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Effectiveness of Boosted Protease Inhibitor-Based Regimens in HIV Type 1-Infected Patients Who Experienced Virological Failure with NNRTI-Based Antiretroviral Therapy in a Resource-Limited Setting

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Abstract

A number of patients have experienced treatment failure while receiving non-nucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral therapy (ART), particularly in resource-limited countries. The need remains for clinical data on protease inhibitor (PI)-based regimens in these patients. A retrospective cohort study was conducted among HIV-1-infected patients who had failed NNRTI-based regimens, were naive to protease inhibitors (PIs), and subsequently initiated a salvage PI-based regimen between January 2004 and December 2006. The study period ended on 30 December 2007. One hundred and forty patients received a single-boosted PI ± optimized background regimen (OBR) and 64 received double-boosted PIs. The median (IQR) duration of follow-up was 19 (13–29) months. The overall virological failure rate at 24 months was 15.2%. No statistically significant difference was detected between the two regimen groups (single-boosted PI ± OBR 16.4% vs. double-boosted PIs 12.5%, log rank $p = 0.818$). At the end of the study, the median (IQR) change in CD4 cell counts for patients in the double-boosted PI group was higher than for patients in the single-boosted PI ± OBR group [149 (53–322) vs. 105 (23–199), respectively, $p = 0.012$]. Patients receiving double-boosted PI regimens displayed a higher frequency of hypertriglyceridemia than those patients who received a single boosted PI ± OBR (31% vs. 11%, respectively, $p = 0.001$). Boosted PI-based regimens showed acceptable virological outcomes among patients who had failed NNRTI-based ART. In the subgroup analysis, patients who received double-boosted PIs demonstrated a superior immunological response but not better virological outcomes compared to the single-boosted PI ± OBR group.

Introduction

Non-nucleoside analog reverse transcriptase inhibitor (NNRTI)-based regimens are currently the preferred treatment option for treatment-naive HIV-1-infected patients globally because of the availability of fixed-dose combination formulations and because these regimens have a lower cost, fewer drug interactions, and a virological response better than, or at least comparable to, that of regimens consisting of a ritonavir-boosted protease inhibitor (PI) plus two nucleoside analog reverse transcriptase inhibitors (NRTIs) (PI-based regimen).[1–3] The prevalence of virological failure in NNRTI-based regimens is 20–26% worldwide.[4–6] Most patients who have failed an NNRTI-based regimen developed resistance to NNRTIs and lamivudine.[7–9] Some patients developed multi-NRTI resistance, including thymidine analog-associated mutations (TAMs) (32–73%), Q151 complex mutations (1–11%), and 69 insertion complex mutations (0–1%).[7–10] A general recommendation of the Department of Health and Human Services (DHHS) in designing a regimen for patients who have failed antiretroviral therapy (ART) is to include at least two, and preferably three, fully active drugs.[2]

The World Health Organization (WHO) guidelines recommend using ritonavir-boosted PIs with a dual NRTI backbone comprising two previously unused NRTIs.[11] Nevertheless, the recommendations of most current guidelines are based solely

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Alimentary Pharmacology & Therapeutics

The predictors of complications in patients with drug-induced liver injury caused by antimicrobial agents

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SUMMARY

Background
Antimicrobials are the leading cause of idiosyncratic drug-induced liver injury in most series.

Aim
To determine the incidence and the predictors of complications in patients with drug-induced liver injury caused by antimicrobial agents requiring hospitalization.

Methods
Medical records of patients with drug-induced liver injury caused by antimicrobial agents were identified by ICD-10, for the period between 2002 and 2006. Clinical information and blood tests during hospitalization were recorded. The causality assessment of drug-induced liver injury was determined by the Roussel UCLAF causality assessment method (RUCAM) scale.

Results
Of 47 594 in-patient admissions per year, the annual incidence of drug-induced liver injury was 0.03%. Male: female ratio was 7:3 with a median age of 47 years. Eighty reactions of drug-induced liver injury were caused by anti-tuberculosis drugs (85%) and by antibiotics (15%). The median (IQR) of RUCAM scale was 6 (5–8). A total of 36% had HIV infection and 9% of patients had diabetes mellitus. Median (IQR) duration of hospitalization was 9 (5–15) days. Serious complications and death were found in 27.5% and 26%, respectively. By a multivariable logistic analysis, the presence of jaundice was found to be significantly associated with an unfavourable outcome.

