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How to solve the problem of hypersensitivity to asparaginase?

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Among various complications associated with L-asparaginase, an essential treatment component of virtually all protocols for childhood acute lymphoblastic leukemia (ALL), clinical hypersensitivity is one that limits continued use of this agent in reacting patients. In the U.S. and many other developed countries, pegaspargase, an *Escherichia coli*-derived (*E. coli*) asparaginase enzyme that is conjugated with polyethylene glycol (PEG), is used as the first-line treatment, whereas *Erwinia* asparaginase (Erwinase), isolated from *Erwinia chrysanthemi*, is used in patients who developed hypersensitivity to any *E. coli* asparaginase preparation: native *E. coli* asparaginase (which is no longer available in U.S.) or pegaspargase. Some studies suggest that Erwinase may not be necessary for some ALL patients who developed hypersensitivity reaction to *E. coli* product, provided that they have already received 50% or more of the prescribed dose and/or treatment is augmented with other chemotherapeutic agents.[1] However, other studies have shown that less intensive asparaginase treatment regimens and even subclinical hypersensitivity (so-called silent inactivation) were associated with inferior outcomes overall;[2] moreover, the optimal number of doses of asparaginase for individual patients is unknown and likely treatment regimen-dependent. Hence, in most clinical trials, patients would be switched to receive Erwinase if they developed hypersensitivity to native *E. coli* asparaginase or pegaspargase.

Because adequate Erwinase treatment requires an onerous thrice weekly schedule, and as many as a third of the patients develop hypersensitivity or infusion reactions to it,[3] a long-acting and less immunogenic *Erwinia* asparaginase (pegcrisantaspase) was developed to address these issues. A Phase I study of this agent was successfully conducted in 10 adults aged 18 to 50 years (median, 40.6 years) without a previous history of allergic reaction to Erwinase;[4] few if any of these patients would have been previously exposed to pegaspargase, a drug seldom used to treat adults with ALL, especially before native asparaginase was discontinued in the U.S. in December 2012. In this issue of *Pediatric Blood & Cancer*, Rau et al.[5] from the Children's Oncology Group reported the results of a Phase II trial of intravenous pegcrisantaspase in pediatric patients with ALL or lymphoblastic lymphoma

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who had a history of grade 2 or more hypersensitivity reactions to pegaspargase. Of the first 4 patients treated, 2 developed a clinical hypersensitivity reaction and 1 had rapid clearance of serum asparaginase activity (i.e., silent inactivation). Serum samples from all 3 of the patients with clinical hypersensitivity or silent inactivation had complement activation and anti-PEG IgG antibodies and lacked detectable anti-Erwinia asparaginase antibodies. Anti-PEG IgM antibodies were detectable only at low levels in 3 patients, including the 1 without a hypersensitivity reaction or silent inactivation. These findings indicated that pre-existing anti-PEG IgG antibodies were responsible for the immune-mediated reactions to pegcrisantaspase in these 3 patients. Each of the 3 patients with a hypersensitivity reaction or silent inactivation were exposed to pegaspargase 1 to 6 weeks prior to administration of pegcrisantaspase, whereas the remaining patient, who lacked reaction or silent inactivation had not been exposed to pegaspargase for 5.5 years, suggesting that anti-PEG-mediated immune reactions may not elicit durable immunologic memory. Regrettably, this “unexpectedly” high frequency of immune reaction resulted in permanent closure of the study to further accrual.

As mentioned by Rau and colleagues,[5] PEG has been used not only in the pharmaceutical industry but also in processed foods and cosmetics. Although PEG has been considered poorly immunogenic over the years, multiple recent studies have shown that anti-PEG IgG and IgM can be detected at low levels in approximately 70% and at high levels in up to 7% of the general population, leading to serious reactions upon first exposure to PEGylated medicines.[6,7] This has stimulated identification of novel genetic markers for predicting the immunogenicity of PEG and PEGylated therapeutics.[7] Hence, it is not surprising that a substantial portion of the general population were found to derive little benefit or to have adverse reactions when treated with any PEG-modified drugs. In the COG AALL07P4 study, which compared 2 forms of PEG-asparaginase, anti-PEG antibodies were detected in 6 (13%) of the 46 patients treated with calaspargase and in 5 (19%) of the 26 treated with pegaspargase; however, among 18 patients who had had an anaphylactic reaction or a hypersensitivity reaction, only 6 had anti-PEG antibodies.[8] It is possible that the use of Tween-20 in the ELISA washing buffer may have affected the sensitivity of the assay.[9] While anti-PEG antibodies undoubtedly contribute to hypersensitivity reactions or silent inactivation, the extent of their involvement requires additional study, with accompanying details as to the type of PEG antigens used to detect anti-PEG antibodies in the ELISAs.

Rau and associates[5] proposed several strategies to circumvent the problems of pegaspargase hypersensitivity, such as the development of alternative “stealth” polymers and saturation of pre-existing anti-PEG antibodies with free, low-molecular-weight PEG prior to administration of subsequent pegaspargase. Whether cross-reactivity of anti-PEG antibodies to other polymers, alternative-molecular-weight PEG or modified PEG would hinder this strategy is unclear. In any event, understanding the details of the source of PEG used for the ELISAs and for the formulation of pegaspargase and pegcrisantaspase would be helpful in resolving issues related to a hypersensitivity.

We contend that existing drugs could be used to treat these patients: that is, native *E. coli* asparaginase for patients without anti-asparaginase antibodies[10] and pegcrisantaspase for those without antibodies to PEG, provided that the pharmaceutical industry is willing to

produce them. Finally, the use of additional immunosuppressive drugs before the administration of pegaspargase, such as rituximab or dexamethasone, may reduce the frequency of hypersensitivity reactions or silent inactivation of pegaspargase.[11,12]

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Abbreviations Key

ALL	acute lymphoblastic leukemia
PEG	polyethylene glycol

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