Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial

Cathriona Grigor, Hilary Capell, Anne Stirling, Alex DMcMahon, Peter Lock, Ramsay Vaillance, Wilma Kincaid, Duncan Porter

Summary

Background Present treatment strategies for rheumatoid arthritis include use of disease-modifying antirheumatic drugs, but a minority of patients achieve a good response. We aimed to test the hypothesis that an improved outcome can be achieved by employing a strategy of intensive outpatient management of patients with rheumatoid arthritis—for sustained, tight control of disease activity—compared with routine outpatient care.

Methods We designed a single-blind, randomised controlled trial in two teaching hospitals. We screened 183 patients for inclusion. 111 were randomly allocated either intensive management or routine care. Primary outcome measures were mean fall in disease activity score and proportion of patients with a good response (defined as a disease activity score <2·4 and a fall in this score from baseline by >1·2). Analysis was by intention-to-treat.

Findings One patient withdrew after randomisation and seven dropped out during the study. Mean fall in disease activity score was greater in the intensive group than in the routine group (−3·5 vs −1·9, difference 1·6 [95% CI 1·1–2·1], p<0·0001). Compared with routine care, patients treated intensively were more likely to have a good response (definition, 45/55 [82%] vs 24/55 [44%], odds ratio 5·8 [95% CI 2·4–13·9], p<0·0001) or be in remission (disease activity score <1·6; 36/55 [65%] vs 9/55 [16%], 9·7 [3·9–23·9], p<0·0001). Three patients assigned routine care and one allocated intensive management died during the study; none was judged attributable to treatment.

Interpretation A strategy of intensive outpatient management of rheumatoid arthritis substantially improves disease activity, radiographic disease progression, physical function, and quality of life at no additional cost.

Introduction Present treatment strategies for rheumatoid arthritis use disease-modifying antirheumatic drugs ( singly or in combination) as early as possible in the disease process, because suppression of disease activity correlates with reduction in radiological joint damage. The challenge is to ascertain whether tight control of the inflammatory response can be achieved and sustained in a large proportion of rheumatoid arthritis patients, and to assess the effect of such management on symptoms and medium-term and long-term outcomes. To date, published trials have focused on specific drug combinations or have used an open study design without masked assessments of disease activity. Moreover, in most trials, combinations of two or more disease-modifying antirheumatic drugs have been used from the outset, whereas many clinicians do not favour this approach in all patients with a new diagnosis of rheumatoid arthritis, preferring instead to step up treatment in those with disease that has proven resistant to monotherapy. We did a randomised controlled trial (with masked assessments) of a therapeutic strategy aiming for sustained, tight control of disease activity compared with routine outpatient care.

Patients and methods

Patients This study was undertaken in two National Health Service (NHS) teaching hospitals in Glasgow, UK. Between August, 1999, and April, 2001, we recruited patients aged between 18 and 75 years who had had rheumatoid arthritis for fewer than 5 years. All patients had active disease, defined by a disease activity score of more than 2·4. We excluded patients who had previously received combination disease-modifying antirheumatic drug treatment, or had relevant concurrent liver (aspartate aminotransferase >80 IU/L, alkaline phosphatase >700 IU/L), renal (creatinine >0·2 mmol/L), or haematological disease (white-cell count <4·0×10⁹/L, platelet count <150×10⁹/L). The local ethics committee in Western Infirmary, Glasgow, approved this protocol. All patients gave written informed consent.

Procedures The treating doctor telephoned an administrative co-ordinator, who randomly assigned patients either intensive or routine management, with randomisation software. Patients assigned to the intensive group were seen every month by the same rheumatologist (CG), and their disease activity score was calculated. This score is a validated composite of erythrocyte sedimentation rate, Ritchie articular index, joint swelling count, and patients’ global assessment of disease activity. 67 Disease activity scores of 3·6, 2·4, and 1·6 represented high, moderate, and low disease activity, respectively. At every
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monotherapy was given in patients with active synovitis, making. Disease-modifying antirheumatic drug
measure of disease activity used in clinical decision
reviewed every 3 months, with no formal composite
working under supervision. These participants were
rheumatologists and included trainee rheumatologists
up clinics, which were led by two consultant
group was supervised in the usual rheumatology follow-
by the rheumatologist.

