

# Treatment of Melanoma-Associated Retinopathy

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## Opinion statement

Melanoma-associated retinopathy is a rare paraneoplastic disorder that is challenging to diagnose and even more difficult to treat. Because of the rarity of the disease, therapy is based on analysis of case series and case reports. Based on evidence from these reports, first-line therapy is cytoreduction of metastatic disease through metastasectomy, chemotherapy, and radiation. This can be combined with intravenous immunoglobulin. For refractory visual symptoms, additional therapies include systemic corticosteroids and plasmapheresis, but the success of these strategies has been limited. Because of the rarity of the disorder, new therapies should be evaluated and reported in the literature to expand our clinical understanding of this autoimmune disease.

## Introduction

Melanoma-associated retinopathy (MAR) is a rare autoimmune retinopathy [1••]. The paraneoplastic disorder occurs in association with cutaneous malignant melanoma. It is characterized by the sudden occurrence of visual deficits, positive visual phenomena (photopsias), and night blindness in people with no previous history of visual problems. Progressive visual loss can eventually develop. MAR can occur months to years after the initial diagnosis of malignant melanoma and is often progressive [2].

MAR is in the class of autoimmune retinopathies (AIR). In addition to MAR, the other major types of AIR are cancer-associated retinopathy (CAR) and non-paraneoplastic autoimmune retinopathy (npAIR) [1••]. All these disorders are similar, but they may differ in the type of antiretinal antibodies produced. CAR was the first identified AIR and is typically associated with small cell lung cancer. It has also been seen in

lung, ovarian, and colon cancers [1••]. In patients without malignancies who have evidence of an AIR, the diagnosis of npAIR is given. These patients typically have a personal or family history of autoimmune disorders.

There are no specific treatment regimens for the AIRs [3]. Because they are autoimmune in nature, immunosuppression is typically the treatment strategy, but because they are quite rare disorders, there is a lack of clinical studies evaluating different treatment regimens. Immunosuppressive strategies using systemic and local corticosteroids, intravenous immunoglobulin (IVIG), and other immunomodulating drugs have been employed [4•]. Patients with CAR have had the best results with immunosuppressive strategies. Patients with MAR have had less favorable results with similar regimens. The rarity of the disorder has created a lack of clinical data supporting effective therapies. To

better understand the therapeutic aspirations for the treatment of MAR, it is first important to understand the pathogenesis and diagnosis of this disorder.

