

# Enzyme-linked immunosorbent assays for monitoring TNF-alpha inhibitors and antibody levels in people with rheumatoid arthritis: a systematic review and economic evaluation

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## Scientific summary

TNF-alpha inhibitors and antibodies in rheumatoid arthritis

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# Scientific summary

## Background

Rheumatoid arthritis is a systemic, chronic, inflammatory, autoimmune disease that typically affects synovial joints. In rheumatoid arthritis, the body produces an excess of a protein called tumour necrosis factor- $\alpha$ , which causes inflammation, pain and damage to the bones and joints, resulting in increasing disability and reduced quality of life.

People with severe disease may be treated with biological disease-modifying antirheumatic drugs, including tumour necrosis factor- $\alpha$  inhibitors such as adalimumab (Humira<sup>®</sup>; AbbVie Inc., North Chicago, IL, USA), etanercept (Enbrel<sup>®</sup>; Pfizer, Inc., New York, NY, USA), infliximab (Remicade<sup>®</sup>; Merck Sharp & Dohme Limited, Hoddesdon, UK), certolizumab pegol (Cimzia<sup>®</sup>; UCB Pharma Limited, Slough, UK) and golimumab (Simponi<sup>®</sup>; Merck Sharp & Dohme Limited). Tumour necrosis factor- $\alpha$  inhibitors block the action of tumour necrosis factor- $\alpha$  and, therefore, reduce inflammation. In some people the disease does not respond to treatment (primary non-responders) and in others response to treatment is lost over time (secondary non-responders). The loss of response may be caused by several factors, including an antibody response elicited by the biologics and fluctuations in the circulating drug levels.

Commercial enzyme-linked immunosorbent assays, such as Promonitor (Grifols-Progenika, Derio, Spain), IDKmonitor (manufactured by Immundiagnostik AG, Bensheim, Germany, and distributed by BioHit Healthcare, Cheshire, UK), LISA-TRACKER (Theradiag, Croissy-Beaubourg, France), RIDASCREEN (R-Biopharm AG, Darmstadt, Germany), MabTrack (Sanquin, Amsterdam, the Netherlands) and those from Sanquin Diagnostic Services (Amsterdam, the Netherlands), can be used to detect and measure drug concentrations and anti-drug antibody levels in the serum or plasma of people treated with tumour necrosis factor- $\alpha$  inhibitors. These tests may inform whether or not adjustments to treatment are required, help clinicians to understand the reasons for absence or a loss of treatment response and optimise dosage for those who are already responding.

Therapeutic drug monitoring for rheumatoid arthritis is not routine in most clinical practices in the UK. Monitoring a patient's response to these treatments typically involves clinical assessment according to response criteria, such as Disease Activity Score in 28 joints.

## Objectives

The objectives of this study were to investigate whether or not using enzyme-linked immunosorbent assay tests to measure the levels of the drug and anti-drug antibodies for monitoring response to TNF- $\alpha$  inhibitors in people with rheumatoid arthritis who had either achieved treatment target (remission or low disease activity) or experienced a primary or a secondary non-response to treatment is clinically effective, and to investigate whether or not adding enzyme-linked immunosorbent assay testing to standard of care represents a cost-effective use of NHS resources.

## Review of clinical effectiveness studies

### Methods

A clinical effectiveness systematic review was conducted following the Centre for Reviews and Dissemination and the National Institute for Health and Care Excellence guidance.

The following bibliographic databases were searched from inception to July 2018, and again in November 2018: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Web of Science, ClinicalTrials.gov, World Health Organization International Clinical Trials Registry and EU Clinical Trials Register. These searches were supplemented by consultation with experts in the field, and reference-checking of relevant systematic reviews and included studies.

