NICE advice

RIDASCREEN tests for monitoring infliximab in inflammatory bowel disease

Medtech innovation briefing
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This advice should be read in conjunction with DG22.

Summary

- The **technologies** described in this briefing are the RIDASCREEN IFX Monitoring and RIDASCREEN Anti-IFX Antibodies tests. They are used for measuring free infliximab in the body and for measuring antibodies against infliximab, respectively, in serum or plasma samples.
- The **innovative aspect** of these tests is that they provide information on individual responses to infliximab with the aim of helping to guide future treatment and dosage.
- The intended **place in therapy** would be in addition to standard practice during maintenance therapy for inflammatory bowel diseases, before the next intravenous infusion, in order to guide drug dosage.

- The **main points from the evidence** summarised in this briefing are from 5 studies (1 prospective observational cohort and 4 assay correlation studies, n=587 samples). One study found that an infliximab concentration threshold of at least 2.7 micrograms/ml using the RIDASCREEN IFX Monitoring test was associated with mucosal healing in patients with ulcerative colitis. One study reported a coefficient of variations of 5% at both 3 and 7 micrograms/ml using the RIDASCREEN IFX Monitoring test.
- **Key uncertainties** around the evidence are that there are few studies that report clinical outcomes.
- The **costs** of the RIDASCREEN IFX Monitoring and RIDASCREEN Anti-IFX Antibodies tests are £795 and £986, respectively, for up to 40 duplicate or 80 singlicate tests (exclusive of VAT). The additional costs compared with standard care may be offset if the test were shown to optimise drug therapy or to improve disease management.

The technology

The RIDASCREEN IFX Monitoring test (R-Biopharm) is an enzyme-linked immunosorbent assay (ELISA) to measure the levels of infliximab (both the branded Remicade and its biosimilars Inflectra and Remsima) in human plasma or serum samples. The RIDASCREEN Anti-IFX Antibodies test is also an ELISA to detect antibodies against infliximab. This briefing focuses on their use to guide treatment with infliximab when used to treat inflammatory bowel disease (IBD).

People process infliximab differently, such that some people's IBD responds well to treatment whereas others have a lesser response or no response at all (primary non-responders). Some people's IBD initially responds to infliximab treatment but then stops (secondary loss of response). The RIDASCREEN IFX Monitoring test measures the amount of available (free) infliximab in the blood to determine whether the levels are high enough for infliximab to be an effective treatment for IBD. If the levels are too low, the RIDASCREEN Anti-IFX Antibodies test can be used to determine if this is because antibodies against infliximab are present in the blood.

Each RIDASCREEN test comes in a single kit, which includes a 96-well microtitre plate, 12 single-use 8-microwell strips, and all necessary reagents for up to 40 duplicate or 80 singlicate tests on serum or plasma samples. For every test, 16 microwells are used for calibration and quality control using 6 standards and 2 control samples in duplicate. Other reagents provided with the kit include diluent, conjugates, substrate, wash fluid and a stop

reagent.

Table 1 Comparative specifications of the RIDASCREEN tests

	RIDASCREEN IFX Monitoring	**RIDASCREEN Anti-IFX Antibodies**
ELISA type	Sandwich ELISA	Bridging-type ELISA
Analyte detected	Free infliximab drug	Free anti-infliximab antibodies
Microwell coating	TNF-alpha molecules	Infliximab
Detection reagents	Conjugate: peroxidase conjugated, monoclonal antibody (MA-IFXB7) Substrate: hydrogen peroxide/ tetramethylbenzidine	Conjugate 1: biotin conjugated infliximab Conjugate 2: peroxidase conjugated streptavidin Substrate: hydrogen peroxide/ tetramethylbenzidine
Controls	Low positive: 30 ng/ml IFX Positive: 70 ng/ml IFX	Low positive: 0.375 ng/ml Anti-IFX antibody (MA-IFX10F9) Positive: 3 ng/ml Anti-IFX antibody (MA-IFX10F9)
Sample dilutions/ measurement range	1:100 / 0.5 to 12 micrograms/ml IFX 1:400 / 2.0 to 48 micrograms/ml IFX	1:25 / 2.5 to 125 ng/ml ATI 1:200 / 20 to 1,000 ng/ml ATI
Total incubation times	1 hour 40 minutes	1 hour 55 minutes

Abbreviations: ATI, antibodies to infliximab; ELISA, enzyme-linked immunosorbent assay; IFX, infliximab; TNF, tumour necrosis factor.

