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ORIGINAL ARTICLE

Effects of Locomotion Training on the Physical Functions and Quality of Life in Patients with Rheumatoid Arthritis: A Pilot Clinical Trial

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Objectives: This study investigated the effects of locomotion training on physical functions and quality of life in patients with rheumatoid arthritis (RA). **Methods:** Thirty-five patients with RA underwent locomotion training for 6 months. Health data collected from the subjects at baseline and after 6 months were the Health Assessment Questionnaire Disability Index (HAQ-DI), pain Visual Analog Scale, 10-m walking test, Timed Up-and-Go (TUG) test, single-leg standing test, Short Form-8 score with physical and mental component summaries, and 25-question Geriatric Locomotive Function Scale. The primary endpoint was a change in HAQ-DI at 6 months. **Results:** In terms of the primary outcome, the HAQ-DI significantly improved from 0.48 ± 0.69 at baseline to 0.27 ± 0.36 at 6 months (P=0.011). The significant secondary outcomes were a change in TUG test for comfortable walking from 9.8 ± 2.1 s at baseline to 8.9 ± 2.0 s at 6 months (P=0.002) and increased single-leg standing times for the right and left legs from 24.7 ± 23.5 s and 22.6 ± 22.8 s at baseline to 30.9 ± 22.1 s and 32.4 ± 24.1 s at 6 months (P=0.004, P <0.001), respectively. **Conclusions:** The findings suggest that locomotion training for 6 months may improve the HAQ-DI in patients with RA.

Key Words: locomotion training; physical function; pilot study; quality of life; rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that causes pain, swelling, stiffness, and loss of function in joints throughout the body. The disease results in progressive joint destruction and deformity, with varying degrees of deterioration in the quality of life (QOL) and limitations in the performance of daily activities and work.[1–3] Therefore, patients with RA have lower health-related QOL than healthy individuals.[4,5] We believe that physical activity is an important factor in determining the QOL of patients with RA.

The European League Against Rheumatism (EULAR) recommendations for pain management in inflammatory arthritis advise patients to exercise.[6] In patients with RA, exercises such as general exercise, aerobic exercise, and strength and resistance training improve physical function and health status.[7–11]

Locomotive syndrome (LS), sarcopenia, and frailty are known concepts of disability. The Japanese Orthopaedic Association (JOA) has proposed the term "locomotive syndrome" to describe the condition that places a person at high risk of requiring support, nursing care, and/or long-term care, secondary to the decline of organs and tissues used for movement, including bones, joints, ligaments, muscles, the spinal cord, and the peripheral nerves.[12] Sarcopenia is a

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syndrome defined as the presence of low grip strength and/or low walking speed and loss of skeletal muscle mass in older people. Frailty is the presence of unintentional weight loss, self-reported exhaustion, low physical activity, low grip strength, and low walking speed. The co-existence of LS, sarcopenia, and frailty was shown to be 2.0% in a cohort of 963 Japanese people aged 60 years or more.[13)]

The JOA recommends locomotion training to improve and sustain standing and gait functions in middle-aged and old people. To prevent LS, the recommended locomotion training consists of holding a single-leg stance with eyes open and performing squats, heel raises, and forward lunges. In previous studies, these exercises resulted in improved physical functions such as mobility, strength, balance, and gait.[14–18)] Literature reports also indicated that the prevalence of LS was higher in patients with RA than in the general population.[19–21)] We believe that the locomotion training recommended by the JOA (Locotre), unlike aerobic exercise and general resistance exercise, is low-intensity training that can be safely performed at home by RA patients. However, the effects of Locotre in patients with RA are unknown. Information about the effects of Locotre may be used to improve the physical function of patients. Therefore, the aim of the present study was to understand the effects of Locotre on the physical functions and QOL in patients with RA.

MATERIALS AND METHODS

Study Design and Patients

This study was an observational pilot study. Locotre was performed by RA patients for 6 months. The primary endpoint was the change in the Health Assessment Questionnaire Disability Index (HAQ-DI) at 6 months, whereas secondary endpoints included changes in the pain Visual Analog Scale (VAS), 10-m walking time, Timed Up-and-Go (TUG) test, single-leg standing time, the 25-question Geriatric Locomotive Function Scale (GLFS-25), and the Short Form-8 (SF-8) health survey. Inclusion criteria were fulfillment of the 1987 American College of Rheumatology (ACR) classification criteria and/or the 2010 ACR/EULAR criteria[22,23)] and, to avoid the effects of inflammation, the presence of low disease activity and/or a maximum C-reactive protein (CRP) level of 0.3 mg/dL. Exclusion criteria included already having an exercise habit, dementia, heart disease (severe valvular disease or New York Heart Association functional classification ≥II), lung disease (forced vital capacity <60% or high-resolution computed tomographic scanning findings of interstitial lung disease grade 3),[24)] severe cerebral disease, and/or joint arthroplasty.

