



Topical Corticosteroids in Treatment of Atopic Dermatitis: An Overview of Their Current Status

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Authors' contributions

This work was carried out in collaboration among all authors. Author KS drafted the manuscript. Authors NB and KS designed the study and performed critical appraisal of the work. Authors AT and SS designed the figures and managed literature searches. Author RS contributed in unerring and systematic presentation of work. All authors read and approved the final manuscript.

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ABSTRACT

Atopic dermatitis (AD) is a common skin disease characterized by epidermal changes with immune regulatory abnormalities. The pathogenesis of AD involves skin barrier defects, genetic factors and immune deregulation. The AD therapy includes skin hydration, anti-inflammatory agents, antibacterial medications and treatment of pruritus. Currently, topical corticosteroids (TCs) are the most frequently used drugs for the treatment of AD due to their potent immunosuppressive action. However, TCs are associated with several local and systemic side effects. The topical steroid addiction and phobia are among the major challenges with TC therapy. Over the years, efforts are being made to reduce side effects which involve adjustment of dosing, minimizing use in vulnerable areas, avoiding prolonged drug usage and application of novel drug delivery systems. The present review provides an overview of the current and upcoming delivery systems of TCs along with novel approaches being employed to improve the drug delivery in the treatment of AD.

Keywords: *Atopic dermatitis; inflammation; topical corticosteroids; novel drug delivery systems; side effects; steroid phobia.*

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1. INTRODUCTION

Atopic dermatitis (AD) is a common skin disease characterized by intense pruritus and cutaneous inflammation [1]. Over the past 30 years, cases of the disease have been increased by 2-3 fold worldwide [2]. Topical corticosteroids (TCs) are widely used as a prescribed treatment choice in chronic exacerbations of AD [3]. The use of TCs as a therapy for AD is based on their potent immunosuppressive, anti-inflammatory and antihistaminic effects. TCs target the viable epidermis and dermis of skin where inflammation takes place [4]. TCs are commercially available in conventional dosage forms i.e. ointments, creams, lotions and gels. However, due to limitations such as poor permeation, skin irritation and local side effects associated with conventional delivery vehicles for topical steroids, several novel drug delivery systems are being evaluated for their potential in improving drug permeation and patient compliance. For topical drug delivery, the carrier system selected should provide the required solubility and chemical stability of the active pharmaceutical ingredient along with hydration of the stratum corneum [5]. The vehicle plays an important role in treatment adherence in the case of topical drug delivery as the skin condition generally worsens in case of AD due to local side effects associated with topical steroids [6]. Due to these reasons, progress in the field of new delivery systems for TCs is being done to achieve both patient's preferences and address unique anatomical characteristics of the skin.

2. PATHOPHYSIOLOGY OF AD

The cause of AD is multifactorial which involves genetics, skin barrier dysfunction, impaired immune response and environmental factors. The predisposing factors of the disease include low birth weight, maternal smoking, early respiratory infections and allergen contacts. The genetic abnormalities lead to loss of function mutation in filaggrin, which is essential for skin's normal barrier function and deficiency of this protein leads to physical barrier defects predisposing patients to increased inflammation and transepidermal water loss [7,8]. Due to defective skin barrier function and reduced immune response for defence against the bacteria, colonization of *Staphylococcus aureus* is increased in skin lesions [9]. *S. aureus* is capable of secreting toxins known as superantigens which bind directly without antigen processing to constitutively expressed HLA-DR molecules on macrophages or dendritic cells

resulting in the release of proinflammatory cytokines via subsequent activation of T cells [10]. Intense scratching and cutaneous hyper-reactivity results in a vicious circle of continuous mechanical stimulation and dysregulated cytokine release by keratinocytes. The impaired epidermal barrier also allows penetration of external antigens which induce skin inflammation. The interaction of external antigens with the local antigen-presenting cells and immune effector cells leads to the elicitation of immune responses [11]. The immunological pathways leading to AD are described in Fig. 1.

Inflammatory and immunological pathways involved in AD. Allergens invade epidermis due to defective skin barrier and are taken up by FcεRI-bearing dendritic cells such as Langerhans cells (LC), processed and presented to allergen-specific T cells. This leads to increased proliferation of allergen-specific T cells. Keratinocytes release pro-inflammatory cytokines which contribute to the inflammation of the skin. Inflammatory dendritic epidermal cells (IDEC), which are recruited from monocytes of the peripheral blood and eosinophils release interleukin 12 (IL-12) and promote immune response the T helper type 1 cells (Th1) in which tumour necrosis factor (TNF) producing T cells predominate.

3. MANAGEMENT OF AD

AD results in very dry skin with reduced protective abilities. Severe pruritus leads to habitual scratching of the affected area, which makes it even itchier. Repeated scratching may cause open sores and cracks. This increases the risk of infections including staphylococcal and streptococcal bacterial skin infections, warts, herpes simplex and mollus contagiosum. The itch-scratch cycle can also cause poor sleep quality. The clinical manifestations of AD are described in Fig. 2 [12-14].

The treatment of AD involves treating the skin abnormalities such as xerosis, pruritus, infection and inflammation. TCs are the mainstay for the treatment of AD. Although the development of calcineurin inhibitors has provided alternatives to TCs these are expensive and not effective in every case. Hence, TCs continue to have an important role in therapy [15-19].

4. CLASSIFICATION OF TCs

TCs have been classified in seven classes depending on their potency (Fig. 3) in which the

Class I TC formulations are the most potent and associated with maximum side effects whereas Class VII is the least potent [20]. This classification is based on cutaneous vasoconstriction assays as corticosteroids

reduce the expression of proteins with vasodilatory effects which lead to skin blanching. The assays performed to determine the degree and duration of skin blanching that occur due to application of TCs [21].

