

Annual Scientific Meeting 2018

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Date: 23-24 June 2018
Venue: Sheraton Hong Kong Hotel & Towers, Tsim Sha Tsui, Hong Kong
Organiser: Hong Kong Society of Dermatology and Venereology

Therapy of pemphigus I: the Japanese guideline

Speaker: Jun Yamagami
Department of Dermatology, School of Medicine, Keio University, Japan

Updated guidelines were published in 2010 in order to improve the quality of management of pemphigus. The speaker shared his experience about fundamental treatment strategy against pemphigus based on the guidelines.

The general goal in the treatment of pemphigus is to achieve and maintain remission. Remission is defined as the absence of new or established lesions using minimal therapy, in most cases less than 10 mg prednisone daily and/ or minimal adjuvant therapy. In order to accomplish this goal, adequate initial therapy is of utmost importance as inadequate treatment may result in disease recurrence during steroid tapering.

The initial therapy typically consists of high dose oral prednisone. Disease activity should be evaluated according to clinical symptoms and scoring system like the Pemphigus Disease Area Index. If insufficient therapeutic effects are noted

after two weeks of initial treatment, additional therapies such as high-dose intravenous immunoglobulin therapy, plasma exchange or pulse steroid therapy should be considered.

Once the disease is under control, tapering of steroid should be initiated and maintenance therapy with minimal dose of steroid and/or immunosuppressive agent should be continued. The serum antibody titre such as the desmoglein ELISA index is useful for the assessment of disease activity in the maintenance stage.

Learning points:

Adequate initial therapy is important for prompt control of pemphigus and to prevent early disease recurrence during tapering of steroid. Maintenance therapy consists of minimal dosage of oral steroid and/or immunosuppressive agent.

Therapy of pemphigus II: newer modalities

Speaker: John R Stanley
Department of Dermatology, University of Pennsylvania, USA

The basic principle of therapy for pemphigus is to eliminate the autoantibodies and its production by B cells which may lead to a cure. Current therapies for pemphigus such as prednisone, azathioprine, mycophenolate and IVIG decrease autoantibodies in a non-targeted way. These immunosuppressive therapies rarely

permanently eliminate the pathogenic autoantibodies.

Rituximab is an anti-CD20 monoclonal antibody that eliminates existing B cells except stem B-cells. The regenerated repertoire from stem B-cells do not develop autoantibodies and hence often leads to a permanent remission of pemphigus. A higher dose and earlier therapy are more effective. Previous study showed that it can be used as primary therapy for pemphigus with promising results.

An even specific targeted therapy that eliminates only anti-desmoglein B cells by using engineered chimeric autoantibody receptor (CAAR) T cells is being tested in preclinical therapy. It may be highly effective in permanent elimination of autoantibodies and hence lead to disease cure.

Learning points:

Treatment of pemphigus disease should aim to eliminate autoantibodies which often leads to a cure. Promising new modalities of targeted treatment including rituximab (anti-CD20 monoclonal antibody) and chimeric autoantibody receptor (CAAR) T cells may improve the clinical outcomes of pemphigus in future.

Anticancer drug-induced skin reactions: clinical manifestations and management

Speaker: Wen-Hung Chung
Chang Gung Memorial Hospital, Taiwan

Toxic erythema of chemotherapy is commonly due to cytarabine, doxorubicin and fluorouracil. This is treated by drug discontinuation and supportive care. For example, papulopustular eruptions which are usually due to epidermal growth factor receptor inhibitors can be managed by use of sunscreens, emollients,

topical steroids and doxycycline. Hand foot skin reaction is typically due to multikinase inhibitors (i.e. sorafenib and sunitinib). Risk factors include elderly female patients with history of total body radiation. Ice packing, topical steroids, urea cream, NSAID and pyridoxine are recommended.

Immunotherapy-induced side effects are due to reduced peripheral tissue tolerance. They are usually low grade and involve the skin (predominantly manifesting as a psoriasiform and lichenoid dermatitis) and has a good prognosis. Systemic steroids can be used for the abnormal T cell reaction. Occasionally, toxic epidermal necrolysis can occur.

Learning points:

Classical chemotherapy side effects include toxic erythema of chemotherapy. With the advent of newer targeted therapy and immunotherapy, the spectrum of side effects has changed. Clinicians therefore need to keep update with latest developments.