and drug-related toxic effects were managed empirically
precluded this approach. We recorded adverse events,
protocol (figure 1), unless they declined or toxic effects
an escalation of their oral treatment according to a
month 3, patients with a score of more than 2·4 received
remained more than 2·4. At every assessment after
was not injected intra-articularly, we gave the balance by
120 mg of triamcinolone acetonide per visit. Within the first
monthly assessment, we injected any swollen joint
amenable to intra-articular steroid, unless the joint had
been injected within the previous 3 months or the
patient declined. We injected a maximum of three joints
per assessment, up to a total dose of 120 mg
triamcinolone acetonide per visit. Within the first
3 months of starting a new disease-modifying anti-
reumatic drug, if 120 mg of triamcinolone acetonide
was not injected intra-articularly, we gave the balance by
intramuscular injection if the disease activity score
remained more than 2·4. At every assessment after
month 3, patients with a score of more than 2·4 received
an escalation of their oral treatment according to a
protocol (figure 1), unless they declined or toxic effects
precluded this approach. We recorded adverse events,
and drug-related toxic effects were managed empirically
by the rheumatologist.

Treatment for patients assigned to the routine care
group was supervised in the usual rheumatology follow-
up clinics, which were led by two consultant
rheumatologists and included trainee rheumatologists
working under supervision. These participants were
reviewed every 3 months, with no formal composite
measure of disease activity used in clinical decision
making. Disease-modifying antirheumatic drug
monotherapy was given in patients with active synovitis,
and failure of treatment (because of toxic effects or lack
of effect) resulted in a change to alternative
monotherapy, or addition of a second or third drug at
the discretion of the attending rheumatologist. Intra-
articular injections of corticosteroid were given to
patients assigned routine care with the same restrictions
as those in the intensive group.

Every 3 months, a metrologist assessed patients from
both groups. To ensure masked assessments, the
metrologist knew of the aim and details of the study
design, but was unaware of patients’ assigned
treatment groups. Before every assessment, patients
were sent a letter stating that they should make no
mention of their drug treatment or the identity of their
doctors. Assessments were undertaken without the case
record and on a different clinic day from that attended
by the intensive group for their monthly visits—hence
all patients (intensive and routine) attended the
assessment clinic every 3 months. The assessing
metrologist did not attend the other outpatient clinics, at
which the intensive group attended every month, and
did not take part in intensive treatment. No intra-
articular injections were allowed in the month preceding
the assessments.

Primary outcome measures were mean fall in disease
activity score, and the proportion of patients with a good
response (European League Against Rheumatism
[EULAR] definition—ie, disease activity score <2·4 and a
fall in score from baseline by >1·2). Secondary outcome
measures consisted of the proportion of patients in
remission (EULAR definition—ie, disease activity scores
<1·6), American College of Rheumatology (ACR)
response rates, and other constituents of the EULAR
core measures of disease activity and outcome, namely
visual analogue pain score, assessor’s global assessment
of disease activity, and patient’s function measured by
the health assessment questionnaire (at 0 and
18 months). ACR 20, 50, and 70 responses are defined
as at least 20%, 50%, and 70% improvement in joint
swelling and joint tenderness counts, and three of five
other variables (ie, erythrocyte sedimentation rate,
health assessment questionnaire, pain score, and
assessors’ and patients’ global assessments). We used
the short form-12 questionnaire (a reliable, valid, and
responsive measure of health status in rheumatoid
arthritis) to measure health-related quality of life. Two
radiologists scored radiographs of hands and feet at
0 and 18 months with the van der Heijde modification
of the Sharp score.30 Films were scored with the
sequence of radiographs known, but the radiologists
were masked to treatment groups.

