IJMS
Vol 43, No 3, May 2018

Review Article

Delayed Complications and Long-Term Management of Sulfur Mustard Poisoning: A Narrative Review of Recent Advances by Iranian Researchers Part II: Clinical Management and Therapy

CME Article

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Received: 30 August 2017
Revised: 15 November 2017
Accepted: 26 November 2017

What's Known

- Almost all sulfur mustard (SM) victims suffer from delayed complications of this poisoning. These patients receive supportive and symptomatic treatments based on a decision by the physicians
- To date, there has been no standard treatments for these patients.

What's New

- A narrative review of recently approved treatment protocols by ophthalmologists, dermatologists, and pulmonologists who were involved in clinical management of SM victims.
- Leveraging on Professor Balali-Mood's extensive experience in treating the veterans of the Iraqi SM attack, his continuous research, and clinical management of patients.

Abstract

The present study aimed to review and discuss the recommended and recently suggested protocols by Iranian researchers for a long-term treatment of delayed complications of sulfur mustard (DCSM) in veterans. As indicated clinically, patients who suffer from delayed ocular complications of sulfur mustard (DOCS) benefit from treatments for dry eyes, therapeutic contact lenses, amniotic membrane transplantation; blepharorrhaphy, tarsorrhaphy, limbal stem cell transplantation; corneal transplantation, topical steroids, and immunosuppressive. In spite of penetrating keratoplasty, lamellar keratoplasty and keratolimbal allograft had a good long-term survival.

Delayed respiratory complications (DRCS) are the most common effects and life-threatening in Iranian veterans. The recommended treatment protocols include regular clinical evaluations, respiratory physiotherapy and rehabilitation, N-acetyl cysteine; warm humidified air, long-acting β2-agonists, and inhaled corticosteroids. Azithromycin has also been effective in improving clinical conditions, pulmonary function tests, inflammatory indexes, and life quality of the veterans. Interferon gamma (IFN-γ) and helium: oxygen combination were also used in severe DRCS with good results. Some of the delayed cutaneous complications (DCCS) such as itching affects the quality of life of victims. Regular but not frequent showering and bathing, applying sunscreen compounds, topical corticosteroids, and systemic antihistamines reduce the problems of DCCS patients. Several compounds such as capsaicin cream, pimecrolimus, IFN-γ, phenol-menthol; Aloe vera/olive oil cream, cetirizine, doxepine, and hydroxyzine were evaluated in DCCS patients with some benefits. The physicians in charge of veterans emphasize the importance of a healthy lifestyle, appropriate financial/social/cultural supports, and a degree of reassurance and supportive care on the clinical improvement of patients.

Please cite this article as: Etemad L, Moshiri M, Balali-Mood M. Delayed Complications and Long-Term Management of Sulfur Mustard Poisoning: A Narrative Review of Recent Advances by Iranian Researchers Part II: Clinical Management and Therapy. Iran J Med Sci. 2018;43(3):235-247.

Keywords ● Chemical warfare agents ● Sulfur mustard ● Vision, ocular ● Respiratory system

Introduction

In the first part of this paper, we comprehensively reviewed the toxicity mechanisms of sulfur mustard (SM) and the delayed complications of SM (DCSM) in different organs of the body with a particular reference to Iranian veterans. In this part, we aim to review and discuss recent protocols recommended for DCSM treatment.

Since there is still no approved antidote for sulfur mustard (SM) poisoning, clinical management of DCSM exposure on different organs of pulmonary, skin, ocular, neuro-psychiatric, immune, and cardiovascular systems are supportive and symptomatic (table 1). Therefore, most patients with DCSM receive several medicines which might put them at the risk of drug-drug interaction and/or adverse drug reactions.

