EDITORIAL

In the Treatment of Rheumatoid Arthritis, Old is The New Way Forward

Durga Prasanna Misra, Anupam Wakhlu*, Vikas Agarwal

The landscape of the management of Rheumatoid arthritis (RA) has undergone sweeping changes over the past three decades with the advent of anti-TNF agents in the late 1980's. The ever expanding armamentarium of biologics now includes agents that work via other mechanisms as well, including tocilizumab, abatacept and rituximab. In the past decade and a half, a number of trials have emerged which address the issue of management of RA with conventional DMARDs (cDMARDs) versus biologic DMARDs (bDMARDs). Use of bDMARDs, more so in developing countries, is limited by problems of affordability and availability; even those who can afford may not do so for sustained periods of time. So a moot point to consider is whether cDMARDs in combination can have an effect that is comparable to bDMARDs.

The TICORA trial (1) revolutionised the management of RA by demonstrating that,in patients with disease duration less than 5 years, "treating to target" with cDMARDs enabled good control disease activity (ACR70 response of 71%) as compared to routine care, along with significantly better retardation of radiologic progression. Such high ACR 70 responses have not been obtained since then with use of bDMARDs as well, hence the relevance of this in the context of the current discussion. This was further emphasized by the CAMERA2 trial, wherein intensive management with methotrexate (MTX), in combination with cyclosporine if needed, resulted in more and sustained periods of remission versus conventional therapy in patients with early RA. Hence, it is treating to target that is of importance, rather than the drugs used to do the same. Since one coat does not fit all, management must be tailored to the individual patient as per the resources available.

Up to a third of patients with early RA would attain remission with methotrexate alone. Initial monotherapy, whether with methotrexate, leflunomide or sulfasalazine, results in ACR 50 responses in almost 30% patients (1). For the management of early drug-naive RA, use of combination of cDMARDs up front results in significantly better responses than monotherapy, as shown by the TICORA (2), CAMERA (3), FinRACO (4,5) and COBRA (6) studies. The BeSt trial (7) was particularly notable, as it was the first to demonstrate that up front combination of cDMARDs was equally efficiacious as the combination of anti-TNF agents and MTX, both in attaining remission, which was sustained over time, and limiting radiographic disease progression; the only advantage of bDMARDswas the earlier time to response. In resource-constrained scenarios, as in developing countries, whether waiting a little longer for response is really a consideration when preferring cDMARDs over biologics, merits consideration. The TEAR (8) trial showed that combining MTX with sulfasalazine (SSZ) and hydroxychloroquine (HCQ) was as efficacious as MTX with etanercept (ETAN) in controlling disease activity at 1 year as well as 2 years; however the group

From the Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, and *Department of Rheumatology, King George Medical University, Lucknow
Correspondence to : Dr Vikas Agarwal Additional Professor, Clinical Immunology, SGPGIMS, Lucknow 226014

receiving ETAN had a significant reduction in modified Sharpe Score of -0.51 as compared to the other group. Translating the same to the world of the clinician, such a small difference in radiologic progression would hardly be of clinical relevance, unless sustained over a number of years altogether. It must be remembered that the scenario in the clinic is much different from that of strictly protocol driven clinical trials, wherein changes in medication to achieve remission would more likely than not be made early if the patient is not having an adequate response to the ongoing treatment regimen. Hence it would not be reasonable to conclude that cDMARDs are a reasonable treatment option for early, drug naïve RA in their efficacy in attaining remission as well as retarding radiologic progression.

Head-to-head trials of monotherapy with biologics versus cDMARDs are uncommon; those that are available suggest that methotrexate monotherapy is comparable to adalimumab (9) or ETAN (10) monotherapy. Most trials of bDMARDs have a background of MTX, so how much benefit is attributable to the biologic agent alone is a matter of conjecture.

Having discussed the management of early drug-naïve RA, let us now review the evidence pool for patients failing MTX monotherapy. The SWEFOT trial (11,12) showed that stepping up to MTX-SSZ-HCQ was comparable to addition of ETAN in MTX non-responders in terms of clinical responses at 2 years, although the biologic-treated group had lesser radiographic progression. The RACAT trial (13,14) showed that adding SSZ-HCQ was comparable to adding ETAN in MTX non-responders in terms of clinical response and radiographic progression at 24 weeks. The recently published NeoRACOtrial (15) showed that at 5 years, triple cDMARD combination with or without infliximab had comparable clinical and radiographic progression at 5 years. This suggests that the effect of combination cDMARDs is sustainable over a longer term.

A recent landmark trial -TACIT trial (16) compared use of intensive treatment regimen with cDMARDs versus use of anti-TNF agents, in patients with active RA fulfilling criteria for starting anti-TNF agents according to British guidelines. They found cDMARDs to be non-inferior in attaining disease remission, as well as associated with substantially reduced costs. This further reaffirms the point that management of RA using cDMARDs is feasible, sustainable and cost effective.

A known devil is better than an unknown angel! With extensive experience in the use of cDMARDs, the adverse effect profile is well described. The same cannot be said for biologics. Conflicting literature exists on the risk of malignancy and tuberculosis reactivation with anti-TNF agents, the latter being of more serious concern in the developing world where latent tuberculosis is almost universal. Rare infections are being reported with greater frequency with bDMARDs, as in the case of leprosy with anti TNF agents in North America (17) (where the disease is almost non-existent) and progressive multifocal leukoencephalopathy with rituximab. Hence we feel one should be more cautious in using biologics up front, wherein one serious infection can potentially neutralize the possible benefit of an earlier clinical response.

To conclude, combination of conventional DMARDs is a reasonable, cost effective alternative to the upfront use of biologic DMARDs in the management of early drug-naïve RA as well as that having failed initial methotrexate monotherapy. Prohibitive costs, serious risks of infection and malignancy are barriers to more widespread use of biologic agents in developing countries, where insurance cover is scarce and nationalized health services are not widely available.

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