We obtained data on resource use from case-note
review and patients’ diaries. We measured hospital
resource use in terms of the number of outpatient visits,
inpatient stays by specialty, and prescription costs of
disease-modifying antirheumatic drugs or non-steroidal
anti-inflammatory drugs. Community resource use was

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### Table: Protocol for escalation of disease-modifying antirheumatic therapy in patients with persisting disease activity

<table>
<thead>
<tr>
<th>Step</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Change to alternative disease-modifying antirheumatic drug therapy (leflunomide or sodium aurothiomalate)</td>
</tr>
<tr>
<td>2.</td>
<td>Add to prednisolone in enteric-coated tablets 7·5 mg daily</td>
</tr>
<tr>
<td>3.</td>
<td>Triple therapy with weekly increments of sulfasalazine dose (maximum 5 g per day in divided doses if tolerated)</td>
</tr>
<tr>
<td>4.</td>
<td>Triple therapy with monthly increments of methotrexate dose by 2·5–5·0 mg per week (maximum 25 mg per week)</td>
</tr>
<tr>
<td>5.</td>
<td>Sulfasalazine 500 mg daily, increasing every week to target dose of 40 mg/kg per day (or maximum tolerated dose)</td>
</tr>
</tbody>
</table>

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Figure 1: Protocol for escalation of disease-modifying antirheumatic therapy in patients with persisting disease activity
obtained with 1-month prospective patients’ diaries at 0, 6, and 12 months. We defined community resources as visits to the family practitioner, practice nurse, or other health professionals, and blood-test monitoring. We assumed that the rate of resource use was constant for every subsequent month after completion of the previous patient’s diary. Perspective of the economics evaluation was from the NHS, although we also measured travel costs by self-completed patients’ questionnaires. We costed resource use with published unit-cost data. For example, the unit cost for a rheumatology inpatient bed per day and an outpatient attendance was £232 and £33, respectively. We calculated incremental cost differences between each arm of the trial for patients who completed the trial. All costs have been expressed in 2001–02 prices. No discounting was applied because of the short study timeframe.

Statistical analysis
We did an intention-to-treat analysis; patients who died, were lost to follow-up, or withdrew from the trial were designated as non-responders. We assessed the mean fall in disease activity score with Student’s t test and the proportion of patients with a good response with the Mantel-Haenszel procedure, with SAS version 8.02. A difference in disease activity score of 1·1 was clinically significant, and the SD of the fall in score in a previous trial was 0·7. With a significance of p<0·01 and a power of 95%, 21 patients per group needed to be analysed. However, to detect an increase in the number of good responders from 40% to 70%, for a trial of 95% power at p<0·01, 53 patients per group would need to be analysed. To assess interobserver variability, we calculated the correlation between the two radiologists’ scores; median change in joint-space narrowing score, erosion score, and total Sharp score was measured by Mann-Whitney non-parametric analysis. We used non-parametric bootstrapping techniques to calculate 95% CIs around cost differences with the percentile method. Sensitivity analysis was used to vary the unit-cost data.

Role of the funding source
The study was funded by the Chief Scientist’s Office, Scottish Executive, and provided feedback on study design, but had no role in data collection, data analysis, data interpretation, writing of the report, or decision to submit the paper for publication.

Results
We screened 183 patients for the study; after exclusions, 55 were assigned intensive management and 55 routine care (figure 2). Baseline characteristics and measures of disease activity in the two groups were similar, although patients randomly assigned to the intensive group had slightly higher erythrocyte sedimentation rates and C-reactive protein concentrations, but slightly less radiological damage, than those in the routine group (table 1). Differences in baseline measures of disease activity were not deemed to be clinically significant. Adherence to follow-up was excellent (figure 2). At the 18-month assessment, patients in the intensive group had a higher rate of EULAR good response, remission, and ACR 70 response than the routine group (table 2). Figure 3 shows the fall in disease activity scores for both groups during the study. The mean fall in disease activity score was significantly greater in the intensive group than in the routine care group, and this difference was sustained throughout the trial. Patients in the intensive group showed significantly greater improvements in all disease activity variables (except C-reactive protein), physical function, and quality of life (table 3).
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99 sets of radiographs were scored at baseline and 18 months (47 in routine group, 52 in intensive group); seven patients died or were lost to follow-up, and baseline or follow-up films were lost in four patients. Patients in the intensive group had reduced progression of joint-space narrowing (table 3). Correlation between the two radiologists’ scoring of the change in total Sharp score was 0.84 (p<0.0001).