Conclusion
Although rare, antimicrobial agents-related drug-induced liver injury requiring hospitalization has a high mortality rate. The presence of jaundice predicts poor outcome.

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Parenteral Bisphosphonates for Osteoporosis in Patients With Primary Biliary Cirrhosis

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We aimed to describe the effects of parenteral bisphosphonates on bone mineral density (BMD) changes in primary biliary cirrhosis (PBC) patients with osteoporosis. Seventeen PBC patients with osteoporosis diagnosed between 1996 and 2005 were enrolled retrospectively. All patients received one of the following parenteral bisphosphonates: zoledronic acid, pamidronate disodium, or ibandronate sodium. The median (interquartile range) age of patients at osteoporosis diagnosis was 62.2 (56.4–67.9) and 94% were women. After treatment, percent change of lumbar spine bone mineral density (LS-BMD) and proximal femur BMD (PF-BMD) of patients with PBC was 2.9% and 0.4%, respectively. Eight patients (47%) showed a greater LS-BMD and/or PF-BMD with percent change of LS-BMD and PF-BMD of 8.7% and 0.8%, respectively. No serious adverse events were found. In PBC patients with osteoporosis, parenteral bisphosphonates can stabilize BMD for 47% of patients. More prospective studies are needed to evaluate the efficacy of specific parenteral bisphosphonates in patients with PBC and osteoporosis.

Keywords: bone disease, primary biliary cirrhosis, treatment, parenteral bisphosphonates

INTRODUCTION

Bone loss is a well-recognized complication of primary biliary cirrhosis (PBC). The prevalence of osteoporosis among PBC patients ranges from 20% to 32% in large series.[1–3] Osteoporosis is clinically important and frequently identified in patients with cirrhosis. It is usually progressive and bone loss occurs at a rate of -0.008 ± 0.002 g/cm^2/yr for the lumbar spine and -0.003 ± 0.003 g/cm^2/yr for the hip.[1] It can lead to spinal fractures and significant patient morbidity.[4] Osteomalacia which is related to the abnormal intestinal absorption of cholecalciferol and 25-hydroxycholecalciferol, may be found in the presence of severe cholestasis, when patients are jaundiced.[4] In a Mayo Clinic study of patients with end-stage PBC and primary sclerosing cholangitis undergoing liver transplantation, there were no patients with osteomalacia identified by bone biopsy.[5]

Bone mineral density (BMD) is used for detection of osteoporosis and is measured by dual-energy x-ray absorptiometry which is currently the best predictor of fracture risk.[4] Osteoporosis is defined by a BMD measured at less than 2.5 standard deviations below the normal peak bone mass (T score of -2.5), whereas osteopenia is defined by a BMD measured by a T score of less than -1 standard deviation below normal peak bone mass.[6] In a recent study involving 176 patients with PBC in our institution, the prevalence of osteoporosis was 20%, which was more than 30 times higher than expected.[1] Age, body mass index, the severity of liver disease, treatment with glucocorticoids for more than 3 months, and history of fractures were indicators of osteoporosis.[1,3] Another study showed that BMD was significantly correlated with age and postmenopausal status but it was not correlated with

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Case Report: Autochthonous Visceral Leishmaniasis in a Human Immunodeficiency Virus (HIV)-Infected Patient: The First in Thailand and Review of the Literature

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Abstract. We report a case of visceral leishmaniasis in a human immunodeficiency virus (HIV)-infected 37-year-old Thai fisherman who presented with nephritonephrotic syndrome, fever, anemia, and thrombocytopenia. Bone marrow biopsy revealed many amastigotes within macrophages. Kidney biopsy showed membranoproliferative glomerulonephritis. Polymerase chain reaction (PCR) and nucleotide sequence analysis of the internal transcribed spacer 1 of the small subunit ribosomal RNA gene in blood and kidney biopsy specimens showed *Leishmania* species previously described in a Thai patient with visceral leishmaniasis. Only four autochthonous cases of leishmaniasis have been reported in Thailand since 1996. To the best of our knowledge, this is the first report of autochthonous visceral leishmaniasis in an HIV-infected Thai. With an increasing number of patients with autochthonous leishmaniasis in association with the presence of potential vector, it remains to be determined whether this vector-borne disease will become an emerging infectious disease in Thailand.

