What is new in dermatotherapy?

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Introduction

Dermatology is an ever-expanding discipline with the discovery of new entities daily. Similarly, the pathogenesis of diseases better understood these days is attributable to the research activities being conducted globally. Thus, dermatotherapy is bound to prosper and progress with the discovery of new molecules apart from newer applications and indications of older molecules. A comprehensive English language literature search from 2015 to August 2020 across multiple databases (PubMed, EMBASE, MEDLINE and Cochrane) for keywords (alone and in combination) was performed. Terms such as "what is new," "recent advances in therapy," "recent treatment," "novel treatment" and "dermatology" were considered. In this review, we have summarized the newer medical therapeutic options (in alphabetical order) for a wide gamut of dermatological conditions with the proposed mechanism of action of the molecule (wherever applicable).

Apremilast for newer indications

Mechanism of action: It is a phosphodiesterase inhibitor that binds to phosphodiesterase-IV and Toll-like receptor-4 in peripheral blood cells which leads to an increase in levels of cyclic adenosine monophosphate which reduces the pro-inflammatory cytokines (tumor necrosis factor-alpha, interleukin-23, interleukin-12, leukotriene B-4) and increases levels of anti-inflammatory cytokine interleukin-10.

It is used in Behcet's disease,[1] hidradenitis suppurativa,[2] atopic dermatitis[3] and recalcitrant pyoderma gangrenosum.[4,5] It can be used in moderate hidradenitis suppurativa at a dose of 30 mg twice daily for 16 weeks. In Behcet's disease, it is used for the treatment of oral ulcers at a dose of 30 mg twice daily for 12 weeks. Apremilast reverses the increased phosphodiesterase 4 activity of immune cells in atopic dermatitis, thus bringing a considerable decrease in cytokines released from T-cells. In a case of pyoderma gangrenosum, apremilast 30 mg twice daily was added to a regimen of oral prednisone 7.5 mg daily and subcutaneous methotrexate 18 mg weekly, for 4 months. The improvement in the ulcers was appreciable.[5]

Beta blockers in prevention of formation of keloids in autoimmune blistering dermatosis

Mechanism of action: There are three types of beta-adrenergic receptors. β1 receptors act on the myocardium, β2 on the blood vessels and bronchi; and β3 receptors on the adipocytes. Vascular endothelial growth factor serves as an endothelial cell mitogen, increases the vascular permeability and deposition of extracellular fibrin matrix. It is also expressed in higher quantities in the dermis, keratinocytes and fibroblasts of keloids when compared to normal skin. So beta-blockers could arrest the progression of scars towards keloids, by blocking vascular endothelial growth factor. Moreover, they can also prevent the formation of keloids by activating extracellular kinase which accelerates inflammatory cell migration and proliferation and inhibiting apoptosis. Thus, beta-blockers have been proposed to have a role in the prevention of formation of keloids.[6]

Biologics (newer molecules)

The recently discovered molecules have been summarized in Table 1.[7-24]

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Intralesional bleomycin for lymphangioma circumscriptum

Bleomycin is an antineoplastic, antibacterial and antiviral drug.

Mechanism of action: It breaks the backbone of DNA by generating free radicals and also has a sclerosant action on endothelial cells. It chelates iron, forms a pseudoenzyme and reacts with oxygen; thereby generating superoxide and free