Thirty-five patients with RA who fulfilled the inclusion criteria and provided informed consent were enrolled consecutively between December 2019 and February 2020. The following clinical data were collected: age, sex, disease duration, anti-cyclic citrullinated peptide antibody positivity, use of biological disease-modifying antirheumatic drugs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs), methotrexate use, glucocorticoid use, CRP level, and the Disease Activity Score 28 erythrocyte sedimentation rate (DAS28-ESR). The clinical data were measured by the attending physician.

This study was conducted in accordance with the principles stated in the Declaration of Helsinki, and written informed consent was obtained from all patients. The Ethics Committee for Clinical Research of Kamagaya General Hospital approved this study (approval number: TGE01199-064).

Locotre

Locotre[25)] education was provided on a one-to-one basis by a physical therapist with the assistance of a video available on a DVD. The patients were given the DVD to help them perform the exercises at home. The patients underwent Locotre for 6 months. The training records were self-reported in a rehabilitation notebook. The details of the exercises and instructions were as follows:

1. Single-leg standing with eyes open (1 min for each leg × three sets per day)

Always perform the exercise where there is something to grab onto to prevent a fall.

2. Squats (five times × three sets per day)

Ensure that the knees do not extend beyond the tips of the toes. If unable to perform squats, sit on a chair with hands on the table and repeatedly stand up and sit down.

3. Heel raises (ten times × three sets per day)

Raise heels while standing on both legs. If unstable, hold the back of a chair.

4. Forward lunges (ten times × three sets per day)

Stand with both feet on the ground with hands on hips. Slowly take a large lunge forward with one leg.

Physical Functions and QOL Assessments

The physical functions and QOL assessments were performed using HAQ-DI, the pain VAS, 10-m walking time, TUG test, single-leg standing time, GLFS-25, and SF-8 at baseline, 3 months, and 6 months. The HAQ-DI is a patient-reported measure of physical disability used as a standard assessment.[26,27)] It includes questions related to 20 activities of daily living, such as dressing, grooming, arising, eating,

walking, maintaining hygiene, reaching objects, maintaining grip, opening things, and performing daily activities. We have classified the eight subscales of HAQ-DI as follows: HAQ-DI associated with upper limb (HAQ-U)—dressing, eating, reach, and grip; and HAQ-DI associated with lower limb (HAQ-L)—arising, walking, hygiene, and activities. In the HAQ-DI, questions were scored from 0 to 3, with higher scores indicating greater disability (0: without any difficulty, 1: with some difficulty, 2: with much difficulty, and 3: unable to perform). The scores were then averaged to give an overall HAQ-DI within the range of 0–3. The times for the 10-m walking test (s/m) and TUG test (s) were twice measured at comfortable and maximum walking speeds, and the longer time was recorded. The TUG test recorded the time that the patient required to stand up from a chair, walk 3 m to cross a line marked on the floor, turn around, and walk back and sit down on the chair.[28] The single-leg standing time was measured twice for the right and left legs, respectively, and the longer time for each was recorded.[29] The GLFS-25 was designed to identify Japanese individuals with high-risk conditions who may soon require care services because of problems with locomotive organs and tissues. The GLFS-25 is a self-administered assessment of 25 items: 4 regarding pain during the previous month, 16 regarding activities of daily living during the previous month, 3 regarding social functions, and 2 regarding mental health status during the previous month. These items are scored from no impairment (0 points) to severe impairment (4 points), and the scores are added to obtain a total score (0–100).[30] The SF-8 is an alternate form of the SF-36, which is widely used to assess health-related QOL.[31] The SF-8 includes eight items: general health, physical functioning, role physical, bodily pain, vitality, social functioning, mental health, and role emotional. It also includes two summaries: the physical component summary (PCS) and the mental component summary (MCS). We used the SF-8 because it provides useful information with minimal administration time and burden on the respondent. Norm-based scoring was used for the analysis. The physical functions of the patients were evaluated by physical therapists. These physical therapists were different from those who provided coaching during the locomotion training.

