Safety of Long-Term Monthly Cycles of Methylprednisolone in Combination with Interferon Beta-1a IM in Treatment-Naïve Early Relapsing-Remitting Multiple Sclerosis Patients in the MECOMBIN Study

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Methods

The MECOMBIN trial was an investigator-initiated, multicenter, double-blind, randomized-placebo-controlled trial in treatment-naive IRMS patients with an EDSS score of 0–4.0 and at least 1 relapse in the previous year.

Three months after initiating IM IFN-β1a therapy, patients were randomized to MP 500 mg per day for 3 days monthly or placebo, for at least 3 and no more than 4 years.

Patients were followed clinically every 3 months.

Adverse event monitoring was performed throughout the study by an independent data monitoring committee at the Copenhagen University Hospital, Rigshospitalet, Department of Neurology.

Conclusions

- Monthly MP pulses of 1.5 g for up to 3 years do not reduce BMD or induce adrenal suppression.
- MP did not increase risk of serious or non-serious infections.
- Monthly cycles of high-dose MP in combination with IFN-β1a induce the clinical and radiological remission in both the placebo group and study drug group.
- Blood pressure should be measured regularly during pulsating MP treatment.
- Short-term MP AEs are troublesome and pose a considerable compliance problem.

Patient disposition

Figure 1. Patient disposition

Table 1. Baseline Characteristics in MECOMBIN Study

<table>
<thead>
<tr>
<th>MP (n=172)</th>
<th>Placebo (n=169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>44.7 (0.1–65)</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>82:90 (48%)</td>
</tr>
<tr>
<td>MS duration, years</td>
<td>1.067 (0.1–38)</td>
</tr>
<tr>
<td>BMD: lumbar spine (mean, g/cm²)</td>
<td>1.063 (0.1–38)</td>
</tr>
<tr>
<td>BMD: hip (mean, g/cm²)</td>
<td>1.170 (0.1–38)</td>
</tr>
</tbody>
</table>

Table 2. Adverse Event of Interest (Intent to Treat [ITT])

<table>
<thead>
<tr>
<th>MP (n=172)</th>
<th>Placebo (n=169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>1438</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>24</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>4</td>
</tr>
<tr>
<td>Acne</td>
<td>19 (11.1)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 (3.5)</td>
</tr>
<tr>
<td>Back pain</td>
<td>8 (4.7)</td>
</tr>
</tbody>
</table>

Table 3. Serious Adverse Event Profile (ITT)

<table>
<thead>
<tr>
<th>MP (n=171)</th>
<th>Placebo (n=167)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>1434</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>24</td>
</tr>
<tr>
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<td>4</td>
</tr>
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References


Study supported by Biogen Idec, Inc.
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September 9–12, 2009
Düsseldorf, Germany

Methods

• The MECOMBIN trial was an investigator-initiated, multicenter, double-blind, randomized, placebo-controlled trial in treatment-naïve RMS patients with an EDSS score ≤3.5 and at least 1 year of disease duration.

• Three months after initiating IFN-β1a treatment, patients were randomized to MP-50 mg per day for 3 days monthly placebo, or for at least 3 years without further changes in drug dosage.

• Laboratory assessments were performed locally every 6 months and included:

  • Hematology: hemoglobin (Hb), platelet count, complete blood cell count with differentials, and thrombocytes.
  • Biochemistry: sodium, potassium, creatinine, albumin, urea, bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, glucose, and adrenocorticotropin (ACTH) 1-24 and 1-41.
  • Urinalysis: protein, leukocytes, nitrites, and glucose.

• Blood and urine samples were collected at randomization and every 3 months, and every 3 months, and every 3 months.

• Bone density measurements by dual energy X-ray absorptiometry (DEXA) were performed at randomization (month 3) and 3 years after randomization.

Conclusions

• Monthly MP pulses of 1.5 g for up to 3 years do not reduce BMD or induce adrenocortical dysfunction.

• MP did not increase risk of serious or non-serious infections.

• Monthly cycles of high-dose MP in combination with IFN-β1a induce the classical short-term AEs, but seem safe and raise no concerns for use in treatment-naïve RMS patients.

• Blood pressure should be measured regularly during pulsed MP treatment.

