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# Cleveland Clinic

## Clinical Rx Forum

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### 5-Aminolevulinic Acid for Malignant Glioma Detection

By: Sylvie Hall, Pharm.D., MPH

**Background:** Gliomas are infiltrative tumors that occur in the brain and spinal cord, originating from glial cells and surrounding neurons.<sup>1</sup> Resection is typically first-line treatment if the tumor is accessible and the patient is eligible for neurosurgery. The goal of surgery is to maximize the amount of tumor removed while preserving neurologic function, making it important for the surgeon to be able to clearly visualize the boundaries of malignant tissue. Various strategies have been used to aid in tumor resection including magnetic resonance imaging (MRI)-guided surgery, neuronavigation, and fluorescein sodium staining, however these methods were not always beneficial.<sup>2,3</sup> Therefore, 5-aminolevulinic acid (5-ALA) (Gleolan®: NX Development Corp) was investigated as a potential optical imaging agent to visualize World Health Organization (WHO) Class III and IV malignant gliomas and was eventually approved by the Food and Drug Admin-

istration (FDA) for this indication in 2017.<sup>4</sup>

**Mechanism of Action:** 5-aminolevulinic acid is an endogenous metabolite formed within the hemoglobin metabolic pathway from succinyl-CoA and glycine.<sup>1,5</sup> Upon oral administration, exogenous 5-ALA crosses the blood-brain barrier where it is taken up by malignant glioma cells and metabolized to the fluorescent metabolite protoporphyrin IX (PpIX). The accumulation of PpIX in tumor cells emits a red fluorescence when viewed under a specialized surgical microscope, while nonmalignant tissue maintains a blue appearance thus enabling the surgeon to approximate the tumor boundaries.

**Key Clinical Trial:** The FDA approval of 5-ALA was based on a randomized phase III trial which compared fluorescence-guided resection using 5-ALA to

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### Denosumab for Bone Disease in Multiple Myeloma

By: Bethany Hipp, Pharm.D.

**Background:** Multiple myeloma (MM) is a hematologic malignancy that presents most frequently in adults aged 65-74 years old and accounts for 1.8% of all cancers.<sup>1</sup> It is characterized by the proliferation of abnormal plasma cells in the bone marrow or the presence of a plasmacytoma and monoclonal paraproteins known as M-spikes.<sup>2,3</sup> Symptoms of active myeloma include elevated serum calcium, renal insufficiency, anemia, and bone lesions (CRAB symptoms).<sup>2</sup> Bone disease occurs in approximately 80-90% of patients

with MM due to the enhancement of osteoclastic resorption and the suppression of osteoblastic development.<sup>2,4</sup> Skeletal-related events (SREs) such as pathological fractures and spinal cord compression are associated with increased morbidity and mortality.<sup>4</sup> The National Comprehensive Cancer Network (NCCN) Guidelines on MM have recommended the initiation of treatment with zoledronic acid (Zometa®) for all patients receiving primary myeloma therapy, however the

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conventional microsurgery with white light.<sup>3</sup> The study objective was to assess the effect of 5-ALA on the degree of surgical resection, progression-free survival, overall survival, and morbidity. Patients (N=322) between the ages of 18 and 72 years old newly diagnosed with untreated malignant glioma were randomly assigned to fluorescence-guided surgery with 5-ALA (n=139) or white light surgery (n=131). The primary endpoints consisted of the proportion of patients with histologically confirmed malignant glioma on central neuropathological review without residual contrast-enhancing tumor on post-operative MRI and progression-free survival at 6 months. Secondary endpoints were residual tumor volume detected on MRI, overall survival, type and severity of neurological deficits after surgery, and toxic effects. In terms of primary outcome, 29% more patients in the 5-ALA group were without detectable tumor on post-operative MRI compared to the control group (95% CI 17-40; p=0.0001). Progression-free survival at 6 months was better among the 5-ALA group compared to control (41% vs 21.1%; p=0.003). Residual tumor volume was significantly smaller in 5-ALA patients than white light patients (0 cm<sup>3</sup> [range: 0-25.7] vs 0.7 cm<sup>3</sup> [range: 0-32.6] respectively; p<0.0001). Additionally, fewer 5-ALA patients required repeat surgery. However, there was no significant difference in overall survival between the two groups with those in the 5-ALA group having an overall survival of 13.5 months (range: 12-14.7 months) and those in the control group having overall survival of 15.2 months (range: 12.9-17.5 months). Assessment of the total stroke scale scores during weeks 1 and 6 after surgery demonstrated no significant between-group differences in neurological impairment. The authors concluded that 5-ALA guided resection achieved a clinical benefit in terms of completeness of tumor removal and progression-free survival.

