PEER PERSPECTIVES
IN THE TREATMENT OF ALL

ISSUE 1

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

INSIDE THIS ISSUE:

- The importance of asparaginase as a foundational component of ALL treatment
- Strategies for managing patients receiving asparaginase
- Exploring the efficacy, safety, and dosing schedules for an ALL treatment in adult and pediatric patients 1 month or older

FEATURING

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"Asparaginase is an essential component of ALL treatment."

Scott Howard, MD, MSc

OPTIMIZING THE TREATMENT OF ALL WITH ASPARAGINASE THERAPY

[a]Dr Howard is a paid consultant of Jazz Pharmaceuticals. This content is intended for informational purposes only and is not a substitute for your clinical knowledge or professional judgment. The views and opinions expressed in this article are those of the author and Jazz Pharmaceuticals and do not necessarily reflect the opinions of The University of Tennessee Health Science Center.

PEER PERSPECTIVES IN THE TREATMENT OF ALL

WITH **SCOTT HOWARD, MD, MSc**

Q. Why is it important to consider using an asparaginase as part of the treatment regimen for patients with ALL?

A. In my opinion, every protocol for ALL should include asparaginase therapy. Asparaginase, as part of a multi-agent treatment regimen, has been shown to improve survival in patients with ALL.[1] Multiple randomized trials have shown that asparaginase treatment improves outcomes, including increasing rates of disease-free survival (DFS) and event-free survival.[1] Furthermore, studies have shown that the risk for relapse increases in patients who experience treatment interruptions and do not complete their prescribed course of asparaginase therapy.[2,3]

Q. In your opinion, what are the biggest challenges in treating and managing patients with ALL who are receiving asparaginase therapy?

A. The main challenge in treating patients with asparaginase is managing hypersensitivity to *Escherichia coli (E. coli)*-derived asparaginase when it occurs to ensure patients can receive all their prescribed doses both safely and effectively.[4,5] In fact, patients who have missed doses because of hypersensitivity to *E. coli*-derived asparaginase and who have lacked access to a non *E. coli*-derived asparaginase due to a global shortage have a higher risk of relapse.[2,3]

Q. How common are hypersensitivity reactions (HSRs) due to *E. coli* asparaginase treatment in patients with ALL?

A. HSRs affect up to 30% of patients with ALL who are treated with *E. coli*-derived asparaginase.[2,6-9] Most of these patients who develop HSRs to *E. coli*-derived asparaginase also develop anti-asparaginase antibodies that may reduce the effectiveness of this therapy.[1,4] Since HSRs can occur at any time during treatment, patients should be monitored for allergic reactions every time they are exposed to asparaginase.[10] In my experience, HSRs tend to arise more frequently after patients have been re-exposed to asparaginase for the second or third time. The key risk factor for developing HSRs and/or anti-asparaginase antibodies is exposing patients intermittently to asparaginase, which can provoke the immune system to generating antibodies.[4,11,12]

Q. What are the symptoms of HSRs?

A. In my experience, there are 3 symptoms that almost always signify HSRs: urticaria, wheezing, and swollen lips.[10,13,14] About half of the time, other symptoms, such as flushing, may be due to an HSR.[10] If it is unclear whether a patient is experiencing an HSR, I typically stop the asparaginase infusion and wait 30 minutes to see if additional classic symptoms have developed.

Q. What is your approach to managing hypersensitivity in your patients with ALL?

A. With the availability of a reliable supply of a recombinant *Erwinia*-derived asparaginase treatment option with minimal immunologic cross-reactivity to *E. coli*-derived asparaginase, I switch my patients to this treatment option whenever there are clinically evident signs of hypersensitivity to the *E. coli*-derived asparaginase therapy.[15] Typically, I consider switching to an *Erwinia*-derived asparaginase within 2 or 3 days after a patient develops hypersensitivity to their *E. coli*-derived asparaginase in order to avoid treatment interruptions and to help ensure that the patient can complete their entire course of asparaginase therapy.

