Contemporary treatment principles for early rheumatoid arthritis: a consensus statement

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Objective. RA has a substantial impact on both patients and healthcare systems. Our objective is to advance the understanding of modern management principles in light of recent evidence concerning the condition’s diagnosis and treatment.

Methods. A group of practicing UK rheumatologists formulated contemporary management principles and clinical practice recommendations concerning both diagnosis and treatment. Areas of clinical uncertainty were documented, leading to research recommendations.

Results. A fundamental concept governing treatment of RA is minimization of cumulative inflammation, referred to as the inflammation–time area under the curve (AUC). To achieve this, four core principles of management were identified: (i) detect and refer patients early, even if the diagnosis is uncertain: patients should be referred at the first suspicion of persistent inflammatory polyarthritis and rheumatology departments should provide rapid access to a diagnostic and prognostic service; (ii) treat RA immediately: optimizing outcomes with conventional DMARDs and biologics requires that effective treatment be started early—ideally within 3 months of symptom onset; (iii) tight control of inflammation in RA improves outcome: frequent assessments and an objective protocol should be used to make treatment changes that maintain low-disease activity/remission at an agreed target; (iv) consider the risk–benefit ratio and tailor treatment to each patient: differing patient, disease and drug characteristics require long-term monitoring of risks and benefits with adaptations of treatments to suit individual circumstances.

Conclusion. These principles focus on effective control of the inflammatory process in RA, but optimal uptake may require changes in service provision to accommodate appropriate care pathways.

KEY WORDS: Rheumatoid arthritis, Early rheumatoid arthritis, DMARD, Corticosteroid, Anti-TNF therapy, Tight control, Step-down therapy.

Introduction

RA leads to irreversible joint damage [1], serious extra-articular manifestations [2] and considerable comorbidities including osteoporosis and cardiovascular disease [3]. These complications contribute to the increased mortality rates among RA patients [4].

In the European Union, the prevalence of RA, from individual country-based studies, is reported to range from 0.24 to 1.42% (source: European Commission). In England and Wales, RA affects more than 420 000 people [5], over two-thirds of whom develop symptoms before the age of 60 years [6]. Cooper [7] estimated that the mean direct and indirect costs per patient with RA were £3575 and £3638 per annum, respectively. In a recent survey, 86% of the employed people with RA had already experienced or anticipated experiencing barriers to remaining in employment [8].

It is now well accepted that initiating treatment early after diagnosis offers the opportunity to improve clinical, functional and other outcomes in RA patients. However, time to first treatment with a DMARD is still not optimal in the UK, and new developments in research directed at tight control of inflammation have practical implications for the way rheumatologists and front-line clinicians practice. Against this background, a group of rheumatologists examined how RA management principles should evolve in the light of emerging evidence about pathogenesis, diagnosis, treatment and prognosis, and aimed to propose a contemporary set of principles and recommendations for the assessment and treatment of early RA.

Methods

A group of practicing rheumatologists with an interest in early RA, drawn from different geographical areas of the UK, met in two meetings (early and mid-2007). The group discussed evidence and experience concerning diagnosis and treatment, and formulated four core principles and three key clinical practice recommendations for best practice in RA management. Areas of clinical uncertainty related to these principles were documented, leading to research recommendations. A systematic literature review was conducted for the principle of tight control, by means of a Medline search using the terms ‘rheumatoid arthritis’, ‘tight’ and ‘step-up’, supplemented by a manual search of abstracts from British Society for Rheumatology (BSR), European League against Rheumatism (EULAR) and ACR meetings (2004–08) and relevant references suggested by the consensus group.

In total, this document provides a contemporary synthesis and interpretation of clinical trials concerned with the management of early RA. The core principles and key clinical practice recommendations are aimed at practicing clinicians [rheumatologists, general practitioners (GPs) and allied health professionals] and at professionals involved in commissioning care and pathway design and are intended as a heuristic complement to more practically focused guidelines [9, 10]. The research recommendations will provide an appreciation of the uncertainties and limitations of current evidence.
The key clinical practice recommendations may require changes in configuration of services. This in part reflects a disconnection between the published literature and current clinical practice. Therefore, the key clinical practice recommendations may not only provide topics for clinical service evaluation and audit, but also inform relevant discussions between service purchasers and providers.

