RHEUMATOLOGY

Rheumatology 2012;51:iv21–iv26
doi:10.1093/rheumatology/kes088

Economic benefits of optimizing anchor therapy for rheumatoid arthritis

Bruno Fautrel[1]

Abstract

The total cost of RA is substantial, particularly in patients with high levels of disability. There are considerable differences in cost between countries, driven in part by differences in the use of biologic therapies. Economic evaluations are needed to assess the extra cost of using these treatments and the benefits obtained, to ensure appropriate allocation of limited health care resources. The BeSt trial, evaluating four treatment strategies, found comparable medium-term efficacy but substantially higher costs with early biologic therapy. A systematic review of such cost-effectiveness analyses concluded that biologic therapy should be used after therapy has failed with less costly alternatives such as synthetic DMARDs and glucocorticoids. Optimizing such relatively low-cost therapy to improve outcomes may delay the need for biologic therapy, thereby saving costs. A simple model has confirmed the value of this approach. The addition of modified-release prednisone 5 mg/day to existing synthetic DMARD therapy in patients with active disease resulted in improvement in DAS-28 to below the threshold level for initiation of reimbursed biologic therapy in 28–34% of patients. On a conservative estimate (i.e. assuming no further benefits beyond the 12 weeks of the study and a 12-week wait-and-see approach to starting biologic therapy), cost savings amounted to nearly €400 per patient. While treatment decisions should never be based only on cost considerations, prolonging disease control by optimizing the use of non-biologic treatments may bring benefits to patients and also economic benefits by delaying the need for biologic treatments.

Key words: rheumatoid arthritis, disease-modifying antirheumatic drugs (DMARDs), biologic therapies, glucocorticoids, cost-effectiveness, cost savings.

The economic burden of RA

The total cost of RA is substantial, with new and ambitious goals for the disease adding to the cost. RA is now seen as a medical emergency, requiring prompt treatment using a tight control strategy that is aimed at achieving remission [1–3]. Although the value to the patient is priceless, efficacious treatments for RA do have a quantifiable cost. Analysis of the QUEST-RA database of over 6000 patients from 70 centres in 25 countries found that lower disease activity scores were generally achieved in countries with higher per capita gross domestic product (GDP), though this association with national wealth was more striking than the association with use of any particular medication for the disease [4].

A systematic review of cost-of-illness studies in RA found mean annual health care cost of €4170 per patient, with indirect costs (sick leave, lost productivity) taking total cost to €14 906 per patient per year [5]. In early arthritis, health care costs account for a high proportion of total costs, as shown in the Etude et Suivi de POlyarthrites Indifférenciées Récentes (ESPOIR) study in France [6]. Annual direct costs for the 577 patients with economic data available amounted to a mean of €2854, with mean indirect costs of €1476.

A key determinant of cost is functional ability [7, 8]. In separate analyses of nearly 200 patients in Sweden and over 800 patients in the UK, costs increased as the score on the HAQ increased (indicating increasing disability); the increase in indirect costs of lost productivity was particularly marked. The cost of RA also varies with country, averaging €15 000 per patient per year in countries in Western Europe, compared with €3800 in countries of

[1]Department of Rheumatology, University of Pierre and Marie Curie, Paris, France.

Submitted 15 December 2011; revised version accepted 13 March 2012.

Correspondence to: Bruno Fautrel, Department of Rheumatology, University of Pierre and Marie Curie – Paris 6, AP-HP, Pitie Salpetrière University Hospital, 83 Boulevard de l'Hôpital, 75013 Paris, France.
E-mail: bruno.fautrel@psl.aphp.fr

Central and Eastern Europe [9]. In this review of the literature and health technology assessments, there were also wide variations in cost within these regions, with the total annual cost of RA per patient in France, for example, more than double that in Spain.

