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Tight Disease Control in Rheumatoid Arthritis – What, Why and How?

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Introduction

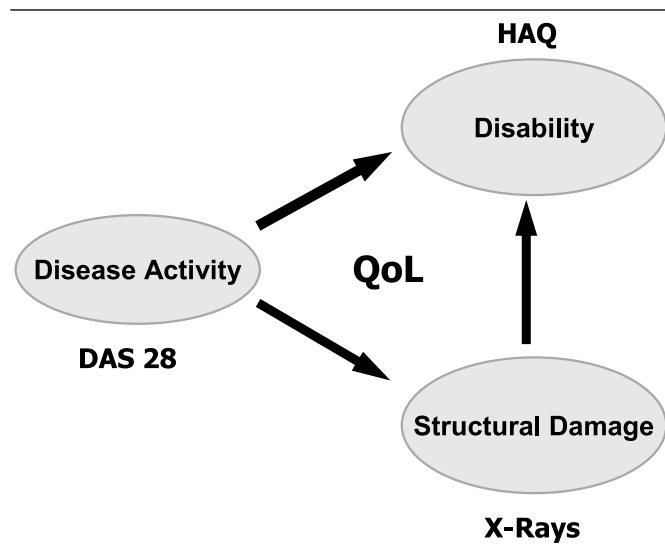
Rheumatoid Arthritis (RA) is the commonest inflammatory joint disease seen in clinical practice. It is an autoimmune disorder that shortens life expectancy. Passive treatment has now given way to active intervention. Much of this stems from aggressive use of disease modifying anti-rheumatic drugs (DMARDs), often in combination, to achieve tight disease control. Also, better understanding of the disease pathobiology has led to the development of several biologic agents. These agents are being employed not only for refractory, difficult to treat disease but also, increasingly, for early RA. The present article focuses on 'disease control' in RA- what is disease activity, how is it measured, the need for tight disease control and the ways to achieve this goal.

Disease Activity In RA- What is it and How is it Measured?

The advent of effective treatments like biologics has stimulated interest in quantitative measurements in Rheumatology- the science of 'Metrology'. The concept of measurement in Rheumatology is more esoteric because, more often than not, the instruments used are questionnaires to be filled in by the patient. This is in contradistinction to quantification possible in other areas of medicine e.g. proteinuria or GFR in kidney diseases, ejection

fraction or valve areas in cardiac illnesses, where numerical values are available to aid comparison and decision making. To complicate matters, most of these patients reported questionnaires are not available or validated in Hindi or other Indian languages. Notwithstanding this drawback, there is enough data to show that patient questionnaires are a scientifically validated way to assess disease activity in Rheumatology.

In general, 2 types of measures are employed in Rheumatology: Status Measures and Response Measures. The former assess disease activity at a specific point in time and are more applicable to individuals and in the clinic. Response measures assess how disease activity changes over time, for example, response to medication.¹ Response measures by their very nature require longitudinal observation and are more useful in clinical trials to study groups of patients. Disease activity score (DAS) and remission are considered to be status measures. In contrast, the American College of Rheumatology- ACR 20/50/70 criteria are response measures. DAS score is a continuous numerical index while the ACR criteria are a categorical mean. It must be pointed out that DAS can also be used as a response measure (as part of the so called EULAR-European League against Rheumatism- response criteria), although it is most often used as a status measure. The EULAR response criteria

Figure 1 : Domains in RA and their measurement tools

DAS= Disease Activity Score; HAQ=Health Assessment Questionnaire; QoL=Quality of life

classify individual patients as non-, moderate, or good responders, dependent on the extent of change in DAS and the level of disease activity reached.

