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Implementation of Treat to Target in Rheumatoid Arthritis through a Learning Collaborative: Results of the TRACTION Randomized Controlled Trial

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Abstract

Background—Treat to target (TTT) is an accepted paradigm for management of rheumatoid arthritis (RA), but some evidence suggests poor adherence. We tested the effects of a group-based multi-site improvement Learning Collaborative (LC) on adherence to TTT.

Methods—We conducted a cluster-randomized quality improvement trial with wait-list control across 11 rheumatology sites in the US. The intervention entailed a 9-month group-based LC that incorporated rapid-cycle improvement methods. A composite TTT implementation score was a percentage of four required items documented in the visit notes for each patient at two time points, as evaluated by trained staff. The mean change in the implementation score for TTT across all patients for intervention sites was compared with control sites after accounting for intra-cluster correlation using linear mixed models.

Results—Five sites with a total of 23 participating rheumatology providers were randomized to intervention and six sites with 23 participating rheumatology providers were randomized to the wait-list control. The intervention included 320 patients and the control 321 patients. At baseline, the mean TTT implementation score was 11% in both arms; after the 9-month intervention, the

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TTT implementation score was 57% in intervention and 25% in control (change in score of 46% in the intervention arm and 14% in control; $p = 0.004$). We did not observe excess resource use or excess adverse events in the intervention arm.

Conclusions—An LC resulted in substantial improvements in adherence to TTT for management of RA. This study supports the use of an educational collaborative to improve quality.

INTRODUCTION

Randomized controlled clinical trials have consistently demonstrated that a strategy of treating to target (TTT), results in better outcomes compared with usual care in rheumatoid arthritis (RA). Specifically, this strategy is implemented by using disease activity measures at every visit and escalating therapy in eligible patients with active disease above the target disease activity level.(1–8) This is a similar strategy to what is recommended for diabetes and hypertension: setting a target for treatment, measuring progress towards achieving the target regularly, and altering treatments until reaching and maintaining target. The TTT strategy for RA is based on a number of principles and recommendations articulated by an international working group and embraced by a US-based professional society.(9, 10) (11) These include: identification of a disease activity target; recording of a disease activity score using a validated measure; and when appropriate, documentation of shared-decision making and reasons why TTT was not implemented. Several lines of evidence suggest that TTT is not practiced consistently across rheumatology settings. The largest US-based RA registry, CORRONA, examined the management of patients at high risk for poor outcomes (i.e. with moderate disease activity and a poor prognosis or with high disease activity).(12, 13) Despite having active disease, only one-third to one-half of patients depending on their level of disease activity received treatment changes over the subsequent 6–12 months. A large Australian cross-sectional study identified various reasons rheumatologists do not adjust RA treatments at visits where patients were found to be in moderate or high disease activity, such as irreversible joint damage and patient preferences.(14)

Most attempts to align physician's behavior with recommended management in chronic illness have demonstrated marginal benefits.(15) While many studies have evaluated educational interventions for providers, methods are generally weak and studies rarely report on adherence with guideline-based treatment.(16) However, there is some limited evidence that quality collaboratives produce improvement.(17) These collaboratives often include setting out principles that characterize best practices, forming teams that include health care providers and staff, rapid cycle testing of changes in care that align with the agreed upon principles, frequent measurement of key indicators for care improvement, and collaboration across practice sites to share best practices.(18) This process has been tested in many clinical settings and is often conducted as part of a group-based multi-site educational collaborative, often described as a Learning Collaborative.(19) Despite prior success with the care of diabetes,(20) HIV,(21) and childhood asthma,(22) Learning Collaboratives have not been widely pursued in sub-specialty medical care; we designed a Learning Collaborative to improve care for patients with RA.

Since implementing TTT broadly requires health care delivery redesign across practices with different workflows and team members, we pursued a trial of a Learning Collaborative across 11 practices, the Treat-to-target in RA: Collaboration To Improve adOption and adhereNce (TRACTION) Trial. The goal of TRACTION was to test the effectiveness of a Learning Collaborative to improve implementation of TTT principles for RA.

