Promonitor for monitoring response to biologics in rheumatoid arthritis

Medtech innovation briefing
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Summary

- The technology described in this briefing is Promonitor. It is used to monitor response to biologic therapies.

- The innovative aspect is that each sample only needs to be run once, potentially allowing for a higher throughput of tests.

- The intended place in therapy would be in addition to current methods of monitoring drug response in people with rheumatoid arthritis.

- The main points from the evidence summarised in this briefing are from 4 prospective studies (2 in Europe and 2 in Asia) and 1 study comparing 3 devices, including a total of 495 adults in specialist centres. They show that drug levels can predict disease response.

- Key uncertainties around the evidence are that the evidence base is still developing with no studies yet showing the direct effect of monitoring. In addition, there are no agreed cut-off levels for adjusting drug treatment, and no standard NHS drug monitoring pathway.

- The cost of Promonitor is £700 per unit (exclusive of VAT). The resource impact would be to add costs to standard care. These costs may be offset if drug monitoring led to reductions in drug costs through dose reduction or stopping ineffective therapy.
The technology

Promonitor (Grifols–Progenika) is a portfolio of assays, run on an enzyme-linked immunosorbent assay (ELISA) technology platform, that measure drug levels (etanercept, infliximab, infliximab biosimilars, adalimumab, rituximab, golimumab) and their correlating anti-drug antibodies (anti-etanercept, anti-infliximab, anti-adalimumab, anti-rituximab, anti-golimumab). The focus of this briefing is the use of Promonitor tests to monitor response to biologic treatments for rheumatoid arthritis. Monitoring drug response can help determine which drug works best for the patient.

A serum sample is needed for the test. Each assay is supplied separately and includes an ELISA plate, all necessary buffers, antibody, substrate and stop solutions, cover films, and a package insert and information sheet.

Promonitor tests can be run with or without automation platforms and may be used with any ELISA platform or the Tritutus or SQII platforms.

The company also offers Promonitor Quick, which is a qualitative point-of-care test to detect anti-infliximab antibodies in whole blood (finger-prick or venous) or serum.

The company is developing assays to measure response to other biologic drugs (and their anti-drug antibodies), specifically tocilizumab, certolizumab pegol and vedolizumab.

Innovations

Unlike current ELISA-based tests, which are run in duplicate, each Promonitor test needs to be run once. This is designed to improve efficiency.

Current NHS pathway

The NICE guideline on rheumatoid arthritis in adults recommends that disease activity should be monitored regularly (using a composite score such as DAS28). It recommends changing treatment if the disease is not responding, but makes no specific recommendations on monitoring response to biologics. However, evidence suggests that monitoring response to biologics is beneficial in clinical practice. In 2013, a systematic review and meta-analysis of 17 studies (865 patients) showed that anti-drug antibodies reduced drug response by up to 80% (Garces et al. 2013).
Promonitor would be used in addition to current inflammatory markers, visual analogue scale (VAS) and DAS28 (disease activity score) tools. In 2014, Garces et al. published a preliminary algorithm for monitoring drug response in people with rheumatoid arthritis having biologic therapies.

**Population, setting and intended user**

Promonitor would be used in addition to existing investigations to guide treatment of rheumatoid arthritis with biologics. Samples would be analysed in a specialist laboratory by staff with experience of ELISA and training in Promonitor (the company provides training at no extra cost). Results would be interpreted by rheumatology specialist teams.

Promonitor Quick may be used in secondary care outpatient clinics.

Promonitor is used in 5 hospitals in the UK.

