59th Annual Meeting of the American Academy of Dermatology

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Date:	3-7 March, 2001
Venue:	Washington Convention Centre, Washington D.C. USA
Organizer:	American Academy of Dermatology

Thalidomide 2001

Speaker: Dr. Jorizzo

Thalidomide is currently being rediscovered because of its multiple therapeutic effects. The anti-inflammatory effect of thalidomide has been widely used in different skin diseases and symptoms. Recently, the drug was approved in the United States for the treatment of erythema nodosum leprosum (ENL). It is useful in ENL reactions, including neuritis and iritis and is helpful in weaning patients off corticosteroids. Thalidomide is also used in patients with mucocutaneous involvement in Behcet's disease. In human immunodeficiency virus (HIV) -infected patients, thalidomide is useful in HIV-wasting syndrome and HIV-related severe aphthous stomatitis. It has also been used successfully in chronic graft-versus-host disease and refractory lupus erythematosus. However, it is not indicated as hypnotic and as an anti-viral agent.

Other skin conditions including neutrophilic vascular reactions such as pyoderma gangrenosum, Sweet's disease and small vessel vasculitis have been treated successfully as well. Furthermore, in patients with actinic prurigo and porphyria cutanea tarda, thalidomide has also been used. In lichen planus, higher dose of thalidomide is required.

Mechanism of Actions

Thalidomide has both immunomodulatory and anti-inflammatory effects. Current evidence indicates that thalidomide inhibits tumour necrosis factor (TNF)-α production by accelerating the degradation of TNF-α RNA transcripts. It also induces down-regulation of integrins and reduces IgM production. Thalidomide inhibits angiogenesis. However, it is not possible to identify a single dominant mechanism, since the action of cytokines and the effect of thalidomide appear to be complex.

Precaution

Thalidomide is not mutagenic. It is not indicated in patients with past history of thalidomide hypersensitivity. Patient with neutropenia is also contra-indicated. Thalidomide should only be prescribed with caution in patients who are taking central nervous system-depressing agents and peripheral neuropathy associated agents. Thalidomide affects mainly sensory fibres in the lower limb, but it does not produce major motor neuropathy. In some patients, electrophysiologic monitoring for peripheral neuropathy is indicated with thalidomide therapy. Thalidomide is teratogenic. A comprehensive program should be established to control access to the drug, including registration of prescribing physicians, dispensing pharmacies, and patients; mandatory informed consent and education procedures; and limitation of the quantity of drug dispensed.

Side effects

Side effects include headache, fever, irregular heart beats, hypotension, neutropenia, drowsiness, toxic erythema, mood alteration, dizziness and gastro-intestinal intolerance such as constipation.

Learning points:

With appropriate safeguards, thalidomide may benefit patients with a broad variety of diseases for which existing treatments are inadequate.

Treatment of Psoriasis: What's New?

Speakers: Drs. M. Lebwohl, A. Menter, K. Wolff, B. Berman, K. Washenik

During one of the symposiums in the AAD, treatment of psoriasis was discussed. For severe psoriasis, treatment options frequently used nowadays include: (1) Rotational therapy between various drugs/ phototherapies every few years; (2) Sequential therapy; and (3) Combination therapy. Safety of the combination is often the most important issue. A note of caution is to avoid the combination of high dose methotrexate and cyclosporine. As both drugs may decrease the elimination of the other. Sometimes it will be useful to use combination therapy to induce an initial response and switch back to monotherapy again for maintenance in order to reduce the possibility of treatment failure and reduce the cost.

A retrospective study with 6-thioguanine, at the dose of 20 mg twice per week up to 120 mg daily, showed that 78% of patient has significant improvement. The side effect included mild myelosuppression (up to 50% of cases). One rare complication was veno-occlusive disease, which might lead to liver failure.

Bexarotene (Targretin) is a selective retinoid receptor agonist. Its half-life is about seven hours and may be used at 300 mg per day. One needs to watch out for hyperlipidaemia, which may require concomitant use of lipid lowering agent. One other possible side effect is glaucoma.

One may consider the use of occlusive therapy/ wrapping for resistant localized plaque. Topical tarcolimus may be considered especially in area not suitable for long term topical steroid (for example, the eyelid and intertriginous region). Foam is a new vehicle for delivering topical steroid. For example, clobetasol (Olux) and betamethasone (Luxiq) are the new preparations. The penetration is better than lotion form and is well tolerated by patients.

There are also many encouraging new treatments being studied. Ascomycin, a macrolactam immuno-modulator, was tested in five cohorts (5 mg daily up to 30 mg bd). The high dose group started to show response in two weeks after starting treatment and psoriasis area and severity index (PASI) scores improved about 75% in those on dose of 20-30 mg bd. So far there was no major side effect and the most frequent side effect was "feeling of heat". It may be useful in patients who cannot tolerate other treatment due to side effects or renal toxicity.

