Intensive management of early rheumatoid arthritis: the TICORA and TEAR studies

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ABSTRACT

Observations form other biological models, principally Type 1 DM, led to the formation of a hypothesis that tight control of synovial inflammation using an intensive management strategy would lead to improved outcomes for patients with early RA. The TICORA study tested this hypothesis by randomising patient to routine or intensive management. It demonstrated that frequent review, formal assessment of disease activity and escalation of therapy in patients with persistent disease activity led to substantial increases in the rate of remission, reduced physical disability and radiographic progression. Its follow up study, TEAR, tested whether these results could be improved further by employing triple therapy from the outset, but the results suggested that a step-up strategy (moving to triple therapy only in those patients who have persistent disease activity on monotherapy) was as effective as parallel triple therapy. The studies have contributed to a consensus that early RA must be treated early and intensively, with the aim of achieving low disease activity or remission in all patients. The challenge to the clinical community is to ensure that this strategy is implemented in every rheumatologist's practice.

Introduction

Evidence from well-designed randomised controlled trials has confirmed that the progression of rheumatoid arthritis could be ameliorated by treatment with a number of disease-modifying anti-rheumatic drugs (1). It is also recognised, however, that DMARD monotherapy has significant limitations: the drugs are not effective in all patients; the therapeutic window is narrow, and many patients develop adverse effects; and as a result, drug discontinuation rates are high (2) (although drug persistence with methotrexate (MTX) is significantly higher than with the other DMARDS). Given this background, it was by no means certain that combining one or more DMARD made sense, but important new evidence emerged in the 1990s that some DMARD combinations, especially 'triple' therapy with methotrexate (MTX) sulfasalazine (SSZ) and hydroxychloroquine (HCQ), were more effective than monotherapy (3-5).

The prevailing wisdom was that the outcome of RA was determined by the accumulation of damage over many years, and that reducing the inflammatory burden over time should be the priority. Parallels could be drawn with hypertension – in this 'disease' therapeutics were directed towards the sustained reduction of blood pressure using as many drugs as necessary to achieve this aim. Physicians were less interested in which drug(s) were used than they were in achieving their therapeutic goal. Type 1 diabetes mellitus (T1DM) provided another informative biological model: the Diabetes Control and Complications Trial had shown that tight glycaemic control, through the use of multiple insulin injections each day, resulted in a dramatic reduction in microvascular complications such as retinopathy (6). As such, the treatment was not designed to cure the underlying cause of T1DM, but to ameliorate the effects of the consequent metabolic dysregulation. The parallels with RA were intriguing and the hypothesis emerged that tight control of synovial inflammation, irrespective of which drugs are used to achieve this, would be associated with an improvement in medium/long term outcomes. The research questions that needed to be addressed were:

1. Can tight control be achieved?
2. If so, would it lead to improved RA outcomes?
3. If so, would the improvements come at an acceptable cost (financial and clinical)

Tight Control in Rheumatoid Arthritis study

The Tight Control in RA (TICORA) study was designed to address these questions (7). It was an open label, randomised controlled trial comparing two strategies of care. Patients were randomised to either: routine management, undertaken in the rheumatology clinics of two teaching hospitals in Glasgow under the supervision of teams of consultant rheumatologists; or intensive management comprising several components of care:

1. Monthly review
2. Formal assessment of disease activity using the Disease Activity Score (DAS)
3. Escalation of DMARD therapy in patients with persistent disease activity (DAS>2.4) according to a treatment protocol
4. Liberal use of intramuscular triamcinolone in the first three months of a new DMARD being prescribed, and intra-articular injections of triamcinolone into swollen joints

One hundred and ten patients with disease duration less than five years (median 19–20 months) were randomised and assessed every three months by the same metrologist, who was blinded to treatment allocation. The results demonstrated a striking improvement in disease activity such that 65% of patients in the intensive group were in DAS clinical remission (DAS<1.6) after 18 months, compared to 16% of the routine group (Odds ratio [95% CI] for remission = 9·7 [3.9, 23.9], $p<0.0001$). The differences were seen across all clinical measures of disease activity. These improvements were associated by a large improvement in physical function measured using the Health Assessment Questionnaire, and a significant reduction in the rate of radiographic progression.

Importantly, these improvements did not come at the cost of increased toxicity: intriguingly, there were *fewer* adverse events reported by patients in the intensive group (even though they were reviewed more often, and were receiving more DMARDs). A similar observation was made in the COBRA trial (4), but the explanation is not entirely clear although there are several possibilities – for instance, it is possible that patients in remission are less prone to adverse events (such as infection, which may then be attributed to a drug side effect), or more likely to stop other medication such as non-steroidal anti-inflammatory drugs. Neither were the clinical improvements in the intensive group 'bought' at too high a financial cost – a health economic evaluation of the study found that the intervention was cost neutral, shifting resource utilisation from Primary Care and in-patient care to out-patients. In other words, it is not increased resources that are required to implement an intensive management strategy in early RA, but service re-design.

