <3.8 g/dL at week 0. (27)

- An observational cohort study involving 168 patients with CD who had failed/not tolerated infliximab was designed to assess the long-term clinical benefit of adalimumab, focusing on the influence of trough serum concentration and antibodies against adalimumab on clinical response, adalimumab dose escalation and discontinuation. All patients were loaded with adalimumab and 102 (65%) needed to have their dose escalated. Adalimumab trough serum concentration increased after dose escalation from 4.8mcg/ml to 9.4mcg/mL and this increase correlated well with the clinical response to escalation (5.9mcg/ml for responders vs. 0.0mcg/ml for non-responders, P< 0.0001). (24)

Vedolizumab represents a new class of immunosuppressant for use in CD. It is a gut-selective immunosuppressant humanized monoclonal antibody that binds specifically to the α4β7 integrin, which is preferentially expressed on gut homing T helper lymphocytes. It is recommended by NICE as an option for patients with CD whose ant-TNF agent is not effective, no longer effective or not suitable. In the pivotal licensing studies (GEMINI studies), patients using infliximab and adalimumab had to undergo 60 and 30 day washout periods respectively before being switched to vedolizumab. (30-32)

**Cost effectiveness of a therapeutic drug monitoring guided approach to dose escalation**

We found three analyses which investigated the cost-effectiveness of monitoring levels of infliximab or adalimumab (TDM) to help decide whether dose-escalation is a potentially cost effective strategy. (33-35) The studies suggest similar clinical effectiveness of both approaches. The TDM guided approach was suggested to be more cost-effective than the conventional approach but the published models were not based on the UK healthcare system. These papers are described below:
A 1 year, single (tertiary) centre, prospective randomised controlled study randomised 236 patients (1:1) to receive concentration based dosing (n=128) or clinically guided dosing (n=123) of infliximab. Patients were adults with moderate to severe stable CD (n=178) or UC (n=85). Of the CD patients, 50% were male, 24% were smokers, they had median disease duration of 12.5 years and they were mostly using infliximab as monotherapy. The study aimed to compare efficacy, cost effectiveness and safety of concentration based dosing to clinically guided dosing of infliximab in patients on standard maintenance regimens of infliximab at the time of randomisation. The primary end point was the proportion of patients in each group in clinical and biological remission (HBI score of <4 and CRP level of <5mg/L) at 1 year after dose escalation. A similar proportion of patients in both groups achieved remission; 66% in the concentration based dosing group and 69% in the clinical based dosing group (p=0.686) indicating no significant difference between the approaches. Note that these statistics include patients with UC as well as CD, but a subgroup analysis showed no significant difference between the treatment arms for each of these patient groups. Concentration based dosing yielded less QALY compared with clinically guided dosing (0.8227 vs. 0.8421) but was less expensive (€20,723 vs. €21,023) per patient per year. It should be noted that the cost effectiveness calculations are not based on the UK healthcare system. (34)

Another RCT (single blinded) 12 week trial (n=69) aimed to investigate the cost effectiveness of a TDM guided algorithmic approach to optimise infliximab therapy in patients with CD failing standard maintenance dosing of infliximab. This TDM algorithm based approach was compared with a conventional empirically or clinically guided approach to dose escalation. Patients were mostly female (61%) with an average age of 37 years and median disease duration of 9 years and mostly luminal CD (90%). Patients were equally randomised to either receive infliximab 5mg every 4 weeks, rather than every 8 weeks (n=36), or to have their treatment guided by their serum concentrations of infliximab and infliximab antibodies tested at the time of treatment failure (n=33) in accordance with an algorithm. The primary objective was to demonstrate that using the algorithm based approach was less expensive and as effective as the conventional dose escalation approach. Response rates were 58% in the algorithm group and 53% in the dose escalation group (RR 1.091, 95% CI 0.713 to 1.673, p=0.810) indicating a non-significant difference. Costs were calculated as being lower for the algorithm group compared with the dose escalation group (€4617 vs. €1373, p<0.001) but this calculation was based on the Danish healthcare system. Withdrawal due to lack of effect was more common in the dose escalation group (20% vs. 10%). Interestingly, 70% of patients with secondary failure had therapeutic infliximab levels and undetectable antibodies, which suggests a pharmacodynamic mechanism for treatment failure. (33)

