Evidence that the Strategy is More Important than the Agent to Treat Rheumatoid Arthritis
Data from Clinical Trials of Combinations of Non-Biologic DMARDs, with Protocol-Driven Intensification of Therapy for Tight Control or Treat-to-Target

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Abstract
Eight major “strategy trials” in rheumatoid arthritis (RA) are reviewed, with protocol-driven escalation of combinations of methotrexate and other small molecule non-biological disease modifying antirheumatic drugs (DMARDs). All documented the value of intensive treatment adjusted according to quantitative data, generally a disease activity score (DAS) or its 28 joint count version (DAS28). Three of the 8 trials, TICORA, Dutch DAS-driven care, and CAMERA, may be termed “pure strategy trials,” to compare a protocol-driven “intensive” strategy to usual care. Five other trials, BeSt, CIMESTRA, TICORA 2, Step-down versus step-up, and TEAR, may be termed “hybrid trials,” in which an initial parallel design was supplemented with incremental protocol-driven intensification of treatment. A strategy of aiming for low disease activity or remission appears more important than the specific agent used. In group data, the proportion of good responses seen in these trials with combinations of non-biologic, small molecule DMARDs are comparable to data from clinical trials of biological agents although responses appear more rapid with biological agents, and certain individual patients may require a biologic agent for adequate control. These trials also illustrate the value of a quantitative index, monitored frequently for rational intensification of therapy. The data make a compelling case for both routine monitoring with a quantitative index and consideration of routine adjustment of therapy at each visit. Combinations of methotrexate with other non-biologic DMARDs and glucocorticoids, toward a target of low disease activity or remission, may improve outcomes for patients with RA at levels similar to biologic agents in many patients.

Traditional clinical trials are designed to analyze the efficacy of a treatment compared to a placebo or other “control” treatment over a defined period, using a “parallel” design. Contemporary trials designed for registration of new therapies use a parallel design to meet the requirement that a new medication have statistically significantly greater efficacy than a control medication or placebo, with an acceptable profile for adverse events. This type of clinical trial may provide unequivocal evidence that a therapy under study is efficacious compared to a placebo. A clinical trial with statistically significant results documents that a given therapy is superior to placebo or control treatment. However, the trial data provide only limited information concerning how the particular therapy might be used in clinical care of a specific individual patient with a rheumatic disease (unlike, perhaps, in many patients with infectious or neoplastic diseases). When should the therapy be introduced to patient care? Why is it preferred over another therapy? Can it be discontinued? When might that take place? The absence of definitive answers to these queries reflect limitations of the traditional parallel-design, placebo-controlled clinical trial methodology, which have been noted over several decades but remain underrecognized.

Data from traditional, parallel clinical trials do provide important information for individual patients and individual physicians to assess which therapy to use at which time, as a “shared clinical decision,” as advocated by the European League Against Rheumatism (EULAR) recommendations concerning therapy of rheumatoid arthritis (RA). These recommendations state that “the treatment of rheumatoid arthritis must be based on a shared decision between patient and rheumatologist. Not only must
the patient be informed of the therapeutic options and the reasons for recommending a particular therapeutic approach by weighing benefit and risk, but the patient should participate in the decision as to which treatment should be applied." These comments reflect that in most situations in the treatment of rheumatic diseases, there is not a single "best" therapy, but a range of acceptable and even desirable options, from which one or several may be selected on the basis of a shared decision between doctor and patient.

In recent years, additional types of clinical trial designs have been introduced in an effort to improve information concerning optimal treatment of individual patients with RA. The "step up" design involves patients who had experienced incomplete responses to an agent, usually methotrexate (MTX) in RA, who are then randomized to receive MTX plus another DMARD or biological agent in combination or MTX plus placebo. Since MTX emerged in the 1990s as the "anchor drug" for RA, taken by many more patients than any other RA medication, it is generally the most frequently used DMARD in combination with other non-biological and biological DMARDs. The step-up design has provided an opportunity to document that a number of DMARDs—including cyclosporine, leflunomide, hydroxychloroquine, and sulfasalazine, which may have lesser efficacy than MTX as monotherapy—can provide incremental benefit when added to MTX as combination therapy. It also has been used to document the efficacy of biological agents.