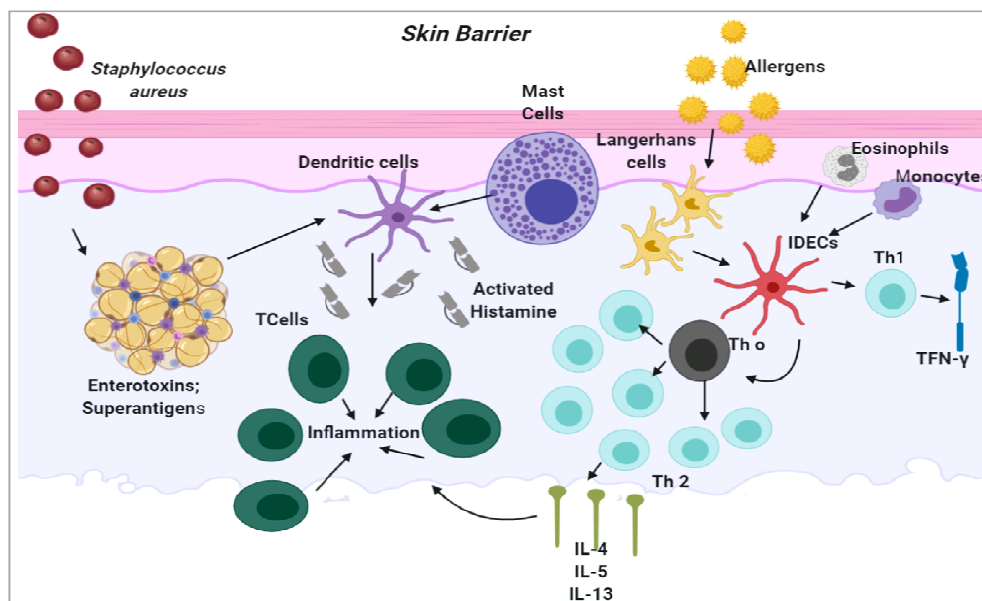


Fig. 1. Inflammatory and immunological pathways involved in AD

Lichenification: Thick, leathery skin due to scratching and rubbing	Papules: Small, raised bumps that may open when scratched, becoming crusty and infected	Ichthyosis: Dry, rectangular scales on the skin
Hyper-Linear palms: Increased number of skin cases on the palms	Urticaria: Red, raised bumps, often after the exposure to an allergen	Keratosis pilaris: Small, rough bumps, generally on the face, upper arm and thigh
Cheilitis: Inflammation of the skin on and around the lips	Atopic pleat: An extra fold of skin that develop under the eyes	Dark circle under eyes: May result from allergies and atropy
Hyper pigmented eyelids: Scaling dark colored eyelids darker due to inflammation	Prurigo nodules: Small thickened bumps of skin caused by repeated picking of the same skin site	

Fig. 2. Clinical manifestations of AD

Group I (Super potent)
• Clobetasol propionate cream (0.05%), Diflorasone diacetate ointment (0.05%)
Group II (High potency)
• Amcinonide ointment (0.1%), Betamethasone dipropionate ointment (0.05%), Desoxamethasone [cream or ointment] (0.025%), Fluocinonide (cream, ointment or gel) (0.05%), Halcinonide cream (0.1%)
Group III (Upper mid-strength)
• Betamethasone dipropionate ointment (0.05%), Betamethasone valerate ointment (0.1%), Diflorasone diacetate ointment (0.05%), Triamcinolone acetonide ointment (0.1%)
Group IV (Mid-strength)
• Desoximethasone (cream) (0.05%), Fluocinonide acetonide ointment (0.025%), Hydrocortisone valerate ointment (0.2%), Triamcinolone acetonide ointment (0.1%)
Group V (Lower mid-strength)
• Betamethasone dipropionate lotion (0.02%), Betamethasone valerate cream (0.1%), Fluocinonide acetonide cream (0.025%), Hydrocortisone butyrate cream (0.1%), Hydrocortisone valerate cream (0.2%), Triamcinolone acetonide lotion (0.1%)
Group VI (Low potency)
• Betamethasone valerate lotion (0.05%), Desonide cream (0.05%), Fluocinonide acetonide solution (0.01%)
Group VII (Least potent)
• Dexamethasone sodium phosphate cream (0.1%), Hydrocortisone acetate cream (1%), Methylprednisolone acetate cream (0.25%)

Fig. 3. Classification of topical corticosteroids based on their potency

5. MECHANISM OF ACTION OF TCs IN AD

Application of corticosteroids results in vasoconstriction of upper dermis blood vessels which reduces the release of inflammatory mediators in the applied area. The corticosteroids induce phospholipase A2 inhibitory proteins known as lipocortins which further control the biosynthesis of inflammation mediators including prostaglandins and leukotrienes and inhibit arachidonic acid which is a common precursor of inflammation. Corticosteroids also inhibit transcription factors such as activator protein 1 and nuclear factor $\kappa\beta$ which are involved in the activation of proinflammatory genes. The corticosteroids decrease the release of proinflammatory cytokine interleukin-1 α from keratinocytes [22]. Other proposed mechanisms for anti-inflammatory effects of TCs include inhibition of phagocytosis and stabilization of lysosomal membranes of phagocytic cells [23]. The immunosuppressive effects of TCs involve inhibition of humoral factors responsible for an inflammatory response along with suppression of maturation, differentiation, and proliferation of all immune cells (Fig. 4).

6. GENERAL GUIDELINES TO BE FOLLOWED DURING TC THERAPY

The factors to be considered for selection of TCs in AD include the anatomic area of application, severity of the disease, patient's age and potency of corticosteroid molecule. It should be noted that all TCs are included under pregnancy category C and should be prescribed with caution during lactation. It is recommended that superpotent TCs should be used only in a prescribed amount for duration not longer than 14 days. Also, the use of superpotent steroids under occlusion is not recommended. It is suggested that after 2 weeks, patients should switch to lower potency or non-steroidal preparations for maintenance therapy [24].

The amount of steroid plays an important role in the treatment efficacy and avoiding adverse effects due to overuse [25]. Fingertip unit is a simple technique in which patients can be counselled regarding the correct amount of TC to be used. The suggested dose of FTU is dependent upon the body region being treated and one fingertip unit (FTU) is equal to approximately 0.5 grams. The number of fingertip units generally required for adequate coverage of specific body area in adults and children has been presented in Table 1 [26-28].

