Cost-Effectiveness of Combination Nonbiologic Disease-Modifying Antirheumatic Drug Strategies in Patients with Early Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To compare the costs and benefits of alternative combination strategies of disease-modifying antirheumatic drugs (DMARD) and DMARD monotherapy in patients with early, active rheumatoid arthritis (RA).

Methods. Data were drawn from randomized controlled trials that compared DMARD monotherapy or any DMARD combination strategy, with or without combined steroid therapy. Mixed treatment comparison methods were used to estimate the relative effectiveness of the different strategies. A mathematical model was developed to compare the longterm costs and benefits of the alternative strategies, combining data from a variety of sources. Costs were considered from a health sector viewpoint and benefits were expressed in terms of quality-adjusted life-years (QALY).

Results. If decision makers use a threshold of £20,000 (US$29,000) per QALY, then the strategies most likely to be cost-effective are either DMARD combination therapy with downward titration (probability of being optimal = 0.50) or intensive, triple DMARD combination therapy (probability of being optimal = 0.43). The intensive DMARD strategy generated an additional cost of £27,392 per additional QALY gained compared to the downward titration strategy. Other combination strategies were unlikely to be considered cost-effective compared to DMARD monotherapy. Results were robust to a range of scenario sensitivity analyses.

Conclusion. Combination DMARD therapy is likely to be cost-effective compared to DMARD monotherapy where treatment entails rapid downward dose titration or intensive, triple DMARD therapy. (First Release May 15 2011; J Rheumatol 2011;38:1593–600; doi:10.3899/jrheum.101327)

Key Indexing Terms:
RHEUMATOID ARTHRITIS COST-BENEFIT ANALYSIS QUALITY OF LIFE

Because rheumatoid arthritis (RA) is common[1] and has considerable societal and economic effect[2], its optimal management is of major importance to healthcare providers. Current initial management involves using nonbiologic disease-modifying antirheumatic drugs (DMARD) and glucocorticoids early to retard disease progression. Antiinflammatories and analgesics are used to improve symptoms. These drug treatments are relatively inexpensive and represent a small component of the overall RA treatment costs[3]. The advent of newer "biologic" treatments has had a substantial effect on patient care. Although the efficacy of tumor necrosis factor-α (TNF-α) inhibitors — infliximab, adalimumab, and etanercept — is established in randomized controlled trials (RCT)[4,5,6] and confirmed in metaanalyses[7], their optimal position in the care pathway is controversial, in part because of their high cost. Healthcare providers such as the UK National Health Service (NHS) allow biologics only after ≥ 2 DMARD have been tried and have failed[4].

One crucial unresolved question is the optimal initial use of conventional DMARD. Several recent trials hint at increased benefits from initial DMARD combination therapies compared to sequential DMARD monotherapy[5,6,7]. Traditionally, the focus of pharmacological treatment for RA has been gradual drug escalation, with DMARD and steroids introduced sequentially and doses titrated upward[8]. While this traditional approach can see patients achieve disease control, there is now evidence, from both clinical trials and clinical practice[5,6,7,9], that either slow introduction of DMARD or slow escalation of the dose leads to unsatisfactory longterm results. A failure to quickly achieve disease control from the outset can result in poorer symptom control and irreversible damage to patients' joints[10].

While there are differences in the acquisition costs of individual DMARD and steroids, their ability to prevent or delay the possible need for biologic therapy will result in potential-

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ly large differences in treatment costs over a patient's lifetime. Therefore, while it is important to compare these strategies in terms of their cost-effectiveness, doing so as part of the published clinical trials will be limited by the timeframe and the numbers of strategies in the trial[6,11,12]. We seek to estimate the cost-effectiveness of a range of alternative DMARD treatment strategies over a lifetime.