Iranian researchers of various specialties (e.g. ophthalmologists, pulmonologists, dermatologist) who have been involved in treating long-term effects and delayed complications of SM veterans have recently published national treatment protocols. Here, it is aimed to review the protocols and recent advances of long-term treatment of delayed complications of SM poisoning to find the best and the optimum solution for the veterans. This review has already been published as a chapter of a book on mustard compounds.[1]

Management of Ocular Complications

As for other DCSM, management of delayed ocular complications of SM (DOCS) is supportive and almost all require long-term follow-up to control the symptoms and signs such as dryness, feelings of granulation, itching, burning sensation; photophobia, tearing, ocular pain, chronic conjunctivitis; peri-limbal hyperpigmentation, corneal thinning, vascular tortuosity, limbal ischemia; corneal opacity, corneal vascularization, and corneal epithelial defect.[1-4]

Table 1: Recommended treatment for the delayed complications of sulfur mustard

Ocular	Artificial tears Tear-duct plugs Therapeutic contact lenses Amniotic membrane transplantation Temporary or permanent punctual plug Blepharorrhaphy Tarsorrhaphy Limbal stem cell transplantation Corneal transplantation Topical steroids (in relapse episode) Immunosuppressive (if need)
Respiratory	Annual evaluation by PE, PFT, CXR, and tuberculin skin testing Respiratory physiotherapy rehabilitations Mucolytic agents (NAC) Warm humidified air Long-acting β2-agonists Inhaled corticosteroids Cancer screening programs
Skin	Reduce taking shower and bath Topical corticosteroids Systemic antihistamines Sunscreen compounds

NAC: N-acetyl cysteine; PE: Physical exams; PFT: Pulmonary function tests; CXR: Chest radiography

Recommended supportive treatments for eye dryness, a common symptom of DOCS, are preservative-free artificial tears, tear-duct plugs, and some types of contact lenses.[3,5-8] Keratitis due to DOCS can be controlled by repairing ocular surface instability and tearing deficiency.[1] Depending on the severity of keratitis, the following treatments are applied: preservative-free artificial tears, immunosuppressive, and therapeutic contact lenses.[1] Some suggest surgical interventions for DOCS include amniotic membrane transplantation, temporary or permanent punctual plugs, surgical repair of the eyelid (blepharorrhaphy); tarsorrhaphy, transplantation of direct family members' limbal stem cell, and corneal transplantation.[6,9] Following allogeneic transplantations, immunosuppressive therapy is required to prevent rejection.[6-9] Episodes of relapsed inflammation can be managed by topical steroids;[9] however, continuous administration of topical steroids is forbidden due to complications as a result of its long-term use (e.g. glaucoma, cataracts, and increased risk of infection).[3,9,10] In severe cases, systemic corticosteroids are administrated especially when topical steroids are ineffective. If both types of corticosteroids (topical and systemic) fail to control inflammation of limbus or cornea, systemic immunosuppressives such as azathioprine and cyclosporine A are indicated.[9]

The effect of primary ocular treatment on the frequency of DOCS is doubtful. We could not find any research that compared DOCS of veterans treated by various regimens. However, most authors believe that the quality of early treatment is effective on the frequency of DOCS. However, they do not recommend any consensus treatment plan. There are some reports on animal studies on DOCS. The treatment of SM intoxicated rabbits by topical ophthalmic solution of dexamethasone or diclofenac erased early clinical symptoms and revealed severe damage to the cornea, but both regimens could not alleviate corneal erosions and revealed only a short delay in epithelial regeneration (table 2).[11-15] Long-term treatment with topical doxycycline in SM intoxicated rabbits reduced metalloproteinases activity, as inflammatory index[16] in the tear fluid. Moreover, not only it reduced the acute injury but was also suggested as a preventive therapy for ameliorating the DOCS. However, researchers

Table 2: Suggested treatment for delayed ocular complications of sulfur mustard (SM) by different authors

First author(reference)	Design	Precipitants	Evaluation	Result
Amir[11]	SM (390 μg/L for 2 min) SM+Dexa (x4/d) SM+Dic (x4/d)	Rabbit	Clinical symptoms TP and PGE of AC Cellular infiltration of cornea Corneal erosions Epithelial regeneration	Dexa and Dic were effective Dexa=Dic<<SM Dexa=Dic<<SM Both were not effective A short delay
Gonzalez[12]	Diltiazem (10 mM) pretreatment to NM	Rabbit	Intraocular pressure Pupil diameter Palpebral closure Conjunctival symptoms TP of AC	Reduced (effective) Not effective Attenuated Reduced and delayed (effective) Not effective
Gross[13]	DLSP pretreatment to SM	Human epidermal keratinocytes	GST level Survival Glutathione level	Not effective Not effective Not effective
Horwitz[14]	Doxycycline (2 mg/ml) x4/d	Rabbit	MMP-9 and 2 in tear and cornea	Reduced (effective)
Javadi[15]	Retrospective, case series: Limbal stem cell transplantation: lrCLAL vs. KLAL Corneal transplantation techniques: PK vs. Lk	99 veterans with delayed-onset SM keratitis	The clinical outcomes and graft survival rates.	The rejection-free graft survival rate: lrCLAL=39.1% vs. KLAL=80.7% PK=39.0% vs. LK=90.3%

