Hematologic abnormalities in patients exposed to monthly triple-dose gadolinium for a year

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Disclosures

The BECOME study was supported by Bayer Schering Pharma, distributors of IFN, but was investigator-initiated and remains the intellectual property of Principal Investigator’s Institution.

The current retrospective study is supported by Guerbet.

Gadopentetate Dimeglumine is FDA approved but was not approved at the 0.3 mmol/kg dose utilized in this study.
Background/ Purpose

It has been well-documented that gadolinium (Gd) deposition occurs in the brain even in patients with normal renal function, but there has been little data to suggest a long-term physiologic effect.\textsuperscript{1-3}

In the BECOME trial, MS patients underwent monthly triple-dose gadolinium enhanced MRI up to 78 dose equivalents over two years.\textsuperscript{4}

During the trial patients were monitored with blood chemistries, urinalysis, and hematology.

The purpose of this study is to retrospectively investigate for any increased frequency in biochemical abnormalities associated with the administration of monthly triple-doses of gadopentetate dimeglumine.
BECOME Study Patient Demographics

Seventy-five patients with relapsing-remitting MS (79%) or a clinically isolated syndrome consistent MS (21%) were randomized and followed by monthly brain MRI with triple dose Gd contrast (0.3 mmol/kg) for 13 months (up to 39 dose-equivalents).

Biochemical and hematologic markers were collected at each monthly time-point.

There were no significant differences in baseline characteristics between treatment groups.

Of the original cohort, data from 67 patients was available for retrospective analysis of monthly gadolinium deposition.

### Table 1. Baseline characteristics of the 75 patients randomized in the BECOME study

<table>
<thead>
<tr>
<th></th>
<th>IFNβ 1b (n = 36)</th>
<th>GA (n = 39)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (range)</td>
<td>36 (18-49)</td>
<td>36 (22-55)</td>
<td>0.96*</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>27 (75)</td>
<td>25 (64)</td>
<td>0.33*</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>15 (42)</td>
<td>24 (62)</td>
<td>0.12*</td>
</tr>
<tr>
<td>Black</td>
<td>10 (28)</td>
<td>11 (28)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>10 (28)</td>
<td>4 (10)</td>
<td></td>
</tr>
<tr>
<td>Indian-Asian</td>
<td>1 (3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Subtype of MS, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsing-remitting</td>
<td>31 (86)</td>
<td>30 (77)</td>
<td></td>
</tr>
<tr>
<td>Clinically isolated syndrome</td>
<td>5 (14)</td>
<td>9 (23)</td>
<td>0.38*</td>
</tr>
<tr>
<td>Time since onset of MS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median years (range)</td>
<td>0.9 (0.1-24)</td>
<td>1.2 (0.2-34)</td>
<td>0.35*</td>
</tr>
<tr>
<td>Annualized relapse rate, median (range)</td>
<td>1.8 (0-7.5)</td>
<td>1.9 (0.13-7.0)</td>
<td>0.53*</td>
</tr>
<tr>
<td>EDSS, median (range)</td>
<td>2.0 (0-5)</td>
<td>2.0 (0-5.5)</td>
<td>0.98*</td>
</tr>
<tr>
<td>Enhancement on MRIs predrug, n (%)</td>
<td>26 (72)</td>
<td>27 (69)</td>
<td>0.81*</td>
</tr>
<tr>
<td>CAL at entry, mean (median)</td>
<td>4.7 (1.75)</td>
<td>3.1 (1)</td>
<td>0.31*</td>
</tr>
<tr>
<td>MSFC, median (range)</td>
<td>0.13 (−1.5 to 1.0)</td>
<td>0.13 (−2.7 to 1.16)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

*Test p value for treatment group comparison.
*Fisher exact test p value for treatment group comparison.
*Rank sum test p value for treatment group comparison.
IFNβ 1b = interferon beta 1b; GA = glatiramer acetate; MS = multiple sclerosis; EDSS = Expanded Disability Status Scale; CAL = combined active lesion count (see Methods for details); MSFC = Multiple Sclerosis Functional Composite.
Metrics and Analysis

Biochemical and hematologic markers (as defined in Table 2) were collected at each monthly time-point.

“Generalized Estimating Equations” was used to test for an association between increased cumulative dosage of Gd and increased frequency of biochemical and hematologic abnormalities (as defined by standard laboratory reference range).