Please refer to the manufacturer's instructions for further detailed information on the tests.

Both tests need additional equipment to be used, specifically: precision micropipettes and standard pipettes, a microplate washer or multichannel pipette, a 37°C incubator and a spectrophotometer (450 nm) or microplate reader (for manual mode). This equipment is readily available in most pathology laboratories. The manufacturer can supply its own microplate reader, the Dynex DS2, if needed.

For each sample, the concentration of free infliximab or antibodies against infliximab is calculated using the 6 standards. Laboratories with semi-automated ELISA platforms will have the software to do this calculation automatically. However, the evaluation software RIDASOFT Win.net is available for free from the company if needed.

R-Biopharm has recently developed RIDA QUICK IFX Monitoring, which is a rapid lateral flow test to quantify infliximab trough levels within 20 minutes. The company also has a number of other ELISAs including RIDASCREEN ADM Monitoring for the quantitative determination of another TNF-alpha inhibitor, adalimumab. However, these tests are beyond the scope of this briefing.

Innovations

The tests are designed to guide further treatment using information on how a person's body processes and responds to infliximab, which is known to vary significantly between people. This may be more precise than current management options such as empiric dose intensification, switching agents or immunomodulation.

RIDASCREEN tests are the commercially available products which were described in the NICE diagnostics guidance on therapeutic monitoring of TNF-alpha inhibitors in Crohn's disease as the Leuven in-house ELISA.

Current NHS pathway or current care pathway

The current diagnostic and care pathways for Crohn's disease are described in the NICE diagnostics guidance on therapeutic monitoring of TNF-alpha inhibitors in Crohn's disease.

NICE technology appraisal guidance on infliximab, adalimumab and golimumab describes the current management pathway for ulcerative colitis.

NICE recommends initial induction treatment with infliximab of intravenous infusion at 0, 2 and 6 weeks. No further treatment should be offered if the disease does not respond to this induction treatment. The specialist commentators who contributed to this briefing indicated that current practice would include measurement of infliximab levels in people whose disease has not responded at this point, using a test such as RIDASCREEN IFX Monitoring.

People whose disease responds to the induction treatment will progress to maintenance treatment. If their disease stops responding over time, treatment decisions are based on 'trial and error'. This includes shortening the interval between dosing, increasing the dose, switching to a different drug treatment and immunomodulation.

NICE diagnostics guidance on therapeutic monitoring of TNF-alpha inhibitors in Crohn's disease considers the use of these tests during the maintenance phase of treatment, but concludes that there is insufficient evidence to recommend their routine use in the NHS.

The RIDASCREEN Anti-IFX Antibodies test cannot measure antibodies against infliximab in samples that have a high level of infliximab: it can only be done if there is less than 1 microgram/ml in the sample. Therefore, a reflex testing strategy should be used. The RIDASCREEN IFX Monitoring test is done first; if the drug is undetectable, the Anti-IFX Antibodies test is used.

NICE is aware of the following CE-marked devices that appear to fulfil a similar function to the RIDASCREEN IFX Monitoring and Anti-IFX Antibodies tests:

- LISA-TRACKER ELISA kits (Theradiag; see NICE guidance)
- IDKmonitor ELISA kits (Immundiagnostik; see NICE guidance)
- Promonitor ELISA kits (Proteomika, Progenika; see NICE guidance)
- Anser IFX (Prometheus Laboratories)
- SHIKARI Q-Inflixi (Matriks Biotek)
- Level Infliximab and ADA Infliximab (Sanquin).

Population, setting and intended user

The RIDASCREEN tests would be used in addition to existing investigations to guide treatment of IBD with infliximab. Treatment with infliximab is managed by clinicians with experience of tumour necrosis factor-alpha (TNF-alpha) inhibitors and of managing IBD, such as gastroenterologists.