**Costs**

**Table 1 Technology costs**

<table>
<thead>
<tr>
<th>Description</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of ELISA plate</td>
<td>£700.00</td>
</tr>
<tr>
<td>Cost per test (singlicate, 88 tests per plate)</td>
<td>£7.95</td>
</tr>
<tr>
<td>Cost per test (duplicate, 40 tests per plate)</td>
<td>£17.50</td>
</tr>
<tr>
<td>Cost per patient (singlicate)</td>
<td>£24.46</td>
</tr>
<tr>
<td>Cost per patient (duplicate)</td>
<td>£50.52</td>
</tr>
<tr>
<td>Annual cost per patient (2 cycles)</td>
<td>Singlicate: £48.92; duplicate: £101.04</td>
</tr>
<tr>
<td>Annual cost per patient (3 cycles)</td>
<td>Singlicate: £73.38; duplicate: £151.46</td>
</tr>
</tbody>
</table>

**Costs of standard care**

Currently, treatment and response is based on subjective clinical assessment using diagnostic markers for inflammation and VAS and DAS28 assessment.

This type of monitoring requires a blood test, biochemistry profile and follow-up with a specialist nurse.
Resource consequences

Using Promonitor may lead to reduced prescribing costs and better outcomes for people through more efficient prescribing and dosage of biologics.

Proper use of Promonitor will need a therapeutic drug monitoring strategy to be developed for use in the NHS. This should be used for consistency in interpreting results and establish therapeutic cut-offs for each biologic.

Regulatory information

Promonitor was CE marked as an in-vitro diagnostic in September 2012.

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).

No equality issues were identified.

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

This briefing summarises 4 studies (n=495): 3 prospective studies and 1 study comparing 3 devices.

Table 2 summarises the clinical evidence as well as its strengths and limitations.
Overall assessment of the evidence

Few studies have compared alternative tests or evaluated the effect of monitoring. Further evidence about this would be helpful, because there is unpredictability in the action of biologics for rheumatoid arthritis and subjective outcomes are often used to guide treatment.

The evidence for Promonitor does not define the cut-off levels or help define a potentially standard monitoring pathway for people on biologics. This may need significant work and collaboration across specialist centres.

Table 2 Summary of selected studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and location</th>
<th>Intervention and comparator(s)</th>
<th>Key outcomes</th>
<th>Strengths and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al. (2016)</td>
<td>Prospective study in 64 people with rheumatoid arthritis. All people included were considered to be in remission or LDA and had a DAS28 score of &lt;3.2 Location: Taiwan.</td>
<td>Adalimumab and anti-adalimumab levels were measured using Promonitor and therapeutic response was measured using the DAS28 tool. This was used to calculate the optimal cut-off drug levels for predicting persistent remission.</td>
<td>At baseline, 25 (39.1%) and 39 (60.9%) patients had achieved remission and LDA, respectively. After this, patients had 24 weeks of adalimumab dose-halving. Persistent remission was observed in 23 patients, remission turned LDA in 2 patients, persistent LDA in 24 patients and disease flare in 15 (23.5%) patients. Baseline adalimumab levels were significantly higher in patients with persistent remission (median 10.5 mcg/ml) or LDA (4.5 mcg/ml) than in those with disease flare (0.9 mcg/ml). An ADA level above the cut-off value of 6.4 mcg/ml might predict persistent remission after dose-halving with high sensitivity and specificity.</td>
<td>This study was done in a Taiwanese population and so may not be wholly applicable to a UK population. The area under the receiver operating curve calculated is very high (0.998 and 0.995 for remission and LDA respectively) and should be interpreted with caution.</td>
</tr>
</tbody>
</table>
**Study size, design and location**

Observational prospective study in 331 people (160 having adalimumab and 171 having etanercept) with rheumatoid arthritis.

Location: UK.

**Intervention and comparator(s)**

ADA levels and drug levels were measured at 3, 6 and 12 months after starting therapy. These results were compared with treatment response (measured by DAS28).

**Key outcomes**

At 12 months’ follow-up, ADAs were detected in 24.8% of patients having adalimumab (31/125) and in no patients having etanercept.

ADA-positive patients had lower median dosages of methotrexate compared with anti-drug antibody-negative patients (15 mg/week vs 20 mg/week; p=0.01) and had a longer disease duration (14.0 vs 7.7 years; p=0.03).

