Published in final edited form as:

J Thromb Thrombolysis. 2018 May ; 45(4): 512–515. doi:10.1007/s11239-018-1637-y.

Effectiveness and safety of oral anticoagulants in patients with sickle cell disease and venous thromboembolism: a retrospective cohort study

Megan Z. Roberts¹, G. Eric Gaskill², Julie Kanter-Washko³, T. Rogers Kyle III³, Brittany C. Jones³, Nicole M. Bohm³

¹Samford University McWhorter School of Pharmacy, 800 Lakeshore Drive, Birmingham, AL 35229, USA

²University of Utah Health Care, Salt Lake City, UT 84132, USA

³Medical University of South Carolina, Charleston, SC 29425, USA

Abstract

Patients with sickle cell disease (SCD) experience initial and recurrent venous thromboembolism (VTE) more commonly and at a younger age than the general population, and it confers a higher mortality for patients with SCD. However, limited evidence is available to guide anticoagulant use for VTE treatment in this population. The primary objective of this study is to characterize the effectiveness and safety of direct oral anticoagulants (DOAC) and warfarin for VTE treatment among patients with SCD. This single-center retrospective study includes adult patients with SCD who were diagnosed with VTE. Data was obtained from review of electronic health records for the 6 months after VTE diagnosis. Among the 22 patients treated initially with a DOAC, 6 (27%) developed recurrent VTE, none experienced major bleeding, and 3 (14%) experienced clinically relevant non-major bleeding (CRNMB). Similarly, of 15 patients initially treated with warfarin, 3 (20%) developed a recurrent VTE, 1 (7%) experienced major bleeding, and 2 (13%) experienced CRNMB. Twelve patients received more than one oral anticoagulant during the study period, most commonly due to a recurrent VTE, concern for non-adherence, or subtherapeutic INR. Overall, the incidence of VTE recurrence and bleeding events were similar between groups, but occurred at a higher rate than those found in major clinical trials of anticoagulant agents. Prescribers should continue to individualize therapeutic decision-making regarding oral anticoagulant therapy for VTE treatment for individuals with SCD based on patient-specific factors and anticipated ability to adhere to the drug regimen or required monitoring.

Megan Z. Roberts, mrober19@samford.edu.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable standards.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s11239-018-1637-y>) contains supplementary material, which is available to authorized users.

Keywords

Sickle cell; Anticoagulants; Factor Xa inhibitors; Venous thromboembolism; Warfarin

Introduction

Among patients with sickle cell disease (SCD), the frequency of venous thromboembolism (VTE) is greater and the age of onset is younger than the general population [1–4]. These patients also experience a higher rate of VTE recurrence (25–29%) [3, 5] and increased mortality compared to patients without SCD [6, 7].

The high VTE incidence and recurrence among patients with SCD is attributed to a pro-thrombotic state induced by iron overload and alterations in nearly every component of hemostasis [4]. In addition, the common use of central venous catheters (CVC) and frequent hospitalizations and surgeries contribute to the increased incidence of VTE [4].

Despite the heightened incidence, recurrence, and mortality of VTE in SCD, there is limited evidence to guide treatment. Current oral anticoagulant options within VTE treatment guidelines include warfarin or direct oral anticoagulants (DOACs): apixaban, dabigatran, edoxaban, or rivaroxaban [8]. Warfarin use is constrained by its narrow therapeutic index, unpredictable pharmacokinetics and pharmacodynamics, and food and drug interactions [9]. A single institution study of warfarin in patients with SCD and upper extremity deep vein thrombosis (UEDVT) found a low time within the therapeutic INR range (TTR) of 25% [5]. The inflammatory manifestations of SCD [10] also pose concern for alterations in warfarin pharmacokinetics based on in vitro data [11]. Thus, the potential use of DOACs for patients with SCD is appealing, theoretically avoiding the need for monitoring due to predictable pharmacokinetics [9]. Results of a murine model of SCD suggest that DOACs could be used in SCD to reduce thrombotic complications [12]. A single study has evaluated the use of DOACs among patients with SCD and VTE, demonstrating clinical failure in 2 of 7 patients [13]. The goal of this study is to evaluate the effectiveness and safety of warfarin and DOACs for VTE treatment among patients with SCD.

Materials and methods

Study population and design

This retrospective study was conducted using patient records from an academic healthcare system from July 1, 2012 to June 30, 2016. Patients were identified based ICD codes for SCD and VTE and medication orders for oral anticoagulant agents or anticoagulant reversal agents. Inclusion criteria were confirmed for patients 18 years of age or older with SCD diagnosis established by hemoglobin electrophoresis, incidence of a new, acute VTE verified by diagnostic imaging, and administration of a DOAC or warfarin in the inpatient setting or prescription from affiliated outpatient provider clinics. Individuals who were pregnant, treated for an isolated distal VTE, or receiving anticoagulant agents for indications other than VTE were excluded. Institutional Review Board approval was obtained.