METHODS

Trial Design

We conducted a cluster-randomized wait-list controlled clinical trial to test the effects of the Learning Collaborative for TTT between January 2014 and October 2015. (The wait-list control sites received the intervention subsequent to October 2015.) Eleven US rheumatology practice sites were recruited to participate; nine were affiliated with academic medical centers and five participated in rheumatology fellowship training programs. We made contact with over 70 sites by e-mail and then interviewed 25 sites by telephone. The 11 sites were diverse in geography, patient populations, and organization (see Supplemental Table 1 for further site details). None was actively engaged in TTT at baseline, based on a baseline interview of the team leaders by the Principal Investigator (DHS) that asked about the four aspects of the outcome measure (see below). Sites were randomized to active intervention or wait-list control. Four sites described using disease activity measures at baseline and they were evenly distributed across arms through stratified randomization, achieved through a random number generator provided by the study statistician (BL). Randomization occurred at the site level since the intervention targeted practice sites, not patients or individual providers. Sites and providers were not masked to their treatment assignment.

Research activities were approved by the Institutional Review Board of Partners Healthcare. The funder had no role in the study except for monitoring progress.

Patient Sample

All sites were given the same instructions for selecting patients. A sample of at least 40 patients with RA was provided by each site, representing patients from providers who attended at least one learning session and contributed to the monthly medical record review. A minimum of 5 patients per provider was required. Patients had to have visits within the baseline and follow-up periods described below. The medical records of these patients were included in the final review by study staff, not local site personnel. Baseline visits were defined as the first visit during the four-month period, September to December 2014, prior to the start of the intervention. The follow-up visits were defined as the first visit during the last four-months of the study period, September to December 2015.

Intervention

The intervention consisted of a Learning Collaborative, which we have described elsewhere. (23) In brief, the Learning Collaborative involved the faculty developing a set of principles and associated concepts that describe the goals for implementing TTT principles, described herein as TTT (see Supplemental Figure 1). The concepts are used by sites to guide rapid-

cycle tests of change. The principles and concepts were taught in the first learning session, which was conducted as a face-to-face one-day meeting. The first learning session also aimed to facilitate team building by sites and cross-site collaborative relationships, and eight subsequent monthly learning sessions were conducted via webinar. Each learning session included sites sharing a set of agreed upon metrics collected through a local medical record review. As well, a Learning Collaborative faculty member presented a question and answer session regarding the principles and concepts of TTT. More details of the learning sessions are provided in the Appendix (see Supplemental Table 2). We asked all team members from each site to attend all learning sessions, but this was not always possible. All learning sessions were recorded and made available on a web-based collaborative tool. The tool was developed using commercially available software (SharePoint by Microsoft; Seattle, WA) that helped manage contents being shared across teams (i.e., key resources, rapid-cycle tests of change), displayed monthly improvement metrics, and provided a discussion board with conversation “threads.”

We reviewed the medical records (including visit notes, laboratory and radiology orders, and medication lists) from patients with RA seen by rheumatology practices involved in the Learning Collaborative from each site.

Trial Outcomes

The primary trial outcome was the change in a composite TTT implementation score. The score included four items directly stemming from the principles and concepts of TTT: 1) specifying a disease activity target; 2) recording RA disease activity, using one of four recommended measures (e.g., DAS28, SDAI, CDAI, or RAPID3), with results described numerically or by category (i.e., remission, low, moderate, or high) (24); 3) when a decision was being made (i.e., change in target or change in treatment), documenting shared-decision making; and 4) basing treatment decisions on target and disease activity measure or describing reasons why TTT was not adhered to. Each item was determined as absent or present based on a medical record review by trained study staff (inter-rater kappa = 94% (95% confidence interval 90–99%), and intra-rater reliability kappa = 98% (95% confidence interval 95–99%)). We calculated the TTT implementation score for each patient as a percentage of TTT items noted in the visit note at baseline and follow-up visits.