• Short-term MP AEs are troublesome and pose a considerable compliance problem.

• The beneficial clinical effects taken into account, compliance might be better in routine clinical settings, especially if treatment is scheduled to last only 1–2 years.

• Our safety results reproduce those of the NRDRMS study, which sustains the benign AE profile of high-dose cyclic MP treatment.

References

2. Ravnborg M, Sorensen, PS, Andersson, M, et al. Presentation at the American Academy of Neurology; April 2009; Seattle, WA.

Study supported by Biogen Idec, Inc.
Background
The MECOMBIN trial was an investigator-initiated, multicenter, double-blind, randomized-placebo-controlled trial in treatment-naïve patients with RRMS. The primary endpoint of the MECOMBIN study was time to disability progression sustained over 6 months. The Expanded Disability Status Scale (EDSS), was not met.

Results
Three months after initiating IFN-β1a therapy, patients were randomized to MP 500 mg per day for 3 days every 3 months or placebo. For at least 3 and no more than 4 years.

• The beneficial clinical effects taken into account, compliance might be

-0.99
1.035
-0.99

MP
Placebo

MP
Placebo

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Objective
To present the safety of monthly oral 3-day 500-mg pulses of MP in combination with IFN-β1a in patients with RRMS in the MECOMBIN trial.

Table 1. Baseline Characteristics in MECOMBIN Study

<table>
<thead>
<tr>
<th>Baseline Characteristic, Median (range)</th>
<th>MP (n=172)</th>
<th>Placebo (n=169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>41 (22–63)</td>
<td>39 (21–65)</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>51.9 (61/172)</td>
<td>54.2 (91/169)</td>
</tr>
<tr>
<td>MS duration, years</td>
<td>2.85 (0–11.7)</td>
<td>3.25 (0–13.7)</td>
</tr>
<tr>
<td>MS lesion, years</td>
<td>1.23 (1–5)</td>
<td>1.23 (1–5)</td>
</tr>
<tr>
<td>MS expansion, years</td>
<td>1.23 (1–5)</td>
<td>1.23 (1–5)</td>
</tr>
</tbody>
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Methods
The MECOMBIN trial was an investigator-initiated, multicenter, double-blind, randomized-placebo-controlled trial in treatment-naïve patients with RRMS. The primary endpoint of the MECOMBIN study was time to disability progression sustained over 6 months. The Expanded Disability Status Scale (EDSS), was not met.

• To present the safety of monthly oral 3-day 500-mg pulses of MP in combination with IFN-β1a throughout the study were randomized to MP (n=172) or placebo (n=169).

- Baseline characteristics and patient disposition were comparable between the 2 groups (Table 1 and Figure 1).

Baseline median adrenal function (nmol/L)

Δ

Median change in BMD lumbar spine (%)

Month 39 BMD lumbar spine (mean, g/cm²)

Patients who reduced the study drug dosage due to AEs (No.)

Fractures (No. events)

MP plus IM IFN-β1a for the treatment of RRMS, is similar regime was applied to treatment-naïve RRMS patients for 3 to 4 years.

Background
Treatment of IFN-β1a and MP with IM IFN-β1a might offer a synergistic effect on disease activity in relapsing-remitting multiple sclerosis (RRMS).

• A recent report indicates that repetitive pulses of MP with IFN-β1a for the treatment of RRMS, is similar regime was applied to treatment-naïve RRMS patients for 3 to 4 years.

• Continuous treatment with even small doses of methylprednisolone (MP) can be associated with several serious side effects including adrenal gland suppression, high blood pressure, potassium loss, cataracts, optic neuritis, worsening of diabetes, psychiatric disturbances, hyperglycemia, and, of course, immunosuppression.

- The number of patients who reported 1 or more AEs was 166 in the MP group and 156 in the placebo group.

- There was no increased incidence of infections in the MP group, and no opportunistic infections were reported.

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- The number of patients who reported 1 or more AEs was 166 in the MP group and 156 in the placebo group.

Conclusions
• Monthly MP pulses of 1.5 g for up to 3 years do not reduce BMD or induce adrenal dysfunction.

- Baseline adrenal function.

- Blood pressure should be measured regularly during pulsed MP treatment.

- Short-term MP AEs are troublesome and pose a considerable

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