RENEW Study Update XVIII: Ongoing Evaluation of the Safety and Tolerability of Mitoxantrone in Worsening Multiple Sclerosis

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P500

Abstract

Background: The Registry to Evaluate Novantrone Effects in Worsening Multiple Sclerosis (RENEW) study is a multicenter, open-label, observational study designed to evaluate the safety of mitoxantrone in worsening RRMS (WRRMS), SPMS, and PRMS in the postmarketing setting.

Objective: To provide an update on the ongoing RENEW study.

Methods: The RENEW study included patients aged 18–65 years with WRRMS, SPMS, or PRMS who had initiated treatment with mitoxantrone 12 mg/m^2 and were expected to follow package insert dosing and monitoring recommendations. Patients were evaluated before treatment initiation and monitored for up to 5 years. During the treatment period, complete blood cell and platelet counts and liver function tests were conducted every 3 months and left ventricular ejection fraction (LVEF) was measured at baseline, at visit 8, at the end of the treatment period, and whenever clinically indicated. After completion of treatment, LVEF and laboratory parameters were measured annually for up to 5 years after treatment initiation.

Results: 509 patients were enrolled in the RENEW study at 46 US centers. The current 18th update includes new data collected between July 17, 2007–January 25, 2008 and an update from the cumulative study which began in April 2001. Through January 25, 2008, treatment has concluded in 470 patients and continues in 39 patients. Of those who have discontinued treatment, 174 patients continued to be followed up. During the current reporting period, no new cases of leukemia, congestive heart failure, treatment-phase serious adverse events, amenorrhea, or serious infections were reported; however, 2 deaths (unrelated to treatment, n=1; unknown relationship, n=1), 2 patients with decreases in LVEF relative to baseline but remaining ≥50%, and 6 relapses were reported. Cumulative data for the entire study period will be presented.

Conclusions: The RENEW study continues to provide important data on the use and safety profile of mitoxantrone in patients with worsening forms of MS in the postmarketing setting.

Introduction

- Multiple sclerosis (MS) is a chronic and progressive disease that results in varying degrees of neurologic disability.
- Mitoxantrone is an immunosuppressive agent that is approved to treat patients with worsening relapsing-remitting MS (WRRMS), secondary-progressive MS (SPMS), and progressive-relapsing MS (PRMS).[1]
- The Registry to Evaluate Novantrone Effects in Worsening Multiple Sclerosis (RENEW) is a multicenter, open-label, observational study designed to evaluate the safety of mitoxantrone therapy in patients with WRRMS, SPMS, and PRMS. Patients were monitored for 2–3 years during treatment and 2–3 years during the follow-up phase, for a total of more than 5 years.

Objective

- This poster presents the cumulative validated data from the beginning of the study in April 2001 through the recent report ending January 25, 2008.

Methods

- A total of 509 patients with MS receiving mitoxantrone were enrolled at 46 centers across the United States.

Inclusion Criteria

- Patients were eligible for the study if they had a clinically defined or laboratory-supported diagnosis of WRRMS, SPMS, or PRMS and had initiated mitoxantrone (12 mg/m^2) treatment within 3 months of site Institutional Review Board approval.
- Patients' treating physicians were expected to follow the dosing and monitoring recommendations specified in the medication package insert.
- Additional entry criteria for the study included age 18–65 years, platelet count >100,000 cells/mm^3, and granulocyte count >2000 cells/mm^3.

Exclusion Criteria

- Had primary-progressive MS, a history of congestive heart failure (CHF), or left ventricular ejection fraction (LVEF) <50%
- Had received previous treatment with mitoxantrone, other anthracenediones or anthracyclines, mediastinal radiotherapy, or total lymphatic irradiation
- Presented with levels of aspartate transaminase or alanine transaminase >2-fold higher than the upper limit of normal (ULN), or bilirubin levels >2 x ULN
- Were pregnant or nursing
- Had current urinary tract or other severe untreated infections

Assessments

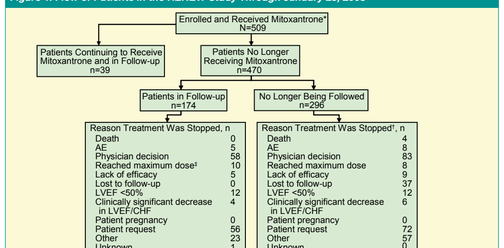
- Patients were medically evaluated before treatment initiation. After this initial examination, liver function tests, complete blood cell counts, and platelet counts were conducted every 3 months during the treatment period.
- LVEF was measured at baseline, at visit 8, at the end of the treatment period, whenever clinically indicated, and annually after completion of treatment for up to 5 years from the first dose of mitoxantrone.
- All tests will be continued annually during the posttherapy follow-up period.
- Relapses are captured per the investigator's discretion.
- Patients are monitored for 5 years from the date of treatment initiation.

