

# Evidence Report: The efficacy and safety of mitoxantrone (Novantrone) in the treatment of multiple sclerosis

Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology



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## ABSTRACT

**Objective:** The chemotherapeutic agent mitoxantrone was approved for use in multiple sclerosis (MS) in 2000. After a review of all the available evidence, the original report of the Therapeutics and Technology Assessment Subcommittee in 2003 concluded that mitoxantrone probably reduced clinical attack rates, MRI activity, and disease progression. Subsequent reports of decreased systolic function, heart failure, and leukemia prompted the US Food and Drug Administration to institute a “black box” warning in 2005. This review was undertaken to examine the available literature on the efficacy and safety of mitoxantrone use in patients with MS since the initial report.

**Methods:** Relevant articles were obtained through a review of the medical literature and the strength of the available evidence was graded according to the American Academy of Neurology evidence classification scheme.

**Results:** The accumulated Class III and IV evidence suggests an increased incidence of systolic dysfunction and therapy-related acute leukemia (TRAL) with mitoxantrone therapy. Systolic dysfunction occurs in ~12% of patients with MS treated with mitoxantrone, congestive heart failure occurs in ~0.4%, and leukemia occurs in ~0.8%. The number needed to harm is 8 for systolic dysfunction and 123 for TRAL. There is no new efficacy evidence that would change the recommendation from the previous report.

**Conclusions:** The risk of systolic dysfunction and leukemia in patients treated with mitoxantrone is higher than suggested at the time of the previous report, although comprehensive postmarketing surveillance data are lacking. *Neurology*® 2010;74:1463-1470

## GLOSSARY

**AAN** = American Academy of Neurology; **CHF** = congestive heart failure; **CML** = chronic myeloid leukemia; **FDA** = Food and Drug Administration; **LVEF** = left ventricular ejection fraction; **MIMS** = Mitoxantrone in Multiple Sclerosis Group; **MS** = multiple sclerosis; **MX** = mitoxantrone hydrochloride; **NNH** = number needed to harm; **RRMS** = relapsing-remitting multiple sclerosis; **SPMS** = secondary-progressive multiple sclerosis; **TRAL** = therapy-related acute leukemia; **TTA** = Therapeutics and Technology Assessment.

Mitoxantrone hydrochloride (MX) (Novantrone®; EMD Serono, Inc., Rockland, MA) is an anthracenedione initially developed as an antineoplastic agent. MX reduces lymphocyte proliferation through several mechanisms of action, including intercalation into DNA strands inducing strand breakage and inhibition of the DNA repair enzyme topoisomerase II.<sup>1</sup> On the basis of the European Mitoxantrone in Multiple Sclerosis Group (MIMS) phase III study, the final report of which was published in 2002,<sup>2</sup> the US

Food and Drug Administration (FDA) extended approval for the treatment of aggressive relapsing-remitting multiple sclerosis (RRMS), secondary-progressive multiple sclerosis (SPMS), and progressive-relapsing multiple sclerosis in 2000. MX is usually given IV at a dose of 12 mg/m<sup>2</sup> every 3 months until a maximum cumulative lifetime dose of 140 mg/m<sup>2</sup> is reached. The Therapeutics and Technology Assessment (TTA) Subcommittee of the American Academy of Neurology (AAN) reviewed the literature on MX use in multiple

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Appendices e-1–e-4 and references e1–e15 are available on the *Neurology*® Web site at [www.neurology.org](http://www.neurology.org).

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*Disclosure:* Author disclosures are provided at the end of the article.

sclerosis (MS) in 2003.<sup>3</sup> At that time, the TTA Subcommittee reached Level B recommendations that MX was probably effective in modestly reducing clinical attack rate, MRI activity, and disease progression. (The MIMS trial was considered to represent Class II/III evidence because of incomplete blinding.) The TTA also recommended that the results of the MIMS phase III study be replicated before widespread adoption of MX as a disease-modifying agent, given the potential for treatment-related acute leukemia (TRAL) and cardiotoxicity to outweigh the clinical benefits.

