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

Victor Rivera,[1] Ahmad AL-Sabbagh,[2] Randy Bennett,[2] Patricia Coyle,[3] Daniel Mikol,[4] Hillel Panitch,[5] Edward Fox,[6] Loren Rolak,[7] William Sheremata,[8] Stanton Elias[9]

[1]Baylor College of Medicine, Houston, TX, USA; [2]EMD Serono, Rockland, MA, USA; [3]Stony Brook University Hospital, Stony Brook, NY, USA; [4]University of Michigan, Ann Arbor, MI, USA; [5]Fletcher Allen Health Care, Burlington, VT, USA; [6]Central Texas Neurology Consultants, Round Rock, TX, USA; [7]Marshfield Clinic, Marshfield, WI, USA; [8]Multiple Sclerosis Center, University of Miami School of Medicine, Miami, FL, USA; [9]Department of Neurology, Henry Ford Health Science Center, Detroit, MI, USA

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Introduction and Purpose

- Multiple sclerosis (MS) is a chronic disease affecting the central nervous system that can ultimately lead to severe neurologic disability.
- The immunosuppressive agent mitoxantrone has been approved for the treatment of patients with worsening relapsing-remitting MS (WRRMS), progressive-relapsing MS (PRMS), or secondary-progressive MS (SPMS) whose neurologic status is significantly abnormal between relapses.
- 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 therapy in patients with worsening MS. Patients are monitored for 2–3 years during treatment and 2–3 years during the follow-up phase, for a total of more than 5 years during treatment and follow-up. The first patient reached the 5-year endpoint in March 2006, and the last patient will reach 5 years in January 2008.
- Objectives of the ongoing RENEW study are to
  - Evaluate the long-term effects of mitoxantrone on cardiac function
  - Evaluate the acute hematologic toxicity of mitoxantrone as manifested by serious infectious complications
  - Collect and evaluate serious adverse event (SAE) data
  - Determine the distribution of cumulative mitoxantrone doses administered
  - Monitor clinical relapses during and following mitoxantrone therapy
- Data have been collected on an ongoing basis since commencement of the study. The previous reporting periods included data gathered and validated through January 16, 2006.
- This poster presents cumulative validated data from the beginning of the study in April 2001 through the recent reporting period, ending on January 15, 2007.

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, PRMS, or SPMS and had initiated mitoxantrone (12 mg/m²) treatment within 3 months of site Institutional Review Board approval.
- As indicated in the study protocol, all patients are 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/mm³, and granulocyte count >2000 cells/mm³.

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 × ULN
- Were pregnant or nursing
- Had current urinary tract or other severe untreated infections

Assessments

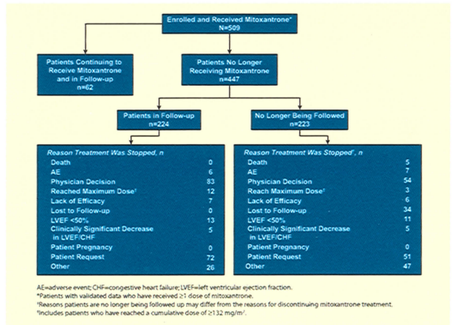
- Patients were medically evaluated before treatment initiation. After this initial examination, liver function tests, complete blood cell counts, and platelet counts were conducted every 3 months during the treatment period.
- LVEF was measured at baseline, before each dose, whenever clinically indicated, 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 post therapy follow-up period.
- All patients will be 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 received at least 1 dose of mitoxantrone through January 15, 2007. These data represent a total of 1104.7 patient years on study.
- Today of the 509 patients, 62 patients continue mitoxantrone, and 447 have stopped treatment; representing a total of 736.9 patient years on mitoxantrone.
- Follow-up data continue to be collected for 224 of the 447 patients who have stopped treatment **(Figure 1)**. The safety population reported herein includes 508 patients who received ≥1 dose of mitoxantrone and had a validated post baseline visit.

Figure 1. Flow of Patients in the RENEW Study Through January 15, 2007



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/m².

Demographics

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

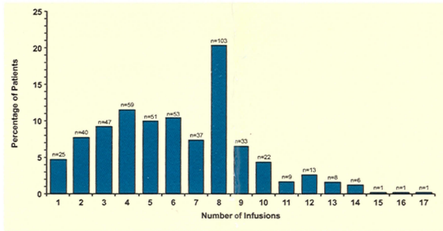
Table 1. Patient Characteristics at Baseline

Patients enrolled,* n	509
Demographic characteristics	
Women, %	67.8
Mean age, y (range)	46 (19–68)
White, %	88.6
History of MS	
Median EDSS score (range)	6.0 (0.0–9.0)
Median years since onset (range)	11.8 (0.4–45.3)
Median years since diagnosis (range)	8.6 (0.0–39.9)
Median years since most recent relapse (range)	0.4 (0.0–20.3)
Patients with no prior treatment for MS, n (%)	16 (3.1)
Cardiac	
Mean LVEF, % (range)	62 (50–83)

EDSS=Expanded Disability Status Scale; LVEF=left ventricular ejection fraction; MS=multiple sclerosis.
*Patients with validated data that received 1 dose of mitoxatrone.

