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CASE REPORT

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Sustained resolution of anticoagulation related iron deficiency anemia with the use of apixaban

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[Correction added on 30 December 2019, after first online publication: The honoraria Dr. Alghamry received were deleted from the funding information and moved under the conflict of interest section in this current version.]

Abstract

Successful resolution of iron deficiency anemia in the context of anticoagulation with rivaroxaban was seen when apixaban is used alternatively. Prospective cohort studies utilizing similar or different approaches are required.

KEYWORDS

anticoagulation, apixaban, atrial fibrillation, iron deficiency anemia, rivaroxaban

1 | INTRODUCTION

Apixaban is the only nonvitamin K antagonist oral anticoagulant available in Australia without increased gastrointestinal tract bleeding compared to warfarin when used in nonvalvular atrial fibrillation. We present a series of iron deficiency anemia cases where switching to apixaban was the cornerstone of management and demonstrated sustained resolution of anemia.

Nonvitamin K antagonist oral anticoagulants (NOACs), including direct thrombin and factor Xa inhibitors, have demonstrated noninferiority to warfarin in the prevention of stroke and systemic embolism in nonvalvular atrial fibrillation (NVAF) and the treatment of venous thromboembolism (VTE).[1-7] In comparison with conventional anticoagulation, NOACs are associated with fewer drug interactions and obviate the need for laboratory monitoring. Furthermore, they are associated with lower mortality and morbidity from major bleeding events. However, their use is correlated with a significant increase in gastrointestinal tract (GIT) bleeding risk when compared to warfarin.[8]

Gastrointestinal tract bleeding represents one third of the major bleeding complications attributed to anticoagulation, and the increased risk is more common with rivaroxaban and dabigatran when compared to warfarin.[9] Apixaban has the most favorable GIT bleeding risk profile and is recently recommended as the NOAC of choice in high-risk GIT bleeding patients by the Australian atrial fibrillation management guidelines.[10] Iron

deficiency anemia (IDA) in developed countries is usually related to overt or covert GIT blood loss.[11] There is limited research investigating the association between the use of NOACs and IDA in the absence of major GIT bleeding. Uncertainty regarding anticoagulation management persists in these patients when endoscopic assessment reveals no reversible pathology.

We present a case series of five patients with symptomatic IDA while anticoagulated with successful resolution of IDA following institution of apixaban along with the other standard treatment of IDA (Table 1). Patients included in this case series were consecutively admitted with IDA under the care of the last author in a single center. They were subsequently followed up in the outpatient setting.

The Prince Charles Hospital Human Research Ethics Committee issued a waiver for full ethics review in compliance with National Health and Medical Research Council guidelines (Project ID 50462).

2 | CASES

The first patient was an 84-year-old women admitted with symptomatic IDA without overt blood loss. She was commenced on rivaroxaban at the time of diagnosis of NVAF, 6 months prior to this presentation. Relevant medical history included gastroesophageal reflux disease (GERD), hypertension, moderate chronic obstructive pulmonary disease, and moderate aortic stenosis. Aside from standard dose proton-pump inhibitor (PPI) therapy, she was not on any other medications that would alter bleeding risk. Iron was replaced intravenously, and rivaroxaban was replaced by apixaban. Outpatient combined esophagogastroduodenoscopy (EGD) and colonoscopy revealed two polyps measuring 5-7 mm with no other cause of blood loss. On follow-up, she was asymptomatic with normal serum hemoglobin (Hb) and ferritin levels.

The second patient was a 69-year-old man admitted with symptomatic IDA and melena, 2 weeks after commencement of rivaroxaban following the diagnosis of NVAF. Relevant medical history included tissue aortic valve replacement, hypertension and peripheral vascular disease. No other medications that could alter bleeding risk were noted. Inpatient pan-endoscopy revealed gastritis, diverticulosis and five polyps measuring 4-6 mm but no obvious macroscopic source of blood loss. He was managed with blood and iron replacement, and rivaroxaban was switched to apixaban while an inpatient. Proton-pump inhibitor therapy was commenced on discharge. No further overt blood loss was reported on subsequent follow-up.

The third patient was an 85-year-old woman admitted with symptomatic IDA while on rivaroxaban for NVAF in addition to aspirin for known coronary artery disease. No other medications that could alter bleeding risk were noted.

TABLE 1 Summary table showing initial hemoglobin (g/L), ferritin (mg/L), timing of endoscopy including findings, and gastroprotective therapy status of nine patients presenting with iron deficiency anemia and ongoing indication for anticoagulation with subsequent results on follow-up

	Index admission						Initial outpatient follow-up			Subsequent outpatient follow-up		
Patient	NOAC	Gastroprotective therapy (Admission/ Discharge)	Hb g/L	Ferritin mg/L	HAS-BLED score	Endoscopy timing from index admission (months)-findings	Months	Hb g/L	Ferritin mg/L	Months	Hb g/L	Ferritin mg/L
1	Rivaroxaban	Yes/Yes	97	11	2	3 (m) - 2 TAs	6	141	608	24	119	NA
2	Rivaroxaban	No/Yes	58	14	3	0 (m) - Gastritis, 5 HPs	5	129	142	20	129	142
3	Rivaroxaban	No/No	77	25	2	3 (m) - Gastritis, 12 TAs & 1 TVA	6	122	45	12	128	NA
4	Rivaroxaban	Yes/Yes	98	25	2	0 (m) - 1 angioectasia, 1 SSA	3	121	189	12	128	36
5	Rivaroxaban	Yes/Yes	86	31	2	2 (m) - 5 TA & 1 HP	6	122	120	24	108	151

Note: All patients were treated with intravenous iron replacement therapy and replacing rivaroxaban with apixaban at the index admission. Reference ranges: Hemoglobin 120-160 g/L; ferritin 30-370 μg/L.