Secondary outcomes included: 1) percent of patients with any positive change in implementation score between baseline and follow-up, and 2) proportion of patients with full implementation of all TTT items at the follow-up. We assessed resource use by examining all visits for RA for patients in the sample over the nine-month study period. We examined RA treatments used, and monitoring laboratory tests (i.e., complete blood count, liver function tests, or serum creatinine), acute phase reactants (i.e., erythrocyte sedimentation rate or C-reactive protein) and diagnostic imaging performed (i.e., DXA, plain radiographs, CT scans, or magnetic resonance imaging). We also examined all visits during the study period for possible medication related adverse events, such as rashes, oral ulcers, alopecia, infections requiring antibiotics, liver toxicity as manifest by abnormal liver function tests and/or abnormal liver imaging, cytopenias as manifest by complete blood counts below the lower limits of normal, renal insufficiency defined as a 50% decrease in

creatinine clearance, cancer, gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, unexplained weight loss/gain, abdominal pain or dyspepsia), and other miscellaneous side effects.

Post-hoc secondary outcomes included the percent of visits with a change in DMARD and the percentage of subjects in different disease activity categories at follow-up.

Statistical Power Considerations

The trial was powered based on the primary outcome – the estimated difference in change in TTT implementation score between the intervention and the control sites. Several assumptions underpinned our sample size calculations. First, we assumed that the control group would have no or only small change (5%) in TTT implementation score during the 9 months period compared with a change in the intervention group of approximately 20%; these assumptions were based on the improvement level observed in a similar trial using a Learning Collaborative.⁽²⁵⁾ Second, we knew that the average number of providers in each of the 11 practice sites would be four, and that there would be moderate intra-cluster correlation (ICC) among patients within a given provider and site; we assumed an ICC of approximately 0.2 based on prior work.⁽²⁶⁾ Finally, the statistically significant alpha level was set at a two-sided p-value of 0.05. Based on these assumptions, we estimated that the required number of patients per provider would be five to ensure 80% power.

Statistical Analysis

We hypothesized that adherence with TTT would improve to a greater extent in patients seen in rheumatology sites randomized to the Learning Collaborative intervention compared with wait list control patients. Thus, the primary analysis compared the mean change in the TTT implementation score over 9 months across patients in the intervention sites was compared with the mean change for the patients in the control sites after accounting for intra-site and intra-provider correlation using linear mixed models.⁽²⁷⁾ Any patient covariates that were imbalanced at the baseline visit were considered for the model, including age, gender, baseline disease activity, baseline RA drugs, and disease duration. For the secondary binary outcomes (e.g., improvement versus no improvement and complete implementation versus incomplete), we used generalized linear mixed models for binary outcomes that accounted for clustering within sites and within providers.⁽²⁸⁾ Analysis of adverse events and resource utilization was performed using Poisson regressions for resource use and adverse events as the outcome variables. Similar to the primary analyses, we adjusted for intra-site and intra-provider correlation.

RESULTS

The CONSORT diagram shows that one site dropped out after randomization but before any activities began, leaving a total of eleven participating sites (see Supplemental Figure 2). The characteristics of the 641 patients with RA included in the trial are shown in Table 1. They represent a typical RA population with a mean age of 60 years, 78% were female, and 79% demonstrated at least one positive serologic test for RA. Patient characteristics were well

balanced across treatment arms; as well, the structure, staff and insurance mix were diverse and well balanced (see Supplemental Table 1).

