

Is non-biological treatment of rheumatoid arthritis as good as biologics?

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recent years, evidence has emerged that combination therapy with conventional DMARDs is not inferior to biologics in the management of RA and is a feasible cost-effective option.

Key words: Rheumatoid arthritis; Disease modifying drugs; Biologics; Methotrexate; Sulfasalazine; Leflunomide; Cyclosporine; Hydroxychloroquine; Tumor necrosis factor; Remission; Radiologic outcome

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Core tip: In developing world cost of treatment remains a major concern. Recent evidences are emerging that support the equal efficacy of conventional disease modifying anti-rheumatic drugs (DMARDs) as compared to biological DMARDs. In this review we have presented evidences supporting conventional DMARDs in management of rheumatoid arthritis.

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Abstract

The management of rheumatoid arthritis (RA) in the past three decades has undergone a paradigm shift from symptomatic relief to a "treat-to-target" approach. This has been possible through use of various conventional and biologic disease modifying anti-rheumatic drugs (DMARDs) which target disease pathogenesis at a molecular level. Cost and infection risk preclude regular use of biologics in resource-constrained settings. In the

INTRODUCTION

The management of rheumatoid arthritis (RA) has witnessed sweeping changes in the past three decades. The emergence of disease modifying anti-rheumatic drugs (DMARDs), has resulted in slowing or halting the progression of RA, including radiographic progression and has resulted in better quality of life and clinical outcomes. In early 1980s, standard of care was oral or intramuscular gold or d-penicillamine, and methotrexate (MTX) had not yet seen the light of day

as a DMARD. Over the next one-and-a-half decades, MTX emerged as a safe, cheap and most compliant drug with convenience of once weekly dosing. Soon it became the first line DMARD for RA. Subsequent studies reported those combination therapy of multiple DMARDs are more effective in achieving treatment targets owing to their synergistic action with a favorable efficacy/toxicity profile. Till late 1980s DMARD therapy was based on "No harm" due to drugs principle, therefore, aggressive strategies targeting remission were hardly realized.

With the advances in the understanding of the pathogenesis of RA, tumor necrosis factor- α (TNF- α) emerged as a major cytokine causing damage to the joint. Development of anti-TNF- α monoclonal antibodies and its efficacy in management of RA revolutionized the management in early 1980s. These drugs, called as biologics, were highly effective with more rapid onset of action than conventional DMARDs and achieving remission in quite a large proportion of patients. Subsequently, newer biologics with different therapeutics targets were found to be effective in RA and led to the broadening of the treatment armamentarium. However, the superior efficacy of biologics was accompanied with risk of serious infections and malignancy. Moreover, prohibitive cost of biologics made it inaccessible to the majority of patients in the developing countries. This compelled researchers to evaluate the efficacy/safety profile of combination DMARDs and to adopt aggressive strategies such as "treat to target" using both combination DMARDs and biologics in head-on trials over last decade.

Keeping these in view, recent years have seen many clinical trials comparing the relative efficacy of triple drug therapy with conventional DMARDs (cDMARDs) and biologic DMARDs (bDMARDs).

MEASURING DISEASE ACTIVITY

It is important to know how to measure disease activity in RA as most clinical trials employ these as outcome measures. This can be measured by a number of indices including the disease activity score (DAS), DAS28, simplified disease activity index, clinical disease activity index, rheumatoid arthritis disease activity index, patient activity scale and routine assessment patient index data. Each assesses a various combination of factors including number of tender joints, number of swollen joints, acute phase reactants [erythrocyte sedimentation rate, C-reactive protein (CRP)], patient global assessment and physician global assessment. Each of these has varying definitions of remission, low disease activity, moderate disease activity and high disease activity. A good degree of correlation exists between the various measures. Recently, the ACR and EULAR have jointly defined "remission" in RA clinical trials as no more than one tender or swollen joint, CRP less than 1 mg/dL and patient global assessment ≤ 1 (on a scale of 0-10). Such stringent criteria lend

credence to the fact that as low a disease activity as possible should be the aim of treating RA^[1,2].

"TREAT-TO-TARGET" APPROACH

Before the era of biologics, remission in majority of RA was not achievable due to fear of toxicity and restricted the use of combination of cDMARDs.

