# Resistant rheumatoid arthritis clinics—a necessary development?

Rheumatologists have always been aware of the limitations of the therapy available to them. For many years the drugs used on patients with rheumatoid arthritis (RA) produced such a high withdrawal rate due to both toxicity and the lack of efficacy that there was some doubt whether they had any impact on the underlying disease at all. With better study design and more efficient use of drugs it is now clear that disease-modifying anti-

rheumatic drugs (DMARDs) do alter the disease course as evidenced by retardation of bony erosions and improvement in function [1]. However, conventional therapy has many well-recognized toxicities and is still incompletely effective, with few patients entering remission. A major change in prescribing in rheumatology is about to occur with the licensing of several new drugs including the pyrimidine synthesis inhibitor leflunomide (Arava) and two tumour necrosis factor (TNF) blocking agents etanacept (Enbrel) and infliximab (Remicade). This is in addition to the COX-2 specific inhibitors celecoxib (Celebrex) and rofecoxib (Vioxx). It is likely that in the next few months all the above will be available in Europe. These drugs represent a significant improvement over their existing comparator therapies and have in common that they will be more expensive.

With a price of at least £6000 per annum, the cost is a particular issue for the biologics. Furthermore, patient expectation has been fuelled by information available on the Internet, leading to clinical pressure for rheumatologists to prescribe these drugs. However, long-term toxicity data are lacking. Thus, there is great concern about how these drugs will be prescribed and the debate is just beginning in this area [2].

Recently there have been attempts at an international level to produce consensus guidelines for the use of TNF blockade, but none of these is completely appropriate for the UK. However, there is a group of patients for whom it has been possible to agree that TNF therapy should be available, i.e. those who have (a) no reasonable alternative (they have failed conventional DMARD therapy) and (b) an unacceptable level of disease activity. However, even such a restricted approach raises problems, as a working definition of 'unacceptable disease activity' and also a 'failure of standard regime of conventional drugs' needs to be agreed upon. This Editorial explores how the organization of resistant arthritis clinics can provide one answer for producing working definitions of these concepts.

Until recently standard treatment for RA consisted of sequential monotherapy with different DMARDs which replace each other as the individual drugs become toxic or ineffective. A review of combination therapy given from onset concluded that there was no evidence that blanket combination therapy was effective [3]. However, add-on studies in which a second drug was added to patients who were partial responders to a single agent, and other studies in which triple combination therapies (all including corticosteroids) were used, have also shown (at least) a statistical benefit over their monotherapy comparator. O'Dell and colleagues [4] have shown that triple therapy of methotrexate, hydroxychloroquine and sulphasalazine produces a significantly better 50% response than comparators and in a subsequent study indicated that all three components of the combination appear to be required for full response (personal communication). Therefore, a reasonable conclusion from the recent data is that whilst evidence for blanket combination from onset of disease (apart from corticosteroids) has not been provided, there are now sufficient data to indicate that for patients selected for failure of monotherapy, combinations of drugs are more effective. Therefore, one working definition of failed conventional therapy is a failure to respond to triple therapy (methotrexate, hydroxychloroquine and sulphasalazine) which has been prescribed at adequate doses for sufficient periods of time (see below).

Patients failing the standard approach have the option of alternative DMARDs including cyclosporin A, which has been shown to have an additive effect with methotrexate [5]. The approval of leflunomide, which has a different range of side-effects to methotrexate and sulphasalazine, will allow its use either singly or in combination [6, 7]. Thus, in the future another layer of combination therapy is likely to become a standard before patients can be labelled as having 'failed conventional therapy'.

In the past the levels of non-response determining unacceptable disease activity have been set rather low because they were the only hurdles that the past inadequate therapies available could hope to clear [8]. With more alternatives and better therapies available, the level of acceptable response will be set higher and in due course the currently Utopian concept of aiming for remission may be achieved. The standard composite score used most frequently is the American College of Rheumatology (ACR) Improvement Criteria (see Table 1).

When responses were poor the traditional measures of determining disease activity, i.e. swollen and tender joints and raised acute-phase response [C-reactive protein (CRP)] were adequate as these measures have been shown to correlate with erosions, bone density and decline in function [10, 11]. However, with better therapy and improved responses they may well be superseded by methods which directly image the primary site of disease and are of higher sensitivity. For example, ultrasonography can detect subclinical disease, and magnetic resonance imaging (MRI) is becoming increasingly available as a tool for research assessment of synovitis [12]. A 20% improvement in disease activity, as defined by the ACR guidelines, is the minimum response which can be reliably distinguished from placebo [8]. From a clinical perspective a more satisfactory response is a

Table 1. Assessment of response: modified ACR criteria [9]

| Criteria | | Criteria | |
|---|---|---|---|
| 1 | Swollen joint count | 3 a | HAQ |
| 2 | Tender joint count | b | Patient VAS for pain |
| | | c | Patient VAS for disease activity |
| | | d | Physician global assessment VAS |
| | | e | CRP/ESR |

ACR response score: patient satisfies 20 or 50% response score if >20 or 50% improvement on baseline for 1, 2 and at least three criteria from 3 (a–e).

