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Zelsuvmi: a promising treatment for molluscum contagiosum

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Abstract

Molluscum contagiosum (MC) is a common skin infection caused by a poxvirus, primarily affecting children and immunocompromised adults. It manifests as single or multiple raised, pearl-like papules and is highly contagious, spreading through skin contact or contaminated objects. Traditional treatments include cryosurgery, curettage, and pulsed dye laser ablation. However, in early 2024, berdazimer topical gel, 10.3% (ZELSUVMI[TM]), was approved as the first topical treatment for MC. This review explores the potential of Zelsuvmi gel as a significant advancement in treatment due to its nitric oxide (NO)-producing properties. NO is a naturally occurring molecule in the body with multiple roles, including immune defense, antimicrobial activity, and modulation of apoptosis, inflammation, and cytokine production. The novel mechanism of action of Zelsuvmi, utilizing NO's antiviral properties, has demonstrated compelling efficacy in clinical settings. The article also considers the broader implications of this treatment, not only for current dermatological practice but also for future research into innovative therapies for viral skin infections. Through an evaluation of clinical data, this review highlights Zelsuvmi's potential to transform treatment approaches for MC, offering a non-invasive, effective option that may influence both clinical management and future prevention strategies.

Keywords

Molluscum contagiosum, contagious disease, Zelsuvmi, berdazimer

Introduction

Molluscum contagiosum (MC), also called water warts [1], is a dermatological condition caused by the molluscum contagiosum virus (MCV) [2], a double-strand DNA poxiviridae virus having humans as its exclusive host [3]. This viral infection primarily affects the epidermis, the top layer of the skin, where it

undergoes replication. The incubation period of the virus varies between two to six weeks, during which the infected individual may not show any symptoms [4]. However, as the virus replicates in the cytoplasm, characteristic manifestations emerge in the form of small, skin-colored to pink, round lesions with central indentations, termed umbilicated lesions [5], which exhibit diverse characteristics, including erythematous, nodular, giant, conglomerated, inflamed, or pedunculated appearances [6]. This condition predominantly targets young children and immunocompromised adults [5]. Though the infection can manifest on any area of the skin, it often appears on the face, neck, arms, legs, or genital region. The clinical presentation typically involves 10 to 30 lesions, which may be sore, swollen, and pruritic [7] but in severe conditions, it can exceed up to 100 lesions [8, 9]. Additionally, MC lesions may occur in atypical locations [3] including the palms and soles, the areola [10, 11], conjunctiva [12], lips [13], eyelids [14], periocular lesions around eyes [6], and other areas [15].

MCV is distinctive in evading immune surveillance by inhibiting or dampening several immune pathways via the production of viral proteins. This results in decreasing local inflammatory response which contributes to the prolonged survival of MCV in the epidermis [15]. Several viral genes have been identified that can alter the activation of nuclear factor kB (NF-kB) [16–19], a nuclear protein complex that stimulates the innate and acquired immune systems by promoting the production of pro-inflammatory cytokines [20]. MC, a highly contagious viral infection, can be transmitted through skin-to-skin contact or contact with contaminated items like towels or toys. In some cases, this can be congenital. This occurs when the virus is transmitted vertically during delivery [21, 22], with circular lesions typically found on the scalp [22]. This infection impacts a significant number of individuals in the United States annually, with approximately 6 million people affected each year [5, 23].

Despite extensive research, there's still insufficient data to determine its exact prevalence, leading to variable results across different studies. For instance, a meta-analysis revealed an overall prevalence of 8.28% in children, with higher frequencies in warm climates [24]. Studies on seroprevalence have yielded variable results in different populations. For example, in Australia, a study found a 23% seropositivity rate for MCV [25], while in Germany, it was 14.8% [26], 6% in Japan, and 30.3% in the UK [26], all utilizing ELISA methodologies to detect antibodies targeting specific viral proteins [23–25]. Moreover, MC is a self-limiting infection that can persist for a period of 6–12 months [6, 27], although, some cases can persist for more than 3 or 4 years [27].