Two reviewers independently assessed titles and abstracts, as well as full-text papers, using prespecified inclusion and exclusion criteria. References were included if the study participants were individuals with rheumatoid arthritis who were receiving treatment with a tumour necrosis factor- $\alpha$  inhibitor (adalimumab, etanercept, infliximab, certolizumab pegol or golimumab) and had achieved treatment target (remission or low disease activity) or had experienced a primary or a secondary non-response. Enzyme-linked immunosorbent assay test kits and diagnostic services that were used to monitor response to tumour necrosis factor- $\alpha$  inhibitor treatments in people with rheumatoid arthritis were eligible for inclusion. The testing must have been compared with standard of care for people with rheumatoid arthritis, in which treatment decisions are based on clinical judgements and monitoring using a composite score, such as Disease Activity Score in 28 joints. Clinical outcomes included changes in disease activity; the rates and duration of disease response, relapse and remission; and the rates of hospitalisation, surgical intervention and adverse effects. Other outcomes included health-related quality of life.

Data extraction and quality appraisal [using the Cochrane ROBINS-1 (Risk Of Bias In Non-randomised Studies – of Interventions) tool for non-randomised controlled and observational studies] were performed by one reviewer and checked by a second reviewer.

## Results

The review criteria were broadened to include studies in which people with rheumatoid arthritis made up < 70% of the study population. Two studies (in four publications) were identified: INGEBIO [reported in three abstracts: Ucar E, Gorostiza I, Gomez C, Perez C, Dios J, Alvarez B, *et al.* Prospective, intervention, multicenter study of utility of biologic drug monitoring with respect to the efficacy and cost of adalimumab tapering in patients with rheumatic diseases: preliminary results of INGEBIO study. *Ann Rheum Dis* 2017;**76**:826; Arango CG, Vivar MLG, Angulo EU, Gorostiza I, Perez CE, De Dios JR, *et al.* Prospective, intervention, multicenter, non-inferiority study of utility of therapeutic drug monitoring with respect to the efficacy and cost of adalimumab tapering in patients with rheumatic diseases. *Arthritis Rheumatol* 2017;**69**(Suppl. 10); and Gorostiza I, Angulo EU, Arango CG, Perez CE, De Dios JR, Alvarez B, *et al.* Prospective, intervention, multicenter study of utility of biologic drug monitoring with respect to the efficacy and cost of adalimumab tapering in patients with rheumatic diseases (34-week descriptive data). *Arthritis Rheumatol* 2016;**68**(Suppl. 10):835–6] and Pascual-Salcedo *et al.* [Pascual-Salcedo D, Plasencia C, Gonzalez Del Valle L, Lopez Casla T, Arribas F, Villalba A, *et al.* Therapeutic drug monitoring (TDM) in rheumatic day clinic enables to reduce pharmaceutical cost maintaining clinical efficacy. *Ann Rheum Dis* 2013;**72**:A227]. Both studies were conducted in Spain and recruited people on biological therapies who had achieved remission or low disease activity. INGEBIO investigated Promonitor enzyme-linked immunosorbent assay kits for monitoring the levels of drug and anti-drug antibodies, whereas Pascual-Salcedo *et al.* used Sanquin enzyme-linked immunosorbent assay kits; the type of test kits used by Sanquin Diagnostic Services (MabTrack or those developed by Sanquin) was not reported. No studies were identified that evaluated IDKmonitor, LISA-TRACKER or RIDASCREEN.

The INGEBIO study was a non-randomised, multicentre trial that compared therapeutic drug monitoring with standard of care in patients with rheumatoid arthritis ( $n = 63$ ), psoriatic arthritis ( $n = 54$ ) and ankylosing spondylitis ( $n = 52$ ) who had achieved remission or low disease activity and were treated with adalimumab. Data were not available for the rheumatoid arthritis subgroup. Study results were reported in three abstracts. The findings showed that there was a non-significant reduction in the risk of flare in the intervention group compared with the control group. In particular, participants' health-related

quality-of-life outcomes were better in the intervention group than in the control group at all visits, with statistically significant results being observed at two out of eight visits. The study had serious limitations in relation to the National Institute for Health and Care Excellence scope: only one-third of participants had rheumatoid arthritis, most of the analyses were not by intention to treat, follow-up was only 18 months and there was no explicit algorithm to guide clinicians in using the test results to inform treatment in the intervention arm. The study was judged to be at a serious risk of bias.