Combination therapies also have been analyzed in trials using a parallel design, in which a combination of DMARDs versus monotherapy is given in parallel from the initiation of therapy, rather than awaiting an incomplete response to MTX (or another DMARD). Twenty-one examples of these types of trials of combination therapy are summarized in an accompanying article in this supplement.9

A potentially more intensive type of trial design may be termed a "strategy trial." In this design, patients are treated with combinations of DMARDs versus monotherapy but with additional protocol-driven adjustment of treatment at frequent visits toward a target, generally a disease activity score—DAS10 or DAS2811—indicating low disease activity or remission. Eight "strategy trials" have been reported in RA (Table 1), all of which documented significant advantages to careful patient monitoring with intensification of therapy, compared to traditional therapy that was unchanged over longer periods. Three may be termed "pure strategy trials," with a design to compare a protocol-driven "intensive" strategy to usual care.12-14 Five others may be termed "hybrid trials," in which an initial parallel design involved randomization to one of two or four arms, but with incremental protocol-driven intensification of the treatment, based on swollen joints or DAS scores, or other quantitative measure.15-19 All eight trials indicate that a strategy of aiming for low disease activity or remission appears more important than the agent used,20 as summarized in this article.

**TICORA (Tight COntrol for Rheumatoid Arthritis) Study**

The TICORA study was a single-blind, randomized controlled trial conducted in Glasgow, Scotland, and reported in 2004, in which 111 patients with early RA were randomized to either intensive management or routine care.12 All patients were treated initially with sulfasalazine. Patients in the intensive group were seen monthly by the same rheumatologist, with calculation of a DAS at every visit. At every assessment after month 3, patients whose DAS was greater than 2.4 had escalation of their treatment according to a protocol, from initial sulfasalazine to combination DMARDs, with MTX, hydroxychloroquine, and prednisolone 7.5 mg/day.12 In addition, any swollen joint was injected with intra-articular triamcinolone acetonide, up to a maximum of three joints or total dose of 120 mg.

Patients assigned to routine care were seen every 3 months, without a formal DAS score to guide clinical decision-making. DMARDs were given sequentially as monotherapy rather than in combination, but intra-articular corticosteroid injections were allowed. The primary outcomes were mean decrease in DAS and the proportion of patients with a good clinical response, defined as DAS < 2.4 and decrease by > 1.2 units (on a scale of 0 to 10).

At the end of the 18-month trial, among 52 intensive group patients, 18 (35%) were receiving monotherapy and 34 (65%) combination therapy, including 27 (52%) triple therapy. Among 51 patients in the routine care group, 45 (88%) were receiving monotherapy and only 6 (12%) combination therapy, including 2 triple therapy (4%).

These differences in therapies were associated with substantial differences in outcomes. In the intensive group, the mean decrease in DAS was 3.5 units (on a 0 to 10 scale) versus 1.9 units in the routine group (p < 0.0001). Among patients in the intensive group, 45/55 (82%) had a good response, compared to 24/55 (44%) in the routine care group [odds ratio (OR) 5.8; limits of 95% confidence interval (CI) 2.4-13.9; p < 0.0001]. Overall, 36/55 (65%) of patients in the intensive group had DAS < 1.6, the criterion for remission, compared to 9/55 (16%) in the routine care group (OR 9.7; limits of 95% CI, 3.9-23.9; p < 0.0001). Change in total Sharp radiographic score was 4.5 in the intensive group compared to 8.5 in the routine care group at the conclusion of the study (p = 0.02). No meaningful differences in adverse events were observed.12