Leishmaniasis is a vector-borne infection caused by an obligate intracellular protozoon, *Leishmania* sp., which is transmitted by phlebotomine sandflies.[1–3] It occurs worldwide in tropical and subtropical regions including the Middle East, India, China, Africa, and southern and central America. Thailand is not a known endemic area for leishmaniasis. Most imported cases were reported between 1960 and 1986 in Thai workers returning from the Middle East.[4,5] The first reported indigenous patient with leishmaniasis was a 3-year-old girl living at Suratthani Province of southern Thailand in 1996.[6] Several autochthonous cases with leishmaniasis were recently seen in northern, central, and southern Thailand.[7–9] Interestingly, these patients were from provinces where a potential sandfly vector has never been reported.[10–12] We describe the first report of visceral leishmaniasis in a human immunodeficiency virus (HIV)-infected patient and review all previous reports of autochthonous cases of leishmaniasis in Thailand.

CASE REPORT

A 37-year-old Thai fisherman with known HIV infection presented with progressive leg edema, ascites, and low-grade fever of 8 weeks duration. Seven weeks prior to admission (PTA), he was hospitalized at Chantaburi Provincial Hospital with a diagnosis of nephritonephrotic syndrome (hypertension, edema, heavy proteinuria, microscopic hematuria, azotemia, hypoalbuminemia, and hypercholesterolemia). He was treated with prednisolone 50 mg/day. Two weeks PTA, he had not improved and developed thrombocytopenia (platelet count of 85,000/μL) and anemia (hematocrit decreased from 29% to 23.4%). Bone marrow aspiration and biopsy were performed and revealed decreased cellularity and many "yeast-like" organisms 1–2 μM in size. Fungal cultures of both specimens did not grow any fungi. He was then transferred to King Chulalonkorn Memorial Hospital in Bangkok for further evaluation. The patient was born at Chantaburi, eastern Thailand. He had never been outside Thailand except for having worked as a fisherman in the Indian Ocean and northern Indonesian sea from 1999 to 2001. The HIV was diagnosed at 33 years of age presenting with active tuberculosis. He received a standard 6-month course of therapy comprised of isoniazid, rifampin, pyrazinamide, and ethambutol and also started on stavudine, lamivudine, nevirapine, and cotrimoxazole. His CD4 cell counts increased from 40 to 129 cells/μL and plasma HIV RNA levels became undetectable at 8 weeks PTA. He was also found to have chronic hepatitis C infection and a history of intravenous drug use. He smoked and drank alcohol daily. Physical examination showed a temperature of 38.5°C, moderate pallor, mild hepatomegaly, and moderate pedal edema. Blood complement levels of C3 and C4 were decreased. A kidney biopsy was performed and revealed membranoproliferative glomerulonephritis with focal segmental glomerulosclerosis. However, no organisms were demonstrated on Giemsa's staining in the renal biopsy slides. A review of the histopathology of the bone marrow revealed, amastigotes of *Leishmania* sp. within macrophages and bar-shaped kinetoplast were also seen (Figure 1). The blood and kidney biopsy specimens were sent to the Department of Parasitology, Chulalongkorn University, for identification of the species of *Leishmania*. The samples were then tested for *Leishmania* using the primers specific for 18S ribosomal RNA (rRNA) genes as described by Le Fichoux and others[13] and for species differentiation using the primers specific for internal transcribed spacer1 (ITS1) regions of the rRNA as described by Uliana and others.[14] Both specimens obtained from our patient were positive for *Leishmania*. Nucleotide sequences of the amplified PCR products for the 18S rRNA gene were identical to the sequence of *Leishmania* sp. previously reported in GenBank (GenBank accession no. AF303938). The species of *Leishmania* identified by nucleotide sequences of the amplified PCR products of the ITS1 region of the rRNA gene was identical to the new species of *Leishmania* (GenBank accession no. EF200011) (Figure 2), previously reported from a Thai patient with visceral leishmaniasis by Sukmee and others.[8] Nucleotide sequences of the 18S rRNA gene and the ITS1 region of the rRNA gene of this report were submitted to GenBank under accession nos. GQ226033 and GQ226034. The patient gradually improved clinically along with his bone marrow and renal status after treatment with amphotericin B deoxycholate (2 mg/kg every other day) for 2 weeks. He was discharged on oral itraconazole (400 mg/day). He

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Rabies Exposure Risk among Foreign Backpackers in Southeast Asia

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Abstract. Rabies remains a problem in Southeast Asia where large numbers of backpackers visit each year. During May–June 2008, a survey study was conducted of foreign backpackers in Bangkok, Thailand to assess their risk of rabies exposure. Eight hundred seventy (870) questionnaires were collected and analyzed. The median age of the backpackers was 25.5 years. Most of them were European (68.4%), followed by North American (13.2%). Although 80.7% had sought health information before traveling, only 55.6% had received information about rabies. Only 18.1% had completed pre-exposure rabies vaccination (3 shots) before travel, whereas 70.9% had not been vaccinated for rabies at all. In this study, the incidence of being licked was 3.56%, and of being bitten 0.69%, on average stays of 30.06 days in Southeast Asia. More than a half (54%) of exposures occurred in the first 10 days after arrival in Southeast Asia.