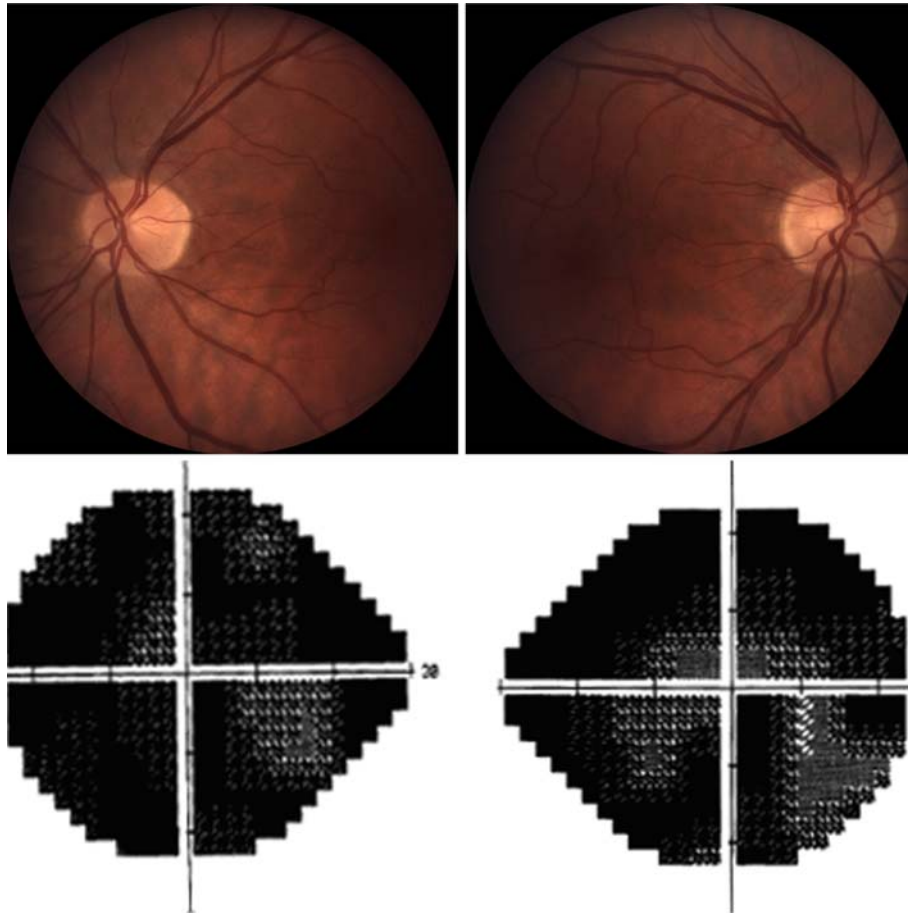
### Pathogenesis of MAR

As mentioned previously, the AIRs result from the development of antiretinal antibodies. These antibodies can vary in each type of AIR. In MAR, pathogenesis is thought to be the result of antiretinal antibodies that are shared by malignant melanoma antigens. Initially, the targets of these antibodies were difficult to discern. Retinal immunohistochemical stains in MAR patients reveal that the target antigens are located within the bipolar layer. Contrary to CAR, the antibodies in MAR were not easily identified on Western Blot analysis. Even so, significant evaluation of patients with MAR

has revealed a number of retinal targets, including a 35-kDa Müller glial cell protein [5], a 22-kDa neuronal antigen [6], transducin [7], and most recently, mitofilin and titin [8]. Immune reactions in response to the antibodies cause retinal degeneration. The resulting effect is that signal transduction is decreased and visual symptoms occur. A recent study showed that these antibodies can be active in patients with melanoma who are without ocular symptoms [9]. The study also revealed that antibody activity was higher in patients with advanced disease.

### Clinical findings in MAR

In all patients with MAR, a deficit in visual acuity is clinically present (Fig. 1). Funduscopic examination may not reveal any correlative findings. The electroretinogram (ERG) is a major diagnostic tool in the diag-



