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MEETING REPORT

The 8th International Congress on Cutaneous Adverse Drug Reactions, Taiwan, 2013: Focus on Severe Cutaneous Adverse Reactions

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1 Introduction

The International Congress on Cutaneous Adverse Drug Reactions (cADR) was first held in 1994. This important scientific event is the world's largest meeting on this subject. Registration is open to everyone and anyone can submit papers for consideration.

The 8th International Congress on Cutaneous Adverse Drug Reactions was held in Taipei, Taiwan, on 16–17 November 2013. The location was of special significance, not only because of the important scientific contribution of the Taiwanese research group to the field, but also because it was the first time the congress was held outside of Europe.

The meeting was organized by the Taiwanese Dermatological Association and the Chang Gung Memorial Hospital, Department of Dermatology, Taipei, Taiwan, and immediately followed the World SCAR (Severe Cutaneous Adverse Drug Reactions) meeting at the same venue. The scientific programme was drawn up by an international committee appointed by the Chair, Dr. Wen-Hung Chung. The full programme is available on the official congress website: http://www.iscar2013.com

More than 1,000 participants from 20 countries attended the congress, including many scientists and clinicians from China, Taiwan, Hong Kong, Japan, Korea, Thailand, Philippines and Singapore. Keynote speakers came from Europe, North America, Australia, Africa and Asia. Global experts from various SCAR groups (Japan-SCAR, Southeast Asia-SCAR and RegiSCAR), and representatives of pharmaceutical companies, patient associations and regulatory agencies from Taiwan, Japan and the US (the FDA) attended.

This report summarizes some of the insights and updates from the meeting, with emphasis on recent progress in the field.

2 Plenary Session

Professor Jean-Claude Roujeau, Université Paris-Est Créteil (UPEC), Créteil, France, gave an overview of the new discoveries on SCAR in the past decades. He spoke about the finding of CD8+ cells and natural killing T cells in the skin blister fluid of patients with toxic epidermal necrolysis (TEN) [1], and about the discovery that granulysin is the main cytokine responsible for the apoptosis of epithelial cells in TEN [2]. He highlighted the progress in translating discoveries from the laboratory to the bedside, citing the advent of the pharmoco-immune concept suggesting that a drug could be presented to the T-cell receptor (TCR) and

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activates a specific clone. The concept is supported by recent findings of direct links between medications and both human leukocyte antigen (HLA) and TCR. Professor Roujeau emphasized the need to involve pharmaceutical companies and regulatory agencies in supporting research and helping patients in order to relieve the financial burden of severe cADR on public health agencies [3].

Professor Knut Brockow, Department of Dermatology and Allergy Biederstein, Klinikum rechts der Isar, Technische Universität München, and President of the Drug Allergy Interest Group of the European Academy of Allergy and Clinical Immunology (EAACI), reported on the use of prick and intradermal skin tests in the diagnosis of immediate drug reactions, emphasizing that the predictive value of skin tests varies with the drug tested. He described the possibility of immediate drug desensitization in case of drug hypersensitivity [4].

Professor Tetsuo Shiohara, Department of Dermatology, Kyorin University School of Medicine, Japan, described the essential role of human herpesvirus 6 (HHV-6) and other herpes viruses (HHV-7, Epstein-Barr virus [EBV] and cytomegalovirus [CMV]) reactivation in the development of drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS), and the practical implications of this discovery for the treatment of these patients with antiviral therapy (ganciclovir and intravenous immunoglobulin [IVIG]) [5].

Professor Sewon Kang, Department of Dermatology, Johns Hopkins School of Medicine, Baltimore, MD, USA, discussed the link between inflammation and scarring, and the central role of matrix degrading metalloproteinases in the process [6].