We developed a decision analytic model to estimate the lifetime costs and effects of a number of treatment strategies based on nonbiologic DMARD for the treatment of patients with early RA in the UK NHS setting. Relevant strategies and their short-term effectiveness were based on published RCT. The model also draws on observational evidence from the British Society for Rheumatology Biologics Registry (BSRBR)[13] to extrapolate beyond the short timeframe covered by clinical trials and to incorporate all relevant differences in costs and benefits. This evaluation was a key component in the recent UK National Institute for Health and Clinical Excellence (NICE) Clinical Guideline for Rheumatoid Arthritis[14]. Although the research is focused on the costs and benefits for the NHS in England and Wales, the methods used by NICE are recognized by the World Health Organization[15] and have international relevance.

MATERIALS AND METHODS

Model overview. The decision analytic model structure (Figure 1) shares several characteristics with models used in previous published economic evaluations for therapies in RA[16]. It tracks the course of disease for hypothetical, individual patients, one at a time, along each of the alternative DMARD treatment pathways. Each pathway has several components, each of which draws on a specific set of evidence, described in detail in the following sections. These stages comprise the initial treatment response assessed at 6 months, the duration of the DMARD treatment strategy for responders, the progression of disease while treatment continues, and the future treatments likely to be provided over the remaining patient lifetime after withdrawal from the initial DMARD treatment strategy. This final component reflects current guidance in the UK NHS in relation to biologic therapies[4] and is important to the assessment of the cost-effectiveness of treatments in early disease, because different strategies will result in patients becoming eligible for biologic and other therapies (and their associated costs and benefits) at different times.

The model tracks the course of disease in terms of Health Assessment Questionnaire (HAQ) profiles. The cost implications of each HAQ profile are then estimated together with the treatment costs for each of the strategies. An NHS perspective is adopted for costs. The model expresses health benefits in terms of quality-adjusted life-years (QALY), a generic measure that incorporates a variety of different types of health effects into a single measure that can be used to make comparisons across a broad range of health conditions. QALY for each treatment strategy are estimated by converting from the HAQ profile.

All future costs and health benefits were discounted at 3.5% per annum. The mean costs and QALY of each of the combination DMARD treatment strategies are compared to standard, sequential DMARD monotherapy and to each other. No mortality effect is modeled, because no evidence suggests a differential effect on mortality between treatments.

Treatment strategies. Systematic searches of the published literature were conducted to identify all evidence of the effectiveness of combination nonbi-