x4/d: Four times a day; AC: Anterior chamber; Dexa: Dexamethasone; Dic: Diclofenac; DLSP: DL-sulforaphane; GST: Glutathione-S-transferases; KLAL: Keratolimbal allograft; Lk: Lamellar keratoplasty; lrCLAL: Living-related conjunctival-limbal allograft; MMP: Matrix metalloproteinases; NM: Nitrogen mustard; PGE: Prostaglandin E; PK: Penetrating keratoplasty; TP: Total protein

believed that doxycycline was only effective in the pre-neovascularization stage.[16]

Corneal argon laser photocoagulation was not quite successful in controlling corneal vascularization.[9,15,17,18] Penetrating keratoplasty (PK) was applied for chronic and delayed mustard gas keratitis (table 2). A follow-up of DOCS patients who underwent PK revealed that about 22% of the grafts failed, and nearly 60% of subepithelial or endothelial grafts were rejected. Due to the limitation of the limbal blood supply of SM veterans, this type of keratoplasty has not shown effective results and has a poor prognosis in DOCS.[9,15,17,18] However, the follow-up of DOCS patients who underwent lamellar keratoplasty (LK) and keratolimbal allograft (KLAL) had a better long-term prognosis and these methods were suggested for long-term corneal and limbal complications of SM.[15]

Management of Respiratory Complications

Delayed respiratory complications of SM (DRCS), unlike ocular complication, had no asymptomatic phase. SM intoxicated patients suffered from a continually progressive pulmonary complication that started from the initial exposure.[3] DRCS are the most common causes of a long-term disability of SM intoxicated victims,[1] and adversely affect patients' quality of life.[19] Nearly all of the moderate to severe SM victims suffered from some degrees of DRCS.[20] DRCS are present in various types: chronic obstructive pulmonary disease (COPD) (35%), bronchiectasis (32.5%), asthma (25%); large airway narrowing (15%), pulmonary fibrosis (7.5%), and simple chronic bronchitis (5%).[20] DRCS patients with COPD have a greater reduction of FEV1 per year; consequently, they had a worse prognosis than non-SM COPD patients.[21]

The protocol for the management of DRCS, as shown in table 1, includes reducing restrictions and stenosis caused by scarring and trying to reverse the reversible obstructive airways by inhaled corticosteroids and long-acting β2-agonists.[3] Also, frequent physical examination and if required chest radiography, pulmonary function tests, and tuberculin skin test should be performed to evaluate the progression of DRCS. Additionally, the patients should be monitored for early detection and treatment of cancer, infections, or exacerbation.[3] Although there are several suggested protocols for the treatment of DRCS patients, individual variations may be involved because of the genetic tendency, underlying diseases, health status, the duration and frequency of exposure to SM; emergent and follow-up medical care, smoking, exposures to other pulmonary irritating compounds, and different types of DRCS. Therefore, physicians should select the treatment on a case-by-case basis.[22]

Respiratory physiotherapy rehabilitations that include postural drainage of sputum and percussion and vibration of the chest wall, during deep breathing and voluntary coughing, are

important medical modalities in the treatment of DRCS (table 1).[22] This manipulation also improves the spirometric parameters.[23] There is no suggestion on any special respiratory physiotherapy for DRCS patients and it is applied similar to other chronic pulmonary diseases.[1]

Warm humidified air and various types of mucolytic agents such as N-acetyl cysteine (NAC) are recommended for the treatment of DRCS (table 1).[24] NAC with both antioxidant and mucolytic properties can improve the pulmonary function tests, quality of life, and reduce bronchial infections and exacerbations (table 2).[25] NAC also affects the fibrozing alveolitis of patients with DRCS,[24] similar to other COPD patients, as it reduces the release of inflammatory mediators.[1]

Ghanei et al.[25] (2008) treated 144 DRCS patients with NAC (1,200 mg daily) or placebo for 4 months (table 3).[19,21,25-33] All patients had SM-induced bronchiolitis obliterans. The NAC treated group showed a significant improvement in dyspnea, wake-up dyspnea, cough, spirometric components, and reduced sputum compared to the control group. NAC also reduced their oxidative stress and inflammatory response. In another study, Shohrati et al.[30] (2008) reported that 4 months treatment of DRCS patients with 1,800 mg daily NAC, improved their clinical conditions and spirometric parameters (table 3).