Another cost effectiveness analysis was designed to investigate whether an algorithm and testing-based dose escalation strategy is more cost effective than an empiric dose escalation strategy. This analysis utilised data from primary or subgroup analyses from randomised clinical trials or from observational studies involving patients with moderate to severe active CD. Similar rates of remission (63% vs. 66%) and response (28% vs. 26%) were achieved though the testing-based strategy resulted in a higher percentage of surgeries (48% vs. 34%) and lower percentage use of high-dose biological therapy (41% vs. 54%). The testing strategy yielded similar QALYs compared with the empiric strategy (0.801 vs. 0.800, respectively) but was less expensive ($31,870 vs. $37,266, respectively). (35)

The involvement of patients in decision making, particularly where they have concerns regarding relapse where doses are to be de-escalated or treatment discontinuation considered.

We found no papers which focussed on the involvement of patients in decision making regarding de-escalation of their infliximab or adalimumab dosing. The NICE guidance recommends to discussing with patients (and/or their parents or carers if appropriate), options for managing their disease when they are in remission, including both no treatment and treatment. The discussion should include the risk of inflammatory exacerbations (with and without drug treatment) and the potential side effects of drug treatment. The person's views should be recorded in their notes. (13)
## APPENDIX TABLE 1: Studies involving use of escalated doses infliximab or adalimumab in patients with CD (including studies which included attempts at de-escalation).