In March 2005, the FDA instituted changes to the MX product labeling, including a “black box” warning about cardiotoxicity and TRAL.<sup>1</sup> This warning was prompted by postmarketing reports of cardiotoxicity at cumulative doses <100 mg/m<sup>2</sup> as well as reports of TRAL.<sup>4</sup> Evaluation of left ventricular ejection fraction (LVEF) prior to initiating therapy and before each subsequent dose was advised. Previously, cardiac monitoring had only been recommended prior to therapy and after each infusion once a cumulative dose of ≥100 mg/m<sup>2</sup> had been reached. In July 2008, the FDA made the further recommendation that patients receive annual cardiac function testing after completing MX therapy because of the potential for delayed cardiotoxicity. The purpose of this update is to review the literature since the original TTA report, specifically focusing on the efficacy and safety of MX use in patients with MS.

### DESCRIPTION OF THE ANALYTIC PROCESS

The OVID MEDLINE and the Cochrane Controlled Trials Database were searched using the keywords mitoxantrone and multiple sclerosis. All articles published in English before July 2009 with both of these terms were retrieved (i.e., only articles pertaining to MX use in MS were considered). Recently published articles were also sought through manual searches of neurology journals and reference lists of relevant publications. Abstracts from the AAN annual meetings and the European Committee for Treatment and Research in Multiple Sclerosis Annual Conferences from 2002 to 2009 were also manually reviewed for case reports of leukemia following MX therapy.

For assessment of efficacy, only controlled clinical trials or cohort studies (Class I and Class II evidence for therapeutic articles; see appendix e-3a on the *Neurology*<sup>®</sup> Web site at [www.neurology.org](http://www.neurology.org)) with defined clinical or MRI endpoints published since the first TTA review were included in the analysis. For assessment of cardiotoxicity and TRAL, all published information, including case series or case reports and abstracts from poster or oral presentations,

was reviewed (Class I–Class IV evidence for screening articles; see appendix e-3b).

A total of 434 articles and abstracts was retrieved through electronic searches and manual searching of abstracts and recent journal volumes. Seventeen efficacy studies published after the last TTA report were identified, including 2 Class I or II studies and 15 Class III or IV studies. Only the Class I and II studies were included in our evaluation. Eleven published Class III studies provided sufficient details to assess cardiotoxicity. TRAL was reported in 31 studies (including 4 poster/oral presentation abstracts), predominantly in small case series or individual case reports (Class III–IV).

**ANALYSIS OF EVIDENCE Efficacy.** No large-scale randomized controlled trial has replicated the MIMS study since the original TTA report. An MRI sub-study of the MIMS trial did not show a benefit of MX on the primary endpoint (Class II evidence).<sup>5</sup> A trial designed to assess the safety of MX induction before glatiramer acetate monotherapy demonstrated a greater reduction in contrast-enhancing lesions in patients treated with MX over 15 months, although no effect on relapses or Expanded Disability Status Scale progression was detected (Class I evidence).<sup>6</sup> Therefore, the original recommendation remains Level B.

**Safety. Cardiotoxicity.** Cardiotoxicity (characterized by decreased LVEF and/or congestive heart failure [CHF]) is a well-documented complication of MX use in cancer. CHF develops in 2.6% of MX-treated patients with cancer.<sup>1</sup> As noted in the original TTA report on MX use in MS,<sup>3</sup> an early review of cardiotoxicity in MX-treated patients with MS was reported in 2002.<sup>7</sup> This report included information from the MIMS trial,<sup>2</sup> an open-label multicenter study from France,<sup>8</sup> and a cohort from a single German center.<sup>9</sup> Of the total 1,378 patients, 2 developed CHF. Follow-up LVEF assessments were performed in 779 patients; of these, 17 patients (2.2%) developed asymptomatic LVEF <50%.