Table 1: Newer biologics

Biologic	Mechanism of action	Indication	Remarks
Ixekizumab[7]	It is a humanized IgG4 subclass monoclonal activity with neutralizing activity against IL-17RA. It is given at a dose of 160 mg subcutaneous at week 0 and 80 mg on weeks 2, 4, 6, 8, 10 and 12 followed by 80 mg every 4 weeks	Plaque psoriasis, psoriatic arthritis	FDA approved for plaque psoriasis (March 2016) and psoriatic arthritis (December 2017)
Brodalumab[8]	It is a human monoclonal IgG2K antibody against IL-17RA. It is given at a dose of 210 mg subcutaneously at week 0, 1 and 2 and 210 mg every 2 weeks	Plaque psoriasis	FDA approved (July 2016)
Guselkumab[9]	It is a human monoclonal IgG1 lambda monoclonal antibody against the IL-23 receptor. It is given subcutaneously 100 mg at week 0, 4 and every 8 weeks thereafter	Plaque psoriasis	FDA approved (July 2017)
Tildrakizumab[10]	It is a human monoclonal IgG1/K antibody against the IL-23 receptor. It is given subcutaneously 100 mg at weeks 0, 4 and 100 mg every 12 weeks	Plaque psoriasis	FDA approved (March 2018)
Risankizumab[11]	It is a human monoclonal IgG antibody against IL-23. It is given subcutaneously at 150 mg week 0, 4 and every 12 weeks thereafter	Plaque psoriasis	FDA approved (April 2019)
Bimekizumab[12]	It is a human monoclonal IgG antibody against IL-17A and IL-17F. It is given subcutaneously at a loading dose of 320 mg and 160 mg every 4 weeks thereafter	Plaque psoriasis, psoriatic arthritis	It is in the Phase 3 trial
Mirikizumab[13]	It is a human monoclonal antibody IgG4 antibody against IL-23. It is given at a dose of 300 mg once in 4 weeks	Plaque psoriasis, psoriatic arthritis	It is in the Phase 3 trial
Dupilumab[14-16]	It is a fully-humanized monoclonal antibody inhibiting IL4 and IL3 through the binding of the alpha subunit of the IL4 receptor. Moreover, it decreases the IgE secretion by the downregulating eosinophil chemotaxis and TH2-associated chemokine activity (CCL17, CCL18, CCL22, and CCL26), inhibiting pre-activated B cells, directing B cells to switch to IgG4 synthesis. It may improve pruritus by decreasing peripheral itch sensory neuron signaling through its direct effects on IL-4 and IL-13 and through its effects on eosinophils which results in decreased IL-31 secretion	Atopic dermatitis, prurigonodularis, bullous pemphigoid	FDA approved for atopic dermatitis in March 2017
Lebrikizumab[17]	It is a humanized monoclonal antibody inhibiting IL-13. It is given at a dose of 125 mg subcutaneously once weekly for 12 weeks	Atopic dermatitis	It is in the Phase 3 trial
Nemolizumab[18]	It is a humanized monoclonal antibody inhibiting IL-31. It is given at a dose of 0.5-1 mg/kg subcutaneously for 6-12 months	Atopic dermatitis	It is in the Phase 3 trial
Spartalizumab[19]	It is a humanized monoclonal antibody, binds to PD-1 and blocks its interaction with PD-L1 and PD-L2. Thus, it acts as an immune checkpoint inhibitor	Melanoma	It is in the Phase 3 trial
Cemiplimab-rwlc[20]	It is a programmed death receptor inhibitor (PD-1/PD-L1). The recommended dosage is 350 mg as an intravenous infusion every 3 weeks	Locally advanced and metastatic squamous cell carcinoma	FDA approved (September 2018)
Selumetinib[21]	It is an inhibitor of mitogen-activated protein kinases thereby reducing ERK phosphorylation	Pediatric patients, 2 years of age and older with NF1 who have symptomatic, inoperable PN	FDA approved (April 2020)
Ligelizumab[22]	It is a humanized monoclonal antibody that binds to IgE and acts as an immunomodulator. It is given subcutaneously at doses of 24 mg, 72 mg, and 240 mg monthly. It requires less frequent injections (in comparison to omalizumab) and at doses of 72 mg, and it is more effective than omalizumab	Chronic spontaneous urticaria	It is in Phase 2B trials
Avelumab[23]	It is a fully human IgG1 anti-PD-L1 monoclonal antibody that blocks the PD-1/PD-L1 interaction. Administered by intravenous infusion once every 2 weeks	Metastatic Merkel cell carcinoma in adults and children aged 12 years and older	FDA approved (March 2017)
Lanadelumab[24]	It is a fully human monoclonal antibody that inhibits active plasma kallikrein and thereby decreases bradykinin. It does not bind to tissue kallkreninkininsystem. It is given subcutaneously 150-300 mg once in 2 weeks	Prevention of attacks of hereditary angioedema	FDA approved (August 2018)

