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 Trial

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Background

- 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, glaucoma, cataracts, peptic ulceration, worsening of diabetes, psychic disturbances, osteoporosis, and, of course, immunosuppression.
- The combination of MP and interferon beta-1a (IFNβ-1a) might offer a synergistic effect on disease activity in relapsing-remitting multiple sclerosis (RRMS).
- A recent report indicates that repetitive pulses of MP with IFNβ-1a for 2 years reduce the disease activity in RRMS patients with break-through disease (NORMIMS).[1]
- In the MECOMBIN study (MP in combination with intramuscular [IM] IFNβ-1a for the treatment of RRMS), a similar regime was applied to treatment-naïve RRMS patients for 3 to 4 years.
  - The MP plus IM IFNβ-1a group had a statistically significant reduction in annualized relapse rate, accumulation of neurologically deficits on the MS Functional Composite, and on T2-lesion load in comparison with the placebo plus IFNβ-1a group.[2]
  - The primary endpoint of the MECOMBIN study, time to disability progression sustained over 6 months on the Expanded Disability Status Scale (EDSS), was not met.
- Prior to the MECOMBIN study, the safety of monthly, high-dose MP pulses administered for more than 3 years has not been studied systematically.

Objective

- To present the safety of monthly oral 3-day 500-mg pulses of MP in combination with IM IFNβ-1a in patients with RRMS in the MECOMBIN trial.

Methods

- The MECOMBIN trial was an investigator-initiated, multicenter, double-blind, randomized, placebo-controlled trial in treatment-naïve RRMS patients with an EDSS score ≤4.0 and at least 1 relapse in the previous year.
- Three months after initiating IM IFNβ-1a 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.
- Symptomatic treatment of MP adverse events (AEs) like palpitations (propranolol), water retention (diuretics), sleeplessness (sedatives), and dyspepsia (H2-blockers) was used at the discretion of the investigator.
- Laboratory assessments were performed locally every 6 months and included:
  - Hematology (hemoglobin [Hb], leucocytes, complete blood cell count with differentials, and thrombocytes).
  - Biochemistry (sodium, potassium, creatinine, albumin, urea, bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, glucose, and hemoglobin A1C [HbA1C]), and urine analyses ([Hb], albumin, ketones, and glucose).
- Blood and urine samples were collected at screening, randomization, and every 3 months.
- Bone density measurements by dual energy X-ray absorptiometry (DEXA) scan were performed at randomization (month 3) and after 3 years (month 39) in accordance with normal standard procedure at each hospital.
  - For the group included within the first year of the trial, an interim safety analysis of DEXA data was performed after 1 year.
- Adrenal function was evaluated by measurements of P-cortisol in an adrenocorticotropic hormone (ACTH) stimulation test before and after ACTH IV.
  - Tests were performed at randomization (month 3) and 3 years (month 39).
- AEs were recorded.

Results

- Three hundred forty-one patients treated with IM IFNβ-1a 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).
- Total number of AEs was higher in the MP-treated group compared with the placebo-treated group (1436 vs 1070; Table 2).
  - The number of patients who reported 1 or more AEs was 166 in the MP group and 156 in the placebo group.
- The number of serious AEs (SAEs) was higher in the placebo group (35 vs 24 in the MP-treated group). No deaths were reported (Table 3).
- AEs that were more frequent in the MP group all represented well-known corticosteroid effects (Table 4).
- No cases of osteonecrosis were reported.
- No cases of gastrointestinal ulceration or bleeding were observed.
- There was no increased incidence of infections in the MP group, and no opportunistic infections were reported.
- Fractures were equally distributed between the groups. One fracture was reported as an SAE due to hospitalization.
- There was no significant difference in bone mineral density (BMD) between groups from randomization to month 39.
  - Lumbar spine BMD (baseline/month 39) was 1.063/1.036 g/cm^2 in the MP group and 1.067/1.035 g/cm^2 in the placebo group.
- There were no significant differences in adrenal function between groups.
  - Results of ACTH stimulation (randomization/month 39) was 381/409 nmol/L in the MP group and 402/388 nmol/L in the placebo group.
- One case of hepatitis occurred in the MP group.
  - Screening was negative for Hepatitis A, B, and C, cytomegalovirus and Ebstein-Barr virus; liver parameters increased 5–30-fold, IFNβ-1a and study drug was discontinued, and the liver tests returned to normal within 3 months; drug-induced hepatitis could not be ruled out.