PEER PERSPECTIVES IN THE TREATMENT OF ALL

Q. What is the role of RYLAZE in your ALL treatment plan?

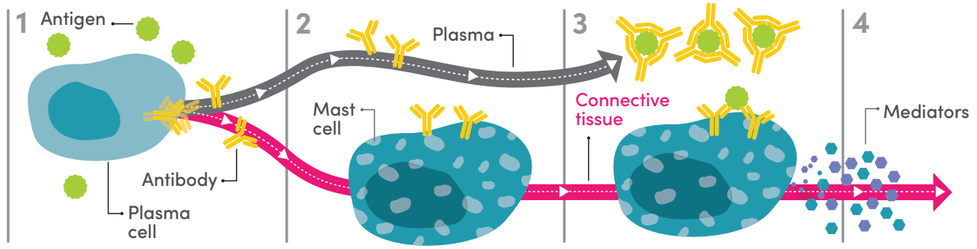
A. Ensuring patients complete their prescribed course of asparaginase therapy without treatment interruption is critical to reducing the risk of relapses.[2,3] RYLAZE plays an essential role as a component in my treatment plan because it is a reliable supply of highly purified asparaginase we can turn to as a replacement therapy when patients develop hypersensitivity to *E. coli*-derived asparaginase therapy.[15,16] With RYLAZE, I no longer need to rely on rechallenging or desensitization protocols to manage hypersensitivity; instead, patients can switch to RYLAZE if an allergic reaction to the *E. coli*-derived asparaginase occurs.[15,17]

> *"In patients who develop an allergic reaction to E. coli-derived asparaginases, we must absolutely consider switching to RYLAZE, which is the only FDA-approved Erwinia asparaginase for the treatment of ALL/LBL available in the United States."*
>
> **— Scott Howard, MD, MSc**

Q. How does RYLAZE differ from other asparaginases?

A. RYLAZE is derived from a novel *Pseudomonas fluorescens* expression platform that produces an enzyme with minimal immunologic cross-reactivity to *E. coli*-derived asparaginases.[18] Therefore, patients who have developed a reaction to *E. coli*-derived asparaginase may not develop hypersensitivity to RYLAZE.[18,19]

PATIENTS WHO HAVE EXPERIENCED AN HSR ARE AT INCREASED RISK OF ANOTHER REACTION WHEN TREATED WITH ASPARAGINASE FROM THE SAME SOURCE[7]



Native *E. coli* asparaginase, a bacterial protein, may trigger an immune response, resulting in proliferation and release of antibodies from plasma B cells[14]

Antibodies may directly bind to the surface of the mast cell, thereby activating it. Antibodies are also present in the plasma[14]

Upon reexposure, the antigen may bind to:

- Antibodies that are present on the surface of the mast cell (characterized by an IgE response or Type 1 reaction)[14]
- Free antibodies (mainly IgG or IgM) may neutralize or clear the antigen[14]

Adapted from Shinnick et al, 2013.[14]

Antigens bound to antibodies on mast cells trigger the release of histamine and other mediators that can cause clinical symptoms, including HSRs[14,20]

RYLAZE is derived from *Pseudomonas fluorescens* and has minimal immunologic cross-reactivity to *E. coli*-derived asparaginases[18]

FDA=Food and Drug Administration; IgE=immunoglobulin E; IgG=immunoglobulin G; IgM=immunoglobulin M; LBL=lymphoblastic lymphoma.

Indication

RYLAZE is indicated as a component of a multi-agent chemotherapeutic regimen given by intramuscular injection for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adult and pediatric patients 1 month or older who have developed hypersensitivity to *E. coli*-derived asparaginase.

Q. What are your thoughts on all dosing options meeting ≥90% standard of NSAA ≥0.1 U/mL?

A. This standard gives me confidence that more than 90% of the time, my patients will achieve and maintain therapeutic levels of asparaginase activity with RYLAZE.[1,17] Results from the RYLAZE open-label, multicohort, multicenter clinical trial demonstrated that all dosing options for RYLAZE met this standard.[15] This included 96% of patients achieving this standard in simulation when receiving the every 48-hour dosing for RYLAZE 25 mg/m^2 intramuscularly (IM).[15] In simulation, the Monday morning, Wednesday morning, and Friday afternoon RYLAZE 25/25/50 mg/m^2 IM dosing option showed that 91.6% of patients would achieve NSAA ≥0.1 U/mL 58 hours after the 25 mg/m^2 Wednesday morning dose and 91.4% of patients would achieve NSAA ≥0.1 U/mL 67 hours after the 50 mg/m^2 Friday afternoon dose.[15]

OPTIMIZED DOSING PROVIDES SUSTAINED ASPARAGINASE ACTIVITY THROUGHOUT THE ENTIRE COURSE OF TREATMENT[15]