The adalimumab level was the best predictor of change in the DAS28 at 12 months.

Etanercept levels were associated with the EULAR response at 12 months (regression coefficient 0.088, 95% CI 0.019 to 0.16, p=0.012), but this difference was not significant after adjustment.

A BMI of ≥30 kg/m² and poor adherence were associated with lower drug levels.

**Strengths and limitations**

Good size study population and serial sampling. Study done in NHS setting. The presence of ADAs and non-trough drug levels were measured by radioimmunoassay instead of Promonitor. The authors stated that radioimmunoassay is less susceptible to drug interferences than ELISA.

Chen et al. 2015

**Study size, design and location**

Observational prospective study in 70 people (36 having adalimumab and 34 having etanercept) with rheumatoid arthritis.

Location: Taiwan.

**Intervention and comparator(s)**

ADAs were measured using bridging ELISA (Promonitor) and radioimmunoassay, and drug levels were measured using sandwich ELISA (Promonitor) at 6 and 12 months after starting drug treatment. Optimal cut-off drug levels for EULAR responses were determined by ROC curve analysis.
### Key outcomes

ADAs were detected in 10 (27.8%) and 13 (36.1%) patients having adalimumab after 12 months using Promonitor and radioimmunoassay, respectively. No anti-drug antibodies were detected in people who had etanercept.

The presence of ADAs was associated with lower EULAR response and lower drug levels compared with those without (both \(p<0.001\)).

Drug trough levels were positively associated with DAS28 decrement (all \(p<0.001\)). The optimal cut-off trough levels for adalimumab were 1.274 mcg/ml and 1.046 mcg/ml, and those for etanercept were 1.242 mcg/ml and 0.800 mcg/ml for good EULAR response assessed at the sixth and twelfth month, respectively.

### Strengths and limitations

This study was done in a Taiwanese population and so may not be wholly applicable to a UK population.

### Schmitz et al. 2015

#### Study size, design and location

Comparative study of 3 ELISA kits for monitoring of infliximab using 30 patient samples.

Location: Netherlands.

#### Intervention and comparator(s)

Promonitor, Lisa Tracker and apDia were all implemented on an automated processing system and were repeated 3 times over 5 days. Therapeutic consequences were evaluated by dividing patients into 4 treatment groups using cut-off levels of 1, 3 and 7 mcg/ml and determining assay concordance.

#### Key outcomes

Within-run and between-run imprecision were acceptable (\(\leq 12\%\) and \(\leq 17\%\), respectively) within the quantification range of the selected ELISA kits. The apDia assay had the best precision and agreement to target values. The Promonitor assay measured the lowest infliximab concentrations, the apDia assay the highest.

#### Strengths and limitations

The authors note that large differences were observed between the 3 assays but it is not clear which would have the greatest clinical applicability. They note that standardisation is needed.

### Laine et al. 2016

#### Study size, design and location

Cost-effectiveness study done in 486 and 1,137 samples from people having adalimumab and infliximab, respectively.

Location: Finland.
Samples were tested for drug levels and ADAs using the Promonitor kit. The authors modelled the impact of using Promonitor for clinical decision making and included: costs for non-optimal treatment; outpatient and specialist visits, laboratory costs; cost of resources; and societal costs.

The Markov model shows that after 3 years, 40% of people having adalimumab and 50% of people having infliximab would need drug treatment modifications. Costs incurred from non-optimal treatment were €1,471 per month and accumulated on clinical follow-up visits.

The authors suggest that drug levels should be monitored regularly for all people having biologics, but that ADAs should only be measured when drug levels are low.

Dose escalation was not included in the model. Long-term health costs and consequences were not considered in the model which spanned 1 year. This study was done in a Finnish population and so may not be wholly applicable to a UK population.