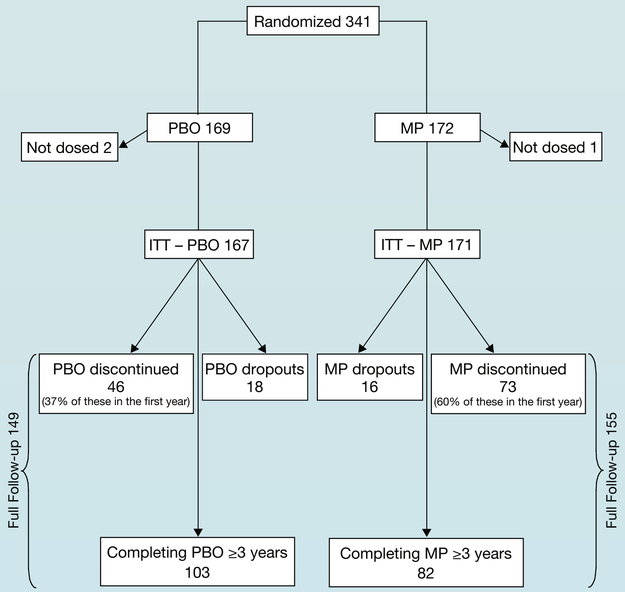
Table 1. Baseline Characteristics in MECOMBIN Study

Baseline Characteristics, Median (range)	MP (n=172)	Placebo (n=169)
Age, years	38 (18–55)	38 (18–56)
Gender (M:F)	38%:62%	33%:67%
MS duration, years	1.2 (0.1–34)	1.2 (0.3–28)
EDSS	2.0 (0–6)	2.0 (0–7)

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

	MP (n=171)	Placebo (n=167)
Adverse events	1436	1070
Infections (No. events)	228	239
Fractures (No. events)	4	3
Patients who reduced the study drug dosage due to AEs (No.)	Awaiting further information	Awaiting further information
Patients discontinuing study drug in first year (No.)	48	22
Baseline BMD lumbar spine (mean, g/cm^2)	1.063	1.067
Month 39 BMD lumbar spine (mean, g/cm^2)	1.036	1.035
Median change in BMD lumbar spine (%)	0.00	-0.99
ΔP-Cortisol at baseline (median; nmol/L)	381	402
ΔP-Cortisol at month 39 (median; nmol/L)	409	388
Baseline median adrenal function (nmol/L)	352	365
Month 39 median adrenal function (nmol/L)	403	393
Diabetes mellitus (No. cases)	2	1

Figure 1. Patient Disposition



MP=methylprednisolone; PBO=placebo.

Table 3. Serious Adverse Event Profile (ITT)

	MP (n=171)	Placebo (n=167)
Serious adverse events	24	35
System organ class		
Ear and labyrinth disorders	1	0
Endocrine disorders	1	0
Eye disorders	2	1
Gastrointestinal disorders	4	3
General disorders and administration-site conditions	1	5
Infections and infestations	1	4
Injury, poisoning, and procedural complications	1	0
Investigations	1	1
Musculoskeletal and connective tissue disorders	1	2
Nervous system disorders	2	4
Pregnancy, puerperium, and perinatal conditions	0	1
Psychiatric disorders	3	0
Renal and urinary disorders	0	1
Reproductive system and breast disorders	0	3
Respiratory, thoracic and mediastinal disorders	0	2
Skin and subcutaneous tissue disorders	2	0
Surgical and medical procedures	2	7
Vascular disorders	2	1

Table 4. Adverse Events Occurring in >5% of Any Group

Adverse Event	MP n (%)	Placebo n (%)
Palpitations	14 (8.2)	5 (3)
Hypertension	13 (7.6)	5 (3)
Dyspepsia	15 (8.8)	2 (1.2)
Nausea	11 (6.4)	7 (4.2)
Fatigue	24 (14.0)	19 (11.4)
Dysgeusia	26 (17.0)	1 (0.6)
Oedema	9 (5.3)	3 (1.8)
Pyrexia	19 (5.8)	6 (3.6)
Influenza-like illness	78 (45.6)	96 (57.5)
Influenza	17 (9.9)	14 (8.4)
Nasopharyngitis	27 (15.8)	28 (16.8)
Sinusitis	5 (2.9)	10 (6.0)
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Liver function tests abnormal	7 (4.1)	11 (6.6)
Weight increase	9 (5.3)	5 (3.0)
Arthralgia	15 (8.8)	13 (7.8)
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Erythema	19 (11.1)	4 (2.4)
Rash	10 (5.8)	11 (6.6)
Flushing	25 (14.6)	0 (0)