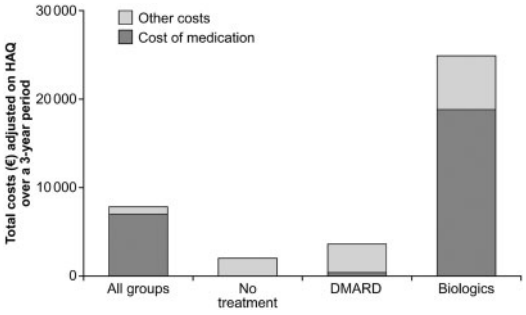
One reason for the difference in health care costs of RA between countries is the varying use of biologic treatments [9]. An analysis of patients in the ESPOIR study in France showed that treatment costs for patients with early arthritis, adjusted for disability level as assessed by HAQ, were markedly higher when treatment included biologic therapy (Fig. 1) [10]. Use of biologic treatments has grown rapidly during the past decade.

Although the use of biologic treatments has contributed to the direct cost of health care for RA, it might also be anticipated that use of an effective treatment could have reduced the costly consequences of the disease. Analysis of the need for total joint replacement in Spain over time showed an increasing trend for patients with OA, but a plateau in such surgery among those with RA, suggesting reduced need following the introduction of biologic therapy [11]. Likewise, a Japanese study of patients with RA showed a decline in total joint replacement surgery since 2003 [12]. A German database study showed a gradual increase in the proportion of employed patients with RA and a marked decrease in days of sick leave due to RA during the last decade [13]. In Sweden, a registry of patients showed a significant reduction in sick leave after receiving a biologic therapy, though no changes were noted in disability pension [14]. It appears that, while substantially increasing health care costs, modern biologic therapies may maintain functional ability and reduce the need for joint replacement surgery, though it may be too early to see any impact on disability benefits. The question remains whether or not expenditure on these costly treatments is an efficient use of limited health care resources. It has been noted that unrestricted use of biologic therapies would be unaffordable, at least in the UK [15].

Allocating limited resources

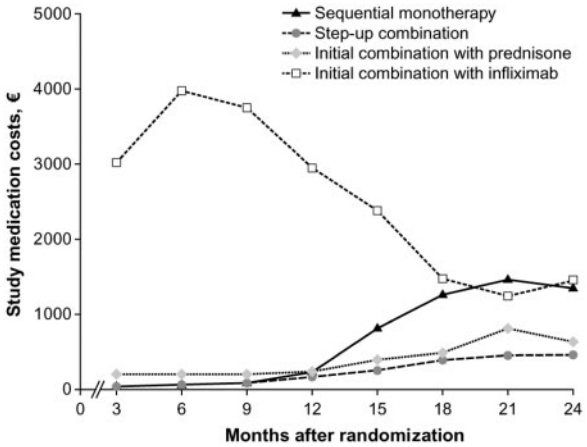
In the ESPOIR study of early RA in France, costs were compared in those who received treatment with biologic therapy within a year of diagnosis and those receiving later biologic therapy [6]. Mean direct costs, adjusted for HAQ score, were markedly higher among those receiving early therapy compared with later therapy, and remained higher throughout the 3 years following diagnosis. Likewise, in the BeSt study that compared four different treatment strategies, the cost of biologic therapy plus MTX was markedly higher than other strategies using non-biologic therapies (sequential synthetic DMARD monotherapy, step-up combination synthetic DMARD and step-down glucocorticoid/combination DMARD) as shown in Fig. 2 [16]. When the outcomes achieved were taken into account, the cost per quality-adjusted life year (QALY) for biologic therapy plus MTX in these newly diagnosed patients was well beyond the limit considered acceptable by most health care systems (Fig. 3), suggesting that the treatment was not

Fig. 1 Direct cost of treatment in the ESPOIR study according to study medication [10].



Reproduced from [10]. BMJ Publishing Group Ltd. © 2010.

Fig. 2 Cost of study medication for the four treatment strategies in the BeSt study [16].



