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Review Article

BERDAZIMER SODIUM IS THE PROMISING DRUG FOR THE TREATMENT OF MOLLUSCUM CONTAGIOSUM

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ABSTRACT

Molluscum Contagiosum (MC) is an infectious dermatosis disease caused by Molluscum Contagiosum Virus (MCV). MC is treated with mechanical, chemical, immunomodulatory, and antiviral drugs. Predominantly, immunodeficiency HIV-positive patients expressing resistance to MC lesions effectively responded to available drug molecules; therefore, there is a need to develop an effective drug molecule for the treatment of MC infection. Berdazimer topical gel, 10.3% has been developed by Novan Inc. (Ligand Pharmaceuticals) under the brand name Zelsuvmi® for treating MC infection in adult and pediatric patients. Berdazimer topical gel, 10.3% is a Nitric Oxide (NO) releasing topical gel comprising novel NO-based technology platform NITRICI™, which stores gaseous NO species on large polymers.

Keywords: Molluscum contagiosum, Berdazimer, Berdazimer sodium topical gel, Zelsuvmi, NITRICI™

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INTRODUCTION

Bateman has first time described and assigned the name of Molluscum Contagiosum (MC), a cutaneous and mucosal eruption which is mainly caused due to a Molluscipox virus in the early nineteen century [1]. Henderson and Paterson mentioned the intracytoplasmic inclusion bodies also known today as molluscum or Henderson Paterson bodies [2]. In the early twentieth century, Juliusberg, Wile, and Kingery were able to extract filterable virus from lesions and show transmissibility [3, 4]. Goodpasture later described the similarities of molluscum and vaccinia [5]. The virus infection cases are reported in humans and animals globally [6-9].

Search Criteria: The review article was critically searched from specialized databases like Google scholar, Elsevier, Pubmed and Mendeley. This paper utilizes existing literature on the subject published after 2014 to create a comprehensive representation of pharmaceutical research. Keywords used to search relevant literature are "Molluscum Contagiosum", "MC infection", "Berdazimer sodium", "Berdazimer sodium topical gel", "Zelsuvmi", "NITRICI™" and "Nitric oxide (NO)-releasing agent" Other selections include articles from Springer, information from Internet sources, and online published articles from Medscape, Statpearls.

MC is a viral infection that commonly occurs in the mucous membranes and skin of children. MC infection cases have increased by up to 20% worldwide, with the trend raising in the United States [10–14]. Children with 2 to 11 y ages having immune system suppression are most commonly infected with MC [15, 16]. Patients suffering from Human Immunodeficiency Virus (H. I. V.) infection and leukemia may be more likely to develop extensive disease [17–19].

MC is manifested by skin infection caused by the largest cutaneous viruses, commonly known as poxvirus [20]. Globally, it has been detected that infecting humans, other primates, and the kangaroo [21-23]. The virus has been efficiently multiplying in the human foreskin [24].

There are four major types of Molluscum Contagiosum Virus (MCV) virus, mainly MCV-1, MCV-1a, MCV-2 and MCV-3, with the latter being extremely rare [24–27]. MCV-1 virus is more common than MCV-2 virus. MCV-1 is mainly responsible for MC infection in pediatric patients and MCV-2 found to infect adult patients and is more prevalent in sexually transmitted cases [28]. Molluscum Contagious infection occurs mostly among children and also affects sexually active adults [29]. MC has received special attention in the past two decades because of its prevalence as an opportunistic infection in HIV patients. MC infection, therefore, consider as first indication of HIV infection [30]. Multiple skin colors are the diagnostic indication of MC infection. Lesions can develop on all over body areas, including palmar and plantar skin. The distribution of lesions is quite irregular, and they are often grouped in clusters or distributed linearly because of self-inoculation by microtrauma or scratching. The diagnosis of MC is commonly performed by dermoscopy and *in vivo* confocal microscopy techniques [31]. Dermatoscope clearly shows a central pore or umbilication, polylobular white-to-yellow amorphous structures, and peripheral crown vessels as an indication of MC infection [32-33]. Reflectance Confocal Microscopy (RCM) is emerging advanced diagnostic tool for diagnosis of Molluscum Contagiosum. Reflectance Confocal Microscopy technique, commonly known as RCM involves round, well-circumscribed lesions with central round-to-cystic areas filled with bright refractile material [34, 35].