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>N=</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Aim</th>
<th>Principal efficacy and safety outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regueiro (17)</td>
<td>Retrospective single centre cohort study</td>
<td>108</td>
<td>• Treatment experienced (had received &gt;8 doses of infliximab over for &gt;1 year)</td>
<td>Patients attending an outpatient clinic who required dose escalation (to 10mg/kg/ decrease in dose interval) were followed up for 30 months.</td>
<td>To determine the proportion of patients and factors associated with dose escalation.</td>
<td>• At 12 months, 31% of patients had required dose escalation (5mg/kg to 10mg/kg).</td>
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<td>Most of these patients (75.9%) whose doses had been escalated remained on infliximab at 30 months.</td>
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<tr>
<td>Chaparro (51)</td>
<td>Retrospective multicentre study</td>
<td>33</td>
<td>• Average age 43</td>
<td>Patients in an outpatient GI clinic setting whose infliximab dose had been escalated (to 10mg/kg and/or decreasing the dose interval from 8 to 6 or 4 weeks) were studied over a 22 month follow up period.</td>
<td>To study efficacy and safety of dose escalation</td>
<td>Dose escalation from 5 to 10mg/kg (n=25), led to 80% response (28% remission and 52% partial response).</td>
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<td></td>
<td></td>
<td></td>
<td>• Disease duration 15 years</td>
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<td></td>
<td>Dose escalation from shortening dose intervals to 4 weekly (n=7) led to 72% response (57% remission and 15% partial response).</td>
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<td></td>
<td></td>
<td></td>
<td>• 51% Male</td>
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<td>Dose escalation from 5 to 10mg/kg AND shortening dose interval from 8 to 6 weekly (n=1) – response not specifically reported.</td>
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<td>• Disease location; 70% ileum/colon.</td>
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<td>Overall, 79% of patients responded to dose escalation; 45.5% had partial response (sustained decrease in HBI) and 33.5% achieved remission (HBI &lt;4).</td>
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<td></td>
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<td>• Smokers; 37%</td>
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<td>The mean time of follow-up with the escalated dosage was 14 months (range 4-39 months) and median was 11 months.</td>
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<td>• 76% on concurrent immunosuppressants</td>
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<td>50% of patients with initial response to dose escalation eventually lost some degree of.</td>
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<td></td>
<td></td>
<td></td>
<td>• Disease severity score – not reported.</td>
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<td></td>
<td>Long term side effects included one herpes zoster infection and an infusion site reaction.</td>
</tr>
<tr>
<td>Lin (38)</td>
<td>Observational retrospective single centre cohort study</td>
<td>30</td>
<td>• Average age 40</td>
<td>Patients who lost response to &gt;6 months of infliximab and had their dose of infliximab escalated (10mg/kg or 6 weekly infusions or both) over a median follow up period of 41 months.</td>
<td>To investigate durability and predictors of response to dose escalation</td>
<td>Following dose escalation, 80% of patients who had lost response to infliximab regained it but eventually, many patients (46.7%) lost response.</td>
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<td></td>
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<td></td>
<td>• Disease duration 13 years</td>
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<td>At the median follow up period of 41 months, 33.3% of patients remained in clinical remission either whilst remaining on escalated doses of infliximab or after de-escalation. The proportion of those who successfully de-escalated was not reported.</td>
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<td></td>
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<td>• 59% Male</td>
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<td>It was estimated that dose escalation extended infliximab therapy by a median duration of 9 months.</td>
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<td>• Disease location; 1/3rd had perianal involvement.</td>
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<td></td>
<td>• Smokers; 10%</td>
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<td>• Excluded if prior TNF use</td>
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<td></td>
<td>• Disease severity score – not reported.</td>
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<tr>
<td>Kopylov (61)</td>
<td>Multicentre retrospective observational study at tertiary centres.</td>
<td>94</td>
<td>• Average age 30</td>
<td>Patients who lost response infliximab were escalated to dosing every 6 weeks (n=55) or double dosed infliximab (n=39, either 10mg/kg every 8 weeks or 5mg/kg every 4 weeks).</td>
<td>To compare the efficacy of the various escalated dosing regimens infliximab</td>
<td>De-escalation was successful in 3 patients in the 6 week regimen group and 2 patients in the double dose group. In these patients, de-escalation was attempted following sustained response to escalated doses after a median duration of 6 (3-9) months. It is not documented how patients were selected for attempts at de-escalation.</td>
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<td>• Disease duration 10 years</td>
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<td>Investigators concluded that dose escalation (regardless of method), achieves a sustained response rate of 50% at 12 months after loss of response to the initial maintenance dose.</td>
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<td>• 50% Male</td>
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<td>• Disease location; 1/3rd had perianal involvement.</td>
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<td>• Smokers; % not available.</td>
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<td>• Excluded if prior TNF use</td>
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<td></td>
<td></td>
<td></td>
<td>• Disease severity score – not reported.</td>
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<tr>
<td>Baert (57)</td>
<td>Multicentre, retrospective cohort study sponsored by Abbott.</td>
<td>720</td>
<td>• Adults with CD who had lost response to infliximab</td>
<td>Patients who required dose escalation (n=208) of adalimumab to 40mg every week after the first 3 months of therapy were followed up to 14 months</td>
<td>To study the incidence and success rate (assessed using HBI* and CRP values) of dose escalation and de-escalation.</td>
<td>A primary response to adalimumab had been achieved in 84% of patients (higher in patient’s naïve to treatment with inhibitors of TNFs).</td>
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<td></td>
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<td></td>
<td>• Average age 24</td>
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<td>Dose escalation rates were 24% over 1 year and 55% over 2 years.</td>
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<td></td>
<td></td>
<td></td>
<td>• Disease duration 11 years</td>
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<td>De-escalation was attempted in 54% of patients after a median of 3 months and was successful in 63% of patients.</td>
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<td></td>
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<td></td>
<td>• 39% Male</td>
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<td>Within a median follow up time of 14 months (3-75), adalimumab</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Smokers; 39%</td>
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<td>• Excluded if prior TNF use</td>
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<td></td>
<td>• Disease severity score – 64% were exposed to anti-</td>
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### Infliximab

#### Adalimumab
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Duration</th>
<th>Follow-up</th>
<th>Patients</th>
<th>Dose Escalation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ma C (17)</td>
<td>Retrospective cohort study</td>
<td>92</td>
<td>14.5 months</td>
<td>75%</td>
<td>Weekly adalimumab escalation</td>
<td>To assess long term safety and efficacy of escalated adalimumab dosing.</td>
</tr>
<tr>
<td>Sutharshan (18)</td>
<td>Prospective, uncontrolled, open label pilot study</td>
<td>14</td>
<td>12 weeks</td>
<td>74</td>
<td>Weekly adalimumab escalation</td>
<td>To assess whether temporary dose escalation would lead to sustained clinical remission.</td>
</tr>
<tr>
<td>Watanabe (19)</td>
<td>52 week placebo controlled RCT with 96 week open label extension in Japan</td>
<td>40*</td>
<td>14 months</td>
<td>74</td>
<td>Weekly adalimumab escalation</td>
<td>To assess long term safety and efficacy of adalimumab in CD, including in the dose escalation subcohort.</td>
</tr>
<tr>
<td>Bougen (16)</td>
<td>Prospective multicentre cohort study</td>
<td>42</td>
<td>14.5 months</td>
<td>13</td>
<td>Weekly adalimumab escalation</td>
<td>Within the 14 weeks after adalimumab escalation, 33.3% achieved clinical remission and 54.8% had a clinical response.</td>
</tr>
</tbody>
</table>

