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Diethyl Azelate for the Treatment of Brown Recluse Spider Bite, a Neglected Orphan Indication: A Commentary

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Where are we two years after this paper[1] was first published? Our Commentary brings an update on the incidence of brown recluse spider bite (loxoscelism), current treatments and future prospects for the development of new drugs for loxoscelism.

Is it "rare" or "medium rare"?

A rare disease is defined as one that affects less than 200,000 people in the United States under The Orphan Drug Act[2]. The jury is still out regarding the question of loxoscelism being a rare or not so rare disease. The U.S. recorded 531,776 annual visits to emergency departments for bites from non-venomous arthropods that included 3,500 cases of moderate to severe envenomations from 2010 to 2014[3]. The estimated annual total lifetime medical and lost work cost of these cases was approximately one billion dollars[4]. A conservative assumption that loxoscelism represented half of these envenomation cases yields some 350 incidents per year with corresponding medical and work costs of one hundred twenty-five million dollars. In 2021, there were 566 brown recluse spider bite cases reported, with one death in the U.S.[5]. These numbers are expected to grow as with the climate change the habitats of brown recluse are gradually moving North. In 2024, the established range of *Loxosceles* species included the Midwest and the South with a large cluster of states reaching from Texas to Georgia up to Illinois[6]. Spider bites are now being reported in the regions previously viewed as nonendemic[7]. The number of reported bites may be imprecise since loxoscelism is notoriously difficult to diagnose despite a handy mnemonic tool[8]. Systemic loxoscelism is less frequent but more deadly than the cutaneous form. Phospholipase D (PLD), also known as sphingomyelinase D, is the principal toxin in the pathophysiology of envenomation[9]. Severe systemic loxoscelism is associated with 3.5% mortality rate and most victims are children[10]. The math can give the impression that brown recluse spider bite is of minimal importance but if you happen to be one of the half million victims of a spider bite, you will probably rush to the emergency room rather than betting on the odds of 1:150 that the bite is innocuous.

Several more recent case reports summarized in Table I illustrate the seriousness of loxoscelism and underscore the fact that medical intervention is frequently delayed. Notably, none of the subjects had past medical history prior to the brown recluse spider bite. The case described in[11] concerns a 51-year-old man who suffered a bite to his left ring finger that progressively worsened over 3 weeks despite treatment with antibiotics and surgical drainage. Based on the

Table 1. Diverse clinical manifestations of loxoscelism

Subject	Bite site	Symptoms/diagnosis	Treatment	Comments	Outcome	Ref.
51 yrs M*	finger	systemic loxoscelism	antibiotics, steroids, surgery	worsening over 3 weeks on antibiotics alone	recovery	11
32 yrs F	shoulder	fever, hemolytic anemia	steroids	autoimmune response	recovery	12
19 yrs M	shin	delayed hemolytic anemia	3x emergency room, 2x hospitalization	unusually late hemolysis	recovery	13
27 yrs M	scapula	sepsis	antibiotics, plasmapheresis	hospital admission on day 8 post-bite	recovery	14
31 yrs M	thigh	myocarditis	steroids, colchicine	first ever reported case of post-bite myocarditis	recovery	15
32 yrs M	lip	pain, fever, COVID-19 positive	dexamethasone, analgesics, antibiotics	got medical help on day 5 post-bite, death on day 56	death	16
44 yrs M	eyebrow	facial pain, vision loss	epinephrine, steroids, blood products	death within 60 h of envenomation	death	5

* age (years); M; male, F; female

suspicion of cutaneous loxoscelism, surgical debridement, decompression and corticosteroid treatment resulted in a complete cure.