The level of remission achieved in the TICORA trial is as high as in any trial involving a biological agent, but no biological agents were used. The mean disease duration was only 19 and 20 months in the two groups, shorter than most (but not all) clinical trials involving biological agents. The investigators concluded that a strategy of intensive outpatient management of rheumatoid arthritis substantially
Table 1: “Strategy” Tight Control Clinical Trials in Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Quality*</th>
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</thead>
<tbody>
<tr>
<td><strong>Pure Intensive Strategy Versus Usual Care</strong></td>
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<tr>
<td>Grigor 200412</td>
<td>N = 111, DAS &gt; 2.4, disease duration &lt; 5 years</td>
<td>• Intensive management: monthly assessment - if DAS &gt; 2.4, escalation of therapy according to step-up protocol</td>
<td>Primary: proportion of patients with a good response (defined as a DAS &lt; 2.4 and a fall in this score from baseline by &gt; 1.2)</td>
<td>Jadad 3</td>
</tr>
<tr>
<td>TICORA study</td>
<td></td>
<td>• Routine care: usual rheumatology follow-up</td>
<td>Secondary: proportion of patients in remission (DAS &lt; 1.6), ACR20/50/70, radiographic progression</td>
<td>Not blinded</td>
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<tr>
<td>2 sites 18-month open label RCT in Glasgow, Scotland</td>
<td></td>
<td>• Intra-articular triamcinolone in all swollen joints</td>
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<tr>
<td>Fransen 200513</td>
<td>N = 384 meet 1987 ACR criteria</td>
<td>• Conventional treatment</td>
<td>Primary: proportion of patients with DAS28 &lt; 3.2 at week 24</td>
<td>Jadad 3</td>
</tr>
<tr>
<td>Multicenter in Netherlands 6 months cluster RCT at 24 sites in the Netherlands</td>
<td></td>
<td>• DAS28 collected at selected visits</td>
<td>Secondary: dose changes in individual DMARDs and changes in patient pain, global disease activity, and disability</td>
<td>Not blinded</td>
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<tr>
<td>Versstappen 200714</td>
<td>N = 299 participants meeting the 1987 ACR criteria, disease duration &lt; 1 year</td>
<td>• Conventional strategy</td>
<td>Primary: remission for at least 3 months—no SJC, ≤ 3TJC, ESR ≤ 20, global VAS ≤ 20</td>
<td>Jadad 3</td>
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<tr>
<td>CAMERA study</td>
<td></td>
<td>• Intensive strategy group according to a computer decision program</td>
<td>Secondary: improvement in single measures; mean change in disease activity</td>
<td>Not blinded</td>
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<tr>
<td>2-yr multicenter open label strategy trial in Denmark</td>
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<tr>
<td>Goekoop-Ruiterman 200515</td>
<td>N = 508 participants meeting the 1987 ACR criteria and TJC, disease duration ≤ 2 years</td>
<td>• Sequential monotherapy</td>
<td>Primary: functional capacity by HAQ and radiographic damage by modified Sharp/Van der Heijde</td>
<td>Jadad 5</td>
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<tr>
<td>BeSt study</td>
<td></td>
<td>• Step-up combination MTX+SSZ+HCQ</td>
<td>Secondary: ACR20/50/70 and clinical remission defined as DAS44 &lt; 1.6</td>
<td>Not blinded</td>
</tr>
<tr>
<td>1- (2-5) yr multicenter RCT in the Netherlands</td>
<td></td>
<td>• Initial combination MTX+SSZ+Prednisone</td>
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<tr>
<td>Hetland 200816</td>
<td>N = 160 participants, disease duration &lt; 6 months</td>
<td>• Initial combination MTX+Infliximab (</td>
<td>Primary: ACR20 response at 2 years</td>
<td>Jadad 3</td>
</tr>
<tr>
<td>CIMESTRA study</td>
<td></td>
<td>• MTX+cyclosporine</td>
<td>Secondary: remission, cumulative dose of betamethasone, and radiographic progression</td>
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<tr>
<td>2 yr multicenter placebo-controlled double-blind RCT in Denmark</td>
<td></td>
<td>• MTX+placebo</td>
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<tr>
<td>Saunders 200817</td>
<td>N = 96, DAS28 &gt; 5.1, disease duration &lt; 5 years</td>
<td>• Monthly assessments in both arms, betamethasone injection into all swollen joints; increase dose of MTX and/ or cyclosporine by predefined protocol</td>
<td>Primary: mean decrease in DAS28 at 12 months</td>
<td>Jadad 3</td>
</tr>
<tr>
<td>TICORA 2</td>
<td></td>
<td></td>
<td>Secondary: EULAR good responses; # in remission: ACR20/50/70</td>
<td>Not blinded</td>
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<tr>
<td>12 month RCT at 3 sites in Glasgow</td>
<td></td>
<td>• “Step-up” SSZ, MTX, HCQ</td>
<td>Primary: DMARD changes</td>
<td>Jadad 1</td>
</tr>
<tr>
<td>Verschueren 200818</td>
<td>N = 71 RA patients with unfavorable prognostic factors 2-years Single site in Belgium</td>
<td>• Parallel triple therapy with SSZ+MTX+HCQ</td>
<td>Secondary: use of steroids, adverse events</td>
<td>Not randomized, not blinded</td>
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<tr>
<td>TEAR study</td>
<td></td>
<td>• Intra-articular triamcinolone in all swollen joints</td>
<td>Primary: change in DAS28 between week 48 and 102</td>
<td>Jadad 5</td>
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<tr>
<td>2-year multicenter RCT in US</td>
<td></td>
<td>• Step-down group: modified COBRA</td>
<td>Secondary: radiographic progression, ACR20/50/70, modified-HAQ</td>
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<td></td>
<td></td>
<td>• Step-up group: monotherapy with MTX, SSZ, HCQ, or AZA</td>
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</table>