The tests would be done after the induction treatment and during maintenance treatment, before infusion with infliximab, in a hospital setting. They would be done in clinical laboratories and run by qualified laboratory staff with appropriate training on the test and system. The laboratory staff should work closely with the treating or referring clinician, in a network, to ensure appropriate use of the tests and interpretation of the results.

Costs

Technology costs

Each tests comes with the necessary reagents for 40 duplicate or 80 singlicate tests on plasma or serum samples. The costs of the tests per patient are:

- IFX Monitoring: duplicate processing (40 samples), £19.88
- IFX Monitoring: singlicate processing (80 samples), £9.94
- Anti-IFX Antibodies: duplicate processing (40 samples), £24.65
- Anti-IFX Antibodies: singlicate processing (80 samples), £12.33.

These costs depend on workload: if there are not enough samples for a full batch, the kit will need to be split. More patient samples (48 singlicate and 88 duplicate) could be processed if a laboratory can verify the use of standards and controls in singlicate.

These costs also do not include the additional equipment needed (pipettes, a microplate washer, an incubator and a spectrophotometer or microplate reader), but this equipment is readily available in most pathology laboratories. Staff costs, maintenance contracts and additional quality assurance needs are also not included. These costs would differ between manual and automated tests.

Table 2 Current costs of the RIDASCREEN tests and components

Description	Cost	Additional information
RIDASCREEN IFX Monitoring test kit	£795	Includes all necessary reagents, 1 96-well microtitre plate and 12 single-use 8-microwell strips
RIDASCREEN Anti-IFX Antibodies test kit	£986	Includes all necessary reagents, 1 96-well microtitre plate and 12 single-use 8-microwell strips
Dynex DS2 (if needed)	£33,000	Price of cash purchase, supplied on request. A rental price is available but depends on the rental period and number of samples to be processed within this period. Consumables would be needed and purchased separately
Maintenance of the Dynex DS2	Approximately £5,000	Per year, for a fully comprehensive service contract

The manufacturer provides training at no extra cost, typically in the form of 2 days' on-site training. Maintenance costs are only needed for the Dynex DS2 microplate reader. Laboratories with existing microplate readers or automated systems will have maintenance charges as per their existing contracts.

Costs of standard care

Although NICE does not recommend routine therapeutic drug monitoring of infliximab for IBD, specialist commentators advise that infliximab is monitored at a number of centres across the UK. For centres that do not monitor infliximab, standard care costs are assumed to comprise the infliximab drug costs only, without therapeutic drug monitoring.

A 100 mg vial of infliximab costs £419.62 (excluding VAT). The treatment cost varies between people because the dose is adjusted based on individual body weight. Costs may vary in different settings because of negotiated procurement discounts.

One specialist commentator noted that these costs are not representative of current practice, in which cheaper biosimilars such as Remsima and Inflectra are regularly used. RIDASCREEN IFX Monitoring and Anti-IFX Antibodies tests can both be used with the

biosimilar alternatives to infliximab.

Resource consequences

In centres where therapeutic drug monitoring of infliximab is not current practice, the use of RIDASCREEN IFX Monitoring and Anti-IFX Antibodies tests would represent additional acquisition costs. However, these costs could be offset by savings from drug therapy optimisation and improved disease management.

The per-patient costs of the RIDASCREEN tests are similar to those presented in the NICE diagnostics guidance on therapeutic monitoring of TNF-alpha inhibitors in Crohn's disease. Therefore, for centres that already offer infliximab testing using one of these methods, the RIDASCREEN tests would be unlikely to represent an additional cost.

The economic models described in the NICE diagnostics guidance show that reflex testing strategies are less costly but less effective than standard care. However, the losses reported by the economic model were uncertain because of the difficulties in measuring quality of life in these populations. These results are likely to be generalisable to the RIDASCREEN tests.

Regulatory information

The RIDASCREEN tests are CE marked as in vitro diagnostic devices. The manufacturer R-Biopharm has current CE certification for the following RIDASCREEN tests:

- RIDASCREEN IFX Monitoring test (CE marked in September 2016)
- RIDASCREEN Anti-IFX Antibodies test (CE marked in February 2016).

Identical versions of these tests that are made by the same company but marketed under the manufacturer name apDia are sold in Belgium, Netherlands, Luxembourg, Iran and Slovenia.