MC exhibits a higher prevalence among immunosuppressed patients, with notable associations observed in HIV patients, where the prevalence rate is estimated to be close to 20% [28]. Additionally, MC may be associated with iatrogenic immunosuppression or primary immunodeficiencies, such as DOCK8 immunodeficiency syndrome [29]. While atopic dermatitis (AD) has been proposed as a risk factor for MC, studies yield mixed findings. Some studies indicate an increased risk in AD patients [30, 31], with prevalence rates reaching up to 62% [32, 33]. It has even been postulated that patients with AD and filaggrin mutation have an increased risk of MCV infection [28]. It is common for patients with MC to develop eczematous plaques around one or more of their lesions. This phenomenon is referred to as "molluscum dermatitis" (MD) or "eczema molluscorum" (EM) and is more frequent in patients with AD. Susceptibility to MD among MC patients is estimated to range from 9% to 47% [33].

Diagnosis of MC can be made via dermoscopy [3], where it is observed as a central pore or umbilication, polylobular white-to-yellow amorphous structures, and peripheral crown vessels [34–36]. Polarized rosettes may also be visible under the dermatoscope [37]. Another emerging diagnostic tool is reflectance confocal microscopy (RCM), which reveals round, well-circumscribed lesions with central round-to-cystic areas filled with bright refractile material [38, 39]. This infection can be difficult to control for both caregivers and patients due to its contagiousness [9]. Lesions caused by MC can be unsightly and persistent and can lead to emotional distress and social stigma [40]. In a patient-centered perspective of MC, the most vexatious aspects to participants were visibility and contagiousness. The most commonly stated psychosocial impacts were self-consciousness (n = 15) and embarrassment (n = 14) [41]. It is a common skin and soft tissue infection (SSTI) in children and results in a significant number of office-based

pediatric visits. With an increase in SSTIs, it is important to treat the individual effectively, appropriately, and cost-consciously [42].

Despite numerous proposed treatments for MC including physical removal, topical medications, and systemic treatment, none have yet been proven effective [9]. There are different ways to physically remove lesions, which include cryotherapy, curettage, and laser therapy [43, 44]. Cryotherapy involves applying a cotton-tipped swab or portable sprayer for 10 s to 20 s to freeze the lesion with liquid nitrogen [3, 43, 44]. It has been found effective in multiple studies, with clearance rates ranging from 70.7% to 100% in a maximum of 16 weeks [45, 46]. Curettage can be done using a curette, punch biopsy, or ear speculum for scraping away the caseous or cheesy material [43, 44, 47, 48]. One study showed that 70% of children were cured while the overall satisfaction rate was 97% [49]. In a randomized trial, 80.3% of patients had complete clearance [47, 48]. Pulse dye laser therapy is another option, but it's costly and limited in availability [4, 50]. Successful use in immunosuppressed patients has been reported [51]. These options require local anesthesia [27, 49, 52] and can cause post-procedural pain, irritation, and scarring [41], blistering and post-inflammatory hypo or hyperpigmentation [4], and risk of bacterial superinfection of blisters [4, 53].

Topical treatments for MC include podophyllotoxin (not for pregnant women), potassium hydroxide, salicylic acid, benzoyl peroxide, and tretinoin [54]. Chemical methods and immunomodulatory methods are also used to treat MC [8]. Cantharidin and potassium hydroxide are effective chemical methods. Cantharidin is an FDA-approved topical agent that produces an intraepidermal blister, followed by resolution [55]. The efficacy of cantharidin in the treatment of MC is variable, with cure rates varying between 15.4% and 100% among different studies [56, 57]. While adverse effects include local erythema, burning sensation, and blisters [27]. Immunomodulatory methods, which stimulate the patient's immune response against the infection, comprise options such as imiquimod, oral cimetidine, interferon alfa, candidin, and diphencyprone [4]. It can be a useful alternative in the treatment of MC based on case reports and uncontrolled studies [58]. However, it's important to note potential side effects, including erythema, itching, burning sensations, and pain, reported in approximately 11% of cases [59].

Top of form antivirals like cidofovir are used in immunosuppressed patients with extensive or refractory disease [60–62]. New treatments for MC, including topical sinecatechins [63], intralesional 5-fluorouracil, hyperthermia [64], and zoster immune globulin [65], are available, albeit lacking FDA approval. There remains no consensus on the best method due to insufficient high-quality data [66]. MC is challenging to control since physical therapies can leave scars, while immunomodulatory and pharmacological treatments can cause unfavorable skin reactions such as blistering, redness, and itching. The need for repeated doctor visits, the possibility of skin discoloration and scarring following surgery, and the increased anxiety experienced by pediatric patients all contribute to these difficulties [67]. Therefore, to adequately treat these complex issues, pharmaceutical interventions must be developed with enhanced efficacy and low side effects.