* HBI = Harvey Bradshaw Index
<table>
<thead>
<tr>
<th>Study description</th>
<th>N=</th>
<th>Patient characteristics</th>
<th>Intervention / aim</th>
<th>Efficacy Outcomes / comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viazis (15)</td>
<td>31</td>
<td>Adults with CD (n=30) or Ulcerative Colitis (n=1) and ‘secondary loss of response’ to either infliximab or adalimumab who required dose escalation. Age, disease duration, sex, smoking status, disease location and severity were not documented. Naïve to prior TNF use. All patients on concomitant azathioprine for 6 months.</td>
<td>Adults who required dose escalation (not defined) to maintain remission were de-escalated if possible (n=16). Median follow up period was 26 months (range 2-26 months).</td>
<td>To evaluate success of de-escalation in patients who had required dose escalation to maintain remission.</td>
</tr>
<tr>
<td>Ghaly (2)</td>
<td>55</td>
<td>Adults with ‘secondary loss of response’ to either infliximab or adalimumab who required dose escalation. Average age 33. Disease duration 9 years. 66% Male. Smokers; 13%. All with prior TNF use. Concomitant immunosuppressants; not documented. Disease location was mostly ileocolonic. Disease severity; not documented.</td>
<td>Adults with ‘secondary loss of response’ to infliximab or adalimumab underwent dose escalation. Infliximab dose intervals were shortened to 6 weeks, 4 weeks and/or the dose was increased to 10mg/kg or patients underwent re-induction of infliximab. Adalimumab doses were escalated to weekly.</td>
<td>To investigate the impact of dose escalation on outcomes of CD (steroid use, need for surgery and physician's perception).</td>
</tr>
</tbody>
</table>

APPENDIX TABLE 2: Studies involving methods of predicting response to dose escalation of infliximab or adalimumab in patients with CD