Since the initial TTA review, a series of Class III studies documented cardiotoxicity in MX-treated patients with MS (table 1), although the reported frequency, severity, and time course of cardiac complications varies markedly. Early cardiotoxicity was reported in 2 Class III studies.<sup>10,11</sup> In the first, LVEF decreased significantly in 5 out of 28 patients (~18%) after 3 doses of MX (12 mg/m<sup>2</sup> every 3 months).<sup>10</sup> In the second study (n = 18), 4 patients developed asymptomatic decreased LVEF after 1–2 MX infusions at cumulative doses ranging from 17.7 to 51.4 mg.<sup>11</sup> Four other patients showed evidence of isolated diastolic dysfunction. Follow-up echocardio-

**Table 1** Cardiotoxicity in patients treated with mitoxantrone hydrochloride

Reference	Class <sup>a</sup>	MX protocol	Cardiac monitoring	Cardiac outcome
10	III	12.5 mg/m <sup>2</sup> q 3 mo, cumulative dose ≤140 mg/m <sup>2</sup>	MUGA prior to fourth dose	5/28 patients asymptomatic ↓ LVEF
11	III	12 mg/m <sup>2</sup> q 3 mo, cumulative dose ≤100 mg/m <sup>2</sup>	TTE prior to each dose	4/18 patients asymptomatic ↓ LVEF after 1-2 doses
12	III	12 mg/m <sup>2</sup> q 1 mo × 3 doses, then q 3 mo, cumulative dose ≤144 mg/m <sup>2</sup>	MUGA every 24 wk	No ↓ LVEF during treatment, late CHF in 3/52 patients
13	III	12 mg/m <sup>2</sup> q 3 mo × 8 doses	TTE at 24 and 48 wk	↓ LVEF in 6/96 patients; 3/96 w/ ↓ LVEF <50% discontinued MX
14	III	12 mg/m <sup>2</sup> q 3 mo × 16 doses	MUGA every 24 wk	↓ LVEF <40% in 2/48 patients at 1 y
15	III	5 mg/m <sup>2</sup> q 3 mo	TTE or MUGA prior to fourth and seventh doses	↓ LVEF <50% in 4/31 patients after 1 y
16	III	12 mg/m <sup>2</sup> q 1 mo × 3 doses, then q 3 mo until cumulative dose 120 mg/m <sup>2</sup>	MUGA after third and sixth dose	118 patient cohort; ↓ LVEF in 25, LVEF <50% in 4 and an AMI in 1 patient
17	III	12 mg/m <sup>2</sup> q 1 mo × 3 doses, then q 3 mo until cumulative dose 108 mg/m <sup>2</sup>	MUGA before fourth, sixth, and ninth dose and 6 mo after therapy	31/102 patients either decrease LVEF ≥10% or LVEF <50%
18	III	10 mg/m <sup>2</sup> q 3 mo × 3 doses, then decreasing frequency over 5 y (cumulative dose <120 mg)	TTE prior to each dose	No ↓ LVEF seen in 73 patients over 5 y
19	III	8 mg/m <sup>2</sup> q 2 mo × 12 doses	TTE at 48 and 96 wk	No ↓ LVEF seen in 50 patients over 96 wk of treatment
20	III	20 mg/m <sup>2</sup> q 1 mo × 6 doses	TTE annually during and for 5 y posttreatment	↓ LVEF in 3/100 patients (1 mo, 1.5 and 5 y posttreatment)

Abbreviations: AMI = acute myocardial infarction; CHF = congestive heart failure; LVEF = left ventricular ejection fraction; MUGA = multigated radionuclide angiography; MX = mitoxantrone hydrochloride; TTE = transthoracic echocardiogram.

<sup>a</sup>See appendix e-3 for descriptions of classification of evidence.

grams showed improvement of LVEF in all patients and 2 patients subsequently resumed MX therapy without further complications.<sup>11</sup>

Another Class III study of a 52-patient cohort reported late development of CHF in 3 patients between 24 and 80 months after discontinuation of MX.<sup>12</sup> One Class III study of 96 patients who received a cumulative dose of 48 mg/m<sup>2</sup> of MX over 1 year reported asymptomatic decreased LVEF in 6 patients.<sup>13</sup> Three of these patients had LVEF <50% at 6 months and discontinued therapy. In another Class III study of 48 patients with SPMS, 2 patients developed asymptomatic and partially reversible LVEF <40% after 1 year (48 mg/m<sup>2</sup>) of MX.<sup>14</sup> A Class III study of 31 patients receiving 5 mg/m<sup>2</sup> of MX every 3 months reported asymptomatic LVEF <50% in 4 patients after ≥12 months of treatment.<sup>15</sup> One Class III study of 118 patients reported decreased LVEF >10% in 25 patients, LVEF <50% in 4 patients, and 1 myocardial infarction.<sup>16</sup> Another Class III study of 102 patients treated with a cumulative dose of 108 mg/m<sup>2</sup> reported asymptomatic decreased LVEF in 31 patients (30%).<sup>17</sup>