Outcomes and definitions

All effectiveness and safety outcomes were evaluated for the 6 months following the index VTE event and identified by review of the electronic health record. VTE was defined as a pulmonary embolism (PE), proximal lower extremity (LEDVT) or upper extremity (UEDVT). The primary effectiveness outcome was the incidence of recurrent VTE. The secondary effectiveness outcome was hospitalization for VTE complications.

Safety outcomes coincide with clinical trials of DOACs [14–16]. The primary safety outcome was incidence of major bleeding and secondary safety outcomes included clinically relevant non-major bleeding (CRNMB) and any bleeding. Drop in hemoglobin or incidence of transfusions as indicators of bleeding were not incorporated for safety analysis, as these are not necessarily indicative of bleeding among patients with SCD [17].

Additional data points were evaluated to further characterize the population. Patients receiving more than one oral anticoagulant during the study period, had outcomes evaluated based solely on the first oral anticoagulant agent received.

Statistical analysis

Descriptive statistics were used to describe baseline characteristics. For differences between the 2 groups, Chi square tests, Fisher's exact tests, and *t* tests were used, as appropriate. A Kaplan–Meier curve and log-rank test were used to describe the time to recurrence between the two groups. *p* values < 0.05 were considered statistically significant. Analyses were performed with Microsoft Excel 2010 and SPSS for Mac®, version 24 (SPSS Inc., Cary, NC).

Results

Thirty-seven patients were included, of whom 22 received a DOAC and 15 received warfarin (Online Resource 1). Within the DOAC group, 15 patients received rivaroxaban, 6 received apixaban, and 1 received dabigatran. One patient reported Pacific Islander, while the remaining were African American. Additional baseline characteristics were similar between groups and without statistically significant differences (Online Resource 2).

All warfarin-treated patients received bridge therapy with enoxaparin (13/15, 87%) or unfractionated heparin (2/15, 13%). The median duration was 24 days (1st–3rd quartile range of 10–46) among the 11 patients for whom bridge therapy was clearly documented. The TTR determined based on standard methods [18] beginning on day 15 of therapy ranged from 0 to 39%. DOAC regimens were concordant with FDA-approved dosing in majority (16/19, 84%) of patients; 3 patients received rivaroxaban at dosages lower than FDA-approved without documented rationale for off-label dosing. None of these 3 patients experienced recurrent VTE. Warfarin and DOAC patients reported non-adherence rates of 64% (9/14) and 50% (8/16), respectively.

The primary effectiveness outcome of recurrent VTE within 6 months occurred in 24% of the study population (Online Resource 3). The rate of VTE recurrence was similar among groups and the overall mean time to recurrence was 89 days (Fig. 1). VTE recurrences

included development of a new PE (56%) and a new DVT (44%). One patient with a recurrent VTE on apixaban was transitioned to enoxaparin as recommended by VTE treatment guidelines [8]. Other patients with recurrent VTE were continued on the current anticoagulant agent (3/9, 33%) or switched to another oral anticoagulant (5/9, 56%). One patient receiving warfarin for bilateral PE treatment died after 124 days; however, cause of the patient's death was not elucidated, due to fatality occurrence outside of the study institution and limited documentation. Although not statistically significant ($p = 0.3$, Fisher's exact test), warfarin treated patients were hospitalized more frequently for VTE complications compared with DOAC treated patients (Online Resource 3 and 4). In addition, concomitant medications with SCD modifying properties or drug–drug interactions were evaluated. Among the 9 patients with recurrent VTE 4 patients were received hydroxyurea and 1 patient was received aspirin. No patient with recurrent VTE received concomitant hydroxyurea and aspirin (Online Resource 4).

Findings of safety outcomes indicate 1 patient in the warfarin group experienced major bleeding, a vitreal hemorrhage. At the time of the hemorrhage, the patient had an INR of 1.36 and aPTT of 105.3 s (goal 60–100 s) while receiving unfractionated heparin at 14 units/kg/h as bridge therapy. In each group, 13% of patients experienced CRNMB, while a greater proportion of the warfarin group experienced any bleeding (53.3 vs. 27.3%, $p = 0.169$, Fisher's exact test). Bleeding events included epistaxis, abnormal vaginal bleeding, lower extremity ulcer site bleeding, and external ear bleeding (Online Resource 3 and 4).

Discussion

DOAC use in patients with SCD reflects current national trends in oral anticoagulant use, but evaluation of use in this population is limited [13]. This study provides additional clinical data regarding use of DOACs and warfarin among patients with SCD [5, 19]. VTE recurrence was similar between DOAC and warfarin groups, but the incidence was 10-fold higher than observed in landmark studies in patients without SCD [14–16].