*Quality was evaluated according to the Jadad scale.29 RCT, randomized controlled trial; MTX, Methotrexate; SSZ, sulfasalazine; HCQ, hydroxychloroquine; AZA, azathioprine; ACR, American College of Rheumatology; DAS28, Disease Activity Score for 28-joint counts; CDAI, Clinical Disease Activity Index; HAQ, Health Assessment Questionnaire; TJC, tender joint count; SJC, swollen joint count; ESR, erythrocyte sedimentation rate.
improves disease activity, radiographic disease progression, physical function, and quality of life at no additional cost.”

**BeSt trial (Dutch acronym for Behandel-Strategieën, “Treatment Strategies”)**

The BeSt trial was a multicenter, randomized clinical trial conducted in The Netherlands and reported initially in 2005, in which 508 patients were randomized to one of four treatment strategies: 1. sequential DMARD monotherapy; 2. step-up combination DMARD therapy; 3. initial combination therapy with tapered high-dose prednisone; and 4. initial combination therapy with infliximab. Treatment adjustments were made every 3 months to a goal of reducing the DAS (with a 44 joint count) to ≤ 2.4, indicating low disease activity. The primary outcomes were functional capacity according to the Dutch HAQ, followed by later radiographic damage.

After 3 months of treatment, mean HAQ scores were 0.6 in groups 1 and 2 versus 0.4 in groups 3 and 4 (p < 0.001), indicating more rapid functional improvement in patients treated with initial combination therapy, which included either prednisone or infliximab, compared to sequential monotherapy or step-up combination therapy. At 1 year, mean HAQ scores were 0.7 in groups 1 and 2 and 0.5 in groups 3 and 4 (p = 0.009). The median increases in total Sharp-van der Heijde radiographic joint score were 2.0, 2.5, 1.0, and 0.5 in groups 1 through 4, respectively (p < 0.001).

After the first year, continued efforts to reach DAS < 2.4 led to tapering of medications in many patients in the initial combination groups, and intensification to combinations in many patients in the initial monotherapy groups. Over years 2 to 5, functional capacity was similar in all groups, and further DAS reduction resulted in HAQ improvement. Radiographic progression was higher in groups 1 and 2 versus groups 3 and 4. Clinical remission was seen in 50% of all patients; 115/508 (23%) of patients achieved drug-free remission at some time during the first 5 years, similar in all groups.

The investigators concluded that initial combination therapy, which included prednisone or infliximab, resulted in earlier functional improvement and less radiographic damage after 1 year than did sequential monotherapy or step-up combination therapy. However, over 2 to 5 years clinical status was similar in the four groups, based on intensive monitoring of all patients, though a statistically significant, albeit relatively small, difference was seen in radiographic scores.