Other Class III studies, however, have not demonstrated such high rates of cardiotoxicity. In one series of 73 patients, no cardiotoxicity was observed, although 2 patients receiving at least 4 doses of MX were lost to follow-up.<sup>18</sup> Similarly, in another Class

III study of 50 prospectively assessed patients, no decrease in LVEF was seen during 2 years of therapy, although cardiac function was not assessed in 3 years of follow-up after discontinuation of MX.<sup>19</sup> A recent Class III study of 100 patients with aggressive RRMS receiving induction MX therapy noted asymptomatic worsening LVEF in 3 patients following MX therapy.<sup>20</sup>

Consolidating these various reports provides an estimated 83/716 (~12%) rate of decreased LVEF and 3/716 (~0.4%) risk of CHF, although the differences in MX regimens and cardiac-monitoring protocols employed in the different centers make this composite figure only a general approximation. The number needed to harm (NNH) for left ventricular dysfunction is 8. This NNH means that for every 8 patients treated with MX, 1 patient will experience some degree of cardiotoxicity.

RENEW, a phase IV study of MX use, is ongoing. As of January 2008, CHF had developed in 2% of the observed 509 patients, according to the latest presented data.<sup>21</sup> Serial cardiac function results were available for 200 patients, of whom 26 (13%) had LVEF <50%.

The iron-chelator dexrazoxane was studied in MX-treated patients with MS to evaluate a mitigating effect on MX-induced cardiotoxicity.<sup>22</sup> The study was an open-label comparison of patients

**Table 2** Reported cases of TRAL in patients treated with mitoxantrone hydrochloride<sup>a</sup>

Reference	Patient age, y/sex	Class <sup>b</sup>	Total dose	TRAL <sup>c</sup>	Interval between MX treatment and TRAL	TRAL outcome	Total no. of patients	TRAL rate, %
25	36/M	IV	87.5 mg	M3	5 y	Remission	1	NA
26, 36	30/F	III	120 mg	M5	12 mo	Death	1378	0.15
	24/F	IV	70 mg/m <sup>2</sup>	NS	NS	NS		
37	32/F	IV	NS	NS	NS	Remission	2 <sup>d</sup>	NA
38	56/M	IV	198 mg	M3	15 mo	Remission	1	NA
29	4 patients	III	31.5- 215 mg	M3	NS	2 relapses	170	2.35
39	34/F	III	72 mg/m <sup>2</sup>	M4	5 mo	Remission	59	1.69
23	28/F	IV	120 mg	M3	16 mo	Remission	1	NA
40	47/F	III	120 mg	M3	26 mo	Death	255	0.4
e1	43/F	IV	120 mg	M3	11 mo	Remission	1	NA
32, 33	48/M	III	160 mg	M1	During	Remission	304	0.33
e2	45/F	III	84 mg; 48 mg/m <sup>2</sup>	M4eo	28 mo	Remission	644	0.15
e3	47/F	III	15 mg (1 dose)	M3	~40 mo	Death	25	4
e4	21/F	III	170 mg	M3	~16 mo	Remission	250	0.8
	37/F		147.5 mg	M3	~7 mo	Remission		
27	42/M	III	60 mg/m <sup>2</sup>	NS	6 mo	Death	134	2.2
	58/M		96 mg/m <sup>2</sup>	M3	18 mo	Death		
	58/M		48 mg/m <sup>2</sup>	M3	3 mo	Death		
e5	28/M	III	66 mg/m <sup>2</sup>	M3	9 mo	Remission	120	0.83
e6	40/F	IV	120 mg	ALL	6 mo	Remission	1	NA
28	NS	III	100 mg/m <sup>2</sup>	NS	During	NS	116	2.5
	NS		30 mg/m <sup>2</sup>	NS	18 mo	NS		
	NS		70 mg/m <sup>2</sup>	NS	24 mo	NS		
e7	58/M	IV	NS	NS	4 mo	Death	1	NA
34	47/F	IV	96 mg/m <sup>2</sup>	CML	19 mo	Remission	1	NA
e8	51/M	IV	90 mg/m <sup>2</sup>	M3	22 mo	Remission	1	NA
	48/F		96 mg/m <sup>2</sup>	M3	During therapy	Remission		
31	52/F	III	30 mg/m <sup>2</sup>	M3	23 mo	Death	142	2.82
	23/M		100 mg/m <sup>2</sup>	M3	2 mo	Remission		
	59/F		70 mg/m <sup>2</sup>	M3	11 mo	Remission		
	33/F		60 mg/m <sup>2</sup>	M3	1 mo	Death		
	30		44/F	III	96 mg/m <sup>2</sup>	M3		
30	63/M	III	48 mg/m <sup>2</sup>	M3	5 y	Remission	152	2.6
	32/F		90 mg/m <sup>2</sup>	M3	11 mo	Remission		
	46/F		60 mg/m <sup>2</sup>	ALL	4 mo	Death		
	e9		35/F	IV	95 mg/m <sup>2</sup>	M4		
e10	54/F	IV	NS	M3	<1 y (exact NS)	Remission	1	N/A
e11	53/F	III	96 mg/m <sup>2</sup>	M3	14 mo	Remission	61	1.64
	53/M		84 mg/m <sup>2</sup>	M2/4	18 mo	Death		
e12	46/F	IV	120 mg	M2	~10 y	Death	1	N/A
e13	NS/M	IV	50 mg/m <sup>2</sup>	M3	NS	NS	158	1.3
	NS/F		140 mg/m <sup>2</sup>	NS	2 y	NS		