Abbreviations: ADA, anti-drug antibody; LDA, low disease activity; EULAR, European League Against Rheumatism response score; ROC, receiver operating characteristic.

Recent and ongoing studies


Specialist commentator comments

Comments on this technology 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.

Five commentators provided comments on this briefing. Four of the specialists were familiar with or had used Promonitor before. One commentator was unfamiliar with this technology but provided comments as a specialist in rheumatoid arthritis.
Level of innovation

Three commentators felt that Promonitor is not novel compared with competitor devices, but 1 noted that they had found it to be the most cost-effective option. One specialist commentator stated that Promonitor is an advancement of current care. Another noted that the evidence base and number of devices for drug monitoring are developing rapidly.

Potential patient impact

Two specialist commentators stated that using Promonitor allows for quick determination of drug effect and dosage. This may allow for quicker determination of drug failure and reduction in adverse events because of inadequate treatment. Three commentators also noted that immunosuppressive drugs may be avoided or reduced, which in turn may reduce cumulative immunosuppression risk. Two specialist commentators stated that Promonitor can be used to predict treatment response and adjust treatment accordingly.

All but 1 of the commentators noted that further investigation was needed to inform proper use of Promonitor and to establish a new care pathway.

One specialist noted that people having treatment for ankylosing spondylitis, psoriatic arthritis, psoriasis and inflammatory bowel disease may also benefit from monitoring with Promonitor. Another felt that some people’s treatment may be changed inappropriately. They observed that Promonitor should only be used alongside other clinical observations to help inform decisions.

Potential system impact

All but 1 of the specialist commentators noted that using Promonitor could save costs through dose reductions. One commentator stated that savings may be notable but depend on clinical engagement and willingness to change practice.

Another stated that cost savings were likely if the same treatment response can be reliably maintained during dose reduction. However, they did not expect a reduction in hospital visits.

One specialist commentator advised that testing would need to be centralised in order to collect enough samples to utilise the high throughput of the test.

All 5 commentators agreed that a programme for dosage reduction would need to be established to realise the potential benefits. Two noted that the evidence to support a new care pathway and
dosage reduction programme is ongoing, but another noted that the cost of implementing these new practices would likely be significant.

General comments

One specialist commentator has implemented Promonitor in their laboratory. They stated that it took 1 day's training for laboratory staff to become familiar with the tests. They explained that most laboratories will have existing equipment that can run Promonitor, but that extra laboratory staff may be needed (as well as additional phlebotomies, a system for communication and verification of results, and clinician time for interpretation).

One commentator has extensive experience with Promonitor, having done a study in 331 people, and stated that the tests are easy to use when the protocols are followed and the company is willing to help with any problems.

One specialist commentator identified the need for evidence that dosage reduction leads to patient benefits in all biologic drugs listed in the indication. They noted that there was less evidence to support dose reduction of newer, non-anti-TNF biologics compared with adalimumab, infliximab and etanercept.

Specialist commentators

The following clinicians contributed to this briefing:

- Dr Martin E Perry, consultant physician and rheumatologist and clinical lead for rheumatology, Effective Prescribing Biologics Programme, National Services Scotland. Dr Perry was provided with Promonitor kits and training from the company at no cost for a pilot study at the centre.

- Dr Meghna Jani, NIHR clinical lecturer in rheumatology, University of Manchester. No relevant conflicts of interest.

- Dr Ray Armstrong, consultant rheumatologist, Southampton General Hospital. No relevant conflicts of interest.

- Professor John Isaacs, professor of clinical rheumatology, Newcastle University. Professor Isaacs has received speaker fees from pharmaceutical companies to lecture on immunogenicity and anti-drug antibodies, and a grant for research that involved the use of Promonitor kits.
• Dr Peter Galloway, consultant medical biochemist, NHS Greater Glasgow and Clyde. No relevant conflicts of interest.

Development of this briefing

This briefing was developed by NICE. 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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