There have been several reports of post-bite hemolysis caused by brown recluse spider venom mediated toxicity to erythrocytes and activation of the complement system[10]. A rare case of loxoscelism-associated hemolytic anemia was reported for a 32-year-old female with a two-day history of a left shoulder papule that had ruptured, forming a small black lesion, along with fever and body aches following a suspected brown recluse spider bite. The patient was treated with antibiotics and developed severe Coombs-positive autoimmune hemolytic anemia. Systemic corticosteroid treatment resulted in an improvement in hemoglobin levels[12]. A more serious case of systemic loxoscelism occurred in a 19-year-old male who was diagnosed with delayed hemolytic anemia 6 days after envenomation. The individual suffered worsening pain, fever, chills, nausea and vomiting, and required three emergency department visits and two hospitalizations[13]. Another case of hemolysis and sepsis was described for a 27-year-old male who was bitten by a brown recluse spider on the right scapula. He was admitted to the hospital on the 8th day post bite with acute hemolytic anemia that was not responsive to red blood cell transfusion and intravenous immunoglobulin treatment. The patient was treated with antibiotics and significantly improved only after plasmapheresis[14].

The first report ever of toxin-mediated myocarditis from a brown recluse spider bite was reported in a 31-year-old man who presented with a diffuse erythematous rash and fever and chills three days after a spider bite. The patient suffered hemolysis, acute kidney injury, mild rhabdomyolysis and myocardial edema. Blood transfusion was not required and the patient was treated with metoprolol and lisinopril for cardiomyopathy and colchicine for acute pericarditis[15].

A fatal outcome of envenomation occurred in Brazil when a 32-year-old man was bitten on a lower lip by a brown recluse. The subject reported severe facial and lower back pain, fever and dyspnea and sought medical assistance five days after the bite and was also confirmed to be positive for COVID-19. Progression of his systemic conditions likely due to the simultaneous insults of the two diseases led to the patient's death[16].

Johns Hopkins Medicine website states "No deaths have been reported in the U.S, from a brown recluse bite"[17]. Boston Children's Hospital website states likewise "No deaths have been reported in the country from a brown recluse bite"[18]. Another source claimed that death from brown recluse spider bites are rare and have been reported only in children[19]. Unfortunately, the threat of mortality from the brown recluse spider bite in the U.S. has been underestimated. One fatal case occurred in 2021 and another death from loxoscelism with an alarmingly short course has been reported in 2024[5]. This case involved a 44-year-old male in El Paso, Texas, who suffered a brown recluse spider bite above the right eyebrow. The patient experienced facial pain, swelling, and progressive right eye vision loss 24 hours prior to the admission to the emergency room. Intravenous epinephrine and dopamine were administered, and intubation was completed for airway protection due to severe facial edema. Despite supportive care including steroids, blood products, treatment for coagulation abnormalities and a bicarbonate drip, the patient continued to deteriorate and died approximately 60 hours after the spider bite.

What happens if you are bitten by a brown recluse today

A. First aid treatments

Most brown recluse spider bites will heal on their own in about a week. First-aid treatments recommended by Mayo Clinic for spider bites includes local cold, rest, elevation of the extremity if possible, over-the-counter pain relievers and antihistamine for itching[20].

B. Non-specific clinical interventions

Current approaches include systemic antihistamines, corticosteroids, antibiotics, analgesics, and nonsteroidal anti-inflammatory drugs (NSAIDs). Such treatments of loxoscelism are controversial because they do nothing to directly address the effects of the spider toxins. A study

with 189 subjects found no evidence that commonly used approaches reduced the median healing time of 17 days or the likelihood of scarring in suspected brown recluse spider bites. Systemic corticosteroids and dapsone were associated with slower healing. Dapsone was associated with an increased probability of scarring, necrosis, and diabetes[21]. A similar opinion reiterated that there is no proven effective therapy for *Loxosceles* bites despite multiple modalities used in the clinic[22]. Overall, even clinical interventions are limited by managing symptoms, not the root cause

C. Targeted clinical interventions in the United States

Antivenins are effective but they have to be administered within the first 12-24 hours of the envenomation. Additionally impeding access, these drugs are intramuscular or intravenous therapies that are best administered in a clinical setting. Antivenin treatment for loxoscelism is not accessible in the U.S. A small market size and a difficult and expensive path to manufacture such products appears to limit commercial interest in the development of brown recluse antivenin. To date, only a black widow spider antivenin is manufactured from horse serum by Merck for the U.S. market. The product comes with warnings that it may cause allergies and even death in a sensitive patient and an anaphylactic reaction to antivenin may occur even following a negative skin or conjunctival test. A dedicated horse farm is used for manufacturing the black widow antivenin. Paradoxically, Merck sells only 300 to 800 vials per year but the product has been in short supply until 2023[23].