PD-1: Programmed death-1, NF1: Neurofibromatosis type 1, PN: Plexiform Neurofibromas, FDA: Food and Drug Administration, IL: Interleukin, IgE : Immunoglobulin E, IgG : Immunoglobulin G, , IgG2K : Monoclonal antibody Immunoglobulin G, CCL : chemokine (C-C motif) ligand

radicals that cleave the DNA. It also inhibits the incorporation of thymidine into the DNA. The procedure consists of reconstitution of bleomycin with 5 mL of distilled water and then mixing 1 mL of the solution with 2 mL of 2% lignocaine and finally injecting with a 26G needle, the endpoint being blanching of the site.[25] Recently, an intralesional combination injection of triamcinolone, bleomycin and bevacizumab was used in the treatment of lymphangioma circumscriptum of the tongue.[26]

Topical cetirizine in androgenetic alopecia

Mechanism of action: Prostaglandin E and F favour hair growth and prostaglandin D2 inhibits hair growth (leading to progression of hair towards miniaturization). It has been found that the levels of prostaglandin D2 synthetase are elevated in the bald scalp when compared to the normal scalp.

Topical cetirizine could be one of the possible promising modalities for androgenetic alopecia by suppressing the prostaglandin D2 and inflammatory infiltrate in the bald scalp, but the evidence is limited and sketchy. A pilot study was conducted among 85 patients (67 cases and 18 controls) to evaluate the efficacy of topical cetirizine versus placebo in patients with androgenetic alopecia. Topical cetirizine was found to increase total hair density, terminal hair density and diameter variation from T0 to T1.[27]

Chlorine dioxide in keratosis pilaris

Chlorine dioxide complex is nontoxic to human use and is an excellent antiseptic and anti-inflammatory product. It is a volatile gas that is toxic at high concentrations, but when it is solubilized in water and applied to human tissue, the side effects are absent due to inactivation by an intracellular defense mechanism. It is found to be an efficacious cleansing agent in keratosis pilaris.

Mechanism of action: It neutralizes the reactive oxygen molecules and degrades the intramolecular and intermolecular disulfide bonds that stabilize the keratin, thereby acting as a keratolytic.[28] It reacts with several specific amino acids, but does not react with or oxidize lipids, carbohydrates, or other organic molecules. Specifically, it reacts with cysteine, tyrosine, tryptophan, methionine, proline, hydroxyproline, and histidine, with most of its biologic activity coming from the reactions with cysteine, methionine, tyrosine, and tryptophan.

Clascoterone cream in acne vulgaris

Clascoterone cream 1%, is a novel investigative topical androgen receptor blocker.

Mechanism of action: Androgens bind to their receptors on the keratinocytes, sebaceous glands and dermal papilla cells, following which it translocates into the cytoplasm and interacts with androgen-regulated genes, thus leading to sebum production and inflammation. Clascoterone inhibits the binding of dihydrotestosterone to the receptors. It can be applied twice daily and to be used in patients of ages 9 years and more. It penetrates the skin and metabolizes to cortexolone, thus limiting the potential side effects.[29]

Crisaborole in atopic dermatitis

It was approved in December of 2016 by the Food and Drug Administration of the United States, for the treatment of atopic dermatitis.[30]

Mechanism of action: Phosphodiesterase increases the levels of inflammatory cytokines through the degradation of cyclic adenosine monophosphate. Crisaborole, when applied topically inhibits phosphodiesterase inhibitor 4 and suppresses the release of cytokines by downregulating nuclear factor kappa B and nuclear factor. Unlike topical corticosteroids and calcineurin inhibitors which have potential adverse side effects with continued use, crisaborole demonstrates a promising safety profile.[31,32]

Gentamicin (topical) in hereditary hypotrichosis of scalp

Hypotrichosis of scalp is characterised by progressive loss of scalp hair. The dominant nonsyndromic hypotrichosis is the result of mutations in *CDSN* and *APCDD1* genes, and the recessive variants are caused due to bi-allelic mutations in *LIPH* and *LSS* genes. These mutations are associated with the development of premature termination codon which leads to the formation of C-terminal truncated corneodesmosin molecules, forming aggregates that are toxic to hair follicles.