Statistical Analyses

The Wilcoxon signed-rank test was used to compare the values of CRP, DAS28-ESR, HAQ-DI, pain VAS, 10-m walking test, TUG test, single-leg standing time, GLFS-25 score, and PCS and MCS in SF-8 at baseline, 3 months, and 6 months. In the subanalysis, the physical functions and QOL assessments at 6 months in the btsDMARDs group (patients treated with bDMARDs or tsDMARDs) and the non-btsDMARDs group (patients not treated with bDMARDs or tsDMARDs) were compared. A minimum sample size of 28 patients was calculated based on a power of 0.8, an α error of 0.05, and an effect size of 0.5. The result of the power analysis with n=35 was 0.88 in this study. The level of significance was set at $P < 0.025$ using the Bonferroni method to solve the problem of multiplicity. The statistical analyses were performed using the R Statistical Package software, version 3.3.2 (http://www.r-project.org/).

RESULTS

Patient demographics and clinical characteristics at baseline, at 3 months, and at 6 months are shown in **Table 1**. The values of CRP at 3 and 6 months were 0.12 ± 0.16 and 0.13 ± 0.22 mg/dL, respectively. The values of DAS28-ESR at 3 and 6 months were 2.52 ± 0.89 and 2.45 ± 0.96, respectively.

Comparison of the physical functions and QOL at baseline, 3 months, and 6 months is provided in **Table 2**. The HAQ-DIs at baseline and at 6 months were 0.48 ± 0.69 and 0.27 ± 0.36, respectively, indicating significant improvement ($P=0.011$). The HAQ-L at 6 months also showed significant improvement ($P=0.001$). The significant secondary outcome variables at 3 months were the 10-m walking test at maximum speed ($P=0.007$), the TUG test at a comfortable walking speed ($P=0.002$), and the single-leg standing time for right ($P=0.004$) and left ($P<0.001$) legs. The significant secondary outcome variables at 6 months were the TUG test at comfortable walking speed ($P=0.002$) and the single-leg standing time for right ($P=0.004$) and left ($P<0.001$) legs.

Table 3 shows the results of the univariate analysis for comparison of physical functions and QOL assessments at baseline and 6 months between the btsDMARDs group and the non-btsDMARDs group. None of the variables were significantly different between the two groups. The adherence to Locotre was 85.7% when based on a possession ratio greater than 80%.

DISCUSSION

This pilot study investigated the effects of Locotre, which is a home-exercise program consisting of low-intensity, lower limb resistance, and balance exercises, on the physical functions and QOL in patients with RA. We observed that Locotre was effective for improving the physical functions and QOL in patients with RA. However, whether or not the

Table 1. Demographics and clinical characteristics of the study population

Variable	Baseline	3 months	6 months	P value
Age, years	70.0 (8.2), 72 (65, 75)			N/A
Sex, female; n (%)	31 (88.6)			N/A
Body mass index, kg/m^2	22.6 (2.9), 22.3 (20.5, 24.2)			N/A
Disease duration, years	14.4 (11.1), 12 (7, 16.5)			N/A
Anti-CCP Ab positive; n (%)	23 (83.3)			N/A
bDMARDs or tsDMARDs use; n (%)	18 (51.4)	18 (51.4)	18 (51.4)	1.000
MTX use; n (%)	25 (71.4)	25 (71.4)	25 (71.4)	1.000
Glucocorticoid use; n (%)	6 (17.1)	6 (17.1)	6 (17.1)	1.000
Analgesic use; n (%)	16 (45.7)	15 (42.9)	15 (42.9)	1.000
CRP, mg/dL	0.14 (0.19), 0.05 (0.025, 0.19)	0.12 (0.16), 0.08 (0.025, 0.15)	0.13 (0.22), 0.04 (0.02, 0.15)	0.193
DAS28-ESR	2.62 (0.81), 2.61 (2.01, 3.04)	2.52 (0.89), 2.53 (1.84, 3.09)	2.45 (0.96), 2.50 (1.95, 3.00)	0.277

Data presented as mean (SD), median (Q1, Q3), or as number (percentage).
SD, standard deviation; Q1, 25th percentile; Q3, 75th percentile; N/A, not applicable; Anti-CCP Ab, anti-cyclic citrullinated peptide antibody; MTX, methotrexate.