Adapted from [16] with permission of John Wiley & Sons, Inc. © 2009.

cost-effective in this patient group [17]. An economic model in early RA that compared the cost-effectiveness of three different treatment strategies also found only limited efficacy benefits with very early use of biologic therapies but substantial additional costs compared with a pyramid strategy starting with synthetic DMARDs [18]. A systematic review of the cost-effectiveness of alternative treatment strategies confirmed that early treatment should be with non-biologic therapies, and that biologic treatments are only cost-effective after failure of therapy with synthetic DMARD treatment (Fig. 4) [19].

Economic benefits of prolonging disease control

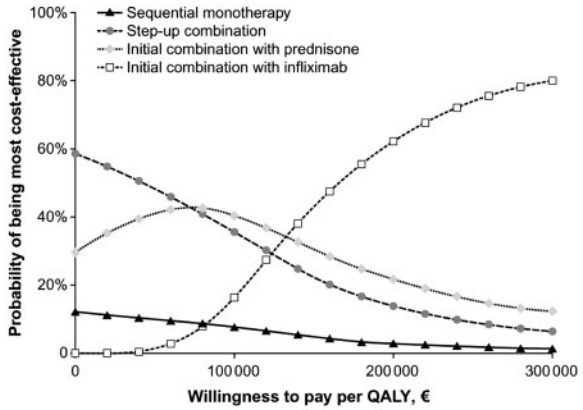
As noted earlier, the cost of managing RA increases with increasing disability [7]. It follows that prolonging disease control early in the course of RA, thereby delaying the

onset of disability and impaired function, may bring economic benefits. While cost alone should never be the key factor in treatment decisions, it follows that economic benefits may be increased if outcomes can be improved by optimizing use of low-cost treatments (i.e. synthetic DMARDs and glucocorticoids).

The COBRA study demonstrated improved disease control and long-term benefits of early treatment with a step-down combination regimen of glucocorticoid, MTX and SSZ, compared with SSZ alone [20–22]. Economic analyses showed that the combination regimen was also the dominant strategy, i.e. it resulted in superior efficacy at lower cost, both when only direct health care costs were considered and when indirect productivity costs were also included [23, 24]. The economic analysis of the BeSt study also showed that initial treatment with prednisone, MTX and SSZ might be a cost-effective strategy compared with other strategies tested except under the most extreme circumstances, i.e. in a model based on the societal perspective and friction cost method [16].

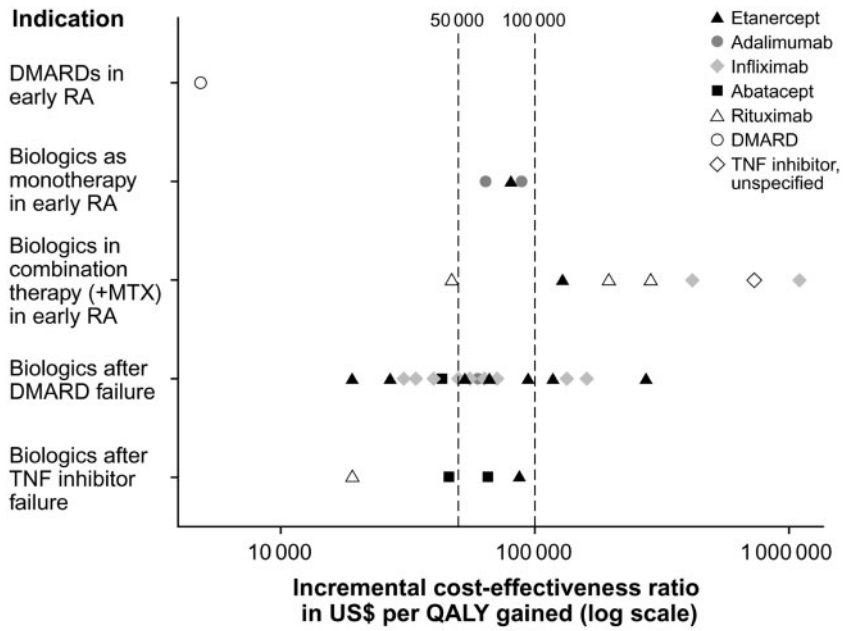
There is increasing evidence suggesting that glucocorticoids enhance clinical outcomes when used with synthetic DMARD monotherapy or combination therapy [25, 26]. Glucocorticoids have been shown to be disease-modifying, at least in early RA [27, 28], and have a good benefit to safety ratio when used at low doses [29]. Recently, a modified-release prednisone preparation has become available that is designed to be taken at bedtime (~22:00 h), with programmed delivery of the active ingredient after a lag period of 4–6 h, to correspond to the natural circadian rhythms in endogenous cortisol secretion [30, 31]. A 12-week study showed superior efficacy with the modified-release prednisone compared with the same dose of conventional prednisone with respect to the duration of morning stiffness and plasma levels of the pro-inflammatory cytokine IL-6 [30]. In a follow-up open-label study, significant improvements from baseline in duration of morning stiffness, plasma levels of IL-6, pain score and DAS were apparent after 9–12 months of treatment with modified-release prednisone instead of the same dose of conventional prednisone [32].