**Safety:** The use of 5-ALA is contraindicated in those with hypersensitivity to 5-ALA or porphyrins and those with acute or chronic types of porphyria.<sup>4</sup> The most common adverse effects of 5-ALA are transient increases in AST/ALT and gamma-GT 24 hours after surgery, but these effects dissipate and have not resulted in liver injury. Other common adverse effects which occurred within a week following surgery included pyrexia, hypotension, nausea, and vomiting. Due to the risk of phototoxicity, patients should have reduced exposure to sunlight or room light and avoid the use of other phototoxic drugs for 24 hours postoperatively.

**Administration:** It is recommended to administer 5-ALA solution 3 hours (range 2 to 4 hours) prior to induction of anesthesia at a dose of 20 mg/kg by mouth.<sup>4,6</sup> It is available as a 1500 mg vial of lyophilized powder which must be reconstituted with 50 mL of drinking water prior to administration. There are no recommendations for renal or hepatic dose adjustments of 5-ALA. It must be used with a standard surgical operating microscope adapted with a blue light-emitting light source and ancillary excitation and emission filters in order to visualize fluorescence.

**Cost and Availability:** The 5-ALA formulation is available as the brand-name product Gleolan® NDC 71469-0231-01.<sup>4</sup> It is supplied as 1500 mg of lyophilized ALA HCl powder (equivalent to 1,170 mg 5-ALA) for oral solution in a glass vial. Gleolan® has a suggested wholesale price of \$3347/vial.<sup>7</sup> A 70 kg patient would require one vial to meet the 20 mg/kg dosage requirement. Although this agent does not have a specific Risk Evaluation Mitigation Strategy (REMS) program, it has limited access. Additionally, it may only be used by neurosurgeons who have completed a manufacturer-provided training program.

**Formulary status:** Aminolevulinic acid is restricted to the Department of Neurosurgery, Brain Tumor and NeuroOncology for use only by physicians who have completed the Gleolan® training program.

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increased incidence of renal disease in MM can pose challenges with bisphosphonate therapy.<sup>1,2</sup> Therefore, denosumab (Xgeva®; Amgen), an agent with a minimal risk of nephrotoxicity, was studied as an alternative agent for the treatment of bone disease in MM and was approved by the Food and Drug Administration (FDA) for this indication in January 2018.<sup>5,6</sup>

**Mechanism of Action:** Denosumab is a monoclonal antibody that targets receptor activator of nuclear factor-kappa ligand (RANKL).<sup>6,7</sup> This protein is secreted by osteoblasts to activate osteoclasts and promote bone resorption. Denosumab inhibits the interaction of RANKL with its receptor RANK to decrease osteoclast formation and prevent SREs.

**Key Clinical Trial:** Denosumab's FDA approval for MM was based on the results of a randomized, double-blind, double-dummy, phase III trial assessing the non-inferiority of denosumab to zoledronic acid for the treatment of bone disease.<sup>8</sup> Patients included in this trial had newly diagnosed MM with at least one documented osteolytic lesion, Eastern Cooperative Oncology Group (ECOG) performance status 0-2, and creatinine clearance (CrCl)  $\geq 30$  mL/min. Patients (N=1718) were randomized 1:1 to receive subcutaneous denosumab 120 mg (n=859) every 4 weeks or intravenous zoledronic acid 4 mg (n=859) every 4 weeks. The primary outcome of this study was to assess whether denosumab was non-inferior to zoledronic acid with respect to time to first on-study SRE. Secondary endpoints included superiority of denosumab with respect to time to first SRE, superiority of denosumab with respect to time to first and subsequent SRE, and overall survival. Denosumab was non-inferior to zoledronic acid for the primary outcome of time to first on-study SRE (HR 0.98 [95% CI 0.85-1.14],  $p=0.010$ ). This effect was consistent across all types of SREs. Overall survival was similar between groups. Incidence of adverse events associated with renal toxicity, including creatinine  $>2$  mg/dL and creatinine doubled from baseline, was higher in the zoledronic group (10% denosumab vs. 17% of zoledronic acid). The authors concluded that denosumab was non-inferior to zoledronic acid for time to SREs and may be considered an alternative option for standard of care for patients with MM associated bone disease.

**Safety:** Denosumab treatment is associated with an increased risk of hypocalcemia, particularly in patients with significant renal dysfunction.<sup>6,7</sup> Close monitoring is recommended within the first weeks of therapy in addition to calcium and vitamin D supplementation as necessary. In addition, there are reports of osteonecrosis of the jaw with denosumab treatment.

