Recent advances in treatment and diagnosis of rheumatoid arthritis

Lisa Waters MRCP and Robert Moots PhD, MD

Rheumatoid arthritis is a chronic, systemic, autoimmune condition that, if inadequately treated, leads to joint destruction, disability and increased mortality. It affects nearly 1 per cent of the adult UK population and, as well as the typical synovial joint problems, is associated with significant co-morbidities, including an increased risk of developing cardiovascular disease, neoplasia and infection.

In the past, treatment for RA was poor: few drugs able to suppress the underlying inflammatory process were available, and even those were withheld until joint damage had become established and disability developed. This should not be surprising, since the pathological processes underlying the disease were largely unknown.

Today, the outlook could not be more different. A combination of both scientific and clinical advances, discussed briefly in this short article, have led to a reasonable expectation that a person newly diagnosed with RA today can expect at least a major suppression of their disease – indeed, full remission in many cases – and live a normal life.

Scientific advances

Intensive and ongoing scientific research has determined that RA is mediated by an inflammatory process that occurs in individuals who are genetically predisposed and then encounter environmental triggers. Such triggers are not yet fully defined, but appear to include cigarette smoking.

This sets up a complex interplay between cells of the immune system, some damaging joints in their own right and others secreting proinflammatory cytokines such as tumour necrosis factor (TNF)-alpha, interleukin (IL)-6 and IL-17 that further mediate inflammation and inflict damage both in the joints and systemically. These major scientific advances have led to the development of novel and highly effective ‘biologic drugs’, specifically designed to inhibit defined molecules and cells.

However, many clinical advances occurring in parallel with these developments have demonstrated that even just using...
standard DMARDs such as methotrexate more intelligently, major inroads can be made into effective therapy.

**Early detection and dynamic therapy**

It makes far more sense to prevent damage rather than react to it. Many studies have accordingly demonstrated that the most effective strategy for the management of RA focuses on early diagnosis (ideally in primary care), rapid referral to a rheumatology unit and early commencement of effective treatment using DMARDs.

Rheumatologists consider there to be a ‘window of opportunity’ of two to three months from the onset of symptoms to the initiation of DMARD therapy during which irreversible damage to joints can be prevented.¹ This has led to many rheumatology units setting up specialist ‘early arthritis clinics’, where patients with suspected RA can be fast tracked for diagnosis and treatment.

Such an approach depends on good relationships between primary and secondary care, with a special onus on GPs to be vigilant.

Once diagnosed, therapy is now dynamic, with drugs and dose escalated according to objective measures of disease activity, typically the Disease Activity Score of 28 joints (DAS 28), until remission is achieved, or at least low disease activity.

The introduction of a ‘treat-to-target’ approach for RA has allowed therapy to catch up with similar such approaches for other chronic diseases such as hypertension and has provided excellent outcomes for patients.

**Diagnosis**

The diagnosis of RA remains a clinical one, with no simple diagnostic test currently available. The American College of Rheumatology (ACR) 1987 criteria – the bedrock for diagnosing this condition – has served well in the past, but the lack of recognition of early disease and hence delay in therapy became a problem when the benefits of early intervention started to emerge. In 2010, therefore, new combined American and European criteria were developed.

<table>
<thead>
<tr>
<th>Target population (who should be tested?)</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>patients who have at least 1 joint with definite clinical synovitis (swelling) with the synovitis not better explained by another disease</td>
<td></td>
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**Classification criteria for RA**

score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA

<table>
<thead>
<tr>
<th>A. joint involvement</th>
<th>Score</th>
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<tbody>
<tr>
<td>1 large joint</td>
<td>1</td>
</tr>
<tr>
<td>2–10 large joints</td>
<td>2</td>
</tr>
<tr>
<td>1–3 small joints (with or without involvement of large joints)</td>
<td>3</td>
</tr>
<tr>
<td>4–10 small joints (with or without involvement of large joints)</td>
<td>5</td>
</tr>
<tr>
<td>&gt;10 joints (at least 1 small joint)</td>
<td></td>
</tr>
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<table>
<thead>
<tr>
<th>B. serology (at least 1 test result is needed for classification)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative RF and negative ACPA</td>
<td>0</td>
</tr>
<tr>
<td>low-positive RF or low-positive ACPA</td>
<td>2</td>
</tr>
<tr>
<td>high-positive RF or high-positive ACPA</td>
<td>3</td>
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</table>

<table>
<thead>
<tr>
<th>C. acute-phase reactants (at least 1 test result is needed for classification)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal CRP and normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>abnormal CRP or abnormal ESR</td>
<td>1</td>
</tr>
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<table>
<thead>
<tr>
<th>D. Duration of symptoms</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>≥6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1. 2010 American and European criteria for the diagnosis of rheumatoid arthritis; RF = rheumatoid factor, ACPA = anticitrullinated protein antibody, CRP = C-reactive protein; ESR = erythrocyte sedimentation rate
European criteria were developed, allowing for earlier detection of disease (see Table 1). Rheumatologists now use a combination of blood tests including rheumatoid factor (RF) or anticitrullinated peptide antibody (ACPA, the new-generation version of RF) together with clinical features to diagnose RA.