The cause of the high recurrence rate cannot be determined from the current data, but it is possible that in addition to the pro-thrombotic conditions associated with SCD [4] and reported non-adherence [20], pharmacokinetics or pharmacodynamics may be altered in this generally younger patient population. Benefits of dose intensification and monitoring drug levels or coagulation assays warrants further investigation, particularly given the use of DOACs in obese patients [21]. The frequency of dosing discordance is consistent with published data [22, 23]. Variation from approved doses may confer altered risk of treatment failure or adverse events.

The low TTR for patients prescribed warfarin in this study is consistent with prior studies in patients with SCD [5]. In this study, the overall rate of patient reported missed doses was 56.6%. This contrasts with the over 60% achievement of INR within the therapeutic window and 80% or greater adherence rates of over 94% of patients in clinical trials [14–16]. Patients with SCD may not adhere well to prescribed treatments; as evidenced by studies describing hydroxyurea adherence [24, 25]. Attributing low TTR to adherence versus other factors that may affect patients with SCD disproportionately such as inflammation, changes

in general activity level, wellness, diet, or drug interactions [12, 26, 27] presents a challenge to treating clinicians. Theoretically, intermittently non-adherent patients may benefit from warfarin, while those with labile INRs for other reasons may benefit from a DOAC.

Safety outcomes were similar between DOAC and warfarin groups and the incidence of major bleeding was comparable to clinical trials [14–16]. A higher incidence of CRNMB in this study population (13.5 vs. 4 to 10%) was not readily explicable.

This is the largest study assessing effectiveness and safety of oral anticoagulant use among patients with SCD, but it includes small population from a single healthcare system. Attribution of outcomes would be best assessed prospectively. In addition, nearly 25% of the study population was lost to follow-up, possibly resulting in the underreporting of outcomes. Receipt of VTE prophylaxis at time of the index VTE event was not assessed within this study, yet is reported as frequently utilized and safe [28]. Further, even if prescribing bias occurred, the high incidence of recurrence engenders a sense of urgency to better treat VTE in SCD.

In conclusion, the rate of VTE recurrence in patients with SCD was high and similar among patients treated with warfarin or a DOAC. Future assessment of treatment, including drug choice, anticoagulation intensity, and adherence are necessary to guide optimal therapy. Until more data becomes available, warfarin and DOACs appear to be equally viable options to treat VTE in patients with SCD, but dosing and adherence should be carefully assessed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The project described was supported by the National Institutes of Health (NIH) National Center for Advancing Translational Science (NCATS) through Grant Number UL1TR001450.

References

1. Bell EJ, Lutsey PL, Basu S, Cushman M, Heckbert SR, Lloyd-Jones DM, Folsom AR (2016) Lifetime risk of venous thromboembolism in two cohort studies. *Am J Med* 129:339.e19 10.1016/j.amjmed.2015.10.014
2. Stein PD, Beemath A, Meyers FA, Skaf E, Olson RE (2006) Deep venous thrombosis and pulmonary embolism in hospitalized patients with sickle cell disease. *Am J Med* 119:897.e7. 10.1016/j.amjmed.2006.08.015
3. Naik RP, Streiff MB, Haywood C Jr, Nelson JA, Lanzkron S (2013) Venous thromboembolism in adults with sickle cell disease: a serious and under-recognized complication. *Am J Med* 126:443–449. 10.1016/j.amjmed.2012.12.016 [PubMed: 23582935]
4. Naik RP, Streiff MB, Lanzkron S (2013) Sickle cell disease and venous thromboembolism: what the anticoagulation expert needs to know. *J Thromb Thrombolysis* 35:352–358. 10.1007/s11239-013-0895-y [PubMed: 23435703]
5. Stone RH, Bress AP, Nutescu EA, Shapiro NL (2016) Upper-extremity deep-vein thrombosis: a retrospective cohort evaluation of thrombotic risk factors at a university teaching hospital antithrombosis clinic. *Ann Pharmacother* 50:637–644 [PubMed: 27189014]