Professor Elizabeth J. Phillips, Vanderbilt University Medical Center, Nashville, TN, USA, and the Institute for Immunology and Infectious Diseases, Murdoch, WA, Australia, described the importance of the HLA-B*57:01 guideline-based test for predicting abacavir hypersensitivity in HIV patients [7]. She presented the recent discovery of the crystal structure of abacavir-HLA-B*5701-peptide [8] that explains the exquisite specificity of HLA-B*5701 for abacavir, and why other HLA alleles that differ by only two amino acids in the HLA-B F binding pocket do not bind abacavir. She spoke about future research directions aimed at designing drugs that do not interact with HLA and will therefore be unlikely to cause hypersensitivity reactions. Such research, carried out at the stage before clinical trials, would exclude high-risk drugs from development [9].

Professor Jean-François Nicolas, Division of Allergology and Clinical Immunology, Lyon University Hospital, France, presented the new developments in in vitro immunobiological assays for the diagnosis of type IV drug allergic hypersensitivity, including novel in vitro tests for drug-induced T-cell activation using cytokine secretion (interferon-g, interleukin [IL]-2, IL-17, tumour necrosis factor-α); cytotoxic potential of effector cells (granzyme B, CD107); and upregulation of cell surface markers (CD69) and the enzyme-linked immunosorbent spot (ELISPOT) method, which analyses the frequency of specific T cells producing type 1, type 2 type 17 cytokines and cytotoxic molecules [10].

Professor Werner J. Pichler, Allergy and Clinical Immunology, Inselspital University Hospital, Bern, Switzerland, discussed the immunological mechanism of drug hypersensitivity. He presented the p-i concept, according to which some drugs that lack hapten characteristics can bind directly and reversibly (non-covalently) to immune receptors and thereby stimulate the cells. He described his work on the analysis of T-cell reactions elicited by drugs, which revealed that the majority are actually off-target effects of drugs on the immune system, and not allergies [11].

3 Networks of Severe Cutaneous Adverse Drug Reactions (SCAR)

A number of international research groups are collaborating on SCAR research projects. This session was a unique opportunity to get acquainted with these groups.

Professor Maja Mockenhaupt, Department of Dermatology, University Freiburg—Medical Center, Freiburg, Germany, introduced the RegiSCAR network, an international registry of SCAR established in 2003. She described the work of the RegiSCAR study group, including the development of an enormous database of systematically validated cases of SCAR, diagnostic algorithms such as ALDEN for causality assessment in Stevens–Johnson syndrome (SJS)/TEN [12], and new data on the prevalence and severity of long-lasting sequelae and disability [13].

Professor Eishin Morita, Department of Dermatology, Shimane University, Faculty of Medicine, Shimane, Japan, and Professor Zenro Ikezawa, Department of Dermatology, International University of Health and Welfare (IUHW), Atami Hospital, Japan, introduced the Japanese Research Committee, J-SCAR, and the Asian SCAR consisting of Japan and Taiwan SCAR groups (J-SCAR and T-SCAR) established in 2010. They described some of the work emanating from the collaboration, including an epidemiologic study of SJS/TEN in Japan, the role of regulatory T cells (Treg) in severe drug eruptions, and a genome-wide association study identifying HLA-A*3101 for carbamazepine-induced drug reactions [14].

Professor Thirumoorthy Thamotharampillai, Dermatology Unit, Singapore General Hospital, Duke-NUS Graduate Medical School, introduced the Southeast Asia network, SEA-SCAR, with ten member countries: Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Thailand, Singapore, and Vietnam.

Professor Arthur Holden introduced the International Serious Adverse Event Consortium (iSAEC), a non-profit organization formed in 2007. This pharmaceutical industry- and FDA-led international consortium focuses on identifying and validating DNA variants useful in predicting the risk of rare drug-induced serious adverse events.

Professor Wen-Hung Chung, Congress Chair, Department of Dermatology, Drug Hypersensitivity Clinical and Research Center, Chang Gung Memorial Hospital, Chang Gung University, Taiwan, presented Taiwan's group, T-SCAR. Landmarks of the T-SCAR include the discovery of the genetic maker of HLA-B*1502 for carbamazepine-induced SJS/TEN in 2004 [15], and the genetic maker of HLA-B*5801 for allopurinol-induced SCAR in 2005 [16]. In 2007, their discoveries led the US and Taiwan FDAs to re-label the drug warning information to include a recommendation to test HLA-B*1502 for persons of Asian ancestry before prescribing carbamazepine.