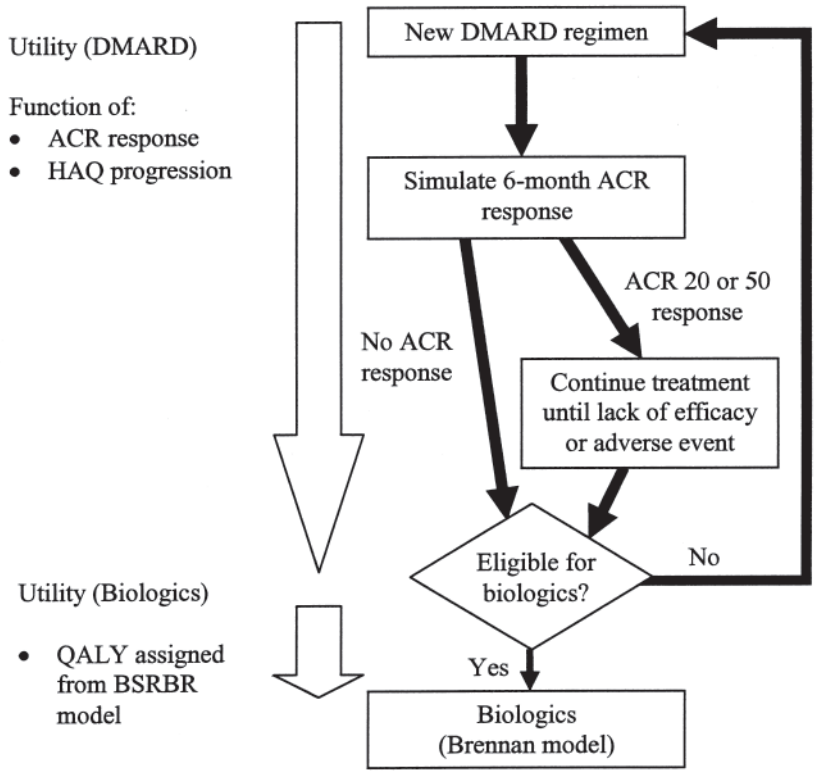

Figure 1. Each individual patient simulated in the model was categorized as an ACR nonresponder or 20 or 50 responder at 6 months. DMARD: disease-modifying antirheumatic drug; ACR: American College of Rheumatology; HAQ: Health Assessment Questionnaire; QALY: quality-adjusted life-years; BSRBR: British Society for Rheumatology Biologics Registry.

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ologic DMARD treatment strategies. Strategies of interest were defined as those in which nonbiologic DMARD were used either in combination with each other or with steroids, but not with biologic drugs. Only RCT published in English and reporting American College of Rheumatology outcomes (ACR20/50) were considered. In addition, patients included in the studies were required to have < 2 years from diagnosis of RA. Full details of the review are provided elsewhere[14].

Thirteen relevant studies were included in the review. The 19 treatment arms of the trials included combination DMARD treatment strategies, and these were categorized into 5 broad strategies (Table 1). A further 10 trial arms considered DMARD monotherapy. Each trial arm contained patients who had active RA for < 2 years.

DMARD monotherapy treatments from the identified trials included methotrexate, sulfasalazine, hydroxychloroquine, and cyclosporine. We decided to group this evidence together into the DMARD monotherapy strategy, and this was based on 2 important considerations. First, a systematic review of DMARD monotherapy treatments in early RA was conducted as part of the NICE Clinical Guideline of Rheumatoid Arthritis[14], and this review found no statistically significant difference between any particular DMARD monotherapy treatment. It was assumed that a class effect was present between specific treatments. Second, including each DMARD monotherapy treatment in the analysis, or restricting the analysis to just methotrexate, would not allow a completed network of evidence. The consequence of this is that it would not be possible to consider all relevant combination DMARD strategies within the mixed treatment comparison.

Treatment response rates. While individual trials make comparisons between 2 or more strategies, providing direct evidence of the relative treatment effect, no single trial exists that has made comparisons between all strategies of interest.

To account for the range of direct and indirect evidence, a mixed treatment comparison method was adopted[28,29] (also known as a network metaanalysis[30]). This method extends the approach of standard metaanalysis but allows the different strategies to be compared to each other, including in situations where no primary trials have made such a comparison, that is, using indirect evidence. Crucially, this approach maintains the randomized estimates from within each individual study. Little variance was found in terms of disease duration (under 2 years) and baseline HAQ across the clinical trials.

Random effects regression models were fitted using Bayesian Markov Chain Monte Carlo (MCMC) Methods in WinBUGS software[31]. The analysis was based on the numbers of patients achieving ACR20 and ACR50 at 6 months in the trials to obtain estimates of the log OR of each treatment strategy relative to each other.

Table 2 shows the estimated OR from the mixed treatment comparison for ACR20 and 50 responses for each of the 5 treatment strategies compared to DMARD monotherapy. It can be seen that all estimates are positive, indicating positive treatment effects for combination strategies, although not all are statistically significant.