If a significant increase in abnormalities was seen at the cohort level, subgroup analysis was performed within each treatment arm to rule out confounding by treatment effect.
Results

A significant increased frequency in abnormalities was seen with regard to: hypophosphatemia, leukopenia, hyperglycemia, and increased RDW.
Hypophosphatemia

Incidence of hypophosphatemia increased significantly over the course of the trial in both treatment arms.

This is not a described effect of either Copaxone or Betaseron, thus it is unlikely that this is an effect of treatment. We observed an increased incidence of hypophosphatemia that reached statistical significance after five months. At month 10 this increasing incidence peaks to include 26% of our study population.

This finding has been described in previous work by the same group.°

Figure (right) displays percent of study population demonstrating hypophosphatemia (defined by lab reference range) at each monthly time-point (MTH). MTH=−1 represents baseline before Gd administration.

**Table:**

<table>
<thead>
<tr>
<th>BIO</th>
<th>TREAT</th>
<th>STAT</th>
<th>EST</th>
<th>CI_LOW</th>
<th>CI_HIGH</th>
<th>P_VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHOS</td>
<td>COPAXONE</td>
<td>ESTIMATOR</td>
<td>0.1869</td>
<td>0.1315</td>
<td>0.2423</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>ODDS RATIO</td>
<td>1.2055</td>
<td>1.1406</td>
<td>1.2742</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BETASERON</td>
<td>ESTIMATOR</td>
<td>0.3501</td>
<td>0.2095</td>
<td>0.4907</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>ODDS RATIO</td>
<td>1.4192</td>
<td>1.2331</td>
<td>1.6334</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Leukopenia

Incidence of low WBC increased significantly over the course of the trial in both treatment arms.

Though this finding is an expected side effect of Betaseron, it is considered an exceptionally rare side effect of Copaxone (0.1-1%). Noteworthy, is that at by months 10 and 11 the frequency in the Copaxone group reached 10 and 12% respectively. This suggests that a proportion of the increased frequency of leukopenia may be attributable to Gd administration.

This suggestion is especially concerning when linked to the known Gd deposition in bone.\(^6^8\)

![PERCENT OF LOW WBC v.s. SCANMTH](image)

Figure (right) displays percent of study population demonstrating leukopenia (defined by lab reference range) at each monthly time-point (MTH). MTH=-1 represents baseline before Gd administration.
Hyperglycemia

Incidence of hyperglycemia increased significantly over the course of the trial when groups were considered together, but this change was not significant in either group individually.

This is not a described treatment effect of either Copaxone or Betaseron, which suggests that it may be an effect of Gd administration.

However, this finding could be the result of treatment with corticosteroids (1 daily gram of methylprednisolone given IV for 5 days) for MS relapses. Furthermore, impaired glucose tolerance has been described in MS.  

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Figure (right) displays percent of study population demonstrating hyperglycemia (defined by lab reference range) at each monthly time-point (MTH). MTH=-1 represents baseline before Gd administration.
Increased Red Blood Cell Distribution Width (RDW)

Incidence of increased RDW increased in the Copaxone group alone.

Though this is not a described effect of Copaxone, however its occurrence in this group alone indicates that it is likely an effect of treatment rather than Gd administration.

Figure (right) displays percent of study population demonstrating increased RDW (defined by lab reference range) at each monthly time-point (MTH). MTH=−1 represents baseline before Gd administration.
Conclusion

We present a retrospective analysis of biochemical and hematologic abnormalities in 63 patients enrolled in the BECOME trial, who received monthly administration of triple dose (0.3 mmol/kg) Gd contrast administration of 13 months.

An increased incidence of 4 abnormalities was observed:

1. Hypophosphatemia
2. Leukopenia
3. Hyperglycemia
4. Increased RDW

Of these, hypophosphatemia and leukopenia (and to a lesser extent, hyperglycemia) are most concerning as potential signs of Gd toxicity.

RDW elevation was only seen in the Copaxone arm and therefore is unlikely to be an effect of Gadolinium.

Since Hypophosphatemia, Leukopenia, and Hyperglycemia were seen in both treatment arms, these are likely related to gadolinium.

2. Errante Y, Cirimele V, Mallio CA et al. Progressive increase of T1 signal intensity of the dentate nucleus on unenhanced magnetic resonance images is associated with cumulative doses of intravenously administered gadodiamide in patients with normal renal function, suggesting dechelation. Invest Radiol 2014;49(10):685-690.