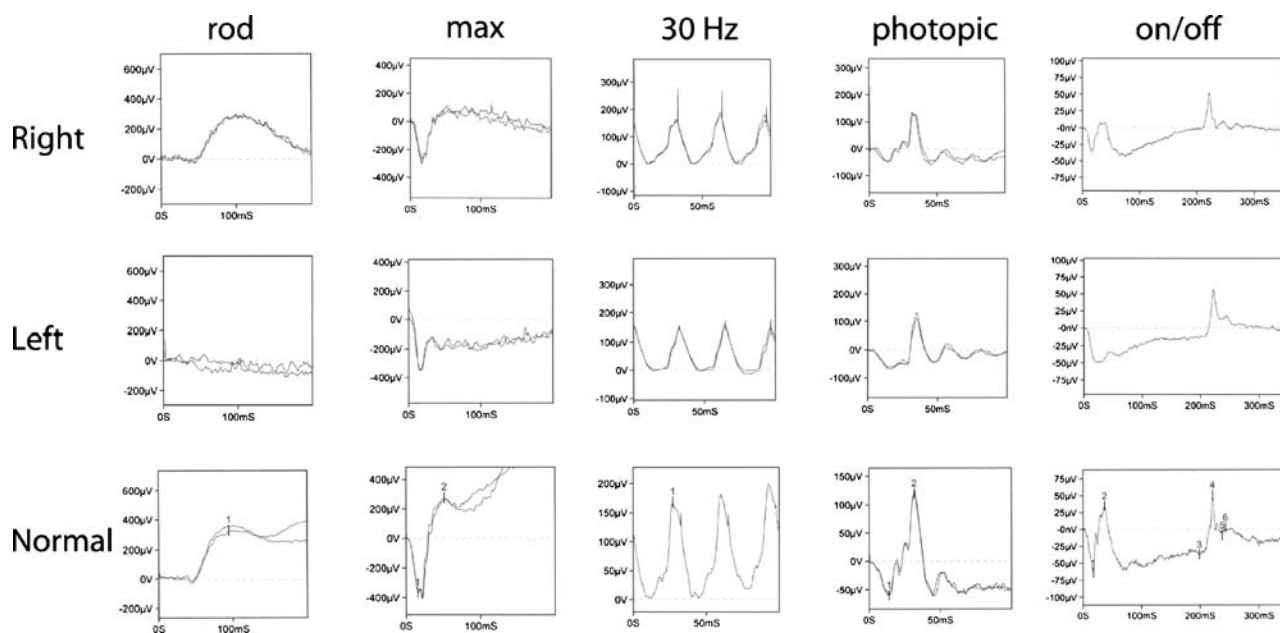
**Figure 1.** Funduscopic photograph of retina of an eye affected by melanoma-associated retinopathy (*upper panels*). No visible abnormalities are seen, but significant visual loss was demonstrated in both eyes, as seen in an automated visual field test (*lower panel*).

nosis and surveillance of MAR. The ERG reveals abolished rod-specific response, a negative maximal response, broadened trough b-wave peak, and complete loss of the ON-bipolar response (Fig. 2, Table 1). Photopic responses are usually much less affected. On the ERG, the dark-adapted A-wave is

usually normal, which suggests normal photoreceptor cell function [2]. Because of the ability of metastatic melanoma to metastasize virtually anywhere in the body, MR imaging of the optic centers in the brain, as well as the eye, should be performed to rule out metastatic disease as a causative factor.

## Treatment

- MAR has proven to be much more difficult to treat than CAR. If possible, removal of the tumor (metastasectomy) is pursued, as this eliminates the stimulus for the production of antibodies. For patients who cannot undergo metastasectomy, immunomodulatory therapies are initiated.
- Because very few patients are reported in the literature, there is no standard regimen for the treatment of MAR. There has been one large review of 62 MAR patients and their responses to treatment. Most other data have been reported in the form of case reports. The reported treatments for MAR and their efficacy will be discussed. All of these therapies are based on case series and case reports, so the recommendations outlined below are Class IV.



**Figure 2.** Electroretinography (ERG) findings of melanoma-associated retinopathy in the left eye. ERG of the right eye is normal except for reduced maximal response (*max*) and slightly reduced ON-bipolar response (*on/off*). ERG of the left eye reveals an abolished rod response, a negative maximal response, photopic responses with a broadened trough b-wave peak, and complete loss of the ON-bipolar response. Normal studies (*bottom*) are shown for comparison. (From Subhadra et al. [12••], with permission.).

