Management of ARIA in lecanemab-treated patients with Alzheimer's disease

Overview

Lecanemab (LEQEMBI, Eisai Inc. and Biogen) is an amyloid beta-directed monoclonal antibody indicated for the treatment of mild cognitive impairment or mild dementia due to Alzheimer's disease.[1] Lecanemab is administered by intravenous infusions every 2 weeks.

ARIA

An important adverse effect to recognize are amyloid-related imaging abnormalities (or ARIA, **Table 1**). ARIA occur in two forms, with edema (ARIA-E, **Table 2**) or with hemorrhagic changes (ARIA-H, **Table 3**). In the phase 3 trial of lecanemab (CLARITY AD),[1] ARIA of any type occurred in 21.5% of patients, including 8.2% who had ARIA-E and ARIA-H concurrently. ARIA-E occured in 12.6% (2.8% symptomatic) of patients overall, while ARIA-H occured in 17.3 % (0.7% symptomatic). Importantly, the risk for ARIA increases with carriage of apolipoprotein E epsilon 4 (APOE4), particularly for those who are homozygous APOE 4/4. ARIA-E occurred in 5.4% (1.4% symptomatic) of APOE4 non carriers, 10.9% (1.7% symptomatic) of APOE4 heterozygous individuals, and 32.6% (9.2% symptomatic) of APOE4 homozygous individuals.[1] Likewise, ARIA-H occurred in 11.9% of non carriers, 14.0% of APOE4 heterozygous individuals, and 39.0% of APOE4 homozygous individuals; with the most common findings being microhemorrhage (14.0%), superficial siderosis (5.6%), and macrohemorrhage (0.6%).[1] A listing of radiographic severity for ARIA is provided in **Table 1**.

Symptoms and evaluation

The most common symptoms attributed to ARIA include: **headache, confusion, visual changes, dizziness, nausea, gait difficulty**. More serious symptoms related to ARIA include: **seizures or status epilepticus, coma/stupor, and other focal neurologic deficits**.[2] Other neurologic symptoms are possible depending on the location and extent of ARIA. Symptoms may be mild (symptoms do not lead to disruption in daily activity and are not acutely or subacutely progressing), moderate (symptoms reduce or affect normal daily activity), or severe (sufficient to require hospitalization, cause incapacitation, increase risk of permanent deficits, significantly impact activities of daily living, or display acute to subacute progression concerning for substantial worsening in short time-period).

Patients on lecanemab with mild symptoms (eg, mild headache, nausea, dizziness) should be scheduled for an urgent clinic visit and have an updated MRI within 24 to 72 hours. If visits/MRI cannot be obtained in a timely manner as an outpatient (eg, on Friday afternoon), these patients should be referred to the Emergency Department. Patients with moderate to severe symptoms (eg, new visual field cut, focal weakness, dysarthria, severe headache or nausea/vomiting, severe confusion beyond recent baseline) should be referred to the Emergency Department.

Management of ARIA

Asymptomatic

In patients who are asymptomatic and where radiographically mild ARIA-E or ARIA-H are discovered on routine surveillance, dosing of lecanemab may continue after shared decision-making with repeat MRI every 4 weeks until ARIA-E resolves or ARIA-H stabilizes. If asymptomatic and radiographically moderate ARIA-E or ARIA-H are found, further dosing should be suspended with repeat MRI every 4 weeks until ARIA-E resolves or ARIA-H stabilizes, at which point shared decision-making would be engaged to decide on whether to resume lecanemab dosing. For patients who

experience two occurrences of radiographically moderate ARIA, dosing should be discontinued. If asymptomatic and radiographically severe ARIA-E or ARIA-H are found, further dosing should be discontinued and patients should be treated with corticosteroids as below and followed clinically and radiographically.

- **Preferred**: IV methylprednisolone 1,000 mg daily for 5 days followed by weekly doses thereafter for 3 more doses with plan to re-image at 1 month.
- **Secondary option**: IVMP x 5 days as above followed by oral prednisone taper 40 mg for one week, 30 mg for one week, 20 mg for one week, and re-image at one month.
- **Prophylaxis**: PJP prophylaxis is not needed unless the patient has a specific cause (other than age and the steroid treatment) to be immunosuppressed. If patients are placed on corticosteroid treatment for longer than 4 weeks, they should initiate a proton pump inhibitor (omeprazole) or H2 inhibitor (ranitidine) for gastrointestinal prophylaxis as well as calcium 1,500 mg (elemental calcium) and vitamin D 800 units daily.