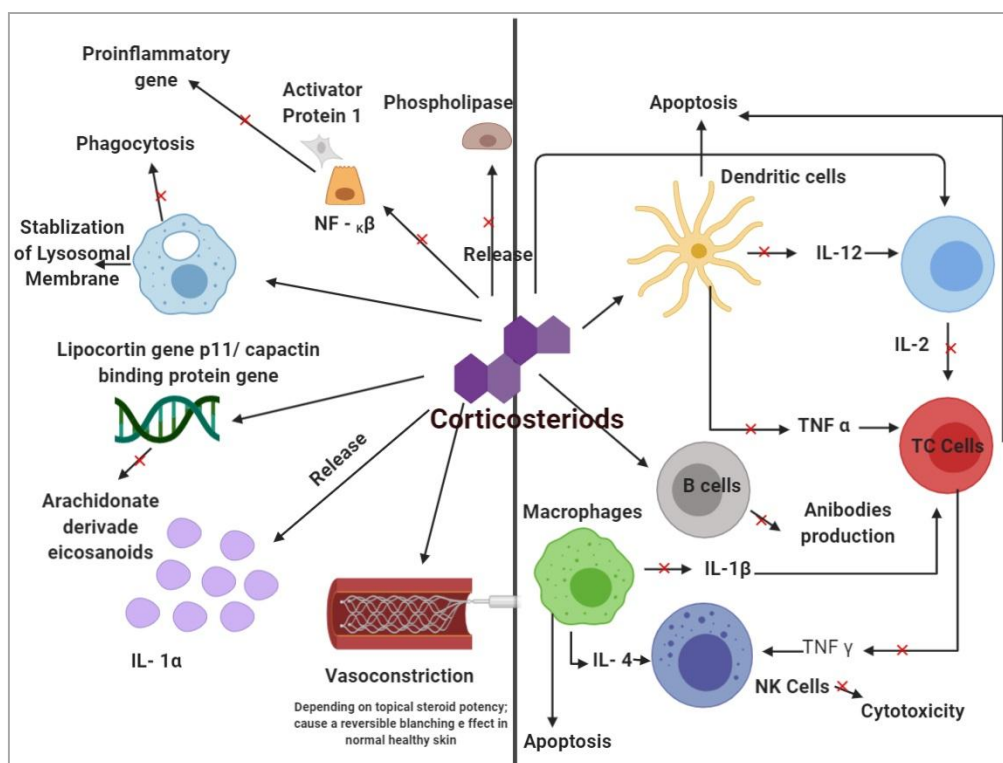


Fig. 4. Mechanism of action of TCs in the treatment of AD

Mechanism of action of TCs in the treatment of AD. IL=Interleukin, TNF=Tumour Necrosis Factor, NK cells=Natural killer cells, NF-κB=Nuclear Factor kappa-light-chain-enhancer of activated B cells.

Table 1. Number of fingertip units required to cover anatomical regions depending on the age of the patient

Area of body	No of fingertip units (FTU) required according to the age of the patient				
	Adults	3-6 month	1-2 years	3-5 years	6-10 years
Face and neck	2.5	1	1.5	1.5	2
Entire arm and hand	4	1	1.5	2	2.5
Entire leg and foot	8	1.5	2	3	4.5
The entire front of the chest and abdomen	7	1	2	3	3.5
Entire back including buttocks	7	1.5	3	3.5	5

7. TOPICAL CORTICOSTEROID MISUSE: TC ADDICTION AND PHOBIA

7.1 Topical Corticosteroid Addiction

Topical corticosteroid addiction (TCA) results from chronic misuse of TCs which results in psychological and cutaneous dependence on the drug and any attempt to withdraw the drug is resisted by the patient [29]. The attempts to stop the drug therapy leads to rebound or flare in the symptoms which becomes both physically and psychologically distressing to the patient. TCs

misuse on the face is a common condition where it is used as a miracle compound with belief that it will correct any imperfection on the face. Although there has been no population-based study to measure the prevalence of TC misuse, a large number of the clinic or hospital-based studies are available. In a multicentric study conducted in 12 dermatology centres in India, it was found that 29% of patients with facial dermatoses were using TC as fairness or general purpose and aftershave cream or 24% were using it for acne. It was also found that potent and superpotent TCs were more frequently used

by the rural/suburban population as compared to the urban population [30]. Similarly, a hospital-based study on 75 patients with steroid-induced rosacea having a history of topical steroid use on their faces for at least 1–3 months was carried out. Facial redness and hotness, telangiectasia, and rebound phenomenon with papulo pustular eruption were the main clinical presentation. Majority of patients were young women who used combinations of potent and very potent topical steroids for pigmentary problems like melasma, freckles and desire of fairer look [31].

Management of TCA involves complete cessation of application of TCs and reversal of the skin damage caused by steroid abuse. Patients need to be counselled regarding the rebound on withdrawal along with providing intensive psychological support. While some advocate a sudden complete cessation of TC use, a slower form of withdrawal with tapering potency of TC is more beneficial in preventing extremely distressing rebound [32]. Corticosteroid withdrawal is characterized by mild erythema and flares for 2 weeks followed by desquamation. The erythema resolves but recurs within a fortnight. A second flare usually occurs within 2 weeks followed again by resolution. Some such flares with decreasing intensity followed by resolutions of longer durations occur before complete cure and the duration of withdrawal period depends on the duration of use of the TC. Therapeutic intervention in such cases is quite difficult however, the use of topical calcineurin inhibitors in some studies found to be quite useful. Tacrolimus ointment (0.075%) was found to be effective for patients with steroid-induced rosacea are solving pruritus, tenderness, and erythema when applied twice daily for 7-10 days [33-34].