MC is intercepted by avoiding direct skin-to-skin contact with an infected patient. Early identification of risk in pregnant women shall avoid abrasion at later stage of delivery, certainly minimize the chances of transmission of MC infection [36, 37].

Currently, there are no treatment procedures for MC, approved by FDA. However, there are many different treatment practices have been reported in the literature, efficacy data is largely dependent on small case series and uncontrolled studies. It is found that significant differences in efficacy between the various treatment modalities are not accurately demonstrated by randomized controlled clinical trials [38]. The decision on whether treatment is necessary shall be based on the needs of the MC-infected patient, the recalcitrance of their infection, and the likelihood of treatments to leave pigmentary alteration or scarring [39, 40]. It is found in many cases that complicated treatment procedures are not required to resolve but natural way of resolution can be awaited. Resolution takes place without complications in normal patients, but immunocompetent patients often take a prolonged period of months to years. When lesions are symptomatic or associated eczema is infuriating, treatment may be prudent. The selection of treatment will be based on various factors, such as the age of the patient and the number and position of the lesions [41, 42].

The treatment for MC includes watchful waiting, procedure-based treatments such as Cryotherapy, Curettage, Needle prick, Pulsed dye laser therapy, chemical agents such as cantharidin, Potassium

hydroxide, Benzoyl peroxide, Trichloroacetic acid, Glycolic acid, Salicylic acid; immune modulator includes Imiquimod, Interferon-alpha, Cimetidine, Antiviral agent like Cidofovir. MC treatments can cause unwanted adverse effects or side effects. Treatment procedures are usually advised for psychological reasons due to refractory lesions. In addition, multiple MC lesions can heal with scar tissue. It is advisable that all treatment procedures should be discussed with patients and their family members [43, 44]. Before performing treatment procedures, a thorough skin examination should be performed to diagnose the infected area and identify all lesions. Curettage is a simple and relatively inexpensive procedure, with the added advantage that the tissue removed can be kept for histopathological analysis in case of diagnostic doubt [45]. EMLA cream, a eutectic mixture of local aesthetics (2.5% lidocaine and 2.5% prilocaine), is very commonly used in children to mitigate the pain caused by the procedure, although its application on MC lesions can cause local, self-resolving purpuric reactions [46, 47]. The umbilicated nucleus of the lesion can be manually removed using the hands or any one of a variety of instruments, including a scalpel, lancet, insulin needle, slide, or forceps. The resulting scarring is similar to that caused by curettage [48]. The umbilicated nucleus of the lesion can be manually removed using the hands or any one of a variety of instruments, including a scalpel, lancet, insulin needle, slide, or forceps. The resulting scarring is similar to that caused by curettage. This technique is of particular interest as it is simple and fast and can be learned by patients, family members, and caregivers and therefore performed at Home [49]. Cryotherapy is an efficient treatment for MC. A cotton-tipped swab dipped in liquid nitrogen is applied on each lesion for 6–10 sec during the procedure. It is preferred to use for multiple trunk MC lesions. However, it is not preferred to use on face MC lesions because it may cause hypo-hyperpigmentation and scar formation. The application should be continued until umbilical formation [50]. Pulsed dye lasers have shown to be promising treatments in case reports and small, uncontrolled studies. It is preferred in child patients, recalcitrant cases, and immunocompromised patients. A novel 585 nm collagen remodeling pulsed dye laser stimulates the release of various growth factors via cell-mediated reaction with T-lymphocytes that promotes collagen remodeling and tightening [51]. Trichloroacetic acid causes tissue destruction by immediate chemical coagulation and superficial necrosis. It is used at concentrations of 20% and 35% and repeatedly applied on the centre of the lesion until a white, frost-like covering forms [52, 53]. Salicylic acid is a keratolytic agent sold at concentrations of 10% to 30%. It can be used in young children, diabetic patients, and those with multiple lesions. Clinical studies on salicylic acid for MC treatment are limited. The combination of 50% salicylic acid paste and 10% PVP-iodine solution is an effective treatment that may accelerate the healing process and is a less expensive and less painful procedure [54]. Topical cantharidin is usually applied every two to four weeks until all lesions are resolved. It should not apply on the face, genital, or perianal areas. Because it may cause transient burning, pain, erythema, and pruritus [55]. Potassium hydroxide (KOH) is an alkali that penetrates and destroys the skin by dissolving keratin. It is used in aqueous solution at concentrations of 5% to 20%, and applied to MC lesions once or twice per day [56, 57]. Orally administered cimetidine as H_2 histamine receptors antagonist. It exerts immunomodulatory effects by stimulating delayed hypersensitivity. In a clinical study of 13 children of less than 10 y of age who were treated with 40 mg/kg of oral cimetidine once per day for 2 mo, complete lesion resolution was observed in 9 of 13 patients [58]. Podophyllotoxin is an effective antimitotic agent in podofilox 0.5% as a solution or gel forms. The safety and efficacy study of podophyllotoxin is unclear in young children. Studies on the use of podophyllotoxin in MC infection are few and limited [59]. İnterferon may be used in MC treatment for immunocompromised patients and refractory lesions [60]. Large and numerous MC lesion can be observed in patients with HIV infection, and the treatments of MC are mostly unsatisfactory in those patients. Cidofovir is a nucleoside analogue antiviral agent that has wide spectrum anti-DNA virus activity, including herpes viruses, papovaviruses, pox viruses, and adenoviruses. It blocks viral DNA synthesis via interacting with viral DNA polymerase [61, 62].