Abbreviations: Hb, Hemoglobin; HP, Hyperplastic Polyp; NA, Not Available; NOAC, Nonvitamin K antagonist oral anticoagulants; SSA, Sessile Serrated Adenoma; TA, Tubular Adenoma; TVA, Tubulovillous Adenoma.

Following iron replacement and cessation of aspirin, given no recent coronary events in the last 12 months, outpatient EGD and colonoscopy were performed. Findings included gastritis with erosions, diverticulosis, one nonbleeding colonic angioectasia, and 13 polyps measuring 3-10 mm, which were removed. Iron deficiency anemia recurred on Rivaroxaban as single antithrombotic therapy 6 month later and iron was again replaced. She was changed to Apixaban, and IDA resolved on subsequent follow-up.

The fourth patient was an 87-year-old man who presented with melena. He had paroxysmal NVAF, for which he was on rivaroxaban for 1 year. Relevant medical history included GERD and hypertension. He was taking standard dose PPI on an as-required basis, but no other medication that would increase bleeding risk. Admission laboratory workup showed IDA. Inpatient EGD revealed one small nonbleeding angiectasia, and colonoscopy showed one polyp measuring 1 cm and diverticulosis, without obvious source of blood loss identified. Apixaban was commenced in place of rivaroxaban, and iron was replaced intravenously. He continued to have sustained resolution of IDA on follow-up.

The last patient was an 83-year-old man admitted with symptomatic IDA. He had NVAF for which he was commenced on rivaroxaban, as an alternative to warfarin, 5 months prior to admission. Additional therapy with Aspirin was used for symptomatic severe coronary artery disease. No other medications known to cause bleeding were noted, and the patient was not on PPI therapy. Other medical history included hairy cell leukemia and chronic kidney impairment. Rivaroxaban was replaced with apixaban, and iron stores were replenished intravenously. Outpatient EGD and colonoscopy revealed six polyps measuring 2-5 mm without any other source of blood loss. On follow-up, serum Hb and ferritin levels were normalized.

3 | DISCUSSION

Nonvitamin K antagonist oral anticoagulants have gained popularity as an alternative to warfarin in the management of thromboembolism prevention in NVAF and VTE over the last 10 years. Their use is likely to increase with the growing evidence of benefit in the prevention of atherothrombosis.[12,13] As a result, certain clinically relevant nonmajor bleeding events, including IDA, impose a management challenge for physicians in the absence of head-to-head comparisons between individual NOACs. Due to the once daily dosing and the order of approval for NVAF and VTE management, rivaroxaban is used frequently by Australian prescribers. This case series demonstrates successful resolution of IDA in the context of anticoagulation with rivaroxaban, when apixaban is used alternatively. Five consecutive patients presented with IDA while on rivaroxaban and received standard IDA management including blood transfusion when indicated and iron replacement intravenously. The use of apixaban in place of rivaroxaban was linked to sustained resolution of IDA for up to 24 months, reflecting resolution or reduction in GIT blood loss.

Iron deficiency anemia as a complication of NOACs use is poorly studied. Rivaroxaban and dabigatran use in NVAF patients was associated with nearly 50% increased risk of GIT bleeding compared with warfarin.[1,2] Conversely, apixaban had similar GIT bleeding risk to warfarin.[3] The increase in upper GIT bleeding risk with rivaroxaban and dabigatran compared with apixaban was also recently demonstrated in a large population based study of US Medicare beneficiaries.[14] The topical anticoagulant effect of NOACs is proposed to be the mechanism of increased GIT bleeding risk compared with warfarin. The direct thrombin inhibitor dabigatran is associated with lower GIT bleeding, a finding attributed to incomplete absorption and increasing concentrations in the lower GIT tract, in addition to the direct caustic effect of its tartaric acid content on the upper GIT mucosa.[15] This effect was also seen when dabigatran was used in a recent randomised controlled trial for an alternative indication.[13] Although rivaroxaban and apixaban have similar mechanisms of action as factor Xa inhibitors, higher peak levels with once daily dosing is hypothesized to be the reason for the GIT bleeding difference between both agents in the AF population.[15] Notably, increased risk of GIT bleeding persisted with twice daily low-dose rivaroxaban use in the prevention of atherothrombosis along with aspirin.[12] A similar safety profile of apixaban for clinically relevant nonmajor bleeding was demonstrated in the pivotal trials of NOAC use against conventional anticoagulation in acute VTE treatment and when therapy is extended in high-risk patients compared with placebo.[4-7,16,17] That was similarly evident on large retrospective population-based cohort analysis recently when apixaban was compared to rivaroxaban in acute VTE management.[18] These findings were incorporated in The European Heart Rhythm Association management guidelines which recommend an alternative NOAC, other than dabigatran or rivaroxaban, for NVAF patients above 75 years of age who had a major GIT bleeding event.[19] Additionally, The Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation suggested using different doses or agents other than high-dose dabigatran or rivaroxaban in patients with prior GIT bleeding.[10] The American College of Chest Physician guidelines refer to the indirect comparisons between NOACs in VTE management, favoring apixaban due to the lower risk of bleeding.[20]