7.2 Topical Corticosteroid Phobia

Topical corticosteroid phobia (TCP) is a new phenomenon that has emerged because of rampant TC abuse. TCP involves a rational or irrational fear of the topical steroids affecting compliance adversely [35]. It leads to a refusal to apply TC formulations or irregular application whenever the patient feels the need or less than useful application. TC phobia among patients as well as doctors was first reported in 1992 in Germany where TC therapy was discredited by physicians because of the risk of drug abuse and indiscriminate use by patients. TCP is commonly encountered in chronic inflammatory skin

disorders, especially AD [36]. This fear is more prevalent among parents of children with AD. A recent study of TCP conducted on caregivers of these patients showed that 38.3% were reluctant to use TC [37]. Another study of childhood eczema found that 50% of parents requested non-steroidal prescriptions due to concerns regarding skin atrophy and growth retardation [38]. Recently, a scale called TOPICOP has been developed by Moret et al. [39] to measure TC phobia among parents of children with AD. To ensure compliance of TC therapy, the health care provider should aim to establish a strong patient-doctor relationship to allay the anxiety of the patients and their guardians. They should communicate to them about the risk-benefit issues of TC.

8. APPROACHES TO REDUCE SIDE EFFECTS ASSOCIATED WITH TCs

The major limitation of TCs is the risk of precipitation of drug-associated side effects leading to noncompliance and corticosteroid phobia among patients. Both local and systemic side effects can occur by TC therapy, the severity of which is determined by potency of formulation and duration of the therapy (Fig. 5) [40-42]. Various strategies to minimize side effects associated with TC treatment are discussed below:

8.1 Adjustment in Dosing

During TC treatment, the development of side effects should be monitored and therapy should be adjusted accordingly. A potent TC can be substituted for one with weaker pharmacological activity or high dose treatment can be changed to low dose treatment. Several regimens have been developed to minimize side effects during long-term therapy such as pulse or weekend only therapy. A study conducted on patients treated with betamethasone dipropionate (0.05%) using optimized vehicle applied on weekends only with three applications dosed 12 h apart showed that 74% of the patient's maintained remission for 12 weeks with no evidence of skin atrophy or hypothalamic-pituitary-adrenal axis suppression. Similar results have been obtained in a larger, multi-centre study conducted over a period of 6 months [43].

8.2 Combination Therapy

Application of high potency TCs in combination with a vitamin D analogue can also minimize side

effects in long-term treatment. A report suggested that calcipotriene is compatible and can be applied with halobetasol ointment or cream in the treatment of psoriasis. However, since calcipotriene is unstable at low pH and vehicle may inactivate calcipotriene so care must be taken on the selection of vehicles in such therapies [44].

8.2.1 Cautious use on vulnerable areas and in paediatric patients

Use of superpotent TCs should be avoided on the vulnerable areas due to increased risk of side effects such as telangiectasia on the face and striae formation on intertriginous sites including the groin, axillae or under the breasts. The potent TCs should be used for very short periods if required at all [38]. Besides, the use of TCs should be reconsidered in case of children as it can lead to severe local and systemic side effects mainly hypothalamic-pituitary-adrenal suppression is a major concern in drug therapy of paediatric patients which may increase the risk for Cushing's syndrome or adrenocortical insufficiency in infants [45]. For that reason, lower potency TCs such as desonide or hydrocortisone is often used in infants and children and on vulnerable skin areas.

8.3 Considering the Benefit: Risk Ratio

The benefit:risk ratio should be considered carefully before selection of TCs [46]. Betamethasone dipropionate and clobetasol propionate are the potent molecules that can control AD very rapidly but possess a high risk of

local and systemic adverse effects. Recently, new steroid molecules are being synthesized that aim to achieve anti-inflammatory effects with minimum adverse effects. The recent TCs being used in the treatment of dermatoses include budesonide, mometasone furoate and prednicarbate. Mometasone furoate has limited skin penetration and is rapidly metabolized to inactive breakdown products which result in minimum duration of effect on skin [45].

8.4 Role of Vehicles in TC Therapy

Vehicles for topical application should allow the adequate release of the active pharmaceutical agent, have good spreadability and should be aesthetically pleasing. Some other important characteristics to be considered when choosing a topical vehicle include drug's solubility, ability to provide desired release rate and stability of the API in the vehicle, the ability of the vehicle to hydrate stratum corneum, along with lack of physical and chemical interaction of the vehicle with drug and skin. The present status of marketed TC dosage forms is given in Table 2 [47].

The potency of each TC has been reported to be influenced by the characteristics of the vehicle used. In general, maximum potency of corticosteroids is observed with ointments and decreases in the following order: ointments> gels> creams> lotions. The summary of the advantages and disadvantages of various vehicles being used for TC delivery are given in Table 3 [48-51].

Table 2. Current status of commercially available TC dosage forms for AD

Drug	Dosage form	Manufacturer
Clobetasol propionate	Aerosol foam	Mylan Pharmaceuticals Inc, USA Perrigo Israel Pharmaceuticals Ltd, Ireland
	Cream	Fougera Pharmaceuticals Inc, USA G and W Laboratories Inc, USA Taro Pharmaceuticals, Israel Hi Tech Pharmaco Inc, USA
	Gel	Fougera Pharmaceuticals Inc, USA Perrigo Co of Tennessee Inc, USA Taro Pharmaceuticals, Israel Teligent Pharma Inc, USA
	Lotion	Actavis Mid Atlantic LLC, USA Taro Pharmaceuticals, Israel Teligent Pharma Inc, USA