INTRODUCTION

Rabies remains a problem in most countries of Southeast Asia, where stray dogs and cats are common. Financial, political, and cultural issues are the main barriers to public health authorities' controlling the disease in animals.[1] Local people and travelers in this area are inevitably at risk of exposure to the rabies virus if bitten or licked by an infected animal. Pre-exposure prophylaxis is an excellent preventive measure against rabies in travelers. However, it is expensive, and the cost-benefit relationship is not clear, so that it has limited application in general travel-medicine practice.[2,3]

Backpackers were considered to be a special group of travelers, who might be at high risk of contracting rabies. However, the risk of rabies exposure among this particular group in Southeast Asia was unknown. Therefore, this study was conducted to determine the incidence and risk of exposure to rabies, i.e., by being bitten or licked by animals, during their travels in Southeast Asia. The secondary objective was to assess their knowledge, attitudes, and practices toward the risk of rabies.

MATERIALS AND METHODS

This was a cross-sectional, questionnaire-based study. Data were collected from foreign backpackers in the Khao San Road area, which is a famous backpacker center in Bangkok, Thailand. The questionnaire was drafted, tested, and revised before actual data collection. The final version of the questionnaire comprised four parts, i.e., general information about the travelers, rabies pre-exposure preparations, knowledge about rabies, and the details of any animal exposure (being bitten/licked). The sample sized was calculated using the estimated risk from a previous study[4] and the estimated number of backpackers in Khao San area from Tourism Authority of Thailand (TAT) data.[5] To achieve a 95% confidence level, we required at least 826 samples.

The study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University.

An accidental sampling method was used in data collection. Backpackers from non-Southeast Asian countries were invited to join the study by answering a written questionnaire. The team of investigators was available to help if needed.

Statistical analysis. All statistical analyses were performed using SPSS for Windows (version 10.0.7, SPSS Inc., Chicago, IL) software. Continuous data were presented as mean with standard deviation (for normally distributed data), or median with range (for non-normally distributed data). Categorical data were presented as numbers and percentage. The student *t* test was used to compare means of two groups, whereas the χ^2 was used for categorical data, as appropriate; a P value of < 0.05 was regarded as statistically significant.

RESULTS

During the period May–June 2008, 870 questionnaires were collected and evaluated. The median age of the respondents was 25.5 years; 52% of the total was male. Most of the backpackers were European (68.4%), followed by North American (13.2%). Their main reason for travel was tourism (91.4%); 27% of the travelers had been traveling in other Southeast Asian countries besides Thailand. The detail demographic data of the study participants are shown in Table 1.

Attitudes and pre-travel preparations for the risk of rabies. Although 80.7% had sought travel health information before travel, only 55.6% had received information about rabies. Only 18.1% of backpackers had completed a course of pre-exposure rabies vaccinations (3 shots) before travel, 11.0% had received only 1 or 2 shots, whereas 70.9% had not been vaccinated for rabies at all. Among those who had not been vaccinated for rabies, 61.8% cited the cost of the vaccine, 11.8% did not know of or were unaware of the risk of rabies, whereas 9.3% thought it unnecessary. The detailed data are shown in Table 2.

Backpackers' knowledge about rabies. Almost all backpackers (95.7%) knew that they could get rabies if bitten by an infected animal. However, only 59% of them knew that being licked on an area of broken skin could also transmit rabies. Ninety-eight percent of backpackers knew that dogs could carry rabies, but only 63.1% of backpackers were aware that cats could also carry rabies. Moreover, 40% of backpackers thought that the bite of a healthy-looking dog/cat posed no risk of rabies. Details of the knowledge assessment are shown in Table 3.