Controlling inflammation: the fundamental concept underlying RA treatment

A single fundamental concept underpins the four core principles (Table 1) outlined in this consensus document: minimizing the cumulative effects of inflammation improves signs and symptoms of RA, increases functional performance and health-related quality of life (HRQoL), and reduces the risk of joint damage and non-articular complications. The area under the inflammation–time curve (AUC) offers a surrogate for cumulative exposure to inflammation (Fig. 1). Wick et al. [11] conceptualized this as the AUC for the disease activity score 28 (DAS28) modified by a mathematical term called the ‘individual constant factor’, which accounts for inter-individual differences in the degree of joint destruction at any given level of inflammation. Even among RA patients in clinical remission, the AUC for DAS predicts radiological progression, irrespective of disease activity at a single time point [12]. Modern imaging studies have supported the concept that sustained suppression of synovitis at the individual joint level results in reduced joint damage [13, 14].

Therefore, lowering the inflammation–time AUC reduces the risk that the patient will develop adverse outcomes. The four core principles in this consensus document all reflect the prima facie validity of this concept.

TABLE 1. Summary of the fundamental concept and core principles of contemporary RA management

<table>
<thead>
<tr>
<th>Fundamental concept</th>
<th>Core principle 1</th>
<th>Core principle 2</th>
<th>Core principle 3</th>
<th>Core principle 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlling inflammation: minimizing cumulative inflammation (inflammation–time AUC) improves signs and symptoms, increases functional performance, HRQoL and reduces risk of non-articular complications</td>
<td>Detect and refer patients early, even if the diagnosis is uncertain</td>
<td>Treat RA immediately</td>
<td>Tight control of inflammation in RA improves outcomes, and requires structured protocols and regular review</td>
<td>Consider the risk–benefit ratio and tailor treatment to each patient</td>
</tr>
</tbody>
</table>

Research recommendation

- Studies to validate a measure of the inflammation–time AUC in routine RA assessment and management. This in turn would provide a new measure of the efficacy of existing and new therapeutic agents. In particular, this would be an important way to compare the effects of treatments that have an extremely rapid onset of action (such as high-dose corticosteroids and anti-TNF agents) with standard DMARD regimes, as each has a markedly different impact on the inflammation–time AUC.

Core principle 1: detect and refer patients early, even if the differential diagnosis is uncertain

The consensus group stressed that all healthcare professionals should refer patients to a specialist rheumatology clinic when they first suspect RA or undifferentiated inflammatory polyarthritis. Currently, rheumatologists in the UK are referred patients from primary care after an interval of 6–10 months after symptom onset [15, 16]. Slightly longer time intervals have been reported from Canada [17].

One reason for not referring patients with undifferentiated inflammatory polyarthritis immediately to secondary care may be a realization that not all such patients will develop persistent arthritis. Indeed, in differing inception cohorts, 6–55% of patients presenting with undifferentiated inflammatory polyarthritis are reported to progress to RA after a year [18]. Predicting, on an individual basis, which patients are going to progress to RA is not simple, particularly as the ACR classification criteria for RA are widely acknowledged to lack sensitivity in this context. Nevertheless, early control of undifferentiated inflammatory polyarthritis may prevent progression to ‘classic RA’ [19] and from moderate to more severe RA [20, 21]. Therefore, the consensus group agreed that patients should be referred immediately when there is a clinical suspicion of undifferentiated inflammatory polyarthritis, to allow prompt treatment and hence minimization of the inflammation–time AUC.

While the differential diagnosis can prove difficult in early RA, three simple and effective criteria could be included in shared care protocols to encourage appropriate referrals by GPs [22]:

- three or more objectively swollen joints on examination;
- morning stiffness lasting > 30 min; and
- involvement of the metacarpal–phalangeal or metatarsal–phalangeal joints, or both (squeeze test positive).

O’Reilly et al. [23] applied these criteria to routine clinical practice in the UK, with an additional criterion that there should be a time limit of no more than 12 months of onset of symptoms before referral. With this caveat, 60–65% of patients identified by these criteria were judged as appropriate referrals to an early arthritis clinic. Approximately half of the patients judged as not suitable for an early arthritis clinic had rheumatological conditions other than undifferentiated inflammatory polyarthritis, which justified a rheumatology referral.