Fig. 3 Probability of being cost-effective for the four treatment strategies investigated in the BeSt study depending on the willingness to pay per QALY from a societal perspective according to the friction cost method [16].



Adapted from [16] with permission of John Wiley & Sons, Inc. © 2009.

Fig. 4 Cost-effectiveness of biologic therapies determined in individual studies [19].



Reproduced from [19] with permission from BMJ Publishing Group Ltd. © 2010.

The tolerability profile of the modified-release preparation appeared unchanged from conventional prednisone [30, 32]. Furthermore, there was no evidence of adverse impact of modified-release prednisone on hypothalamic–pituitary–adrenal (HPA) axis function [33]; rather there are early indications that chronotherapeutic use of prednisone may improve HPA function in patients with RA [34]. There is currently no evidence on the safety profile of modified-release prednisone for periods longer than 1 year. Prolonged use (at least 1 year; mean 6.2 years) of conventional prednisone (or equivalent) at doses of 5–15 mg/day was shown to result in a dose-related increased risk of serious adverse events (fractures, serious infections, gastrointestinal bleed or ulcer, cataracts) in 112 patients with RA compared with a matched cohort of patients with RA not receiving glucocorticoid treatment; doses below 5 mg/day had no discernable impact on serious adverse effects [35]. However, a meta-analysis of randomized controlled trials (six studies all lasting at least 2 years, total of 689 patients) found limited toxicity of low-dose glucocorticoid use compared with placebo for all adverse events [odds ratio (OR) 1.19, 95% CI 0.91, 1.57)] and serious adverse events (OR 1.06, 95% CI 0.67, 1.67) per patient-year [36].

In patients with active RA (mean DAS 5.2) despite therapy with synthetic DMARDs, the addition of modified-release prednisone for 12 weeks has recently been shown to reduce disease activity by a mean DAS of 1.2, compared with a mean of 0.6 in patients who received additional placebo [37, 38]. A simple model based on findings from this study [Circadian Administration of Prednisone in Rheumatoid Arthritis (CAPRA-2)] has been developed that suggests such improvement in disease control, by delaying initiation of biologic therapy, may be cost saving [37].

In the Netherlands, therapy with biologic treatments is reimbursed for patients with a DAS >3.2; in Belgium, the equivalent threshold is >3.7 and in the UK, the threshold is >5.1 [37, 39]. In France, the official guidelines advise introduction of biologic treatments if DAS-28 is >5.1 or in patients with moderate disease activity associated with structural damage progression or dependence on steroids at a dose >0.1–0.15 mg/kg/day. Analysis of patients in the CAPRA-2 study showed the proportion of patients at or below these thresholds (Table 1). Using the Dutch threshold, all patients at the start of the study would have been above the threshold and therefore eligible to receive biologic treatment; after 12 weeks, 28% of patients receiving additional modified-release prednisone had a DAS at or below the threshold compared with 15% of those continuing with synthetic DMARD alone, a difference of 13% (95% CI 4%, 21%). Thus, adding modified-release prednisone to existing therapy for 3 months would have delayed initiation of biologic therapy by at least this duration for 28% of patients, if biologic treatments would otherwise have been started immediately; if a 3-month wait-and-see policy (or additional placebo) were followed, biologic therapy would be delayed for at least 3 months in 13% of patients. A similar reduction in patients requiring biologic treatments would be seen using the threshold levels for Belgium, France and the UK.