**Table 1. Electroretinography (ERG) findings of melanoma-associated retinopathy in both eyes<sup>a</sup>**

	Patient: right eye	Normal	Patient: left eye
<b>Data for full-field ERG</b>			
Rod response amplitude, $\mu V$	300	85–370	Undetectable
Rod response implicit time, <i>ms</i>	100.50	81–119	–
Maximal response a-wave amplitude, $\mu V$	305	147–625	350
Maximal response a-wave implicit time, <i>ms</i>	16	10–17	17.50
Maximal response b-wave amplitude, $\mu V$	415	304–740	230
Maximal response b-wave implicit time, <i>ms</i>	52	33–57	32
Oscillatory potentials	Present	Present	Not present
30-Hz flicker amplitude, $\mu V$	165	65–155	140
30-Hz flicker implicit time, <i>ms</i>	31	23–30	31.75
Single photopic flash a-wave amplitude, $\mu V$	45	20–65	70
Single photopic flash a-wave implicit time, <i>ms</i>	14.25	12–16	16.25
Single photopic flash b-wave amplitude, $\mu V$	180	100–225	180
Single photopic flash b-wave implicit time, <i>ms</i>	31.75	25–32	35
<b>Pattern ERG data</b>			
P50 amplitude, $\mu V$	4.05	2.35–4.84	1.16
N95 amplitude, $\mu V$	6.00	3.78–7.54	3.07
N95:P50 ratio	1.48	> 1.1	1.91

<sup>a</sup>Same patient as in Fig. 2.

## Pharmacologic treatment

- Drug therapy for MAR is aimed at immunomodulation. By altering the immune response involved in MAR, it is hypothesized that improvement can be seen in the visual deficits. Immunomodulation can be achieved through generalized immunosuppression or through alteration of the normal immune response.

## Immunosuppressive therapy

### *Corticosteroids (prednisone, methylprednisolone)*

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|--------------------------|--|
| <b>Standard dosage</b>   | Prednisone is administered orally at a range of doses. In MAR, treatments have consisted of 60 to 80 mg daily. Because little is known about the necessary duration of treatment, a standard time to stay on this dose has not been determined. In one successful case, a patient was treated with 60 mg/d for 1 month and then started on a slow taper over the course of 7 months. Methylprednisolone is an intravenous corticosteroid that has been used for the initiation of treatment. A standard dose has yet to be determined, but a dose of 125 mg given twice daily has been used in the past [2]. Local treatment with subtenon injection of corticosteroids has not been effective and is not typically used for the treatment of MAR. |
| <b>Contraindications</b> | Systemic corticosteroids are relatively well tolerated and virtually no absolute contraindications exist. A number of adverse effects are associated with corticosteroid use and special care should be taken to evaluate patients who are at high risk for these effects.   |

<b>Main drug interactions</b>	Corticosteroids are noted to have a number of drug interactions. Rifampin and a number of antiepileptic medications reduce the efficacy of corticosteroids. Corticosteroids also reduce the therapeutic effects of a number of drugs including hypoglycemic agents, antihypertensives, diuretics, and heparin. Corticosteroids also can potentiate the ability of nonsteroidal anti-inflammatory medications to cause gastrointestinal ulcers.
<b>Main side effects</b>	Corticosteroid use is associated with a number of significant adverse effects involving almost every organ and physiologic system. Dermatologic effects are common and include skin fragility, easy bruisability, striae formation, and impaired wound healing. Major hematologic effects are lymphocyte depletion and promotion of coagulation. Endocrinologic effects are among the more concerning and significant findings in corticosteroid use. Chronic use of high-dose corticosteroids can cause patients to develop a cushingoid habitus (moon facies, buffalo hump, central obesity). Hyperglycemia secondary to increased gluconeogenesis and insulin intolerance is also common and should be monitored in diabetic patients. After cessation of moderate to high doses of steroids, patients can be at risk for adrenal insufficiency due to suppression of the hypophyseal pituitary adrenal axis. Musculoskeletal effects are also common. Osteoporosis and osteopenia are commonly associated with significant corticosteroid use. Corticosteroid myopathy can also occur in patients on chronic steroids. Osteonecrosis or avascular necrosis is another significant musculoskeletal disorder that can develop from long-term steroid use. Gastrointestinal effects are mostly related to ulcerogenesis. Neurologic effects such as mania, insomnia, and sometimes psychosis are more common in elderly patients. Finally, perhaps one of the more concerning adverse effects of corticosteroids involves immunosuppression. High-dose, chronic steroid use places patients at risk for opportunistic infections. It also has been suggested that high-dose steroids used to treat MAR may cause worsening of metastatic disease in melanoma patients [10].
<b>Special points</b>	Corticosteroids are among the most widely used immunosuppressive drugs, and they have shown utility in other autoimmune retinopathies, such as CAR. In MAR, the results have been less promising. Only two patients out of nine reported in a small case series [2] and several case reports [10,11] have responded to systemic corticosteroid therapy. Because of their many adverse effects and relatively low response rate to date, the use of systemic corticosteroids should be reserved for therapy in MAR patients in whom other, more successful options have failed. Because of the small number of reported cases, however, it may be too early to completely disregard systemic corticosteroids as a viable therapeutic option for MAR further investigation is warranted.
<b>Cost/cost-effectiveness</b>	Oral prednisone is generic and is relatively inexpensive. The drug is dosed once daily. The overall cost of its use would be related to the duration of therapy needed, but compared with other MAR therapies, daily oral prednisone is inexpensive. Methylprednisolone is an intravenous medication and is more expensive than prednisone. The drug is usually given only once or over a few days, however, so its overall use is relatively inexpensive when compared with other MAR therapies.