Conclusions

- Monthly MP pulses of 1.5 g for up to 3 years do not reduce BMD or induce adrenal dysfunction.
- MP did not increase risk of serious or non-serious infections.
- Monthly cycles of high-dose MP in combination with IFNβ-1a induce the classical short-term AEs, but seem safe and raise no concerns for use in treatment-naïve RRMS 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.
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References

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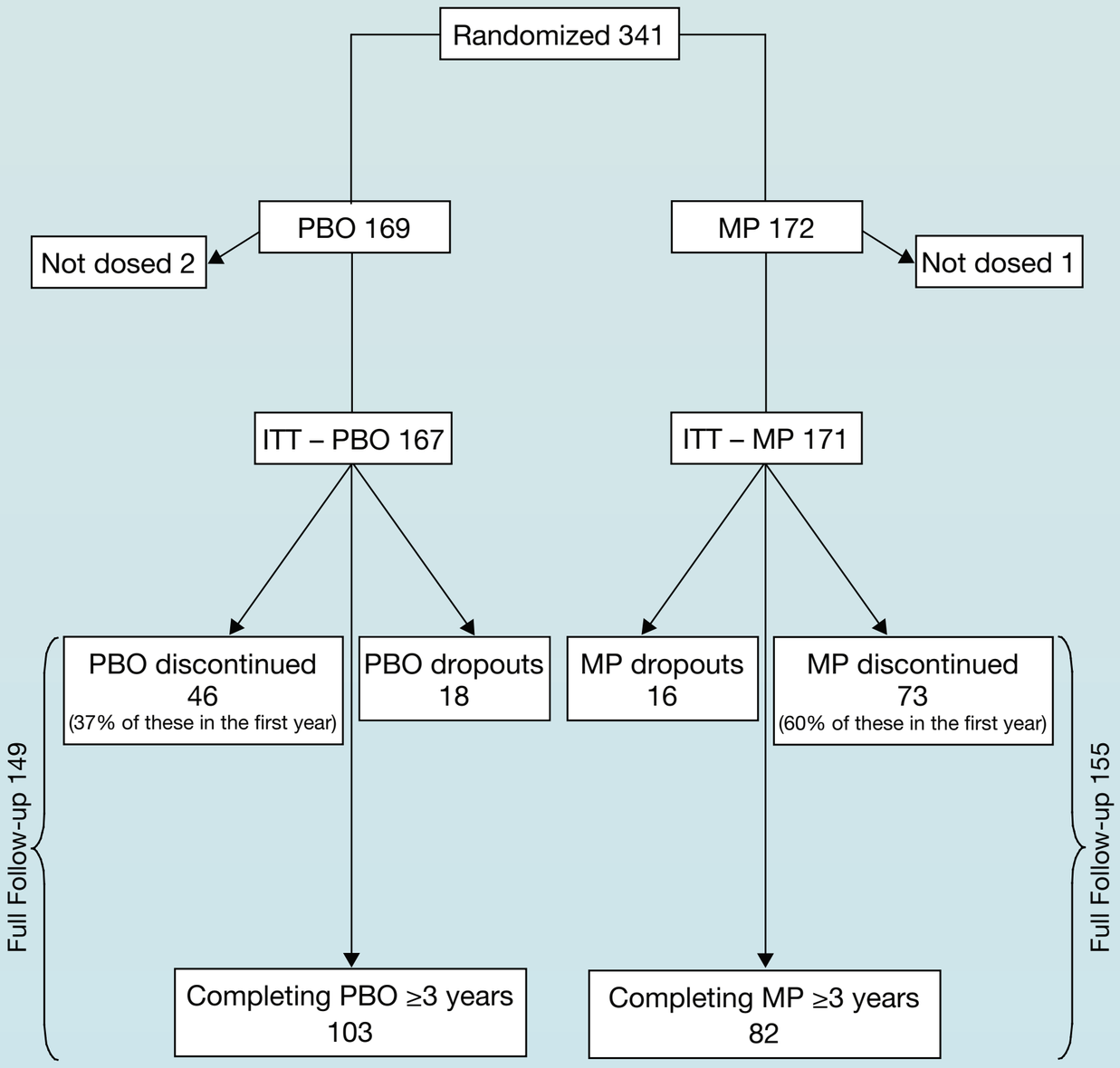

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