Mild to moderate symptoms

In patients with mild to moderate symptoms and radiographically mild-to-moderate ARIA-E or ARIA-H, further dosing should be suspended, and patients should be treated with corticosteroids as above and followed clinically and radiographically. Additional symptomatic management may be targeted to the specific clinical scenario. For patients who experience two occurrences of symptomatic ARIA, dosing should be discontinued.

Severe symptoms

In patients with severe symptoms (regardless of ARIA grade), further dosing should be discontinued and patients should be treated with corticosteroids as above and followed clinically and radiographically. Additional symptomatic management may be targeted to the specific clinical scenario.

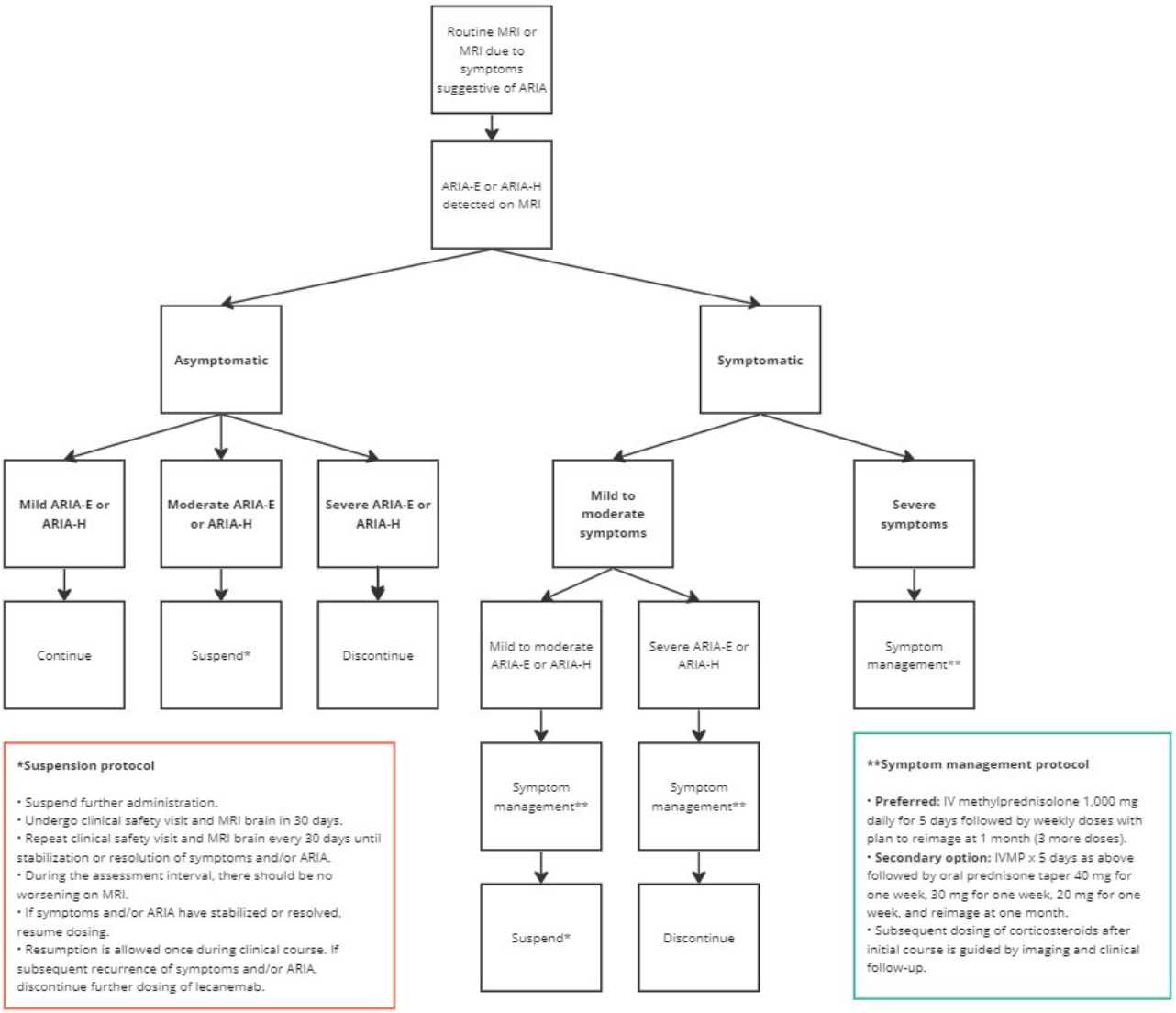
Side effects of methylprednisolone

Administration of IV steroids can lead to avascular necrosis of the hip. Although very rare, this condition should be considered if a patient receiving IV steroid experiences new hip or groin pain. Other significant side effects to be aware of include gastrointestinal ulceration, especially in the setting of an underlying ulcer. Blood glucose levels may rise while on steroids, and individuals with diabetes should be particularly cognizant of glucose levels while on steroids. It is not uncommon for those without known diabetes to develop glucose intolerance after steroids are initiated. Patients are more vulnerable to infections during steroid administration.