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Retrospective review of extra-pulmonary small cell carcinoma at King Chulalongkorn Memorial Hospital cases during 1998–2005

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Abstract

***Objective*:** The aim of this study was to review cases of extra-pulmonary small cell carcinoma (EPSCC), including their clinical manifestations and treatment outcomes.

***Methods*:** We retrospectively reviewed the medical records and pathological reports of patients who were diagnosed with EPSCC from 1998 to 2005.

***Results*:** Overall 21 EPSCC patients were eligible for this study. The most common primary sites were the gastrointestinal organs and the nasal cavity. Eleven patients (52.3%) had limited disease (LD) and 10 patients (47.7%) had extensive disease (ED). Nine patients underwent radical surgery alone, four received only radical radiation and two received only palliative chemotherapy. Two patients received adjuvant radiation or chemotherapy following surgical resection and one received a combination of all three treatment modalities. Three patients declined specific treatment and were treated with best supportive care. The median overall survival in the ED group was only 3 months (range 1–16 months), compared to 30 months (range 20–61 months) for LD. EPSCC of pancreas demonstrated a favorable clinical outcome with treatment, whereas primary EPSCC of the liver, esophagus and rectum had an aggressive natural history and a poor response to treatment.

***Conclusion*:** Our report suggests that EPSCC may have a different biology from that of pulmonary small cell carcinoma. When detected at an early stage, EPSCC may have an excellent prognosis with treatment. Additional studies involving more patients with EPSCC are warranted to further define the optimal roles of each treatment modality.

Key words: extra-pulmonary small cell carcinoma, neuroendocrine, carcinoma of unknown primary.

INTRODUCTION

Small cell carcinoma is an aggressive malignancy that has pathological features typical of poorly differentiated and small round cell carcinoma.[1] Most small cell carcinomas (SCC) possess characteristic neuroendocrine features such as synaptophysin, neuron-specific enolase and chromogranin.[2] The most common site of primary SCC is the pulmonary parenchyma. Other primary organs of this malignancy include those of the gastrointestinal and genitourinary tracts and the head and neck region. Based on the above pattern, SCC can be categorized into two subgroups according to primary tumor location: pulmonary and extra-pulmonary SCC (PSCC and EPSCC).[3]

PSCC is prevalent in middle-aged or elderly men with a strong history of smoking.[4] It is considered to be one of the most aggressive malignancies, as demonstrated by the high frequency of advanced metastatic disease at the time of diagnosis. PSCC consists of two stages,

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High incidence of symptomatic venous thromboembolism in Thai hospitalized medical patients without thromboprophylaxis

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Venous thromboembolism (VTE) is a common preventable cause of mortality during hospitalization. However, prophylaxis is frequently under-utilized due to the belief that it is rare in Asia. The objective of the study was to estimate the incidence of symptomatic VTE in hospitalized nonsurgical Thai patients. We performed a prospective study in medical wards in Chulalongkorn Hospital, a tertiary-care university-based center, from June 2007 to December 2008. We included adult patients admitted beyond 3 days. Patients with VTE before admissions or undergoing major surgery during hospitalization were excluded. According to the usual practice, heparin prophylaxis was not given. However, the program of primary physician education and fast-track diagnostic imaging were implemented. Forty-two VTEs from 7126 susceptible patients [0.59%, 95% confidence interval (CI) 0.41–0.77%] were found; 20 (48%) definite pulmonary embolism, four of which also had symptomatic deep vein thrombosis (DVT), 19 (45%) definite DVT and three sudden deaths from possible pulmonary embolism. Immobilization (74%), active cancer (52%) and rheumatologic diseases (12%), including arthritis of lower extremities and systemic lupus erythematosus with antiphospholipid, were common VTE risk factors, which were present in our patients. The incidences in total cases of arthritis, cancer, mechanical ventilation and congestive heart failure were 7.7, 1.8, 1.5 and 0.5%, respectively. Notably, nine of 23 (39%) pulmonary embolism cases were fatal and two more patients (9.5%) expired from bleeding after treatment (one pulmonary embolism and one DVT). In conclusion, VTE contributes significant hazard to hospitalized nonsurgical Thai patients. Appropriate measures to assure proper thromboprophylaxis in high-risk patients are strongly needed. *Blood Coagul Fibrinolysis* 21:334–338 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Keywords: deep vein thrombosis, incidence, medical patients, prophylaxis, pulmonary embolism, venous thromboembolism

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Introduction

Venous thromboembolism (VTE), presenting as deep vein thrombosis (DVT) and pulmonary embolism, is a common complication during admissions for acute medical illnesses. It remains a significant cause of morbidity and mortality, in particular fatal pulmonary embolism that accounts for 5–10% of all deaths in hospitalized patients [1,2]. In addition to the acute problem, long-term adverse consequences of VTE are chronic debilitating post-thrombotic syndrome and chronic hypoxemia from thromboembolic pulmonary hypertension. These markedly impair patient quality of life and increase healthcare cost.