Salbutamol (a beta agonist) and ipratropium bromide (an anticholinergic) in the form of inhaler have been applied for DRCS patients to achieve a better lung function and reduce the airway hyper-reactivity.[1,34,35] Mehrtash (2002) compared pulmonary function tests after the administration of salbutamol spray alone or in combination with ipratropium bromide in SM veterans. He reported a more remarkable effect, 3 hours later, using the combination therapy compared to single therapy.[36] Ghanei et al. (2007) reported that the combination of inhaled corticosteroids, beclomethasone or fluticasone propionate, long-acting β2-agonists, and salmetrol were effective in the management of chronic bronchiolitis of DRCS patients (table 3).[26]

One important mechanism of both the progression and exacerbation of DRCS is inflammation that includes the accumulation of inflammatory cells in the respiratory tract and the production of inflammatory mediators.[1] Inflammation probably plays an important role in the airway obstruction of DRCS and thus several anti-inflammatory agents are suggested for the treatment of lung problems. It is reported that NSAID may be effective in DRCS.[1]

Corticosteroids have a potent anti-inflammatory property. They are recommended more by inhalation than by systematic route. However, the long-term administration of inhaled corticosteroids do not augment the survival time of DRCS patients, and only have an effect on quality of life.[1] There is an impression that DRCS are not the neutrophil dominated inflammatory disease and are an eosinophilic inflammation; thus, oral corticosteroids could not have a great effect.[37] However, oral corticosteroids are usually advised to patients with respiratory exacerbation.[1] Therefore, oral corticosteroids should be reserved for severe and unresponsive to inhaled corticosteroids cases.[1]

Ghanei et al. (2005) compared pulse therapy, tapered doses of intravenous methylprednisolone acetate (500 mg/day on days 1-3 and 250 mg/day on days 4-6), and oral therapy of corticosteroids, prednisolone. They found no difference in patients' response. Nevertheless, both groups had a better pulmonary function than their own controls (table 3).[28]

Osteopenia and reduction in bone mineral density (BMD) may result in a systemic absorption of high-dose inhaled corticosteroids through the lung parenchyma.[38] Attaran et al. (2007) compared the BMD of 35 SM veterans, treated by beclomethasone dipropionate or fluticasone dipropionate 300-1000 µg/day, with 75 normal individuals for 3-15 years. They reported that BMD in the femoral region has a negative correlation with the severity of bronchial obstruction, but not in the lumbar region. Also, they described a decrease in BMD secondary to long-term therapy with inhaled corticosteroids.[39]

Abtahi et al. (2016) followed up 73 DRCS patients (asthma: 38, COPD: 16, and bronchiolitis obliterative (BO): 19) for 5 years. They treated BO patients with NAC (1,200-1,800 mg/day), inhaled Seretide 125-250/25 (2 puffs BID), and azithromycin (250 mg, three times/week). The other two groups were treated with existing guidelines. They found no significant differences between the basal, final, and yearly decline of FEV1 of BO and COPD patients. Therefore, they recommended therapeutic regimen for BO patients of DRCS (table 3).[21]

The level of transforming growth factor β1 (TGF-b1) in bronchoalveolar lavage and pulmonary samples of DRCS patients were higher than in normal persons and resembled pulmonary fibrosis patients.[40] TGF-beta molecule and receptors have been over-expressed in primary airway fibroblasts of SM veterans.[41-43] Therefore, it seems that TGF-b1 has a fundamental role in the pathogenesis of DCRS, and the treatment of DRCS patients with interferon-gamma (IFN-γ) (i.e. able to reduce TGF-β) may be effective. IFN-γ has shown favorable effects on adjusting cytokines, modifying oxidative stress, improving

