Understanding the Potential Promise and Pitfalls of Intravenous Gentamicin as a Therapy for Epidermolysis Bullosa

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ichthyosis severity.[10] While it has been assumed that Th17 skewing in ichthyotic skin is a response to defects of the stratum corneum barrier,[12] several case reports have demonstrated the potential effectiveness of targeting this pathway with treatment with secukinumab or ustekinumab.[11-13] In addition, the Janus kinase and signal transducer and activator of transcription (JAK-STAT) pathway has been found to be upregulated in skin samples from patients with harlequin ichthyosis, the most severe subtype of ichthyosis,[14] and the inhibition of the JAK-STAT pathway has been effective in a skin model of harlequin ichthyosis.[14]

Importance of Outcome Measurement to Support Innovation

Given the potential for targeting the IL-17/IL-23 and JAK-STAT pathways, there is ongoing interest in randomized clinical trials on the effectiveness of novel treatments, such as secukinumab.[15] The success of studies that explore new treatments to address skin barrier dysfunction and enhanced inflammatory pathways in ichthyoses hinge not only on the effectiveness of these novel treatments, but additionally on the ability to effectively measure whether they are efficacious. Scales, such as the ISS, that can reliably and accurately capture disease severity play an important role as outcomes in these studies. They will enable us to differentiate what treatments provide meaningful clinical benefits for patients with ichthyoses and facilitate comparative effectiveness studies. Furthermore, using these outcomes in clinical settings will enable us to identify which patients are reaching their treatment goals and which require modification of their treatment regimen. The development and assessment of disease severity assessments, as well as patient-reported outcome measures, for ichthyoses can complement the exciting translational research on immune pathway–targeted therapies for ichthyoses, ushering in a new era of treatment for ichthyoses.

ARTICLE INFORMATION

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Understanding the Potential Promise and Pitfalls of Intravenous Gentamicin as a Therapy for Epidermolysis Bullosa

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Epidermolysis bullosa (EB) is a rare inherited disorder of epithelial fragility, primarily manifesting as blisters and erosions of the skin and mucous membranes.[1] Severe subtypes of EB can be complicated by recurrent or nonhealing wounds, scarring, and a range of nonskin complications that affect overall health and quality of life for individuals with the disorder. The current treatment of EB is largely palliative, relying on wound care, nutritional support, and symptom management. Although approaches such as genetically-corrected keratinocytes or fibroblasts are being investigated, particularly for recessive dystrophic EB,[2-4] no disease-modifying therapy for EB is approved or widely available at this time, leaving tremendous unmet need for patients. The dystrophic epidermolysis bullosa research association (commonly known as *debra*), a

patient advocacy organization, has characterized EB as "the worst disease you've never heard of" - a catchphrase that demands attention and signifies the isolation, pain, and suffering those with EB endure for the duration of their lives. The desperation for better treatments is palpable.

Repurposing existing medications for novel applications is a potential means to bridge the treatment gap for rare diseases. One such example is the use of aminoglycosides, not for their antimicrobial properties, but to induce ribosomal readthrough of premature termination codons (PTCs). In the case of genetic disorders, this phenomenon results in protein expression, which if sufficient in quantity could ameliorate primary manifestations of the disorder.[5] In this issue of *JAMA Dermatology*, 2 groups of investigators report the short-term outcomes of intravenous gentamicin as a readthrough therapy for junctional EB (JEB) and EB simplex with muscular dystrophy (EBS-MD). Mosallaei and colleagues[6] evaluated 5 pediatric patients with intermediate or severe JEB owing to nonsense variants in *LAMA3* and *LAMB3*, whereas Martínez-Santamaría and colleagues[7] observed 1 adult with EBS-MD owing to a homozygous nonsense variant in *PLEC*. Although both groups demonstrated that gentamicin induced or augmented the expression of the absent or deficient affected proteins and was well tolerated, the clinical relevance of this intervention is more difficult to estimate.

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What Is Readthrough Therapy?

The translation of DNA into protein consists of a chain of events in which the transfer RNA (tRNA) anticodon associates reversibly with the mRNA codon in the ribosomal decoding center. The codons UAA, UGA, or UAG signal termination of mRNA translation in the ribosome, but this process is never 100% efficient because a near cognate tRNA can bind to the codon, leading to the addition of an amino acid, a phenomenon termed "readthrough."[5] By interacting with the ribosomal decoding center, aminoglycosides promote readthrough with varying degrees of efficiency, depending on the genetic code. For example, the responsiveness of stop codons to readthrough decreases from UGA to UAG to UAA, and the context of a uridine at position−1 and a cytosine at +4 relative to the PTC favors readthrough.[8] Thus, readthrough therapy is variant dependent and should be considered a personalized therapy, requiring in vitro testing of a patient's particular genetic variants prior to treatment.