—Continued

**Table 2** Continued

Reference	Patient age, y/sex	Class <sup>b</sup>	Total dose	TRAL <sup>c</sup>	Interval between MX treatment and TRAL	TRAL outcome	Total no. of patients	TRAL rate, %
e14	59/F	IV	35 mg	M3	NS	Remission	14 <sup>f</sup>	N/A
	58/F		70 mg	M3	NS	Remission		
	59/F		234 mg	M3	NS	Remission		
	28/M		110 mg	M3	NS	Recurrence		
	61/M		100 mg	M3	NS	Remission		
	45/M		176 mg	M3	NS	Remission		
	45/M		81 mg	M3	NS	Remission		
	55/F		64 mg	M3	NS	Death		
	45/F		120 mg	M3	NS	Remission		
e15	49/M	IV	90 mg	M2	NS	Remission	1	N/A
17	54/M	IV	72 mg/m <sup>2</sup>	NS	2 y	Death	108	0.93
	46/F		108 mg/m <sup>2</sup>	NS	1 y	Death		

Abbreviations: ALL = acute lymphoblastic leukemia; CML = chronic myeloid leukemia; MX = mitoxantrone hydrochloride; NS = not stated; TRAL = therapy-related acute leukemia.

<sup>a</sup>This table does not include reference 20, a cohort of 100 patients which overlaps with reference 26, and the RENEW registry (reference 21), which may also contain duplicate cases reported in references listed above.

<sup>b</sup>See appendix e-3 for descriptions of classification of evidence.

<sup>c</sup>By French-American-British subtype unless otherwise stated, leukemia subtype not always specified.

<sup>d</sup>The other patient in this reference is also discussed in references 32 and 33.

<sup>e</sup>The second patient in this reference is not included in the author's own cohort of 61 patients.

<sup>f</sup>This article discusses 14 patients with multiple sclerosis with leukemia; not shown in the table are 2 cases not exposed to MX and 3 cases previously reported in other references.

treated with (n = 28) or without (n = 19) dexrazoxane in conjunction with MX. While a blinded assessor evaluated LVEF using multiple gated acquisition scanning, the 2 arms were recruited separately (Class III). Both patient groups experienced significant decreases in LVEF at 1 year; however, the mean percent change was lower in the dexrazoxane-treated group (−3.8% compared with −8.6%; *p* < 0.001).