The concept of "treat to target" where treatment target is a state of remission or low disease activity emerged from the TICORA trial^[3]. In this trial, patients with RA of duration less than 5 years were randomized to receive either routine care or intensive care (monthly visits with target DAS ≤ 2.4 achieved by protocolised sequential cDMARD therapy). Both Groups had significant improvement in DAS. However the Group treated more intensively to reach a low disease activity had a significantly larger proportion of patients achieving an ACR70 response (71%) as compared to the Group receiving routine care (18%) and retardation of radiographic progression. Such a high ACR70 response has never been achieved even in trials with biologics. Intensive treatment was not associated with increased risk of adverse effects, and was cost-effective. The CAMERA trial^[4] demonstrated that in early RA, intensive treatment approach with MTX (with cyclosporine if needed) resulted in remission in 50% patients (median duration 11 mo in 2 years) as compared to 37% (median duration 9 mo in 2 years) with conventional approach. At 2 years, the intensive treatment Group had an ACR 50 response of 58% compared to 45% in the conventional treatment Group. This again proves that an intensive treatment approach in patients using conventional DMARDs is effective in greater than half the patients in achieving remission. This data emphasized that outcome of RA depends on treating to target and not on the drugs used to achieve this. All patients are different in their treatment response to different drugs, so there is no unifying treatment algorithm which suits all.

Delving into the available evidence pool, the treatment of RA can be discussed separately for DMARD naïve patients and for patients who have failed these DMARDs.

TREATMENT OF EARLY, DRUG-NAÏVE RA

With the change in criteria for diagnosis of RA in 2010 it has become possible to diagnose much early and initiate DMARDs therapy to an optimum dose to target lowest disease activity or remission. As reported in the CAMERA trial^[4], TICORA trial^[3], FIN RACo^[5,6], COBRA study^[7], combination cDMARDs in various combinations not only achieve low disease activity or remission in quite a significant proportion of patients but also resulted in clinical and radiological outcomes in the long term. TICORA^[3] trial resulted in ACR70 response in greater than 70% patients with a combination of conventional DMARDs alone. The FIN RACo^[5] study showed that in early RA, combination therapy was

Table 1 RCTs comparing outcomes in rheumatoid arthritis

Trial	Arms	No. of patients	Mean/median disease duration at presentation	Outcome assessment at	Outcome		
					Clinical	Functional (change in HAQ)	Radiological
TICORA ^[3]	Intensive Conventional	55 55	Approximately 20 mo	18 mo	EGR 82% vs 45% ER 64% vs 16% ACR70 71% vs 18%	NA	Median change TSS 4.5 vs 8.5
CAMERA ^[4]	Intensive	151	< 1 yr	1 yr	Remission for 3 mo 35% vs 14% ACR50 58% vs 43%	NS	NS
	Conventional	148		2 yr	Remission for 3 mo 50% vs 37% ACR50 43% vs 45%		
FINRACO ^[5]	SSZ + MTX + HCQ	87	Approximately 8 mo	2 yr	ACR remission 37% vs 18%	NS	Increase Larsen score 4 vs 12
NEO-RACO ^[20]	SSZ	91	4 mo	5 yr	ACR50 71% vs 58%	NA	Change in SHS NS
	SSZ + MTX + HCQ + IFX	50			Remission-ACR: 60% vs 61%		
BEST ^[8]	SSZ + MTX + HCQ + Placebo	49	2 wk	1 yr	DAS28: 84% vs 89%	0.7; 0.7; 0.9; 0.8	Change in SHS 2; 2.5; 1; 0.5
	Seq Monotherapy	126			LDA 53%; 64%; 71%; 74%		
TEAR ^[10]	Step up MTX + SSZ + Pred MTX + IFX	121 133 128	Approximately 4 mo	2 yr	LDA 75%; 81%; 78%; 82%	0.7; 0.8; 0.9; 0.9	Change in SHS 2; 2; 1; 1
	Immediate ETAN	244			ACR20 45%-50% in all		
TEAR ^[10]	Immediate triple	132	Approximately 4 mo	2 yr	ACR50 35%-40% in all	NS	Change in TSS 0.5; 1.9; 0.7; 1.4
	Step-up ETAN	255			ACR70 10%-20% in all		
	Step-up triple	124					

NS: Not significant; NA: Not available; SHS: Modified sharp score; MTX: Methotrexate; SSZ: Sulfasalazine; HCQ: Hydroxychloroquine; IFX: Infliximab; ETAN: Etanercept; Pred: Prednisolone; LDA: Low disease activity; EGR: EULAR good response; ER: EULAR remission; TSS: Total sharp score; DAS: Disease activity score.

more effective than monotherapy in achieving ACR remission (14% vs 3%) and DAS28 remission (51% vs 16%). In COBRA^[7] trial, initial intensive combination of MTX with sulfasalazine (SSZ) and prednisolone vs SSZ monotherapy alone not only resulted in significant clinical improvement at 28 and 56 wk but also resulted in better radiologic outcome even at 5 years.