The ‘Leiden Predictive Rule’ [24] estimates the probability that a patient with undifferentiated inflammatory polyarthritis will progress to classical RA based on nine simple clinical and laboratory features. These are sex, age, localization of symptoms, morning stiffness, tender joint count, swollen joint count, CRP level, RF positivity and the presence of anti-cyclic citrullinated peptide (anti-CCP) antibodies. Routinely using this rule when assessing patients with possible early-onset polyarthritis potentially simplifies and speeds decision making regarding the use of DMARDs. Some components of the rule might offer a baseline for predicting and monitoring response and adjusting therapy.

The consensus group felt that imaging has an expanding role in diagnosis of patients with early RA, especially given the limitations of the ACR classification criteria and difficulties...
detecting synovitis either by clinical examination or the DAS28 [25]. In contrast, ultrasound (US) often identifies grey scale and Doppler abnormalities in synovium of joints that are clinically normal [26–28]. These features might secure a diagnosis of synovitis where there is a clinical uncertainty.

Research recommendations

- Studies to evaluate the utility of predictive models to determine the likelihood of progression to RA and its subsequent prognosis in individual patients with undifferentiated inflammatory polyarthritis.
- A standardized protocol for US assessment of synovial disease, and where available MRI, should be developed to help diagnosis and prognostic stratification in routine practice.

Core principle 2: treat RA immediately

Inflammation in RA has the capacity to produce numerous negative outcomes very quickly, both systemically and in joints. Many patients enrolled in early RA studies are reported to have erosive damage on plain radiographs within a few months of symptom onset, for example 72% of patients in the BeSt study [29] and 48% in CIMESTRA [30] (mean disease duration being 23 weeks and 4.6 months, respectively). Cartilage does not heal effectively and any damage is likely to lead to permanent sequelae, perhaps in part explaining loss of employment within a year of diagnosis in 28% of respondents in a recent UK survey [8] and in 20% of patients in the ERAN cohort [31]. Others have also found evidence for employment and functional problems associated with RA early in the course of the disease [32, 33].

To avoid damage, treatment must effectively and rapidly minimize the inflammation–time AUC, thus lowering the patient’s cumulative inflammatory burden. Measurable benefits may be achieved by both starting therapy very soon after disease onset and by using drugs with a fast onset of action. Evidence for the benefit of starting treatment quickly comes from DMARD monotherapy studies in which a time of 3–4 months from symptom onset to start of a relatively benign, slow-acting drug regimen appears to be a critical period to achieve a significant impact on outcome. In one study, early RA patients who started on DMARD monotherapy within 3 months of symptom onset had sustained significant improvements in composite disease activity and radiographic scores for 3 years compared with a comparator group starting DMARD monotherapy after 9 months of symptoms [34]. Similarly, patients presenting with a median symptom duration of 4–6 months had significantly better disease activity, function and radiographic outcome at 2 years if DMARD monotherapy was started immediately compared with a historical comparator group where treatment was delayed for a further 4 months [35]. Further, support for the benefits of starting DMARD therapy promptly comes from a subgroup analysis of the FIN–RACo study in which patients were significantly more likely to be in remission at 2 years if SSZ monotherapy was started within 4 months of symptom onset [36].

Interestingly in the same study, the beneficial effect of starting treatment within 4 months was not apparent in the group treated with combination therapy and steroids [36]. This wider window of opportunity in the combination arm may in part reflect the benefit of using a therapeutic regime with a fast speed of onset. This may be achieved with therapies using either step-down steroids or anti-TNFα agents, both of which have been shown to have advantages in early RA over monotherapy DMARD regimes (with a slower onset of action). Both the COBRA study [20, 37] and arm 3 of the BeSt study [29] demonstrate the beneficial disease activity, radiographic and functional effects of step-down steroids compared with either monotherapy (COBRA and arm 1 of BeSt study) or slow step-up DMARD therapy (arm 2 of BeSt study). Although patients and their doctors may not like the idea of using steroids, the COBRA regime involves a rapid reduction of the dose of prednisolone to 7.5 mg within 7 weeks and was the regime of choice in a trial setting for 40% of those who actually received this [38].