**Dutch Study of Intensive Versus Conventional Therapies**

A cluster clinical trial randomized 24 Dutch rheumatology outpatient centers, 12 to systematic monitoring using the DAS28 and 12 to usual care. Patients in the DAS28 group had DAS28 calculated at weeks 0, 4, 12, and 24 by the treating rheumatologist, with a goal that patients would have a DAS28 score of ≤ 3.2, indicating low disease activity, after 24 weeks of observation. Patients in the usual care group did not have systematic DAS28 monitoring and had no guidelines to adapt treatment to reach DAS28 ≤ 3.2. Changes in DMARD treatment were at the discretion of the rheumatologist and the patient.

At baseline, DAS28 was 4.6 in the DAS28 centers and 4.5 in the usual care centers (p = 0.44), and 8/61 patients (13%) in the DAS28 centers had low disease activity versus 10/81 patients (12%) in the usual care centers (p = 0.91). After 24 weeks, the number of patients with low disease activity was increased from 8 to 19 of 61 (31%) in the DAS28 centers, compared to an increase from 10 to 13 of 81 (16%) in the usual care centers (p = 0.028). DMARDs were changed on average in 18% of visits in the DAS28 centers, compared to 8% of visits in the usual care centers (p = 0.013). However, while doses of MTX, sulfasalazine, and corticosteroids were higher in the DAS28 centers than in the usual care centers, the differences were not statistically significant.

The investigators concluded that “in daily practice, systematic monitoring of disease activity in rheumatoid arthritis may lead to more changes in DMARD treatment, resulting in a larger number of patients with low disease activity.”

A significant difference in the primary outcome was seen although differences in therapies were not significant, perhaps because the trial was conducted over only 24 weeks, while the other seven trials in this review were continued over at least 12 months, five of which were over 24 months.

**CAMERA (Computer Assisted Management in Early Rheumatoid Arthritis) Trial**

The CAMERA clinical trial was a 2-year multicenter open label strategy trial of 299 patients with early RA in The Netherlands. Patients were assigned randomly either to an intensive strategy of treatment with MTX according to a strict protocol and a computerized decision program or to conventional MTX treatment. Patients in both groups were treated with a goal of remission, defined as no swollen joints, ≤ 3 tender joints, ESR ≤ 20, patient global visual analog scale (VAS) ≤ 20/100 mm.

Patients in the intensive treatment group came to the outpatient clinic once every month and had adjustment of MTX dosage on the basis of predefined response criteria, using a computerized decision program. Patients in the conventional strategy group came to the outpatient clinic once every 3 months and were treated according to “common practice.” Cyclosporine was added if patients had an inadequate response to maximal tolerated MTX doses.

Seventy-six patients in the intensive strategy group (50%) achieved at least one period of remission during the 2-year trial versus 55 patients (37%) in the conventional strategy group (p = 0.03). Greater efficacy in the intensive treatment group was seen for all measures. A later study indicated more adverse events in the intensive strategy group than in the conventional strategy group, but they were not severe and differences did not lead to withdrawal.

The investigators concluded that “it is possible to substantially enhance the clinical efficacy early in the course.
of the disease by intensifying treatment with MTX, aiming for remission, tailored to the individual patient,” and suggested that “participating rheumatologists indicated that the computerized decision program could be a helpful tool in their daily clinical practice.” They further concluded from the later study that “the previously observed clinical efficacy of an intensive treatment strategy seems to outweigh the observed toxicity profiles.”

**CIMESTRA (Cyclosporine, Methotrexate, Steroid in RA) Clinical Trial**

The CIMESTRA trial was an initial 2-year trial with two treatment arms: 1. MTX plus cyclosporine (combination therapy group); and 2. MTX plus placebo-cyclosporine (monotherapy group). In addition, if patients in either group presented with swollen joints during the first year, they were treated with intra-articular betamethasone injections (7 mg/L, maximum four joints or 4 ml per visit). Furthermore, the MTX dose was escalated by 2.5 mg/week every 4 weeks from 7.5 mg/week up to maximum 20 mg/week, followed by stepwise increase (0.5 mg/kg) in cyclosporine/placebo-cyclosporine every 4 weeks from 2.5 mg/kg up to maximum 4.0 mg/kg of body weight.