After impeccable efforts and research, a nitric oxide (NO)-releasing product containing Zelsuvmi, called SB206, has emerged to be a promising treatment in overcoming current limitations and has undergone a successful phase 3 trial [66]. Zelsuvmi (Zelsuvmi sodium) in January 2024 was declared as the FDA-approved drug for the topical treatment of MC in adults and pediatric patients 1 year of age and older [67] on the basis of 2 phase 3 trials—B-SIMPLE4 and B-SIMPLE2 in which Zelsuvmi was found to reduce lesion counts and was well tolerated [68–70]. This innovative therapy is the first and only topical prescription drug for molluscum that can be used outside of a healthcare facility [71].

Mechanism of action

Zelsuvmi topical gel, marketed as ZELSUVMI^{TM} by Novan Inc., is a medication designed for the treatment of MC. Formulated with 10.3% NO, the gel leverages Novan's innovative NITRICIL^{TM} platform to release NO at the site of application through large polymers [72]. Zelsuvmi is a polymeric substance that features a polysiloxane backbone and covalently bound N-diazeniumdiolate NO donors. Upon exposure to proton

donors such as water, Zelsuvmi releases NO, facilitated by the degradation of the N-diazeniumdiolate entity [40]. Zelsuvmi is an immunomodulator, which means it can regulate the immune system's response to infections [73], and it also exhibits broad-spectrum antimicrobial and antiviral activity [74, 75], likely due to the S-nitrosylation of proteins and cytotoxicity to viral replication from reactive oxygen species [9, 76], making it an effective treatment for a wide range of infections. Clinical studies have demonstrated its effectiveness as an antiviral agent in treating various viral infections [40, 76–78]. Zelsuvmi sodium has been found to effectively reduce the viral load of poxvirus and suppress the expression of the MC immunomodulation protein MC160 by directly targeting MC virions. This suggests that Zelsuvmi's antiviral effects are due to its direct action on the virus itself, rather than the host's immune system [79].

Clinical trials

The effectiveness of ZELSUVMI™ was assessed in 3 multicenter, randomized, double-blind, parallel group, vehicle-controlled trials in patients with MC (trials 1, 2, and 3; NCT04535531 [70], NCT03927703 [69], and NCT03927716 [80], respectively). This study registered 891 subjects for trial 1, 355 subjects for trial 2, and 352 subjects for trial 3. Eligible subjects in trial 1 were randomized in a 1:1 ratio while in trials 2 and 3, subjects were randomized in a 2:1 ratio to receive ZELSUVMI™ with MC lesions once a day for a period of up to 12 weeks. 3 subjects in the three studies were aged less than 2 years, while 96% were aged between 2 and 17 years. The trial population consisted of 51% male, 88% Caucasian, 6% African American, and 6% Other; with regard to ethnicity, 21% of the subjects were Hispanic/Latino, 78% were non-Hispanic/Latino, and 1% were unknown. There was a range of number of persistent MC lesions ranging from 3 to 70 in the subjects' case records. Based on the enrolment criteria concerning baseline MC lesions at the first visit, the mean number of MC lesions was 20.2. The primary endpoint assessment was the percentage of subjects completely cleared at 12 weeks. The criteria for complete clearance means that at the time of evaluation, there were zero total MC lesions in that patient. The secondary endpoint analysis was the rate of complete clearance at 12 weeks [81]. Less robust positive efficacy trends for complete clearance in some subgroups, such as those aged < 6 years, may be due to age-related underdeveloped immune responses. Of note, for patients < 6 years of age, ≥ 90% clearance rates were statistically favorable for zelsuvmi [82].

The results of the Phase 3 clinical trial (B-SIMPLE4) of Zelsuvmi gel are significant for patients with molluscum. In this trial, patients with a mean starting lesion count of approximately 20 were treated with 10.3% Zelsuvmi gel once a day for 12 weeks. The results showed that 32.4% of patients treated with Zelsuvmi (n = 444) had complete clearance of lesions compared to only 19.7% of those treated with a placebo (n = 447). This means that for every 100 patients treated with Zelsuvmi, 32 of them had complete clearance of lesions, whereas only 20 of every 100 patients treated with a placebo had the same outcome. The odds ratio (OR) was 2.0, with a 95% confidence interval (CI) of 1.5–2.8, and a P-value < 0.001, indicating a statistically significant difference in treatment efficacy between the two groups [68].