Drug	Dosage form	Manufacturer
		Galderma Laboratories L P, USA
	Ointment	Fougera Pharmaceuticals Inc, USA G and W Laboratories Inc, USA Glenmark Pharmaceuticals Inc, USA Taro Pharmaceuticals, Israel Hi Tech Pharmaco Co Inc, USA
	Shampoo	Actavis Mid Atlantic LLC, USA Perrigo Israel Pharmaceuticals Ltd, Ireland Galderma Laboratories Inc, USA
	Solution	Fougera Pharmaceuticals Inc, USA G and W Laboratories Inc, USA Novel Laboratories Inc, Somerset Taro Pharmaceuticals, Israel TolmarInc, Fort collins
	Spray	Paddock Laboratories LLC, USA Zydus Pharmaceuticals Inc, USA Galderma Laboratories, USA
Amcinonide	Cream	Fougera Pharmaceuticals Inc, USA Taro Pharmaceuticals, Israel
	Lotion	Fougera Pharmaceuticals Inc, USA
	Ointment	Fougera Pharmaceuticals Inc, USA Taro Pharmaceuticals, Israel
Betamethasone dipropionate	Cream	Actavis Mid Atlantic LLC, USA Fougera Pharmaceuticals Inc, USA Taro Pharmaceuticals, Israel Galderma Laboratories, USA PerrigoInc, USA Merck Sharp And Dohme Corp, USA MSD Pharmaceuticals, India
	Gel	Taro Pharmaceuticals, Israel Fougera Pharmaceuticals Inc, USA
	Lotion	Actavis Mid Atlantic LLC, USA Fougera Pharmaceuticals Inc, USA G and W Laboratories Inc, USA PerrigoInc, Ireland Taro Pharmaceuticals, Israel
	Ointment	Actavis Mid Atlantic LLC, USA Fougera Pharmaceuticals Inc, USA
	Spray	PromiusPharma LLC, USA
	Aerosol foam	Leo Pharma AS, Denmark
Desoximetasone	Cream	AkornInc, USA Lupin Atlantis Holdings SA, Switzerland Actavis Mid Atlantic LLC, USA Fougera Pharmaceuticals Inc, USA PerrigoInc, USA Taro Pharmaceuticals, Israel

Drug	Dosage form	Manufacturer
	Gel	Taro Pharmaceuticals, Israel AkornInc, USA GroupeParimalnc, Canada Perrigo, USA
	Ointment	Lupin Atlantis Holdings SA, Switzerland Actavis Mid Atlantic LLC, USA AkornInc, USA Fougera Pharmaceuticals Inc, USA G and W Laboratories Inc, USA Glenmark Generics Ltd, India GroupeParimalnc, Canada Novel Laboratories Inc, USA Teligent PharmaInc, USA
	Spray	Perrigo Israel Pharmaceuticals Ltd, Ireland Taro Pharmaceuticals, Israel
Fluocinonide	Cream	Fougera Pharmaceuticals Inc, USA G and W Laboratories Inc, USA Taro Pharmaceuticals, Israel Teva Pharmaceuticals Inc, USA Glenmark Generics Ltd, India Perrigo Israel Pharmaceuticals Ltd, Ireland Medicis Pharmaceutical Corp, USA
	Gel	Fougera Pharmaceuticals Inc, USA G and W Laboratories Inc, USA Taro Pharmaceuticals, Israel
	Ointment	Fougera Pharmaceuticals Inc, USA Taro Pharmaceuticals, Israel Teva Pharmaceuticals Inc, USA County Line Pharmaceuticals LLC, USA
	Solution	E FougeraDivAltanaInc, USA G and W Laboratories Inc, USA Taro Pharmaceuticals, Israel Teva Pharmaceuticals Inc, USA County Line Pharmaceuticals LLC, USA
Halcinonide	Cream	Ranbaxy Laboratories Inc, USA
	Ointment	Ranbaxy Laboratories Inc, USA
Betamethasone valerate	Aerosol foam	Perrigo UK Finco Ltd, London Taro Pharmaceuticals, Israel Mylan Pharmaceuticals Inc, USA
	Cream	G and W Laboratories Inc, USA E FougeraDivAltanaInc, USA Taro Pharmaceuticals, Israel Actavis Mid Atlantic LLC, USA GlaxoSmithKline Pharmaceuticals Ltd, India

Drug	Dosage form	Manufacturer
	Lotion	G and W Laboratories Inc, USA E FougeraDivAltanaInc, USA STI Pharma LLC, USA
	Ointment	G and W Laboratories Inc, USA Actavis Mid Atlantic LLC, USA E FougeraDivAltanaInc, USA
Triamcinolone acetonide	Cream	G and W Laboratories Inc, USA Dr Reddy's Laboratories Ltd, India Fougera Pharmaceuticals Inc, USA Glenmark Pharmaceuticals Ltd, India Taro Pharmaceuticals, Israel
	Ointment	G and W Laboratories Inc, USA Dr Reddy's Laboratories Ltd, India Fougera Pharmaceuticals Inc, USA Perrigo UK Finco Ltd, London Taro Pharmaceuticals, Israel TeligentPharmaInc, USA Glenmark Pharmaceuticals Ltd, India
	Lotion	Fougera Pharmaceuticals inc, USA TeligentPharma, USA Fougera Pharmaceuticals Inc, USA G and W Laboratories INC, USA Vintage Pharmaceuticals LLC, USA
Hydrocortisone valerate	Cream	PerrigoInc, USA Taro Pharmaceuticals, Israel
	Ointment	Taro Pharmaceuticals, Israel
Hydrocortisone butyrate	Cream	Taro Pharmaceuticals, Israel Glenmark Generics Ltd, India Precision Dermatology Inc, USA
	Lotion	Precision Dermatology Inc, USA
	Ointment	Taro Pharmaceuticals, Israel Precision Dermatology Inc, USA
	Solution	Taro Pharmaceuticals, Israel
Desonide	Aerosol foam	Aqua Pharmaceuticals, Spain
	Cream	G and W Laboratories Inc, USA PerrigoInc, USA Taro Pharmaceuticals, Israel Galderma Laboratories , USA
	Gel	Bayer Healthcare Pharmaceuticals Inc, USA
	Lotion	Fougera Pharmaceuticals Inc, USA Taro Pharmaceuticals, Israel Galderma Laboratories , USA
	Ointment	Fougera Pharmaceuticals Inc, USA Hi-Tech Pharmaca Co Inc, USA PerrigoInc, USA Taro Pharmaceuticals Inc, USA Galderma Laboratories, USA

