

Rising Like the Phoenix?

Edward F. Plow, Mitali Das

Depending on one’s perspective, αIIbβ3 antagonists can be viewed as a great success story or as an exasperating disappointment.1 Certainly, millions of patients have been treated with the 3 Food and Drug Administration–approved αIIbβ3 antagonists, abciximab, eptifibatide, tirofiban; based on their reduction in mortality in clinical trials, one can calculate that many lives have been saved by these drugs2 and they continue to be administered to prevent thrombotic events, primarily in the setting of percutaneous coronary interventions.3 However, the vision that αIIbβ3 antagonists would be broadly administered as safe, orally active agents to patients at risk for acute coronary syndromes, and other cardiovascular diseases not only failed to materialize but also were abandoned as being unsafe.4–6 Indeed, the perceived side effects of existing αIIbβ3 antagonists, bleeding,6,7 and thrombocytopenia,8–10 in combination with the emergence of alternative and inexpensive antiplatelet and antithrombotic drugs have led to waning use of αIIbβ3 antagonists during the past decade. Thus, the story of αIIbβ3 antagonists seems to be heading toward its closing chapter. To rewrite or extend the ending of this story would require development of a new class of αIIbβ3 antagonists, one with a distinct mechanism of action that would distinguish it from the existing αIIbβ3 antagonists and their associated complications, bleeding, and thrombocytopenia, and, above all, be targeted to a new and broader therapeutic indication. The article by Li et al11 appearing in this issue of ATVB describes the properties and early preclinical testing of RUC-4 as a new αIIbβ3 antagonist.

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RUC-4 (mol wt=386) is closely related to its predecessors RUC-110,12 and RUC-2,10 which were identified through high throughput screens for small molecule inhibitors of fibrinogen binding to αIIbβ3. Like RUC-2, RUC-4 is a potent inhibitor of platelet aggregation; it is specific for αIIbβ3 and does not react with αVβ3. The solubility properties of RUC-4 in physiologically compatible solvents are superior to that of RUC-2. Both compounds work by competing with Mg2+ bound to the metal ion-dependent adhesion site in the integrin β1 domain for a key coordinating site in the β3 subunit (Figure). This displacement locks the receptor in a resting state so that it cannot bind ligand with high affinity and does not undergo the conformational changes associated with ligand binding. Hence, αIIbβ3 does not become activated on binding of RUC-4 and does not express neoepitopes induced by ligand binding13 that may become the targets for naturally occurring antibodies that may lead to the thrombocytopenia observed in some patients treated with αIIbβ3 antagonists.9,14–17 The article presents detailed molecular dynamic simulations to explain and compare the binding mechanisms of RUC-4 and RUC-2 to αIIbβ3 at a structural level.

The remainder of the article deals with an in vivo analysis of RUC-4 in comparison with RUC-2. Because neither RUC-4 nor RUC-2 react with mouse αIIbβ3, mice developed by Blue et al,12 which express human αIIb complexed to murine β3, were used as an initial test of the antiplatelet activity of the 2 agents in vivo. Doses of RUC-2 administered by intraperitoneal injection were found that completely inhibited platelet aggregation induced by high-dose ADP within 15 minutes of injection with a return toward normalization within 45 minutes to 4 hours. Even lower doses of RUC-4, administered by intramuscular injection, also led to the complete inhibition of platelet aggregation within 5 minutes with partial return of aggregation by 4 hours. Indeed, the plasma absorption of RUC-4 through the intramuscular route was more rapid than that of RUC-2 through the intraperitoneal route. With these encouraging results, RUC-4 was moved into test into cynomolgus monkeys. The animals were given intramuscular injections of 4, 2, and 1 mg/kg of RUC-4. The extent and duration of inhibition of platelet aggregation ranged from partial to complete inhibition of platelet aggregation within 15 minutes and paralleled the dose of administered RUC-4 as did the recovery of normal platelet function. None of the animals developed thrombocytopenia, major bleeds, or other overt health problems. In the final set of analyses, the authors returned to murine models and examined the effects of RUC-2 and RUC-4 in 2 models of thrombosis. In a ferric chloride carotid injury model and in a von Willebrand factor mutant mouse model, RUC-4 protected the mouse against the development of thrombosis by intramuscular administration in the former model and intravenous injection in the latter model.

The study presented by Li et al11 identifies RUC-4 as having a favorable preclinical safety and efficacy profile and properties clearly justifying further exploration. Particularly intriguing is the route of its administration, intramuscular, and the rapidity with which full inhibition of platelet aggregation, as rapidly as 15 minutes in subhuman primates, can be achieved. These characteristics open the possibility that a drug with the profile of RUC-4 could be administered by emergency medical personnel to patients with myocardial infarctions where rapid intervention is not only life-saving but also affects subsequent complications.18 The currently Food and Drug Administration–approved αIIbβ3 antagonists requiring intravenous injection and prolonged administration are not amenable to fulfilling this role. Obviously, the present study is only

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Arterioscler Thromb Vasc Biol is available at http://atvb.ahajournals.org
DOI: 10.1161/ATVBAHA.114.304486
Figure. Mechanism of action of RUC-4. A, Ligands bind near metal ion-dependent adhesion site (MIDAS) in the β integrin subunit leading to the activation of resting integrins. B, Unlike conventional αIIbβ3 integrin antagonists, RUC-4 displaces Mg2+ to bind at MIDAS. Because no conformational change ensues, integrins cannot bind ligands and thus remain inhibited.

the initial step in a long road to the development of RUC-4 or its derivatives as a therapeutic drug. Even at the preclinical level, it remains to be shown that the drug does not cause clinically significant bleeds or does not lead to thrombotic episodes because the drug dissipates or has other adverse effects. Moreover, the design of appropriate clinical trials and the cost of such trials represent major hurdles to the drug development in the cardiovascular arena. Nevertheless, an important step has been come to realization—the possibility of a new αIIbβ3 antagonist may have risen.

Acknowledgments

We thank D. Schumick for his assistance in the development of the figure. This work was supported by National Institutes of Health grant P01 HL073311.

Disclosures

None.

References


Key Words: αIIbβ3 • αIIbβ3 antagonist • platelet • platelet aggregation • thrombosis
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Arterioscler Thromb Vasc Biol. 2014;34:2182-2183
doi: 10.1161/ATVBAHA.114.304486
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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