<table>
<thead>
<tr>
<th>Author</th>
<th>Study description</th>
<th>N=</th>
<th>Patient characteristics</th>
<th>Intervention / aim</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
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<tr>
<td>Vande Casteele (TAXIT) (34)</td>
<td>Prospective RCT at a single (tertiary) centre.</td>
<td>263</td>
<td>Adults with moderate to severe CD responding to standard dosing of infliximab. Average age 41. Disease duration 12.5 years. 55% Male. Smokers; 25%. Concomitant immunosuppressants, disease location; not documented.</td>
<td>To compare clinical efficacy, cost effectiveness and safety of concentration based dosing to clinically based dosing of infliximab in patients who were on standard infliximab dosing at the time of randomisation. Some patients in both cohorts required dose escalation. Follow up was to 1 year.</td>
<td>Patients were randomised 1:1 to either the concentration based dosing (n=128) or clinically based dosing (n=123) group of infliximab. Primary end point was the proportion of patients in each group in clinical and biological remission at 1 year after optimisation. Clinical remission was defined as having a Harvey-Bradshaw index score of &lt;4 and biological remission as having a CRP level of &lt;5mg/L. A similar proportion of patients in both groups achieved remission as defined above; 66% in the concentration based dosing group and 69% in the clinical based dosing group (p=0.686) indicating non-significant difference between the approaches (statistics include patients with UC too but a subgroup analysis showed no significant difference between the treatment arms for both of these groups).</td>
</tr>
<tr>
<td>Study (Ref)</td>
<td>Design</td>
<td>Participants</td>
<td>Methods</td>
<td>Outcomes</td>
<td></td>
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</tbody>
</table>
| Steenholdt (29) | Post-hoc analysis of a RCT | 42 | - Age range 21-42  
- Disease duration; 2-14 years  
- Sex; not documented  
- Smokers; 24-33  
- Concomitant immunosuppressants, prior treatment and disease location; not documented. | To explore the association between changes in serum infliximab levels, antibodies (Abs) and clinical outcomes after infliximab dose escalation (5mg/kg every 4 week) for 12 weeks. | - Trough serum infliximab levels and anti-infliximab antibody levels were measured at treatment failure and the end of the trial.  
- Twenty-one patients (50%) regained clinical response on the escalated infliximab dosing regimen.  
- The increase in serum trough levels of infliximab during treatment escalation was higher among responders than non-responders. All responders exhibited an average increase in serum infliximab levels in the magnitude of ≥2.6 μg/mL.  
- Increases in infliximab levels following dose escalation were associated with improved clinical outcomes, indicating insufficient drug levels with standard dosing in a subgroup of patients.  
- Anti-infliximab antibodies were detected in 13 patients (32%) and these became undetectable during infliximab dose escalation whether functional or not. |
| Pariente (25) | Retrospective study | 76 | - Patients with IBD (n=18 with UC, n=55 with CD and n=3 with indeterminate colitis).  
- Average age 34.5  
- Disease duration; 8.6 years  
- 49% Male  
- Smokers; 26%  
- Prior TNF use; 25%  
- 26% on concomitant immunosuppressants  
- Disease location of CD was mostly ileocolonic.  
- Disease severity (HBI and SCCAI) 7.8 and 7) | Patients with IBD who had lost response to infliximab therapy (and whose serum infliximab levels were available) were evaluated in order to assess the clinical value of measuring infliximab trough serum and antibody levels. | 39/76 (51%) of patients had their infliximab dose escalated, 31/76 (41%) continued on standard dosing and 5/76 (7%) were switched to adalimumab. One patient underwent surgery.  
- Clinical response to dose escalation was observed in 27 patients (69%). There was no significant difference in mean infliximab trough level at inclusion (3.3 +/-1.4 mg/mL) in responders compared with non-responders (2.3 +/- 2.2 mg/mL p=0.85).  
- 16/76 patients (22.4%) presented detectable ATI in the serum. Ten ATI-positive patients had an escalation of infliximab therapy and six (60%) demonstrated a clinical response. After escalation of infliximab therapy the ATI concentration decreased in five patients.  
- Authors concluded that clinical response to escalation of infliximab therapy in patients who lost response to the drug was not accurately predicted by measurement of infliximab trough serum and ATI concentrations. |
| Hibi (24) | Open-label prospective multicentre study | 57 | - Average age 29  
- Disease duration; 5.8 years  
- 51% Male  
- Smokers; 32%  
- Patients were TNF naive but most were on other treatments  
- Disease location was mostly ileocolonic.  
- Disease severity (CDAI scores); 285) | The association between clinical efficacy of infliximab and its serum level was investigated (the study included patients who required dose escalation). Co-primary endpoints were: rate of clinical response and remission at week 54. Serum trough level measurements of infliximab were evaluated against clinical response. | Infliximab was administered at 5 mg/kg at weeks 0, 2, and 6. Week 10 responders received infliximab every 8 weeks thereafter. In those with loss of response (n=20) after week 14 the dose was escalated to 5mg/kg every 4 weeks.  
- For those with loss of response, escalated dosing resulted in clinical response and remission rates of 83.3% (15/18) and 55.6% (10/18), respectively, at week 54. A correlation between clinical efficacy and serum trough level was found (P<0.01).  
- Responders had median serum trough infliximab levels of 1.10mcg/mL whereas non-responders had lower median levels of 0.80mcg/mL. Infliximab trough levels were 0.80mcg/mL in patients, whose doses were escalated, suggesting a threshold level for efficacy of 1mcg/mL.  
- The study lacked a control group. |
| Suzuki (27) | Japanese multicentre, open label, dose escalation cohort study | 39 | - Average age 29  
- Disease duration; 8.2 years  
- 74% Male  
- Smokers; 31%  
- Most had ileocolonic CD and many were on concurrent treatments  
- Disease location was mostly ileocolonic.  
- Disease severity (CDAI scores); 293) | Patients with CD who needed dose escalation to 10mg/kg every 8 weeks from week 0 to week 40 were assessed in order to assess the relationship between trough serum levels and clinical efficacy after dose escalation. Serum trough infliximab levels were measured at week 0 and every 8 weeks and correlations between levels and clinical response were made (though not a primary or secondary endpoint). | Remission rate at week 40 (overall) was higher in patients with a trough serum infliximab level of >1 mg/mL (65%) than in those with <1 mg/mL (23%) at week 0.  
- Remission rate was higher in patients with a plasma IL-6 level <2.41 pg/mL versus those with levels of >2.41 pg/mL at week 0  
- Remission rate was higher in patients with a serum albumin level of >3.8 g/dL versus those with <3.8 g/dL at week 0. |
| Velayos (16) | Cost effectiveness | N/a | Data from primary or subgroup analyses from randomized | To investigate whether an algorithm and testing-based dose escalation | Similar rates of remission (63% vs 66%) and response (28% vs 26%) |
Adalimumab