Hidradenitis suppurativa

Speaker: Erin McMeniman
Princess Alexandra Hospital South East Dermatology, Australia

Hidradenitis Suppurativa (HS) is a recurrent autoimmune disease due to follicular occlusion and increased cytokines in the skin. Contrary to conventional belief, it is neither infective nor apocrine gland-related. It usually presents as nodules or abscesses with sinus tract formation in the axillary, mammillary and gluteal regions. Treatments include using antiseptics to prevent secondary infection, topical clindamycin and oral antibiotics to reduce inflammation, and surgery. In the recent years, the arrival of biological therapy has revolutionised the care of HS.

Learning points:

HS is an autoimmune disease with increased skin cytokines. Apart from surgical treatment, medical treatments which target these cytokines are helpful (i.e. TNF alpha blockade by biological therapy).

Mycoplasma genitalium in female

Speaker: David A Lewis

Western Sydney Sexual Health Center, Western Sydney Local Health District and University of Sydney, Australia

Mycoplasma genitalium (MG) has been strongly implicated in non-gonococcal urethritis (NGU), it accounts for 20-35% of non-chlamydial NGU cases in males. It is also found to be significantly associated with urethritis, vaginal discharge, microscopic cervicitis and mucopurulent cervical discharge. However, the association with pelvic inflammatory disease, infertility and ectopic pregnancy is still unclear. There is a need to further investigate the pathogenic role of MG in terms of sequelae, also its pathogenesis and immune activation in both symptomatic and asymptomatic cases.

The prevalence of MG was estimated to be 2% in low-risk populations and 7.3% in high-risk populations. Widespread screening with the current commercial nucleic acid amplification test is not recommended in view of the low MG prevalence in most populations. Further prospective studies are needed to determine whether screening and targeted treatment of MG infection in women can reduce the incidence of adverse sequelae and improve reproductive outcomes.

Azithromycin-resistant MG is a growing problem in countries using Azithromycin 1g for Chlamydia treatment. Therefore, the 5-day extended 1.5 g Azithromycin regimen is preferred (Azithromycin 500 mg daily for day 1, then 250 mg daily for day 2 to 5).

Moxifloxacin should be considered when resistance to Azithromycin is found.

Learning points:

Mycoplasma genitalium should be considered in cases of non-gonococcal urethritis, female urethritis, cervicitis and the preferred treatment is the 5-day extended 1.5 g Azithromycin regimen.

Antimicrobial resistance and new treatment options for gonorrhoea

Speaker: David A Lewis

Western Sydney Sexual Health Center, Western Sydney Local Health District and University of Sydney, Australia

Neisseria gonorrhoeae (NG) has been labelled as one of the microorganisms with a threat level of urgent by CDC in 2013 and one of the pathogens with a high priority for research and development of new antibiotics by WHO in 2017. The emergence and transmission of extensively drug resistant NG has been found in the recent decade. The question of whether "old" antimicrobials can be used as "new drugs" was addressed and the choices that were explored included Spectinomycin, Gentamicin, Ciprofloxacin and Fosfomycin. This would be challenging and will need the development of molecular assays that can diagnose NG and predict the susceptibility of these "old" antimicrobial agents.

Currently, Ertapenem has been used as a treatment for extensively drug resistant NG. Three potential new drugs have been developed in recent or planned clinical trials, which is Solithromycin, Zoliflodacin and Gepotidacin. Nevertheless, with the current situation, the most important action is to reduce the transmission of gonorrhoea and to protect the current drugs that we have by using high doses of Ceftriaxone as monotherapy or as dual therapy with Azithromycin.

Learning points:

The important action in the current era is to reduce the transmission of gonorrhoea and to correctly use the current drugs that we have – high dose Ceftriaxone as monotherapy or dual therapy with Azithromycin.

Diagnosis and management of paediatric vascular malformations

Speaker: Erin McMeniman

Princess Alexandra Hospital South East Dermatology, Australia

It may be challenging to diagnose and manage vascular tumours and malformations in infants. The speaker cited the International Society for the Study of Vascular Anomalies (ISSVA) classification to illustrate how the various vascular tumours and malformations can be better differentiated.