The benefits of rapid and effective suppression of inflammation are equally demonstrated by the trials of anti-TNF agents in early RA [29, 39–43], in which adalimumab, etanercept and infliximab have all been found to produce significantly better outcomes than slower-acting DMARD monotherapy. The relative merits of anti-TNF agents over step-down steroids are less well understood. In the BeSt study, arm 4 (inflimixab and MTX) achieved comparable outcomes to arm 3 (step-down steroid with combination DMARD), with significant improvements in disease activity, function and QoL monotherapy and slow step-up arms [29]. Importantly, these improvements were maintained despite withdrawing infliximab after sustained good disease control was achieved. This observation implies an important principle that effective rapid control of inflammation early in disease may permit biological (and possibly all drugs) free remission. Quinn et al. [40] demonstrated this in a smaller study, in which poor prognosis early RA patients were treated with MTX with or without infliximab for 46 weeks. The inflammation–time AUC for the infliximab group was strikingly different (Fig. 1). In patients treated with both MTX + infliximab, function and QoL were re-gained and maintained after infliximab was stopped. In contrast, these measures remained poor in patients treated with MTX + placebo, reflecting the longer time taken to adequately suppress inflammation in the latter group. Recently, the same effect has been demonstrated for etanercept, where 70% of early RA patients who had achieved remission after 24 weeks of etanercept + MTX therapy remained in remission at 48 weeks despite withdrawal of etanercept at 24 weeks [44].

Considering the dual importance of using a fast-acting therapeutic strategy and starting this quickly, it is striking that currently the average delay in starting the first DMARD in the UK is ~6–12 months after the onset of symptoms [15, 16, 45]. Similarly, across the world long delays are seen in commencing DMARD therapy, with 8.4 months reported in a Canadian cohort [17]; and in a review of over 4000 patients, a median delay of 4–15 months was reported in 15 different countries [46]. Faced with these delays, evidence from FIN–RACo would suggest that initial therapy should include a fast-acting component (corticosteroid) and combination DMARDs [36]. Despite this, DMARD monotherapy remains the most commonly used first-line drug regime in the UK ERAN database [45].

The effects of combination vs monotherapy DMARD strategies have been studied extensively in early and established RA. Interpretation is complicated by confounding issues including trial design flaws with the absence of appropriate control arms, small sample sizes, low doses of drugs and slow step-up regimes [47]. Nevertheless, many studies demonstrate that combination therapies used in early RA are efficacious, and radiological benefit persists independent of future treatment [20, 21]. Acknowledging all of these confounding issues and trial heterogeneity, meta-analysis in early and established RA does suggest a superior efficacy/toxicity ratio of some DMARD combinations compared with monotherapy regimes [48]. Given the current reality that newly presenting patients with RA start initial treatment after 4 months of symptoms, it would seem prudent to minimize the negative impact of this delay by commencing an aggressive first-line strategy including a fast-acting component (i.e. corticosteroid and combination DMARDs or MTX and anti-TNF) to achieve a rapid minimization of the inflammation–time AUC. This means a move away from sequential monotherapy to a step-down treatment algorithm. The emphasis is therefore on effective and rapid control of disease, with the option of withdrawing components of an initial combination regime once good control is achieved. In the UK (where anti-TNF agents cannot be prescribed before two DMARDs have been used), an added advantage of
starting combination DMARDs (with step-down corticosteroids) is that the timeframe for eligibility for anti-TNF agents will be reduced.

**Research recommendations**

- Multi-centre observational studies to determine the effect of symptom duration on outcome, in relation to the choice of first-line treatment, be it DMARD monotherapy, combination therapy or a fast-acting regime with step-down corticosteroids or anti-TNF agents.
- Multi-centre strategy studies using regression analysis modeling to determine which components of baseline clinical and biomarker data best predict, on an individual patient basis, which patients will benefit most from intense step-down corticosteroid or biologic strategies, and how long they should be given to achieve drug-free remission.
- Cost-effectiveness analysis of the use of a DMARD plus anti-TNF vs DMARD plus corticosteroid as first-line therapy for poor prognosis patients, given the likelihood that once ‘target’ low activity is achieved the biologic may be successfully withdrawn [29, 40].