Longer-term course while taking DMARD. Figure 1 shows that each individual patient simulated in the model was categorized as an ACR nonresponder or 20 or 50 responder at 6 months, based on the results in Table 2. Nonresponders move to the next treatment, which may be further DMARD in the case of the DMARD monotherapy and steroid strategies, or biologic therapy for the remaining combination DMARD strategies. For the step-up and intensive step-up combination strategies, the step-up occurs within the first 6 months and so patients who do not respond progress to biologics. We assumed that ACR20 and 50 are equivalent to 20% and 50% improvements in starting HAQ[16]. Treatment responders are assumed to experience annual increases in HAQ of 0.0418 for the duration of treatment, as estimated in a metaanalysis of longterm natural history disease data[13]. When a patient withdraws from a treatment, it is assumed that HAQ increases by the same magnitude as the original 6-month treatment benefit. For treatments that are attempted twice (DMARD monotherapy and steroid combination therapy), a patient's chance of response a second time is the same as the first.

Withdrawal. The 6-month withdrawal rate, either because of lack or loss of efficacy or for adverse events, was estimated for each treatment strategy by taking a weighted average of the patients withdrawn from each relevant arm of the trials. The same probability of withdrawing from treatment was also applied at each subsequent 6-month period. In the DMARD monotherapy arm, both the probability of achieving an ACR 20 or 50 response and the rate of withdrawal were assumed to be the same for both first DMARD and second DMARD treatment before biologics.

Post-DMARD therapy. The model assumes that patients move to biologic treatments, as per current UK NHS guidance, once they have failed 2 DMARD. We took estimates of the costs and QALY for treatments from this point onward from a published study based on analysis of the BSRBR[13]. This provides a lifetime estimate of costs and QALY for patients with early RA.

Quality of life. To convert the estimated HAQ profiles for patients to QALY, we used values from the National Databank for Rheumatic Diseases (NDRD) reported in an analysis of abatacept for RA[32]. The study provides EQ-5D values for each quarter-point on the HAQ scale, with a utility value of 0.857 for those with a HAQ of 0–0.25, and a value of 0.034 for those with a HAQ of 2.75–3. These estimates are based on one of the largest reported datasets (n = 4258) and were therefore preferred to other published regression models[33,34]. These were investigated as part of the sensitivity analysis.

Costs. All unit costs for the drugs are taken from the British National Formulary (BNF56 — Sept 2008). As well as drug costs, the economic model includes doctor/hospital consultation costs and drug administration costs, which are taken from the Personal Social Services Research Unit analysis of health and social care unit costs (PSSRU 2007).

The cost of other resources such as hospitalizations, outpatient visits, and joint replacement surgeries was estimated as a function of HAQ based on a study that used the Resource Utilisation Norfolk Arthritis Register (NOAR)[35]. The estimated annual cost of resources used related to HAQ is £120.23,

Table 1. Combination DMARD strategies.

Treatment Strategy Type	Description	Studies from which Trial Arm Drawn (reference number)
Monotherapy	DMARD monotherapy	(5, 17–25)
Parallel combination	Two or more DMARD given in combination at the same time	(5, 7, 17–23, 26)
Step-up combination	Patients begin with DMARD monotherapy, and a second DMARD is added if an inadequate response is observed (within first 6 months)	(5, 6)
Step-down combination	Initial parallel combination followed by downward dose titration and withdrawal	(24, 27)
Intensive step-up combination	Patients begin with a DMARD parallel combination strategy, and rapid dose increases are made where an inadequate response is observed (within first 6 months)	(6, 26)
Steroid plus monotherapy	Glucocorticoids routinely used alongside a DMARD monotherapy regimen (the other combination strategies use steroids on an "as needed" basis	(7, 25, 27)

DMARD: disease-modifying antirheumatic drug.

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Table 2. Measurement values.