A search of the Medicines and Healthcare products Regulatory Agency website revealed that no manufacturer field safety notices or medical device alerts have been issued for this technology.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

Inflammatory bowel disease (IBD) is usually diagnosed in people in their late teens or early 20s, but can affect people of any age. It is more common in people of white ethnicity. People of Eastern European Jewish family origin are most likely to have IBD. People with Crohn's disease may be unable to carry out normal day-to-day activities and so may be considered to have a disability. Age, race and disability are protected characteristics under the Equality Act 2010.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

The literature search identified 10 studies that reported on the use of the RIDASCREEN tests for monitoring infliximab in inflammatory bowel disease (IBD). These include studies reporting on the earlier, pre-commercialised versions of the tests (Leuven in-house enzyme-linked immunosorbent assay [ELISA] method), because they were considered comparable to the current versions of the test. Studies reporting on these tests under their apDia branding were also included.

Five of these studies (table 3; n=587 serum samples in total) reported relevant clinical outcomes. These comprise 1 prospective observational study (Van Stappen et al. 2016)

and 4 studies that had relevant test comparisons which reported concordance data (Marini et al. 2017, Lee et al. 2016, Malickova et al. 2016, Schmitz et al. 2015).

This briefing excludes 1 randomised controlled trial (TAXIT; Vande Casteele et al. 2015) and 1 test comparison study (Vande Casteele et al. 2012) from full review, because they are summarised in the NICE diagnostics guidance on therapeutic monitoring of TNF-alpha inhibitors in Crohn's disease. Three bench-test studies (Van Stappen et al. 2015a, Van Stappen et al. 2015b, Gils et al. 2016) were also excluded because they did not include clinical outcomes.

Table 3 summarises the clinical evidence as well as its strengths and limitations.

Overall assessment of the evidence

Only 1 relevant additional study (Van Stappen et al. 2016) was identified since the publication of the NICE diagnostics guidance on therapeutic monitoring of TNF-alpha inhibitors in Crohn's disease in February 2016. This study included clinical outcome data on the use of a pre-commercialised version of the RIDASCREEN Anti-IFX Antibodies test. However, clinical outcome data were limited because it was not the primary outcome of the study. No information was reported on how therapeutic drug monitoring had helped with the management of symptoms.

In the absence of a gold-standard reference method for therapeutic drug monitoring of infliximab, there is limited evidence on the accuracy of the RIDASCREEN tests. Therefore, the evidence base is largely focused on correlation studies with other ELISAs for therapeutic drug monitoring of infliximab.

Only the Lee et al. (2016) and Schmitz et al. (2015) studies clearly stated which platforms were used for analysis, or whether the analysis was automated or manual.

The evidence base would be improved by prospective studies evaluating the clinical outcomes associated with using the tests.

Table 3 Summary of the current evidence

Van Stappen et al. 2016

Study size, design and location	N=190 serum samples from 29 anti-TNF-naive patients with ulcerative colitis starting IFX induction. Serum samples were prospectively collected during IFX induction (weeks 0, 2, and 6) and maintenance therapy (week 14 onward for up to 2 years). N=221 serum samples from the 29 patients were taken during the 1-year follow-up for testing 2 ATI tests. Prospective observational study, Belgium.
Intervention and comparator(s)	Intervention: rapid lateral flow-based assay (LFA, RIDA QUICK IFX). Comparator: RIDASCREEN IFX Monitoring. A new drug-tolerant anti-infliximab assay was also compared with a drug-sensitive anti-infliximab assay (Leuven in-house ELISA test, pre-commercialised version of Anti-IFX Antibodies), using 221 serum samples.
Key outcomes	Receiver operating characteristic analysis identified an IFX concentration threshold ≥2.7 micrograms/ml using the RIDASCREEN IFX Monitoring test (AUROC of 0.802, p=0.012, sensitivity 100%, specificity 50%) to be associated with mucosal healing. During the 1-year follow-up, the drug-sensitive anti-infliximab assay detected ATI in 14% (4/29) patients at at least 1 time point. In total, 5/221 (2%) samples were ATI-positive using the drug-sensitive assay. All 4 patients with positive ATI in the drug-sensitive bridging ELISA had at that time no detectable TC. Two out of 8 patients discontinued IFX maintenance treatment because of adverse events associated with ATI development. The drug-sensitive assay detected the ATI at 40 and 17 weeks before the adverse events.
Strengths and limitations	Strengths: the study provides useful clinical outcome data on the use of RIDASCREEN. The patients in this trial are likely to be representative of those who would have IFX in UK practice. Limitations: the analysis was post-hoc which may introduce potential bias. Samples were collected from a small cohort of patients with ulcerative colitis. Results may not be generalisable to Crohn's disease.
Lee et al. 2016	

