Infliximab and anti-infliximab antibody levels in Crohn's disease

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Assessment of infliximab and antibody to infliximab levels is desirable to guide therapy at the point of loss of response

► Steenholdt C, Brynskov J, Thomsen OØ, *et al.* Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. *Gut* 2014;63:919–27.

This study, the first controlled trial comparing dose escalation of infliximab with a treatment algorithm based on drug and antidrug antibody levels in the context of loss of treatment response in Crohn's disease, demonstrates cost benefit and clinical equivalence of an algorithm based approach.

Infliximab (IFX), a human-mouse chimerical antitumour necrosis factor α (anti-TNF α) drug, is a mainstay of treatment of Crohn's disease (CD). Initial response to therapy is often good, but subsequent loss of response (LOR) is common with time. Given the lack of alternative treatments it is desirable to optimise anti-TNF therapy, if possible, to extend its duration of therapeutic effect. Dose escalation of IFX at the point of LOR has been shown to be effective in a percentage of patients, but also has cost and side-effect implications. Measurement of IFX and antibodies to IFX (ATI) levels can be used to guide safety and efficacy of treatment dosing, but the availability and use of these tests is not yet universal. This study hypothesised that treating according to an algorithm based on IFX and ATI levels, rather than 'blindly' escalating the IFX dose at the point of LOR,

would provide cost savings without clinical compromise.

This was a multicentre, randomised, controlled, single blind clinical trial based in Denmark. Eligible patients had a diagnosis of CD with return of active disease following an initial response to IFX. Active disease was defined as Crohn's Disease Activity Index ≥ 220 and/or a minimum of one actively draining fistula. Patients were randomised to receive either conventional dose escalation of IFX with 5 mg/kg every 4 weeks, or tailored treatment according to an algorithm (table 1) based on IFX and ATI levels, for the duration of the 12 week trial. In the algorithm cohort, patients with low IFX levels and positive ATI (Group 1) were switched to adalimumab, while patients with low IFX levels and negative ATI (Group 2) received dose escalation of IFX. Patients with therapeutic IFX levels and absent ATI (Group 3) and those with therapeutic IFX levels and positive for ATI (Group 4) were advised to discontinue IFX and consider other therapies.

Costs per patient were calculated via the robust Danish National Patient Registry and included costs for all healthcare interactions related to CD during the 12 week trial. Drug and antibody levels were analysed using radioimmunoassays, and verified using ELISA and homogenous mobility shift assays. Coprimary end points were the mean healthcare cost per patient (Euros) and clinical response (defined as ≥ 70 point drop in Crohn's Disease Activity Index and/or decrease in draining fistulas $\geq 50\%$) rate.

Ninety-five patients were screened with 69 randomised (33 algorithm and 36 dose escalation). Of the 33 subjects randomised to the algorithm, 14 were not treated per algorithm, 2 withdrew from the study due to lack of drug effect and 17 completed the study correctly following the algorithm. Of the 36 subjects who had dose escalation, 8 withdrew (7 due to lack of effect, 1 due to severe infusion reaction) and 28 completed the trial. The cost per patient of the algorithm group was statistically significantly less (€3141 less, $p < 0.001$) than that of the dose intensification group and there was no statistically significant difference in the clinical response rate (58% vs 53%, respectively, $p = 0.810$). Normal IFX levels with negative ATI were found in 70% of randomised subjects, highlighting the multifactorial nature of LOR.

The study concludes that managing secondary IFX treatment failure by an algorithm based on serum IFX and ATI levels to define the mechanistic basis is more cost-effective than an intensified IFX regimen.

Comment

IFX and ATI testing add value and aid clinical decision making. Whereas inflammatory markers will merely alert us to LOR, drug level testing provides mechanistic information and informs corresponding interventions. The clear difference between costs of the two cohorts is evident even over the short time period of this study. It would be interesting to see cost and health status comparisons over a longer period of follow-up. No definition was provided for 'initial response'

Table 1 Based on the figure presenting the treatment algorithm in Steenholdt *et al*'s paper

	Detectable ATI	Undetectable ATI
Subtherapeutic IFX levels (<0.5 µg/mL)	Group 1 Insufficient IFX bioavailability due to induced immunogenicity. Action—Switch to a different anti-TNF (adalimumab)	Group 2 Insufficient IFX bioavailability due to non-immune mediated pharmacokinetics. Action—Intensify IFX treatment (IFX 5 mg/kg every 4 weeks)
Therapeutic IFX levels (>0.5 µg/mL)	Group 4 Consider: pharmacodynamics; non-functional anti-IFX Abs; false positive test. Action—Repeat IFX drug and Abs levels. If unchanged then act as in group 3	Group 3 Pharmacokinetics: inhibition of TNF-α is ineffective due to non-TNF driven disease. Action—Discontinue IFX. Review clinical condition and consider: alternative anti-TNF; optimise conventional immunosuppressant; glucocorticoid; surgery

ATI, antibodies to infliximab; IFX, infliximab; TNF, tumour necrosis factor.

to IFX, and this is a possible source of bias. It is also important to note that, of the patients randomised to the algorithm, the recommended protocol wasn't followed in over half. This probably reflects the directive to halt the IFX treatment in cases of LOR with therapeutic IFX levels, which isn't necessarily followed in practice, especially if LOR is partial and there is an absence of alternative therapies.

The main cost savings are from the avoidance of doubling IFX dose (and hence cost) in those patients with LOR who wouldn't benefit from dose escalation; namely those with ATI, and those with therapeutic drug levels. This is common sense and good practice. Availability of testing is commissioning group dependent, and the cost per test varies between laboratories. Non-numerical tests are

available for around £45 for the two tests. The cost saving demonstrated here makes a compelling business case to any commissioning group that does not yet recompense such testing.

Competing interests None.

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