Measurement	Value	Uncertainty	Reference
Treatment effectiveness: ACR20 response	OR	CODA samples (95% credible interval)	
Monotherapy	1.00	—	Mixed treatment comparison
Parallel combination	1.72	1.11–2.51	
Step-up combination	1.55	0.46–2.51	
Step-down combination	3.25	0.84–8.87	
Intensive step-up combination	13.02	1.35–50.01	
Steroid plus monotherapy	1.23	0.47–2.53	
Treatment effectiveness: ACR50 response	OR	CODA samples (95% credible interval)	
Monotherapy	1.00	—	Mixed treatment comparison
Parallel combination	2.50	1.14–4.80	
Step-up combination	1.39	0.16–5.30	
Step-down combination	3.34	0.59–10.20	
Intensive step-up combination	25.57	0.55–105.40	
Steroid plus monotherapy	1.72	0.27–5.68	
Treatment withdrawal	6 month probability	Beta distribution (n, p)	
Monotherapy	0.095	66,696	Clinical trials
Parallel combination	0.060	4,176	
Step-up combination	0.020	51,610	
Step-down combination	0.026	4,55	
Intensive step-up combination	0.049	5,173	
Steroid plus monotherapy	0.074	20,262	
HAQ			
ACR20 response: HAQ improvement	37.8%	—	(16)
ACR50 response: HAQ improvement	85.3%	—	
Annual HAQ progression rate	0.0418	—	(13)
Resource use	HAQ group		
Annual cost of NHS resources (hospital days, hospital visits, and joint replacement)	0 = £120.23 0–1 = £261.78 1–2 = £579.94 2–3 = £1,673.41	—	(35) Costed with 2007 PSSRU
6-month strategy costs			
Monotherapy	£251.40	—	BNF56 (September 2008)
Parallel combination	£263.56	—	
Step-up combination	£266.93	—	
Step-down combination	£269.29	—	
Intensive step-up combination	£766.35	—	
Steroid plus monotherapy	£269.98	—	
Patient population characteristics	Value	Normal distribution (SD)	
Age, yrs	54.8	13.6	(3)
Women, %	66.6	—	
Disease duration, yrs	0.68	0.508	
Baseline HAQ	1.11	0.7	
Biologics			
Lifetime cost of biologic therapy	£57,919	—	(13)
Lifetime QALY of biologic therapy	5.1514	—	

ACR: American College of Rheumatology; CODA: Convergence Diagnostic and Output Analysis software; HAQ: Health Assessment Questionnaire; NHS: National Health Service (UK); PSSRU: Personal Social Services Research Unit; BNF: British National Formulary; QALY: quality-adjusted life-years.

£261.78, £579.94, and £1673.41 for a patient with a HAQ in the range of 0, 0–1, 1–2, and 2–3, respectively. It should be noted that the NOAR dataset is not exclusive to patients with RA but includes any inflammatory polyarthritis, and so it may provide lower estimates than that of a true RA cohort.

Analysis of uncertainty. We reflected uncertainties in the cost-effectiveness estimates through a range of sensitivity analyses. Probabilistic sensitivity analysis was performed to reflect the joint uncertainty in model inputs by assigning distributions to model measures and using Monte Carlo simulation[36]. The joint uncertainty in the ACR response probabilities was reflected by extracting the samples directly from the MCMC simulation in WinBUGS. Normal distributions were assigned to the patient baseline characteristics and annual HAQ progression rates. Beta distributions were assigned to withdrawal rates. In addition, a range of 1-way analyses was performed.

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RESULTS

The model was run with 100 patients simulated through 1000 Monte Carlo simulations. Tests for convergence were performed to ensure that enough patients and Monte Carlo simulations were run. Table 3 shows the mean costs and QALY associated with each of the 6 treatment strategies.

The most costly strategy is the intensive DMARD combination strategy, with a mean lifetime cost per patient of £61k. The least costly strategy is the step-down DMARD combination strategy. It should be noted that DMARD monotherapy, while the cheapest strategy in terms of DMARD drug cost, is not the most cost-effective strategy overall. Similarly, the most effective strategies are those that use intensive or step-down DMARD combinations. Monotherapy is more effective over a patient's lifetime compared to several of the combination strategies.