A conservative estimate of the direct economic consequences arising from this delay in biologic therapy in the Netherlands gives a cost saving of almost €400 [37]. This assumes no additional benefit beyond the 3 months of the study, so that 3.25% (i.e. 13%/4) less biologic treatment would be required for the year. At an estimated annual cost of biologic treatment in the Netherlands of €15 000, expenditure on this therapy would be reduced by €487.50. With a daily cost of €1 for modified-release prednisone amounting to additional drug expenditure of €91.25 for 3 months, net savings in drug costs amount to at least €396. The economic benefit would increase if the effect of modified-release prednisone persisted, or if an immediate start in biologic therapy was assumed. However, further research and assessment is required to give a full evaluation of such a strategy, to include also any potential risks of low-dose steroids over long-term use and any impact on indirect costs arising from changes in productivity, sick leave and disability benefits. This model was based on costs and benefits with modified-release prednisone rather than the more commonly used conventional formulation. However, it should be noted that a significant reduction in need for biologic therapy was reported when conventional prednisone at low dose

Table 1 Proportion of patients receiving therapy with synthetic DMARDs dropping below reimbursement thresholds for biologic treatments after addition of modified-release prednisone 5 mg/day or placebo for 12 weeks [37]

	Percentage of patients at or below DAS-28 threshold for reimbursement					
	Threshold 3.2 (Netherlands)		Threshold 3.7 (Belgium)		Threshold 5.1 (UK)	
Time point	MR prednisone	Placebo	MR prednisone	Placebo	MR prednisone	Placebo
Baseline	0	0	3	3	45	45
12 weeks	28	15	42	29	79	68
Improvement	28	15	39	26	34	23
Difference	13		13		11	

MR: modified-release. Adapted from [37] with the permission of John Wiley & Sons, Inc. © 2011.

(10 mg/day) was included in a 2-year MTX-based tight control strategy compared with the MTX-based strategy and placebo, with a reduction in the proportion of patients experiencing adverse events [40].

Conclusions

The total cost of RA is substantial, with marked increase in costs over the past decade, due in substantial part to the use of biologic therapies. The high cost of these therapies is a real challenge to health care systems with limited resources. Biologic treatments are cost-effective in patients who are refractory to conventional treatments. While treatment decisions should never be based only on cost considerations, optimizing the use of anchor therapies such as MTX, other synthetic DMARDs and glucocorticoids may prolong disease control with these much less costly treatments, delaying the need for biologic therapy [15]. Such an optimization approach may save costs, bringing economic as well as patient benefits, although long-term safety issues should also be included in the debate.

Rheumatology key messages

- The cost of managing RA has increased markedly, primarily due to biologic treatments.
- Biologic treatments in RA are only cost-effective in patients who are not adequately controlled with conventional treatments.
- Prolonging disease control of RA by optimizing use of conventional treatments may result in large cost savings.

Acknowledgements

D. Storey of DPS Limited prepared the first draft of the manuscript for the author's review and provided editorial support, funded by Mundipharma International Limited. This supplement has been commissioned and funded by Mundipharma International Limited. It contains papers based on presentations given at a meeting held on 24 May 2011 and a satellite symposium held on 26 May 2011 at the EULAR annual congress, both arranged and sponsored by Mundipharma International Limited. The author received travel expenses to attend and an honorarium for his contribution.

Supplement: This paper forms part of the supplement 'Optimizing use of anchor therapies for rheumatoid arthritis: treating the disease and the patient'. This supplement was commissioned and funded by Mundipharma International Limited.

Disclosure statement: B.F. has received honoraria from Mundipharma International Limited.