Table 3: Suggested treatment for delayed respiratory complications of sulfur mustard (SM) by different authors

First author (reference)	Precipitants/design	Evaluation	Results
Abtahi[21]	BO (n=16): Seretide 125-250/25 (2 puffs BID)+Azithromycin (250 mg, three times/week)+NAC (1200-1800 mg/day). Asthma (n=38), COPD (n=16): Existing guidelines	5 years PFT indices: Basal and final FEV1 Yearly FEV1 decline	 BO=COPD BO=COPD
Ghanei[26]	Randomized clinical trial, 12 weeks on 105 DRCS patients Group 1 (n=52): Fluticasone propionate 500 µ/day+Salmeterol 100 µ/day Group 2 (n=53): Beclomethasone 1000 µ/day+Salbutamol 800 µ/day	FEV1, FVC, FEV1/FVC%, and PEFo Reversibility	Increased: Group 1>Group 2 Group 1>Group 2
Panahi[19]	15 DRCS patients INFG (100 µg) every other day for 6 months	Quality of life, FEV1 Cough, dyspnea, sputum, hemoptysis Serum levels of IL-2, 4, 6, 10, CGRP, MMP-9, TNF-alpha, TGF-beta, and MDA INFG, total and reduced glutathione	Improved Decreased Decreased Increased
Shohrat[27]	3 groups (n=18) of DRCS patients Group 1: Serevent+Flixotide+PR+Tiotropium bromide 18 µg/day Group 2: Serevent+Flixotide+PR Group 3: PR	Cough and nocturnal dyspnea FVC, MMEFR, and PEFI FEV1 CPET	Group 1<Group 3 Group 1>Group 2 Group 1<Group 2 Group 1=2 = 3
Ghanei[28]	Methylprednisolone (500 mg/ day on days 1-3 and 250 mg /day on days 4-6)	PFT indices on admission and on day 8 of therapy	Group 1=Group 2
Ghanei[29]	17 DRCS patients (non-responsive to conventional treatments) Clarithromycin+NAC for 6 months	Cough and sputum, FEV1 and FVC FEV1/FVC	Improved No significant change
Shohrati[30]	144 DRCS, BO classes 1 and 2, Placebo double-blind clinical trial Group 1 (n=72): NAC 1,800 mg/day 2-4 months Group 2 (n=72): Placebo	Dyspnea, wake-up dyspnea, cough, and sputum after 4 months PFT indices after 4 months	Improved Improved
Ghanei[25]	144 DRCS, BO classes 1 and 2, Placebo double-blind clinical trial Group 1 (n=72): NAC 1200 mg/day 2-4 months Group 2 (n=72): Placebo	Dyspnea, wake-up dyspnea, cough, and sputum after 4 months PFT indices after 4 months	Improved Improved
Boskabady[31]	40 DRCS patients for 2 months Study group (n=20): 0.375 mL/kg of nigella seed boiled extract Control group (n=20): Placebo	Wheezing Respiratory symptom score PFT values	Improved Improved Improved
Panahi[32]	36 DRCS patients Study group (n=18): IFNG-1b (200 µg three times per week)+Prednisolone 7.5 mg/day for 6 months Control group (n=18): Prednisolone 7.5 mg/day+Salbutamol+Beclomethasone	FEV1	Improved
Ghanei[33]	Noninvasive positive-pressure ventilation Study group (n=12): 79:21 helium: oxygen Control group (n=12): 79:21 air: oxygen	Systolic blood pressure, Mean arterial pressure, Pulse rate, Respiratory rate, Dyspnea Oxygen saturation, Diastolic blood pressure	Decreased in study group>Control group Increased in study group=Control group

BO: Bronchiolitis obliterans; CGRP: Calcitonin gene related peptide; CPET: Cardiopulmonary exercise test; DRCS: Delay respiratory complications of SM; FEV1: Forced expiratory volume in 1 S; FVC: Forced vital capacity; IL: Interleukin; INFG: Interferon gamma; MDA: Malondialdehyde; MMEFR: Maximal mid-expiratory flow rate 25%-75%; MMP: Matrix metallopeptidase; NAC: N-acetyl cysteine; PEFI: Peak expiratory flow,; PEFo: Peak expiratory force; PFT: Pulmonary function test; PR: Pulmonary rehabilitation 30 minutes/2 times a week; Reversibility: 10% increase of FEV1 in the 2nd month; RV: Residual volume; TGF: Transforming growth factor; TLC: Total lung capacity; TNF: Tumor necrosis factor

respiratory symptoms, and the quality of life of DRCS (table 3).[19,44]