Other side effects include osteopenia/osteoporosis, which usually occur with more prolonged administration. Patients with an underlying psychiatric disorder should be aware of steroid psychosis, although this can occur even without an underlying psychiatric diagnosis. Other side effects include but are not limited to: hypertension, electrolyte imbalances, cataracts, increased intraocular pressure/glaucoma, nervousness, insomnia (especially the night of the infusion), fluid retention/edema, weight gain, and Cushing's syndrome.

Monitoring while taking methylprednisolone

Prior to administering IV steroids, the following should be checked: blood pressure, serum glucose and electrolytes, and urine pregnancy screen when applicable. During administration, particular attention should be paid to symptoms such as hip or groin pain, signs or symptoms of infection, and significant abdominal pain. For patients with known diabetes, close glucose monitoring is required as adjustments in insulin doses may be required both during initiation of the steroids and with discontinuance. Patients should not receive live vaccines while on this treatment.



***Suspension protocol**

- Suspend further administration.
- Undergo clinical safety visit and MRI brain in 30 days.
- Repeat clinical safety visit and MRI brain every 30 days until stabilization or resolution of symptoms and/or ARIA.
- During the assessment interval, there should be no worsening on MRI.
- If symptoms and/or ARIA have stabilized or resolved, resume dosing.
- Resumption is allowed once during clinical course. If subsequent recurrence of symptoms and/or ARIA, discontinue further dosing of lecanemab.

****Symptom management protocol**

- **Preferred:** IV methylprednisolone 1,000 mg daily for 5 days followed by weekly doses with plan to reimage at 1 month (3 more doses).
- **Secondary option:** IVMP x 5 days as above followed by oral prednisone taper 40 mg for one week, 30 mg for one week, 20 mg for one week, and reimage at one month.
- Subsequent dosing of corticosteroids after initial course is guided by imaging and clinical follow-up.

Table 1: ARIA MRI classification criteria

ARIA type	Radiographic severity		
	Mild	**Moderate**	**Severe**
ARIA-E	FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location <5 cm	FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring <10 cm	FLAIR hyperintensity >10 cm with associated gyral swelling and sulcal effacement. One or more separate/ independent sites of involvement may be noted.
ARIA-H microhemorrhage	≤ 4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 areas of superficial siderosis

Table 2: Dosing recommendations for patients with ARIA-E

<table>
<tr><td rowspan="2">Clinical symptom severity[1]</td><td colspan="3">ARIA-E severity on MRI</td></tr>
<tr><td>Mild</td><td>Moderate</td><td>Severe</td></tr>
<tr><td>Asymptomatic</td><td>May continue dosing</td><td>Suspend dosing[2]</td><td rowspan="4">Discontinue dosing[3]</td></tr>
<tr><td>Mild</td><td colspan="2">Suspend dosing[2]</td></tr>
<tr><td>Moderate</td><td colspan="2">Suspend dosing[2]</td></tr>
<tr><td>Severe</td><td colspan="2">Discontinue dosing[3]</td></tr>
</table>

[1] **Mild:** Discomfort noticed, but no disruption of normal daily activity. **Moderate:** Discomfort sufficient to reduce or affect normal daily activity. **Severe:** Incapacitating, with inability to work or to perform normal daily activity.
[2] Suspend until MRI demonstrates radiographic resolution and symptoms, if present, resolve. See suspension protocol.
[3] Discontinue further dosing.

Table 3: Dosing recommendations for patients with ARIA-H

<table>
<tr><th rowspan="2">Clinical symptom severity</th><th colspan="3">ARIA-H severity on MRI</th></tr>
<tr><th>Mild</th><th>Moderate</th><th>Severe</th></tr>
<tr><td>Asymptomatic</td><td>May continue dosing</td><td>Suspend dosing[1]</td><td rowspan="4">Discontinue dosing[2]</td></tr>
<tr><td>Mild</td><td colspan="2">Suspend dosing[1]</td></tr>
<tr><td>Moderate</td><td colspan="2">Suspend dosing[1]</td></tr>
<tr><td>Severe</td><td colspan="2">Discontinue dosing[2]</td></tr>
</table>

[1] Suspend until MRI demonstrates radiographic resolution/stability and symptoms, if present, resolve.
[2] Discontinue further dosing.

References

1. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. *N Engl J Med.* 2023;388(1):9-21.
2. Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: Appropriate Use Recommendations. *J Prev Alzheimers Dis.* 2023;10(3):362-377.

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