Cidofovir is deoxycytidine monophosphate nucleotide analogue. It inhibits viral DNA polymerase, therefore blocking the synthesis of viral DNA. Cidofovir is generally administered intravenously at 5 mg/kg per week for 2 w followed by 5 mg/kg once every two weeks or administered topically at 1%-3% cream or gel, applied daily [63].

The treatment of MC in immunocompromised patients like HIV-infected patients remains a major challenge. HIV-infected patients are treated with various treatment procedures such as Incision, curettage, cryotherapy with liquid nitrogen, electrodesiccation, and CO_2 laser [64, 65]. Topical tretinoin cream may control the spread of MC but frequently causes severe, treatment-limiting irritation. None of the locally destructive modalities is consistently effective in patients with HIV infection. The presence of MC virus in the epidermis adjacent to MC lesions in immunocompromised patients with AIDS may explain the recurrence of the disease after the lesions are removed [66]. Treatment options for MC lesions are listed in table 1.

Table 1: Treatment options for MC and the corresponding degree of evidence

Topical treatment, outpatient	Topical treatment, home	Immunotherapy	Destructive treatment, outpatient	Homeopathic/Natural	References
Silver nitrate	Imiquimod cream 5%	Cimetidine	Cryotherapy	Australian essential oil (Backhousiacitriodora)	[66]
Trichloroacetic acid	Benzoyl peroxide	Cidofovir	Curettage	Tea tree oil	[64]
Podofilin	Hydrogen peroxide	Interferon-α	Manual extrusion		[66]
Cantharidin	Potassium hydroxide	Candidin	Carbon dioxidelaser		[65, 66]
Salicylic acid			Pulsed dyelaser		[64-66]

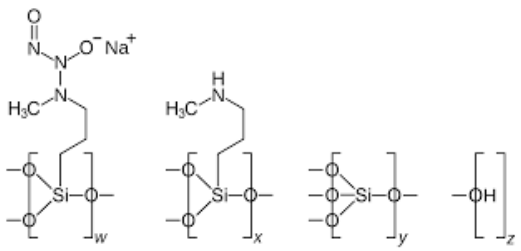

Fig. 1: Structure of berdazimer sodium

Currently, there is no effective systemic treatment for MC infection available worldwide. A recent report described the use of systemic interferon as an unsuccessful attempt. There was a significant need to develop effective drug for the treatment of MC infection. In

January 2024, USFDA approved berdazimer topical gel, 10.3% under the brand name Zelsuvmi™. Novan Inc. (a Ligand Pharmaceuticals company) has developed Zelsuvmi™for the topical treatment of MC in adults and paediatric patients. Berdazimer sodium is a white to off-white powder with the chemical name poly[{[3-(methylamino)propyl]silasesquioxane}-co-{[3-(1-methyl-2-nitroso2-oxidohydrazin-1-yl)propyl] silasesquioxane}-co-silicate (1:3:6 x)], partially hydrolyzed (Si: OH ~ 10: 5), and the following structural and empirical formulas showed in fig. 1.