Results

Patient Disposition

- Enrollment of patients in the RENEW study is complete. A total of 509 patients have received at least 1 dose of mitoxantrone through January 25, 2008.
- Of the 509 patients, 39 patients continue mitoxantrone, and 470 have stopped treatment.
- Follow-up data continue to be collected for 174 of the 470 patients who have stopped treatment **(Figure 1)**.

Figure 1. Flow of Patients in the RENEW Study Through January 25, 2008



AE=adverse event; CHF=congestive heart failure; LVEF=left ventricular ejection fraction.
*Patients with validated data who have received ≥1 dose of mitoxantrone.
†Reasons patients are no longer being followed up may differ from the reasons for discontinuing mitoxantrone treatment.
‡Includes patients who have reached a cumulative dose of ≥132 mg/m^2.

Demographics

- Patient characteristics at baseline are shown in **Table 1**. 97% of patients had received MS medications before study initiation. The most commonly received therapies at baseline (April 2001) were intravenous (IV) methylprednisolone (65%), oral prednisone (49%), intramuscular (IM) interferon beta (IFNβ)-1a (45%), subcutaneous (SC) IFNβ-1b (40%), and SC glatiramer acetate (GA; 40%).

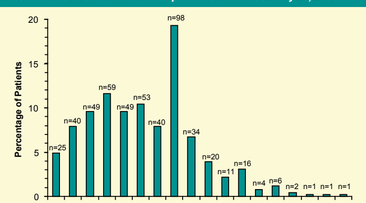
Table 1. Patient Characteristics at Baseline

Characteristic	Overall	Worsening Relapsing-Remitting	Progressive-Relapsing	Secondary-Progressive
Patients enrolled,* n (%)	509 (100.0)	81 (15.9)	33 (6.5)	395 (77.6)
Demographics				
Women, %	67.8	77.8	54.5	66.8
Mean age, y (range)	49 (19–68)	40 (19–63)	47 (30–64)	47 (25–68)
White, %	88.6	85.2	87.9	89.4
History of MS				
Median EDSS score (range)	6.0 (0.0–9.0)	4.0 (1.0–8.0)	6.0 (1.5–8.5)	6.5 (0.0–9.0)
Median years since onset (range)	11.8 (0.4–45.3)	8.0 (0.4–29.2)	11.5 (0.6–34.5)	13.0 (0.6–45.3)
Median years since diagnosis (range)	8.6 (0.0–39.9)	4.8 (0.0–24.6)	7.3 (0.1–26.5)	9.3 (0.1–39.9)
Median years since most recent relapse (range)	0.4 (0.0–20.3)	0.2 (0.0–2.4)	0.2 (0.0–4.6)	0.5 (0.0–20.3)
Patients with no prior treatment for MS, n (%)	16 (3.1)	3 (3.7)	2 (6.1)	11 (2.8)
Cardiac				
Mean LVEF, % (range)	62 (50–83)	62 (50–83)	63 (52–79)	62 (50–83)

EDSS=Expanded Disability Status Scale; LVEF=left ventricular ejection fraction; MS=multiple sclerosis.

- The mean duration of mitoxantrone treatment is 1.5 years (range, 0.0–4.9 y).
- Patients received a mean of 6 infusions (range, 1–18) during the study period **(Figure 2)**. The mean cumulative dose per patient is 69.7 mg/m^2 (range, 8.0–148.6 mg/m^2). Doses <10 mg/m^2 were received by 121 (24%) patients and account for 517 (16%) of all infusions given during the study period.
- The most commonly used concomitant therapies were GA (25%), IV methylprednisolone (21%), IFNβ-1a IM (21%), IFNβ-1b SC (15%), IFNβ-1a SC (12%), and oral prednisone (6%). Less than one third of the patients (29%) received no concomitant therapies during the study.

Figure 2. Number of Infusions of Mitoxantrone per Patient as of January 25, 2008



Serious Adverse Events

- A total of 178 serious adverse events have been reported in 101 patients to date.
- Of these, 106 were considered unrelated to mitoxantrone therapy by investigators, 31 were considered possibly related, 33 were considered probably related, 1 was considered definitely related, and 7 were categorized as having an unknown relationship to treatment **(Table 2)**.

Table 2. Serious Adverse Events Considered Probably or Definitely Related to Mitoxantrone Treatment as of January 25, 2008

Serious Adverse Event	Number of Instances	Relationship to Mitoxantrone
Febrile neutropenia	2	1 Definite, 1 Probable
Decreased ejection fraction	11	Probable
Leukopenia	4	Probable
Pneumonia	3	Probable
Cardiomyopathy	3	Probable
Urinary tract infection	3	Probable
Cardiac failure congestive	2	Probable
Urosepsis	1	Probable
Acute myeloid leukemia	1	Probable
Cellulitis gangrenous	1	Probable
Herpes zoster	1	Probable
Upper respiratory tract infection	1	Probable
Ventricular hypokinesia	1	Probable

Therapy Discontinuation

- Treatment has concluded in 470/509 patients **(Figure 1)**.
- The majority (74%) of the reasons given for stopping study treatment included physician decision, patient request, and other **(Table 3)**.