BeSt trial^[8,9] is a landmark open label trial which included 4 treatment arms (Table 1). Group 1 (sequential monotherapy) treated with initial MTX followed by SSZ followed by leflunomide, etc. Group 2 (step up combination therapy) treated with initial MTX but subsequently stepped up to combination therapy with MTX + SSZ + hydroxychloroquine (HCQ) + prednisolone. Group 3 (initial combination therapy) started with combination therapy from beginning (MTX + SSZ + HCQ + prednisolone) whereas. Group 4 (Initial biologic therapy) started with infliximab with MTX. At 1 year, low disease activity (DAS44 < 2.4) was attained in more than

half the patients (53%, 64%, 71% and 74% in Groups 1, 2, 3 and 4 respectively) with about a third of the patients in remission in all the Groups. Of interest to answering the question posed earlier is a comparison of the results in Groups 3 and 4. At 1 and 2 years, both Groups 3 and 4 achieved similar DAS and HAQ scores at similar rates (both improved quicker than Groups 1 and 2) and had similar radiographic progression. Radiographic progression was numerically greatest in Group 1 and for Groups 1 and 2 taken together compared to combination Groups, although it did not reach statistical significance. This suggested that combination therapy with non-biologic DMARDs has similar efficacy to biologics in treatment naïve RA.

Treatment of early aggressive rheumatoid (TEAR)^[10] trial further sought to explore whether triple therapy with MTX-SSZ-HCQ could be similar to MTX-etanercept (ETAN) (Table 1). This large trial involved 755 patients with poor prognostic factors (RF or anti CCP positive

Table 2 PREMIER study - outcome at 2 years follow-up^[13]

	Ada + MTX	Ada	MTX
ACR20	69%	49%	56%
ACR50	59%	37%	43%
ACR70	47%	28%	28%

Ada: Adalimumab; MTX: Methotrexate.

with erosive disease). The study had four arms: (1) Initial MTX + ETAN; (2) Initial triple therapy (MTX + SSZ + HCQ); (3) Initial MTX for 24 wk followed by step up addition of ETAN for 78 wk if disease activity was not controlled; and (4) Initial MTX for 24 wk followed by step up triple therapy for 78 wk if disease activity was not controlled. The results showed similar outcomes at 1 and 2 years for all the Groups, with a small but significant advantage of the ETAN Groups vs the triple therapy Groups with respect to radiographic progression (change in total Sharp score- Δ TSS - 0.51/year). This again showed that combination DMARD therapy is not inferior to biologics in management of early RA.

Biologics have also been tried in DMARD-naïve RA, however head to head trials with combination cDMARDs are not available. The IMAGE^[11] trial showed that use of rituximab in early RA with background MTX use resulted in ACR20, ACR50 and ACR70 responses of 77%-80%, 59%-65% and 42%-47% as compared to placebo (64%, 42%, 25% response rates respectively). Tocilizumab in drug-naïve RA (AMBITION trial)^[12] had ACR 20, ACR50 and ACR70 response rates of 68%, 45% and 27% respectively. The PREMIER trial^[13] (Table 2) showed that MTX monotherapy was comparable to adalimumab monotherapy. A trial of ETAN (25 mg twice weekly) in early RA compared to MTX monotherapy showed comparable ACR20 (50% vs 60%), ACR50 (about 40% in both) and ACR70 (about 20% in both) responses at 1 year^[14]. In the ASPIRE trial^[15], on a background of MTX, infliximab compared to placebo resulted in better ACR20 (62%-66% vs 53%), ACR50 (45%-50% vs 32%) and ACR70 responses (32%-37% vs 21%). It must be noted that most of these trials had a background MTX, so how much of a benefit was attributable to the biologic agent alone is a matter of debate.

The next question that arises is: Which one is preferable as initial combination therapy? Whether to go for triple therapy "MTX + SSZ + HCQ" or to add bDMARDs. To this regard multiple trials have been conducted and as discussed above, all concluded that if treated to a target, both options yielded similar result.

MANAGEMENT OF RA FAILING INITIAL METHOTREXATE MONOTHERAPY

If initial treatment with MTX monotherapy fails, then what is the best treatment option? Should we go

directly to biologics or try combinations of cDMARDs? A closer look at the 3rd and 4th arms of the TEAR trial shows that 72% patients on MTX monotherapy had to be stepped up in a blinded fashion with addition of either SSZ + HCQ or ETAN due to persisting disease activity (DAS > 3.2). At 12 wk following stepping up as well as at the completion of the trial period (102 wk), both Groups had similar disease activity outcomes, quality of life and radiographic progression^[10].