Some commonly encountered conditions, such as port-wine stain and infantile haemangioma were mentioned by the speaker. Other than diagnosing the vascular conditions, the attending physician should check for any associated developmental anomalies, e.g. the association between port-wine stain and Sturge-Weber syndrome; the association between large segmental haemangioma and PHACES as well as LUMBAR syndromes. For multiple infantile haemangiomas (more than five), one should also screen for any internal organ involvement, especially liver haemangioma.

Regarding prognosis, 30% infantile haemangiomas would involute by the age of three years, 50% by the age of five years and 90% by the age of nine years. The lesion may have remnants in the form of fibrofatty tissue and telangiectasia. From a recent Cochrane review in 2018, oral propranolol has replaced systemic steroid as standard of care in the proliferative phase. Topical timolol, wound care

and vascular laser may be used as appropriate in superficial haemangiomas. Treatment should be considered when there is airway obstruction, congestive heart failure, bleeding, ulceration, lifelong disfigurement or mental distress for child and family.

Learning points:

Treatment of vascular malformations and tumours require a multidisciplinary approach. Oral propranolol has become the standard treatment of infantile haemangioma.

Dermatologic reactions to immune checkpoint inhibitors

Speaker: Vincent Sibaud

Medical Oncology and Dermatology Units, Institut Universitaire du Cancer Toulouse-Oncopole, France

Anti-Programmed cell Death protein 1 / anti-Programmed Death-Ligand 1 (anti-PD-1/PD-L1) and Cytotoxic T Lymphocyte Associated protein 4 (CTLA-4) antibodies are gaining spotlight in oncology treatment. The most common immune-related adverse effects (irAEs) of these therapeutic agents are cutaneous toxicities. Dermatological irAEs appear to be similar for anti-PD-1/PD-L1 and CTLA-4 antibodies. However, the incidence is lower with anti-PD-1/PD-L1. In melanoma patients undergoing anti-PD-L1 therapy, more than 40% of them have dermatological irAEs.

The most common irAEs is non-specific maculopapular rash with pruritus. Lichenoid dermatitis and psoriasiform dermatitis may also be the manifestation of irAEs. Other reported possible irAEs include papulopustular rosacea, bullous pemphigoid, eruptive keratoacanthoma/ SCC and Grover's – like disease. Mucosal involvement may manifest as Sjögren-like xerostomia and oral lichenoid reaction. Hair toxicity leading to alopecia areata is also noted.

Learning points:

Despite the cutaneous irAEs secondary to anti-PD-1/PD-L1 are usually self-limiting, early recognition is important for proper dose adjustment to prevent the more severe irAEs.

Hitting the target in psoriasis with IL-23 inhibition

Speaker: Chin-ho Hong

Department of Dermatology and skin Science, University of British Columbia, Canada

Interleukin 23 (IL- 23) is an essential key regulatory cytokine that promotes T cell differentiation. The differentiated T cells will further produce TNF α and IL-17. New anti-IL 23 blockers are developed to control the upstream pathway of cytokine production.

Guselkumab is one of the anti-IL- 23 blockers which has shown promising results in phase III studies. It has achieved psoriasis severity index PASI 90 and is superior to adalimumab. The PASI response has been sustained for up to two years. Available biologics range from those that act on effector cytokines to those that act on regulatory cytokines. Newer agents are opening a new era in the treatment of psoriasis.

Learning points:

Evidence supporting the efficacy and safety of biologics is growing. New agents such as IL-23 inhibitor guselkumab is emerging with promising result.

Clinicopathological relationship between purely cutaneous Rosai-Dorfman disease and IgG4-related skin disease

Speaker: Wai-fuk Wu

Medical & Health Officer, Social Hygiene Service, Center for Health Protection, Department of Health, Hong Kong

Cutaneous Rosai-Dorfman disease with no systemic involvement is a benign histiocytic disorder while IgG4-related skin disease is a fibroinflammatory condition. These two diseases share some overlapping features, but their relationship remains uncertain. This study showed that they should be regarded as two distinct entities after correlating the clinicopathological and immunohistochemical features as a whole.

Learning points:

Pure cutaneous Rosai-Dorfman disease and IgG4-related skin disease should be regarded as two distinct entities.