Table 3. Most Common Reasons for Treatment Stoppage

	Patients, n (%)
Total number of patients who discontinued mitoxantrone	470 (100)
Number of treatment stoppages attributed to physician decision, patient request, or other reason for discontinuation	349 (74)
Physician decision	141 (28)
Disease stabilization	37 (26)
Administration of 8 doses	25 (18)
Desire to reserve mitoxantrone as a future treatment option	16 (11)
Combination of disease stabilization and desire to reserve mitoxantrone	9 (6)
No specific reason	9 (6)
Reasons other than those listed above	45 (32)
Patient request	128 (25)
Lack of efficacy/worsening of the disease	38 (30)
AEs	12 (10)
Combination of lack of efficacy/worsening of the disease and AEs	7 (6)
No specific reason	25 (20)
Reasons other than those listed above	46 (36)
Other	80 (16)
Change in physician/closing of center/inconvenience of travel/study terminated at center	42 (53)
Financial/medical insurance reasons	9 (11)
Reasons other than those listed above	29 (36)

AEs=adverse events.

- 12 deaths have been reported to date; 1 due to multisystem organ failure secondary to CHF, cardiomyopathy, and reduced LVEF (considered probably related to mitoxantrone); 1 due to acute meningitis, 1 due to septic shock, and 1 due to cerebrovascular accident and carotid artery occlusion (all considered possibly related to mitoxantrone); 2 due to pulmonary embolism, 1 due to cardiopulmonary arrest, 1 due to pneumonia, 1 due to prostate cancer, 1 due to respiratory failure, and 1 due to a traffic accident (all considered unrelated to mitoxantrone); 1 due to pulmonary edema (unknown relationship to mitoxantrone).

Relapses

- To date, 343 relapses have been reported in 247 patients.
- Of these patients, the median time to first relapse was 160 days (range, 3–1215 d). The majority (90%) of relapses did not require hospitalization.

Cardiac Function and Leukemia

- As of January 25, 2008, 405 postbaseline LVEF tests have been performed for 200 patients during the treatment phase of the study, with an LVEF result of <50% reported in 26 patients **(Table 4)**.
- 8 cases of CHF have been reported thus far, with 3 of them requiring hospitalization. One case was not specified as CHF requiring hospitalization or other treatment, and is therefore, not included in **Table 4**.
- Therapy-related leukemia has been reported in 2 patients (1 case of acute myelogenous leukemia probably related and 1 case of chronic myeloid leukemia possibly related to mitoxantrone therapy). One case of promyelocytic leukemia has also been reported but is considered unrelated to mitoxantrone therapy.

Table 4. Cardiac Adverse Events and Postbaseline Test of LVEF in Patients With ≥1 Infusion and ≥1 Additional Visit

	Overall	Worsening Relapsing-Remitting	Progressive-Relapsing	Secondary-Progressive
Number of patients	509	81	33	395
Number of patients with CHF*				
Requiring hospitalization	3	1	0	2
Without hospitalization	4	2	0	2
Number of patients with postbaseline evaluations (%)				
LVEF <50%	26 (5.1)	1 (1.2)	0	25 (6.3)
LVEF <50% and ≥10% decrease relative to baseline LVEF†	24 (4.7)	1 (1.2)	0	23 (5.8)
LVEF ≥50% and ≥10% decrease relative to baseline LVEF	51 (10.0)	7 (8.6)	4 (12.1)	40 (10.1)
LVEF ≥10% increase relative to baseline LVEF	43 (8.4)	6 (7.4)	2 (6.1)	35 (8.9)

CHF=congestive heart failure; LVEF=left ventricular ejection fraction.
*1 case not included because it was not specified whether the CHF required hospitalization or other treatment.
†Test results with LVEF <50% and ≥10% decrease from baseline LVEF are a subset of those with LVEF <50%.

Conclusions

- **The results of the RENEW study to date continue to support the benefit-risk profile of mitoxantrone.**
- **As the risk of cardiotoxicity during mitoxantrone treatment increases with cumulative dose, it is important to monitor cardiac function regularly and before every dose.**
- **Continued observation of patients in the RENEW study will further extend long-term safety and tolerability data on the use of mitoxantrone for the treatment of worsening MS in clinical practice.**

References

1. Novantrone® (mitoxantrone for injection concentrate). Full Prescribing Information, EMD Serono, Rockland, MA, 2006.

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