Thromboelastography Profiles of Hemophilia A patients on Emicizumab

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BACKGROUND

Hemophilia A is an inherited bleeding disorder caused by a deficiency of Factor VIII (FVIII) of the coagulation cascade.

Emicizumab is a new monoclonal antibody, with Factor VIII mimic activity, has been found to be highly effective for bleed prevention and therefore has been approved for treatment patients with Hemophilia A.

Unlike FVIII prophylaxis which is associated with peaks and troughs and is administered intravenously, Emicizumab is associated with a steady state correction of coagulation following four weekly subcutaneous, loading doses.

Traditional FVIII replacement therapy is monitored using the APTT assay. The APTT in patients on Emicizumab is artificially shortened, and as such is inaccurate and cannot be used for monitoring.

Breakthrough bleeding, although very uncommon, may occur in patients on Emicizumab.

Thromboelastography (TEG) is a novel, global coagulation assay that measures coagulation in whole blood by measuring changes in viscosity. Few publications have attempted to determine the effect of Emicizumab on TEG.

This study describes the Tissue Factor activated TEG (TF-TEG) characteristics in twenty-two patients taking Emicizumab, three of whom experienced breakthrough bleeding.

OBJECTIVES

The purpose of this study was to determine the sensitivity of TF-TEG parameters (alpha angle, clot formation time, reaction time, or maximum amplitude) for predicting breakthrough bleeding.

If a sensitive parameter to predict bleeding can be identified, the eventual goal is to use the results of this study to promote the widespread use of TF-TEG to monitor treatment.

METHODS

A retrospective chart-review was conducted on patients treated with Emicizumab at Children’s Hospital of Michigan from 2016 until 2020, following Institutional review board approval.

Medical charts were reviewed to obtain bleeding history at each of the visits and laboratory data.

TEG’s were performed using previously described method with low dose tissue factor as an activator.

TEG parameters (alpha angle, maximum amplitude (MA), reaction time (R), and clot formation time (K)) and APTT were included in the data collected.

RESULTS

Twenty-two patients were included in the study based on the availability of laboratory data and bleeding history.

The average age of patients was 11 years old with a range of 19.7 years, and the average time since the start of Emicizumab was 45 weeks (>6 months).

Five patients had breakthrough bleeding with trauma, while two exhibited spontaneous breakthrough bleeding.

Table 1 shows the means of the TEG parameters in patients on the study. Patients exhibiting breakthrough bleeding showed a 24% increase in K time, as well as a 25% increase in R time suggestive of delayed clot formation compared to those without a bleeding phenotype, making these parameters of the TF-TEG assay the most desirable to use in predicting which patients may have breakthrough bleeding.

Table 1

<table>
<thead>
<tr>
<th>TF-TEG parameter (normal range)</th>
<th>Average TEG profile on factor (n=19)</th>
<th>Average on Emicizumab (no breakthrough bleeding) (n=25)</th>
<th>Average of breakthrough bleeding episodes (n=7)</th>
<th>Percent increased or decreased (breakthrough bleeds vs no breakthrough bleeds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K (1-2 min)</td>
<td>2.7</td>
<td>2.3</td>
<td>2.9</td>
<td>+24%</td>
</tr>
<tr>
<td>R time (3-8 min)</td>
<td>8.6</td>
<td>7.5</td>
<td>9.3</td>
<td>+25%</td>
</tr>
</tbody>
</table>

Table 1

CONCLUSIONS

This is the first study to utilize the TEG to determine its utility to predict breakthrough bleeding in patients on Emicizumab.

Currently, APTT is used in many hospitals without access to TEG.

APTT’s low sensitivity of 29% makes it undesirable as an assay to predict breakthrough bleeding, although the high specificity of 89% may confirm its ability to identify patients who will not exhibit breakthrough bleeding.

The results of this study show that TEG may be helpful in assessing the risk for breakthrough bleeding in patients receiving Emicizumab.

LIMITATIONS

This study has several limitations, including the fact that it is a very small study on a small group of patients.

The TEG was performed at our center using a modified approach of low dose tissue factor which may have increased the sensitivity of the assay.

Further data are warranted to determine if kaolin (the standardized assay) may be used with the same sensitivity.

REFERENCES