Intensive therapy for moderate established rheumatoid arthritis: the TITRATE research programme

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Declared competing interests of authors: James B Galloway has received personal fees and non-financial support from AbbVie Inc. (North Chicago, IL, USA) and from Pfizer Inc. (New York, NY, USA); personal fees from Bristol Myers Squibb™ (New York, NY, USA) and from Janssen Pharmaceuticals (Beerse, Belgium); and grants and personal fees from Celgene Corporation (Summit, NJ, USA) and from UCB Pharma (Brussels, Belgium). Elena Nikiphorou has received speaker honoraria and has participated in advisory boards for Pfizer Inc., AbbVie Inc., Sanofi SA (Paris, France), Gilead Sciences, Inc. (Foster City, CA, USA), Celltrion (Incheon, Republic of Korea) and Eli Lilly and Company (Indianapolis, IN, USA) outside the submitted work. Jackie Sturt has received personal fees from Eli Lilly and Company, and grants and personal fees from Spirit Healthcare Ltd (Leicester, UK).

Published August 2021
DOI: 10.3310/pgfar09080

Scientific summary

The TITRATE research programme

Programme Grants for Applied Research 2021; Vol. 9: No. 8
DOI: 10.3310/pgfar09080

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Scientific summary

Background

Rheumatoid arthritis is a major long-term inflammatory disorder that affects nearly 1% of adults in England. It causes substantial morbidity and impairs quality of life. The TITRATE (Treatment Intensities and Targets in Rheumatoid Arthritis ThErapy) programme evaluated intensive management in patients with moderately active rheumatoid arthritis. Key treatment goals were minimising disease activity and achieving remission, decreasing physical disability and improving health-related quality of life. In active rheumatoid arthritis, intensive management is known to help achieve these goals. However, many patients with established rheumatoid arthritis have moderate disease activity between active disease and remission. The TITRATE programme developed evidence for intensive management in patients with moderate rheumatoid arthritis.

Objectives

- To define how to deliver intensive therapy to patients with moderate established rheumatoid arthritis.
- To establish the clinical effectiveness and cost-effectiveness of intensive therapy in treatment of moderate established rheumatoid arthritis in a clinical trial.
- To evaluate existing evidence supporting such intensive management in observational studies and completed trials.

Methods

The programme involved observational studies, secondary analyses of completed trials, systematic reviews, qualitative studies, a 12-month multicentre clinical trial and a health economic analysis with a 6-month follow-up study.

Observational studies comprised four cross-sectional studies of 1323 rheumatoid arthritis patients at two London specialist outpatient clinics followed for over two decades, one long-term follow-up study of 1693 rheumatoid arthritis patients followed for over a decade at a single London centre and 152 rheumatoid arthritis patients with stable low disease activity remission followed for 12 months at three London centres.

The observational studies were supplemented by secondary analyses of three completed clinical trials in early and established rheumatoid arthritis and involved 668 rheumatoid arthritis patients from many rheumatology outpatient clinics across all regions of England.

Qualitative studies assessed expectations about intensive management in nine patients and five carers from four London rheumatology clinics, and perspectives about intensive management in 15 patients from 10 rheumatology clinics participating in the TITRATE trial.

The TITRATE clinical trial compared intensive management with standard care. A total of 335 rheumatoid arthritis patients attending rheumatology clinics in 39 centres across all English regions were randomised. The patients spanned diverse levels of socioeconomic deprivation and ethnicity. The trial evaluated both clinical and economic outcomes. A 6-month extension study involved 95 patients who had received intensive management.

Clinical assessments focused on the Disease Activity Score for 28 joints based on the erythrocyte sedimentation rate (DAS-ESR). Moderate rheumatoid arthritis scores are 3.2–5.1 and remission is < 2.6. The Health Assessment Questionnaire evaluated physical disability and the EuroQol-5 Dimensions measured health-related quality of life. Treatments spanned conventional disease-modifying antirheumatic drugs, biologics and steroids.

