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BRIEF REPORT

Fatigue after initiating rivaroxaban for venous thromboembolism

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Abstract

Background: Rivaroxaban was the first new oral anticoagulant approved for treatment of venous thromboembolism (VTE). Clinical trials have shown that rivaroxaban is noninferior to conventional anticoagulation for VTE in efficacy and safety. Increased fatigue after the initiation of rivaroxaban has been observed in clinical practice, but data on this potential side effect are lacking.

Objective: The study aimed to evaluate development of fatigue in patients treated for VTE, comparing rivaroxaban to other anticoagulants.

Methods: Patients were prospectively recruited after a diagnosis of VTE. The Fatigue Questionnaire was used to determine the level of fatigue at baseline, at 3 weeks of treatment, and either at 1 month after the discontinuation of treatment if the treatment was discontinued after 3 months or at 6 months if treatment was continued beyond this time. Data was analyzed by a linear mixed model.

Results: A total of 126 patients were included. Mean age was 59 years; 77 (61%) were males. Fifty-seven patients (45%) were diagnosed with deep vein thrombosis, 48 (38%) with pulmonary embolism, and 21 (17%) with both. Predicted changes in fatigue scores from baseline to the last measurement were −0.007 and −2.49 for the rivaroxaban and the other-anticoagulants groups, respectively, neither of which were statistically significant. No difference was detected between rivaroxaban and the other-anticoagulants group at any time point, including subgroup analysis comparing over and under 6 months of treatment duration.

Conclusion: In this small study, our results suggest no increase in the level of fatigue after the initiation of treatment with rivaroxaban for VTE.

KEYWORDS

anticoagulants, fatigue, pulmonary embolism, rivaroxaban, thrombosis, venous thromboembolism, venous thrombosis

Essentials

- Increased fatigue has been observed in clinical practice after initiation of rivaroxaban for venous thromboembolism (VTE).
- Fatigue was assessed with the Chalder Fatigue Score in consecutive patients diagnosed with VTE.
- No significant change in fatigue was detected over time in patients treated with rivaroxaban.
- No difference in fatigue was detected between the rivaroxaban and the other-anticoagulants group.

1 | INTRODUCTION

Venous thromboembolism (VTE) comprises deep venous thrombosis (DVT) and pulmonary embolism (PE) and is treated with anticoagulation for a duration of time ranging from 3 months to indefinitely, depending on the presence or absence of provoking factors, risk of recurrence, and bleeding.[1] Until recently, warfarin was the only oral anticoagulant available.[2] In the past decade, however, 4 new direct oral anticoagulants have been introduced in clinical practice. In phase 3 studies, these agents were found equally effective and safe with regard to risk of recurrence and bleeding.[3–7] Rivaroxaban, a direct oral factor Xa inhibitor, was the first drug to be approved for the treatment of VTE, followed by apixaban, dabigatran, and edoxaban. In addition to their efficacy and safety profile, these agents also demonstrate rapid and stable anticoagulation and reduced need for monitoring. This may in large part explain why the use of these agents has rapidly increased and, in many countries, to a great extent replaced warfarin for the treatment of VTE, with rivaroxaban and apixaban now being the 2 most widely used agents.[8]

Based on clinical observations in the follow-up period as well as personal communication with other treatment providers, a number of patients treated with rivaroxaban reported severe fatigue symptoms. To date, however, no studies have investigated this possible side effect in patients with VTE treated with rivaroxaban.

Thus, the current study aimed to prospectively evaluate the course of fatigue in consecutive patients treated with anticoagulation for VTE, comparing rivaroxaban to other anticoagulants.

2 | MATERIALS AND METHODS

This trial was a substudy to the Long-Term Outcomes of Venous Thromboembolism study (the LOVE study, NCT02268630). The LOVE study is an observational single-center trial conducted at Østfold Hospital Trust aiming to prospectively determine the prevalence of recurrence, bleeding, postthrombotic syndrome and chronic thromboembolic pulmonary hypertension at 2 and 5 years after VTE, as well as changes in health-related quality of life. Consecutive patients ≥ 18 years of age with objectively verified VTE were included if written informed consent was obtained. Patients were excluded if their life expectancy was <6 months. A total of 356 patients were included in the LOVE study between June 2014 and December 2017.