**Core principle 3: tight control of inflammation in RA improves outcomes, and requires structured protocols and regular review**

DMARDs used according to conventional treatment protocols reduce the signs and symptoms of RA, but do not necessarily halt progressive joint destruction or prevent disability [49]. Furthermore, remission rates with DMARDs used conventionally are relatively low, as illustrated by the control arms of numerous studies [37, 50–52]. Against this background, the consensus group suggested that based on the evidence three factors contribute to the optimal use of DMARDs:

- a protocol based on an objective measure of disease activity determines whether treatment is escalated or reduced;
- a low threshold of continuing disease activity triggers a treatment change; and
- treatment decisions are made frequently (monthly).

When all three factors are used together the term ‘tight control’ may be applied. A systematic literature review, supplemented by a manual search of abstracts from EULAR, BSR and ACR meetings revealed four studies in which some or all of the principles of ‘tight control’ were compared with usual care (Table 2) and six studies in which different treatment regimens were compared with each other, using protocols with principles of ‘tight control’ (Table 3).

The impact of recording an objective measure of disease activity in routine practice was demonstrated by Fransen et al. [53]. In this study of patients with established RA, treating physicians were required to record the DAS28 score at three visits over 24 weeks and were advised that they should aim to achieve a score $<3.2$. Even though there was no specific treatment protocol to dictate therapy change, and DMARD changes were only made on 20% of occasions that the DAS28 score was $>3.2$, significantly more patients in this group achieved a DAS28 score $<3.2$ at 24 weeks than a control matched group where there was no requirement to measure DAS28 at each visit.

The BeSt study employed aspects of tight control, in that measurement of the DAS28 dictated mandatory treatment changes at an infrequent assessment interval of 3 months. Two of the BeSt recruiting centres reported [54] outcome at 1 year in early RA patients either recruited to Groups 1 and 2 (of the BeSt study) or managed with similar DMARD protocols according to ‘usual care’, which differed from the study in there being no mandate to change treatment on the basis of an agreed target DAS28 score. Despite patients recruited to the BeSt study having more active disease than the usual care patients (baseline mean DAS28 6.1 and 5.6, respectively), there were significantly greater improvements in HAQ, ESR and DAS28 scores in the BeSt study patients at 1 year, the principal difference appearing to be the principles of ‘tight control’.

The CAMERA study [52] compared the effect of frequent (monthly) visits, an objective measure of disease activity and a

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**Table 2. Summary of trials comparing aspects of the principles of ‘tight control’ with usual care**

<table>
<thead>
<tr>
<th>Study, reference</th>
<th>Active treatment</th>
<th>Frequent assessments</th>
<th>Objective disease activity measure</th>
<th>Mandatory treatment change</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fransen et al. [53]</td>
<td>DMARDs, steroid p.o. allowed</td>
<td>No, 0, 4, 12, 24 weeks</td>
<td>Yes</td>
<td>No</td>
<td>DAS28 $&lt;3.2$</td>
</tr>
<tr>
<td>Goekeoop-Ruiterman et al. [54]</td>
<td>Sequential monotherapy or step-up combination, steroid only very late</td>
<td>No, 3 monthly</td>
<td>Yes</td>
<td>Yes</td>
<td>DAS44 $&lt;2.4$</td>
</tr>
<tr>
<td>(BeSt arms 1 and 2 vs usual care)</td>
<td>MTX monotherapy $\rightarrow$ MTX $\rightarrow$ CyA, no steroid p.o. or IA</td>
<td>Yes, monthly</td>
<td>Yes</td>
<td>Yes</td>
<td>Composite response in SJC, TJC, ESR, VAS</td>
</tr>
<tr>
<td>CAMERA, Verstappen et al. [52]</td>
<td>Step-up combination therapy + steroid IA/IM</td>
<td>Yes, monthly</td>
<td>Yes</td>
<td>Yes</td>
<td>DAS44 $&lt;2.4$</td>
</tr>
<tr>
<td>TICORA, Grigor et al. [51]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3. Summary of trials comparing different treatments delivered in a protocol according to the principles of ‘tight control’**