Disease activity in RA is assessed by several parameters which include duration of morning stiffness, tender joint count, swollen joint count, observer global assessment, patient global assessment, visual analog scale (VAS) for pain, health assessment questionnaire for activities of daily living, ESR, NSAID pill count etc.² Scores which integrate several parameters are now frequently employed e.g. DAS score. DAS 28 is one of the simplified versions of original DAS in common usage. DAS 28 requires four simple inputs: 28 tender joint count (TJC), 28 swollen joint count (SJC), ESR and general health (GH) assessment by the patient on a VAS from 0 to 100. The 28 joints assessed for swelling and tenderness include the 10 PIP joints, 10 MP joints, 2 wrists, 2 elbows, 2 shoulders and the 2 knees.

One of the drawbacks of DAS 28 is the requirement of a DAS calculator which is available online also on the DAS web site (www.das-score.nl). Two composite indices that are derived from the

DAS but do not require a calculator or computer have been constructed- simplified disease activity index (SDAI) and clinical DAI (CDAI). The SDAI index includes five components: SJC (28 joints), TJC (28 joints), C-reactive protein (CRP) in mg/dL (with a range of 0.1-10), patient's global disease activity on a 10-cm VAS, and physician's global assessment on a 10-cm VAS. The index constitutes a simple numerical summation of the values of the individual components of SDAI, and ranges from 0.1 to 86. Four of these components are included in CDAI, which excludes the CRP. CDAI scores may range from 0 to 76. CDAI is the only composite index constructed to measure clinical remission in RA that does not include a laboratory test.^{3,4}

It also needs to be emphasized here that RA is a multidimensional disease and disease activity is one of the domains that can be measured (Figure 1). Other domains that are measured include disability (commonly measured by health assessment questionnaire-HAQ) and disease damage (measured on hand radiographs by scoring methods like Sharp score and its modifications). An all encompassing facet is quality of life, for which generic and disease specific measures like WHO-QoL Bref, RA-QoL etc are available.⁵ A detailed discussion on these is beyond the scope of this write up.

What is tight disease control?

Tight disease control aims to keep disease activity at low levels preferably in remission. The traditionally used ACR criteria for remission⁶ mandate that 5 or more of the following requirements must be fulfilled for at least 2 consecutive months:

- Duration of morning stiffness not exceeding 15 minutes
- No fatigue
- No joint pain (by history)
- No joint tenderness or pain on motion
- No soft tissue swelling in joints or tendon sheaths

- ESR (Westergren method) < 30 mm/h for a female or 20 mm/h for a male

Using DAS 28, RA activity is classified as mild when the DAS 28 is 2.6-3.2, moderate when the score is 3.2-5.1 or high when it is > 5.1. Remission is defined as a DAS 28 < 2.6. A change of 1.2 in DAS 28 is considered a meaningful change.

It has become increasingly apparent that complete remission as defined by the ACR criteria is not common in RA. Instead, the concept of minimal disease activity (MDA) may be more realistic. The original name for this state was low disease activity state (LDAS). Over the course of time, it became apparent that the name LDAS gave the impression that this was referring to a state of low activity and excluded remission. The change of the name to MDA was, in part, to address this misconception. MDA is between high disease activity and remission and any patient in remission is also in MDA.⁷ For DAS 28, the remission cut off is a score < 2.6. It is important to be aware of the fact that patients who meet the DAS28 remission cut point of < 2.6 may have a few tender and/or swollen joints unlike the ACR criteria. The DAS28 definition places the patient in MDA when DAS28 < The cut points for remission for SDAI and CDAI are 3.3 and 2.8 respectively.⁸

Why tight disease control in RA?