In the routine group, of 89 new disease-modifying anti-rheumatic drug courses started during the trial, 38 (43%) were stopped because of drug-related toxic effects, two (2%) owing to lack of effect, and two (2%) because of the patient’s death. The remaining 47 (53%) courses were ongoing. In the intensive group, compared with the routine group, more new disease modifying anti-rheumatic drug courses were started (n=129), fewer were stopped because of toxic effects (n=20, 16%), and more treatment episodes continued beyond the end of the trial (n=104, 81%). Drug-related toxic effects were more common in the routine group than in the intensive group, with 85 adverse events reported in 42 of 55 patients assigned routine care (gastrointestinal [25 events], abnormal liver function [16], dermatological [15], CNS [nine], infective [seven], haematological [six], others [seven]) compared with 46 adverse events in 32 of

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Intensive group (n=55)</th>
<th>Routine group (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td>39 (71%)</td>
<td>38 (69%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>51 (15)</td>
<td>54 (11)</td>
</tr>
<tr>
<td><strong>Disease duration</strong></td>
<td>19 (16)</td>
<td>20 (16)</td>
</tr>
<tr>
<td><strong>Rheumatoid factor</strong></td>
<td>41 (75%)</td>
<td>40 (73%)</td>
</tr>
<tr>
<td><strong>Disease activity</strong></td>
<td>4.9 (0.9)</td>
<td>4.6 (1.0)</td>
</tr>
<tr>
<td><strong>Swollen joint</strong></td>
<td>12 (4)</td>
<td>11 (4)</td>
</tr>
<tr>
<td><strong>Ritchie articular</strong></td>
<td>23 (10)</td>
<td>22 (12)</td>
</tr>
<tr>
<td><strong>PsA score</strong></td>
<td>2.0 (0.8)</td>
<td>1.9 (0.7)</td>
</tr>
<tr>
<td><strong>Short-form-12 physical summary</strong></td>
<td>28 (7)</td>
<td>28 (8)</td>
</tr>
<tr>
<td><strong>Short-form-12 mental health summary</strong></td>
<td>39 (13)</td>
<td>39 (13)</td>
</tr>
<tr>
<td><strong>Median total Sharp score (IQR)</strong></td>
<td>21.5 (10–39.5)</td>
<td>24.5 (13–25–47)</td>
</tr>
<tr>
<td><strong>Total Sharp score</strong></td>
<td>28 (23)</td>
<td>32 (27)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or number of patients (%), unless otherwise indicated. *0=no disability, 3=maximum disability. †Population mean=50.

Table 2: Number of patients responding at 18-month assessment

<table>
<thead>
<tr>
<th></th>
<th>Intensive group (n=55)</th>
<th>Routine group (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACR 70 response</strong></td>
<td>39 (67%)</td>
<td>6 (11%)</td>
</tr>
<tr>
<td><strong>ACR 50 response</strong></td>
<td>46 (84%)</td>
<td>22 (40%)</td>
</tr>
<tr>
<td><strong>ACR 20 response</strong></td>
<td>50 (91%)</td>
<td>35 (64%)</td>
</tr>
<tr>
<td><strong>EULAR remission</strong></td>
<td>36 (65%)</td>
<td>9 (16%)</td>
</tr>
<tr>
<td><strong>EULAR good response</strong></td>
<td>45 (82%)</td>
<td>24 (44%)</td>
</tr>
</tbody>
</table>

Intention-to-treat analysis of all patients randomised, including those who died or withdrew from the study. Analysis of patients completing the study is very similar (data not shown). *Mantel-Haenszel procedure used.

Figure 3: Mean disease activity score

Student’s t test used. Intensive vs routine after month 3, p<0.0001. Error bars show SD.
55 patients in the intensive group (gastrointestinal [18], abnormal liver function [eight], dermatological [ten], CNS [one], infective [five], haematological [two], others [two]). In the intensive group, 20 patients were admitted a total of 25 times (median stay, 6 days; range 1–52) compared with 30 admissions in 20 patients in the routine group (8 days stay, 1–102). Four patients died during the trial, three in the routine group (rheumatoid vasculitis, pneumonia, and myocardial infarction), and one in the intensive group (vulval carcinoma). None of the deaths was judged attributable to treatment. One patient in the routine group developed toxic epidermal necrolysis that was secondary to sulfasalazine treatment, which resulted in permanent bilateral corneal damage.