Drug-induced severe cutaneous adverse reactions in paediatric population

Speaker: Wen-hung Chung

Department of Dermatology, Chang Gung Memorial Hospital, Taiwan

Drug-induced adverse reactions in children are often associated with mucocutaneous manifestations that mimic viral exanthems and erythema multiforme major. Therefore, the attending physician has to bear in mind the possibilities of drug eruption, Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) when encountering maculopapular and morbilliform rash in children.

The speaker illustrated use of ALgorithm of Drug causality for Epidermal Necrosis (ALDEN) in assessing possible culprit drugs for paediatric SJS and TEN cases. Based on his study in Taiwan, antibiotics, anticonvulsants and nonsteroidal anti-inflammatory drugs were the most common drugs for SJS/TEN and drug reaction with eosinophilia and systemic symptoms.

After identification and withdrawal of the culprit drug, multidisciplinary supportive care should be instituted for SJS/TEN patients, such as thermoregulation, airway protection, fluid balance, nutritional support, pain management, venous thromboembolism prophylaxis, monitoring of infection and psychological support. Intensive care in a burns unit may be required. In the acute stage, the speaker suggested to consider early use of systemic immunomodulatory agents, e.g. corticosteroids, cyclosporine. Skin and mucous membrane treatments should also be continued. Clinical trials of high-dose steroid pulse therapy and other biologic agents in SJS/TENS are ongoing.

Learning points:

Though severe cutaneous adverse reactions are uncommon, they can result in severe potential complications. Early diagnosis and timely treatment would reduce the morbidity and mortality.

Pathophysiology of pemphigus

Speaker: John R Stanley

Department of Dermatology, University of Pennsylvania, USA

Blisters in the patients with pemphigus are caused by autoantibodies against desmogleins (Dsgs). In general, patients with pemphigus foliaceus (PF) have anti-Dsg1 antibodies; patients with mucosal pemphigus vulgaris (PV) have anti-Dsg3 antibodies; and patients with

mucocutaneous PV have anti-Dsg1 and anti-Dsg3 antibodies. Therefore, the diagnosis can be made by ELISA assays against Dsg1 and Dsg3. The location of the blisters in pemphigus can also be explained by Dsg compensation. Dsg1 and Dsg3 can compensate for loss of function of the other caused by autoantibodies if they are both present in the same tissue at the same level of epithelium.

Regarding treatment, the rapid response to corticosteroids used for disease control may be due to increase in synthesis of Dsgs thus overcoming their depletion by autoantibodies. This process is mediated by STAT3 signalling.

Learning points:

Pemphigus blisters are caused by anti-Dsg autoantibodies through direct inhibition of cell adhesion. The blister formation is enhanced by signalling pathway. Therapies targeting other signalling pathways may be used to decrease blistering.

Bullous pemphigoid: an updated review

Speaker: Jun Yamagami

Department of Dermatology, School of Medicine, Keio University, Japan

The Japanese government designated "pemphigoid", including bullous pemphigoid (BP), mucous membrane pemphigoid and epidermolysis bullosa acquisita, as nationally occurring intractable disease in 2015. Therefore, Japanese guidelines for the management of pemphigoid were published in 2017. Similar to pemphigus guidelines, the guidelines for BP has defined maintenance of remission as the treatment goal, and has divided treatment into two stages (initial therapy and maintenance therapy). Unlike pemphigus, during initial treatment of BP, mild, moderate

and severe disease are treated differently: Staging of disease severity is by Bullous Pemphigoid Disease Area Index (BPDAI). The guidelines distinguished circumstantial therapies for pemphigoid (not pemphigus), such as superpotent topical steroids, doxycycline and cyclophosphamide.

Dipeptidyl peptidase-4 (DDP-4) inhibitors are oral anti-hyperglycaemic drugs used in the treatment of type 2 diabetes mellitus. Cases of BP in patients after taking DDP-4 inhibitors have been reported. DDP-4i-BP patients usually present with the non-inflammatory phenotype of BP, with less erythema than observed in BP

patients not on DDP-4 inhibitors. In addition, DDP-4i-BP patients have IgG autoantibodies against full-length BP180 but not against the NC16a domain, which is the main target of autoantibodies in typical BP.

Learning points:

The clinical features (less erythema) and IgG autoantibodies against full-length BP180 can be used to diagnose patients with BP caused by DDP-4 inhibitors.