### *Intravenous immunoglobulin*

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<b>Standard dosage</b>	IVIg is given intravenously. The typical dosage is 300–600 mg/kg per month, given every 2–4 weeks for most autoimmune and neurologic disorders. In treating MAR, a more rapid induction treatment has been used. In one case
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series, several patients were given IVIG at a dose of 400 mg/kg per day for 5 days with success [2]. Another case report [12••] gave IVIG as induction treatment at a dose of 100 g/d for 2 days, then monthly as maintenance at the same dose. Because so few cases of MAR have been treated with IVIG, no standard dosage is recommended. The agent is given intravenously at an initial rate of 0.5–1.0 mg/kg per minute. After 15–30 min, the rate is increased to 1.5–2.5 mg/kg per minute, and it can be increased further as tolerated. It usually takes 2–4 h to complete the infusion [13].

<b>Contraindications</b>	IVIG is contraindicated in patients who have had anaphylaxis or a severe immune response to IVIG in the past. The agent should be used with extreme caution in those with IgA deficiency, particularly if it is severe. In IgA-deficient patients, products with low IgA content should be used [13].
<b>Main drug interactions</b>	The only known drug interaction with IVIG is that it can impair the efficacy of live attenuated vaccines such as measles, mumps, and rubella.
<b>Main side effects</b>	The most serious adverse effects experienced with IVIG infusion are anaphylaxis, Stevens-Johnson syndrome, hypotension, acute respiratory distress syndrome, transfusion-related lung injury, stroke, and seizure. Fortunately these are not common. The most commonly experienced adverse effects are headache, pain, nausea, fatigue, and chills. Slowing the infusion or pre-treating with medications such as diphenhydramine and acetaminophen can help alleviate these effects. Of note, patients receiving IVIG formulated in a sucrose stabilizing agent can develop acute renal failure.
<b>Special points</b>	IVIG has shown utility in a number of autoimmune disorders. Specifically, it has shown activity in autoimmune retinopathies. Only a few cases of patients with MAR being treated with IVIG have been reported, but it appears to be the most successful therapy to date. In one case series, three patients were treated with IVIG [2]. Of these three patients, one responded to IVIG alone and the other two responded to the combination of IVIG and cytoreductive surgery. Another recent case report revealed that IVIG was successful in treating a patient with MAR who continued to have visual decline after metastasectomy. Because these data are promising but limited, it is suggested that IVIG should be used in the treatment of MAR if cytoreductive surgery and radiation are not successful.
<b>Cost/cost-effectiveness</b>	IVIG is quite expensive. The cost varies depending on the institution where it is available. Currently at our institution, 30 g of IVIG costs approximately \$2,000 [14]. This cost does not include the cost of administration or staff.

## Interventional procedures

- Interventional procedures for the treatment of MAR are aimed at cytoreduction. Cytoreduction is thought to decrease the amount of antiretinal antibody production by decreasing the amount of tumor. Radiation therapy is the main interventional procedure used in the treatment of MAR.