Determining how to deliver intensive management involved qualitative research of rheumatoid arthritis outpatients and workshops involving patients and carers.

The TITRATE trial studied patients with moderately active established rheumatoid arthritis who were receiving conventional synthetic disease-modifying antirheumatic drugs and were seen in specialist clinics. The trial tested the hypothesis that intensive management using drug therapy and a treatment support programme of non-drug approach given by specialist nurses resulted in higher remission rates than standard care. A comparison group received standard care. The primary outcome was DAS28-ESR remission at 12 months. Secondary outcomes included other remission criteria, fatigue scores, disability (measured by the Health Assessment Questionnaire) and adverse events. Resource use of each participant was determined for health economic assessments. Multivariable logistic and linear regression compared treatment strategies in intention-to-treat analyses, using multiple imputation methods for missing data. Total costs and quality-adjusted life-years, measured using the EuroQol-5 Dimensions, were used to assess the incremental cost-effectiveness ratio of intensive management compared with standard care.

A predefined secondary analysis of the trial evaluated the impact of baseline factors on remissions. A 6-month extension study from the trial examined the persistence of DAS28-ESR remissions.

Subsequent qualitative research evaluated patients' and clinicians' views on intensive treatment. A fidelity assessment evaluated the delivery of intensive management.

Results

Two observational studies showed substantial reductions in disease activity over the last two decades and the reductions were associated with increased treatment intensities. Four cross-sectional surveys between 1996–7 and 2012–14 showed that mean DAS28-ESR scores fell (from 5.2 to 3.7), DAS28-ESR remissions increased (from 8% to 28%) and biologics prescribing increased (from none to 32% of patients). A longitudinal study from 2005 to 2015 also showed that mean DAS28-ESR scores fell (from 4.1 to 3.6), DAS28-ESR remissions increased (from 18% to 27%) and more biologics were prescribed (from 19% to 42% of patients).

A systematic review of intensive management identified 48 superiority trials (intensive management strategies vs. less intensive strategies), six head-to-head trials comparing combination disease-modifying antirheumatic drugs with biologics and one trial comparing both. Superiority trials reported remissions in 3013 of 11,259 intensive management patients and 1211 of 8493 control patients [i.e. intensive management increased remissions (relative risk 2.23, 95% confidence interval 1.90 to 2.61)]. Head-to-head trials reported remissions in 317 of 787 patients receiving biologics and 229 of 671 receiving combination disease-modifying antirheumatic drugs. There was no difference between strategies (relative risk 1.06, 95% confidence interval 0.93 to 1.21).

The impact of remission in moderately active rheumatoid arthritis was evaluated in a longitudinal cohort followed for ≥ 3 years and secondary analyses of two completed trials. Patients with moderately active rheumatoid arthritis were divided into those who subsequently had one or more DAS28-ESR remissions and those who did not. In patients achieving remissions, disability was reduced with substantially lower Health Assessment Questionnaire scores.

Further analyses of the relationships between remission, disability and quality of life were undertaken in the longitudinal cohort and the completed trials. Sustained remissions were infrequent (5–9% of patients) and remission at single time points was more common (35–58% of patients). End-point DAS28-ESR scores post remission showed that 53–61% of patients remained in remission, 9–18% had low disease activity, 21–22% had moderate disease activity and 4–8% had high disease activity. Sustained remissions were most specific for patients with low disability (97–98%) and normal quality of life (93–97%), but lacked sensitivity (low disability 19–29%; normal quality of life 19–36%). Point remission gave a better balance between sensitivity and specificity (low disability, specificity 50–78% and sensitivity 68–89%; normal EuroQol-5 Dimensions, specificity 42–72% and sensitivity 70–93%).

A qualitative study on patients' and carers' views of intensive management highlighted the importance of treatment expectations. Patients placed greatest emphasis on improving their physical symptoms, reducing their pain and increasing their mobility and independence. Patients' views varied about taking more medication, depending on the stability and benefits of their current treatments. Most patients were not receiving drugs that fully controlled their rheumatoid arthritis and they were willing to try more intensive managements, although they were concerned about side effects. Patients realised that intensive management involved more frequent clinic appointments, but these were generally welcomed.