Outcomes

At baseline, the mean TTT implementation score was 11% in both arms. After the 9-month intervention, the TTT implementation score was 57% in the intervention arm and 25% in the control arm. The mean change was 46% in the intervention arm and 14% in control (p for difference in change = 0.004 from linear mixed model) (see Table 2). Each component of the TTT implementation score improved in the intervention arm, but not all improved to the same extent (see Table 2). The proportion of participants for whom presence of a treatment target was documented went from 0.6% at baseline to 45.6% at follow-up in the intervention arm. As well, the recording of the disease activity went from 20.0% to 89.1%; all sites used the CDAI or RAPID3. Shared decision making started out at 51.3% in the intervention group and increased to 85.9%. While there was some improvement noted over time in the wait-list control arm, the improvement in implementation of each component of TTT was not as large as in the intervention arm.

Secondary outcomes differed across treatment arms. A positive change (of any magnitude) in the TTT adherence score was noted in 83.8% (268 of 320) patients in the intervention arm sites and 36.8% (118 of 321) in the control arm sites ($p = 0.0001$). A similar trend was observed when visits were analyzed for having all components of TTT present versus less than all components (see Figure 1). At baseline, almost no patient visits in either arm were adherent with all components of TTT. At follow-up the percent of visits adherent with all four components of TTT were 25.9% in the intervention arm and 5.6% in the control arm ($p = 0.045$).

The number of orders for drug monitoring laboratory tests was similar across control (8.14 tests per patient) and intervention arms (8.10 tests per patient) ($p = 0.67$) (see Table 3). Radiology orders were also very similar between control (0.96 per patient) and intervention arms (0.77 per patient) ($p = 0.96$). Patients in the intervention arm were noted to have fewer adverse events (0.26 per patient) than those in the control arm (0.43 per patient) ($p = 0.043$) (see Table 3).

We abstracted disease activity measure information at follow-up visits from medical records when available and found that a numerically greater percentage of patients in the intervention arm were in remission – 40.5% in intervention vs 26.1% in control ($p = 0.07$). However, since the control arm was not instructed on disease activity measurement, this was only measured on 69 patients in the control arm, but 284 in the intervention arm.

DISCUSSION

Treatment for RA does not always follow the recommended TTT approach. The TRACTION Trial focused on improving implementation of TTT principles for RA using a Learning Collaborative approach to adopt new strategies and improve work-flow. While TTT is a proven strategy in the care of RA, many areas of health care require a similar team

approach for effective care. In this study, we found large benefits, despite using a relatively low intensity approach to the Learning Collaborative, with only one face to face meeting.

The success of TRACTION has potential implications beyond the care of RA. Effective management of diabetes and hypertension also requires a similar treatment approach: setting a treatment target (i.e., hemoglobin A1c or blood pressure) with patient involvement, regular measurement of progress towards the target, and modification of treatments until target is reached and maintained. While our Learning Collaborative focused on RA, it seems clear that the principles and concepts underlying this approach could be transferred to other chronic diseases. In fact, our model is consistent with the goals and strategy of the Million Hearts campaign to reduce cardiovascular disease burden across the US by targeting five areas of goal-based therapy.(29) The program we used for this Learning Collaborative used only one face to face meeting but still produced excellent results. Further evaluation of different intensity Learning Collaboratives will improve our understanding of how to best fit these improvement programs into the lives of busy health care workers.

While the TRACTION Learning Collaborative improved the use of TTT for RA, implementation remained far lower than desired and several prior studies suggest potential reasons. A survey of Australian rheumatologists found that they preferred not adjusting medications for symptoms when they were perceived to be associated with irreversible joint damage.(14) Some might argue that this is a defensible position which could avoid over-treatment. They also cited patient preferences as justification for not adjusting treatments. It may be the case that more engagement of patients regarding choosing targets and identifying best treatments would affect patient preferences.