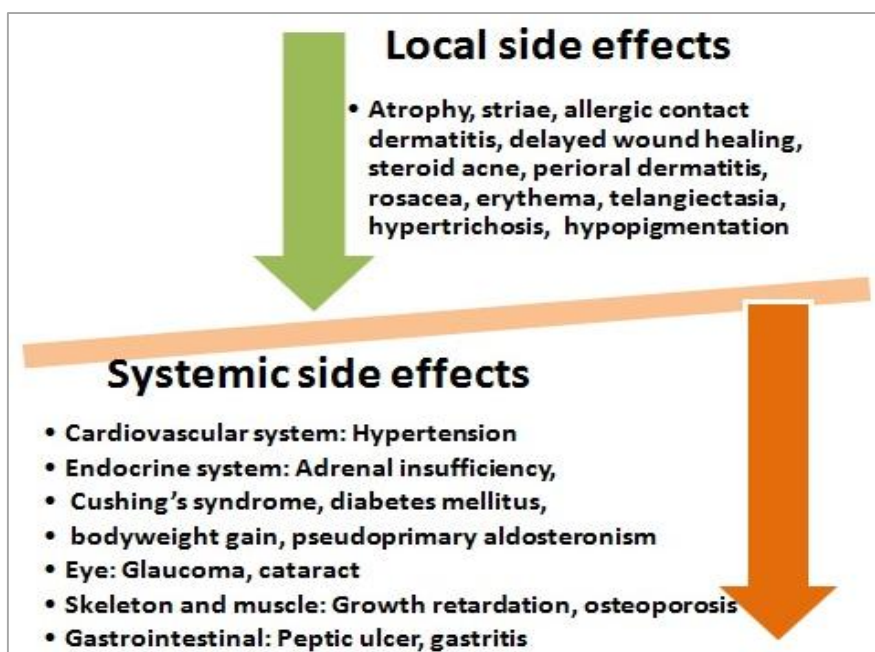


Fig. 5. Side effects associated with TC therapy

Table 3. Advantages and disadvantages of commonly used vehicles for TCs

Formulation	Advantages	Disadvantages
Ointment	Highly occlusive Most potent	Greasy nature and difficult removal from the skin, lack of water washability
Cream	Easy application good patient compliance	The difficulty of spreadability and soiling of clothing with oily creams
Lotion	Easy application good patient compliance	Not suitable for dry skin Stings the inflamed skin
Gel	Easy application Non-greasy Good patient compliance Useful in hair-bearing skin	Has drying effect Stings the inflamed skin
Foam	Improved spreadability Non-greasy Useful in an application on scalp	Costly

9. NOVEL DRUG DELIVERY SYSTEMS FOR DELIVERY OF TCs

To reduce TC associated side effects, several studies are being conducted in the development of novel drug carrier systems. Nanoparticle-based drug delivery can improve percutaneous absorption of therapeutic agents while providing targeted drug delivery and minimizing damage to the skin barrier function. Besides, nanocarriers can target TCs to the viable epidermis, where the prime inflammatory reactions take place. The

nanoparticulate carriers have several advantages over conventional topical formulations, such as protection of unstable active agents against degradation; drug targeting to the skin layers and prolonged active agent release (Table 4).

9.1 Polymeric Nanoparticles

These are composed of biocompatible and biodegradable polymers and have several advantages such as improved drug bioavailability, targeted drug delivery, reduced

toxicity and undesirable effects. In a recent study, di-flucortolone valerate (DFV) loaded lecithin/chitosan nanoparticles showed increased accumulation of drug especially in the stratum corneum and epidermis of rat skin without any significant permeation. The drug retention was twofold higher than commercial cream indicating a potential for dermal delivery of DFV in various skin disorders [52]. Similarly, hydrocortisone loaded chitosan nanoparticles were reported to reduce the severity of the pathological features of AD including decreased production of immunoglobulin E, the release of histamine, and expression of prostaglandin-E2 in the sera and skin of the tested animals [53].

9.2 Lipid Nanoparticles

Lipid nanoparticles are the colloidal carrier systems that possess many advantages over other topical delivery systems applied for delivery of TCs. The lipids used in these carriers are solid at the room as well as body temperatures. Topically applied solid lipid nanoparticle (SLN) based formulations have been reported to improve drug delivery to the desired site and their solid lipid matrix may also modulate drug release, thus controlling the concentration at the site of action. Formulation of solid lipid nanoparticle system containing betamethasone 17-valerate using monostearin and beeswax as the lipid phase resulted in prolonged and localized delivery of the active drugs into the skin. The topical SLNs showed potential for treating skin conditions by targeting corticosteroids to dermal disease sites while minimizing systemic drug absorption [54]. Halobetasol propionate-loaded SLNs were formulated to minimize the adverse effects and for providing a controlled release [55]. *In vitro* skin, deposition and irritation studies showed that the formulation can avoid systemic absorption and lead to better accumulative uptake of the drug compared to marketed preparation. These results indicated that HP-SLN formulation is a promising carrier system for delivery of HP with controlled drug release and potential of skin targeting with no skin irritation. A nanostructured lipid carrier (NLC) based gel for topical delivery of clobetasol propionate was developed and showed improved anti-inflammatory activity via paw oedema technique along with the rapid onset of action and prolonged duration of action as compared to marketed gel [56]. NLCs for topical delivery of fluticasone propionate were reported to improve the safety profile and

decrease the adverse side effects as compared to conventional formulation [57].

9.3 Microemulsions and Nanoemulsions

These formulations have several advantages over other dosage forms such as ease of preparation, high solubilization capacity for both lipophilic and hydrophilic drugs, long-term stability and drug targeting to different layers of skin. Microemulsion based gel of clobetasol propionate aimed for effective dermal drug delivery in the treatment of vitiligo was reported to improve drug permeation and retention into skin layers as compared to marketed product [58]. Clobetasol propionate and calcipotriol loaded nanoemulsion based gel were developed by Kaur et al. [59] for topical treatment. The nanogel showed negligible skin irritation along with increased skin permeation. Physically and chemically stable positively charged prednicarbate nanoemulsion has been studied for the treatment of AD. The use of positively charged carriers in the formulation led to intensive adsorption to the negatively charged skin which increased the retention time and thus the bioavailability [60].

