# Patient-reported adverse events of high-dose intravenous methylprednisolone for relapse treatment in multiple sclerosis (FEEL study)

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## Introduction

Pulses of high dose intravenous methylprednisolone (IVMP) 500–1000 mg/day for 3-5 days is the standard relapse treatment in multiple sclerosis (MS) and other inflammatory conditions. Despite IVMP being generally considered as well tolerated in MS patients, patient-reported adverse events (AEs) are scarcely studied.

The FEEL study is an observational study designed to assess the occurrence, severity and impact of patient-reported AEs during and shortly after IVMP treatment in MS patients experiencing a relapse.

85 patients (mean age 45 yrs.) planned to be treated with IVMP were enrolled from 15 hospitals in the Netherlands between January 2013 and April 2014. The patients completed a self-administered questionnaire, including questions related to the occurrence, severity and impact of symptoms, previously characterized in literature as methylprednisolone (MP) associated side effects, at 4 time points. For the majority of patients information related to the disease and the MP treatment was also provided by the neurologists/ MS nurses. For 47 patients (55%), complete information was available (all patient questionnaires completed and information was obtained from neurologists).

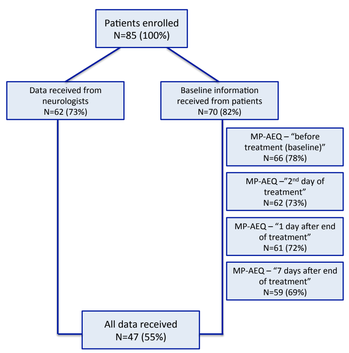
AEs were defined as any worsening of pre-existing symptom or the occurrence of any new symptom after start of treatment. AEs were considered severe when one of the two highest points (a lot, quite a lot) of the 4-point Likert scale were chosen at least once at the question about the severity of the symptom.

## Objective

The FEEL study is an observational study designed to assess the occurrence, severity and impact of patient-reported AEs during and shortly after IVMP treatment in MS patients experiencing a relapse.

## Methods

**Figure 1: Subject disposition. Number and percentages of patients from whom each questionnaire was received, are shown (MPAEQ=Methylprednisolone Adverse Events Questionnaire)**




- 85 patients planned to be treated with IVMP enrolled from 15 hospitals in the Netherlands between January 2013 and April 2014. Subject disposition is shown in Figure 1.
- Methylprednisolone Adverse Events Questionnaire (MP-AEQ) is a self-administered questionnaire, developed in-house. MP-AEQ assesses the occurrence, severity and impact of IVMP AEs on a 4-point Likert scale (a lot, quite a lot, a little, not at all) for 15 symptoms (6 CNS-related and 9 non CNS-related), which have been previously described in the literature as MP associated side effects.
- Participants completed the MP-AEQ at 4 different time points (Figure 1).The questionnaires were in most cases distributed online but part of the questionnaires was completed on paper.
- AEs were defined as any worsening of pre-existing symptom or the occurrence of any new symptom after start of treatment. An AE was considered severe when one of the two highest points were chosen at least once in the question related to severity. AEs were calculated from patients that responded at baseline and at least one follow up questionnaire (N=59, 69%).

## Results

### Baseline characteristics

**Table 1: Baseline characteristics as received from patients (N=70)**

| | |
|---|---|
| Gender | |
| Female | 54 (77%) |
| Male | 16 (23%) |
| Age (mean ± SD (range)) | 45±11 (25 – 67) |
| Receives immunomodulatory treatment? | |
| Yes | 31 (44%) |
| No | 39 (56%) |
| Immunomodulatory treatment | |
| Interferon Beta | 15 (21%) |
| Glatiramer acetate | 7 (10%) |
| Natalizumab | 2 (3%) |
| Fingolimod | 3 (4%) |
| Other | 4 (6%) |
| Number of relapses in the last 2 years | |
| 0 | 16 (23%) |
| 1 | 19 (27%) |
| 2 | 13 (19%) |
| 3 | 9 (13%) |
| 4 | 6 (9%) |
| ≥5 | 6 (9%) |
| Number of periods of treatment with MP during the last 2 years | |
| 0 | 27 (39%) |
| 1 | 21 (30%) |
| 2 | 8 (11%) |
| 3 | 9 (13%) |
| 4 | 3 (4%) |
| 5 | 1 (1%) |

**Table 2: Baseline characteristics as received from neurologists/MS nurses (N=62)**

| | |
|---|---|
| Diagnosis | |
| RRMS or CIS | 51 (82.3%) |
| Progressive MS | 3 (5%) |
| Secondary progressive MS | 1 (2%) |
| Unknown | 7 (11%) |
| Duration of MS, years (mean ± SD (range)) | 9.0 ± 7.5 (0 -28) |
| EDSS score (mean ± SD (range)) | 3.0±1.7 (0.5 – 6.5) |