Table 2. Physical functions, quality-of-life assessments, and comparison of parameters at baseline, 3 months, and 6 months

Variable	Baseline n=35	3 months n=35	6 months n=35
HAQ-DI	0.48 (0.69)	0.34 (0.43)	0.27 (0.36)*
HAQ-U	0.44 (0.9)	0.31 (0.45)	0.29 (0.43)
HAQ-L	0.53 (0.72)	0.34 (0.44)	0.25 (0.32)*
Pain VAS	23.0 (22.1)	22.0 (20.2)	16.7 (148)
10-m walking test			
Comfortable, s/m	0.82 (0.16)	0.79 (0.13)	0.81 (0.13)
Maximum, s/m	0.66 (0.13)	0.63 (0.12)*	0.64 (0.13)
TUG test			
Comfortable, s	9.8 (2.1)	8.9 (2.0)*	8.9 (2.0)*
Maximum, s	7.6 (1.8)	7.1 (1.5)	7.4 (1.5)
Single-leg standing time			
Right leg, s	24.7 (23.5)	33.1 (23.5)*	30.9 (22.1)*
Left leg, s	22.6 (22.8)	31.8 (24.3)**	32.4 (24.1)**
GLFS-25	13.1 (12.7)	11.7 (10.6)	11.8 (9.9)
SF-8			
PCS	47.7 (6.2)	47.4 (5.4)	47.9 (5.9)
MCS	51.4 (5.5)	51.0 (5.6)	50.5 (5.7)

Data presented as mean (SD).
Wilcoxon signed-rank test: *P <0.025, **P <0.001.

patient was treated with btsDMARDs did not affect the improvement of physical functions or QOL. Several previous studies have shown that in patients with RA, exercise was able to increase the physical capacity and improve physical functions without aggravating the disease activity.[32] In this study, Locotre did not affect the disease activity in patients.

Table 3. Results of univariate analysis for comparison of physical functions and quality-of-life assessments at 6 months between the btsDMARDs group and the non-btsDMARDs group: a subanalysis

	Baseline			6 months		
Variable	btsDMARDs group n=18	Non-btsDMARDs group n=17	P value	btsDMARDs group n=18	Non-btsDMARDs group n=17	P value
HAQ-DI	0.31 (0.52)	0.66 (0.82)	0.330	0.22 (0.35)	0.32 (0.37)	0.369
HAQ-U	0.28 (0.53)	0.60 (0.81)	0.261	0.22 (0.40)	0.37 (0.46)	0.314
HAQ-L	0.35 (0.54)	0.72 (0.84)	0.230	0.22 (0.33)	0.28 (0.30)	0.434
Pain VAS	24.4 (19.6)	21.6 (25.0)	0.877	18.8 (14.9)	14.6 (14.8)	0.467
10-m walking test						
Comfortable, s/m	0.79 (0.15)	0.86 (0.16)	0.245	0.77 (0.13)	0.84 (0.12)	0.120
Maximum, s/m	0.64 (0.12)	0.70 (0.13)	0.132	0.61 (0.12)	0.68 (0.13)	0.110
TUG test						
Comfortable, s	9.6 (2.0)	9.9 (2.3)	0.800	8.6 (1.9)	9.3 (2.1)	0.306
Maximum, s	7.1 (2.0)	8.0 (1.7)	0.690	7.0 (1.8)	7.8 (2.0)	0.165
Single-leg standing time						
Right leg, s	27.8 (23.4)	21.4 (23.8)	0.419	32.4 (22.5)	29.3 (22.2)	0.837
Left leg, s	27.3 (23.6)	19.6 (21.9)	0.304	34.2 (25.8)	30.5 (22.8)	0.700
GLFS-25	11.7 (12.3)	14.7 (13.3)	0.595	9.9 (10.1)	13.7 (9.5)	0.123
SF-8						
PCS	47.4 (5.1)	47.9 (7.3)	0.552	48.6 (4.2)	47.1 (7.4)	0.788
MCS	51.9 (6.4)	50.9 (4.4)	0.410	51.8 (5.3)	49.1 (6.0)	0.176

Data presented as mean (SD). Data analysis by Wilcoxon signed-rank test.

In RA, exercise programs are recommended to include moderate- to high-intensity aerobic exercises performed for 30–60 min/session, two to five times per week, along with muscle strengthening exercises with 8–12 repetitions of three sets performed two or three times per week.[7] Although Locotre is a low-intensity exercise that patients are instructed to perform daily as much as possible, it was effective in improving physical function. A comparison of older patients with RA belonging to a moderate- to high-intensity gymnasium-exercise group and those in a low-intensity home-exercise group for 20 weeks showed no significant differences in HAQ-DI, although the gymnasium-exercise group showed significant improvement in HAQ-DI when compared with baseline.[11] In another study,[33] patients who performed strengthening exercises showed significantly increased cross-sectional area of the rectus femoris after 12 weeks, although there was no change in the activity level. In the present study, the HAQ-DI had significantly decreased at 6 months. Therefore, although Locotre is a low-intensity exercise, we believe that long-term training improves HAQ-DI in patients with RA. Moreover, given that HAQ-L, not HAQ-U, improved significantly after 6 months of Locotre, we believe that Locotre reflects exercise of the lower limbs.