Infliximab is an anti-TNFα monoclonal antibody. TNFα is an important inflammatory cytokine, which was increased in psoriatic lesions but not in normal skin. One study of infliximab used 5 mg/week and 10 mg/ week infusion against a placebo. Both PASI and physician's global assessment improved significantly at 10 weeks. The only side effect that was significantly more frequent than placebo was headache.

Alefacept is a monoclonal antibody that binds to CD2 and interferes with the binding of T cell to antigen-presenting cell. Both intravenous and intramuscular injections appeared to be effective and more patient in treatment group obtained >75% improvement in PASI and physician's global assessment. Again the side effect appeared minimal.

UV Excimer laser treatment emits UVB at 308 nm. It can aim at the psoriatic plaques only and may reduce the number of treatment sessions required. Preliminary result showed 72% patients obtained >75% clearance in average of 6.2 treatment sessions and 84% patients showed similar improvement after 10 treatment sessions. It may also reduce the carcinogenic potential, as normal skin is not exposed.

With all the new development and experience, hopefully, the treatment of psoriasis will become more effective in the future.

Learning points:

In using combination therapies in the treatment of refractory psoriasis, the combination of high dose methotrexate and cyclosporine should be cautious, as both drugs may decrease the elimination of the other.

Drug Reactions: A Practical Update for the Clinician

Speaker: Dr. L. E. Shapiro

Erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) belong to a spectrum of life-threatening blistering skin conditions. Mucosal erosion is a prominent feature. EM can present with typical target lesions over acral areas with or without blister formation. EM may also manifest as macules, purpura and erosions. For EM related to herpes simplex infection, it tends to involve acral areas, in contrast to predominant truncal involvement in drug-related EM. The course of SJS is unpredictable; it may either remain static or continue to evolve into TEN in two to five days' time. The differential diagnosis of TEN includes staphylococcus scald skin syndrome, acute generalized exanthematous pustulosis, Kawasaki's disease, and linear IgA disease. The prognosis of TEN depends on age, body surface area involved (>30%), pulse rate (>120/min), blood glucose (>14 mmol/L), bicarbonate (<20 mmol/L), and urea levels (>10 mmol/L) and the presence of co-existing diseases such as malignancy. Patients infected with human immunodeficiency virus (HIV) have an increased risk of developing severe cutaneous drug reactions, including SJS and TEN. Management of TEN includes discontinuation of suspected drug and all other non-essential medications, use of topical steroid and supportive therapy, namely oral hygiene, intravenous fluid and nutritional support, preferably in a burn unit. The use of intravenous immunoglobulins (IVIG) has revolutionized the treatment of TEN. The pathogenesis of TEN involved the up-regulated expression of lytically active Fas ligand (FasL) in keratinocytes. The interaction of FasL and the cell-surface death receptor Fas (CD95) normally expressed on keratinocytes triggers apoptosis of epidermal cells, resulting in separation of large areas of skin at the dermo-epidermal junction. Antibodies contained in IVIG preparations could interfere with Fas-mediated keratinocyte death by blocking the Fas receptor and inhibition of Fas-FasL interaction. The dose of IVIG recommended to treat TEN is 1g/kg per day for three days and it should be given at an early stage of the disease. Cyclosporin has also been reported to be effective in this condition at a dose of 5 mg/kg per day given for seven days.

Drug hypersensitivity syndrome comprises the triad of fever, rash and internal organ involvement occurring after exposure to a drug. This is a rare but serious reaction. Aromatic anticonvulsants, sulfonamides, allopurinal and dapsone are the most frequently involved drugs. Cross-reactivity may be present, particularly among the anticonvulsants. This adverse reaction may present predominantly as severe organ manifestation. The syndrome can present late, ranging from 20 to 40 days after culprit drug is started. The suspected drug should be stopped immediately if a fever accompanies the drug eruption, heralding the syndrome. The drug eruption can range from an exanthematous eruption to the most serious TEN. One of the early features of drug hypersensitivity syndrome is facial edema and redness. The liver is most frequently involved; ranging from mildly elevated transaminase levels to severe hepatitis and marked cholestasis. Other organs such as the kidney, heart and lung may be involved. Eosinophilia can be demonstrated in skin biopsy and peripheral blood. Baseline investigations, such as complete blood count, liver transaminases, serum creatinine and urinalysis should be performed. Systemic cortisteroids are indicated if symptoms are severe. Some patients with the syndrome may flare three to four weeks after initial improvement upon discontinuation of the drug, especially when the corticosteroids have been stopped too abruptly.

Learning points:

IVIG is a promising agent to treat patients with toxic epidermal necrolysis if it is given in the early stage of the skin disease. Systemic hypersensitvity reactions to drugs are characterized by fever, rash and internal organ involvement. Patients who developed suggestive symptoms need to be recognized early and the involved drug discontinued immediately.