The incremental cost-effectiveness ratios (ICER) compared to monotherapy show that the steroid plus DMARD monotherapy strategy is both more costly and less effective. Two strategies, step-up combination and parallel combination, are cost-saving but also less effective. Step-down combination therapy is cost-saving and more effective than monotherapy and is therefore preferable on economic grounds. The remaining strategy, intensive DMARD combination, generates 2.04 additional QALY per patient, at relatively little additional cost (£5050). This results in an ICER of £2482.

Table 3 also allows us to consider which of the 6 treatment strategies may be considered optimal, i.e., to compare between strategies, rather than just with standard DMARD monotherapy. Step-down combination therapy exceeds monotherapy, step-up, parallel, and steroid combinations, that is, it is less costly and more effective. Comparing the remaining strategy (intensive DMARD combination) to step-down treatment, the estimated ICER is £27,392. This information can also be seen in the net benefits column of Table 3. If we assume that decision makers adopt a threshold of £20,000 per QALY, then the value of each strategy can be expressed in monetary terms. The threshold of £20,000 per QALY is multiplied by the QALY generated, net the total cost of the strategy. The optimal strategy is that which generates the greatest net benefit. This is step-down combination therapy (£258k) followed by intensive DMARD combination therapy (£254k). The probabilistic sensitivity analysis shows that given the uncertainty in the model inputs there is considerable overlap between these 2 strategies. At a £20k threshold, the probabilities of step-down or intensive DMARD combination therapies being optimal are 0.50 and 0.43, respectively.

A range of sensitivity analyses was undertaken to test that the results were robust to the assumptions and measurement values used. We tested alternative specifications of the relationship between HAQ and the EQ-5D measure, patient baseline HAQ, and age values, discount rates and frequencies of monitoring required while taking treatment. In addition, the model assumes that all nonresponders at 6 months switch to the next treatment in the strategy, either a further DMARD or biologic therapy. In a sensitivity analysis, nonresponders continue taking treatment until an adverse event or loss of efficacy is experienced. Further, in the main analysis, HAQ score increased while patients remained on DMARD therapy[13] for both DMARD combination and monotherapies. This rate is based on DMARD monotherapy evidence, because there has not been a long-run analysis of the progression of RA in patients receiving combination DMARD. The followup data from the BeSt[5] and COBRA[24] trials suggest that there may not be a significant annual increase in HAQ from 6 months until the end of followup (2 years). Therefore a sensitivity analysis was conducted with the combination strategies having no annual increase in HAQ once they achieved an ACR 20 or 50 response. The key finding, that intensive or step-down DMARD combination strategies are likely to be the most cost-effective alternatives, was robust to all sensitivity analyses.

DISCUSSION

Our analysis suggests that step-down or intensive combinations of DMARD are likely to be the most cost-effective strategies. The step-down combination strategy appears less costly and more effective when compared to DMARD monotherapy. When comparing intensive DMARD combination to step-down DMARD combination therapies, the estimated ICER is £27k. In the NHS in England and Wales, a threshold range of £20,000 to £30,000 per QALY is typically

Table 3. Cost-effectiveness results.

Strategy	Cost	QALY	ICER (compared to monotherapy)	Incremental Analysis*	Net Benefit (£20,000)	Net Benefit Rank
Monotherapy	£55,996	13.73	—	Dominated	£218,604	3
Step-up	£50,791	11.91	£2852	Dominated	£187,409	5
Parallel	£55,573	13.42	£1356	Dominated	£212,827	4
Intensive	£61,046	15.77	£2482	£27,392	£254,354	2
Step-down	£48,849	15.32	Cost saving	Reference strategy	£257,551	1
Steroid	£57,468	11.79	Dominated	Dominated	£178,332	6

* Incremental comparisons are against the next best, nondominated treatment strategy. QALY: quality-adjusted life-years; ICER: incremental cost-effectiveness ratios.

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applied[37]. This should be considered alongside the substantial uncertainty in the estimates.