Costs were lower in the intensive group than in the routine group but did not differ significantly for total hospital cost per patient or total community cost per patient (table 4). Although outpatient and prescribing costs were significantly higher in the intensive treatment arm, higher inpatient costs in the routine group offset these effects. The generalisability of these results depends on local patterns of service delivery and the frequency of admissions. Community costs did not differ between each arm, although there seemed to be a substitution effect, with increased outpatient visits in hospital costs being offset by a reduction in community visits to family practitioners (data not shown). Diagnostic blood-test costs were higher in the intensive arm, associated with increased monitoring costs in primary care. Patients’ travel costs were higher in the intensive arm owing to increased frequency of outpatient visits (table 4). Results of sensitivity analysis were robust to changes in unit-cost data. For example, total hospital and community costs per patient remained lower in the intensive group than in the routine group even after a 20% reduction or a 50% increase in unit costs. Costs associated with the four patients’ deaths were excluded from the analysis; however, their inclusion further favoured the intensive group in terms of total hospital costs per patient (difference = –£854, 95% CI –£3525 to £1426).

Discussion

Our evidence lends support to the hypothesis that tight control of rheumatoid arthritis can be achieved in most patients with early rheumatoid arthritis, with a strategy of intensive treatment. It is noteworthy that, in this era of targeted biological therapies, this tight control was achieved with standard disease-modifying anti-rheumatic drugs without the use of anti-tumour necrosis factor (TNF) treatment.

The strategy used in this trial was multifaceted—treatment consisted of the frequent, objective assessment of patients; the intensive use of intra-articular steroid injections if needed; and the application of a structured protocol for the escalation of treatment in patients with current disease activity. Benefits of this strategy might relate to one particular part but they are most probably multifactorial. First, more than two-thirds of patients who were treated intensively needed to escalate oral treatment to achieve good control, and about half ended the trial on triple therapy with methotrexate, sulfasalazine, and hydroxychloroquine. Second, the mean dose of methotrexate used every week in the intensive group was higher than in the routine group. Third, more intra-articular steroid injections were given in the intensive group, although the additional steroid used was only 20 mg triamcinolone acetonide per month (equivalent to one large joint-injection every 2 months). Fourth, a very low proportion of patients stopped treatment because of drug-related toxic effects in the intensive group, perhaps because frequent outpatient review might have allowed additional patients’

<table>
<thead>
<tr>
<th>Intensive group (n=53)</th>
<th>Routine group (n=50)</th>
<th>Difference (95% CI)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease activity score</td>
<td>–3 (1.1)</td>
<td>–3 (1.4)</td>
<td>1.6 (1.1 to 2.1)</td>
</tr>
<tr>
<td>Joint swelling count</td>
<td>–11 (5)</td>
<td>–8 (5)</td>
<td>3 (1 to 5)</td>
</tr>
<tr>
<td>Joint tenderness count</td>
<td>–20 (9)</td>
<td>–12 (12)</td>
<td>8 (4 to 12)</td>
</tr>
<tr>
<td>Patient global assessment</td>
<td>–51 (30)</td>
<td>–21 (34)</td>
<td>30 (17 to 42)</td>
</tr>
<tr>
<td>Assessor global assessment</td>
<td>–58 (22)</td>
<td>–34 (28)</td>
<td>24 (14 to 34)</td>
</tr>
<tr>
<td>Pain score</td>
<td>–45 (24)</td>
<td>–20 (31)</td>
<td>25 (14 to 36)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>–30 (28)</td>
<td>–12 (24)</td>
<td>18 (8 to 28)</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>–30 (53)</td>
<td>–14 (40)</td>
<td>16 (3 to 34)</td>
</tr>
<tr>
<td>Health assessment questionnaire</td>
<td>–0.97 (0.8)</td>
<td>–0.47 (0.9)</td>
<td>0.5 (0.2 to 0.8)</td>
</tr>
<tr>
<td>Short form-12 physical summary score</td>
<td>9 (12)</td>
<td>4 (11)</td>
<td>5 (3.0 to 8.9)</td>
</tr>
<tr>
<td>Short form-12 mental health summary score</td>
<td>10 (9)</td>
<td>6.0 (18)</td>
<td>5.0 (1.6 to 11.6)</td>
</tr>
<tr>
<td>Erosion score†</td>
<td>0.5 (0–3.375)</td>
<td>3 (0–5.8)</td>
<td>n/a</td>
</tr>
<tr>
<td>Joint space narrowing†</td>
<td>3.75 (1.25–7.5)</td>
<td>4.5 (1.5–9)</td>
<td>n/a</td>
</tr>
<tr>
<td>Total Sharp score</td>
<td>4.5 (1–9.875)</td>
<td>8.5 (2.5–15.5)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Data are mean (SD) unless otherwise indicated. n/a=not applicable. *Students’ t test used. †Median (IQR) increase in score. tMann–Whitney test used.