Intensive therapy resulted in ~50% reduction in radiographic progression, when compared to routine management. Interestingly, the reduction was primarily the result of a lack of new erosions in the intensive group, whilst reduction in joint space narrowing continued apace. Given the striking improvement in remission rate in the intensive group, might a more profound sparing of radiographic progression have been expected? It is possible that conventional DMARDs are more effective in suppressing symptoms and signs than in reducing joint damage, although there is evidence that sustained remission is associated with very low rates of radiographic progression (8). The benefits of intensive therapy take some time to reach maximum effect – the rate of remission in the intensive group continued to rise throughout the 18 month follow up period – and it is also possible that the majority of the radiographic progression occurred early on, before remission was established. If so, this would argue for the use of more intensive induction regimens, although the clinical relevance of an early loss of cartilage, if this is subsequently arrested, may not be too high. Almost complete abrogation of radiographic progression is seen with TNFi/MTX combination therapy, and might suggest that early biologic therapy may have more to offer than intensive management with conventional DMARDs, particularly in the minority of patients with rapid radiographic progression. This may be the case, but in many parts of the world, the early use of biologic therapy is restricted because of costs.

The results strongly supported the hypothesis that the strategy of pursuing tight control is a useful paradigm in directing therapy in patients with RA. Of course, the results raised more questions than were answered. The strategy was multi-faceted, but which component(s) contribute(s) most to the attainment of tight control cannot easily be elucidated: was it the frequency of review? Was it the liberal use of steroid injections? Was it the increased use of combination DMARDs? It was noted that >50% of patients in the intensive group finished the study on triple therapy, whereas this was very uncommon in the routine group. Given the results of the study by O'Dell *et al*. (3), it was possible that triple therapy played a major role in the success of the TICORA study. Moreover, would even better results be achieved if triple therapy were used in all patients from diagnosis?

Triple Therapy in Early Rheumatoid Arthritis study

The Triple Therapy in Early RA (TEAR) study was designed to address this question (9). The study compared two groups of early RA patients (mean disease duration 10–13 months), both of whom were treated with an intensive management strategy based on TICORA (monthly assessment, formal assessment of disease activity and escalation of treatment in patients with persistent disease activity). The only differences were that one arm were treated from the outset with triple therapy (parallel treatment) whereas the other commenced on monotherapy and only escalated treatment if/when there was evidence of persistent disease activity (step-up treatment).

The results provided useful confirmation of the effectiveness of intensive management, with high rates of remission in both groups (~40% DAS28 remission) and substantial reductions in physical disability (-0.8–0.9 HAQ units). However, the use of parallel triple therapy afforded no advantage over the step-up strategy, with no dif-

ferences between the groups in any outcome measure. The study is small, and was not powered to detect small differences between the groups, but trends favoured the step-up group. Many clinicians prefer to employ a step-up strategy because this allows monotherapy in that sub-group of patients who respond well to it, thereby avoiding unnecessary polypharmacy. However, there are proponents of early combination therapy based on several trials in which patients with initial combination therapy fared better than those treated with initial DMARD monotherapy, including the COBRA (4), FinRACo (5) and BeSt studies (10). It may be important that FinRACo and BeSt also employed a 'treat-to-target' approach, with the aim of achieving low disease activity or remission, but neither did so within the context of such an intensive management strategy as was employed in TICORA and TEAR – so, for instance, bridging intramuscular corticosteroid was not allowed in the BeSt protocol, and assessments (and treatment escalation) were performed quarterly rather than monthly.

Discussion

The results of TICORA and TEAR have contributed to the development of international consensus that early, sustained control of disease activity is achievable and desirable, and should be considered 'best practice' (11). They demonstrated that excellent outcomes can be achieved using conventional DMARDs, if these are employed energetically within a strategy of tight control. Of course, many questions remain:

1. Where do biologic drugs fit into the paradigm? TNF inhibitor (TNFi) has revolutionised the management of established RA, but its role in the management of early RA is much less established.
2. How tight should disease control be? Should we be aiming to achieve low disease activity or clinical remission? Are our tools sufficiently sensitive and accurate to allow us to target remission? Will any incremental gains in moving from low disease activity to remission be offset by some cost or risk, and if so will that be acceptable or affordable?
3. Can we develop superior tools to track disease activity using imaging? It is possible that regular musculoskeletal ultrasound examination will prove to be more accurate than clinical assessment in identifying persistent disease activity, and may therefore have a role in directing therapeutic decisions.
4. Can we develop more refined (individualised) treatment strategies that select different drugs or protocols on the basis of biomarker profiles? Attempts to identify such biomarkers have to date led to disappointing results, but considerable efforts continue to be made in this area.

These questions add up to a fascinating and engaging research agenda, but there is a more pressing need: to ensure that best practice is more widely implemented in routine clinical practice. It sometimes requires service re-design, and for clinicians to change their mind set, but the vigorous pursuit of good disease control using an intensive management strategy should no longer be regarded as an option but mandatory for all rheumatologists.

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