The TRACTION trial was a pragmatic cluster randomized controlled trial, with a wait-list for the control arm. This design is often used in quality improvement, and it has associated strengths and limitations. While the trial was appropriately powered, it included only 11 rheumatology practice sites in the US. The sites were geographically diverse and represented different types of practices (academic and non-academic), however, the ability of the TRACTION Learning Collaborative to produce similar changes in other settings requires further testing. The majority of TRACTION sites were affiliated with an academic medical center and the results may not generalize across all types of practice. In addition, the intervention required approximately 20 hours per provider over 9 months, which may limit its generalizability. The primary outcome of TRACTION was a process measure and does not reflect clinical outcomes. The process measure appears valid, however, as at least seven prior trials have demonstrated improved outcomes in RA using a TTT approach.(30) We appreciate that the outcome measure for implementation of TTT was developed for this trial as no valid measures for TTT have been published. However, the four items were based on the original TTT recommendations to ensure face validity. The developer of the TTT recommendations (JSS) agreed that the four aspects of TTT that we were able to measure from chart review were essential aspects to assure content validity (i.e., the extent that a measure represents the full range of the construct). The measure had good reliability as noted by the inter-rater and intra-rater kappas > 0.9. But, it is a clear limitation that the primary outcome of the trial was not based on a previously validated measure. A minority of

subjects had disease activity measured at baseline, limiting our understanding of whether implementation of TTT significantly improved disease activity over the course of the trial.

The TRACTION trial staff reviewed medical records to avoid the potential bias of self-assessment. However, the staff was not masked to the assignment of sites to the intervention or control arms. The high intra- and inter-rater reliability suggests that the outcomes measure, assessed at two visits, was highly reproducible. A final limitation is that adverse events were collected from chart review and thus could have been biased if providers in different treatment arms differentially reported adverse events. Since providers were not aware of our hypotheses regarding adverse events, this seems unlikely. In summary, we found significant improvements in adherence to TTT principles in rheumatology practices participating in a Learning Collaborative. Future work will include dissemination activities with professional organizations to make this opportunity more widely available for other interested rheumatology practice sites. There are similar efforts with Learning Collaboratives for RA ongoing,(31) and our results support considering this approach for other chronic diseases benefitting from TTT strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Practice Sites	Team Members
Cedars Sinai (Venturapali)	Venturapali, Gaggi, Uy, Bustos, Vasquez
Loyola	Tehrani, Ostrowski, Briones, Murphy
North Shore	Grober, Malik, Woodrick, Lynn, Sun, Drevlow, Zaacks, Bilbrey, Chavez, Casey, Gan, Myers
Park Nicollet	Paisansinsup, Shousboe, Glickstein, Steele
University of Kansas	Lindsley, Schmidt, Colbert, Springer, Bhadbhade, Parker, Estephan, McMillian, Heneghan
University of Kentucky	Lohr, Hanaoka, Lightfoot, Jenkins, Baker, Bisono, Wafford, Wiard, Lenert, Howard
University of Houston	Scholz, McCray, Barnes, Tan, Homann
University of Vermont	Hynes, Bethina, Kennedy, Lau, Edwards, Libman, Farely
Univeristy of Virginia	Kimpel, Lewis, D'Souza, Potter, Carlson, Mosteanu, Khalique, Khurana, Swamy
UTMB -- Galveston	Murthy, Musty, Rudrangi, Ganti, Gonzalez, McCullum
Vanderbilt	Annapureddy, Kroop, Hayden

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Figure 1. demonstrates the baseline, follow-up and change in full adherence to treat to target in the TRACTION trial, the secondary outcome.