The long-term strategy was to withdraw MTX in patients who were in remission from year 3 and onwards. Hydroxychloroquine 200 mg/day was added in all patients at week 68, irrespective of disease activity, because a previous study had shown that hydroxychloroquine extended the response seen with combination therapy after withdrawal of MTX. The primary outcome was American College of Rheumatology 20% improvement (ACR20), with secondary ACR50 and ACR70 outcomes.

After 2 years of observations, ACR20, ACR50, and ACR70 responses were seen in 88%, 79%, and 59% of patients in the combination group, respectively, versus 72%, 62%, and 54% in the monotherapy group (p = 0.03, 0.02 and 0.6 between groups). However, other measures did not differ between the two groups: patient global estimate (0 to 100 mm VAS) declined from 50 to 12 in the intensive group versus 52 to 9 in the monotherapy group. The proportion of patients who met criteria for DAS28 remission at the conclusion of the trial was 51% and 50% in the two groups. Sharp-van der Heijde radiographic scores did not differ clinically or statistically significantly between the two groups.

Serum creatinine levels were increased by 7% in the combination group versus 4% in monotherapy, but hypertension was not more prevalent in the combination group.

The investigators concluded that continuous MTX with intra-articular corticosteroid treatment resulted in an excellent clinical response and disease control at 2 years. Addition of cyclosporine during the first 76 weeks resulted in statistically significantly increased proportions of ACR20 and ACR50 responses but did not have any additional effect on remission rate and radiographic outcome. The data suggest a powerful effect for careful monitoring with protocol-required intra-articular betamethasone injections while limited incremental efficacy was associated with addition of cyclosporine to MTX.

**Tight Control of Rheumatoid Arthritis (TICORA) 2 Trial**

The Glasgow group that had conducted the initial TICORA trial conducted a second trial, which may be termed “TICORA 2,” in which the design was modified to include an early parallel triple therapy group with sulfasalazine plus MTX plus hydroxychloroquine to compare to a “step-up” therapy group. The step-up group received initial sulfasalazine monotherapy, followed by MTX after 3 months, raising the MTX dose every 3 months, and hydroxychloroquine after maximum tolerated dose of MTX was reached.

All patients were assessed monthly over 12 months. Again, an aggressive approach was used, with protocol-driven increases in the dosage of DMARDs and injection of swollen joints in both groups with triamcinolone acetonide at a maximum dosage of 80 mg per month, if the DAS28 was > 3.2. The primary outcome was the mean decrease in the DAS28 score at 12 months.

Forty-six patients with early RA with mean disease duration of 11.5 months were randomized to initial parallel triple therapy or step-up therapy. Both groups showed substantial improvements in disease activity and functional outcomes. Greater efficacy was seen for the step-up therapy group, which, however, was not statistically significant compared to the parallel therapy group. At 12 months, the mean decrease in the DAS28 score was 3.3 in the parallel therapy group versus 4.0 in the step-up therapy group (p = 0.163). No significant differences in were seen the proportion of patients with DAS28 remission (33% parallel triple therapy, 45% step-up therapy), DAS28 good response (41% versus 60%), ACR20 (76% versus 77%), ACR50 (51% versus 60%, respectively), or ACR70 (20% versus 30%). Radiologic progression was similar in both groups.

Again, results were as favorable as those seen in trials of biologic agents but without any use of biologic agents. The mean duration of disease at baseline was less than 1 year, which may account for the excellent results. However, the results were not as favorable as in the initial TICORA trial, which the investigators suggested may have resulted from observation over 12 months in this study versus 18 months in the earlier study. The investigators concluded that “highly effective control of disease activity can be achieved using conventional DMARDs as part of an intensive disease management strategy. Within this setting, step-up therapy is at least as effective as parallel triple therapy.”

**Belgian Step Up Versus Step Down Therapy Trial**

Patients with severe early RA were assigned to either a “step-down” modified combination therapy in early RA (COBRA) regimen or a “step-up” tight control therapy. Step-down, modified COBRA patients received sulphasalazine 2 g daily,
MTX 15 mg weekly, and step-down oral prednisolone, initially 60 mg daily, rapid tapering to 7.5 mg over 6 weeks, and discontinuation from week 28. At week 40, patients were randomized to maintenance therapy with either sulfasalazine or MTX if DAS28 was acceptably low.