A patient handbook about intensive management relevant for moderate disease was developed in a patient workshop held at a London centre. Patients suggested that it should focus on the aims of intensive management, its benefits and the importance of patients participating in assessing benefits.

A training manual for nurses delivering intensive management was developed after systematically reviewing the evidence for psychological support and motivational interviews for rheumatoid arthritis patients. Psychological support improved disability, pain and fatigue. Motivational interviewing increased physical activity and treatment concordance. Both were incorporated within the nurses' training.

The TITRATE trial screened 459 patients (335 patients were randomised, 168 patients had intensive management and 167 patients received standard care). A total of 303 (90%) patients provided 12-month outcomes data. With intensive management, 139 (83%) patients attended at least eight separate monthly sessions, 140 patients started another conventional disease-modifying antirheumatic drug, 67 patients started a second or third conventional disease-modifying antirheumatic drug, 72 patients had depot steroids and 45 patients started biologics. With intensive management, patients also received person-centred psychoeducation provided by their specialist nurses. With standard care, 128 patients started another conventional disease-modifying antirheumatic drug, 37 patients started a second or third conventional disease-modifying antirheumatic drug, 50 patients had depot steroids and 24 patients started biologics.

The trial showed that intensive management increased DAS28-ESR 12-month remission rates compared with standard care (32% vs. 18%; $p = 0.004$). Intensive management also increased remission rates using alternative criteria, including the Disease Activity Score for 28 joints based on C-reactive protein levels (21% vs. 10%; $p = 0.008$), Clinical Disease Activity Index (18% vs. 10%; $p = 0.049$) and American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Boolean remissions (13% vs. 6%; $p = 040$). Intensive management also increased DAS28-ESR low disease activity states (48% vs. 32%; $p = 0.005$) and reduced patient-assessed fatigue (mean difference −15, 95% confidence interval −21 to −9; $p < 0.001$) and pain (mean difference −8, 95% CI −15 to −2; $p = 0.007$). Disability, assessed by Health Assessment Questionnaire scores, fell when intensive management patients achieved remission (difference −0.40, 95% confidence interval −0.57 to −0.22). Fourteen patients receiving intensive management and 11 patients receiving standard care experienced one or more serious adverse events or died. These differences were not significant.

Economic analysis of the TITRATE trial showed that the base-case incremental cost-effectiveness ratio was £43,972 (€51,474) from NHS and Personal Social Services perspectives. The probability of meeting the English willingness-to-pay threshold (i.e. £30,000/€35,000) was 17%. The incremental

cost-effectiveness ratio fell to £29,363 (€24,384) after including patients' personal costs and lost working time, and this corresponded to a 50% probability of intensive management being cost-effective at English willingness-to-pay thresholds.

The predefined secondary analysis of the TITRATE trial evaluated baseline predictors of remission. Significant predictors were male sex, baseline DAS28-ESR, Health Assessment Questionnaire scores and body mass index.

The persistence of remission in the 6-month TITRATE extension study showed that in patients receiving intensive management the frequency of remissions declined at 18 months. This decline was least in patients achieving two or more remissions during intensive management. DAS28-ESR levels returned towards low moderate levels and this change was least in patients achieving two or more remissions.

The stability of remission was assessed in a separate observational study of 152 patients with minimal disease activity undergoing treat-to-target treatment management. Over 12 months, 44 patients had sustained remissions, 23 patients were disability-free at all visits, 46 patients had fluctuating disease activity and 51 patients had fluctuating levels of disability.

A qualitative study of the perspectives of patients, nurses and rheumatology practitioners from London centres involved in intensive management in the TITRATE trial showed that monthly appointments were acceptable. Their benefits included regular reviews of medication and the ability of practitioners to establish close relationships with patients. Practitioners felt 'fairly confident' using motivational interviewing techniques. Most patients found optimising their medication based on monthly assessments helpful and that side effects generally resolved.