The observational study, by Pascual-Salcedo *et al.* ( $n = 43$ ), was of limited value in informing whether or not enzyme-linked immunosorbent assay test-based monitoring is clinically effective. The study had a historical control and evaluated the effect of therapeutic drug monitoring on changes in disease activity in participants receiving adalimumab, etanercept or infliximab during a follow-up period of 7 years. Therapeutic drug monitoring was associated with a non-significant reduction in the mean Disease Activity Score in 28 joints (indicating lower disease activity) at 7-year follow-up compared with the historical control group (in whom therapeutic drug monitoring was not carried out). The study was judged to be at a moderate risk of bias, which may have compromised reliability of the findings.

The search also identified an ongoing Norwegian multicentre randomised controlled trial, the Norwegian Drug Monitoring (NOR-DRUM) study (Haavardsholm EA. *The Norwegian Drug Monitoring Study (NOR-DRUM)*. 2018. URL: <https://clinicaltrials.gov/ct2/show/NCT03074656>), which is evaluating the effect of therapeutic drug monitoring in people with rheumatoid arthritis in remission compared with standard of care.

## Review of economic evaluations

### Methods

A systematic review of published economic evaluations of using enzyme-linked immunosorbent assay tests compared with alternatives and standard of care was undertaken. Bibliographic databases, including MEDLINE, EMBASE, Web of Science, NHS Economic Evaluation Database and EconLit, were searched for economic studies from inception to July 2018, and again in November 2018. After two reviewers had completed the screening process, the bibliographies of the included papers were scrutinised for further potentially relevant studies. Studies were quality appraised and their results were tabulated using the Consensus on Health Economic Criteria list.

### Results

In total, five studies were included: two that were selected in the clinical effectiveness review (INGEBIO and Pascual-Salcedo *et al.*) and three model-based economic evaluations (KriECKaert CL, Nair SC, Nurmohamed MT, van Dongen CJ, Lems WF, Lafeber FP, *et al.* Personalised treatment using serum drug levels of adalimumab in patients with rheumatoid arthritis: an evaluation of costs and effects. *Ann Rheum Dis* 2015;**74**:361–8; Laine J, Jokiranta TS, Eklund KK, Väkeväinen M, Puolakka K. Cost-effectiveness of routine measuring of serum drug concentrations and anti-drug antibodies in treatment of rheumatoid arthritis patients with TNF- $\alpha$  blockers. *Biologics* 2016;**10**:67–73; and Gavan S. *An Economic Evaluation of a Biomarker Test to Stratify Treatment for Rheumatoid Arthritis*. PhD thesis. Manchester: University of Manchester; 2017). Promonitor and Sanquin assays and three tumour necrosis factor- $\alpha$  inhibitors (adalimumab, etanercept and infliximab) were considered in the included studies.

No single study addressed the decision problem because not all of the interventions identified by the National Institute for Health and Care Excellence scope were included or because a UK perspective was not used. The study by Gavan, which was conducted in England, most closely matched the decision problem. A discrete event simulation model used in this study was parameterised with data from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. However, the study did not consider any specific assays, and only treatment with adalimumab was evaluated. Gavan concluded that routine use of adalimumab drug and antibody testing in people with rheumatoid arthritis in

remission was cost-effective compared with current practice, but was unlikely to be cost-effective relative to dose reduction without testing. Findings from the studies of Krieckaert *et al.* and Laine *et al.*, conducted outside the UK, suggested that enzyme-linked immunosorbent assay monitoring could be cost-saving.

## Independent economic evaluation

### Methods

Owing to limited evidence identified in the clinical effectiveness systematic review, studies excluded from the review were also considered, for example those evaluating the concentration–response relationship. An additional systematic literature review to identify randomised controlled trials evaluating any tests used to monitor anti-tumour necrosis factor- $\alpha$  treatments in people with rheumatoid arthritis was performed. No relevant sources were found. Searches to identify cost and utility studies were conducted.

Outcomes from the only head-to-head study included in the systematic review, INGEBIO, were used in all analyses reported here. In INGEBIO, both mean time in remission (reported in Ucar *et al.*) and mean time in remission or low disease activity (reported in Arango 2017 *et al.*) were estimated in patients from the intervention and the control arms. Therefore, two separate scenario analyses were conducted.