The step-up group started disease-modifying anti-rheumatic drug (DMARD) monotherapy with MTX, sulfasalazine, hydroxychloroquine, or azathioprine, with subsequent combinations of these DMARDs. Patients in both groups were evaluated by a rheumatologist after 4 to 6 weeks and at least once every 4 months thereafter. Treatment was adjusted to DAS28-CRP, with a goal of remission (< 2.6) or at least low disease activity (< 3.2). In addition to DAS28, HAQ scores, DMARD changes, and steroid use were recorded every 4 months for 2 years.18

Nineteen patients received step-down and 52 step-up treatment; patients were not randomized. Over first year of treatment, 84.2% in the step-down group versus 60% in the step-up group completed the year without unplanned DMARD changes or dosage adjustments. Over the 2-year follow-up period, the proportion of patients without unplanned DMARD changes (73.3% versus 55%) and without adjustment of the DMARD dosage (40% versus 30%) was higher in the step-down group, but differences were not statistically significant.18

MTX proved to be the most effective maintenance therapy after step-down. The DAS response, proportion of patients in remission, HAQ response, and proportion of patients without disability at 4 months was higher in the step-down group. The number of adverse events did not differ significantly in the two groups.18 The investigators concluded that a step-down treatment strategy for early RA is more effective than a step-up approach.18 However, most adjustments occurred every 4 months in the step-up group, compared to more frequent adjustments, including monthly, in studies indicating greater efficacy to a step-up strategy, so that step-up therapy may not have been optimal.

**TEAR (Treatment of Early Aggressive Rheumatoid Arthritis) Clinical Trial**

TEAR (Treatment of Early Aggressive Rheumatoid Arthritis) is a 2-year, randomized, double-blind trial in the USA,19 in which patients were randomized initially to one of four treatment arms: 1. initial treatment with MTX plus etanercept; 2. initial oral triple therapy (MTX plus sulfasalazine plus hydroxychloroquine); 3. step-up from MTX monotherapy to MTX plus etanercept at week 24 if the DAS28-ESR was > 3.2; and 4. step-up from MTX monotherapy to triple therapy (MTX+SSZ+HCQ) if the DAS28-ESR was > 3.2. Matching placebos were included in all treatment arms. The primary outcome was change in DAS28-ESR values from week 48 to week 102.

At week 24, which was the beginning of the step-up period, reduction in the mean DAS28-ESR was 4.2 in the two immediate-treatment groups versus 3.6 in the step-up groups (p < 0.0001). However, the step-up groups showed improvement in the mean DAS28-ESR by week 36, and by week 48, the mean DAS28-ESR was similar in all groups. No significant differences were seen across the four treatment groups in DAS28-ESR between week 48 and week 102 (p = 0.28), whether patients were treated initially with MTX plus etanercept or triple therapy (p = 0.48) or with initial combinations versus step-up therapy (p = 0.55). Overall, 56% of all patients had a DAS28 score ≤ 2.6 at some point during follow-up: 56.6% in the immediate etanercept group, 59.1% in immediate triple therapy group, 52.9% in the step-up to etanercept group, and 56.5% in the step-up to triple therapy group (p = 0.93).

Radiographic progression, defined as a change of 0.5 units from week 0 to week 102 (less than 1% of the total possible score), was seen in only 33.6% of all participants; 79.4%, 64.9%, 71.1%, and 68.3% of patients in the four groups showed no radiographic progression (p = 0.33). When patients were collapsed into two groups, 76.8% of those who received MTX plus etanercept had no radiographic progression, with a mean difference of 0.6 units, compared to 66.4% of those who received triple therapy (p = 0.02), with a mean difference of 1.69 units (p = 0.047). However, these differences would not be detectable clinically on a scale of 0 to 448.25 The investigators concluded that “initial use of MTX monotherapy with the addition of sulfasalazine plus hydroxychloroquine or etanercept, if necessary, after 6 months is a reasonable therapeutic strategy for patients with early RA.”19

**Discussion**

These data indicate statistically significantly better outcomes in eight clinical trials in patients managed with combination non-biological DMARDs according to an aggressive “treat to target strategy” compared to traditional therapeutic approaches. In three clinical trials, many differences were not statistically significant; one was conducted over only 24 weeks,13 another over 1 year,17 while the other six were conducted over at least 18 months, five of which were over 24 months. In the step-down versus step-up trial,18 “intensive” clinical adjustments of therapy were conducted every 4 months, compared to every 1 to 3 months in the other trials (Table 1).

