Perspectives

Ticagrelor: A promising role in preventing multi-organ failure among patients with sepsis due to resistant gram-positive cocci

Shio-Shin Jeana,b, Shun-Chung Hsuehc, Juey-Jen Hwangd,e, Po-Ren Hsuehf,g,*

a Department of Emergency, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
b Department of Emergency Medicine, Department of Emergency and Critical Care Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan
c Department of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
d Cardiovascular Center, National Taiwan University Hospital Yunlin Branch, Yunlin County, Taiwan
e Cardiovascular Division, Department of Internal Medicine, National Taiwan University College of Medicine and Hospital, Taipei, Taiwan
f Department of Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan
g Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

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Despite recent advances in optimal antibiotic choice and intensive care support, substantial case-fatality rates are frequently encountered among patients with severe sepsis.1–6 Infections and septicemia — with a complex dysregulated mechanism that is as yet poorly understood — are usually associated with activation of platelets, a subsequent platelet-leukocyte heterotypic aggregation,
ultimately causing multi-organ failure.\textsuperscript{2,6} Of particular note is the receptor P2Y\textsubscript{12} on platelets, which was shown to play a pivotal role in amplifying the release of pro-inflammatory chemokines from the granules within platelets, perpetuating the inflammatory response related to tumor necrosis factor-\(\alpha\) and interleukin-6, and causing platelet-mediated inflammation.\textsuperscript{2,7,8} By contrast, adenosine has an inhibitory effect on responses of platelets as well as broad effects on some pathways involved in innate immunity. Consequently, adenosine was considered to exert a protective effect against pulmonary injury in murine experiment models.\textsuperscript{9} Based on the aforementioned theories, as seen in one retrospective investigation evaluating the incidence and severity of community-acquired pneumonia (CAP) among heterogeneous CAP patients,\textsuperscript{10} the anti-platelet agent characteristic of antagonizing the function of the P2Y\textsubscript{12} receptor (while assisting the retention of adenosine within cells) favorably prevents sepsis-related organ dysfunction and reduces case-fatality rates.

Ticagrelor, an effective agent that reversibly inhibits P2Y\textsubscript{12} receptor and adenosine transport ENT1 (type 1 equilibrative nucleoside transporter), was approved in 2011 for the prevention of severe cardiovascular events among patients with significant coronary ischemia or stroke.\textsuperscript{2,11} With a single ticagrelor dose ranging from 45 to 90 mg, a dose-proportional increased inhibition of platelet aggregation was demonstrated.\textsuperscript{1} Compared with the other P2Y\textsubscript{12} receptor antagonist clopidogrel (irreversibly and non-competitively binds to the P2Y\textsubscript{12} receptor, but has no known effect on adenosine metabolism), ticagrelor showed significantly greater efficacy in inhibiting platelet aggregation.\textsuperscript{1} Unsurprisingly, it also showed greater clinical efficacy in reducing rates of mortality due to vascular causes (myocardial infarction, cerebrovascular accident, etc.), without significantly increasing the rates of overall major bleeding events (NCT00391872).\textsuperscript{11}

Apart from reports on the prominent anti-platelet effect of ticagrelor, a post hoc analysis in the PLATO (Platelet Inhibition and Patient Outcomes) trial demonstrated reduced rates of mortality-owing to events of pneumonia or worsening pulmonary function-in patients who received ticagrelor therapy when compared to those in patients who received clopidogrel.\textsuperscript{1} In addition, with respect to the in vitro efficacy of ticagrelor against bacteria, Lancellotti et al. observed that ticagrelor and its major metabolites (M5 AR-C133913, M7, M8 AR-C124910) possessed in vitro efficacy of ticagrelor against bacteria, Lancellotti et al. demonstrated that for Asian patients, the maximal concentration in serum on day 1 and day 7 after 90 mg ticagrelor administration twice daily (following 90 mg administration on day 1) was only 0.82 \(\mu g/mL\) and 1.27 \(\mu g/mL\), respectively.\textsuperscript{12} Hiasa et al. also demonstrated that for Asian patients, the maximal concentration in serum on day 1 and day 28, after 90 mg ticagrelor administration twice daily for stable coronary arterial disease, was only 0.61 \(\mu g/mL\) and 0.93 \(\mu g/mL\), respectively, in Japanese patients (\(n = 33\)); and 0.76 \(\mu g/mL\) and 1.38 \(\mu g/mL\), respectively, in non-Japanese patients (\(n = 7\)).\textsuperscript{13} To address the great discrepancy between MBC and low serum concentration in patients, Lancellotti et al. proposed that the antibacterial activity of ticagrelor at infection sites may still be achieved through local, possibly platelet-driven, drug accumulation.\textsuperscript{12}

Although ticagrelor is possibly in vitro active against drug-resistant GPC, as also reported by Lancellotti et al., it was in vitro ineffective against gram-negative bacteria (\textit{Escherichia coli} ATCC 8739, and \textit{Pseudomonas aeruginosa} PAK laboratory strain), even at concentrations up to 80 \(\mu g/mL\).\textsuperscript{12} However, Rahman et al. demonstrated that at a dose of 100 mg/kg in mice, ticagrelor could reduce pulmonary neutrophil recruitment and attenuate lung injury severity to a considerable degree in a murine model with abdominal sepsis (induced by cecal ligation and puncture for tested mice).\textsuperscript{16}

In conclusion, through inhibition of the P2Y\textsubscript{12} receptor in conjunction with enhancement of adenosine reuptake, ticagrelor strongly inhibits platelet aggregation and further platelet-leukocyte heterotypic aggregation that are universally catastrophic to organ function in sepsis patients. This drug might have a promising role in reducing the severity of lung injury caused by GPC sepsis. The optimal dose of ticagrelor as a supplementary option to decrease the severity of multi-organ failure (including lung damage) among patients with significant GPC infections, however, remains to be investigated. Furthermore, in vitro susceptibility studies on the action of ticagrelor against clinically important resistant GPC isolates (particularly vancomycin-resistant \textit{E. faecium}) obtained from different geographical areas, and in vivo studies comparing the incidence of colonization/infection due to GPC among patients receiving ticagrelor and other anti-platelet agents, are necessary. Further investigations on attenuation of organ failure severity by ticagrelor addition for patients with severe septicemia may be warranted.
Conflicts of interest

All authors have no conflicts of interest to declare.

References