Advances in Dermatology

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ABSTRACT

Advance in dermatological therapeutics has led to a dramatic increase in treatment options for skin diseases. Some of these agents are already available while others are on the horizon. An updated review is necessary so that we could take advantage of these new tools. The pharmacology and the use of agents that affect cutaneous immunological system will be discussed. These include the newer topical steroid, tacrolimus, ascomycin, imiquimod and narrow band UVB. The evidences that compare the use of terbinafine and itraconazole are reviewed and finally the use of finasteride for androgenetic alopecia is also assessed.

Keywords: review, advance, dermatological therapy

INTRODUCTION

Therapeutic options in Dermatology have dramatically increased in the last several years. Dermatologists could now use agents with low side effects but excellent efficacy to treat a wide range of dermatological diseases. The aim of this article is to review these new therapeutic modalities. Treatments currently under development will also be briefly mentioned. Several areas will be covered and are listed as follow:

1. New topical steroid: which is more superior?
2. Advance in the management of atopic eczema and psoriasis
3. Imiquimod: a new agent for viral wart
4. Finasteride: an effective treatment for androgenetic alopecia
5. Terbinafine versus Itraconazole: which is better?

New topical steroid: which is more superior?

For decades, topical steroids have been used in the treatment of inflammatory dermatitis. Since the introduction of compound F, new derivative had been developed with the aim of improving the clinical efficacy of topical steroid. Several measures were found to be successful in achieving such a task. These included the chemical modification of the steroid structure, the addition of a penetration enhancing agent such as salicylic acid, and the use of an appropriate vehicle. Unfortunately the increase in clinical efficacy was associated with a wide range of side effects. Besides localized problems such as skin atrophy and hypertrichosis, potent preparation could also lead to systemic problems such as pituitary-adrenal suppression and Cushing's syndrome. More recently, a new generation of topical steroid is developed with the aim of dissociating the adverse effects from the clinical efficacy. These so-called 'soft steroids' are slowly absorbed cutaneously but rapidly broken down by hepatic metabolism. Topical steroids belonging to this group of agents include mometasone furoate, fluticasone propionate and methylpredisolone aceponate. Their slow absorption properties have posed a major problem for pharmacokinetic studies. Instead of previously used vasoconstriction test, most studies on these compounds were conducted on rats or rabbits with subcutaneous or intraperitoneal administration. Previous investigations indicated that while the potency of this group of steroid was similar to that of a class III topical steroid (UK classification with class I being the weakest), the risk of adverse effect was equivalent to that of a class I.[1] Furthermore, with the exception of fluticasone, the other two could be used in a once daily regimen in the

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treatment of inflammatory dermatitis, allowing a further improvement in drug compliance. Although these agents were thought to share a similar degree of clinical efficacy,[2,3,4] data comparing their use in the treatment of inflammatory skin diseases is limited. Prakash and Benfield in a recent review article suggested that mometasone was superior to fluticasone in the treatment of psoriasis, but the reference they quoted was from unpublished data.[5] In allergic rhinitis, mometasone nasal spray was found to be equally effective when compared with fluticasone.[6] In vivo and in vitro studies indicated that mometasone furoate and methylpredisolone aceponate were similar in terms of vasoconstriction, effect on collagen synthesis and skin atrophy.[7,8]

The low side effect profile of this group of new topical steroid allows the use of occlusive therapy in the management of atopic eczema in children. Wet wrap[9,10] is a form of occlusive dressing that has gained increased popularity in Hong Kong in the last several years. Patients have a bath at night followed by application of topical steroid (usually diluted preparation of one of the new steroid) to the affected area and emollient to the unaffected area. A wet dressing is then applied to the limbs and trunk followed by a dry dressing afterwards. To further improve sleep quality, a sedating antihistamine is given. Wet wrap improves eczema by several means. It prevents scratching, enhances steroid absorption and also allows the skin to rehydrate. By cooling the skin, it further relieves the itch of eczema. Our group has shown that this method is highly effective in the treatment of resistant cases of atopic eczema.[11] We are currently performing a study that compares the clinical efficacy of mometasone and fluticasone when used under wet wrap dressing.