Pharmacokinetics

In a study of 34 children, plasma hydrolyzed MAP3 (hMAP3), a structural marker for Zelsuvmi, and nitrate levels were measured. Zelsuvmi was applied for two weeks, once daily. On day 1, none of the subjects had measurable plasma hMAP3 concentrations, but two subjects showed it on day 15. The mean plasma nitrate levels were similar on days 1 and 15. Methemoglobin levels remained constant throughout the study [83]. While the pharmacodynamics of the drug are unknown [84].

Adverse effects

Adverse events were generally low, with mild application-site pain (burning or stinging sensation) being reported in 14.4% of patients in the Zelsuvmi group versus 4.7% in the placebo group, and erythema being reported in 5.6% of patients in the Zelsuvmi group versus 1.1% in the placebo group [76]. In rare cases, patients may experience body aches or pain, chills, cough, ear congestion, fever, headache, loss of voice, sneezing, stuffy or runny nose, unusual tiredness or weakness, or vomiting. If any of these occur, it is

important to seek medical attention immediately. Additionally, blistering, burning, crusting, dryness, and flaking of the skin, as well as itching, scaling, severe redness, soreness, or swelling of the skin may occur but are not very common [84].

Nonclinical toxicology

Currently, we do not have enough data comparing the exposure of Zelsuvmi in humans after using Zelsuvmi topically. While a dermal mouse was assessed for the carcinogenic potential of Zelsuvmi gel. No drug-related tumor findings were associated with daily topical administration of Zelsuvmi gel to mice at doses up to 4% Zelsuvmi gel. As far as mutagenicity (the ability to induce genetic mutation) [85] is concerned. Zelsuvmi was found to be mutagenic in a bacterial mutagenicity assay (Ames assay), but was not clastogenic (causing breaks in chromosomes) [86] in an in vitro chromosomal aberration assay in human peripheral blood lymphocytes. Additionally, there were no Zelsuvmi-related effects on male or female fertility or early embryonic parameters in rats at oral doses up to 189 mg/kg/day [79].

Limitation

Although it offers a non-invasive option for managing the condition, it comes with several limitations. Zelsuvmi gel may not result in complete clearance of lesions in all patients. Clinical trials have shown variability in patient response, with some achieving full resolution while others experience partial or no improvement. This may be due to differences in individual immune responses or the severity of the infection [84, 87]. There is insufficient data on the effects of Zelsuvmi during pregnancy and lactation. The potential risks to unborn babies or nursing infants are not fully understood [83]. The recommended treatment duration is up to 12 weeks, which may not be sufficient for all patients depending on their condition's severity. Zelsuvmi is strictly for topical use and should not be applied near the eyes, mouth, or vagina. Its safety in children under 1 year has not been established [87].

Conclusions

Therefore, MC is a common contagious skin infection in children and adults with weak immunity that can be difficult to treat. Previously available treatments had limitations such as being ineffective, requiring anesthesia, or causing scarring. However, a new topical medication called Zelsuvmi has been FDA-approved for the treatment of MC. Clinical trials have shown that Zelsuvmi is effective and well-tolerated, with the most common side effects being mild application-site pain and redness. Despite efforts, the duration of the application and resolution of disease has not been reduced yet. Further research is needed to identify potential areas for optimization. By reducing the application duration, users could experience significant benefits such as increased productivity, reduced wait times, and improved overall satisfaction. Overall, this new medication offers a promising option for patients with MC.

Abbreviations

AD: atopic dermatitis

MC: molluscum contagiosum

MCV: molluscum contagiosum virus

NO: nitric oxide

Declarations

Author contributions

FL: Conceptualization, Formal analysis, Investigation, Writing—original draft. MH and MM: Formal analysis, Investigation, Writing—review & editing. RA: Data curation, Formal analysis, Investigation, Writing—original draft. NUA and QUA: Conceptualization, Investigation, Methodology, Writing—original draft. BG:

Conceptualization, Formal analysis, Project administration, Resources, Validation, Supervision, Writing—review & editing. All the authors have equal contributions to this work and agreed to the publication.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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