<table>
<thead>
<tr>
<th>Study, reference</th>
<th>Treatment comparisons</th>
<th>Frequent assessments</th>
<th>Objective disease activity measure</th>
<th>Mandatory treatment change</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIN-RACo, Mottonen et al. [50]</td>
<td>Sequential monotherapy $\pm$ steroid p.o. vs combination DMARD $\pm$ steroid p.o.</td>
<td>No, 3 monthly</td>
<td>Yes</td>
<td>Yes</td>
<td>50% improvement in two out of SJC, TJC, ESR or CRP</td>
</tr>
<tr>
<td>BeSt, Goekeoop-Ruiterman et al. [29]</td>
<td>Monotherapy vs step-up vs step-down with steroid vs MTX $+$ infliximab</td>
<td>No, 3 monthly</td>
<td>Yes</td>
<td>Yes</td>
<td>DAS44 $&lt;2.4$</td>
</tr>
<tr>
<td>Verschuuren et al. [56]</td>
<td>Modified COBRA vs step-up MTX $+$ CyA $+$ steroid IA vs MTX $+$ steroid IA</td>
<td>No, 4 monthly</td>
<td>Yes</td>
<td>Yes</td>
<td>DAS28 $&lt;2.6$ or $&lt;3.2$</td>
</tr>
<tr>
<td>CIMESTRA, Hatland et al. [30]</td>
<td>Step-up with steroid IA/IM vs combination with MTX + cyA</td>
<td>No, 4 weekly</td>
<td>Yes</td>
<td>Yes</td>
<td>No swollen joints</td>
</tr>
<tr>
<td>TEAR, Saunders et al. [57]</td>
<td>FIN-RACo $+$ infliximab (6 months) vs FIN-RACo alone</td>
<td>Yes, monthly</td>
<td>Yes</td>
<td>Yes</td>
<td>DAS28 $&lt;3.2$</td>
</tr>
<tr>
<td>NEO-RACO, Leirisalo-Repo et al. [58]</td>
<td></td>
<td>No, 3 monthly</td>
<td>Yes</td>
<td>Yes</td>
<td>Remission, strict criteria</td>
</tr>
</tbody>
</table>

p.o.: per orum; IM: intra-muscular; SJC: swollen joint count; TJC: tender joint count.

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mandatory treatment change (escalating MTX monotherapy) to a specific target, with conventional 3-monthly follow-up practice without mandatory objective measures or treatment changes. At 2 years, 41% of the tight control group were in remission compared with 24% of the conventional group.

The intensive arm of TICORA [51] employed all three factors with an aggressive treatment escalation regime including IA steroids. The protocol used monthly DAS assessment to determine whether to escalate or reduce treatment using combination DMARD and steroid therapy to achieve a DAS44 score <2.4. Patients managed according to this intensive regimen were 5.8 times more likely to have a good response and 9.7 times more likely to be in remission than those receiving conventional care. The benefits of this model of tight control are illustrated by the observation that sustained good outcome >18 months deteriorated when patients reverted to conventional care [55].

Table 3 illustrates those studies that have compared different intensities of DMARD or anti-TNF treatments, but where the same principles of ‘tight control’ have been applied uniformly to all treatment groups within the study. The first of these was the FIN-RACo study [50], where the aim was to achieve remission, and a protocol based on changes in joint counts, ESR and CRP dictated treatment changes on a 3-monthly basis of assessments. In this setting, DMARD combination and prednisolone were superior to DMARD monotherapy with or without prednisolone, and long-term benefits up to 5 years were reported [21]. Similarly in the BeSt study [29], a DAS44 determined measure of disease activity every 3 months, aimed at a target <2.4, found that combination DMARD treatment with prednisolone or infliximab (arms 3 and 4) were superior to DMARD monotherapy or delayed step-up therapy. Furthermore, Verschueren et al. [56] showed the benefit of a modified COBRA regimen (step-down steroid with MTX and SSZ) over step-down DMARD therapy, even though the step-down group had significantly more severe disease activity and worse prognostic markers at baseline. In contrast, CIMESTRA [30], TEAR [57] and NEO-RACO [58] showed less clear-cut benefits of one version of treatment over another. Of all the studies in Table 3, these were the only ones where the protocol required that swollen joints were injected with cortico-

Research recommendations

- Development of a standardized protocol for use in routine practice, including an appropriate ‘RA index’ as a measure of disease activity that prompts a change in treatment. To create an ‘RA index’, the relation between the inflammation–time AUC and different measures of disease activity, function and QoL requires further understanding. The consensus panel felt it important to consider whether to integrate patient-centric outcomes, clinical and serological scores and imaging results in this and, where included, to determine the relative weight to give each variable. Whatever the chosen objective measure, the consensus panel felt that the protocol should include an ambitious target for treatment, perhaps remission, and that the frequency of assessment should be regular.