HAQ, health assessment questionnaire; VAS, visual analogue score; ESR, erythrocyte sedimentation rate.

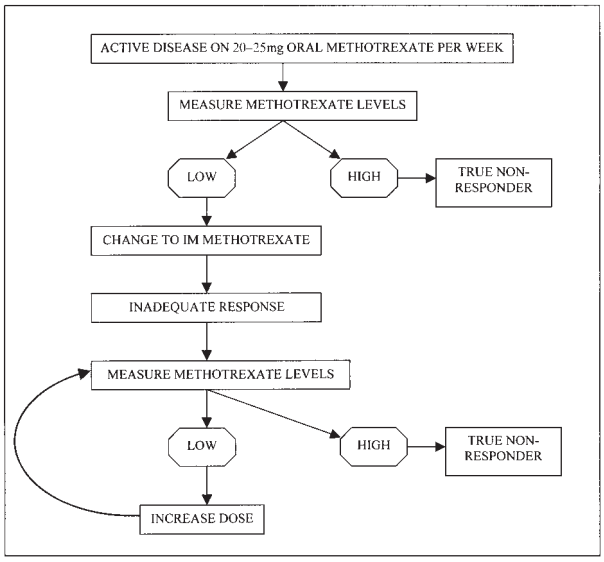


FIG. 1. Algorithm for determining methotrexate non-response.

50% improvement. However, even a 50% reduction in activity in an individual patient with very active disease can still leave an unacceptable level of activity. This residual activity can be recorded by also using the disease activity score (DAS) which not only provides a snapshot of disease activity but is also an indication of the absolute disease activity at any particular time (Table 2).

Thus, by including both these approaches an appropriate definition of unacceptable activity could initially be defined as a failure to improve by 20% on ACR criteria and/or a DAS indicating a moderate or poor response.

The magnitude of cost implications of using the new therapies demands that an attempt is made to agree indications for their use. The minimum proposed criteria of an unacceptable disease activity and a failure of conventional therapy need confirmation/assessment in a clinical setting. To achieve this, intensive monitoring of patients is required and ideally an algorithm for treatment would be used. A patient not responding

TABLE 2. Assessment of response: EULAR response criteria [13, 14]

$DAS = 0.56 \times \sqrt{28T} + 0.28 \times \sqrt{28S} + 0.70 \times \ln ESR + 0.014 \times GH$
28T = 28 tender joint count
28S = 28 swollen joint count
ESR = erythrocyte sedimentation rate
GH = patient global assessment of general health VAS (0–100 mm)

EULAR response criteria based on the DAS:

| | Improvement[a] | | |
|---|---|---|---|
| | $>1.2$ | $\leqslant 1.2$ and $\geqslant 0.6$ | $\leqslant 0.6$ |
| DAS[b] $\leqslant 2.4$ | Good response | | |
| $2.4 < DAS \leqslant 3.7$ | | Moderate response | |
| $DAS > 3.7$ | | | No response |

[a]Improvement in DAS compared with baseline.
[b]Attained level of disease activity.

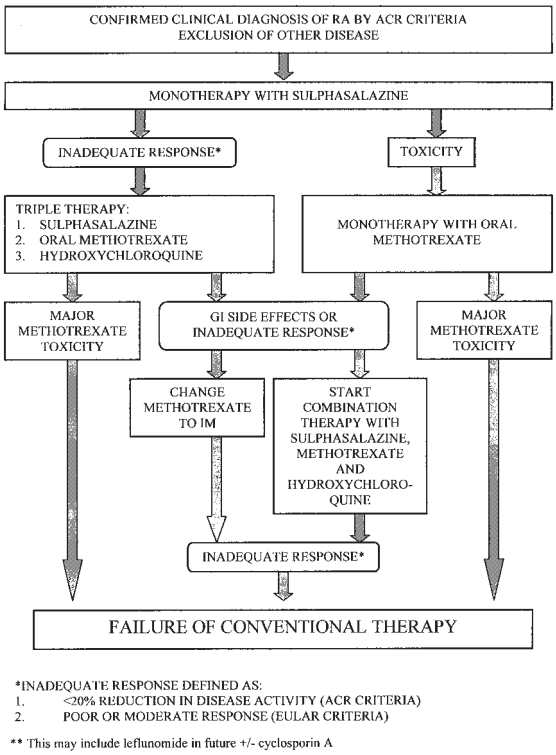


FIG. 2. Optimization of conventional therapy/determination of failure of conventional therapy.