Berdazimer sodium is a polymeric drug substance comprising a polysiloxane backbone (Si-O-Si bonds) with covalently bound N-diazeniumdiolate NO donors throughout. Exposure to a proton donor like water, promotes NO release from the polymeric drug substance via decomposition of the N-diazeniumdiolates [67].

Novan Inc. has discovered a NO-based technology platform (NITRICIL™), which stores gaseous NO species on large polymers, in the development of berdazimer topical gel, 10.3%. Zelsuvmi®consists of berdazimer sodium gel, a new molecular entity (NME), and a proton-donating hydrogel. Mixing the two gels prior to the topical application to MC lesions releases NO, a pharmacologically active agent. NITRICIL™ technology allow to control the level of NO storage, the rate of release, and the molecule size for targeted delivery. The result is stabilized, druggable NO that is optimized for a specific indication. NITRICIL™provides the stable storage of large quantities of NO onto the polymeric drug substance scaffold and bypass the challenges associated with conventional low molecular weight NO donors. SB206 gel combines berdazimer sodium, a NO-releasing macromolecule, with a buffered hydrogel for topical administration. SB206 gel releases NO, which has bactericidal and virucidal activity, presumably through direct damage to various biomolecules by oxidation and nitration reactions. NO is a short-lived, lipophilic gas, that is endogenously produced and important for defending against infection. Inducible Nitric Oxide synthase (INOS) is the main enzyme for the synthesis of NO. In general, endogenous NO is considered protective against viruses, being produced by immune effector cells and critical to the innate immune response. NO may possess direct antiviral effects, covering impairment of viral enzymes through nitrosylation, destruction of viral DNA through oxidative and nitrosative stress, and repression of viral transcription factors. NO is also important to the modulation of vascular physiology, including vasodilation, leading to improved oxygenation. However, NO can have different physiological effects depending on the tissue and concentration, with high concentrations leading to apoptosis and cell cycle arrest. NO is also one of the key components in the formation of the tumor microenvironment caused by chronic infection and plays a role in cancer initiation and progression. The cytotoxic effect of exogenously administered NO has been investigated in a various literature report, using a number of delivery systems. In a study of gaseous NO to manage wound infection, no cytotoxic effects were observed at levels of up to 200 ppm (6.7 mmol, potentially much lower than the concentration of NO released from berdazimer sodium in the clinic to human dermal fibroblasts, keratinocytes and endothelial cells. In a study using NO-releasing nanoparticles, human lung fibroblasts were treated for 24 h and only minimal cytotoxicity was observed. NO-releasing patches have been tested for wound healing, and were shown to safely deliver up to 400 ppm (13 mmol) NO. Earlier studies tested NO-releasing cream containing ingredients nitrate and ascorbic acid effect on the skin of volunteers, and showed that the NO was pro-inflammatory and toxic to DNA, leading to the accumulation of p53 and subsequent apoptosis. A study using NO-loaded Zeolite ointment showed impairment of 3T3 fibroblast viability in a 24-hour cell culture assay, and that the cytotoxicity resulted from the NO release rather than the ointment itself. However, this cytotoxic effect was not recapitulated in the context of wound healing in obese rats [68].

Berdazimer sodium is a NO-releasing agent. The mechanism of action Berdazimer sodium is not very well known so far. The pharmacodynamics of Berdazimer sodium are not known very well. Plasma hydrolyzed MAP3 (hMAP3), a structural marker for berdazimer, and nitrate levels were evaluated in n=34 subjects 2 to 12 y of age with Molluscum contagiosum.

Subjects applied Berdazimer sodium once a daily for two weeks to a total treatment area of 484 cm^2 (mean lesion count=34), applying a mean dose of approximately 3 ml/d mean plasma nitrate levels were similar on days 1 and 15 and remained relatively flat during the PK sampling period (baseline through 1-, 3-, and 6 h post-application). There were no apparent differences in methemoglobin levels throughout the study signs of carcinogenicity, Mutagenesis, and Impairment of Fertility were detected in pre-clinical studies [69-73].