Advance in the management of atopic eczema and psoriasis

Retinoids are vitamin A analogs that work by acting on the nuclear receptors and in doing so affect gene expression.[12] Retinoid nuclear receptors are present in a large variety of cells, and as a result, the use of retinoids in the treatment of skin disease could lead to a significant degree of side effects. To reduce such adverse effect, retinoids that would selectively affect the relevant biological system are developed. Tazarotene is the first topical retinoid found to be effective in the treatment of psoriasis.[13] It was also designed with the aim of selectivity for the retinoic acid receptor (RAR) over the retinoid X receptors (RXRs). Previous study indicated that it was as effective as a potent steroid (UK classification III with I being the weakest). It could cause mild to moderate irritation and could be used in combination with other modalities such as phototherapy, topical steroid and calcipotriene.[14]

Topical tacrolimus (FK506) and ascomycin (SDZ ASM 981) are two new topical agents currently under investigation for the treatment of inflammatory dermatitis. Tacrolimus was first isolated from the fermentation broth of a soil sample in Japan in 1984. It is a macrolide lactone that works very much similar to cyclosporin but exhibits 10 to 100 times greater immunosuppressive activity.[15] It inhibits T lymphocyte proliferation by blocking cytokine gene expression. It also prevents histamine release from mast cells and basophils. There is evidence that tacrolimus affects the epidermal cytokine network and in doing so alters the Th1/Th2 balance, an immunological abnormality that was thought to be an important etiological factor in atopic eczema. Tacrolimus has been used successfully in the treatment of solid organ transplantation.[16] Unlike cyclosporin that was found not to be suitable for topical use, the small molecular weight of tacrolimus allows it to be used as a topical ointment. The European tacrolimus multicenter atopic eczema study group performed a randomized, double-blind, placebo controlled study that compared the effect of different concentration of tacrolimus ointment (0.03 to 0.3%) with vehicle alone in the treatment of atopic eczema.[17] Their result indicated that topical tacrolimus was significantly better than vehicle in the treatment of atopic eczema. The effect seemed to be dose related but the differences were not statistically significant. Plasma levels were below the detectable limit in most cases and burning sensation was the only significant adverse effect. Topical tacrolimus was found to be ineffective in the treatment of psoriasis.[18] In a randomized controlled clinical study, Zonneveld compared the efficacy of tacrolimus with calcipotriol and placebo in the treatment of psoriasis. They found that non-occlusive topical tacrolimus was not effective in the treatment of psoriasis. The reason was not known but the relative large molecular weight might have prevent effective penetration of the tacrolimus into the thick psoriatic skin. Other possible applications for topical tacrolimus include contact dermatitis, alopecia areata, lichen planus and urticaria pigmentosum.[15] Systemically, tacrolimus has been used in the treatment of psoriasis, pyoderma gangrenosum and Behcet's disease.[15]

Ascomycin derivatives represent a group of new macrolactams that exhibit strong anti-inflammatory activity. SDZ ASM 981 is one of such new agents that is currently under clinical studies for the treatment of inflammatory skin disease. SDZ ASM 981 is a potent cytokine inhibitor that affects the transcription and therefore production of both Th1 and Th2 related cytokines.[19] In doing so, it expresses potent immunosuppressive and anti-inflammatory activities. Previous study also indicated its role in suppressing mast cell activity.[19] With a molecular weight of 810 d, topical SDZ ASM 981 would only be absorbed in inflammatory skin condition such as atopic eczema where there is a disruption of the epidermal skin barrier.[20] For thick psoriatic skin, it has to be used under semi-occlusive condition in order to increase the cutaneous absorption for it to be effective.[21] Looking at the effect of SDZ ASM 981 on the treatment of atopic eczema, Van Leent et al performed a randomized, double blind, placebo-controlled study on 38 adult patients.[20] Their result indicated that SDZ ASM 981 twice-daily application was significantly better than placebo and once daily application. Neither skin irritation nor any other local adverse effect was observed. Besides atopic eczema and psoriasis, topical SDZ ASM 981 has also been shown to be effective in the treatment of allergic contact dermatitis.[22] In vivo study comparing the anti-inflammatory activity of SDZ ASM 981 and ultrapotent topical steroid clobetasol-17-propionate indicated that they were equally effective.[23]

Both tacrolimus and ascomycin derivatives have a much lower degree of adverse effect as compared with topical steroid. For example, they do not cause skin atrophy and are not well absorbed systemically. As a result, they may eventually replace topical steroid as the first line treatment for inflammatory skin conditions.