Core principle 4: consider the risk–benefit ratio and tailor treatment to each patient

Optimizing therapy means balancing the risks and benefits of the various treatment options to meet the achievable goals for each patient: maintaining the best possible state of well-being from day-to-day; and minimizing the risk of future progression of joint damage and co-morbidities. To this end, guidelines can be useful clinically. However, the RA population is heterogeneous [10] and clinicians will still need to tailor management to the patient taking into account concurrent disease, non-articular complications and any age-related differences in pharmacokinetics, pharmacodynamics and adverse events. In the future, genetic testing may aid the identification of RA patients and predict the effectiveness and tolerability of DMARDs and biologics in individual patients [59–61]. However, the group felt that these were not yet appropriate for routine clinical use.

Ideally, treatment plans should be agreed with the patient. Professionals should be aware of possible discordance between the patient’s views on their state of well-being and goals vs those of the clinician [62]. Because of this, assessments should incorporate a range of tests to assess disease activity and its impact on QoL and well-being, including pain and fatigue, or formal HRQoL measures. Above all else, good communication between patients and members of the multi-disciplinary team is vital, especially in situations where the patient may be reluctant to accept certain therapies.

There is an anecdotal concern that combination DMARDs are more toxic than monotherapy regimes. This has been studied in a meta-analysis of standard DMARD and biologic combinations vs monotherapy in early and established RA. Overall toxicity based on patients withdrawn due to adverse events was greater for combinations (relative risk 1.37; 95% CI 0.28, 0.45). However, certain combinations have favourable efficacy/toxicity ratios and in these cases combination strategies should not be avoided on grounds of perceived toxicity [48]. Patient choice and specific situations, such as pregnancy or a desire to conceive, may require individualized use of DMARDs, but the principle of an acceptable strategy that effectively minimizes the inflammation–time AUC applies to all patients.

Imaging systems potentially offer valuable insights into targeting treatments to individual patients and decisions regarding treatment withdrawal. Many RA patients receiving DMARDs demonstrate active inflammation on imaging despite being in clinical remission [26–28, 63]. This subclinical synovitis may not be benign, given that 19% of these patients experienced deterioration in radiographic joint damage at 12 months [64]. Importantly, US imaging may provide a new individualized tool to predict joint damage, and hence tailor treatment regimens. Single time point and time-integrated US measures of synovial disease have been found to correlate with radiographic-defined damage in some RA cohorts [14, 64, 65]. Although a single time point observation would have greatest clinical utility, this has not been found to be predictive by all [65, 66], possibly explained by variability in quality of the equipment and US scores used.

Research recommendations

Multi-centre observational studies to identify individual genotypes and/or phenotypes that:

(i) will respond best to specific therapies; and
(ii) represent a benign or aggressive disease course; and
(iii) will be at high or low risk of toxicity from specific therapies.

If these answers were available, individual treatment plans could be derived for each patient, with the intention of achieving a rapid and sustained suppression of inflammation, with minimal toxicity.

Key clinical practice recommendations to facilitate rapid diagnosis and effective treatment

The consensus group made three key clinical practice recommendations to implement these four core principles (Tables 1 and 4) in clinical practice.

Key recommendation 1: increase awareness among the public and professionals. As there appears to be a significant
delay from the onset of symptoms of RA to first contact with a GP, the consensus group highlighted a particular need to raise awareness of the importance of starting treatment quickly among the public. The group advocated a public education campaign that highlights the benefits associated with early treatment, and provides clear information on the symptoms that should prompt patients to seek their doctor’s advice. Although a logical proposal, it is acknowledged that currently there is little evidence to support changes in outcomes following any specific educational approach.

Steps should be taken to provide similar education to GPs and other members of the community health care team, allied health professional and medical staff who encounter patients with musculoskeletal disease. This educational programme should challenge the view that treatment should be delayed until there is an unequivocal RA diagnosis or damage has occurred. The programme should stress that a patient with possible early onset undifferentiated inflammatory polyarthritis has an ‘urgent’ medical problem that requires rapid referral. A close working relationship between rheumatologists and both primary and secondary care colleagues would facilitate dissemination of this message. Perhaps the creation in 2008 of a new standardized clinical coding system (‘Read’ code) in the UK for ‘suspected inflammatory arthritis’ will promote early referral.