Table 1**Baseline Characteristics of Patients Included in TRACTION Trial**

	Control (n = 321)	Intervention (n = 320)	P-value
<i>N (%) unless noted</i>			
Age *, years, mean (SD)	59.7 (14.3)	60.2 (27.5)	0.75
BMI *, kg/m ² , mean (SD)	30.1 (7.5)	29.4 (7.5)	0.24
Female sex	250 (77.9)	253 (79.1)	0.72
RA duration *, years			0.12
2	22 (16.1)	50 (25.6)	
2–5	39 (28.5)	49 (25.1)	
6–10	30 (21.9)	47 (24.1)	
>10	46 (33.6)	49 (25.1)	
Serologic status *			0.15
Positive	193 (76.3)	216 (81.5)	
Negative	60 (23.7)	49 (18.5)	
Use of synthetic DMARDs	248 (77.3)	259 (80.9)	0.25
Use of biologic DMARDs	131 (40.8)	148 (46.3)	0.16
Comorbidity index, mean (SD)	1.33 (0.6)	1.28 (0.5)	0.24
Joint erosion			0.19
Yes	109 (53.4)	142 (59.7)	
No	95 (46.6)	96 (40.3)	
Total medications			0.16
0	0 (0)	1 (0.3)	
1–5	42 (13.1)	53 (16.6)	
6–10	104 (32.4)	117 (36.6)	
10+	175 (54.5)	149 (46.6)	

Notes:

* Some data were missing for the following variables: age, missing = 64; body mass index, missing = 52; rheumatoid arthritis duration, missing = 309; serologic status, missing = 123; and joint erosions, missing = 199.

Abbreviations: BMI, body mass index; RA, rheumatoid arthritis; DMARD, disease modifying anti-rheumatic drug.

Table 2**Implementation of Treat to Target and Components at Patient Visits in TRACTION Trial**

	Control (n = 321)			Intervention (n = 320)			P-value* for difference in change
	Baseline	Follow-up	Change	Baseline	Follow-up	Change	
Primary Outcome							
Implementation score	11.0%	24.7%	13.7%	11.1%	57.1%	46.0%	0.004
Visits with components present							
Treatment target	0%	12.5%	12.5%	0.6%	45.6%	45.0%	0.065
Disease activity measure	30.2%	52.3%	22.1%	20.0%	89.1%	69.1%	0.002
Shared decision-making [†]	24.5%	43.0%	18.5%	51.3%	85.9%	34.6%	<0.001
Treatment decision [‡]	0%	8.4%	8.4%	0.6%	27.8%	27.2%	0.064

* P-values for difference in change were calculated in linear mixed models for the primary outcome and generalized linear mixed model for binary outcomes for the components; both sets of models accounted for clustering within sites and within providers. (28)

[†] The shared decision-making criteria did not apply to all visits when no decisions were being made about changing targets or changing treatments. The number of visits when shared decision-making applied for the control group was baseline 102 and follow-up 100; for the intervention group, 115 baseline visits and 184 follow-up visits had shared decision-making.

[‡] Treatment decision based on target and disease activity measure.

Table 3**Resource Use and Adverse Events During TRACTION Trial**

	Control (n = 321)	Intervention (n = 320)	P-value *
<i>Number of tests or adverse events (mean number per patient)</i>			
Monitoring laboratory tests [†]	2614 (8.14)	2591 (8.10)	0.67
C-reactive protein or erythrocyte sedimentation rate	788 (2.45)	607 (1.90)	0.66
Plain x-ray of musculoskeletal system	308 (0.96)	247 (0.77)	0.96
Computed tomography of musculoskeletal system	6 (0.019)	12 (0.038)	0.50
Magnetic resonance imaging of musculoskeletal system	14 (0.044)	16 (0.050)	0.77
Rheumatology visits	922 (2.87)	753 (2.35)	0.36
Adverse events [‡]	138 (0.43)	83 (0.26)	0.04

Notes:

* P-values were calculated in Poisson regression for count data after accounting for clustering within sites and within providers. (28)

[†] Complete blood count and/or basic metabolic panel and/or liver function tests.[‡] Adverse events included infections (n = 14 in intervention and 34 in control), cutaneous reactions (n = 13 in intervention and 21 in control), liver test abnormalities (n = 9 in intervention and 10 in control), renal test abnormalities (n = 1 in intervention), gastrointestinal symptoms (n = 22 in intervention and 28 in control), and other miscellaneous (n = 24 in intervention and 45 in control).