4 Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis: New Insights

Several studies were presented on SJS and TEN. International assessment protocols and treatment regimens for patients with SJS/TEN were described, including experience with cyclosporine, systemic corticosteroids, and plasmapheresis. The findings of a study assessing the management protocols of patients with TEN in various burn centers and dermatology departments in North America was presented: IVIG was found to be the most common systemic treatment; most centers reported experience with amniotic membrane therapy; and most stressed the need for international treatment guidelines for patients with TEN. The promising preliminary results of a unique, prospective, randomized, open-label trial currently underway in Taiwan were described. In this study comparing the use of etanercept versus systemic corticosteroids in patients with SJS/TEN, the average duration to reach maximal skin detachment and complete skin healing was shorter in the etanercept group. In vitro investigations demonstrated that etanercept, steroids or thalidomide significantly decreased granulysin expression of blister cells. Etanercept did not, however, increase the cytotoxic effect to keratinocytes found with thalidomide. Furthermore, etanercept upregulated Treg and decreased granulysin expression in patients with SJS/TEN. A review of the activities of the French referral center for the management of SJS/TEN described the comprehensive treatment by the dermatological intensive care unit that contributed to a better survival in the past 10 years. A survival analysis of patents with SJS/TEN disclosed high in-hospital mortality and a marked number of deaths following discharge [13].

5 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): New Insights

A number of papers were presented on DRESS, called DIHS in Japan. Important discoveries were discussed on the role of viral reactivation, specifically HHV-6, in the pathogenesis of DRESS [5, 17], and recent studies demonstrating that FoxP3+ Treg cells are expanded during the acute stage, providing potential mechanisms by which herpesviruses could be reactivated [18]. Presentations included new guidelines for treating DRESS based on the presence and severity of symptoms and the assessment of a major viral reactivation [19], and studies documenting the occurrence of autoimmune diseases and the production of autoantibodies following the resolution of DRESS/DIHS in a period ranging from several months to years [20]. The autoimmune diseases included diabetes mellitus type 1, lupus erythematosus, Hashimoto's thyroiditis, enteropathy, sclerodermiform lesions type graft-versus-host disease (GVHD), and bullous pemphigoid. A discussion ensued on the need for anti-inflammatory effects from systemic corticosteroids for reducing the risk of autoimmune diseases in patients with DRESS versus the risk of infectious diseases such treatment may induce.

Other interesting papers dealt with epidemiology, clinical assessment, management and outcome of cADRs, pharmacogenomics and animal models, and clinicopathology and immunology studies. Enlightening reports were heard from the FDA and industry regulatory organizations, and from patient associations.

6 Consensus on Important Issues Related to SCAR

During the international congress, a meeting was held to discuss interesting cases from different countries and some of the important issues and controversies related to SCAR. Fifty drug hypersensitivity experts and researchers from different countries and SCAR research groups, including RegiSCAR, J-SCAR and SEA-SCAR, took part in this questionnaire-based face-to-face discussion. There was consensus on several issues (Table 1): that DRESS and DIHS are the same entity; anticonvulsants and allopurinol are the two most commons causes of SJS/TEN and DRESS/DIHS; there is no indication for empirical antibiotic treatment for SJS/TEN or DRESS; systemic steroids are used most commonly for SJS/TEN, at an initial dose of 0.5–1 mg/kg/day; debridement of necrotic skin for SJS/TEN is not necessary; and the need for an international SCAR organization.