In patients with SM lung injuries, neutrophilic (non-eosinophilic) inflammation is predominant. Thus, macrolide antibiotics can play an anti-inflammatory role by modulating the production of pro-inflammatory cytokines and mediators, and improve macrophage functions.[37,45] Gao

(2008, 2010) evaluated different macrolides (roxithromycin, clarithromycin, azithromycin, and erythromycin) on phagocytotic and chemotactic of SM treated monocyte and the production of various inflammatory cytokines/mediators. Reduced chemotaxis and phagocytosis of SM treated monocyte were restored by all types of macrolides. Also, over-expressed inflammatory cytokines and over-stated nitric oxide (NO) production, induced by SM, were reduced up to 70% by the antibiotics. Therefore, they suggested that treatment with macrolide can enhance clearance of apoptotic material in the airway and leads to the reduction of airway inflammation.[45,46] Ghanei et al. (2008) reported that adding azithromycin to the protocol of DRCS patients who have not responded to full dose prednisone is not effective.[47] However, according to the results of another clinical trial, they recommended 6 months treatment with clarithromycin and NAC to reduce chronic bronchitis and bronchiolitis of DRCS patients (table 3).[29]

Oxidant versus antioxidant balance has an important role in DRCS pathogenesis.[30,48] Thus, antioxidants were evaluated in the treatment of DRCS. Compared to the placebo control group, 45 DRCS patients who received combined curcuminoids (1,500 mg/day) and piperine (15 mg/day) for a period of 4 weeks had higher glutathione and lower malonedialdehyde concentration at the end of the trial. More tolerable signs and symptoms based on COPD assessment scoring tests were reported.[49] The curcuminoids+piperine treated patients had better FEV1/FVC and lower inflammatory mediators, including interleukins 6 and 8, tumor necrosis factor-alpha, transforming growth factor-beta; high-sensitivity C-reactive protein, calcitonin gene-related peptide, and substance P.[50]

Magnesium ion is effective in asthmatic patients as a bronchodilator because of relaxing the smooth muscles of the respiratory system.[51] It also stabilizes mast cells that released bronco-constrictor mediators, thus it decreases bronchial responsiveness of the bronchial tree.[1,52-54]

SM can induce pulmonary artery hypertension.[55] Sildenafil is a phosphodiesterase type 5 inhibitor that relaxes vascular smooth muscles (vasodilatation) through increasing nitric oxide contents. It is approved for the treatment of pulmonary artery hypertension and can be used for reducing pulmonary artery pressure of DRCS.[24,55]

Bayat et al. (2006) evaluated the effect of Thymus vulgaris extract (oral drop 2%) on dyspnea, cough, amount of sputum, and spirometric parameters. They concluded that this compound had a significant effect on veterans signs and symptoms.[56]

The preventive effect of Nigella sativa on tracheal responsiveness and lung inflammation of SM intoxicated guinea pigs has been reported.[57,58] Because of anticholinergic and antihistaminic effects of Nigella sativa seed, Boskabady (2011) evaluated bronchodilator and anti-inflammatory effects of Nigella sativa seed on 40 DRCS patients in a randomized, double-blind, placebo-controlled trial for 2 months. They reported improvement in all respiratory symptoms, chest wheezing, and pulmonary function tests values in the Nigella sativa seed treated group.[31]

Ghanei et al. (2011) evaluated circulatory and pulmonary criteria of DRCS patients, treated with acute respiratory decompensation by 79:21 helium: oxygen inhaled through non-invasive positive-pressure ventilation in comparison with 79:21 air: oxygen. The helium: oxygen treated group had a higher reduction in systolic, diastolic and mean arterial pressure, pulse rate, respiratory rate and dyspnea; and had also a higher arterial oxygen saturation than the air: oxygen treated group.[33]