The current evidence-based clinical practice guideline [3] emphasizes that prevention of VTE is critical for at-risk hospitalized medical patients and programs to implement it in clinical practices are strongly required. However, thromboprophylaxis is frequently under-prescribed in Thailand. According to the analysis of the VTE risk and prophylaxis in the acute medical care setting (ENDORSE study), a multinational, observational and cross-sectional study, only 15 (3.7%) out of 406 at-risk medical patients in Thailand received appropriate prophylaxis [4].

The significant factor causing underused VTE prophylaxis in Thailand is the prior data indicating the much lower incidence of VTE in Asian compared with those of Western populations. Studies 3 decades ago showed that the rates of perioperative thrombosis in Thais were 10-fold less than those of Caucasians [5,6]. The underlying causes of this striking difference, either genetic or environmental, remain to be determined. However, more recent investigations in Asia [7,8], including Thai patients, demonstrated that VTE incidences after orthopedic surgery were close to western individuals [8]. Furthermore, studies from Hong Kong suggested that the risk of total DVT, with or without symptoms, in hospitalized medical patients was at least 1.0% [9]. However, another study in the same ethnic group estimated the symptomatic VTE incidence of 2–3 in 1000 patients [10]. Nevertheless, data in Thai medical patients are lacking. Other data influencing physicians' decisions come from two meta-analyses in Western patients showing that pharmacological VTE prophylaxis could not significantly decrease overall mortality in

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Ventricular Geometry, Strain, and Rotational Mechanics in Pulmonary Hypertension

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Background—We tested the hypothesis that right ventricular (RV) pressure overload affects RV function and further influences left ventricular (LV) geometry, which adversely affects LV twist mechanics and segmental function.

Methods and Results—Echocardiographic images were prospectively acquired in 44 patients (age, 46±12 years; 82% women) with evidence of pulmonary hypertension (estimated pulmonary artery systolic pressure, 71±23 mm Hg) and in 44 age- and gender-matched healthy subjects. Patients with intrinsic LV diseases were excluded. RV lateral wall longitudinal strain (LS) and interventricular septal (IVS) LS were reduced in the pulmonary hypertension group compared with control subjects (−15.9±7.6% versus −25.5±6.1%, $P<0.001$; and −17.3±4.4% versus −20.2±3.9%, $P=0.002$, respectively), whereas LV lateral wall LS was preserved. RV lateral wall LS and IVS LS, but not LV lateral wall LS, correlated with pulmonary artery systolic pressure ($r=0.56$, $P<0.01$; $r=0.32$, $P<0.01$) and LV eccentricity index ($r=0.57$, $P<0.01$; $r=0.57$, $P<0.01$). IVS and LV lateral wall circumferential strain (CS) were both reduced in the pulmonary hypertension group. Although IVS CS and LV lateral wall CS correlated with pulmonary artery systolic pressure and LV eccentricity index, after adjustment of CS for LV eccentricity index, differences between groups persisted for IVS CS ($P<0.01$) but not LV lateral wall CS ($P=0.09$). LV torsion was decreased in patients with pulmonary hypertension compared with control subjects (9.6±4.9° versus 14.7±4.9°, $P<0.001$). LV torsion inversely correlated with pulmonary artery systolic pressure ($r=-0.39$, $P<0.01$) and LV eccentricity index ($r=-0.3$, $P<0.01$). LV untwisting rates were similar in both groups ($P=0.7$).