Contrary to the common perception that brown recluse spider bites are rare and carry a low risk, reports of severe outcomes including deaths continue to appear in the literature. There is an urgent need for a safe and effective therapy of the brown recluse envenomation, especially its systemic effects. At a first blush, loxoscelism may not look like an economically attractive therapeutic target but the Orphan Drug Act, the Animal Rule and other regulatory incentives in fact make drug development programs for brown recluse spider bite treatment economically viable, especially if the product is used as an easy accessible first aid kit in case of unidentified spider bites.

D. Targeted clinical interventions outside the United States

Loxoscelism antivenin is available in Mexico and several South American countries, where loxoscelism is endemic. A large prospective study in Mexico included 146 patients diagnosed with loxoscelism, mostly the cutaneous form (96.6%). Over half of the patients (50.7%) received polyvalent antivenin within 41.6 ± 27.4 hours from the time of the bite. After discharge, most of the patients (90.9%) were treated with corticosteroids, antihistamines and analgesics as needed. Necrosis was significantly lower among the patients who were admitted earlier and those who received antivenin[24]. Another study involved three patients with loxoscelism who received the *Loxosceles* antivenin (immunoglobulin (Ig)G F(ab')2 fragments) preparation Reclusmyn. Two patients had a satisfactory outcome without severe skin or systemic damage. Despite early administration of antivenin one patient developed extensive skin lesions that healed in 4 weeks[25].

Something old and something new

Several new treatments reported in the past few have not achieved success to date. A proposed novel therapy for loxoscelism using trichloroacetic acid (TCA)[26] was met with criticism due to TCA being an injurious corrosive dermal irritant[27]. Following in vitro and in vivo studies, tetracycline administration was proposed as a treatment of human systemic loxoscelism[28]. A tetracycline ointment entered human testing in Phase III clinical trials a while ago[29], but the outcome is as yet unclear.

Early interest in PLD inhibitors as potential treatments for loxoscelism[30] has largely waned as other diseases offer more attractive markets. A Korean team at Yonsei University used computer-aided drug design to identify a potent and selective PLD1 inhibitor as a potential treatment for colorectal cancer[31]. Biogen reported a discovery of PLD inhibitors with improved drug-like properties and central nervous system penetrance in animal models with utility for neurodegenerative diseases, including Alzheimer's and the amyotrophic lateral sclerosis[32].

As described in the original manuscript, diethyl azelate (DEA) may be useful for the treatment of loxoscelism based on its effects on clinically relevant endpoints such as inhibition of PLD, prevention of hemolysis, and pain reduction. Topical DEA resolved the consequences of human LOX envenomation in two weeks. In vitro, DEA inhibited hemolysis caused by the brown recluse spider venom and recombinant recluse PLD, and suppressed phospholipase A2 (PLA2) activity in a dose-dependent manner[1]. Further evidence of the potential of DEA for the treatment of loxoscelism shown in a video detailing the clinical course of an intentionally induced brown recluse bite and its treatment with DEA is available elsewhere[33].

DEA represents a new class of NSAIDs. Like NSAIDs, DEA reduces inflammation and pain in part by suppressing the release and production of inflammatory cytokines[14] and the inhibition of endogenous PLA2 signaling responsible for pain sensation. On the other hand, unlike many NSAIDs, DEA apparently does not interact with COX. Instead, the anti-inflammatory actions of DEA are likely due to reversible fluidization of the plasma membrane and consequent modulation of the inflammatory signaling[34, 35]. Collectively we refer to molecules such as DEA as Membrane Active Immunomodulators (MAIMs) that use the entire cell plasma membrane as their target. MAIMs alter membrane

fluidity and shift the innate feedback loop regulating fluidity homeostasis mechanism, which we have named the Adaptive Membrane Fluidity Modulation (AMFM). DEA displayed activity in seemingly unrelated cases; modulated activities of pathogen-associated molecular pattern receptors, mitigated effects of cholera toxin and anthrax lethal toxin, and was effective in vivo against antibiotic resistant *Staphylococcus aureus*[35] and *Mycobacterium ulcerans*[36]. In a human study in overweight males, orally administered DEA significantly reduced fasting glucose and insulin in subjects with insulin resistance, and improved the diagnostic lipid ratios[37].