The recommended treatments for SM lung exacerbation have resemblance to other COPD exacerbations. Inhaled corticosteroids or brief time systemic corticosteroids, oxygen supplement therapy, mucolytics; chest physiotherapy, appropriate antibiotics, and morphine are components of the treatment.[24] Ghanei recommended oral or intravenous corticosteroids in DRCS exacerbation and in un-responded patients; IFN-γ is added to the regimen.[59]

Management of Skin Complications

Reported delayed cutaneous complications of SM (DCCS) includes itching, hyper and hypopigmentation, dermal scarring; dry skin, multiple cherry angiomas, and atrophy.[60] The management of almost all DCCS are supportive and symptomatic (table 1).[1]

Itching is the most common symptom of DCCS.[3,5,61-63] Patients should avoid frequent showering and bathing.[1] However, topical corticosteroids and systemic antihistamines are the standard treatment for skin itching (table 1)[1] and skin atrophy is a side effect of prolonged use of corticosteroids. The adverse effect depends on the type of corticosteroids, the vehicle, and the location of its application.[3] Other adverse effects of prolonged use of corticosteroids include the exacerbation of skin infections, rosacea, acne, striae; purpura, dyspigmentation, and

perioral dermatitis. Systemic reactions such as hyperglycemia, glaucoma, adrenal insufficiency, and delayed wound healing have been reported following the long-term application of topical corticosteroids.[64]

Due to the adverse effects of the long-term application of corticosteroids, several compounds are evaluated and suggested for controlling the itching of DCCS. Panahi et al. (2008-2012) compared betamethasone cream 0.1% versus capsaicin cream 0.025%, pimecrolimus, IFN-γ 50 μg/m^2, and Aloe vera/olive oil cream in Iranian veterans with DCCS in four distinct clinical trials (table 4).[65-74] Capsaicin reduced the scaling of pruritus and skin dryness less than betamethasone, but the burning sensation in the capsaicin-treated group was higher than the controls and 35% of the patients suffered from a burning sensation and its intolerable odor.[71] Pimecrolimus is an inhibitor of T-cell activation by the calcineurin pathway and reduces the release of numerous inflammatory cytokines. It is used in the treatment of atopic dermatitis (eczema). Pimecrolimus reduced pruritus score, burning sensation, and skin dryness as much as betamethasone. The severity of vesicle, hypo- and hyper-pigmentation, erythema, lichenification, fissure, and excoriation did not change by pimecrolimus or betamethasone administration.[70] A trial has shown that Aloe vera/olive oil cream was as effective as betamethasone in controlling the pruritus, burning sensation, and skin dryness. Nevertheless, excoriation and fissure were only reduced by Aloe vera/olive oil cream. Aloe vera and/or betamethasone could not change erythema, blisters, hypo- and hyper-pigmentation lesions and lichenification of the skin of DCCS patients (table 4).[68] Hydrophilic decontamination formulation of CC-2 (DRDE/WH-03) that was fortified with Aloe vera gel has shown appropriate wound healing efficacy in mice model.[75]

There is a positive correlation between concentrations of IFN-γ, TGF-beta and TNF-alpha, and pruritus severity.[67] The administration of subcutaneous IFN-γ (three times per week) was compared to the topical cream of betamethasone 0.1%. IFN-γ showed greater reductions in both

Table 4: Suggested treatment for delayed cutaneous complications of sulfur mustard by different authors

First author(reference)	Design	Evaluation	Results
Panahi[65]	6-week RDBCT, 80 DCCS Study group (n=40): 1% phenol+1% menthol (BID) Control group (n=40): Placebo	Pruritus score	Study group<Control group
Panahi[66]	6-week RDBCT Study group (n=40): Doxepin cream 5% BID Control group (n=35): Beta. cream 0.1% BID	Pruritus score and DLQI	Improved by both regimens
Panahi[68]	6-week RDBCT Study group (n=31): Aloe vera/olive oil cream BID Control group (n=32): Beta. cream 0.1% BID	Pruritic score Fissure, excoriation	Study group=Control group Study group<Control group
Panahi[69]	4-week RDBCT Study group (n=20): IFN-gamma (50 μg/m^2), SC, 3 times per week Control group (n=20): Beta. cream 0.1% daily	SCORAD DLQI	Study group<Control group Study group<Control group
Panahi[70]	6-week RDBCT Study group (n=35): Pimecrolimus cream 1% BID Control group (n=35): Beta. cream 0.1% BID	Pruritus score	Study group=Control group
Panahi[71]	6-week RDBCT Study group (n=32): Capsaicin cream 0.025% BID Control group (n=32): Beta. cream 0.1% BID	Pruritus, scaling, and skin dryness Burning sensation	Study group=Control group Not improved by capsaicin
Shohrati[72]	3-week RDBCT, 90 DCCS Group 1 (n=30): Beta. %1 cream Group 2 (n=30): Unna's Boot cream Group 3 (n=30): Placebo cream	Pruritus score	Improved: Group 1=Group 2>Group 3
Shohrati[73]	4-week RDBCT, DCCS Group 1: Cetirizine 10 mg/day Group 2: Doxepine 10 mg/day Group 3: Hydroxyzine 25 mg/day	Pruritic score	Improved Group 3>Group 2>Group 1
Shohrati[74]	4-Week RDBCT, 50 DCCS Group 1 (n=25): Doxepine 10 mg/day Group 2 (n=25): Hydroxyzine 25 mg/day	Pruritic score	Improved Group 1=Group 2