Conclusions—Chronic RV pressure overload directly affects RV longitudinal systolic deformation. RV pressure overload further influences IVS and LV geometry, which impairs LV torsion and segmental LS and CS, more for the IVS than for the free wall of the LV. **(*Circulation*. 2010;121:259-266.)**

Key Words: echocardiography ■ hypertension, pulmonary ■ myocardial contraction ■ torsional force

The right (RV) and left (LV) ventricles share the interventricular septum (IVS) and are contained within the pericardial sac, inducing interdependence in ventricular structure and function.[1,2] Chronic right ventricular (RV) pressure overload leads to a leftward shift and flattening of the IVS.[1–4] The degree of severity of chronic RV pressure overload has traditionally relied on the degree of pulmonary artery systolic pressure (PASP) rise, yet patients may present with a wide range of disease severity within a similar range of elevated PASP. Little is known about the impact of RV pressure overload and ventricular geometric alteration on biventricular systolic deformation and LV twist and untwist mechanics in the setting of pulmonary hypertension (PH). Currently, ventricular strain and torsion analysis assessed by speckle tracking echocardiography may provide insights into the impact of RV pressure overload on ventricular interdependence and subsequent LV performance beyond structural and volumetric analyses. Accordingly, by using this echocardiographic technique, we sought to test the hypotheses that RV systolic pressure directly affects RV performance and that RV pressure/volume overload influences LV geometry, which in turn influences LV segmental function and torsion. We also hypothesized that these alterations will be more marked in the septum than in the lateral LV wall.

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Methods

Patients

Detailed transthoracic echocardiographic data were prospectively collected from 62 patients diagnosed with PH, defined by the Third World Symposium on Pulmonary Arterial Hypertension,[5] and family members of patients with familial pulmonary arterial hypertension (PAH). Of these 62 consecutive participants who provided informed consent, we included 51 patients with PH and family members who

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Stability of Plasma Anti-Xa Activity in Low-Molecular-Weight Heparin Monitoring

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Low-molecular-weight heparin (LMWH) is now the standard of care for prophylaxis and treatment of thromboembolic disorders. Only cases with renal failure, morbid obesity or extreme age require anti-Xa monitoring to assure the therapeutic level achievement. Because of infrequent requests, the test is usually sent to the reference laboratories and specimen handling may be delayed. Because LMWHs can be kept at ambient temperature for several days, we proposed that anti-Xa levels in plasma samples are similarly steady. Patients' plasma that was requested for anti-Xa activity was left at room temperature to repeat the test 24 hours later and compare with the result of immediate assay. The study included 86 fresh specimens from 56 participants. All patients received enoxaparin with anti-Xa levels ranging from 0.1 to 2.5 U/mL. Notably, anti-Xa activities significantly rose on the second occasions ($P = 8.4 \times 10^{-10}$). The mean change of anti-Xa was $+0.15 \pm 0.21$ U/mL ($+24.9\% \pm 37.4\%$). Children (age <15 years) showed more marked alterations than adults ($+40.9\%$ vs. $+18.2\%$, $P = .008$). There was no statistical difference in the degrees of changes between sexes and diagnoses. The data suggest that specimens sent for anti-Xa require prompt handling to prevent falsely elevated values. This observation is new and future research is needed to find the mechanism of this alteration.

Keywords: factor Xa; inhibitors; in vitro diagnostic systems; low-molecular-weight heparins

Introduction

Deep vein thrombosis (DVT) is a common disorder worldwide. This can lead to both potentially fatal pulmonary embolism (PE), and the chronic debilitating postthrombotic syndrome. Low-molecular-weight heparin (LMWH) is currently the standard initial treatment of DVT as it can be used daily via subcutaneous route as outpatients.[1] Apart from this convenience, subcutaneous LMWH is proven to be more effective and safe in a meta-analysis of randomized trials compared with intravenous standard heparin.[2] Furthermore, long-term LMWH has been shown to be the drug-of-choice for DVT in cancer patients. Not only it significantly reduces DVT recurrences,[3] but also prolonged survival in cases without demonstrable metastasis when compared with warfarin.[4,5]

In general, LMWH does not require monitoring. However, it is excreted via kidneys and may be accumulated after repeated injections in the presence of severe renal dysfunction. Deep vein thrombosis is more common in the elderly patients. These patients may have creatinine clearance below 30 mL/min, even with normal serum creatinine. This can lead to severe bleeding complications after regular doses of LMWH.[6] In addition, the optimal doses for pediatric patients have not been clearly defined. Therefore, dose modification and/or anti-Xa monitoring is necessary in these cases. In addition, LMWH dosing according to total body weights may overestimate the dose for patients with morbid obesity and anti-Xa assay is also recommended.[7]

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Effects of lifestyle modification on oxidized LDL, reactive oxygen species production and endothelial cell viability in patients with coronary artery disease

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ABSTRACT

Objectives: We evaluated the effects of lifestyle modification (LM) on lipid profile, oxidative stress and serum-stimulated human coronary artery endothelial cell (HCAEC) viability in coronary artery disease (CAD) patients after 6 months.