**Table 3: Information related to treatment with IVMP as received by the neurologists/MS nurses (N=62)**

| | |
|---|---|
| Patient was treated for a relapse | |
| Yes | 52 (84%) |
| No | 4 (7%) |
| Unknown | 6 (10%) |
| Location of treatment | |
| Daycare | 36 (58%) |
| Nursing ward | 18 (29%) |
| Home | 1 (2%) |
| Unknown | 7 (11%) |
| MP treatment schedule | |
| 1000mg/d for 3 days | 35 (56%) |
| 1000mg/d for 5 days | 14 (23%) |
| 500mg/d for 5 days | 6 (10%) |
| 500mg/d for 3 days | 1 (2%) |
| Unknown | 6 (10%) |
| Total MP dose received, mg (mean ± SD (range)) | 3420±952 (1500-5000) |
| Completed MP treatment? | |
| Yes | 40 (65%) |
| No | 1 (2%) |
| Unknown | 21 (34%) |

- The majority of patients was female, with a mean age of 45 years, a mean EDSS score of 3 and an average of 9 years of disease duration.
- Half of the patients had experienced 2 or more relapses in the last 2 years and 59% had received MP at least once during the last 2 years.
- The majority of patients was treated with MP because of a relapse (84%) and received 1000mg/d for 3 days (56%).

### Patient-reported adverse events

- Out of the 15 symptoms surveyed, patients experienced on average 4 AEs (range 0-12).
- Out of the 6 CNS-related symptoms surveyed, patients experienced on average 2 AEs (range 0-6).
- Out of the 9 non-CNS-related symptoms surveyed, patients experienced on average 3 AEs (range 0-8).

**Figure 2: Percentages of patients experiencing an AE. AEs are divided into CNS-related ones and non CNS related**

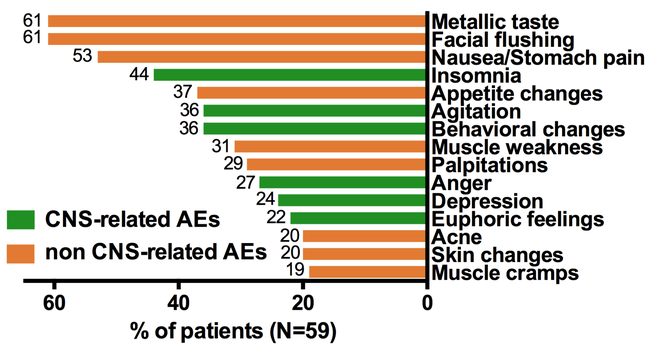



**Figure 3: Percentages of patients experiencing an AE and considering it as severe.**

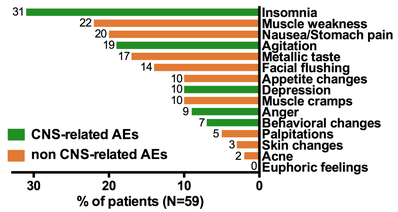
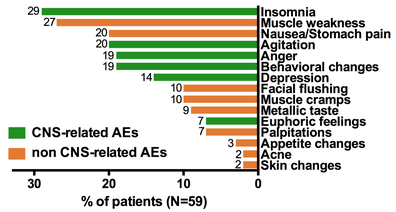



**Figure 4: Percentages of patients experiencing an AE which affected their daily activities.**




- The 5 most frequently reported AEs were metallic taste, facial flushing, nausea/stomach pain, insomnia and appetite changes (Figure 2).
- The 5 AEs most commonly reported as severe were insomnia, muscle weakness, nausea/stomach pain, agitation and metallic taste (Figure 3). From them, insomnia and agitation are the most commonly CNS-related AEs reported as severe and from the non CNS-related ones, muscle weakness, nausea/stomach pain, and metallic taste.
- Insomnia, muscle weakness, nausea/stomach pain, agitation, anger and behavioral changes were the AEs that were most commonly mentioned to affect the daily activities of the patients (Figure 4). The majority of them are CNS-related AEs.
- In the 5x1000mg/day group (N=12) muscle weakness, palpitations, agitation, anger, behavioral changes and appetite changes occurred nearly twice as often as in the 3x1000mg/day group (N=30), with minor differences in the other AEs. However, due to the small number of patients these result should be interpreted with care.
- In addition to the previously mentioned AEs, 1 week after the end of treatment, 18 patients (31%) reported to have gained weight and 6 patients (10%) reported to have experienced an infection (3/6 bladder infection, 5% of the total number of patients).
- 9% of the patients stated that they are thinking of refusing treatment with IVMP every time they are treated, and an additional 12% thought about it sometimes.
- Finally, 93% of the patients reported to have a cannula at their vein during the treatment period (for 3 to 5 days), 11% reported to be bothered by it and 34% reported that this interfered with their daily activities.

## Conclusions

MS patients treated with high-dose IVMP for a relapse report experiencing on average 4 AEs and on average 2 CNS-related AEs during and shortly after treatment.

The most frequently reported AEs are metallic taste, facial flushing, nausea/stomach pain, insomnia and appetite changes, with insomnia, muscle weakness, nausea/stomach pain, agitation and metallic taste most commonly reported as severe.

Apart from muscle weakness and stomach pain, CNS-related AEs (insomnia, agitation, anger, behavioral changes and depression) appear to affect the daily activities of patients the most, in up to 29% (insomnia) of the patients. Moreover, the cannula staying at the vein of the patients during the 3-5 days of treatment also seems to be a burden for their daily activities.

The above mentioned AEs add to the MS-related symptoms and these results suggest that, from a patient perspective, there is the need for an improved treatment of MS relapses with less-side effects.