Table 3: Change in disease activity, radiographic damage, physical function, and quality of life between 0 and 18 months

Figure 4: Mean dose of triamcinolone acetonide used every 3 months. Error bars show SD.
etanercept.19 anti-TNF treatment.18 The speed of disease activity was less impressive than results obtained in trials of less striking than that on clinical disease activity, and narrowing. The effect on radiographic progression was damage was recorded, but not in joint-space progression of erosive disease and total radiographic substantially enhanced quality of life. Reduced treatment in early rheumatoid arthritis), and disease-modifying antirheumatic drug therapy in compared with other randomised controlled trials of group had great improvements in physical function patient-centred outcomes. The people in the intensive management could be studied further. Improvement in disease activity in the routine group might have been unusually poor, but comparison of our results with other published randomised controlled trials16–19 suggests otherwise. For instance, the ACR 20 response in the routine group compared favourably with that reported in trials of sulfasalazine,16 leflunomide,17 methotrexate,18 and etanercept.19

Our results also lend support to the hypothesis that tight control of disease activity improves medium-term patient-centred outcomes. The people in the intensive group had great improvements in physical function compared with other randomised controlled trials of disease-modifying antirheumatic drug therapy in rheumatoid arthritis (including trials of anti-TNF treatment in early rheumatoid arthritis), and substantially enhanced quality of life. Reduced progression of erosive disease and total radiographic damage was recorded, but not in joint-space narrowing. The effect on radiographic progression was less striking than that on clinical disease activity, and was less impressive than results obtained in trials of anti-TNF treatment.18 The speed of disease activity control with anti-TNF treatment could be important, but conventional disease-modifying antirheumatic drugs might simply be less effective in reducing radiographic progression, even when used intensively. Implications for the management of patients with rheumatoid arthritis are considerable. Despite initial concerns, cost did not differ between intensive management of patients and routine treatment. Whether the improvement in patients’ outcomes will translate into longer-term savings, such as a reduction in work disability, the need for joint-replacement surgery, or the need for institutional care, remains to be seen. More importantly, our results show that a strategy of optimising current techniques and treatment regimens can deliver substantial patients’ benefits within a cost-neutral framework—ie, an unambiguously cost-effective intervention from an NHS perspective. By comparison, the UK National Institute for Clinical Excellence estimated an incremental cost-effectiveness ratio of £27 000 to £35 000 per quality-adjusted life year for anti-TNF treatment.20 Substantial budgets are being diverted to fund the use of these drugs in patients with rheumatoid arthritis, yet we have shown that good results can be achieved by application of a strategy of tight control in early rheumatoid arthritis at no additional cost, with conventional disease-modifying antirheumatic drugs, intra-articular steroid, and frequent clinical assessments to target persistent disease activity. Whether this intensive strategy would have equivalent or superior results to anti-TNF treatment needs to be the focus of a randomised controlled trial. Our results might be further improved by the incorporation of anti-TNF treatment into the strategy.