Clinical trial Data from two adequate and well-controlled trials NI-MC302 and NI-MC304 (trials-302 and-304) provided substantial evidence of the effectiveness of berdazimer gel, 10.3% for the topical treatment of MC in the target population. Both trials assessed as their primary efficacy endpoint the proportion of subjects with complete clearance of all treatable MC lesions at Week 12, and as a key secondary efficacy endpoint the complete clearance rate of all treatable MC lesions at Week 8. The primary efficacy endpoint results from Study NI-MC304 were statistically significant ($p<0.0001$; treatment difference of 12.8%, 95% CI (7.1%, 18.6%)), consistent across subgroups and sensitivity analyses, and supported by the findings on the key secondary endpoint at Week 8. Thus, efficacy has been demonstrated in Study NI-MC304. In Study NI-MC302, although the results for the primary endpoint analysis at Week 12 just missed the significance threshold ($p=0.0510$), the point estimates and treatment effect estimate were similar to those observed in Study NI-MC304 (treatment difference of 9.2%, 95% CI (-0.04%, 18.4%)) and the secondary endpoint (complete clearance at Week 8) was supportive of the Week 12 result. The prespecified method of handling missing data in Study NI-MC302 was conservative, and many sensitivity analyses that used reasonable alternative methods of handling missing data had nominally significant findings. In addition, exploratory endpoints that evaluated change or percent change in lesion counts, rather than a dichotomized response endpoint, support an efficacy finding for Study NI-MC302. The complete evaluation of the efficacy results, including primary endpoint results, sensitivity and supplementary analyses, and secondary and exploratory endpoint results, were persuasive and confirm that efficacy had been demonstrated in Study NI-MC302. Thus, Studies NI-MC304 and NI-MC302 are adequate and well-controlled trials that demonstrate substantial evidence of effectiveness.

The substantial evidence of effectiveness was demonstrated through two adequate and well-controlled trials (Studies NI-MC302 and-304). The primary efficacy endpoint results from Study NI-MC304 were statistically significant ($p<0.0001$; treatment difference of 12.8%, 95% CI [7.1%, 18.6%]), consistent across subgroups and sensitivity analyses, and supported by the findings on the key secondary endpoint at Week 8. Thus, efficacy has been demonstrated in Study NI-MC304.

In Study NI-MC302, although the results for the primary endpoint analysis at Week 12 just missed the significance threshold ($p=0.0510$), the point estimates and treatment effect estimate were similar to those observed in Study NI-MC304 (treatment difference of 9.2%, 95% CI [-0.04%, 18.4%]) and the secondary endpoint (complete clearance at Week 8) was supportive of the Week 12 result. The prespecified method of handling missing data in Study NI-MC302 was conservative, and many sensitivity analyses that used reasonable alternative methods of handling missing data had nominally significant findings. In addition, exploratory endpoints that evaluated change or percent change in lesion counts, rather than a dichotomized response endpoint, support an efficacy finding for Study NI-MC302. The complete evaluation of the efficacy results, including primary endpoint results, sensitivity and supplementary analyses, and secondary and exploratory endpoint results, were persuasive and confirmed that efficacy had been demonstrated in the study NI-MC302 [74-79].

CONCLUSION

MC is skin disease caused by a virus characterized by distinctive raised, skin-toned-to-pink-colored lesions called Mollusca that can cause pain, inflammation, itching, and bacterial infection. Berdazimer topical gel, 10.3% has received USFDA approval under brand name Zelsuvmi™for the treatment of molluscum infections.

Berdazimer sodium is the first novel drug for the treatment of MC in adult patients and pediatric patients one year of age and older. Zelsuvmi™ has developed by Novan Inc. (Ligand Pharmaceuticals) as a NO-releasing agent. Berdazimer sodium is shown to have antiviral effects, mechanism of action is not known. NO-based technology platform (NITRICIL™) has been developed by Novan Inc. NITRICIL™ stores gaseous NO species on large polymers in the development of berdazimer topical gel, 10.3%.

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AUTHORS CONTRIBUTIONS

VD was actively involved in conceptualizing and designing the review, literature search, data acquisition, manuscript preparation, editing, and review. AK supported in the review work design, manuscript preparation, and review of the manuscript.

CONFLICT OF INTERESTS

The authors declare no conflict of interest, financial or otherwise.

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