adequately to monotherapy would follow the introduction of a new one according to guidelines. Such a rigid assessment of patients is difficult in a busy out-patient clinical setting. Therefore, for the last 12 months we have run a 'resistant RA' clinic which was primarily set up to assess patients for stem-cell transplantation. It identifies and manages patients who have persistent disease despite routine treatment. The indications and the numbers of patients suitable for the clinic have increased with time. The vast majority of these patients have had unsuccessful therapy with sulphasalazine, methotrexate and combinations (many are recruited from the YEAR protocol of monotherapy progressing to combination with sulphasalazine and methotrexate). Patients who are tolerant of methotrexate, but have not responded adequately, have their oral dose increased to 25 mg/week, which if not successful after 8 weeks (as defined by ACR 20 or DAS) is then switched to an intramuscular preparation with blood levels measured before and after (Fig. 1). This is an attempt to assess the importance of bio-availability in the non-response. Such an approach should identify apparent (responding to intramuscular methotrexate) and true (not responding to intramuscular methotrexate) non-responders. Patients who fail triple therapy with adequate methotrexate levels will be eligible for the next stage, which could be leflunomide before proceeding to biologics (Fig. 2).

The approach outlined for these clinics will have the advantage of ensuring that: (1) patients have adequate exposure to conventional therapy; (2) a standard

approach, which is analysable, is used; (3) expensive biological therapies are restricted in the first instance to those who not only will have most benefit from them but in whom the long-term toxicity is virtually certainly to be outweighed by the known risks of their active disease. Furthermore, if patients do go into remission, the criteria for continuing therapy can be established. Finally, it is now known that around 30% of patients have non-response to biologics and non-response should be identified rapidly. Such patients may be appropriate for experimental approaches including stem-cell rescue from high-dose immunosuppression.

Clearly the above represents only one possible approach out of many. However, it provides the starting point for rheumatologists and it is crucial that they have thought through the implications of the advent of these therapies before they are licensed. The next few months may be the only time that a logical debate will be a possibility.

S. Bingham and P. Emery

*Rheumatology and Rehabilitation Research Unit, University of Leeds, 36 Clarendon Road, Leeds LS2 9NZ, UK*

## References

1. Stenger AA, Van Leeuwen MA, Houtman PM, Brayn GA, Speerstra F, Barendsen BC *et al.* Early effective suppression of inflammation in rheumatoid arthritis reduces radiographic progression. Br J Rheumatol 1998;37:1157–63.
2. Emery P, Panayi G, Sturrock R, Williams B. Targeted therapies in rheumatoid arthritis: the need for action. Rheumatology 1999;38:911–2.
3. Felson DT, Anderson JJ, Meenan RF. The efficacy and toxicity of combination therapy in rheumatoid arthritis. A meta-analysis. Arthritis Rheum 1994;37:1487–91.
4. O'Dell J, Haire C, Erikson N. Treatment of rheumatoid arthritis with methotrexate alone, sulphasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med 1996;334:1287–91.
5. Tugwell P, Pincus T, Yocum D, Stein M, Gluck O, Kraag G *et al.* Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. The Methotrexate-Cyclosporine Combination Study Group. N Engl J Med 1995;333:137–41.
6. Smolen J, Kalden J, Scott D, Rozman B, Kvien T, Larsen A *et al.* Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double blind, randomised, multicentre trial. Lancet 1999;353:259–66.
7. Weinblatt ME, Kremer JM, Coblyn JS *et al.* Combination therapy with leflunomide-methotrexate in refractory rheumatoid arthritis. Arthritis Rheum 1999; in press.
8. Felson DT, Anderson JJ, Lange ML, Wells G, LaValley MP. Should improvement in rheumatoid arthritis clinical trials be defined as fifty percent or seventy percent improvement in core set measures, rather than twenty percent? Arthritis Rheum 1998;41:1564–70.
9. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C *et al.* ACR preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727–35.
10. Devlin J, Gough A, Huissoon A, Perkins P, Holder R, Reece R *et al.* The acute phase in early rheumatoid arthritis. C-reactive protein levels correlate with functional outcome. J Rheumatol 1997;24:9–13.
11. Gough A, Sambrook P, Devlin J, Huissoon A, Njeh C, Robbins S *et al.* Osteoclastic activation is the principle mechanism leading to secondary osteoporosis in rheumatoid arthritis. J Rheumatol 1998;25:1282–9.
12. Conaghan P, Wakefield R, O'Connor P, Gibbon W, Brown C, McGonagle D *et al.* MCPJ assessment in early RA: a comparison between X-ray, MRI, high-resolution ultrasound (HRUS) and clinical examination. Arthritis Rheum 1998;41(suppl.):S246.
13. Prevoo M, van't Hof M, Kuper H, van Leeuwen A, van de Putte L, van Riel P. Modified disease activity scores that include twenty-eight joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;39: 44–8.
14. Van Riel PL, van Gestel AM, van de Putte LBA. Development and validation of response criteria in rheumatoid arthritis: steps towards an international consensus on prognostic markers. Br J Rheumatol 1996;35(suppl. 2):4–7.