There is abundant data to show that apart from morbidity, the mortality is also increased in RA with an average shortening of life span by 10 years. The saving grace is that despite being a disease with unfavorable prognosis, suppression of disease activity does correlate with reduction in radiological joint damage.⁹ In the landmark TICORA study, patients were assigned to 2 groups, intensive treatment and conventional care. The intensive treatment group developed less radiographic damage than the control group after 18 months of follow up, suggesting an association between remission (or low disease activity) and further joint destruction.¹⁰ Similarly, Dutch investigators have shown that control of disease activity has a salubrious influence

on radiological progression, after adjustment for time effects and baseline predictors of radiological destruction and their interactions with time.¹¹ Similar data has been obtained from the recent PREMIER, ASPIRE and the TEMPO trials which reveals that higher remission rates are associated with arrest of radiographic progression and better physical function.¹²⁻¹⁴ It needs to be emphasized that maintenance of durable remission/MDA is as important as achieving remission/MDA.

Also, time is of essence in RA. Intervention should be early since there is irrefutable evidence to show that irreversible damage occurs within the first 2 years of the disease. The rate of progression in the first year of disease is significantly higher than that in later years, indicating the need for early intervention. Apart from the clinical and radiological benefits, early DMARD therapy also favorably influences mortality, which has been shown to be lower in patients who present early compared to those who present late.¹⁵ The concept of 'window period' is now firmly entrenched in RA akin to the concept in myocardial infarction. This window of opportunity in the treatment of RA describes a period of time early in course of RA when the disease is more responsive to therapy. The window period is a moving target and some authorities reckon that this may be as little as 3-4 months from the onset of symptoms.¹⁶ The duration of the disease too has a bearing on responsiveness to treatment. Patients with a longer duration of disease do not respond as well to treatment compared with patients with early disease. Trials of TNF blockers in RA too provide proof of concept that intensive intervention early in the course of RA can have a bearing on long term radiographic progression. In patients with a disease duration of less than three years, the use of a TNF blocking drug (adalimumab, etanercept, or infliximab) in combination with methotrexate revealed an increased rate of clinical remission and slowing of radiographic progression compared with methotrexate monotherapy.^{12,13,17} The available evidence, thus, overwhelmingly supports the case for early intervention in RA.

Despite the evidence that early treatment fetches the best dividends in RA, it is also pertinent to point out that patients in India present late and it is never too late to start treatment, though earlier is better.

How to achieve control in RA?

This is perhaps the most contentious area in this field. There is unanimity of opinion on the need to objectively measure disease activity, and control disease effectively. However, opinion on the tools to achieve this is divided.

There are robust data to show that compared with existing DMARDs, the biologic agents are capable of higher response rates, greater remission rates, slower radiographic damage over time, and fewer cardiovascular deaths, particularly when initiated early in the disease course.^{12,13,17,18} However, resource constraints make it unlikely that these agents would be used as the first line agents in India. I would, therefore, in this article, focus on the conventional DMARDs and how they can be used to achieve tight control. DMARDs can be instituted in various ways:

Step-up approach

Therapy is started with a single DMARD, other agents are added one by one till response is achieved.

Step-down approach

Several DMARDs are started together till remission; one agent is then continued and others withdrawn.

Saw-tooth approach

Therapy is started with a single DMARD which is substituted by another agent in case of toxicity or when it ceases to be effective.

Parallel approach

Several DMARDs are started simultaneously and continued.

Three landmark trials need mention: COBRA, TICORA and BeST. The COBRA

(Combinatietherapie Bij Reumatoide Artritis) trial was a randomized, double-blind, multicenter trial representing step down DMARD use.¹⁹ In this trial 155 patients with early RA were treated with either sulfasalazine (SSZ) monotherapy or combination therapy, comprising SSZ (2 g/day), methotrexate (MTX; 7.5 mg/week) and prednisolone (initially 60 mg/day, tapered in 6-weekly steps to 7.5 mg/day). The COBRA combination was found to be superior to SSZ monotherapy in suppressing disease activity and radiological progression of early RA. After a 5-year follow-up, it was seen that the initial 6-month cycle of intensive combination treatment (COBRA therapy) resulted in a sustained reduction in the rate of radiological progression, independent of subsequent antirheumatic therapy.²⁰ To put things in perspective, it needs to be mentioned that despite impressive results most rheumatologists are reluctant to embrace the COBRA protocol due to reasons like high dose of steroids (prednisolone ~60 mg/day initially), pill burden, complexity of regimen etc.²¹