Our analysis also suggests that a strategy of monotherapy plus glucocorticoids is more costly and less effective when compared to DMARD monotherapy. This is because patients in the model receiving the monotherapy plus glucocorticoid strategy reach biologic treatments more quickly than those receiving DMARD monotherapy alone, and so fewer QALY have accrued. However, it is important to note that intensive, step-up, step-down, and parallel DMARD combinations all contain glucocorticoids as part of the regimen, and so they contribute to the effectiveness of a combination DMARD strategy.

One of the 2 trials that provided evidence for a step-down combination[24] provided a cost-effectiveness analysis in a Dutch setting and also found step-down combination DMARD strategy to dominate monotherapy. The Tight Control for Rheumatoid Arthritis (TICORA) trial that populated the intensive DMARD combination strategy included a cost-effectiveness analysis[6] that found the intensive arm to be more effective at no additional cost. In the TICORA study there were higher inpatient costs in the comparator step-up arm, which exceeded the higher prescribing costs in the intensive arm. In our analysis, the extra admissions (including admissions due to adverse events) have not been directly estimated, and therefore the cost of intensive combination DMARD strategy was higher than the step-up combination DMARD strategy.

Our findings have several limitations. Most importantly, we grouped similar treatment strategies together rather than considering every individual trial arm separately. Indeed, such individual treatment arm comparisons are not feasible, given the limited links between the various trials. Inevitably, there is some judgment required in making such groupings, because trials are not identical in terms of drug choice, dosage, monitoring, and protocol criteria. Not all experts believe we should treat DMARD as a class, and a strong body of opinion holds that methotrexate is superior to other DMARD such as sulfasalazine. While this viewpoint is understandable, there are no supporting clinical trial data to show whether methotrexate is more effective. A second limitation is the historic design of the economic data on the future costs of treating RA, which relied heavily on information from Norfolk. Because clinical practice is always changing, some of these calculations, particularly those relating to inpatient admissions, may be less relevant in the future. Finally, the treatment costs depend on the stage at which biologics are used. Widespread use of biologics for milder disease will have different cost implications from the more conservative approach followed in the UK.

It is important to note that trials included in this analysis required patients to meet the ACR criteria for RA[38], and to have had active disease (defined in different ways in the trials, but usually includes numbers of tender and swollen joints, elevated acute-phase markers, morning stiffness, or composite scores). The ACR criteria were not designed for early RA, and may not perform well in identifying early inflammatory arthritis that may evolve into RA[39,40]. Current recommendations for the management of early idiopathic inflammatory arthritis advocate the introduction of DMARD in patients with persistent synovitis before they meet ACR criteria for RA[41].

The current analysis cannot comment on the cost-effectiveness of various DMARD strategies in cases of early inflammatory arthritis that do not meet ACR criteria for RA, or for disease that does meet the criteria but is inactive. At present, the most appropriate and cost-effective DMARD strategies for either milder inactive RA or undifferentiated inflammatory arthritis are unknown. Recently published UK RA management guidelines recommended further research in this area[14].

Guidance for movement to biologics is often based on a specific level of disease (such as a Disease Activity Score of 5.1 as defined in the NICE guidelines for anti-TNF-α[4]). The model has not included a switching mechanism based on a level of disease activity, and so may not fully reflect current clinical behavior. The lack of longterm data on HAQ level when on combination treatments means that the full benefits of combination treatments may not have been fully captured. Our analysis models the NICE guidance that recommends patients progress to biologic therapy only after failure on 2 DMARD. Our analysis does not provide an evaluation comparing biologic therapies to DMARD combinations in patients with early RA. Further research is also required to assess the longterm disease activity of patients on monotherapy DMARD and combination DMARD, as this has a substantial effect on the QALY that a patient accrues while taking the treatment.

We have provided health economic evidence to support the clinical evidence favoring specific combination strategies as early treatment of active RA. Further cost-effectiveness analyses are required to extend this work in comparing the use of biologic therapies with DMARD combination strategies, and there may be benefit in assessing alternative sequences of medical interventions through head-to-head trial evidence.

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