The choice of the modelling approaches was driven by the limited clinical evidence available, the multifactorial nature of decisions to adjust treatment in rheumatoid arthritis patients, uncertainty in the testing strategies, as well as the prices of tumour necrosis factor- $\alpha$  inhibitors and their uptake in the UK. Threshold and cost–utility analyses based on a decision tree model were conducted. The former approach allowed the estimation of the annual cost of enzyme-linked immunosorbent assay testing at which the addition of therapeutic drug monitoring to standard of care would result in zero net monetary benefit for a range of plausible acquisition costs of biologics and the willingness-to-pay thresholds of £20,000 and £30,000 per quality-adjusted life-year gained usually considered by the National Institute for Health and Care Excellence. In the cost–utility analyses, list prices for the tumour necrosis factor- $\alpha$  inhibitors and the costs of enzyme-linked immunosorbent assay kits provided by manufacturers were used; other testing costs were modelled following Jani *et al.* (Jani M, Gavan S, Chinoy H, Dixon WG, Harrison B, Moran A, *et al.* A microcosting study of immunogenicity and tumour necrosis factor alpha inhibitor drug level tests for therapeutic drug monitoring in clinical practice. *Rheumatology* 2016;55:2131–7). The costs of managing health states, flares and adverse events were also included. Quality-adjusted life-years were estimated from health-state utilities, and disutilities of flares and adverse events.

Unit costs were obtained from the *British National Formulary* and *NHS Reference Costs*, from documents provided by test manufacturers, and from published and unpublished sources. They were inflated to 2017–18 prices using the Hospital and Community Health Services pay and prices index. Where the conversion from other currencies to Great British pounds was required, International Monetary Fund purchasing power parity was used. Costs were measured from the NHS and Personal Social Services perspective. Given an 18-month time horizon adopted in the model, no discounting was applied to costs and quality-adjusted life-years.

Owing to a substantial variation in clinical practice with respect to treatment, drug dose tapering and flare management, as well as uncertainty in tumour necrosis factor-testing strategies in people with rheumatoid arthritis, the specification of the base-case scenario was extremely difficult. The effect of such variations on the economic outcomes was evaluated in numerous clinically relevant sensitivity analyses.

## Results

### Adalimumab and Promonitor: threshold analyses

Results based on a shorter follow-up (Ucar *et al.*) suggest that testing would need to be < £225 per patient-year in order for therapeutic drug monitoring to be judged as cost-effective at the willingness-to-pay threshold of £20,000 per quality-adjusted life-year gained and the annual acquisition cost of adalimumab (Humira); at the willingness-to-pay threshold of £30,000 per quality-adjusted life-year gained, the cost of testing should be < £274 per patient-year. For the annual acquisition cost of £1000 per patient-year, the corresponding threshold values for the cost of testing were £197 and £246 per patient-year, respectively.

According to the results based on a longer follow-up (Arango *et al.*) and the list price of Humira, the cost of testing should not exceed £18 per year to be considered as cost-effective at the willingness-to-pay threshold of £20,000 per quality-adjusted life-year gained. However, the other threshold values obtained for these data were negative, signifying that, for the outcomes presented in Arango *et al.*, there were no (positive) values of the cost of testing at which it would be cost-effective.

### Adalimumab and Promonitor: cost-utility analyses

The results obtained by Ucar *et al.* suggest that the intervention was likely to be cost-effective. However, standard of care was dominant when outcomes from Arango *et al.* were utilised.

### Adalimumab and Promonitor: sensitivity analyses

In the analyses that assumed that monitoring solely affects flare rate (following Gavan), incremental cost-effectiveness ratios were either slightly under £30,000 per quality-adjusted life-year gained, signifying the borderline cost-effectiveness of the intervention, or exceeded this threshold substantially.