Proportion of patients with NSAA ≥0.1 U/mL by simulation[15]

RYLAZE IM Dosing Options	Trough Sampling Time	Proportion with NSAA ≥0.1 U/mL (95% CI)[a]
Q48 25 mg/m^2	48 hours	96.0% (94.4%-97.2%)
Monday morning, Wednesday morning, and Friday afternoon 25/25/50 mg/m^2	**Friday afternoon:** 58 hours after 25 mg/m^2 Wednesday morning dose[b]	91.6% (90.4-92.8%)
	Monday morning: 67 hours after 50 mg/m^2 Friday afternoon dose[c]	91.4% (90.1%-92.6%)

[a]Based on 2,000 virtual subjects.[15]
[b]Based on maximum interval of 58 hours between the Wednesday morning and Friday afternoon doses.[15]
[c]Based on maximum interval of 67 hours between the Friday afternoon and Monday morning doses.[15]

Activity of ≥0.1 U/mL has been demonstrated to correlate with asparagine depletion and to serum levels that predict clinical efficacy.[1,17]

CI=confidence interval; IM=intramuscular; NSAA=nadir serum asparaginase activity; Q48=every 48; U=unit.

RYLAZE AALL1931 study overview

- **In collaboration with COG**, AALL1931 evaluated the efficacy and safety of RYLAZE as part of a multiagent chemotherapeutic regimen for ALL and lymphoblastic lymphoma patients with a hypersensitivity reaction to *E. coli* asparaginase[15,21]
  - A standard was set that at least 90% of patients should achieve and maintain NSAA ≥0.1 U/mL[15]
- AALL1931 was an open-label, multicohort, multicenter trial that evaluated 167 patients aged 1-25 years treated via IM route of administration[15]
- **Determination of efficacy** was to demonstrate that at least 90% of patients will achieve and maintain NSAA ≥0.1 U/mL[15]
- **Determination of safety** was the occurrence of treatment-emergent adverse events up to 30 days after last dose[21]
- **The dosing regimen** was designed to determine dosing options that provide sustained asparaginase activity throughout the entire course of treatment.[15,21] A treatment course consisted of RYLAZE at various dosages administered IM every Monday, Wednesday, and Friday for a total of 6 doses to replace each dose of pegaspargase[15]

IMPORTANT SAFETY INFORMATION

Contraindications

RYLAZE is contraindicated in patients with: history of serious hypersensitivity reactions to *Erwinia asparaginase*, including anaphylaxis; history of serious pancreatitis during previous asparaginase therapy; history of serious thrombosis during previous asparaginase therapy; history of serious hemorrhagic events during previous asparaginase therapy; or severe hepatic impairment.

RYLAZE®
asparaginase erwinia chrysanthemi (recombinant)-rywn for injection 10mg/0.5mL per vial

Please see Important Safety Information on page 7. Please see full Prescribing Information.

Q. What do the safety results from the clinical trial tell you about RYLAZE?

A. The safety profile of RYLAZE is consistent with other asparaginase therapies.[15] In the RYLAZE clinical trial, permanent discontinuation due to an adverse reaction occurred in 10% of patients who received RYLAZE IM at the recommended dosages.[15] Adverse reactions resulting in permanent discontinuation included pancreatitis (5%), drug hypersensitivity (4%), and infection (1%).[15] All patients treated with the recommended dosages of RYLAZE as a component of multi-agent chemotherapy experienced neutropenia, anemia, or thrombocytopenia.[15] The most common nonhematological adverse reactions (incidence >20%) in patients were abnormal liver tests, nausea, musculoskeletal pain, infection, fatigue, headache, febrile neutropenia, pyrexia, hemorrhage, stomatitis, abdominal pain, decreased appetite, drug hypersensitivity, hyperglycemia, diarrhea, pancreatitis, and hypokalemia.[15]