In the earliest trial, TICORA,12 which was conducted between 1999 and 2001, after 18 months at the conclusion of the trial, 88% of patients in the routine care group were taking monotherapy, compared to 35% in the intensive management group.13 It is likely that the proportion of patients taking combination therapy would be higher in both groups at this time, but differences between intensive and routine care might remain substantial.

The data reviewed in this article make a strong case that combinations of non-biological DMARDs, generally including MTX, may have efficacy as great as seen with biological agents in groups of patients. Nevertheless, it must be noted...
that results in groups may not pertain to every individual patient. Indeed, some patients appear to have aggressive and intractable disease activity, which does not respond to any non-biological DMARD singly or in combination but does respond to a biological DMARD, often in combination with MTX. Probably no more than 20% of patients are in this category, but these patients must be recognized using clinical indices and treated to reach an appropriate target. Furthermore, patients treated with biological agents generally experience more rapid improvement in clinical measures, which may provide an advantage even if results are similar 2 years after baseline. Results of clinical trials over 6 to 24 months are not necessarily applicable to 5 to 10 year results. Finally, patient and physician preferences may favor triple therapy or a biological agent.

A cost-utility analysis of the BeSt trial concluded that the value of sustained productivity in patients treated with infliximab may have compensated for the additional medication costs. The investigators concluded that the “using the friction cost method, costs to achieve this improvement are generally considered too high, and initial combination therapy with prednisone should be preferred. However, depending on the extent to which productivity is valued, infliximab costs could be largely compensated for by savings on productivity.” They recognized that further observation was needed to adequately assess pharmaco-economic conclusions. These observations further emphasize the importance of shared decisions in the EULAR recommendations for treatment of individual patients with RA, as results in groups in clinical trial are not invariably applicable to every individual patient.

The design and results of strategy trials all depend on quantitative clinical data in an index to monitor RA patients, rather than traditional non-quantitative narrative descriptions or “clinical judgment” alone. However, despite findings in these strategy clinical trials documenting effectiveness of “treat to target” with traditional DMARDs, most rheumatologists continue not to collect quantitative clinical measures or use an index to monitor their patients with RA. A recent survey of the ACR membership indicated that the highest proportion of rheumatologists scoring any quantitative index is about 29% for DAS28 or RAPID3. In most medical records of RA patients at this time, the only quantitative data are laboratory tests, which have limited value to monitor patient status.

Evidence for the efficacy of intensification of therapy also provides evidence of the value of quantitative clinical measurement in rheumatology care. It would not be possible to make optimal rational escalations of therapy without quantitative measurement of an index, generally DAS28. However, the clinical disease activity index (CDAI) and routine assessment of patient index data (RAPID3) (an index only of patient reported measures) are correlated significantly with DAS28 and probably by inference could be used. It is possible to have patients complete a multidimensional health assessment questionnaire (MDHAQ) with a RAPID3 score while waiting to see the doctor, as a simple tool in usual care, to be certain that some quantitative data are collected at every visit. This practice in no way prevents collection of a DAS28, CDAI, ultrasound, or any other measure or index that appears appropriate to the treating rheumatologist.

We may conclude that the data presented in this report make a compelling case for three changes in rheumatology care at many sites: 1. routine monitoring of an index in patient care at each visit; 2. adjustment of therapy toward a target of low disease activity or remission; 3. consideration of attempting to gain control of disease activity through a combination of non-biological DMARDs before turning to a biological agent in incomplete responders to MTX and other DMARDs. Such practices could result in considerably improved outcomes for patients with RA and other rheumatic diseases.

Disclosure Statement
None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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