It is perhaps the TICORA study that is most applicable to the Indian setting. In the TICORA study, patients with recent onset RA were randomly assigned to receive routine DMARD treatment at the discretion of the treating rheumatologist, or intensive treatment with monthly assessment of clinical disease activity.¹⁰ The DMARDs employed were SSZ, MTX, hydroxychloroquine singly to begin with. The investigators in addition to frequent, objective assessment of patients made intensive use of intraarticular steroid injections if needed; and the application of a structured protocol for the escalation of treatment (step up) in face of active disease. Combinations were employed in patients where disease activity was not controlled with single drugs, with prednisolone added to the treatment if response was suboptimal despite triple drug therapy. The people in the intensive group had greater improvements in physical function and substantially enhanced quality of life. Reduced progression of erosive disease and total radiographic damage was recorded, but not in joint-

space narrowing. The lesson that emerges from TICORA trial is that even in this era of targeted biological therapies tight control can be achieved with standard DMARD drugs without the use of anti-TNF treatments.

The third landmark trial is the BeST trial.²² The BeST trial evaluated the efficacy of 4 commonly used treatment strategies in over 500 patients with early RA, who were allocated to one of four treatment groups. Group 1 received sequential monotherapy, group 2 received step-up combination therapy, group 3 was assigned initial combination therapy with tapered high-dose prednisone, and group 4 was treated with initial combination therapy with infliximab. Patients were monitored every 3 months and treatments were adjusted to achieve and maintain disease activity scores (DAS 44) < 2.4. The trial design closely resembled clinical practice, allowing physicians many possibilities to adjust therapy, including the nine allowed DMARDs. The main clinical disease activity findings after 2 years were more rapid clinical improvement during year 1 in both groups that got initial combination therapy, but similar clinical improvement in all four groups at the end of year 2 (P = 0.257). However, patients in the two combination therapy groups had less progression of radiographic joint damage. Continuous DAS < 2.4 from month 6 to month 24 was observed in 22% of patients who received sequential monotherapy, in 21% who received step-up combination therapy, in 28% of those assigned combination DMARDs with initial high-dose prednisone, and in 40% of those assigned combination therapy with infliximab.

Each approach, whether step down or step-up, has its merits and demerits. What might be the conclusion for the clinician? The key message is that tight disease control is important, no matter how it is achieved. The middle of road approach would be step-up combination DMARD therapy with methotrexate (MTX) as the initial anchor drug. It might not be the most effective approach but reduces the risk of overtreating those patients who might otherwise have responded

to monotherapy.²³ It is important to step-up MTX quickly rather than a laid back approach and some centers adopt weekly escalation protocol in 2.5 mg steps up to 20 or 25 mg, with regular monitoring. Current guidelines too recommend a rapid dose escalation of MTX, titrated to patient response and side effects, to minimize the area under the curve of inflammation, which correlates closely with the progression of erosions and other surrogates for damage.^{24,25} When using higher doses of MTX (25-40 mg), it might be preferable to shift to parenteral route since bioavailability data demonstrates that the parenteral route delivers a higher and more consistent serum methotrexate concentration than the oral route.²⁶ It needs to be highlighted that DMARD therapy should be part of an aggressive package of care incorporating escalating doses of MTX and combination therapy rather than sequential monotherapy. Biologic therapy is employed in case of sub-optimal relief with conventional DMARDs. Systemic glucocorticoids are considered adjuncts to the DMARD strategy.²⁵

Conclusions

The currently available data mandate that disease activity in RA should be measured frequently and objectively, and the treatment titrated to match disease activity. Tight disease control should be the goal using DMARDs singly or in combination. The need of the hour is to strike a balance between efficacy, toxicity and cost!

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