If possible, initiation of therapy should be delayed until dental health is optimized. Additional adverse events include hypersensitivity and atypical femoral fractures.

**Dosing and Administration:** The recommended dose of denosumab for MM prevention of SREs is 120 mg subcutaneously every 4 weeks.<sup>6</sup> There is no recommended dosage adjustment for renal dysfunction, however use in patients with a CrCl  $<30$  mL/min has not been evaluated. Subcutaneous injection can be given in the upper arm, upper thigh, or abdomen. The original container should be stored in the refrigerator and brought to room temperature immediately prior to administration.

**Cost and Availability:** Denosumab (Xgeva®; Amgen) is available as a 120 mg/1.7 mL vial of solution for subcutaneous injection.<sup>6</sup> The average wholesale price is about \$2,660 per vial leading to an annual treatment cost of approximately \$31,927 per patient.<sup>7</sup> In addition, denosumab (Prolia®; Amgen) is available for the treatment of osteoporosis and bone loss associated with androgen deprivation therapy and aromatase inhibitor therapy as a 60 mg/1 mL vial of solution for subcutaneous injection.

**Formulary Status:** Expansion of the restriction for Xgeva® (denosumab) is currently under review.

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# Shingrix®: The Preferred Shingles Vaccine

By: Pooja Cerrato, Pharm.D., BCPS

**Background:** Over 90% of the adult population has been exposed to varicella-zoster virus (VZV), the virus responsible for chickenpox. As such, the risk of herpes-zoster (HZ) infection, also known as shingles, remains high.<sup>1,2</sup> Herpes zoster occurs from reactivation of VZV via the dorsal-root or cranial-nerve ganglion years after the primary infection. The hallmark of HZ is a painful, unilateral vesicular rash with a dermatomal distribution. The risk of HZ increases with age likely due to age-related decline in the immune response.<sup>2</sup> While the incidence in the general population is 2 to 4.6 cases per 1000 person-years, this rises to 10 to 12.8 cases per 1000 person-years in those ≥ 80 years of age.<sup>3</sup> The most common complication of HZ infection is post-herpetic neuralgia (PHN), but the virus can affect the ocular, cutaneous, and visceral systems as well.<sup>1,2</sup> In 2006, zoster vaccine live (ZVL) (Zostavax®;Merck), a live, attenuated vaccine, was approved by the Food and Drug Administration (FDA) for the prevention of HZ in patients ≥ 50 years of age.<sup>4</sup> Due to various limitations of ZVL (e.g., low efficacy rate, contraindication in immunosuppressed individuals), recombinant zoster vaccine (RZV) (Shingrix®;GlaxoSmithKline) was investigated as an alternative and received FDA-approval for the same indication in October 2017.<sup>5</sup>

**Comparative Vaccine Efficacy :** Clinical trials which evaluated ZVL and RZV compared each individual vaccine to placebo; there are currently no head-to-head studies evaluating these vaccines.<sup>2,3,6,7</sup> However those studies demonstrated a higher efficacy rate with a lower occurrence of PHN for patients who received RZV. For example, a 70% efficacy rate was reported for patients 50 to 59 years of age who received ZVL as part of the ZEST trial (also known as “the Zostavax Efficacy and Safety Trial”), while patients of the same age group who received RZV during the ZOE-50 trial (entitled “The Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults”) achieved a 97% efficacy rate.<sup>2,7</sup> Similarly, in ZOE-70 (entitled “Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older”), the efficacy rate for RZV was 90% in patients ages 70 to 79 year old, while ZVL was found to be only 41% effective in SPS (also known as “the Shingles Prevention Study”) for patients in that same age group.<sup>3,6</sup> For patients in the 80 years age group who participated in ZOE-70 and SPS, vaccine efficacy was 89% versus 18% for RZV and ZVL, respectively. In regards to PHN, RZV was 93% effective in preventing PHN in patients aged 70 to 79, while ZVL

was only 55% effective in preventing this complication in patients in the same age group. The RZV vaccine efficacy rate 4 years post-vaccination was 87.9%, similar to years 1 through 3.<sup>3</sup> Conversely, the efficacy rate of ZVL 6 years post-vaccination was < 35% and in most cases it was found to be no longer effective 9 to 11 years after administration.<sup>8</sup>