**Karmiris (47)**
Observational Cohort study

- Average age 36
- Disease duration; 10.5 years
- 29% Male
- Smokers; 41%
- Most were on concurrent immunosuppressants.
- Disease location was mostly ileocolonic.
- Disease severity; not documented.

**Ma C (17)**
Retrospective cohort study

- Average age 43.5
- Disease duration 11 years
- 46% Male
- Smokers; 20%
- 50% with prior TNF use
- All patients had failed immunosuppressants
- Disease location was mostly ileal or colonic and 29% had perianal involvement.
- Disease severity (Montreal classification); 38% penetrating, 27% structuring, 34% non-structuring and non penetrating.

**Roblin (48)**
Prospective observational study

- Average age 43
- Disease duration; 7.4 years
- 50% Male
- Concomitant immunosuppressants; 12%

<table>
<thead>
<tr>
<th>Steenholdt</th>
<th>Randomised, controlled, single blind, trial</th>
<th>69</th>
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<tbody>
<tr>
<td>Analysis</td>
<td>clinical trials or observational studies involving patients with moderate to severe active CD.</td>
<td></td>
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<tr>
<td>Strategy</td>
<td>strategy is more cost effective than an empiric dose escalation strategy.</td>
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<tr>
<td>Findings</td>
<td>were achieved through differential use of available interventions.</td>
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<td></td>
<td>The testing-based strategy resulted in a higher percentage of surgeries (48% vs 34%) and lower percentage use of high-dose biological therapy (41% vs 54%).</td>
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<tr>
<td></td>
<td>The testing strategy yielded similar QALYs compared with the empiric strategy (0.801 vs 0.800, respectively) but was less expensive ($31,870 vs $37,266, respectively).</td>
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</table>

Adults with CD on infliximab with treatment failure requiring optimisation of their infliximab regimen. Patients were equally randomised to either receive infliximab 5mg every 4 weeks, rather than every 8 weeks (n=36), or to have their treatment guided by their serum concentrations of infliximab and infliximab antibodies tested at the time of treatment failure (n=33) in accordance with an algorithm. The study aimed, over 12 weeks, to investigate the cost effectiveness of an algorithm guided approach to dose escalation based on therapeutic drug monitoring.

The primary objective was to demonstrate that treatment of patients with CD with loss of response to infliximab maintenance therapy using the algorithm based on drug level and antibody monitoring was less expensive and as effective as conventional dose escalation approach.

Response rates for the IRR population were 58% in the algorithm group and 53% in the dose escalation group (RR 1.091, 95% CI 0.713 to 1.673, p=0.810) indicating a non-significant difference but with a trend favouring the algorithm group.

Costs were calculating as being lower for the algorithm group compared with the dose escalation group (€4617 vs. €1373, p<0.001) but this calculation was based on the Danish healthcare system.

However, 70% of patients with secondary failure had therapeutic infliximab levels and undetectable antibodies, which suggests a pharmacodynamic mechanism for treatment failure.

Withdrawal due to lack of effect was more common in the dose escalation group (20% vs. 10%) but findings were similar for the protocol population.

All patients were loaded with adalimumab and 102 (65%) needed to have their dose escalated.