Study size, design and location	N=12 serum samples, comprising 3 control samples from 2 healthy men and 1 woman, and 9 physiological interference samples. Physiological interference samples were from patients with positive rheumatoid factor (n=3) and with para-proteins (n=6). IFX was added to each of the serum control and physiological interference samples to achieve final infliximab concentrations of 0, 0.2, 2.0, 3.0 and 7.0 micrograms/ml. Pharmacological interference samples were prepared using adalimumab and etanercept and were diluted to achieve therapeutic concentrations of 20 mg/ml and 25 mg/ml respectively. Assay correlation study, Australia.
Intervention and comparator(s)	Comparison of 3 ELISAs for the detection of serum IFX trough levels: RIDASCREEN IFX Monitoring (R-Biopharm), Promonitor-IFX (Grifols) and LISA-Tracker Infliximab (Theradiag).
Key outcomes	RIDASCREEN IFX Monitoring had poorer agreement compared with other methods and consistently produced readings lower than the known concentration of the prepared samples. RIDASCREEN IFX Monitoring produced accurate negative readings at an IFX concentration of 0 micrograms/ml. To calculate the CV, 7 samples were analysed at concentrations of 3 and 7 micrograms/ml. CVs at both were 5%. Low concentrations of ATI caused little effect (in vitro binding) on the IFX results, while higher concentrations resulted in reduced IFX drug levels in a dose-dependent fashion. Falsely low readings were observed in the presence of etanercept, while no significant interference was observed with adalimumab.
Strengths and limitations	Strengths: a blinded set of samples were aliquoted from the original samples before sending to the respective laboratories, therefore reducing potential for operator bias. Limitations: samples were sent to different laboratories for analysis and details of their analysis techniques (platforms used and automated or manual processes) were not described. The para-protein interference samples were considered not entirely relevant to the IBD population because they are not common findings in this patient group.

Marini et al. (2017)	
Study size, design and location	N=56 serum test samples for IFX concentration. N=32 serum test samples for ATI. Samples were from IBD patients (with and without IFX exposure) and healthy volunteers. Samples based on normal human serum were spiked with an IFX concentration of 5 micrograms/ml. Assay correlation study, US.
Intervention and comparator(s)	Intervention: Janssen (in-house) IFX and ATI (original and drug-tolerant versions) assays used in clinical trials of IFX. Comparators: RIDASCREEN IFX Monitoring and an in-house version of the RIDASCREEN Anti-IFX Antibodies test. Commercialised IFX and ATI assays from Sanquin (Level Infliximab and ADA Infliximab), LabCorp (MSD ECLIA), and Dynacare (Promonitor-IFX ELISAs).
Key outcomes	No cross-reactivity was observed for the RIDASCREEN IFX Monitoring test with other anti-TNFs drugs prepared at 5 micrograms/ml of (adalimumab, certolizumab pegol, golimumab or siltuximab). The presence of ATI affected the selectivity of the RIDASCREEN IFX Monitoring test in a titre-dependent manner. However, TNF-alpha concentrations (0.5 to 50 ng/ml) did not affect IFX detection in the assay. The in-house version of the RIDASCREEN Anti-IFX Antibodies test produced inconclusive results in the presence of ≥2 micrograms/ml IFX concentrations.
Strengths and limitations	Strengths: sample analysis of all ELISAs was done in a blinded manner, which would reduce reviewer bias. Limitations: the study only compared the Janssen methods to each of the commercialised tests; little comparison was made between each of the commercialised tests. The study was funded by Janssen and therefore reporting bias may be introduced.
Malickova et al. 2016	