Phototherapy has long been used for the treatment of skin diseases. Phototherapy induces immunosuppression by altering the population of cutaneous antigen presenting cells. There is a decrease in the Langerhan cells but an increase in the non-Langerhan cell antigen presenting cells. As a result, suppresser T cells are stimulated while there is a reduction in the helper T cells. Among the disease treated with phototherapy, psoriasis was one of the most responsive. Studies looking at the action spectrum of phototherapy for psoriasis indicated that much of the shorter wavelength of the broad spectrum UVB was ineffective for treatment of psoriasis.[24] One of the main characteristic differences between UVB and UVA is that for UVB, the energy required to induce erythema is lower than the energy required to induce tanning whereas the reverse applies for UVA.[25] This unique property of broad spectrum UVB serve as a mean to protect the skin from excessive sun damage. As a result, the efficacy of broad spectrum UVB for the treatment of skin disease is limited. Narrow band UVB (311nm) has a wavelength that approaches the UVA spectrum and is therefore 5 to 10 times less potent than broad spectrum UVB for erythema induction.[26] It is more immunosuppressive and probably more carcinogenic than the broad s pectrum UVB. Some studies indicated that it has similar efficacy when compared with PUVA for the treatment of psoriasis and atopic eczema.[27,28] Further examination of these data indicated that while there is no statistical difference between the clinical efficacy of narrow band UVB and PUVA, PUVA induces a greater degree of improvement. Its advantages over PUVA include possible lower carcinogenic risk, ability to be used in childhood and pregnancy, the lack of psoralen-induced nausea and no need to have photoprotective measures after treatment.[29]

Imiquimod: a new agent for viral wart

With the exception of interferon injection, most of the previous treatment modalities for viral wart involved tissue destruction rather than actual viral eradication. Such treatments include the use of cryotherapy, cauterization and laser surgery which destroy the infected tissue and in doing so remove the viral particles. However as viral particles could be present in clinically inapparent areas, relapse is common. Imiquimod is a new topical agent that expresses anti-viral and anti-tumor activity. By inducing various cytokines production (INFα, TNFα, IL1,6,8), imiquimod leads to an increase in cutaneous immunity and eliminates human papilloma virus as a consequence.[30] Edwards et al compared the safety and effectiveness of topical 5% and 1% imiquimod cream with vehicle cream in the treatment of external genital warts.[31] Patients were instructed to apply the cream overnight three times a week for 16 weeks. Of the 311 patients enrolled into the study, 50% of those received 5%, 21% of those on 1%, and 11% of those received the vehicle experienced eradication of the warts. Local erythema was the most common adverse reaction. There was no difference in the incidence of flu-like symptoms among the three groups. Further researches are currently underway studying its role in the treatment of other skin

diseases including plane warts, molluscum contagiosum and skin tumors.

Finasteride: an effective treatment for androgenetic alopecia

There is little doubt that androgen plays an important role in the etiology of androgenetic alopecia. It is well established that eunuchs did not become bald and patients with testicular insufficiency before puberty have no baldness. However, as androgen is vital to other biological functions in male, development of new agents for the treatment of this condition has been restricted. Indeed until recently the therapeutic options for the treatment of androgenetic alopecia was limited to topical minoxidil and hair transplant.