Q. What do you take into consideration when deciding whether to switch a patient with ALL to RYLAZE?

A. For me, it is essential that appropriate patients who develop hypersensitivity to their *E. coli*-derived asparaginase treatment are switched to and get the right dose of RYLAZE so that they can complete their course of asparaginase therapy.[15,17] The key point to remember when switching a patient from a long-acting *E. coli*-derived asparaginase to RYLAZE is that you are replacing the intended duration of treatment with either Q48 at 25 mg/m^2 IM or Monday morning/Wednesday morning/Friday afternoon at 25/25/50 mg/m^2 IM of RYLAZE.[15,a] For example, if a patient is scheduled to receive 4 doses of pegaspargase in Weeks 1, 3, 5 and 7, which is an intended duration of 8 weeks of therapy, I will replace this treatment regimen with 8 weeks of RYLAZE. With RYLAZE, I have 2 dosing options to choose from: either replace 1 dose of pegaspargase with 7 doses of RYLAZE 25 mg/m^2 when administered IM every 48 hours (Monday, Wednesday, Friday, Sunday, Tuesday, Thursday, Saturday) or with 6 doses of RYLAZE when administering 25 mg/m^2 IM on Monday morning and Wednesday morning, and 50 mg/m^2 IM on Friday afternoon.[15,b] The advantage of having these 2 dosing regimens for RYLAZE is that patients and providers can select one of these 2 options that works best for their scheduling needs.

"I was very happy when the FDA approved the dosing schedule where RYLAZE can be administered IM on Monday morning and Wednesday morning at 25 mg/m^2 and on Friday afternoon at 50 mg/m^2, in addition to the Q48 25 mg/m^2 IM dosing option. These optimized dosing options help ensure patients maintain the adequate asparaginase activity needed to keep fighting ALL, and offers an option for patients treated at centers without access to an infusion center on weekends."

— Scott Howard, MD, MSc

[a]Administer the Friday afternoon dose 53 to 58 hours after the Wednesday morning dose (eg, 8:00 am on Monday and Wednesday, and 1:00 pm to 6:00 pm on Friday).
[b]See the full Prescribing Information for the long-acting asparaginase product to determine the total duration of administration of RYLAZE as replacement therapy.

IMPORTANT DOSING INFORMATION

Recommended Premedication

Premedicate patients with acetaminophen, an H-1 receptor blocker (such as diphenhydramine), and an H-2 receptor blocker (such as famotidine) 30-60 minutes prior to administration of RYLAZE to decrease the risk and severity of hypersensitivity reactions.

Recommended Monitoring and Dosage Modifications for Adverse Reactions

Monitor patient's bilirubin, transaminases, glucose, and clinical examinations prior to treatment every 2-3 weeks and as indicated clinically. If results are abnormal, monitor patients until recovery from the cycle of therapy. If an adverse reaction occurs, modify treatment according to Table 2 in the full Prescribing Information.

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Warnings and Precautions

Hypersensitivity Reactions
Hypersensitivity reactions after the use of RYLAZE occurred in 29% of patients in clinical trials, and it was severe in 6% of patients. Anaphylaxis was observed in 2% of patients after intramuscular administration. Discontinuation of RYLAZE due to hypersensitivity reactions occurred in 5% of patients. Hypersensitivity reactions were higher in patients who received intravenous asparaginase erwinia chrysanthemi (recombinant)-rywn. The intravenous route of administration is not approved.

In patients administered RYLAZE intramuscularly in clinical trials, the median number of doses of RYLAZE that patients received prior to the onset of the first hypersensitivity reaction was 12 doses (range: 1-64 doses). The most commonly observed reaction was rash (19%), and 1 patient (1%) experienced a severe rash.

Hypersensitivity reactions observed with L-asparaginase class products include angioedema, urticaria, lip swelling, eye swelling, rash or erythema, blood pressure decreased, bronchospasm, dyspnea, and pruritus.

Premedicate patients prior to administration of RYLAZE as recommended. Because of the risk of serious allergic reactions (e.g., life-threatening anaphylaxis), administer RYLAZE in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (e.g., epinephrine, oxygen, intravenous steroids, antihistamines). Discontinue RYLAZE in patients with serious hypersensitivity reactions.

Pancreatitis
Pancreatitis, including elevated amylase or lipase, was reported in 20% of patients in clinical trials of RYLAZE and was severe in 8%. Symptomatic pancreatitis occurred in 7% of patients, and it was severe in 6% of patients. Elevated amylase or lipase without symptomatic pancreatitis was observed in 13% of patients treated with RYLAZE. Hemorrhagic or necrotizing pancreatitis have been reported with L-asparaginase class products.