9.4 Liposomes

These vesicular carrier systems are made of phospholipid layers. These phospholipids have similarity to skin lipids leading to several advantages in the field of dermal drug delivery. The liposomes possess very low toxicity, biodegradability and strong tissue affinity. Liposomes also promote restoration of skin barrier leading to reduction of inflammation, penetration of irritants and allergenic substances through the skin. Pharmacokinetic evaluation of triamcinolone acetonide and hydrocortisone liposomes was reported to have higher drug accumulation in skin and lower systemic absorption as compared with conventional preparations [61].

9.5 Transferosomes

Transferosomes can play an important role in the delivery of drugs that are unable to efficiently penetrate the stratum corneum via passive diffusion [62]. Potential of transferosomes for dermal delivery of different corticosteroids i.e. hydrocortisone, dexamethasone and triamcinolone acetonide has been investigated by Cevc et al. [63]. The deformable carriers were reported to improve the targetability of all tested corticosteroids into the viable skin.

Table 4. The role of novel drug delivery systems in the delivery of TCs to the skin for the treatment of dermal disorders

Drug delivery system	Drug	Significance	References
Lipid Nanoparticles	Betamethasone 17-Valerate	Improved drug retention in the upper layers of the skin while reducing the undesirable systemic side effects	[54]
	Halobetasol propionate	Lesser skin irritancy, greater occlusivity and slow drug release as compared to a marketed product	[55]
	Mometasone furoate	Better drug retention with sustained drug release	[64]
	Fluticasone propionate	Enhanced drug permeation, reduced dosing frequency and sustained the drug release	[57]
	Prednicarbate	The improved extent of prednicarbate uptake by human skin <i>in vitro</i> and targeting to the epidermis	[65]
	Clobetasol propionate	Improved anti-inflammatory activity, rapid onset of action and prolonged duration of action	[56]
	Fluocinolone acetonide	Enhanced drug solubility, favoured deposition into the epidermis, reduced risk of systemic side effects	[66]
Microemulsion	Clobetasol propionate	Better retention in the skin and minimal irritation potential than marketed formulation	[58]
	Betamethasone Dipropionate	Improved drug deposition and anti-inflammatory activity as compared to marketed formulation	[67]
	Hydrocortisone	Increased drug penetration through stratum corneum, occlusive action thus improving skin barrier function	[68]
Nanoemulsion	Clobetasol propionate	Negligible skin irritation despite increased penetration into the skin	[59]
	Prednicarbate	Improved drug retention	[60]
	Hydrocortisone	Improved skin permeation as compared to an aqueous suspension of hydrocortisone	[69]
Liposomes	Betamethasone valerate	Better drug accumulation in the desired skin strata with higher inhibition of oedema and erythema in AD induced rat model	[70]
	Diflucortolone valerate	Better drug retention and inhibition of erythema and oedema in animal skin	[71]
	Hydrocortisone	Improved skin retention	[61]
	Triamcinolone acetonide	Improved skin retention and reduced side effects	[61]
	Clobetasol propionate	Epidermal targeting and improved benefit/ risk ratio	[61]
Polymeric nanoparticles	Betamethasone dipropionate	Increase the antiinflammatory action, improved corticosteroid benefit:risk ration	[73]
	Diflucortolone valerate	Sustained release of drug and improved accumulation in stratum corneum and epidermis in a lower dose	[52]
	hydrocortisone	Reduction in severity of pathological features of AD including the production of immunoglobulin E, release of histamine, expression of prostaglandin-E2 and vascular endothelial growth factor a	[55]
	Clobetasole propionate	Epidermal targeting and increased benefit/ risk ratio	[74]
Transfersomes	Dexamethasone	Faster penetration through hair follicles and potential for dermal delivery of poorly soluble drugs.NPs showed no cytotoxic and oxidative stress induction on normal human keratinocytes and exhibited pH-dependent drug release.	[75]
	Triamcinolone acetonide	The improved risk-benefit ratio in humans	[63]
	Hydrocortisone	Superior drug-targeting to skin	
	Dexamethasone	Superior drug-targeting to skin	

Table 5. Recent patents in the field of TC drug delivery

Patent No and publishing date	Description	References
US 7 66858B2 (February, 2010)	The pharmaceutical composition for TC used in association with a diffusing enzyme for the treatment of phimosis.	[76]
US 7,897,587 B2 (March, 2011)	A topical formulation of a steroid compound for improved solubility in combinations of the solvents propylene glycol and propylene carbonate	[77]
US 0136430 A1 (May, 2009)	Combination of an antihistamine with a corticosteroid which is more effective than either one used separately in the treatment of AD.	[78]
US 0115828 A1 (May, 2012)	The active ingredients, namely chitosan, corticosteroid in the form of hydrocortisone acetate and an antibacterial agent in the form of miconazole are incorporated in the cream base for use in treating bacterial skin infections and skin inflammation.	[79]
US 0184732 A1 (July, 2010)	A method of long-term therapy using corticosteroids to treat tissue damage associated with graft-versus-host disease in a patient undergone hematopoietic cell transplantation, and host-versus-graft disease in a patient undergone organ allograft transplantation.	[80]
US 0233892 A1 (September, 2009)	The present invention generally relates to a topical composition such as a dermatological cream, containing the corticosteroid compound hydrocortisone butyrate.	[81]
US 0183749 A1 (July, 2010)	Methods of delivering corticosteroids or metabolites thereof for treatment and prevention of tissue damage resulting from acute radiation injury in the gastrointestinal tract with locally effective therapeutic agents.	[82]
US 8,653,055 B2 (February, 2014)	Novel compositions of water-insoluble corticosteroid drug in combination with antimicrobial agents and very low concentrations of polymers and surfactants for topical and ophthalmic treatment.	[83]
US 9,050,368 B2 (June, 2015)	Methods for treatment, prevention or alleviation the symptoms of and inflammation associated with inflammatory diseases and conditions of the gastrointestinal tract are provided along with pharmaceutical compositions useful for the methods of the present invention	[84]
US 9,522,189 B2 (December, 2016)	A composition comprising: a benefit agent; at least one polymer including a poly(monoStearoyl glycerol-co-Succinate) polymer; at least one lower alcohol; and at least one co-solvent; and a method for enhancing topical delivery of a benefit agent are disclosed.	[85]
US 0015704 A1 (January, 2016)	A combination which comprises corticosteroid and a dual muscarinic antagonist-B2adrenergic agonist compound. or any pharmaceutically acceptable salt or Solvate thereof.	[86]
US 0324699 A1 (December, 2009)	Homogeneous pharmaceutical compositions for the treatment of, for example, rhinitis, asthma and/or chronic obstructive pulmonary disease comprising a corticosteroid and an antihistamine, a polar lipid liposome and a pharmaceutical-acceptable aqueous carrier	[87]