**Leukemia.** TRAL is a recognized complication of chemotherapy.<sup>23</sup> Most cancer patients are treated with combinations of chemotherapeutic agents, including MX, and in this population TRAL occurs in 2%–12% of patients, with a median time of 22 months between onset of MX therapy and TRAL.<sup>23,24</sup>

The first case report of TRAL in a patient with MS was published in 1998.<sup>25</sup> An early review estimated that the risk of TRAL in the MS population was 0.07% after a mean follow-up of 36 months in 1,378 patients.<sup>26</sup> These data were based on the MIMS study<sup>2</sup> (124 patients) and the aforementioned multicenter French<sup>8</sup> (802 patients) and single-center German<sup>9</sup> studies (452 patients). No TRAL was seen in the MIMS or German cohorts, but one case was seen in the French study. The authors note in an addendum to the article that a second patient in the French cohort also developed TRAL, making the corrected rate 0.25% at 3.1

years in that 802-patient cohort, or 0.15% of the overall 1,378 patients (table 2).<sup>26</sup>

Subsequently, a number of Class III and IV case series and case reports have reported 56–57 individual cases of TRAL in MX-treated patients with MS (table 2; one patient may be duplicated in references 29 and 38). In contrast to the low incidence reported earlier, recent reports (3 as abstracts) have documented rates of TRAL between ~2% and 3%.<sup>27–31</sup> Additionally, in one of these cohorts, all 3 affected patients died despite adequate treatment,<sup>28</sup> in contrast to the majority of reported cases where leukemia remission was achieved following chemotherapy and/or bone marrow transplantation (see table 2). The majority of TRAL cases in the MS population occur within a few years of MX use, the original case report being an outlier at 5 years post-therapy (see table 2).

Other case series reported lower rates of TRAL. In a Class III retrospective study of 100 consecutive French patients who received induction monthly MX boluses for 6 months (max 72 mg/m<sup>2</sup>), one patient (previously reported in a larger cohort<sup>26</sup>) developed acute myelogenous leukemia.<sup>20</sup> A Class III retrospective survey of 304 patients treated at a single center in France<sup>32</sup> identified only one previously reported case of TRAL.<sup>33</sup> The latest presented update of the United States RENEW registry reported leu-

kemia in 3/509 patients; however, only 2 were thought to be TRAL.<sup>21</sup>

In addition, one case has recently been published of a patient developing chronic myeloid leukemia (CML) 16 months after MX therapy.<sup>34</sup> CML is not a recognized TRAL in either the cancer or MS population and it is unclear whether this malignancy resulted from the MX therapy.

Combining all of the reports listed in table 2 in which a denominator is available, the incidence of TRAL in patients with MS is 33/4,076 (~0.81%). The NNH for the development of TRAL is 123. This figure is only an approximation, however, given the heterogeneity in the length of follow-up documented in the various case series. Nevertheless, this result is very similar to the findings of a recent large retrospective review from 35 Italian MS Centers that reported 21 cases of TRAL in 2,854 (0.74%) patients treated with MX (Class III).<sup>35</sup> These authors also demonstrated a strong dose-response relationship, with the incidence rate ratio increasing from 1.84 at doses  $\leq 60$  mg/m<sup>2</sup> to 2.74 at doses  $\geq 82.4$  mg/m<sup>2</sup>. (It is unclear which of these 21 cases have been previously reported in the references listed in table 2.) Fifteen deaths occurred in the 51 patients (29%) whose outcome was reported; however, it is not known how many other patients in remission subsequently died.

**Conclusions.** While the Class III and IV evidence available provides conflicting estimates of both the frequency and severity of MX-related cardiotoxicity, asymptomatic decreased systolic function occurs in approximately 12% of patients treated with MX, and CHF occurs in approximately 0.4%. The literature on TRAL in MX-treated patients with MS is also limited to Class III and IV evidence; however, the cumulative incidence appears to be ~0.8%. Both TRAL and systolic dysfunction can occur at any time after initiation of MX, including early in the treatment course.

The evidence regarding toxicity suggests the risk of systolic dysfunction associated with the use of MX in patients with MS results in an NNH of 8, and the risk of TRAL with MX therapy results in an NNH of 123. This demonstrates that the risk of both cardiotoxicity and leukemia is likely higher than earlier estimates.