7 Summary

The 8th International Congress on Cutaneous Adverse Drug Reactions was an invaluable opportunity to broaden

Table 1 Consensus among the 50 participants of the World SCAR 2013 meeting (percentages denote percent of the total group)

Questions	Answers				
Region of participant	57 %	27 %	8 %	4 %	4 %
	Asia	Europe	North and South America	Africa	Other
Field of speciality	60 %	10 %	8 %	4 %	18 %
	Dermatology	Basic research	Rheumatology/immunology	Ophthalmology	Other
DRESS and DIHS the same entity	85 %	13 %	2 %		
	Same entity	Different entity	I don't know		
Department in your institute treating patients with SJS/TEN	72 %	24 %	2 %	2 %	
	Dermatology	Burn Unit/ICU	Internal medicine	Rheumatology/immunology	
Main type of SCAR seen at your institute	56 %	42 %	2 %		
	SJS/TEN	DRESS/DIHS	Other		
Number of SJS/TEN cases treated in your institute annually	35 %	28 %	22 %	9 %	6 %
	<5	10–20	5–10	20–30	>30
Number of DRESS/DIHS cases treated in your institute annually	32 %	32 %	17 %	13 %	6 %
	<5	5–10	10–20	20–30	>30
The most common drug inducing SJS/TEN	48 %	22 %	16 %	8 %	6 %
	Anticonvulsants	Allopurinol	NSAIDS	Antibiotics	Anti-HIV and anti-TB
The most common drug inducing DRESS/DIHS	43 %	39 %	7 %	7 %	4 %
	Anticonvulsants	Allopurinol	Antibiotics	Anti-HIV and anti-TB	Other
Empirical antibiotic treatment for SJS/TEN	73 %	18 %	9 %		
	No	Yes	I don't know		
Empirical antibiotic treatment for DRESS/DIHS	84 %	8 %	8 %		
	No	Yes	I don't know		
The most common treatment for SJS/TEN	58 %	25 %	10 %	2 %	5 %
	Systemic steroids	Only supportive care	Cyclosporine	Anti-TNF agent	Other
The initial dose of systemic steroids for SJS/TEN	53 %	22 %	22 %	3 %	
	0.5–1 mg/kg/day	1–1.5 mg/kg/day	1.5–2 mg/kg/day	0.5 mg/kg/day	
Duration of treatment with systemic steroids for SJS/TEN	53 %	16 %	9 %	9 %	13 %
	Depends on the stage of the disease	>2 weeks	3 weeks	<5 days	Other
Genetic testing prior to treatment with carbamazepine or allopurinol	31 %	60 %	9 %		
	Yes	No	I don't know		
Consultation with ophthalmology for SJS/TEN	100 %				
	Yes				
Debridement of necrotic skin in SJS/TEN	64 %	29 %	7 %		
	No	Yes	I don't know		

Table 1 continued

Questions	Answers					
Important future SCAR research topics	23 % Management and therapeutics	23 % Immune mechanisms	18 % Genetics and biomarkers	18 % Epidemiology and causality	18 % Other	
Need for an international SCAR organization	83 % Yes	15 % No comment	2 % No			

DRESS drug reaction with eosinophilia and systemic symptoms, *DIHS* drug-induced hypersensitivity syndrome, *ICU* intensive care unit, *NSAIDs* non-steroidal anti-inflammatory drugs, *SCAR* Severe Cutaneous Adverse Drug Reactions, *SJS* Stevens–Johnson Syndrome, *TB* tuberculosis, *TEN* toxic epidermal necrolysis, *TNF* tumour necrosis factor

our understanding and knowledge of the current trends in SCAR research and treatment in different countries, and to exchange experiences and information with colleagues from around the world.

Interesting programs of visits to professional and cultural sites were conducted, including to the Drug Hypersensitivity Clinical and Research Center in Chang Gung Memorial Hospital. The center, established in 2012, provides a multidisciplinary approach for the management of patients with adverse drug reactions and combines clinical and basic research with major international collaborations.

We are deeply grateful to our hosts, Dr. Weng-Hung Chung, Chair, Dr. Rosaline Chung-Yee Hui, Vice-Chair, and Dr. Chih-Hsun Yang, President of the Taiwan Dermatological Association, for their warm and generous hospitality and for providing the opportunity to meet our fellow scientists.

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