Standard treatment for IDA includes blood transfusion and iron replacement either orally, as first-line therapy, or intravenously for more profound IDA or in elderly patients. All patients included in our case series were treated with intravenous iron to replace deficits. Recent RCT data show that intravenous ferric carboxymaltose used to treat IDA produced a sustained increase in hemoglobin starting at day seven and

peaking at day 35.[21] Similar response was noted when intravenous iron replacement was utilized in chronic kidney disease patients with IDA.[22] Our case series had variable longitudinal follow-up, from 2-24 months, following the hospital presentation in which intravenous ferric carboxymaltose was utilized to replenish iron stores. Anticoagulation with apixaban was resumed in all cases, with significant improvement in hemoglobin levels on follow-up, which argues against the continuation of occult blood loss.

Most of the reported cases had polyps removed during outpatient colonoscopy, which may in part explain the sustained response to changing their anticoagulant, but the initial response prior to endoscopic evaluation is more reflective of lower volume or no blood loss related to the change of anticoagulant. In a significant proportion of patients, IDA remains occult despite endoscopic investigation.[23] This raises the possibility of alternative causes such as anticoagulation choice. Furthermore, in our patient cohort, no polyps >10 mm were resected on colonoscopy. Polyps measuring <10 mm are typically not the sole cause of IDA.[24]

Gastroprotective therapy was commenced, if not previously utilized, in all patients in our case series based on the current available guidelines.[25] The effect of proton-pump inhibitor therapy on reducing GIT bleeding risk with rivaroxaban and dabigatran is unknown and remains a subject of ongoing randomised control trials.[26,27] Patients 1, 4, and 5 were on established gastroprotective regimens for alternative reasons prior to the GIT bleeding event, and this remained unchanged following IDA management. Patient 3 did not receive gastroprotective therapy at her choice and experienced resolution of IDA despite this. It is unlikely that gastroprotective therapy would have confounded the bleeding risk in these patients. Apart from the change of antithrombotic therapy, and the addition of proton-pump inhibitors when absent, there was no other medications intervention that would confound our results. Nonsteroidal anti-inflammatory drugs were not used by any of the patients in this case series prior to or after the index hospitalization. Baseline 1-year risk of major bleeding was low in this cohort, ranging between 4.1% and 5.8% based on HAS-BLED score.[28]

This case series has several limitations. As a case series, it is not powered to assess for association between altering anticoagulation and the resolution of iron deficiency. This case series serves to highlight the possibility that specific NOACs may influence bleeding risk in IDA and generate further hypothesis testing in large-scale trials. In several cases, there may be alternative pathology such as gastritis and polyp-associated bleeding that may account for the resolution of occult bleeding. Treatment of these with polypectomy and gastroprotective therapy may have contributed to the resolution of IDA. The follow-up period is variable among patients and longer-term follow-up might reveal recurrence of IDA on Apixaban. However, in the majority of cases, Rivaroxaban was commenced few months prior to developing symptomatic anemia and patients were followed up for a longer duration of time while on Apixaban with no recurrence which implies less occult blood loss if any with Apixaban. Further studies can extend the follow-up period to assess for sustained resolution of iron deficiency, which would signify that resolution of IDA is not solely related to standard IDA treatment but also switching of NOACs.

We conducted a literature search looking for management approach for similar patients that yielded no results. Head-to-head comparisons between NOACs are currently taking place in approved clinical settings to compare efficacy and safety (ClinicalTrials.gov NCT03266783 and ClinicalTrials.gov NCT02829957), and the last author based his management of these patients on the available data from RCTs in the absence of any guideline recommendations at the time. Eliminating the cause of covert blood loss in these patients is challenging, and cessation of anticoagulation when patients develop GIT bleeding is associated with poor outcome.[29] Prospective cohort studies including similar patients utilizing similar or different approaches are required to provide evidence-based answers for the commonly encountered nonmajor bleeding complications of NOACs use.

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CONFLICT OF INTEREST

Dr Alaa Alghamry received honoraria and speaking fees from Bristol-Myers Squibb (BMS) and Pfizer and travel fees from Boehringer Ingelheim.

AUTHOR CONTRIBUTIONS

AC: involved in data collection, data analysis, and drafting of the article. AB: involved in drafting of the article. SKDME: involved in drafting of the article. AA: involved in drafting of the article, supervision of the project, and overall specialist for the patient cohort.

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