References

1 Emery P, Salmon M. Early rheumatoid arthritis: time to aim for remission? Ann Rheum Dis 1995;54:944–7.

2 Pincus T. Rheumatoid arthritis: a medical emergency? Scand J Rheumatol Suppl 1994;100:21–30.

3 Weinblatt ME. Rheumatoid arthritis: treat now, not later! Ann Intern Med 1996;124:773–4.

4 Sokka T, Kautiainen H, Pincus T *et al*. Disparities in rheumatoid arthritis disease activity according to gross domestic product in 25 countries in the QUEST-RA database. Ann Rheum Dis 2009;68:1666–72.

5 Franke LC, Ament AJ, van de Laar MA, Boonen A, Severens JL. Cost-of-illness of rheumatoid arthritis and ankylosing spondylitis. Clin Exp Rheumatol 2009; 27(4 Suppl. 55):S118–23.

6 Fautrel B, Lucier S, de Rosa M *et al*. Initiation rapide ou tardive des biothérapies dans les polyarthrites débutantes: impact économiques, à partir des données de al cohorte ESPOIR [Early or later initiation of biologics in early rheumatoid arthritis, based on the ESPOIR cohort data.]. Rev Rhum 2010;77S:A68.

7 Kobelt G, Jönsson L, Lindgren P, Young A, Eberhardt K. Modeling the progression of rheumatoid arthritis: a two-country model to estimate costs and consequences of rheumatoid arthritis. Arthritis Rheum 2002;46:2310–9.

8 Kobelt G, Woronoff AS, Richard B, Peeters P, Sany J. Disease status, costs and quality of life of patients with rheumatoid arthritis in France: the ECO-PR Study. Joint Bone Spine 2008;75:408–15.

9 Lundkvist J, Kastäng F, Kobelt G. The burden of rheumatoid arthritis and access to treatment: health burden and costs. Eur J Health Econ 2011;8(Suppl. 2):S49–60.

10 Fautrel B, Lucier S, Laroche ML *et al*. Costs for early rheumatoid arthritis patients by type of treatments in France: results from the ESPOIR cohort. Ann Rheum Dis 2010;69(Suppl. 3):351.

11 Descalzo M, Carmona L, Tobias A. Total joint replacement surgery of hip and knee in the biologics era: a time-trend analysis from 1997-2005. Arthritis Rheum 2007; 56(Suppl.):Abstract 834.

12 Momohara S, Inoue E, Ikari K *et al*. Decrease in orthopaedic operations, including total joint replacements, in patients with rheumatoid arthritis between 2001 and 2007: data from Japanese outpatients in a single institute-based large observational cohort (IORRA). Ann Rheum Dis 2010; 69:312–3.

13 Huscher D, Ziegler S, Koetter I *et al*. Increasing intensity of treatment and decreasing work disability 2011 to 2007 in patients with rheumatoid arthritis in Germany. Arthritis Rheum 2008;58(Suppl):Abstract 787.

14 Olofsson T, Englund M, Saxne T *et al*. Decrease in sick leave among RA patients the first 12 months after start of treatment with TNF-antagonists A population-based cohort study. Ann Rheum Dis 2010;69(Suppl. 3):57.

15 Deighton C, Hyrich K, Ding T *et al*. BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biologic therapy. Rheumatology 2010;49:1197–9.

16 van den Hout WB, Goekoop-Ruiterman YPM, Allaart CF *et al*. Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. Arthritis Rheum 2009;61:291–9.

17 Boers M. The cost-utility analysis of the BeSt trial: is a camel in fact a horse with abnormalities in the distribution

of dorsal fat? Comment on the article by van den Hout et al. Arthritis Rheum 2009;61:1616–7.

18 Finckh A, Bansback N, Marra CA *et al*. Treatment of very early rheumatoid arthritis with symptomatic therapy, disease-modifying antirheumatic drugs, or biologic agents: a cost-effectiveness analysis. Ann Intern Med 2009;151:612–21.