**CLINICAL CONTEXT** Recommendations on MX use reflecting the potential for harm would require a risk-benefit analysis and are beyond the scope of an evidence-based guideline. In the absence of such an analysis, it is reasonable for clinicians to follow the recommendations outlined in the product monograph and include ejection fraction assessments before initiating treatment and administering each dose of MX and

yearly after discontinuation of treatment. It is not known whether patients treated with MX with asymptomatic decreased LVEF will experience long-term sequelae. The long-term sequelae of asymptomatic cardiotoxicity is not clear. It is reasonable for clinicians to monitor patients for TRAL after MX therapy with periodic complete blood cell counts, although the optimal timing of such monitoring is not known.

Clinicians contemplating MX administration for an individual patient with MS must weigh the potential for benefit against the potential for harm given the ~12% risk of systolic dysfunction and ~0.8% risk of TRAL and the availability of alternative therapies with less severe toxicities (e.g., interferon- $\beta$  and glatiramer acetate) for patients with RRMS.

## RECOMMENDATIONS FOR FUTURE RESEARCH

- The best evidence for MX use in MS remains the MIMS trial. The first report of the TTA in 2003 recommended that the results of this trial be replicated, and this has not occurred to date. No Class I evidence exists to support the use of MX in the MS population.
- Future trials using MX induction followed by standard disease-modifying agents should be considered. Any future trial should include a prospective, long-term safety analysis.
- While the rate of symptomatic cardiotoxicity and TRAL appears low, more reports are arising to suggest that these risks are higher than indicated by the initial evidence. It is imperative that long-term, prospective postmarketing data be compiled to better quantify the risks of MX therapy.

## DISCLOSURE

Dr. Marriott has served on a scientific advisory board for Biogen Idec; has received funding for travel from EMD Serono, Inc. and Biogen Idec; and has received a speaker honorarium from Teva Pharmaceutical Industries Ltd. Dr. Miyasaki has served on a scientific advisory board for Teva Pharmaceutical Industries Ltd.; has received honoraria for educational activities not funded by industry; serves on the editorial board of *Movement Disorders*; has received speaker honoraria from Biovail Corporation; serves/has served as a consultant to Ortho-McNeil-Janssen Pharmaceuticals, Inc., Merz Pharmaceuticals, LLC, Schering-Plough Corp., the NIH (Independent Medical Monitor), Ontario Drug Benefits, and Common Drug Review, Canada; and receives research support from Teva Pharmaceutical Industries Ltd., Boehringer Ingelheim, Solvay Pharmaceuticals, Inc., Solstice Neurosciences, Inc., Impax Laboratories, Neurogen, Medivation, Inc., the National Parkinson Foundation, the Parkinson Society Canada, the Michael J. Fox Foundation, and the Huntington Study Group. Dr. Gronseth serves as an editorial advisory board member of *Neurology Now*; serves on a speakers' bureau for Boehringer Ingelheim; and receives honoraria from Boehringer Ingelheim and the American Academy of Neurology. Dr. O'Connor has served on scientific advisory boards for Novartis, Sanofi-Aventis, Bayer Schering Pharma, Genentech, Inc., and Roche; has received funding for travel from Biogen Idec, Teva Pharmaceutical Industries Ltd.; has received speaker honoraria from Biogen Idec; serves as a consultant for Biogen Idec, Bayer Schering Pharma, Daiichi Sankyo, Abbott, Genzyme Corporation, BioMS Medical, Schering-Plough Corp., Novartis, EMD Serono, Inc., Sanofi-Aventis, Teva Pharmaceutical Industries Ltd., and Genentech, Inc.; has received research support from Biogen Idec, Schering-

Plough Corp., BioMS Medical, Genentech, Inc., Bayer Schering Pharma, Novartis, Sanofi-Aventis, Roche, and the NIH (1 U01 NS 45719-01 A1 [Site PI]); and estimates that 25% of his clinical effort is spent on evoked potentials in MS diagnosis.

## DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

## CONFLICT OF INTEREST

The American Academy of Neurology is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interests to influence the recommendation of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guidelines have been reviewed by at least three AAN committees, a network of neurologists, *Neurology*<sup>®</sup> peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at [www.aan.com](http://www.aan.com).

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