Mean cost per patient (£)

<table>
<thead>
<tr>
<th></th>
<th>Routine (n=50)</th>
<th>Intensive (n=53)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient</td>
<td>401</td>
<td>698</td>
<td>298 (241 to 354)</td>
</tr>
<tr>
<td>Inpatient</td>
<td>1611</td>
<td>571</td>
<td>-1040 (-3198 to 279)</td>
</tr>
<tr>
<td>Prescribing</td>
<td>452</td>
<td>649</td>
<td>197 (90 to 300)</td>
</tr>
<tr>
<td>Total</td>
<td>2464</td>
<td>1919</td>
<td>-544 (-2737 to 1784)</td>
</tr>
<tr>
<td>Patient travel costs</td>
<td>73</td>
<td>129</td>
<td>56 (12 to 99)</td>
</tr>
<tr>
<td>Community costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health professional visits</td>
<td>1240</td>
<td>859</td>
<td>-391 (-698 to -90)</td>
</tr>
<tr>
<td>Diagnostic tests</td>
<td>341</td>
<td>586</td>
<td>247 (-42 to 516)</td>
</tr>
<tr>
<td>Total community costs</td>
<td>1590</td>
<td>1427</td>
<td>-162 (-462 to 274)</td>
</tr>
</tbody>
</table>

Numbers are rounded to the nearest £.

Table 4: Total hospital, community, and patient costs per patient between 0 and 18 months

education, reassurance, adjunctive treatment (such as prochlorperazine early in the course of sulfasalazine), and flexible dose adjustments. The relative importance of the various components of intensive outpatient management could be studied further.

Whether the improvement in patients’ outcomes will translate into longer-term savings, such as a reduction in work disability, the need for joint-replacement surgery, or the need for institutional care, remains to be seen. More importantly, our results show that a strategy of optimising current techniques and treatment regimens can deliver substantial patients’ benefits within a cost-neutral framework—ie, an unambiguously cost-effective intervention from an NHS perspective. By comparison, the UK National Institute for Clinical Excellence estimated an incremental cost-effectiveness ratio of £27 000 to £35 000 per quality-adjusted life year for anti-TNF treatment.20 Substantial budgets are being diverted to fund the use of these drugs in patients with rheumatoid arthritis, yet we have shown that good results can be achieved by application of a strategy of tight control in early rheumatoid arthritis at no additional cost, with conventional disease-modifying antirheumatic drugs, intra-articular steroid, and frequent clinical assessments to target persistent disease activity. Whether this intensive strategy would have equivalent or superior results to anti-TNF treatment needs to be the focus of a randomised controlled trial. Our results might be further improved by the incorporation of anti-TNF treatment into the strategy.

Mean cost per patient (£)

<table>
<thead>
<tr>
<th></th>
<th>Routine (n=50)</th>
<th>Intensive (n=53)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient</td>
<td>401</td>
<td>698</td>
<td>298 (241 to 354)</td>
</tr>
<tr>
<td>Inpatient</td>
<td>1611</td>
<td>571</td>
<td>-1040 (-3198 to 279)</td>
</tr>
<tr>
<td>Prescribing</td>
<td>452</td>
<td>649</td>
<td>197 (90 to 300)</td>
</tr>
<tr>
<td>Total</td>
<td>2464</td>
<td>1919</td>
<td>-544 (-2737 to 1784)</td>
</tr>
<tr>
<td>Patient travel costs</td>
<td>73</td>
<td>129</td>
<td>56 (12 to 99)</td>
</tr>
<tr>
<td>Community costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health professional visits</td>
<td>1240</td>
<td>859</td>
<td>-391 (-698 to -90)</td>
</tr>
<tr>
<td>Diagnostic tests</td>
<td>341</td>
<td>586</td>
<td>247 (-42 to 516)</td>
</tr>
<tr>
<td>Total community costs</td>
<td>1590</td>
<td>1427</td>
<td>-162 (-462 to 274)</td>
</tr>
</tbody>
</table>

Numbers are rounded to the nearest £.

Table 4: Total hospital, community, and patient costs per patient between 0 and 18 months

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References
7 Verhoeven AC, Boers M, van Der Linden S. Responsiveness