Assessments of the fidelity of 10% of intensive management TITRATE trial sessions showed that health-care practitioners followed some but not all recommended approaches. Health-care practitioners were good at providing solicited information, using listening skills and asking patients' open questions. Affirming patients' strengths and abilities, evoking and reinforcing change talk and identify patients' main problems were also used effectively. Other areas, such as helping patients change their behaviour, were often overlooked.

Conclusions

Intensive management delivered by trained practitioners was clinically effective in moderately active patients with established RA and its benefits were generalisable across English rheumatology clinics. It substantially increased remissions at 12 months and also significantly reduced fatigue without increasing adverse reactions.

Qualitative research showed that patients and nurses found that the intensive management approach taken in the TITRATE programme was acceptable to patients and could be delivered by the nurses without major challenges. However, monthly assessments may not be essential. Future research should identify the optimal frequency of assessments.

The health economic benefits were more complex. Within-trial estimates confirmed patient and societal value of intensive management; however, the incremental cost-effectiveness ratio from an NHS and Personal Social Service perspective was above the current willingness-to-pay thresholds for medical costs in England. Further economic evaluation is needed beyond the 12-month follow-up period to define overall benefits of intensive management, as within-trial assessments underestimate the benefits of improved earlier treatment and potentially reduce biologic longer-term drug use.

Maintaining remissions after intensive management was incomplete in the TITRATE trial and in an observational study of patients receiving treat-to-target management. Low disease activity may be an easier target.

The real-world observational studies show that treatment intensity has increased over two decades with far greater biologic use. Consequently, mean DAS28-ESR scores have decreased and more patients achieve remissions. These findings suggest that intensive management approaches are increasingly followed. However, as our observational studies showed, when patients with moderate rheumatoid arthritis achieve one or more remissions, their outcomes are better and opportunities remain to increase treatment intensities.

The systematic review of previous trials showed that intensive management increases remissions in active rheumatoid arthritis. These trials suggest that there is no reason to favour one intensive management strategy over another. Custom and practice and health economic considerations together suggest a good case to use combinations of conventional disease-modifying antirheumatic drugs initially and reserving biologics for patients who do not respond to this approach.

The main limitations of the trial comprised (1) focusing on remissions at single time points rather than sustained responses, (2) uncertainty about relative benefits of different aspects of intensive management and (3) doubt about optimal treatment for patients who did not respond to intensive management.

The balance of evidence suggest that intensive management, no matter how it is delivered, does not benefit all rheumatoid arthritis patients with established disease. Findings in both previous trials and the TITRATE trial suggest that current intensive management strategies benefit approximately half of patients. In the TITRATE trial, patients with high body mass indices, particularly those who also had high baseline Health Assessment Questionnaire scores, were unlikely to respond to intensive management. There is growing evidence from observational studies that obesity is associated with poor outcomes. The implications for management need further investigation.

Although achieving remission reduced disability in the TITRATE trial, many patients still had considerable disability. Other approaches to minimising disability in patients with established rheumatoid arthritis are needed in addition to intensive management aimed at optimising drug therapy. The best clinical approaches to minimising disability needs further research. This research should evaluate a range of different options, including non-drug treatments.

Trial registration

This trial is registered as ISRCTN70160382.

Funding

This project was funded by the National Institute for Health Research (NIHR) Programme Grants for Applied Research programme and will be published in full in *Programme Grants for Applied Research*; Vol. 9, No. 8. See the NIHR Journals Library website for further project information.

Programme Grants for Applied Research

ISSN 2050-4322 (Print)

ISSN 2050-4330 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

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This report

The research reported in this issue of the journal was funded by PGfAR as project number RP-PG-0610-10066. The contractual start date was in October 2012. The final report began editorial review in July 2019 and was accepted for publication in February 2021. As the funder, the PGfAR programme agreed the research questions and study designs in advance with the investigators. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The PGfAR editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

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