Mechanism of action: Topical gentamicin (0.1%) when applied twice daily for 6 months can prevent progressive hair loss caused due to the accumulation of the corneodesmosin aggregates. It can rescue the synthesis of corneodesmosin by the read-through activity of nonsense mutation (continuation of the transcription of DNA beyond a normal stop signal or terminator sequence) and restoring the full length of corneodesmosin biosynthesis in hypotrichosis of the scalp keratinocytes.[33]

Gentian violet for newer indications

The topical application of gentian violet has been found to induce apoptosis and kill the cutaneous T cell lymphoma cells. Gentian violet has been found to possess anti-bacterial, anti-fungal, anti-helminithic, anti-trypanosomal, anti-angiogenic and anti-tumor properties. Intralesional gentian violet has been reported to be useful in primary cutaneous diffuse B-cell lymphoma.

Mechanism of action: It activates the extrinsic apoptotic pathway by increasing caspase 8, death receptors 4 and 5, tumor necrosis factor receptor and Fas ligand. This has been published as an *in-vitro* study and these preclinical findings open up the avenues for research on antineoplastic features of gentian violet. In a recently published report, recalcitrant, localized patch disease in a patient with stage IB (T2, N0, M0) cutaneous T cell lymphoma clinically responded to treatment with topical gentian violet (1% solution),.[34]

Gentian violet has also been found to be useful in erythema multiforme. Angiopoietin 2 is an angiogenic mediator associated with inflammation and vascular leak. Angiopoietin 2 is highly expressed in lesions of erythema multiforme and the vascular leak helps in blister formation. It is also postulated that nicotinamide adenine dinucleotide phosphate oxidase genes are linked to angiogenesis and regulate angiopoietin 2. Gentian violet acts as a nicotinamide adenine dinucleotide phosphate oxidase inhibitor thereby downregulating the production of angiopoietin 2.[35]

Glycopyrronium and sofpironium bromide gel in axillary hyperhidrosis

Glycopyrronium tosylate is a topical anticholinergic approved by the US Food and Drug Administration for primary axillary hyperhidrosis for age > 9 years. It is applied once daily in the axilla with a pre-moistened towelette for 4 weeks.[36]

Sofpironium bromide is an ester analog of glycopyrrolate that inhibits muscarinic receptors including sweat glands. It was developed according to the principles of retrometabolic drug design, in which the goal is to develop an active compound that is readily metabolized *in vivo* to an inactive moiety in a single, predictable reaction. This novel formulation containing 5%, 10% or 15% active drug, can induce a significant clinical reduction in axillary hyperhidrosis.[37]

Hepatitis B vaccine in warts

Intralesional Hepatitis B virus vaccine is a potential therapeutic alternative in the treatment of warts. Patients are given 0.2 mL of the vaccine in the largest wart, every 2 weeks for a maximum of five sessions. The exact mechanism of action is not known but the most likely mechanism is the stimulation of Th1 immune response with release of cytokines such as interleukin -2, interleukin -12 and interferon gamma. [38]

Hydrogen peroxide for seborrheic keratosis

Seborrheic keratosis is a benign growth in elderly individuals. Hydrogen peroxide 40% lotion when applied topically, helps in the resolution of seborrheic keratosis, and the molecule is FDA approved for the condition.