A Swedish study attempted to look at whether addition of infliximab was a better option to adding SSZ + HCQ in patients with inability to achieve low disease activity with MTX alone. The initial 1 year randomized trial showed similar outcomes with both approaches at 6 mo, but significantly better outcomes for the infliximab Group at 1 year (EULAR good response was attained in 26% triple therapy Group and 39% infliximab + MTX Group at 1 year). However at 18 and 24 mo of follow up this significance of difference was lost. This led the investigators to conclude that for those patients who fail initial MTX monotherapy, add-on therapy with conventional DMARDs serves as an appropriate treatment option. Of note, the triple therapy Group had a significantly higher radiographic progression of disease compared to the infliximab Group^[16,17].

A recently published trial with a randomized double-blind design further compared addition of SSZ + HCQ verses addition of ETAN in failure of MTX monotherapy (RACAT Trial). At 24 wk, the patients having inadequate response were switched over to the other Group. Both Groups showed similar reductions in DAS 28 at 24 and 48 wk, with no significant differences in radiographic progression or quality of life. There was no significant difference in response after switching between the two Groups. This led the investigators to conclude that triple therapy with conventional DMARDs was non-inferior to ETAN + MTX in patients with RA having active disease in spite of MTX monotherapy^[18,19].

Another recent study, the NEO-RACo trial^[20] showed that at 5 years, treatment with combination cDMARDs (MTX, SSZ, hydroxychloroquine and low dose prednisolone) with or without infliximab during the first 6 mo had similar ACR remission rates (60% vs 61%) and DAS 28 remission rates (84% vs 89%) and radiologic outcomes. This again suggests that combination of cDMARDs is as effective as use of bDMARDs even on long term follow up.

SAFETY PROFILE

Although no form of therapy is absolutely safe, experience with conventional DMARDs is long-term over decades and side effect profile is well known. MTX and SSZ usage entails a risk of cytopenias and liver toxicity but if monitored properly does not pose a real threat. HCQ is a relatively safe drug and only need yearly

eye check up to look for retinal toxicity which is rarely encountered.

Biologic agents in general carry a definite increased infection risk, as they act by perturbing crucial pathways in anti-microbial defense like interleukin-6 and TNF- α . This is of greater importance in developing countries. Of note reactivation of tuberculosis is a definite threat in developing countries and there is still controversy regarding proper screening methods for this in literature. Most studies regarding anti TNF- α are from the North American and Scandinavian regions, where prevalence of TB is low^[21,22]. Extrapolating the same data to developing countries where tuberculosis is rampant needs caution. Moreover, case reports of unusual infections like leprosy with use of anti TNF- α in developed countries, where these infections were unheard of previously, rang the warning bell^[23]. RA has increased risk of lymphomas; furthermore, anti-TNF- α agent therapy also has been associated with risk of lymphoma and solid tumors^[24]. Risk of demyelinating diseases as multiple sclerosis and flare of autoimmunity are also concerns with anti-TNF- α agents^[21,22]. Although data regarding these are not very robust at present, we have to remember most of the biologic trials have been short term and exact risk of malignancy needs long-term follow up. Tocilizumab is associated with transaminitis, dyslipidemia and neutropenia which require monitoring for patients on follow-up^[12]. Postmarketing surveillance had revealed Rituximab carries a small risk of fatal progressive multifocal leucoencephalopathy^[25].

We feel worldwide experience with biologics is more limited than with cDMARDs, and they need to be used over few decades for estimating exact risk of malignancy and other long-term side effects. There is industry pressure to embrace biologics early and use it more liberally and multiple guidelines are being formulated supporting these. But in absence of a clearcut efficacy benefit and a definite risk of infection and malignancy, we have to be careful while using these and exercise more caution atleast in developing countries where cost both of biologics and any complication arising out of its use is significant.

CONCLUSION

Although biologics have revolutionized the field of RA treatment, their overwhelming costs, risk of serious infections and limited availability result in their inaccessibility to a majority of the population in resource constrained healthcare settings. Triple therapy, whether used initially or as rescue therapy in patients with MTX failure, has similar efficacy to combination of anti-TNF- α agents with MTX, and this has been demonstrated across various populations. There is paucity of data comparing biologics other than anti-TNF- α agents with conventional DMARDs, and this remains to be addressed in future clinical trials.

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