Inform patients of the signs and symptoms of pancreatitis, which, if left untreated, could be fatal. Evaluate patients with symptoms compatible with pancreatitis to establish a diagnosis. Assess serum amylase and lipase levels in patients with any signs or symptoms of pancreatitis. Discontinue RYLAZE in patients with severe or hemorrhagic pancreatitis. In the case of mild pancreatitis, withhold RYLAZE until the signs and symptoms subside and amylase and/or lipase levels return to 1.5 times the ULN. After resolution of mild pancreatitis, treatment with RYLAZE may be resumed.

Thrombosis
Serious thrombotic events, including sagittal sinus thrombosis and pulmonary embolism, have been reported in 1% of patients following treatment with RYLAZE. Discontinue RYLAZE for a thrombotic event, and administer appropriate antithrombotic therapy. Consider resumption of treatment with RYLAZE only if the patient had an uncomplicated thrombosis.

Hemorrhage
Bleeding was reported in 25% of patients treated with RYLAZE, and it was severe in 2%. Most commonly observed reactions were bruising (12%) and nose bleed (9%).

In patients treated with L-asparaginase class products, hemorrhage may be associated with increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenemia. Consider appropriate replacement therapy in patients with severe or symptomatic coagulopathy.

Hepatotoxicity, including Hepatic Veno-Occlusive Disease
Elevated bilirubin and/or transaminases occurred in 75% of patients treated with RYLAZE in clinical trials, and 26% had Grade ≥3 elevations. Elevated bilirubin occurred in 28% of patients treated with RYLAZE in clinical trials, and 2% had Grade ≥3 elevations. Elevated transaminases occurred in 73% of patients treated with RYLAZE in clinical trials, and 25% had Grade ≥3 elevations.

Hepatotoxicity, including severe, life-threatening, and potential fatal cases of hepatic veno-occlusive disease (VOD), have been observed in patients treated with asparaginase class products in combination with standard chemotherapy, including during the induction phase of multiphase chemotherapy. Do not administer RYLAZE to patients with severe hepatic impairment. Inform patients of the signs and symptoms of hepatotoxicity.

Evaluate bilirubin and transaminases prior to each cycle of RYLAZE and at least weekly during cycles of treatment that include RYLAZE, through four weeks after the last dose of RYLAZE. Monitor frequently for signs and symptoms of hepatic VOD, which may include rapid weight gain, fluid retention with ascites, hepatomegaly (which may be painful), and rapid increase of bilirubin. For patients who develop abnormal liver tests after RYLAZE, more frequent monitoring for liver test abnormalities and clinical signs and symptoms of VOD is recommended. In the event of serious liver toxicity, including VOD, discontinue treatment with RYLAZE and provide supportive care.

Adverse Reactions

The most common adverse reactions (incidence >20%) with RYLAZE are abnormal liver test, nausea, musculoskeletal pain, infection, fatigue, headache, febrile neutropenia, pyrexia, hemorrhage, stomatitis, abdominal pain, decreased appetite, drug hypersensitivity, hyperglycemia, diarrhea, pancreatitis, and hypokalemia.

Use in Specific Populations

Pregnancy and Lactation
RYLAZE can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective non-hormonal contraceptive methods during treatment with RYLAZE and for 3 months after the last dose. Advise women not to breastfeed during treatment with RYLAZE and for 1 week after the last dose.

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asparaginase erwinia chrysanthemi (recombinant)-rywn for injection 10mg/0.5mL per vial

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"RYLAZE is an essential component in the treatment for ALL by restoring reliable access to a non E. coli-derived asparaginase, giving me confidence that I can provide patients with sustained asparaginase activity throughout their entire course of treatment."

— Scott Howard, MD, MSc

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Dr Howard is a leading expert in treating patients with ALL, both as a physician and researcher.

Scott Howard, MD, MSc, is Professor at the University of Tennessee College of Health Sciences in Memphis. Dr Howard earned his medical degree at The University of Alabama School of Medicine at Birmingham. He received his Master of Science degree in epidemiology and completed his residency in pediatrics and internal medicine at the University of Tennessee College of Health Sciences, followed by a pediatric hematology/oncology fellowship at St. Jude Children's Research Hospital in Memphis. Dr Howard's research focuses on the management of acute lymphoblastic leukemia, relapsed leukemia, supportive care, and adapting treatment regimens to local conditions in low- and middle-income countries. He is a member of the American Society of Clinical Oncology, the American Society of Pediatric Hematology/Oncology, and the International Pediatric Oncology Society.

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