Study size, design and location	N=42 serum samples from IBD patients (n=22) having Remsima (biosimilar IFX). 22 serum samples were measured at week 2 of the induction treatment, 15 serum samples at week 6 and 5 samples at week 14. Assay correlation study, US.
Intervention and comparator(s)	Comparison of 3 ELISAs for the detection of serum IFX trough levels: RIDASCREEN IFX Monitoring (R-Biopharm), SHIKARI Q-Inflixi (Matriks Biotek) and LISA-Tracker Duo Infliximab (Theradiag).
Key outcomes	At the cut-off value of 3 micrograms/ml IFX, the RIDASCREEN IFX test showed good correlation with the LISA-Tracker Duo (Kappa=0.76, r=0.92). At the cut-off value of 3 micrograms/ml IFX, the SHIKARI Q-Inflixi showed good correlation with the RIDASCREEN IFX test (Kappa=0.76, r=0.86). IFX levels measured by RIDASCREEN IFX Monitoring did not predict treatment responsiveness at week 2 after the induction phase treatment (p=0.71). Similar results were obtained for week 6 measurements.
Strengths and limitations	Strengths: this is the only study to investigate the correlation of 3 IFX ELISAs using the biosimilar Remsima. Limitations: very limited data were described about the clinical performance evaluation of the assays. Insufficient details of sample blinding may introduce reviewer bias. There were discrepancies between the Spearman's rank correlation coefficient values reported in the text and figures for RIDASCREEN IFX compared with LISA-Tracker Duo. The correct sample dilution was also not used.
Schmitz et al. 2015	
Study size, design and location	N=34 blood samples (30 samples from patients with Crohn's disease or ulcerative colitis, collected immediately before a new IFX infusion, and 4 spiked plasma samples of IFX concentrations 10, 5.0, 2.5 and 0.5 micrograms/ml). Comparative performance evaluation study, The Netherlands.

Intervention and comparator(s)	Comparison of 3 ELISAs for the detection of infliximab: Infliximab ELISA (apDia), Theradiag (LISA-Tracker Infliximab), Progenika (Promonitor-IFX). All ELISA tests were implemented on the automated DSX 4-plate ELISA Processing System (Dynex Technologies).
Key outcomes	Imprecision results were determined using patient samples at 3 levels by triplicate measurements on 5 different days. The within-run imprecision of the apDia Infliximab ELISA at low (0.68 micrograms/ml), middle (2.8 micrograms/ml) and high (5.9 micrograms /ml) levels of infliximab were 6.1%, 1.9% and 2.4%, respectively. The between-run imprecision of the apDia Infliximab ELISA at low (0.68 micrograms/ml), middle (2.8 micrograms/ml) and high (5.9 micrograms/ml) levels of infliximab were 6.3%, 7.1% and 6.0%, respectively. The agreement of the apDia ELISA to the target values of the spiked samples ranged between 96% and 108%.
Strengths and limitations	Strengths: robust methods were used to determine imprecision values as triplicate measurements were made on 5 different days. Results were anonymised following IFX measurement, reducing the potential for reporter bias. Limitations: there were a relatively small number of samples analysed.
Abbreviations: ATI, antibodies to infliximab; AUROC, area under receiver operating characteristic; CI, confidence interval; CV, coefficient of variation; ELISA, enzyme-linked immunosorbent assay; IBD, inflammatory bowel disease; IFX, infliximab; LFA, lateral flow assay; TC, trough concentration; TNF, tumour necrosis factor.	

Recent and ongoing studies

Two of the specialist commentators highlighted an analytical evaluation study of the RIDASCREEN IFX Monitoring test. This was presented as a poster at the British Society of Gastroenterology Conference in 2016, and is due to be published as a paper in 2017.

Specialist commentator comments

Comments on these technologies were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

All 4 specialist commentators were familiar with the RIDASCREEN tests and 2 had used them for research purposes. Three specialist commentators routinely use therapeutic drug monitoring, but none uses the RIDASCREEN tests.

Level of innovation

Three specialist commentators considered the RIDASCREEN tests to have little innovation because similar technologies already exist and are readily available. One added that RIDASCREEN is only a minor variation on existing tests. The fourth commentator highlighted that the University of Leuven uses the RIDASCREEN tests, and this is one of the leading and reputable centres in this field.