### Radiation therapy

Radiation therapy is used as palliative and curative therapy in a number of different malignancies. Traditionally, melanoma has been thought to be a fairly radioresistant tumor, and long-term remissions are not possible with radiation therapy alone. Clinical practice has shown that metastatic melanoma can be successfully radiated for palliation [15].

<b>Standard procedure</b>	In MAR, radiation therapy can be used as a cytoreductive technique to reduce tumor burden and thus antiretinal antibody production. The procedure is noninvasive and utilizes external beam techniques. External beam therapy works by delivering a beam of high-energy x-rays directed at a tumor. Before the procedure, the patient undergoes a simulation (usually facilitated by CT) to determine the area that will be treated. Radiation dosing is determined based on the type, size, and location of the tumor.
<b>Contraindications</b>	Radiation therapy is usually well tolerated and is noninvasive, so contraindications to therapy are few. Most are related to tumor location. If the tumor is too close to a vital organ such as the heart, radiation may cause too much damage to the organ and result in death. Additionally, patients who have received radiation in the past may not be able to receive more radiation therapy because of cumulative toxicity from prior radiation.
<b>Complications</b>	Complications and adverse effects of radiation therapy are related to the region being irradiated and the dose of radiation used [15]. The procedure itself is pain-free. Radiation is toxic to essentially all organs. The skin is the most commonly involved organ. Acutely, the skin can become erythematous and irritated. Desquamation can occur in some cases. Other epithelial tissues that are commonly involved include the oral mucosa and gastrointestinal tract. Tissues exposed to repeated radiation or high doses of radiation can develop fibrosis. This is commonly seen in the lung. Hair loss and even cognitive decline can develop with brain radiation. Fatigue is one of the most common adverse reactions from radiation therapy. Death from radiation therapy is very rare and is usually related to toxicity of vital organs, such as the heart.
<b>Special points</b>	The use of radiation therapy in MAR was shown to be effective in one patient reported in a case series [2]. There are no clinical studies or other large case series evaluating the procedure. Because of its ease of use and the fact that it is relatively well tolerated, the use of radiation therapy for cytoreduction should be considered as one of the first-line therapies for MAR. It is particularly useful in patients who are not candidates for surgery or cytoreductive chemotherapy because of their performance status.
<b>Cost/cost-effectiveness</b>	The cost of radiation therapy depends on the dose of radiation needed, the number of treatments required, and the extent of disease that must be radiated. In general, radiation therapy is fairly expensive and is comparable to the cost of surgery.

## Surgery

- Metastasectomy is a cytoreductive surgery that involves the surgical removal of metastatic disease. This results in an overall decrease in tumor burden. In MAR, cytoreductive surgery by the means of metastasectomy reduces tumor burden and is thus hypothesized to decrease the source for antiretinal antibody production.

### *Metastasectomy*

<b>Standard procedure</b>	The procedure varies based on the site of metastasis. Melanoma is difficult to control surgically because of its ability to metastasize virtually anywhere. Superficial lesions would be easier to access and the surgery would be less technically difficult. In melanoma, common sites for metastasectomy include lymph nodes, soft tissues (muscle and fat), and skin. These regions
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make up about 40% of the metastatic sites for malignant melanoma [16]. Pulmonary metastases are also commonly seen they are more difficult to remove than more superficial lesions but surgical intervention is possible. The most common procedure involves video-assisted thoracoscopic surgery (VATS) with resection of the lesion. Intra-abdominal metastases, though less common than pulmonary metastases, are also present in metastatic melanoma. In the gastrointestinal tract, the small bowel is the most common site for intra-abdominal metastases, followed by the colon and then the stomach. The liver is also a common intra-abdominal metastatic site. Metastasectomy is not typically performed in the bowel or stomach unless there is concern about obstruction. Solitary liver metastases are amenable to surgical resection with reasonable results. Intracranial metastases make up another common group of melanoma metastases. Solitary lesions can be removed with some success, but morbidity and mortality from this procedure can be significant.

