An extensive database analysis demonstrates significant increase in platelet quantity in unselected hospitalized patients following treatment with oseltamivir

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An extensive database analysis demonstrates significant increase in platelet quantity in unselected hospitalized patients following treatment with oseltamivir

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Dr. Aniko Szabo - performed statistics and data analysis
Dr. Laura Michaelis - Supervised study and edited the manuscript
Dr. Juliana Perez Botero - Supervised study and edited the manuscript
Dr. Karin Hofmeister - Supervised study and edited the manuscript

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Thrombocytopenia is a known risk factor for morbidity in individuals with various health conditions, including malignancy. Thrombocytopenia can lead to adverse outcomes including increased bleeding risk and mortality.\(^{(1-3)}\) Preventing and correcting thrombocytopenia may mitigate these consequences and improve patient outcomes.\(^{(3)}\) One proposed mechanism for remedying thrombocytopenia is to prolong the lifespan of platelets by interfering with normal platelet clearance. In addition to apoptosis, platelets are marked as aged and removed from circulation by hepatocytes and hepatic Kupffer cells in a highly coordinated process triggered by the loss of the terminal carbohydrate moiety sialic acid (platelet desialylation).\(^{(4)}\)

Neuraminidases cleave the glycosidic link and remove the terminal sialic acid. This allows the platelet to bind to the hepatic Ashwell-Morel receptor\(^{(5)}\) (likely also the macrophage galactose lectin (MGL) on Kupffer cells) and be removed from circulation.\(^{(6)}\) Thus, oseltamivir, a known neuraminidase inhibitor commonly used in treatment of influenza, may have off-target effects by halting platelet desialylation and attenuating platelet apoptosis and phagocytosis.\(^{(7)}\)

Based on this mechanistic observation, there is clinical interest in applying this finding to treat immune thrombocytopenia (ITP). Previous in vitro and in vivo studies have specifically demonstrated desialylation’s important role in ITP’s clearance of platelets, and its possibilities as a therapeutic target in ITP.\(^{(8-11)}\)

Previously, only a small pilot study\(^{(11)}\) had demonstrated an increase in platelets in response to oseltamivir in patients with ITP until a recent multicenter, randomized phase II study. In this study, individuals with ITP were randomly assigned to either dexamethasone monotherapy or dexamethasone in combination with a 4-day course of oseltamivir. Researchers randomized 96 patients and reported the combination group achieved significantly higher response rates at both 14 days and 6 months.\(^{(12)}\)

We were interested in whether we could confirm that treatment with oseltamivir is independently associated with a significant change in platelet counts before and after treatment. Using a large database, we hypothesized that receiving oseltamivir would increase platelet levels.

We obtained approval for a review of electronic medical records from the Medical College of Wisconsin Institutional Review Board. Using TriNetX software, we extracted data from patient charts. In our analysis, we included patients treated in the Medical College of Wisconsin system if they (1) had at least one clinical encounter between January 1, 2010, and December 31, 2020, (2) were over 18 years old, (3) were administered oseltamivir, (4) had platelet count measured at least once a maximum of 30 days before receiving oseltamivir and a post measurement a maximum of 30 days following oseltamivir administration. The platelet count before and after oseltamivir administration was recorded.
We interrogated patient charts for demographic data and variables that could affect platelet levels including a positive influenza polymerase chain reaction (PCR) test within 10 days of oseltamivir administration. We utilized ICD10 codes to identify the variables of interest. We employed a multivariable nested random effects model to account for the variance of the repeated measurements within the same treatment episode and multiple episodes within the same patient. We performed analysis using SAS 9.4 (SAS Institute, Cary, NC).

We identified 2,168 patients who met enrollment criteria. Table 1 includes demographic information as well as comorbid conditions. Some patients had multiple treatment episodes over the 10 years which were at least 90 days apart, creating 2,397 patient treatment episodes. We completed t-test analysis on the log-transformed fold change of the platelet level. On average there was a 1.14-fold increase in platelet levels after therapy with oseltamivir, with an average increase of 14%. We then broke the population down into four quartiles using baseline platelet levels. The 1st quartile was composed of 603 patients with a baseline platelet level equal to or less than 153x10^3/µL. The mean fold change for those individuals was 1.40, meaning after oseltamivir treatment, platelet level showed an increase of 40%, on average. Compared with all patients we analyzed, the cohort of patients in the lowest quartile were found to have the highest fold change in platelets after oseltamivir administration (Figure 1).

In the current climate of scarce blood products, novel mechanisms to prevent or ameliorate severe thrombocytopenia are critical. Similar to other studies, our results show an increase in platelet counts after oseltamivir administration, particularly in patients with the lowest baseline platelet count.

One possible explanation could be that oseltamivir increases platelets at a set amount regardless of the initial platelet count, and that the apparently more significant elevations in patients with more severe thrombocytopenia could be explained by starting with a lower platelet count from which to calculate log-fold and percentage increase.

Another possibility could be differing levels of platelet desialylation between the quartiles contributing to different baseline platelet levels, as shown by research demonstrating an inverse correlation between platelet count and the extent of specifically O-glycan desialylation in murine models. For example, the patients in the first quartile could have higher levels of platelet desialylation compared to other quartiles, explaining both that quartiles’ lower platelet baseline and its superior response to the sialidase inhibitor oseltamivir, as there are more therapeutic targets available in this group. A recent prospective cohort study showed that higher levels of desialylation can be found in certain diseases including connective tissue disease, aplastic anemia, and myelodysplastic syndromes. As our search did not specify these precise co-morbid conditions, it is possible that quartile 1 contained more patients with these “high-desialylation” diseases, which could be responsible for the lower baseline platelet levels. More research identifying the specific mechanisms of oseltamivir mechanistic activity at differing platelet levels would be beneficial.
Limitations of our work include those inherent to the retrospective cohort design, including inability to determine if the effect of oseltamivir is secondary to the anti-influenza effect or to the glycan effect on platelets. Notably, however, only 27% of the cases in our database had a positive influenza test. Those patients testing positive did not have a significantly different increase in platelets compared to the overall population. This finding supports the hypothesis that the increase in platelets is not associated with recovery from the respiratory illness.

Ultimately, the large sample size in our observational study adds power to the premise that the neuraminidase inhibitor oseltamivir could benefit individuals with severe thrombocytopenia even in situations other than immune-mediated thrombocytopenia. We believe this data provides support for clinical trials that would prospectively test such a hypothesis.
References
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<tr>
<td>Glycoprotein use</td>
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Figure 1 Legend: Fold change (left axis) and percent change (right axis) of platelet counts following Oseltamivir therapy. Each point represents one subject, ordered from lowest to highest baseline platelet count along the x-axis. The box-and-whisker plots summarize the median and interquartile range from each quartile of baseline platelet count. The dashed blue line represents no change (fold-change = 1, percent-change = 0%). The solid red line connects the means within each quartile of baseline platelet count.