Beta.: Betamethasone; BID: Twice a day; DLQI: Dermatology life quality index; DCCS: Delay cutaneous complications of SM; RDBCT: Randomized double-blinded clinical trial,; SC: Subcutaneously; SCORAD: Scoring atopic dermatitis

atopic dermatitis score and dermatology life quality index (table 4). Patients complained of no major adverse effects from IFN-γ, and also researchers found no hematobiochemical abnormalities including markers of hematologic, renal, and hepatic functions.[69]

The efficacy of cetirizine 10 mg/day, doxepine 10 mg/day, and hydroxyzine 25 mg/day, in relieving pruritus of DCCS patients, was evaluated in a 4-week double-blind clinical trial in Iranian SM veterans. All compounds reduced the pruritus scoring after one month; however, cetirizine showed lower effectiveness and sedation (table 3).[73]

The combination of phenol 1% and menthol 1% reduced the skin pruritus of SM veterans significantly better than placebo (table 4). However, the patients complained of its intolerable odor.[65]

Skin dryness is one of DCCS that can be treated by soothing creams and emollients.[3] Moreover, several compounds, as above-mentioned, were suggested for this purpose.[68,70,71,73]

Dyspigmentation on non-covered areas, hands, and face leads to cosmetic problems in DCCS patients.[3,76] Sunscreen lotions or creams are recommended for hyper- and hypo-pigmentation areas.[3,77] Sunscreen protects hypopigmentation areas from UVA/UVB hazards secondary to inadequate amounts of melanin pigment. The combination of topical glucocorticoids, azelaic acid, hydroquinone, kojic acid, ascorbic acid, and tretinoin can be used to treat hyperpigmentation induced by SM.[3] Hypopigmentation, induced by SM, can be treated as for vitiligo by applying procedures such as ReCellÒ that inducts living and functional melanocytes and other skin cells.[3]

As mentioned, for the management of respiratory complications, gamma interferon is also proposed for the management of SM skin complications considering its noticeable role of TGF-b in the pathogenesis of chronic inflammatory skin lesions of DCCS.[78]

Psychiatric and Social Problems of SM veterans

Since SM intoxication is a major stressor, some veterans suffer from PTSD (post-traumatic stress disorder). Physicians should continually assess the signs and symptoms of PTSD (e.g. obsessive-compulsive disorder, anxiety, somatization, depression, hostility).[3] A healthy lifestyle of the patients, appropriate financial/social/cultural support, reassurance, and supportive care are important in their clinical management.[1] Iranian veterans have benefited from social, financial, and cultural support including spiritual and religious practices.[79,80]

Conclusion

Various therapeutic methods for the clinical management of DCSM in Iranian veterans have been applied over the past few decades. Iranian researchers of various specialties (e.g. ophthalmologists, pulmonologists, and dermatologist), who have been involved in treating long-term effects and delayed complications of SM veterans, have recently published national treatment protocols. We have reviewed the recent advances of long-term treatment of delayed complications of SM poisoning including the protocols. It is concluded that the majority of treatments are still supportive and symptomatic. The veterans have benefited from a clinical management of different specialties based on the national treatment protocols.

Acknowledgment

The authors received no specific funding for this work.

Conflict of Interest: None declared.

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