**Contraindications** Contraindications to the procedures are related to whether or not the patient is a good surgical candidate, which depends on the nature of the surgery and the degree of invasiveness. For instance, a localized resection of a skin lesion or lymph node would be more easily tolerated than resection of a liver mass.

**Complications** Surgical complications in general are related to bleeding, infection, and damage to surrounding tissue and neurovasculature. Once again, these vary and are related to the degree of surgical intervention.

**Special points** The largest case series of patients with MAR included 62 patients [2]. Metastasectomy was associated with the best results in this series. Of the eight patients who responded to treatment, four had undergone cytoreductive surgery as an attempt to treat their MAR. The treatment was done in combination with the use of IVIG in two of the patients. Because of these data, it is widely agreed that if metastasectomy is possible, it should be the first line of therapy.

**Cost/cost-effectiveness** The cost of cytoreductive surgery is variable, but it is more expensive than other methods of therapy. To estimate the price, one would have to account for the cost of the procedure itself (including anesthesia) and the cost of hospitalization if the procedure requires an inpatient stay.

## Other treatments

- Other treatments for MAR revolve around the ongoing theme of immunomodulation and reducing antiretinal antibodies. Plasmapheresis has shown some success in treating patients with MAR.

### *Plasmapheresis*

**Standard procedure** Plasmapheresis is a form of therapeutic apheresis in which plasma is removed from the patient and replaced with donated plasma or normal saline and albumin. With each cycle of plasmapheresis, the estimated circulating plasma volume is removed from the patient and replaced with the equivalent amount of normal saline and 5% albumin [17]. For this procedure, special intravenous access is required. The access needs to allow for the venous removal of blood while simultaneously allowing for venous infusion of solute. This is typically achieved through the use of a temporary dual-lumen venous catheter. The procedure is performed over several hours. It is not known how many cycles of plasmapheresis should be performed to treat MAR.



<b>Contraindications</b>	There are no absolute contraindications to plasmapheresis. Because of concerns about fatal bleeding or hypotension, it is relatively contraindicated in patients with coagulopathy, severe thrombocytopenia, or sepsis.
<b>Complications</b>	The major side effects of plasmapheresis include transfusion reaction, urticarial reaction, citrate-related nausea and vomiting, bleeding, and hypotensive reactions [18]. Transfusion reactions and urticarial reactions are seen in patients getting donor plasma. Bleeding is typically related to the venous access placement.
<b>Special points</b>	Plasmapheresis is used in a wide variety of autoimmune and neurologic disorders. The desired mechanism of action is to remove autoantibodies, circulating immune complexes, and cytokines. It is hypothesized that this procedure could remove the antiretinal antibodies produced in MAR. It also could remove cytokines and immune complexes that contribute to the immunologic response. Only three MAR patients who have been treated with plasmapheresis are reported in the literature [2]. Of these three patients, one was treated with plasmapheresis alone and did not respond to therapy. One patient was treated with plasmapheresis, prednisone, azathioprine, and gabapentin. This patient had only mild improvement in ERG findings and on visual tests. The final patient, who received both intravenous methylprednisolone and plasmapheresis, had a favorable response. It is not clear if the plasmapheresis, the corticosteroids, or the combination of the two created the response. Because of the limited data about plasmapheresis and the mixed results, it is not recommended as early therapy for MAR. It could be considered for nonresponders or those who do not qualify for other therapies.
<b>Cost/cost-effectiveness</b>	Plasmapheresis is labor-intensive and requires a number of personnel including specialized nursing staff and knowledgeable blood bank personnel. Exact costs vary based on the facility, but it is generally very expensive.

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## Disclosure

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No potential conflicts of interest relevant to this article were reported.

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