19 Schoels M, Wong J, Scott DL *et al*. Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69:995–1003.

20 Boers M, Verhoeven AC, Markusse HM *et al*. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350: 309–18.

21 Landewé RB, Boers M, Verhoeven AC *et al*. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46:347–56.

22 van Tuyl LHD, Boers M, Lems WF *et al*. Survival, comorbidities and joint damage 11 years after the COBRA combination therapy trial in early rheumatoid arthritis. Ann Rheum Dis 2010;69:807–12.

23 Korthals-de Bos I, Van Tulder M, Boers M *et al*. Indirect and total costs of early rheumatoid arthritis: a randomized comparison of combined step-down prednisolone, methotrexate, and sulfasalazine with sulfasalazine alone. J Rheumatol 2004;31:1709–16.

24 Verhoeven AC, Bibo JC, Boers M, Engel GL, van der Linden S. Cost-effectiveness and cost-utility of combination therapy in early rheumatoid arthritis: randomized comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone. COBRA Trial Group. Combinatietherapie Bij Reumatoïde Artritis. Br J Rheumatol 1998;37:1102–9.

25 Gorter SL, Bijlsma JW, Cutolo M *et al*. Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69:1010–4.

26 Smolen JS, Landewé R, Breeveld FC *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biologic disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964–75.

27 Graudal N, Jürgens G. Similar effects of disease-modifying antirheumatic drugs, glucocorticoids, and biologic agents on radiographic progression in rheumatoid arthritis: meta-analysis of 70 randomized placebo-controlled or drug-controlled studies, including 112 comparisons. Arthritis Rheum 2010;62:2852–63.

28 Kirwan J, Bijlsma JW, Boers M, Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev 2007;4:CD006356.

29 da Silva JAP, Jacobs JWG, Kirwan JR *et al*. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Ann Rheum Dis 2006;65:285–93.

30 Buttgereit F, Doering G, Schaeffler A *et al*. Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. Lancet 2008;371:205–14.

31 Straub RH, Cutolo M. Circadian rhythms in rheumatoid arthritis: implications for pathophysiology and therapeutic management. Arthritis Rheum 2007;56:399–408.

32 Buttgereit F, Doering G, Schaeffler A *et al*. Targeting pathophysiological rhythms: prednisone chronotherapy shows sustained efficacy in rheumatoid arthritis. Ann Rheum Dis 2010;69:1275–80.

33 Alten R, Doering G, Cutolo M *et al*. Hypothalamus-pituitary-adrenal axis function in patients with rheumatoid arthritis treated with night-time-release prednisone. J Rheumatol 2010;37: 2025–31.

34 Kirwan JR. Targeting the time of day for glucocorticoid delivery in rheumatoid arthritis. Int J Clin Rheumatol 2011; 6:273–9.

35 Saag KG, Koehnke R, Caldwell JR *et al*. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med 1994;96: 115–23.

36 Ravindran V, Rachapalli S, Choy EH. Safety of medium- to long-term glucocorticoid therapy in rheumatoid arthritis: a meta-analysis. Rheumatology 2009;48: 807–11.

37 Boers M, Buttgereit F. A simple model that suggests possible cost savings when modified-release prednisone 5mg/day is added to current treatment in patients with active rheumatoid arthritis. Arthritis Rheum 2011; 63(10 Suppl.):S359(Abstract 914).

38 Buttgereit F, Mehta DP, Kirwan JR *et al*. Low-dose glucocorticoid chronotherapy of rheumatoid arthritis: 12 week efficacy data of 5 mg modified-release (MR) prednisone. Ann Rheum Dis 2010; 69(Suppl. 3):220.

39 National Institute for Health and Clinical Excellence. Rheumatoid arthritis: the management of rheumatoid arthritis in adults. NICE Clinical Guideline. http://www.nice.org.uk/CG79, Vol. 79. London: NICE 2009 (29 March 2012, date last accessed).

40 Bakker MF, Jacobs JW, Welsing PM *et al*. Low-dose prednisone inclusion into a MTX-based tight control strategy for early rheumatoid arthritis: better control of disease and erosive joint damage. Results from the double-blind randomized CAMERA-II trial. Ann Rheum Dis 2011; 70(Suppl. 3):114.