Mechanism of Action - The exact mechanism is not known. With the application of hydrogen peroxide 40% lotion on the lesion, it may lead to oxidation of tissues, generation of reactive oxygen species, lipid peroxidation and generating high oxygen concentrations, eventually leading to destruction of the lesions of seborrhoeic keratosis.[39]

Lidocaine for peristomal dermatitis

Lidocaine gel is applied on the affected area and cleansed followed by a warm water rinse. Lidocaine's anti-inflammatory effect decreases erythema, weepiness and stinging sensation caused due to usage of adhesives. It also increases bag adherence and reduces leakage.[40]

Losartan for epidermolysis bullosa

Genetic loss of collagen VII leads to recessive dystrophic epidermolysis bullosa. It is a skin fragility disorder characterized by life-long blistering, progressive fibrosis and contractures. Losartan appears to be beneficial in such diseases with progressive fibrosis.

Mechanism of action: In dystrophic epidermolysis bullosa, transforming growth factor-beta and inflammation are the major drivers for fibrosis. Losartan, an angiotensin 1 receptor antagonist reduces transforming growth factor-beta signalling in dystrophic epidermolysis bullosa dermal fibroblasts, thereby improving clinical symptoms and quality of life.[41]

Melatonin in atopic dermatitis

Sleep disturbance is common in children with atopic dermatitis. Melatonin has sleep-inducing properties and is anti-inflammatory both of which help in atopic dermatitis.

Mechanism of action: Melatonin regulates circadian rhythm and improves sleep latency. Melatonin also has an anti-inflammatory effect by inducing synthesis of interleukin-2, interleukin-6 and interleukin-12. It upregulates the antioxidant enzymes, thereby neutralizing free radicals and protecting cell membranes, possibly leading to improvement of the condition of the patient. It is a safe drug and can be given at a dose of 3 mg/day for 4 weeks in the night as an adjunct. In a randomized, double-blinded, placebo-controlled trial conducted on 70 children (6-12 years) diagnosed with atopic dermatitis, melatonin supplementation had beneficial effects on disease severity, serum total IgE levels, and Children's Sleep Habits Questionnaire.[42] Melatonin supplementation has been found to be a safe and effective modality to improve the sleep-onset latency and severity of disease in children with atopic dermatitis

Metformin (topical) in melasma

Topical metformin can be prepared by mixing 30 g of metformin powder with 70% alcohol and propylene glycol in 30% weight: volume ratio and the prepared 30% lotion is dispensed in an amber colored bottle. It can be applied once at night.

Mechanism of action: Metformin has a melanopenic action when applied topically. It decreases the cyclic adenosine monophosphate accumulation and phosphorylation of cyclic adenosine monophosphate responsive element binding protein, leading to decreased expression of MITF (microphthalmia associated transcription factor) and other melanogenic proteins like tyrosinase-related protein-1, tyrosinase-related protein-2 and tyrosinase. It also inhibits diacylglycerol and prevents the anchorage of protein kinase to melanosomes.[43]

Minocycline for newer indications

Topical minocycline

Oral minocycline has been used in mild to moderate cases of acne vulgaris but it has its limitations in the form of causing pigmentation. To overcome the above side effect,

a novel topical 4% minocycline foam preparation has been made which can be used to treat inflammatory lesions of non-nodular moderate to severe acne in adults and children aged 9 years or older. It is non-photoallergic and has been approved by the Food and Drug Administration of the United States in October 2019.[44]

Oral minoxidil

The dosage of oral minoxidil for hypertension is 5–100 mg. Low dose oral minoxidil (0.5 to 1 mg/day) can be given to treat chemotherapy-induced alopecia, monilethrix, female and male pattern alopecia.[45-48] In women with alopecia, it is given at a dose of 0.25–1.25 mg/day and in men with alopecia, it is given at a dose of 2.5–5 mg/day.

Mechanism of action: It is a potassium channel opener that causes hyperpolarization of the membranes, leading to vasodilation. It decreases the entry of calcium into the cells, thereby inhibiting epidermal growth factor-induced inhibition of hair growth. It also activates prostaglandin-1 synthetase enzymes that stimulate hair growth.