Adalimumab trough serum concentration increased after dose escalation from 4.8mcg/ml to 9.4mcg/mL and this increase correlated well with the clinical response to escalation (5.9mcg/ml for responder’s vs. 0.0mcg/ml for non-responders, P< 0.0001).

Need for concurrent steroids at the time of escalation predicted non-response to dose escalation.

Elevated CRP >10.0 mg/L levels were associated with a 3-fold increased risk of tertitary loss of response. Time to loss of response was also shorter among patients with a high CRP at escalation.

No other risk factors (including disease classification, behaviour, phenotype, activity or concurrent medications at the time of escalation) were found to predict response to escalation.

Authors suggested that patients with a high inflammatory disease burden are less likely to respond to dose escalation because of the refractory nature of their CD.

They suggest that elevated CRP (interpreted in light of the clinical context) can be an adjunct in the assessment of secondary loss of response and in deciding between adalimumab dose optimisation vs. switching out of class.
<table>
<thead>
<tr>
<th><strong>Infliximab or adalimumab</strong></th>
<th><strong>Reference</strong></th>
</tr>
</thead>
</table>
| **Ghaly**<sup>(27)</sup> | Observational, multicentre, retrospective study at 6 Australian (tertiary) hospitals. 55 patients. | *Average age 33*  
*Disease duration 9 years*  
*66% Male*  
*Smokers; 13%*  
*All with prior TNF use*  
*Concomitant immunosuppressants; not documented*  
*Disease location was mostly ileocolonic.*  
*Disease severity; not documented.*  
*Patients with secondary loss of response to either infliximab or adalimumab who required dose escalation. To investigate the impact of dose escalation on outcomes of CD (corticosteroid use, need for surgery and physicians perception).*  
*The only predictor of durable steroid free remission over 12 month following dose tailoring was the absence of prolonged, continuous use of corticosteroids for >6 months in the 5 years prior to dose tailoring (OR 3.5, 95% CI 1.05 to 12.05, p<0.042).* |
| **Yanai**<sup>(28)</sup> | Subanalysis of a retrospective study in Israel. 247 patients. | *Patients with active flare of IBD (55% CD).*  
*Average age 34*  
*Disease duration; 10 years*  
*43% Male*  
*Smokers; 15%*  
*22% had prior anti-TNF agents*  
*32% were on concurrent immunosuppressants.*  
*Crohn's Disease location was mostly ileocolonic or small bowel.*  
*Disease severity; not documented.*  
*To examine correlation between trough levels of anti-TNF agents or antibody titres and clinical outcomes to define predictors for loss of response in patients with IBD (55% with CD) with suspected loss of response to infliximab or adalimumab. Follow up was to 24 months.*  
*Trough levels of adalimumab >4.5 mcg/mL and infliximab >3.8 mcg/mL identified patients who failed to respond to an increase in drug dosage or a switch to another anti-TNF agent with 90% specificity; these were set as adequate trough levels. Adequate trough levels predicted response with more than 75% specificity.*  
*Levels of antibodies against adalimumab >4 mcg/mL equivalent or antibodies against infliximab >9 mcg/mL identified patients who did not respond to an increased drug dosage with 90% specificity. Dose escalation was more effective for patients with no or low titters of ADAs (p=0.02).*  
*Patients with adequate trough levels had a longer duration of response when they switched to a different class of agent than when anti-TNF was dose escalated (p=0.002).*  
*Authors concluded that trough levels of drug or antibody titres may guide therapeutic decisions for more than two-thirds of patients with IBD with either clinically suspected or definite inflammatory loss of response to therapy.* |

**Reference**


(27) Suzuki Y, Matsui T, Ito H. Circulating Interleukin 6 and Albumin, and Infliximab Levels Are Good Predictors of Recovering Efficacy After Dose Escalation Infliximab Therapy in Patients with Loss of Response to Treatment for Crohn's Disease: A Prospective Clinical Trial. Inflammatory Bowel Disease 2015; 21(9):2114-2122.


(32) Personal Communication with Takeda (switching to vedolizumab from anti TNF therapies in CD). October 2015.


(38) Torres J, Boyapati RK. Systematic Review of Effects of Withdrawal of Immunomodulators or Biologic Agents From Patients with Inflammatory Bowel Disease. Gastroenterology 2015; In press:Published Online, September 2015. (Abstract)

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