Patients were included in the fatigue substudy from 2016 after a protocol amendment in response to clinical observations of severe fatigue in some patients following the initiation of rivaroxaban. We included all patients, regardless of whether they were treated with rivaroxaban or other anticoagulants for comparative purposes using the same inclusion criteria as the main study cohort. Fatigue was measured using the Fatigue Questionnaire, which was originally developed by Chalder et al.[9] The Fatigue Questionnaire consists of 11 questions divided into 2 dimensions: physical fatigue (7 items) and mental fatigue (4 items). Four response options are used (0-4), and higher scores indicate higher levels of fatigue. Combining the scores of physical and mental fatigue produces a score for total fatigue, with a maximum score of 33. The questionnaire has been translated into Norwegian and psychometrically tested for validity, reliability, sensitivity, and responsiveness in the Norwegian general population, as well as certain disease cohorts, such as inflammatory bowel disease and non-Hodgkin lymphoma.[10,11]

Fatigue scores were obtained at baseline, at 3 weeks of treatment, and either at 1 month after the discontinuation of treatment if the treatment was discontinued after 3 months or at 6 months if treatment was continued beyond this time. In other words, the last time point included 2 rivaroxaban subgroups; 1 was not on anticoagulation at the time of measurement, and 1 was still on anticoagulation after 6 months. The questionnaires were sent to the patients by mail, to be completed by the patients and returned to the hospital.

The Fatigue Questionnaire was introduced after the protocol was amended in 2016 and was therefore completed by only a subset of patients. Inclusion criteria were identical to the main study cohort. No

TABLE 1 Baseline patient characteristics

Characteristics	Rivaroxaban > 6 months (n = 59)	Rivaroxaban < 6 months (n = 28)[a]	Other anticoagulants (n = 38)
Sex, n			
Male	39	14	23
Female	20	12	15
Mean Age, y	59.6	53.1	62.9
Diagnosis, n			
DVT	27	21	9
PE	23	6	18
DVT + PE	9	1	11
Cancer	0	0	5

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.
[a]One patient on rivaroxaban <6 months was lost to follow-up.

TABLE 2 Mean scores (standard deviation) for total, physical, and mental fatigue at the 3 time points in the study population receiving rivaroxaban or other anticoagulants

Fatigue score (SD)	Rivaroxaban ≥ 6 months			Rivaroxaban < 6 months			Other anticoagulants		
	T0 n = 59	T1 n = 59	T2 n = 49	T0 n = 28	T1 n = 28	T2 n = 17	T0 n = 38	T1 n = 38	T2 n = 28
Mental fatigue	4.5 (1.4)	4.6 (1.5)	5.3 (1.8)	3.9 (1.2)	4.5 (2.1)	4.5 (1.1)	4.9 (1.5)	5.0 (1.7)	4.5 (1.0)
Physical fatigue	11.1 (3.5)	10.6 (3.1)	10.7 (3.9)	10.5 (4.4)	9.9 (3.7)	9.1 (2.6)	11.6 (4.5)	11.0 (3.9)	9.1 (3.0)
Total fatigue	15.6 (4.2)	15.3 (3.8)	16.0 (5.1)	14.5 (5.1)	14.5 (4.3)	13.7 (3.2)	16.4 (5.5)	16 (5.1)	13.6 (3.4)

Abbreviations: SD, standard deviation; T0, baseline; T1, 3 weeks; T2, 4-6 months.

formal hypothesis was planned to be tested in this study; however, a sample size of 70 patients receiving rivaroxaban and completing the Fatigue Questionnaire at 3 time points was set a priori to see if we could capture any signal of increased fatigue after rivaroxaban initiation.

Multiple measurements on the same patients are obviously correlated. This was accounted for by analyzing the data on fatigue score by a linear mixed model, using time and type of treatment (rivaroxaban or other anticoagulants) as explanatory variables and individuals as random effects. An interaction term allowed for different trends over time for the 2 treatment groups. The model was reduced by likelihood ratio tests. The linear mixed model implicitly assumes normal data. The model was checked by quantile-quantile and residual plots and gave no cause for concern. The subgroup analysis for rivaroxaban treatment duration was also analyzed by a linear mixed-effects model using treatment over 6 month versus under 6 month and time as independent variables.

3 | RESULTS AND DISCUSSION

Fatigue scores were obtained from 174 patients at baseline, 126 at 2 time points (rivaroxaban group: n = 88) and 95 at 3 time-points (rivaroxaban group: n = 67). As the aim of the study was to analyze the development of fatigue over time, only patients with at least 2 separate fatigue measurements were included in the statistical analysis, corresponding to a response rate of 72% and 55% at the second and third time points, respectively, and a total of 126 patients included in the analysis. Of these patients, 88 were treated with rivaroxaban, 18 with apixaban, 11 with enoxaparin, 7 with warfarin, and 2 with dabigatran. Of the 11 patients receiving enoxaparin, 5 had a diagnosis of cancer at the initiation of anticoagulant therapy.

Of the patients who completed the Fatigue Questionnaire at the third time point, 17 completed the questionnaire 1 month after cessation of treatment, that is, at 4 months; 49 were still being treated with rivaroxaban at 6 months; and 28 were treated with other anticoagulation, excluding 1 patient lost to follow-up.