Molecules (newer) for hereditary angioedema

Some of the newer molecules have been summarized in Table 2.[49-52]

Topical mupirocin for balanitis circumscripta plasmacellularis - Zoon's balanitis

Zoon's balanitis is a chronic, idiopathic benign inflammatory mucositis. Various treatment modalities like topical calcineurin inhibitors, fusidic acid, steroids, photodynamic therapy, cryotherapy and circumcision have been used. Successful treatment of Zoon's balanitis has been observed with topical 2% mupirocin when applied for 3 months.

Mechanism of Action – Zoon's balanitis results from a complex interplay of various factors like chronic irritant dermatitis, heat, hypospadias and *Mycobacterium smegmatis* infection. Mupirocin acts by irreversible inhibition of isoleucyl-transfer RNA synthetase, thereby inhibiting bacterial protein and RNA synthesis. The effectiveness of mupirocin in Zoon's balanitis raises the possibility that this condition could be triggered by a bacterial infection or a superantigen.[53]

Narrow band ultraviolet b for verruca plana

Narrow band ultraviolet B is effective in extensive verruca plana. A dose of 0.3 J/cm2 was given in an 11-year-old boy without any significant adverse effects apart from the darkening of the skin in verruca plana. Complete resolution was noted after 12 exposures.

Mechanism of action: It is unknown, but a possible explanation is inhibition of replication of viral DNA due to narrowband ultraviolet B, leading to cell cycle arrest.[54]

Normal saline injection for steroid-induced atrophy

Saline injection has been used for lipoatrophy[55] and steroid-induced atrophy.

Mechanism of action: Steroid does not dissolve the adipocytes but allows the escape of triglycerides from the cells through the enlargement of cell pores. Normal-saline injection converts the precipitated steroid into a solution. Eventually, macrophages treat the solution as foreign bodies, leading to the removal of steroids from the affected area.[56]

Ozenoxacin cream for impetigo

Impetigo is a superficial bacterial infection caused by *Staphylococcus* and *Streptococcus* species. Ozenoxacin 1% cream applied twice daily for 5 days helps in the treatment of impetigo.

Mechanism of Action –Ozenoxacin a non-fluorinated quinolone that is bacteriostatic and bactericidal against most of the gram-positive pathogenic organisms. It inhibits bacterial DNA replication enzymes like DNA gyrase A and topoisomerase IV.[57,58]

Ranitidine in molluscum contagiosum

Molluscum contagiosum is a common viral infection. Ranitidine at a dose of 5 mg/kg/day in two divided doses is an effective alternative for widespread molluscum in immunocompetent children.

Mechanism of action: The exact mechanism is not clear. Previously, cimetidine has been shown to provide benefit by immunomodulatory effects (enhancement of T cell immunity by inhibition of suppressor lymphocyte function). This

Table 2: Newer molecules for hereditary angioedema

Molecule	Mechanism of action	Indication	Remarks
Berinert[49]	It is a plasma-derived C1 esterase inhibitor. It is given intravenously at 20 international units per kg body weight per dose	On-demand treatment of hereditary angioedema	FDA approved (October 2009)
Ruconest[50]	It is a recombinant C1 esterase inhibitor. It is given intravenously as a slow infusion over 5 min at a dosage of 50 IU per kg	Treatment of acute attacks of hereditary angioedema	FDA approved (July 2014)
Haegarda[51]	It is a plasma-derived concentrate of a C1 esterase inhibitor. It is given subcutaneously at a dose of 60 IU per kg body weight twice weekly	Prevention of attacks of hereditary angioedema	FDA approved (June 2017)
BCX7353 (Berotralstat)[52]	It is an orally available small-molecule inhibitor of human plasma kallikrein. It is given at 35 mg QID for 28 days	Prevention and treatment of attacks of hereditary angioedema	It is in phase 3 trial

FDA: Food and Drug Administration, QID : four times daily

has been extrapolated to ranitidine, and the molecule has been utilized in the treatment of molluscum contagiosum. Ranitidine has an immunostimulatory effect by increasing the cluster of differentiation 4 (CD4) lymphocytes and decreasing the cluster of differentiation 8 lymphocytes. It is also supposed to increase the activity of natural killer, lymphokine-activated killer cells and interferon activated killer cells. Ranitidine may exert its antiviral effects, by increasing the activity of these cells.[59] But, we must remember that cluster of differentiation 8 lymphocytes have an important role to play, in contributing towards antiviral immunity. Since the evidence of the role of ranitidine in molluscum contagiosum remains sketchy, studies with a larger sample size must be done, to have a clear idea regarding the utility of this molecule.