6. Novelli EM, Huynh C, Gladwin MT, Moore CG, Ragni MV (2012) Pulmonary embolism in sickle cell disease: a case-control study. *J Thromb Haemost* 10:760–766. 10.1111/j1538-7836.2012.04697.x [PubMed: 22417249]
7. Vichinsky EP, Neumayr LD, Earles AN et al. (2000) Causes and outcomes of the acute chest syndrome in sickle cell disease: National Acute Chest Syndrome Study Group. *N Engl J Med* 342:1855–1865. 10.1056/NEJM200006223422502 [PubMed: 10861320]
8. Kearon C, Akl EA, Ornelas J et al. (2016) Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel Report. *Chest* 149:315–352. 10.1016/j.chest.2015.11.026 [PubMed: 26867832]
9. Comerota AJ, Ramacciotti E (2016) A Comprehensive overview of direct oral anticoagulants for the management of venous thromboembolism. *Am J Med Sci* 352:92–106. 10.1016/j.amjms.2016.03.018 [PubMed: 27432042]
10. Sparkenbaugh E, Pawlinski R (2013) Interplay between coagulation and vascular inflammation in sickle cell disease. *Br J Haematol* 162:3–14. 10.1111/bjh.12336 [PubMed: 23593937]
11. Muntane-Relat J, Ourlin JC, Domergue J, Maurel P (1995) Differential effects of cytokines on the inducible expression of CYP1A1, CYP1A2, CYP3A4 in human hepatocytes in primary culture. *Hepatology* 22:1143–1153 [PubMed: 7557864]
12. Sparkenbaugh EM, Chanrathammachart P, Mickelson J et al. (2014) Differential contribution of FXa and thrombin to vascular inflammation in a mouse model of sickle cell disease. *Blood* 123:1747–1756. 10.1182/blood-2013-08-523936 [PubMed: 24449213]
13. Bhat S, Han J (2017) Outcomes of rivaroxaban use in patients with sickle cell disease. *Ann Pharmacother* 51:357–358. 10.1177/1060028016681129 [PubMed: 27881693]
14. Agnelli G, Buller HR, Cohen A et al. (2013) Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 369:799–808. 10.1056/NEJMoa1302507 [PubMed: 23808982]
15. Boursachs R, Berkowitz SD, Brenner B et al. (2010) Oral rivaroxaban for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 363:2499–2510. 10.1056/NEJMoa1007903 [PubMed: 21128814]
16. Buller HR, Prins MH, Lensin AW et al. (2012) Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 366:1287–1297. 10.1056/NEJMoa1113572 [PubMed: 22449293]
17. Novelli EM, Gladwin MT (2016) Crises in sickle cell disease. *Chest* 149:1082–1093. 10.1016/j.chest.2015.12.016 [PubMed: 26836899]
18. Rosendaal FR, Cannegieter SC, van der Meer FJ et al. (1993) A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 69:236–239 [PubMed: 8470047]
19. Wolters HJ, ten Cate H, Thomas LL, Brandjes DP, van der Ende A, van der Heiden Y, Stadius van Eps LW (1995) Low-intensity oral anticoagulation in sickle-cell disease reverses the prethrombotic state: promise for treatment. *Br J Haematol* 90:715–717 [PubMed: 7647016]
20. Chen SY, Wu N, Gulseth M, LaMori J, Bookhar BK, Boulanger L, Fields L, Schein J (2013) One-year adherence to warfarin treatment for venous thromboembolism in high-risk patients and its association with long-term risk of recurrent events. *J Manag Care Pharm* 19:291–301. 10.18553/jmcp.2013.19.4.291 [PubMed: 23627575]
21. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S (2016) Use of direct oral anticoagulants in obese patients: guidance for the SSC of the ISTH. *J Thromb Haemost* 14:1308–1313. 10.1111/jth.13323 [PubMed: 27299806]
22. Tran E, Duckett A, Fisher S, Bohm N (2017) Appropriateness of direct oral anticoagulant dosing for venous thromboembolism treatment. *J Thromb Thrombolysis* 43:505–513 [PubMed: 28271315]
23. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA (2017) Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. *J Am Coll Cardiol* 69:2779–2790. 10.1016/j.jacc.2017.03.600 [PubMed: 28595692]
24. Candrilli SD, O'Brien SH, Ware RE, Nahata MC, Seiber EE, Balkrishnan R (2011) Hydroxyurea adherence and associated outcomes among Medicaid enrollees with sickle cell disease. *Am J Hematol* 86:273–277. 10.1002/ajh.21968 [PubMed: 21328441]

25. Ritho J, Liu H, Hartzema AG, Lottenberg R (2011) Hydroxyurea use in patients with sickle cell disease in a Medicaid population. *Am J Hematol* 86:888–890. 10.1002/ajh.22134 [PubMed: 21922530]
26. Rouleau-Mailloux E, Shahabi P, Dumas S et al. (2016) Impact of regular activity on weekly warfarin dose requirement. *J Thromb Thrombolysis* 41:328–335. 10.1007/s11239-015-1248-9 [PubMed: 26238769]
27. Ansell J, Hirsh J, Hylek E, et al (2008) Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 133:160–198. 10.1378/chest.08-0670
28. Kelley D, Jones LT, Wu J, Bohm N (2017) Evaluating the safety and effectiveness of venous thromboembolism prophylaxis in patients with sickle cell disease. *J Thromb Thrombolysis* 43:463–468. 10.1007/s11239-016-1463-z [PubMed: 27943026]

Fig. 1.
Time to venous thromboembolism recurrence