- The mean duration of mitoxantrone treatment is 1.4 years (range, 0.0–4.5 y). At the time of this report, individual patients have been treated for up to 4.5 years.
- Patients have received a mean of 6 infusions (range, 1–17) during the study period **(Figure 2)**. The mean cumulative dose per patient is 68.9 mg/m² (range, 8.0–148.6 mg/m²). Doses <10 mg/m² were received by 121 (24%) patients and account for 499 (16%) of all infusions given during the study period.
- Of the 508 patients included in the safety analysis, the most commonly used concomitant therapies were GA (25%), IFN–β-1a IM (21%), IV methylprednisolone (21%), IFN–β-1b SC (14%), IFN–β-1a SC (12%), and oral prednisone (6%). One third of patients received no concomitant therapies during the study.

Figure 2. Number of Infusions of Mitoxantrone per Patient as of January 15, 2007



Serious Adverse Events

- A total of 174 SAEs have been reported in 98 patients to date.
- Of these, 103 were considered unrelated to mitoxantrone therapy by investigators, 31 were considered possibly related, 33 were considered probably related, 1 was considered definitely related, and 5 were categorized as having an unknown relationship to treatment **(Table 2)**.
- There did not appear to be a correlation between the occurrence of SAEs and the cumulative dose of mitoxantrone received.

Table 2. Serious Adverse Events Considered Probably or Definitely Related to Mitoxantrone Treatment as of January 15, 2007

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 447/509 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	447
Number of treatment stoppages attributed to physician decision, patient request, or other reason for discontinuation	333 (74.0)
Physician decision	137 (31.0)
Following administration of 8 doses	24 (17.5)
Disease stabilization	36 (26.3)
Desire to reserve mitoxantrone as a future treatment option	16 (11.7)
Combination of disease stabilization and desire to reserve mitoxantrone	9 (6.6)
No specific reason	9 (6.6)
Reasons other than those listed above	43 (10.0)
Patient request	123 (27.0)
Lack of efficacy/worsening of disease	36 (29.3)
AEs	12 (9.8)
Combination of lack of efficacy/worsening of disease and AEs	6 (4.9)
No specific reason	24 (19.5)
Reasons other than those listed above	45 (10.0)
Other	73 (16.3)
Change in physician/closing of center/inconvenience of travel/study terminated at center	38 (52.1)
Financial/medical insurance	8 (11.0)
Reasons other than those listed above	27 (6.0)

AEs=adverse events.

- 10 deaths have been reported to date.
- During the current reporting period, 2 deaths were reported; 1 due to prostate cancer (considered unrelated to mitoxantrone) and 1 due to cerebrovascular accident and carotid artery occlusion (considered possibly related to mitoxantrone).
- During the previous reporting periods, 8 deaths were reported; 1 due to multisystem organ failure secondary to CHF, cardiomyopathy, and reduced LVEF (considered probably related to mitoxantrone); 1 due to acute meningitis and 1 due to septic shock (both considered possibly related to mitoxantrone); 2 due to pulmonary embolism, 1 due to cardiopulmonary arrest, 1 due to pneumonia, and 1 due to respiratory failure (all considered unrelated to mitoxantrone).

Relapses

- To date, 327 relapses have been reported in 241 patients.
- Of these patients, the median time to first relapse was 158 days (range, 3–1215 d). The majority of relapses (90%) did not require hospitalization.

Cardiac Function and Leukemia

- At the time of this report, 382 postbaseline LVEF tests had been performed for 197 patients during the treatment phase of the study, with an LVEF result of <50% reported in 26 patients.
- 8 cases of CHF have been reported thus far; 5 in patients with SPMS, and 3 in patients with WRRMS **(Table 4)**. One case was not specified as a CHF requiring hospitalization or other treatment, and is therefore not included in the table.
  - Hospitalization was necessary in 3 cases.
- 1 case of treatment-associated acute myeloid leukemia has been reported in a patient who had received 6 infusions of mitoxantrone for a total cumulative dose of 73.5 mg/m².
- Mitoxantrone treatment continues in 62/509 patients, and an additional 224 patients are being followed up in the safety extension.

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

	Overall	WRRMS	PRMS	SPMS
Number of patients	508	80	33	395
Total number of cardiac events concurrent with treatment	28			
Number of patients with CHF*				
Requiring hospitalization	3	1	0	2
Without hospitalization	4	2	0	2
Number of patients with postbaseline LVEF evaluations (%)				
LVEF <50%	26 (5.1)	1 (1.3)	0	25 (6.3)
LVEF <50% and ≥10% decrease relative to baseline LVEF†	24 (4.7)	1 (1.3)	0	23 (5.8)
LVEF ≥50% and ≥10% decrease relative to baseline LVEF	49 (9.6)	7 (8.8)	4 (12.1)	38 (9.6)
LVEF ≥10% increase relative to baseline LVEF	42 (8.3)	6 (7.5)	2 (6.1)	34 (8.6)

CHF=congestive heart failure; LVEF=left ventricular ejection fraction; PRMS=progressive-relapsing multiple sclerosis; SPMS=secondary-progressive multiple sclerosis; WRRMS=worsening relapsing-remitting multiple sclerosis.
*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%.

Discussion and Conclusions

- In a population representing 736.9 patient years on mitoxantrone, 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 on a regular basis and before every dose (as indicated in the package insert).
- One case of treatment-related leukemia has been reported to date.
- 327 relapses have been reported in 241 patients; of these patients, the median time to first relapse was 158 days (range, 3–1215 d).
- 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.

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