Topical rapamycin and calcitriol for angiofibromas in tuberous sclerosis

Tuberous sclerosis is characterized by dysfunction of hamartin tuber heterodimer causing suppression of mammalian targets of rapamycin, resulting in hamartomas. The rapamycin calcitriol combination is made by combining 1 g of rapamycin powder, 1 g of 0.3% calcitriol ointment with 998 g of petroleum. It is stored at 4°C and it is to be used within 3 months. The ointment can be applied twice daily for 24 weeks. It helps in faster resolution of erythema. The reduction in the size of papules is significant and the durability is longer (after discontinuation of treatment).[60]

Mechanism of action: In addition to mammalian target of rapamycin pathway over-activation, mammalian target of rapamycin independent transforming growth factor-beta signalling also plays a role in tuberous sclerosis. Vitamin D analogs reduce transforming growth factor-beta induced fibroblast proliferation. It can also downregulate the mammalian target of rapamycin signaling pathway by up-regulation of DNA damage-inducible transcript 4, thereby potentiating the actions of rapamycin.

Sarecycline in acne

Sarecycline is a narrow spectrum tetracycline and when compared to broad-spectrum tetracyclines, it has lesser gastrointestinal disturbances. It was approved by the United States Food and Drug Administration in October 2018 for moderate to severe acne vulgaris at a single daily dose of 1.5 mg/kg/day.[61]

Serlopitant for psoriatic pruritus

There is an over-expression of neurokinin 1 receptor and substance P in pruritic skin of psoriasis. The intensity of itching correlates with the number of substance P positive nerve fibers. Serlopitant is a potent neurokinin 1 receptor antagonist that helps in the reduction of pruritus. It is given at a dose of 5 mg once daily and does not have somnolence which is a side effect of the antihistamines. In a recently published data of phase 2 trial, 204 patients were randomized to receive serlopitant, 5 mg, or placebo daily for 8 weeks. Serlopitant was found to significantly reduce the pruritus associated with mild to moderate psoriasis,.[62]

Silymarin prevents the rise of alanine aminotransferase and aspartate transaminase liver enzymes in patients taking isotretinoin

Silybum marianum, also known as milk thistle belongs to the *Asteraceae* family. Silymarin is extracted from the plant.

Mechanism of action: It inhibits free radicals, promotes DNA polymerase and increases glutathione levels thereby preventing further liver damage. It also binds to hepatocytes, thereby altering the cellular uptake of toxins by altering the phospholipid bilayer. It is given at a dose of 140 mg/day.[63]

Topical timolol in chronic, recalcitrant fissures and erosions of hand eczema

Hand eczema is characterized by inflammation, scaling, vesicles and hyperkeratosis. Keratinocytes express beta 2 receptors which help in cutaneous homeostasis. Timolol increases the migration of keratinocytes, phosphorylation of extracellular signal-related kinases and increases the re-epithelization. It restores the damaged skin barrier. Application of 1–2 drops of timolol 0.5% ophthalmic solution at bedtime, is useful in hand eczema.[64]

Tofacitinib in alopecia areata and atopic dermatitis

Topical and oral tofacitinib is used in the treatment of atopic dermatitis. Being Janus kinase inhibitors, topical 2% formulation helps in alleviating the need for oral medications for localised disease. Oral tofacitinib 5 mg to 10 mg twice daily can be given in alopecia universalis.

