

## **Successful treatment of warfarin-induced skin necrosis using oral rivaroxaban: a case report**

### **Point by point responses to reviewers' comments**

#### **Comment for the author:**

Reviewer #1: This is an interesting case report. I have some suggestions to improve the clarity of the presentation.

1. The authors conclude that necrosis was caused by warfarin: they should specify which algorithm was used for causality assessment. The Naranjo algorithm? I only suggest the Naranjo algorithm. In any case, it is essential that the authors clarify the method for causality assessment they selected and discuss its limitations.

2. Figure 3 reports only some of the parameters of interest. I think that it should be revised including also the other coagulation tests, the clinical manifestations and the time of warfarin administration.

3. The authors state in abstract, discussion and conclusions that “Direct administration of oral anticoagulants instead of warfarin is important in patients with decreased activity of protein S and C.” They probably mean “administration of direct oral anticoagulants instead of warfarin is important in patients with decreased activity of protein S and C.” Please check.

4. The figures, at least in the version that was made available to me, were of low resolution/quality and could be improved. Figure legends should be clear with no need to look for explanations in the text.

**Response:** We are sincerely grateful for your helpful comments. Please find responses to all the points you raised below.

**Response to comment 1.** Thank you once again. As requested, we have shown our assessment

using the Naranjo algorithm in the manuscript:

- Page 5, line 104-106

Based on the Naranjo algorithm, we diagnosed the patient with warfarin-induced skin necrosis.

Question	Yes	No	Do not Know	Score
1. Are there previous conclusive reports on this reaction?	<u>+1</u>	0	0	1
2. Did the adverse event appear after the suspected drug was administered?	<u>+2</u>	-1	0	2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	<u>+1</u>	0	0	1
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	<u>0</u>	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	<u>+2</u>	0	2
6. Did the reaction reappear when a placebo was given?	-1	+1	<u>0</u>	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	<u>0</u>	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	<u>0</u>	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	<u>0</u>	0	0
10. Was the adverse event confirmed by any objective evidence?	<u>+1</u>	0	0	1
Total score:				<b>7</b>

**Response to comment 2.** Thank you for your advice. As requested, we have added a table on other coagulation tests and warfarin administration period. The activities of protein S and C over time are shown in Figure 3:

“Figure 3 Clinical course. The course of treatment with prednisolone and anticoagulants as well as the activities of proteins C and S are shown.”

**Response to comment 3.** Thank you for pointing this out. As you recommended, we have changed the conclusions as follows:

- Page 2, line 44-45

## Abstract

**Conclusion:** “Direct administration of oral anticoagulants instead of warfarin is important in

patients with decreased activity of protein S and C” has been changed to

“Administration of direct oral anticoagulants (DOACs) instead of warfarin is important in patients with decreased protein S and C activity.”

- Page 2, line 49-50

**Core tip:** “Direct administration of oral anticoagulants instead of warfarin is important in patients with decreased activity of protein S and C.” has also been changed to

“Administration of DOACs instead of warfarin is important in patients with decreased protein S and C activity.”

- Page 7, line 171-173

### **Conclusion**

“It is important to directly administer oral anticoagulants instead of warfarin in patients with decreased activities of proteins S and C, which are vitamin K-dependent coagulation inhibitors.”  
has been changed to

“It is important to administer DOACs instead of warfarin in patients with decreased activities of protein S and C, which are vitamin K-dependent coagulation inhibitors.”

**Response to comment 4.** Thank you for your advice. The figures we submitted had good resolution/quality except Figure 2. Therefore, we have improved the resolution/quality of Figure 2 alone.

Reviewer #2: To: Editorial Board World Journal of Clinical Cases Title: “Successful treatment of warfarin-induced skin necrosis using oral rivaroxaban: a case report” Dear Editor, I read this manuscript and I think that the paper is good and well written.

**Response:** Our deepest appreciation to you for your favorable review of our case report.