In this study, the single-leg standing time for the right and left legs improved at 3 and 6 months. In a previous study, Locotre for 3 months led to improved single-leg standing time in elderly Japanese people.[17] Considering these results, Locotre may effectively improve some motor function in elderly people in general as well as in patients with RA. However, whereas the 10-m walking test at maximum walking speed was significantly improved at 3 months, the improvement was not significant at 6 months. The results of the 10-m walking test at maximum speed of two patients decreased by more than 0.1 s/m from 3 months to 6 months. These patients had decrease in exercise frequency. We believe that decrease in exercise frequency may be more likely to decrease 10-m walking test result at maximum speed.

In a previous study of individuals with pre-sarcopenia/sarcopenia who underwent Locotre for 6 months, although the average GLFS-25 score of the exercise group was significantly lower than that of the control group, the change in GLFS-25 from baseline was −0.2.[34] In the current study, the change in GLFS-25 from baseline was −1.3, but this was not significant. Although the GLFS-25 scores at baseline were

different between these studies, improvement of the GLFS-25 may be difficult in elderly subjects with sarcopenia or RA despite the use of Locotre for 6 months. Moreover, a program of habitual exercise (>30 min with light sweating) in a 2-year study significantly improved the GLFS-25 scores in middle-aged and elderly men.[35] We believe that the differences in the results of the current study and those of previous reports are attributable to the GLFS-25 score at baseline, the period of exercise, and the intensity of exercise. The GLFS-25 scores of the patients in the present study were higher than those of the patients in previous reports. The results may differ if patients with mild physical dysfunction start Locotre.

In the present study, a DVD video recording was used to assist the subjects in performing Locotre. In previous studies, live instruction by physical therapists or video assistance was more effective and less expensive than handouts alone or pamphlets used for exercise program education.[36–38] Hashizume et al.[37] reported that mobility and muscle training provided by video reduced lower back pain and improved both the single-leg standing time and the 6-m walking time after 3 months in elderly patients. In the current study, the locomotion training improved the 10-m walking time (at maximum speed), improved the TUG test result (at a comfortable speed), and improved the single-leg standing times at 3 months in patients with RA. Given that the Locotre program focuses on the lower limbs, the improvements observed in this study, such as those for walking and standing, were not unexpected.

In patients with RA, maintaining a regular exercise program is commonly a challenge because of disease-specific barriers such as pain, stiffness, and fatigue. To ensure regular exercise, enhancing self-efficacy for exercise is important.[39] We believe that the intensity of Locotre and the use of video instruction may contribute to the maintenance of long-term exercise.

The present study has some limitations that should be acknowledged. First, the sample size was relatively small. Nevertheless, we believe that our study provides important insights as a pilot study. Further research needs to be conducted on larger samples with reference to our results. Second, in this study, patient symptoms other than pain were not examined. Physical exercise can improve various symptoms of patients such as fatigue, stiffness, and sleep disturbance.[40–42] Although the improvement of these symptoms may have affected physical functions, the symptoms themselves were not assessed, and the results of this study revealed only the effectiveness of exercise in patients with RA. Finally, most of our patients had low disease activity. Given that exercise has limited impact on such patients, its effects on disease activity were difficult to quantify.

In conclusion, this study showed that a 6-month program of Locotre exercise in patients with RA improved some physical functions including the HAQ-DI but did not improve QOL and GLFS-25. Therefore, Locotre may be a therapeutic option for improving some physical functions in patients with RA.

CONFLICTS OF INTEREST

T.M. received honorariums for lectures from Asahi-Kasei, Astellas, Bristol-Myers, Chugai, Daiichi Sankyo, Eli Lilly, Janssen, and Mochida. K.Y. received honorariums for lectures from AbbVie, Astellas, Ayumi, Bristol-Meyers, Eisai, Hisamitsu, Mochida, and Takeda. K.I. received honorariums for lectures from AbbVie, Astellas, Bristol-Myers, Chugai, Eisai, Eli Lilly, Janssen, Takeda, Tanabe-Mitsubishi, and UCB. The other authors report no conflicts of interest.

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