**Safety:** Adverse reactions following RZV administration were common, mild-moderate intensity, and short-lived (lasting 2-3 days).<sup>2,3,5</sup> The most common local adverse events following at least one dose of RZV administration in the ZOE-50 and ZOE-70 trials included pain (78%), myalgia (45%), fatigue (45%), and redness (38%). Local pain was more common in patients that received RZV compared with ZVL. Systemic adverse events occurring in >50% of patients receiving RZV included myalgia, fatigue, and headache. Adverse event rates did not significantly change following administration of the second dose. Since there are no data to determine if RZV administration is safe in pregnant and lactating women, the Advisory Committee on Immunization Practices (ACIP) recommends delaying administration in this population.<sup>8</sup> Additionally, the ACIP supports the use of RZV in patients taking < 20 mg of prednisone (or steroid equivalent) per day, those anticipating immunosuppression, or who have recovered from an immunocompromising condition. However, the ACIP does not yet have a recommendation on the use of RZV in patients who are actively immunocompromised including those taking moderate-high dose steroids regimens. Phase III trials evaluating safety and efficacy in certain immunocompromised patient populations are underway.

**Dosing and Administration:** Recombinant zoster vaccine is supplied as two vials: lyophilized varicella zoster glycoprotein E (gE) powder and manufacturer-supplied vaccine diluent which contains the AS01<sub>B</sub> adjuvant suspension. The vaccine must be reconstituted prior to administration by combining the gE antigen with the adjuvant suspension.<sup>5</sup> The 0.5 milliliter (mL) intramuscular dose should be injected into the deltoid region of the upper arm immediately or within 6 hours of reconstitution if refrigerated. Prior to reconstitution, the vaccine should be stored in the refrigerator. The RZV is administered as a two-dose series (0, 2-6 months). The vaccine series does not need to be reinitiated if more than 6 months have passed after the first dose.<sup>8</sup> However it is important to consider that a 0,12 month regimen of RZV compared to the

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0,2 month and 0,6 month regimens did not meet non-inferiority standards in terms of eliciting an immune response.<sup>9</sup> If the second dose of RZV is given less than 4 weeks after the first, it must be repeated.<sup>8</sup> Two doses are needed regardless of prior history of HZ or prior receipt of ZVL. RZV should not be given < 2 months after receipt of ZVL. Patients with an acute episode of HZ infection should wait until symptoms have resolved before receiving RZV.

### **Concomitant Use with Other Vaccines:**

The Centers for Disease Control and Prevention (CDC) guidelines state that recombinant and adjuvanted vaccines, such as RZV, can be given concurrently, at different anatomic sites, with other adult vaccines.<sup>8</sup> A study confirmed that RZV can be safely administered with Fluarix Quadrivalent (QIV) with no compromise in efficacy of either vaccine or safety concerns.<sup>5</sup> Unpublished data evaluating the concurrent administration of RZV with pneumococcal polysaccharide vaccine (Pneumovax<sup>®</sup> 23) met all immunogenicity and safety endpoints.<sup>10</sup> A similar unpublished study evaluating concurrent administration of RZV with Tdap (tetanus/diphtheria/acellular pertussis vaccine) (Boostrix<sup>®</sup>) met all immunogenicity and safety endpoints except non-inferiority of humoral response to antigen pertactin.<sup>11</sup> The clinical significance of this result is unclear. Administration of RZV in combination with other adjuvanted vaccines such as Fluad<sup>®</sup> has not been studied.

**ACIP Recommendations:** In January 2018, the ACIP published three recommendations<sup>8</sup>:

1. Recombinant zoster vaccine (RZV) should be administered for immunocompetent adults aged  $\geq 50$  years.
2. RZV should be given to those patients previously vaccinated with ZVL.
3. RZV is the preferred vaccine over ZVL for the prevention of HZ and related complications.

The ACIP will continue to monitor RZV in the post-licensure period for adverse events, duration of protection, adherence to a 2-dose regimen, and single dose administration efficacy.

### **Important Counseling Points:**

It is important to know the differences between RZV and ZVL in order to appropriately counsel patients. Important points to communicate are that RZV is more effective than ZVL, but injections with RZV may be associated with more pain, redness, and swelling. Furthermore, RZV requires two doses, whereas ZVL only required one. Unlike ZVL which was recommended by the ACIP for patients  $\geq 60$  years of age, RZV is recommended for those  $\geq 50$  years of age.

**Formulary Status:** Zoster vaccine recombinant was added to the CCHS Formulary in April 2018.

It is restricted to:

1. Immunocompetent patients  $\geq 50$  years of age
2. Immunocompetent patients  $\geq 50$  years of age undergoing pre-transplant evaluation
3. Post-transplant hematopoietic stem cell transplantation patients, solid organ transplant patients, and immunocompromised patients pending formal ACIP recommendations on a case-by-case basis in collaboration with Infectious Diseases

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