Use of gentamycin to induce translational readthrough of PTC variants and restore functional protein expression has been studied as a potential treatment of genetic disorders, with most of the clinical work done in Duchenne muscular dystrophy[9] and cystic fibrosis.[10] A limitation of the use of aminoglycosides for translational readthrough is potentially low readthrough efficiency, resulting in relatively low protein levels, coupled with the relatively high risk of nephro- and/or ototoxicity.[11] To overcome these drawbacks, second-generation aminoglycosides, nonaminoglycoside readthrough products, enhancers, and nonsense mediated decay inhibitors are being developed. The cytotoxic effects of aminoglycosides may be reduced by coadministration with different compounds, such as aspartic acid or melatonin.

What Are the Best Ways to Document Readthrough Therapy's Effects in EB?

For readthrough therapy to be effective in patients, a sufficient quantity of restored protein is needed to improve its functionality in cells and tissues. This is particularly important for structural proteins expressed in large organs, such as skin or muscle. Although immunofluorescence microscopy (IFM) is most often used to assess protein expression, this method does not evaluate protein functionality. The 5 patients with JEB treated by Mosallaei and colleagues[6] showed remarkable protein reexpression in the skin on IFM that lasted over the 3-month period, and correlated with 85% wound closure in 93% of monitored wounds. The adult woman with EBS-MD treated by Martínez-Santamaría and colleagues[7] had mild mucocutaneous involvement but marked muscular involvement when gentamicin therapy was initiated. She received two 14-day courses of 7.5 mg/kg/d of intravenous gentamicin with 7 months in between courses. Reexpression of plectin that lasted for 4 to 5 months in skin was demonstrated, but plectin expression was not assessed in skeletal muscle, perhaps owing to the more invasive nature of muscle biopsies.

Although demonstrating a relevant change in the target biomarkers, laminin 332 and plectin, is important in these proof-of-concept studies, demonstrating clinically meaningful benefit that correlates with biomarker improvement is imperative for clinical trials. Mosallaei and colleagues[6] assessed changes in pain, itch, and quality of life. However, these data were incomplete and variable, making the interpretation of clinical relevance for the patients difficult. Martínez-Santamaría and colleagues[7] showed modest, albeit short-lived improvements in neuromuscular and ventilatory function and a reduction in muscle pain in their patient. No improvement in the performance of core daily activities was documented in either study.

These reports highlight the heterogenous nature of EB, which makes assessing outcomes especially challenging. Mosallaei and colleagues[6] and Martínez-Santamaría and colleagues[7] both used the EB Disease Activity and Scarring Index (EBDASI)[12] as an outcome measure, but the small changes seen in the overall scores are difficult to interpret in the absence of a comparator or control. Because signs and symptoms of EB can fluctuate in a patient over time, establishing a baseline prior to assessing for change is imperative in a rigorous clinical trial. Both studies used different instruments to measure outcomes relevant to EB subtype and important to patients, such as pain and quality of life. However, such instruments need to be specific to the age and developmental status of the patient (eg, infant, child, adolescent, or adult) to have confidence in their accuracy. Although the heterogeneity of EB warrants the use of an a la carte approach to selecting outcome assessments for clinical studies that reflect the manifestations and symptoms of that particular EB subtype, core outcome measures that evaluate the common features of EB should be used in a uniform way to compare out-

comes across studies. There is a need for well-chosen, broadly supported, and agreed on core outcomes and assessments by stakeholders, including patients, investigators, and regulatory authorities.

Cautious Optimism, but More Work Is Needed

The safety of any emerging therapy is paramount, and it is heartening to note no adverse effects were seen in either report. In addition, no antibodies against the reexpressed proteins were detected. These results should be viewed cautiously, however, in light of the short-term nature of both studies. Like other forms of severe EB, JEB and EBS-MD are chronic, progressive, and debilitating disorders. To modify their natural history, a treatment such as gentamicin would ideally be started at an early age and repeated at regular intervals to stabilize the condition over a patient's lifetime. Stopping therapy would presumably lead to a resumption in disease progression or even death, as in the case of severe JEB. Initiating treatment at an early age may mitigate the confounding nature of irreversible tissue damage (fibrosis or dystrophy) that accumulates in individuals with EB. The chronic changes of EB are unlikely to be overcome by restoring protein expression alone, and make the benefit of treatment difficult to assess. Because therapies such as gentamicin were not designed for long-term use, additional studies on the feasibility, possible accumulative toxic effects, risk of microbial resistance—a particular concern in EB because chronic wounds are often colonized with bacteria, as well as benefits of longer-term therapy are needed before this approach can be fully endorsed. If considered as an off-label therapy, the balance between the potential burden of intervention (adverse effects, logistic effort, infusions) and its potential benefits (improving quality of life) should be weighed thoughtfully.

All forms of EB are considered orphan disorders. Yet in the family of EB, JEB and EBS-MD have received less attention than recessive dystrophic EB, where many different approaches to treatment are currently being investigated. For the reasons cited herein, performing rigorous therapeutic studies for EB is extremely challenging. Although the studies discussed herein have both strengths and weaknesses, the investigators should be applauded for taking advantage of a readily available systemic treatment to target cutaneous and extracutaneous symptoms of patients who have very limited treatment options at this time.

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