Five alpha-reductase (5AR) is the enzyme responsible for converting testosterone to its active metabolite dihydrotestosterone (DHT). There are two 5AR isoenzymes: type I is present in the skin, scalp and testicles whereas type II is located in the hair follicle and prostate. Patients with 5AR II deficiency do not develop male pattern baldness. Finasteride is a 5AR II inhibitor that lowers the serum, prostate and scalp DHT. Finasteride 5mg per day has been used for the treatment of benign prostate hypertrophy for the last 6-7 years. More recently, it was used at a lower dose (1mg) to treat androgenetic alopecia. Kaufman et al performed a randomized, placebo controlled, double-blind study looking at the effect of finasteride 1mg in the treatment of androgenetic alopecia.[32] A total of 1553 men with Hamilton class II to V were recruited into the two years study. Scalp hair counts, patients and investigators assessments and review of photographs by an expert panel were used to assess the clinical end points. At the end of 24 months, patients receiving finasteride had increase in hair count by 16% as compared with the placebo group. Adverse events related to sexual function were reported in 4.2% of patients on finasteride as compared to 2.2% of control. Only 1.4% of those on finasteride and 1% in the placebo group stopped treatment because of sexual adverse effects. Such effects discontinued after termination of the study. There is currently no study that compares the efficacy of finasteride with topical minoxidil. As the two agents work in a different manner with different side effect profile, combination therapy seems to be a logical approach.

Terbinafine versus Itraconazole: which is better?

Since the introduction of terbinafine and itraconazole into the treatment of fungal infections, there have been much debates comparing the cost and effectiveness of these two agents. Terbinafine is a fungicidal agent that belongs to the allylamine group of compound. It is effective against dermatophyte but not yeast nor mould infections.[33] It has minimal side effects that include gastrointestinal upset, loss of taste, less commonly skin eruption and liver impairment. Itraconazole belongs to the azole group of drug and is fungistatic in nature.[33] It could cause nausea, abdominal pain, dyspepsia and headache. It is effective against both yeast and dermatophyte infection. As it stays in target tissues after systemic clearance, high dose intermittent therapy has been used for the treatment of onychomycosis in order to reduce the adverse effect and cost.

Small studies comparing the efficacy of the two agents in the treatment of fungal infection often produced mixed results. Jahangir compared the two agents in the treatment of tinea capitis among 55 patients.[34] Cure rates at week 12 were 85.7 and 77.8% for itraconazole and terbinafine respectively ($p>0.05$). A recent meta-analysis study comparing the two drugs in the treatment of onychomycosis suggested that terbinafine was superior with diseas e free nail in 35 to 50% of cases after a standard course as compared with 25 to 40% achieved by itraconazole.[35] Other clinical studies have shown similar findings.[36,37] De Backer compared the efficacy of twelve weeks of continuous terbinafine versus itraconazole in the treatment of dermatophyte onychomycosis in 372 patients.[37] Their results indicated that terbinafine was superior with 73% mycological cure as compared to 45.8% in the itraconazole group. In the **L**amisil versus intermittent **I**traconazole treatment of toenail **ON**ychomycosis study (LION),[38] a European multi-center trial, 496 patients with onychomycosis were recruited. They received either terbinafine 250mg daily for 12-16 weeks or itraconazole 200mg BD for a week every 4 weeks for 12-16 weeks. Efficacy end point in terms of mycological cure was defined as negative microscopy and negative mycological cultures of target toenail at 72 weeks. For the terbinafine group, the cure rates were 75.7% and 80.85% for 12 and 16 weeks respectively whereas the cure rates were 38.3% and 49.1% for the itraconazole group at week 12 and week 16.

There seems to be little doubt that terbinafine, a fungicidal agent, is superior in the treatment of dermatophyte onychomycosis. The key issue that needs to be addressed is the role of yeast or mould as a pathogen in onychomycosis. This particularly applies to patients whose nail culture yields mixed-growth. Some suggested that itraconazole would be superior in the treatment of mixed infection. Others suggested that mixed-growth reflects contamination or clinical insignificant yeast/mould infection. Further study is necessary to look into this issue.

Learning points:

Narrow band UVB showed comparable clinical efficacy to PUVA in the treatment of psoriasis and atopic eczema. Its advantages over PUVA include possible lower carcinogenic risk, ability to be used in childhood and pregnancy, the lack of psoralen-induced nausea and no need to have photoprotective measures after treatment.

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