Mean age was 59 years (standard deviation, 12.25), and 77 of the patients (61%) were male. Fifty-seven (45%) were diagnosed with DVT, 48 (38%) with PE, and 21 (17%) had both DVT and PE. Baseline patient characteristics are summarized in Table 1. Average fatigue scores are demonstrated in Table 2.

Our results suggest a constant level in mean fatigue score over time for patients treated with rivaroxaban (Figure 1), including when analyzed for subgroups of treatment duration >6 months versus <6 months. No significant difference was detected between the treatment groups at any of the 3 measuring points (Table 2), including at the third measuring time point when comparing patients being treated with rivaroxaban at 6 months to patients assessed 1 month after treatment cessation (Table 3). Predicted changes in fatigue scores from baseline to the last measurement were −0.007 and −2.49 for the rivaroxaban and the other-anticoagulants groups, respectively, which were not statistically significant (Table 3). Change for the rivaroxaban group can be read from Table 3 as the sum of the time2 and time2:riv effects. The non–rivaroxaban treatment group showed a trend toward lower levels of fatigue from the second to the third time point but without being significant (Figure 1).

Although our results found no increase in fatigue, individual patients reported an increase in the level of fatigue after the initiation of rivaroxaban, but this was also observed in patients receiving other anticoagulants. We cannot conclude whether the observed increase in fatigue in some patients is attributable to the treatment or the underlying VTE. However, Kovacs et al[12] also found no difference in fatigue score when comparing short-term warfarin use to placebo despite observations of fatigue in the clinical setting. This

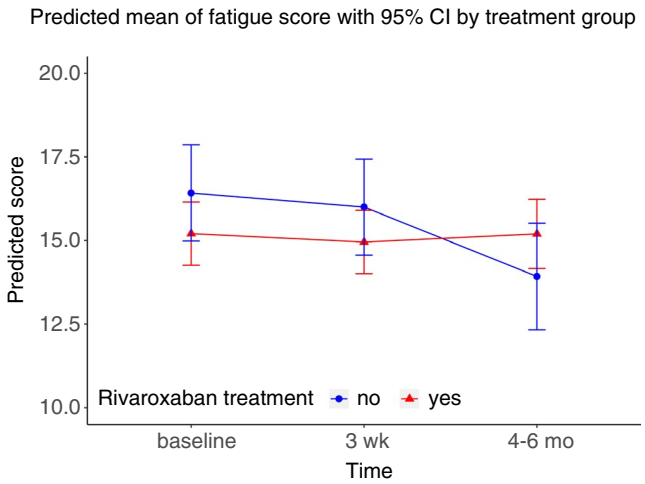

FIGURE 1 Predicted mean of fatigue score with 95% confidence interval by treatment groups

TABLE 3 Parameter estimates for mixed-effects regression model for fatigue score

Parameter	Estimate	SE	*df*	*t* value	*P* value
(Intercept)	16.42	0.73	217	22.41	<.0001
Time1	−0.42	0.71	217	−0.59	.55
Time2	2.49	0.79	217	3.14	.002
riv	−1.22	0.88	124	−1.39	.17
Time1:riv	0.17	0.85	217	0.20	.84
Time2:riv	2.49	0.95	217	2.63	.009

Note: Reference group: first measuring point (time 0) and other anticoagulants (riv = 0).

Abbreviations: *df*, degrees of freedom; SE, standard error.

may indicate that the underlying thrombosis, not the anticoagulation itself, is a factor in the fatigue development.

The Fatigue Questionnaire has not previously been validated in a Norwegian VTE population, which represents a limitation to the study. Other limitations include a small sample size and missing/incomplete measurements from ≥1 time points. The latter is a well-known shortcoming of longitudinal studies, but the linear mixed model does make optimal use of the data by using all measurements and not only the complete cases. The lack of adjustment for comorbid conditions represents another limitation to the group comparison analysis.

In conclusion, in this small study, our results suggest no increase in the level of fatigue after the initiation of treatment with rivaroxaban for VTE. However, in individual patients, an increase in fatigue score was observed, confirming occasional observations of fatigue in the clinical setting. Although occasionally practiced, it remains unknown whether switching to another oral anticoagulant could relieve these patients' fatigue.

AUTHOR CONTRIBUTION

WG, KU, and LPJ-J designed the study. TKK, EF, and CTJ were responsible for data collection. MA did the statistical analysis. RH assisted on the statistical analysis and participated in the revision of the manuscript. TKK, TLB, and WG wrote the manuscript, and EF, CTJ, and LPJ-J were responsible for critical revision.

RELATIONSHIP DISCLOSURE

WG reports grants and lecture honoraria from Novartis, Bayer, and Pfizer/BMS and lecture and advisory board honoraria from MSD, Novartis, and Amgen outside the submitted work. All other authors declare nothing to report.

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