DEA is expected to strike loxoscelism at multiple levels because it affects not only the enzymatic activity of PLD but also its substrates, membrane phospholipids, and the host immune response to the venom. One particular product of PLD activity, cyclic phosphatidic acid, contributes to the pathology of loxoscelism because it inhibits a nuclear receptor, peroxisome proliferator-activated receptor gamma (PPAR gamma) that affects cell proliferation, apoptosis, inflammation, energy homeostasis and metabolic functions. On the other hand, activation of PPAR gamma causes insulin sensitization and enhances glucose metabolism[38]. Since DEA mitigates insulin resistance in humans[37] it may also counter negative effects of cyclic phosphatidic acid signaling upon a rapid conversion of DEA to azelaic acid[39], which reportedly induces PPAR gamma in human keratinocytes[40].

DEA putatively modulates the host response to the venom by dint of its anti-inflammatory and immunomodulatory properties. We have shown that DEA downregulated matrix metalloproteinases, which are also abundant in the recluse spider venom, and inhibited pro-inflammatory interleukins IL-6 and IL-8, CXCL1/GRO-alpha and CCL2/MCP-1 (35), all of which are upregulated in loxoscelism[41].

Topical DEA might control pain associated with the recluse bite[42] because it inhibits PLA2 and the resulting inflammatory response mediated by arachidonic acid released from plasma membrane phospholipids by PLA2. Pain relief may also result from DEA effects on monosialotetrahexosylganglioside 1 (GM1)-enriched lipid rafts[35] and PLD2 signaling. An intriguing link between lipid rafts structure and PLD2 was discovered in pain control, whereby signaling from the membrane-associated mechanosensitive enzyme PLD2 that resides in a membrane-lipid site comprised of cholesterol, ganglioside GM1 is coupled to the mechanically activated ion channel TREK-1 responsible for downstream signaling[1, 43].

DEA may therefore deliver a "one-two punch" by preventing or reducing PLD toxicity at both the level of the skin and the entire host system. About 4% of the topically applied azelaic acid (the parent compound of DEA) is systemically absorbed and excreted unchanged in the urine[44]. Given that DEA is expected to be systemically absorbed at least to the same extent as azelaic acid, we can do simple back of the envelope calculations. Approximately 1% DEA completely inhibited hemolysis due to PLD activity of brown recluse venom in vitro, and the full-strength topical DEA resolved loxoscelism in a human subject[1]. Therefore, topical DEA can be viewed both as a toxicity mitigator at the bite site and a systemic modulator of the pain and damage to the victim's body by the venom.

We have patented the use of DEA for the treatment of brown recluse spider bite[45], musculoskeletal pain[46], insulin resistance[47] and Type 2 diabetes[48]. Overall, DEA is a highly "druggable" small molecule with a favorable safety profile. It is not mutagenic, undergoes rapid metabolism in mammalian hepatocytes, and is rapidly eliminated from plasma upon oral dosing in rodents[39]. DEA has shown safety and efficacy in human studies upon oral[37] and topical[1] administration. Last but not least, DEA is economical to manufacture and has a long shelf life.

Conclusions

In the two years since we published our paper demonstrating the utility of DEA for the treatment of brown recluse bite the state of the art has not advanced. Given the high potential for negative outcomes of loxoscelism and a lack of specific and safe treatments, DEA is ideally suited for a first aid type therapy with an undeniably large market potential.

Conflicts of Interest

EI and RTS are the owners and officers of New Frontier Labs, LLC.

Authors' Contributions

Both authors contributed equally to the writing of the manuscript.

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