The intervention dominated standard of care in those analyses that excluded the cost of phlebotomy appointments and were based on Ucar *et al.*, whereas it was more costly and resulted in a smaller gain in quality-adjusted life-years (with incremental cost-effectiveness ratios under £20,000 per quality-adjusted life-year) in the analyses parameterised from Arango *et al.* When this cost was factored in, the intervention was either dominated by standard of care or likely to be cost-effective depending on the evidence source used (Arango *et al.* or Ucar *et al.*).

Under the assumption of 6-monthly testing, standard of care was dominant in the analysis for Arango *et al.*, whereas the incremental cost-effectiveness ratio for Ucar *et al.* was £36,756 per quality-adjusted life-year gained.

In all other scenario analyses, the incremental cost-effectiveness ratios were under £20,000 per quality-adjusted life-year when estimated from Ucar *et al.*, whereas standard of care was dominant in the analyses for Arango *et al.*

Regardless of the level of discount for Humira, therapeutic drug monitoring was either cost-effective or dominated by standard of care, depending on the data source that was used (Ucar *et al.* or Arango *et al.*).

One-way deterministic sensitivity analyses were conducted for flare rates, time in remission or low disease activity, the costs of disease management and the proportion of patients in whom the biologic was tapered. In these analyses, parameterised from Arango *et al.*, the outcomes varied from the intervention being dominated by standard of care to incremental cost-effectiveness ratios of < £30,000 per quality-adjusted life-year, located in the south-west quadrant of the cost-effectiveness plane.

## Adalimumab and Promonitor: exploratory analyses based on the INGEBIO full study report

The use of clinical data from the INGEBIO full study report (provided by Grifols-Progenika) resulted in outcomes that varied from the intervention being dominant (when one test per patient-year was assumed or the cost of phlebotomy appointments was excluded) to the incremental cost-effectiveness ratios exceeding £160,000 per quality-adjusted life-year gained, signifying that the intervention was highly unlikely to be cost-effective.

## Etanercept or infliximab, and Promonitor: exploratory analyses

In the cost-utility analyses for etanercept [Enbrel® and Erelzi® (Sandoz Limited, Camberley, UK)] and infliximab (Flixabi®, Biogen Biosimilars, Cambridge, MA, USA; and Renflexis®, Samsung Bioepis, Incheon, Republic of Korea) standard of care was dominant when the outcomes were taken from Arango *et al.*, whereas the results for Ucar *et al.* indicated that the intervention was likely to be cost-effective. When it was assumed that therapeutic drug monitoring solely affects flare rates, incremental cost-effectiveness ratios for these treatments varied within the range £27,944–111,450 per quality-adjusted life-year gained.

Importantly, the results of all analyses reported here are based on very small and uncertain differences in outcomes, with the incremental quality-adjusted life-years of < 0.01.

## Conclusions

There is limited evidence and much uncertainty in relation to the clinical effectiveness and cost-effectiveness of enzyme-linked immunosorbent assay test-based therapeutic drug monitoring in rheumatoid arthritis. The evidence used in the model was from the poorly reported INGEBIO study (a non-randomised controlled trial from Spain, in which less than 40% of participants were rheumatoid arthritis patients), heavily supplemented by input from other studies and expert advice. The results of the economic analysis should, therefore, be viewed as exploratory and highly speculative.

## Suggested future work

Further controlled trials are required to assess the impact of using the different enzyme-linked immunosorbent assay tests for monitoring anti-tumour necrosis factor- $\alpha$  therapies in rheumatoid arthritis patients who have achieved remission or low disease activity, and in people being treated with the full range of anti-tumour necrosis factor therapies. The identified ongoing trial (NOR-DRUM) evaluates the effect of therapeutic drug monitoring in this population. Future trials are warranted to assess the clinical effectiveness of enzyme-linked immunosorbent assay tests for monitoring anti-tumour necrosis factor therapies in patients who have developed clinical inefficacy (primary or secondary non-response).

The review identified limited evidence on health-care resource use and utilities, relevant to the population considered in this assessment. This warrants further research on medium-/long-term cost and health outcomes of therapeutic drug monitoring in people with rheumatoid arthritis.

## Study registration

The study is registered as PROSPERO CRD42018105195.

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