Interestingly, ACPA antibodies has been found to precede the onset of symptoms and, with higher specificity than the older RF test, this may help uncover further new pathogenic insights into this disease.

The use of musculoskeletal ultrasonography as the ‘stethoscope’ for rheumatologists has proliferated in recent years, providing better sensitivity for the detection of synovitis and erosions than clinical examination or plain radiographs (see Figure 1).

Current recommended management of RA is outlined in Figure 2.

**DMARDs**
For many years patients with RA relied heavily on glucocorticoids for treatment. While clearly suppressing disease, the attendant side-effects were a major problem. In addition, hot wax treatments, hydrotherapy, bed rest and physiotherapy were key components of symptomatic therapy.

Since then, many studies have highlighted the benefits of early diagnosis and treatment of RA. Early DMARD initiation has been shown to result in both lower disease activity and less radiographic progression, and methotrexate has become the anchor therapy in treatment of RA.

Other DMARDs commonly used by rheumatologists include hydroxychloroquine, sulfasalazine and leflunomide. Studies have shown that combination therapy of two or more DMARDs plus corticosteroid in early disease offers optimal reduction in joint damage and earlier remission.

Other DMARDs such as azathioprine, gold, ciclosporin and penicillamine are now only rarely used due their unfavourable risk/benefit ratio.

**Glucocorticoids**
Despite optimising the use of DMARDs and the development of biologic drugs, glucocorticoids still have a firm role to play in...
the management of RA, especially at presentation and for flares, due to their rapid and effective mode of action. However, low doses for short durations are preferred to minimise the risk of steroid-related side-effects.

Biologics

The last 10 years have been an exciting time in the treatment of RA. Better understanding of the pathophysiology has informed the development of many biological therapies designed to specifically target key components of inflammation that can effectively prevent disease progression and improve patient outcomes.

As proteins, these drugs are administered by sc injection or iv infusion and act by:

- inhibiting TNF-alpha – etanercept (Enbrel), adalimumab (Humira), certolizumab (Cimzia), golimumab (Simponi) and infliximab (Remicade)
- inhibiting IL-6 – tocilizumab (RoActemra)
- blocking activation of T cells – abatacept (Orencia)
- depleting B lymphocytes – rituximab (MabThera).

Rheumatologists are able to use these drugs when disease activity is high and when DMARDs have not been effective, in line with NICE guidance.

These drugs, especially in combination with methotrexate, are the most effective in halting progression of disease. As a result numerous trials with other biologics have followed showing the value of these drugs in inducing remission and halting radiographic progression for patients with RA.

The introduction of biologics was initially associated with marked safety concerns. However, the establishment of the British Society for Rheumatology Biologics Registry (and surveillance programmes in other countries) has provided much reassurance, indicating a small increased risk of infections in comparison to DMARDs, especially in the first six months of treatment, and the potential for reactivation of latent tuberculosis (and other intracellular infections) that can be mitigated by pretherapy screening by chest X-ray and examining for prior exposure to mycobacteria by blood testing.

Reassuringly, data from registries worldwide have not confirmed the theoretical risk for malignancy, with the exception of a faint potential signal for nonmelanomatous skin cancer.

NICE has developed clear pathways for the use of biologic drugs in RA. Patients must have severe disease and have failed to respond to or been intolerant of at least two DMARDs including methotrexate, in an effective dose, before being eligible for treatment.

These drugs are not yet recommended by NICE for treatment in early disease.

Conclusion

This short review has only been able to touch on some of the many significant developments in the treatment of RA in a relatively short period of time. Despite the cure remaining elusive, rheumatologists now have a wide range of effective drugs that will control disease, result in less (or even prevent) joint damage, reduce co-morbidities and increase quality of life to a level that could not have been envisaged before.

Progress continues even further, with new biologics under evaluation such as inhibitors of IL-17 (secukinumab), GM-CSF (mavrilimumab) and small molecules (tofacitinib) and new trials informing the optimal use of drugs, both new and old, just around the corner.

References


Declaration of interests

None to declare.

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Guidelines