Patent No and publishing date	Description	References
US 0249060 A1 (September, 2010)	A new topical formulation is provided, with high chemical stability, of for example a low dose clobetasol propionate, Suitable for the topical treatment of skin and mucous membrane conditions associated with disorders including psoriasis, eczema, and other forms of dermatitis	[88]
US 0349981 A1 (November, 2014)	Topical pharmaceutical compositions are described comprising bexarotene, a corticosteroid and a carrier or vehicle useful for the treatment of skin disorders.	[89]
US 8,546,362 B2 (October, 2013)	The active ingredients, namely chitosan, a corticosteroid betamethasone valerate, and an antibacterial agent Neomycin Sulphate, are incorporated in the cream base for use in treating bacterial skin infections and skin inflammation due to allergy & itching, & wounds on human skin involving contacting human skin with the above-identified composition.	[90]
US 2010/0130460 A1 (May 2010)	Topical formulations comprising an androstane steroid, propylene glycol, and benzyl alcohol in an amount effective to dissolve the androstane steroid compound, wherein the amount of benzyl alcohol is not effective to act as a penetration enhancer. The formulations are useful for the treatment of inflammatory and/or pruritic manifestations of corticosteroid-responsive dermatoses.	[91]
US 0240621 A1 (September, 2010)	Topical pharmaceutical compositions comprising fusidic acid and mometasone or halobetasol or their esters, processes for preparing the same, and the use of Such compositions for prevention and treatment of dermal infections.	[92]
US 0053161 A1 (March, 2012)	Solution formulations comprising a corticosteroid, cyclodextrin, and xanthan gum are disclosed. The formulations are intended for topical application to the eye, ear, or nose.	[93]
US 0124538 A1 (May, 2010)	Topically applicable compositions were useful for the depigmentation of the skin containing fluocinoloneacetone, de-pigmenting agent, formulated into physiologically acceptable carrier therefor.	[94]
US 0050329 A1 (February, 2015)	A pharmaceutical composition comprising liposomal formulation providing human patients a fast, strong, and durable anti-inflammatory effect for at least 2 weeks at a dose of at most 5 mg/kg body weight of prednisolone or an equipotent dose corticosteroid other than prednisolone at a treatment frequency of at most once per two weeks.	[95]
US 8,173,671 B2 (May, 2012)	Topical ophthalmic and otic solution compositions of moxifloxacin and dexamethasone phosphate are disclosed.	[96]
US 0238535 A1 (September, 2012)	A new topical formulation is provided with high chemical stability with low dose clobetasol propionate, suitable for the topical treatment of skin and mucous membrane conditions associated with disorders including psoriasis, eczema, and other forms of dermatitis.	[97]
US 0215735 A1 (August, 2009)	Solution formulations containing a corticosteroid, cyclodextrin, and Xanthan gum are disclosed. The formulations are intended for topical application to the eye, ear or nose	[98]

10. RECENT PATENTS IN THE FIELD OF TCs

Since new formulations and treatment options for TC drug delivery are being studied extensively, the number of patents in the field of treatment using TCs is increasing enormously. A combination of an antihistamine with a corticosteroid disclosed in US patent 0136430 A1 by Harry and Dugger claims to provide a synergistic effect in the treatment of AD. The inventors claim that composition results in the disappearance of the atopic dermatitis lesion within one to five days with little or no relapse. The patent also discloses the pharmaceutical composition and the methods of utilizing the preparation [76]. Another US patent discloses a composition for treating fungal skin infections and skin inflammation, along with skin rejuvenation containing a biopolymer and a combination of active pharmaceutical ingredients i.e. miconazole and hydrocortisone acetate for treating bacterial skin infections and skin inflammations along with skin rejuvenation. The active ingredients in the formulation are incorporated into the cream base for use [77]. AUS patent by Smith discloses a novel topical formulation with the high chemical stability of low dose clobetasol propionate which is suitable for topical treatment of skin and mucous membrane conditions including psoriasis, eczema and other forms of dermatitis. The formulation comprises propylene glycol-based aqueous vehicle as a solvent and moisture-retaining agent and macrogol-glycerol hydroxyl stearate as a non-ionic emulsifier which is capable of holding surprisingly low concentrations of clobetasol. The formulation claims to have good chemical stability and hence, long durability [78]. A summary of some of the important patents related to TCs in the last decade is provided in Table 5.

11. CONCLUSION

TCs are the first-line treatment for AD due to their potent immunosuppressive, anti-inflammatory, and antihistaminic effects. However, the current therapy of atopic dermatitis with TCs is insufficient due to the risk of side effects. Therefore, it is necessary to utilize novel approaches to minimize drug-related side effects and steroid phobia among the patients. Improved dermal absorption of established TC may be obtained by a novel vehicle system which can reduce the side effects. Recently, lipid

and polymeric based nanocarriers such as liposomes, transfersomes, ethosomes, microemulsions and nanoparticles are being studied intensively and the potential of these carrier systems have also been proved in several studies.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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