Key recommendation 2: create systems to ensure early diagnosis and treatment. The optimal care of early inflammatory polyarthritis requires a systematic approach to diagnosis, and tailored treatment on the basis of likely prognosis and measured disease activity [67]. Good practice would include systems that allow easy and rapid access to a rheumatological service. This may mean reconfiguring some services and priorities, developing local protocols and guidelines and ideally formulating an early arthritis care pathway with local commissioners and primary care. Such a pathway should include:

- agreed referral criteria, such as those outlined as part of Core principle 1 [22];
- a simple process that ‘fast-tracks’ appropriate patients and offers short waiting times; and
- a standard set of diagnostic and prognostic investigations available to the early arthritis clinic on the day of assessment, including RF, anti-CCP antibodies, acute phase markers, US or MRI (where appropriate expertise and standardized assessments are available) and radiographs.

Although not uniformly available, it was felt important that anti-CCP antibodies were measured. In PROMPT, prevention of progression from undifferentiated arthritis to RA was achieved only by MTX in anti-CCP-positive patients [19]. These data suggest that patients with early undifferentiated inflammatory arthritis, who are anti-CCP positive should be treated with MTX, even though they have yet to fulfil standard diagnostic criteria for RA.

Key recommendation 3: titrate treatment regularly depending on disease activity. Rheumatologists and, if available, GPs or specialist nurses, should assess and record an objective measure of disease activity, such as DAS28, at baseline and regularly thereafter with appropriate training. DMARD and/or biological therapy should be titrated to maintain control over an agreed ‘target’, thereby minimizing the inflammation–time AUC. The chosen ‘target’ of treatment may vary considerably between patients, and include not only standard measures such as DAS28, or an inflammatory marker, but also disability, QoL and employability. Frequent review, ideally monthly, is central to the principle of ‘tight’ control. This is contrary to current ‘routine care’ arrangements in the UK, where restrictions on secondary care follow-up appointments are being imposed to permit more new attendances. An understanding of this key component of ‘tight’ control should lead to changes in service provision for patients with early RA, with frequent review being provided for at least the first 18 months, given the finding in TICORA that the benefits of ‘tight’ control were lost if routine 3-monthly care was resumed at this stage [55].

Conclusions

To make the most of the opportunity offered by contemporary treatment strategies, patients with early RA should be started on effective treatment as early as possible in order to minimize the inflammation–time AUC.

To achieve this we recommend:

(i) a change in behaviour of the public, to seek help promptly, based on the understanding that inflammatory arthritis can be treated very effectively if therapies are started quickly;
(ii) early referral according to an early arthritis care pathway, ideally at the first suspicion of persistent inflammatory polyarthritis;
(iii) rapid diagnostic and prognostic assessment to tailor treatment to individual patients;
(iv) initial therapy with a fast-acting component such as step-down corticosteroids or anti-TNF drugs in combination with DMARDs; and
(v) continued treatment on the principles of ‘tight’ control in which frequent assessments of an objective measure of disease activity lead to protocol-directed escalation or withdrawal of therapy to achieve an agreed ‘target’.

To implement these recommendations, the National Health Service and rheumatologists should develop services that allow easy and rapid access to a dedicated early arthritis assessment and management service, with the provision of frequent review to achieve acceptable low-disease activity as quickly as possible.

No document can be definitive and the principles outlined in this article will need to be reconsidered in the light of new clinical, genetic and experimental evidence as it arises. Nevertheless, the group hopes that clarifying the core principles that underlie the assessment and management of undifferentiated inflammatory polyarthritis and RA will inform and empower patients, health care professionals and providers to implement the best possible framework and management strategy to ensure optimal outcomes for each patient.

Rheumatology key messages

- A fundamental concept governing treatment of RA is minimization of cumulative inflammation: the inflammation–time AUC.
- Early detection and referral of patients is central to the goal of starting treatment immediately.
- Rheumatologists and, if available, GPs or specialist nurses (with appropriate training) should assess and record an objective measure of disease activity, such as DAS28, at baseline and regularly thereafter.

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