One commentator considered that ELISA technologies will likely be superseded in the near future by fully automated immunoassays, which offer higher throughput and efficiencies of scale.

Potential patient impact

Two specialist commentators considered that therapeutic drug monitoring is widely recognised as best practice in managing IBD, but that this isn't currently reflected in national guidelines. One added that 3 centres in the UK already offering routine testing using tests other than RIDASCREEN.

Three commentators indicated that the RIDASCREEN tests allow a personalised approach to drug optimisation, which is better for patients than empirical dose escalation. One added that this is particularly useful in patients whose disease doesn't respond (primary non-response) or stops responding (secondary loss of response). Additionally, 2 commentators considered that the tests reduce exposure to unnecessary, potentially harmful drugs in certain patients.

One specialist commentator described an analysis in their practice which demonstrated

that in most people with secondary loss of response, the amount of infliximab in the blood had reached the therapeutic level. This means that the lack of response was not caused by a shortage of infliximab, so an increased dose wouldn't help.

One commentator added that patients who test positive for antibodies against infliximab are at an increased risk of infusion reactions. They felt that therapeutic drug monitoring may help to achieve a better response to infliximab treatment. This could help eliminate disease-related symptoms and improve quality of life with as few side effects as possible.

Potential system impact

Three specialist commentators considered that no changes in facilities or infrastructure would be needed because similar technologies are already used in the NHS. One commentator disagreed, and felt that any centre choosing to adopt the RIDASCREEN tests would need some infrastructural changes before implementation. Additional training may also be needed for any extra equipment (such as the Dynex DS2).

Another commentator highlighted that interpreting the results of the tests needs considerable expertise and understanding of their limitations, and appropriate network facilities and software would be needed to transfer patient results.

All 4 specialist commentators considered that the RIDASCREEN tests could lead to cost savings for the NHS. Three added that cost analyses should take the cheaper costs of biosimilars into account.

One commentator described that from their experience, the test cost was negligible compared with the annual cost of infliximab per patient. Costs savings can be achieved by dose de-escalation, drug optimisation and better outcomes for patients. They considered that using the tests may also reduce future hospital admissions.

General comments

One specialist commentator explained that, for the RIDASCREEN Anti-IFX Antibodies test kit, they run singlicate patient samples but at 2 different dilutions (1:25 and 1:200), so the maximum number of patient samples per plate in this instance is 40. Another commentator advised that sample dilutions for infliximab measurement may later affect the number of samples that will need repeat testing for absolute values.

One commentator highlighted that routine use of the RIDASCREEN tests is subject to the same limitations noted in the NICE diagnostics guidance on therapeutic monitoring of TNF-alpha inhibitors in Crohn's disease, and further research is needed to address this issue.

Two commentators highlighted that a full analytical verification of the RIDASCREEN tests on existing microplate readers would be needed before offering a clinical service. One added that laboratories using an automated or semi-automated ELISA platform would need to ensure acceptability of the in-built software, in use and implement sufficient quality control procedures and validation criteria for ongoing quality assurance. One commentator further advised that manual methods would not be recommended for routine services.

Specialist commentators

The following clinicians contributed to this briefing:

- Ms Zehra Arkir, consultant clinical scientist, Viapath, St Thomas' Hospital. Ms Arkir was a stakeholder on the analytical evaluation of similar assays evaluated in NICE diagnostics guidance on therapeutic monitoring of TNF-alpha inhibitors in Crohn's disease. She has conducted analytical evaluations of the RIDASCREEN tests which were provided free of charge by R-Biopharm.
- Ms Mandy Robinson, advanced nurse practitioner/inflammatory bowel disease nurse, Newcastle-upon-Tyne Hospitals NHS Trust (no conflicts of interest declared).
- Dr Ally Speight, consultant gastroenterologist, Newcastle-upon-Tyne Hospitals NHS Trust (no conflicts of interest declared).
- Mr Nick Unsworth, senior clinical scientist, Imperial College Healthcare NHS Trust. Mr Unsworth has previously done analytical evaluations of the RIDASCREEN tests, which were provided free of charge by R-Biopharm.

Development of this briefing

This briefing was developed for NICE by Newcastle and York external assessment centre. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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