Mechanism of action: Janus kinase-signal transducer and activator of transcription-dependent cytokines, interferon-γ and interleukin-15 drive activation of an autoreactive cluster of differentiation 8 (CD8) T cells that are crucial in the pathogenesis of alopecia areata. Tofacitinib is an inhibitor of the enzyme Janus kinase 1 and Janus kinase 3, thus interfering with the Janus kinase-signal transduction and activation of a transcription signaling pathway. Therefore, it blocks a cluster of differentiation 8 (CD8) cell-mediated destruction of hair follicles in alopecia areata.[65,66]

Tranexamic acid (5%) for post-acne erythema

Post-inflammatory erythema occurs due to the release of inflammatory mediators and cytokines.

Mechanism of action: Tranexamic acid suppresses tumor necrosis factor-alpha and interleukin-6 and angiogenesis. The injectable tranexamic acid is diluted with 0.9% sodium chloride and the obtained solution (tranexamic acid 5%) can be applied topically once at night. The solution can retain its potency for 90 days.[67]

Tranexamic acid for Stevens-Johnson syndrome/toxic epidermal necrolysis

Mucosal involvement in Stevens-Johnson syndrome/toxic epidermal necrolysis often leads to oral hemorrhages which is troublesome to manage. A solution of 5% tranexamic acid applied to gauze and placed in the buccal cavity, can be used as a technique to manage oral hemorrhagic lesions associated with Stevens-Johnson syndrome-Toxic epidermal necrolysis.

Mechanism of action: Tranexamic acid is a synthetic lysine analog that inhibits the conversion of plasminogen to plasmin, by preventing the attachment of plasminogen to fibrin molecules. Moreover, it also inhibits plasmin activity directly, at higher doses. It has been noted that tranexamic acid inhibits fibrin cleavage as well. The 5% solution of tranexamic acid can be made by diluting the intravenous preparation (500 mg in 5 mL) with 5 mL of sterile water. This solution can be used for controlling oral mucosal hemorrhage in Stevens-Johnson syndrome-toxic epidermal necrolysis.[68]

Trifarotene cream for acne

Trifarotene is a novel topical retinoid that can be applied once daily at night for truncal and facial acne vulgaris.[69] It was approved by the Food and Drug Administration of the United States in October 2019.

Mechanism of action: It is an agonist of the retinoic acid receptor with significant activity at the gamma subtype of retinoic acid receptors. Stimulation of retinoic acid receptors results in gene modulation which is involved in cell differentiation and inflammation. Tretinoin acts on retinoic acid receptor-alpha and retinoic acid receptor-beta receptors and adapalene acts on retinoic acid receptor-beta receptors, the resultant therapeutic effect being comedolytic. Trifarotene as mentioned acts on the retinoic acid receptor -gamma receptor; and the side effects such as irritation, pruritus and burning which are noted with tretinoin and adapalene, are not seen with trifarotene.

Valacyclovir as a modality for zosteriform mycosis fungoides

Zosteriform mycosis fungoides is a rare variant characterized by lesions in a zosteriform distribution. It is thought to be triggered by the varicella zoster virus. Valacyclovir, when given at a dosage of 500 mg daily, helps in resolution of the disease. In an isolated case report, an elderly African-American female with recurrent zosteriform mycosis fungoides, was given valacyclovir 1000 mg daily. On extended antiviral therapy, her erythema and pruritus resolved within two months, leaving only pigmentary changes in a zosteriform distribution.[70]

Zoliflodacin in gonorrhea

Zoliflodacin is a newer molecule in trials to treat uncomplicated gonorrhea. It is given as a single dose of 2–3 g orally.

Mechanism of action: It acts by inhibiting microbial biosynthesis by arresting cleaved covalent gyrase complex and formation of fused circular DNA required for synthesis.[71]

Conclusion

In this article, we have summarized the newer therapeutic options in dermatological conditions. We have considered enumerating the newer uses of older molecules; apart from enlisting the names and indications of the recently approved molecules. However, we would like to mention that the aforementioned options should be considered, only after giving due importance to the availability, side-effect profile and the cost factor.

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Conflicts of interest

There are no conflicts of interest.

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