Design and methods: Thirty patients with CAD were randomly assigned to LM intervention ($n=15$) and usual care control ($n=15$) groups. LM-intervened patients were instructed to consume low-fat, high-antioxidants and fiber diets. Moderate exercise and stress management were also advised. Group support to maintain patients' compliance was applied.

Results: Serum cholesterol, triglyceride, oxidized LDL and protein carbonyl were decreased in LM group. Serum triglyceride was increased in control group. HCAEC viability was increased, while intracellular reactive oxygen species was decreased, by serum from the LM group.

Conclusion: LM is capable of improving lipid profile, reducing oxidative stress and increasing HCAEC survival in the patients with CAD, hence lowering a risk for the future cardiovascular event.

Introduction

Coronary artery disease (CAD) is one of the life-threatening diseases in all countries [1]. In 2004, the WHO reported that CAD is the leading cause of death with an estimation of 7.20 million people (12.2% of all death) died from the disease. Dyslipidemia, hypertension, obesity, diabetes mellitus, metabolic syndrome, smoking and sedentary lifestyle are well-known risk factors for CAD [2–7]. Dyslipidemia defined as increases in circulating total cholesterol, triglyceride, low-density lipoprotein (LDL) and decrease in high-density lipoprotein (HDL), is a prerequisite event in the development of atherosclerosis. It is well recognized that LDL oxidized by free radicals, called oxidized LDL (oxLDL), plays a critical role in the formation and progression of atherosclerotic plaques [8]. Increased plasma oxLDL is documented in CAD patients, and it is an independent predictor of developing cardiac events [9].

A decade ago, lifestyle modification (LM) was introduced as an alternative treatment for CAD in order to reduce mortality and improve quality of life of the patients. The LM approach basically focuses on dietary control, optimal exercise, weight reduction and stress management, aiming at normalization of the CAD risk factors. Amelioration of metabolic CAD risk factors by LM has been demonstrated in patients with metabolic syndrome [10]. In obese adults, LM effectively reduces body weight and markers of vascular inflammation and insulin resistance [11] as well as decreases metabolic CAD risk factors [12]. Intervention of LM is also capable of improving cardiovascular risk indices in HIV-infected patients with metabolic syndrome [13]. We previously reported that short-term intensive LM program increased circulating antioxidants and reduced oxidative stress in patients with CAD [14]. A short-term diet and exercise intervention (3 weeks) significantly reduced serum lipids and body mass index (BMI) in diabetic men, and their sera were shown to reduce reactive oxygen species (ROS) production in human coronary artery endothelial cells (HCAECs) [15]. Also in metabolic syndrome men, serum-stimulated ROS production in HCAECs was decreased after three-week diet and exercise intervention [16]. Hitherto, the effects of lifestyle change on serum oxLDL and intracellular production of ROS in CAD patients have not been investigated.

We aimed to evaluate the efficacy of LM intervention in ameliorating dyslipidemia and oxidative stress in CAD patients. Furthermore, an *in vitro* model was employed to examine the effects of sera from LM-intervened patients on HCAECs survival and ROS production.

Patients, materials and methods

Participants

Sixty patients with CAD admitted at King Chulalongkorn Memorial Hospital, Bangkok, Thailand, were initially recruited for the study. The

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MAJOR ARTICLE

Postexposure Rabies Prophylaxis Completed in 1 Week: Preliminary Study

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(See the report by Shantavasinkul et al., on pages 77–9.)

Background. Patients exposed to a rabid animal often travel long distances to receive postexposure prophylaxis (PEP), which requires 4 or 5 visits. Reducing the number of clinic visits would not only reduce costs for the patient but may also help increase compliance to receive complete PEP. We made an effort to develop PEP completed in 1 week.

Methods. We administered the 4-site intradermal injections of 0.1 mL of purified Vero cell rabies vaccine to the deltoids and thighs on days 0, 3, and 7, with and without equine rabies immunoglobulin (40 IU/kg). A control group received the World Health Organization–approved and widely used Thai Red Cross regimen (2-site intradermal injections on days 0, 3, and 7 and 1 injection on days 28 and 90) with equine rabies immunoglobulin. We then determined rabies neutralizing antibody (NAb) up to day 360.

Results. Geometric mean titers for subjects receiving the 4-site intradermal regimen, with or without equine rabies immunoglobulin, had significantly higher NAb values than did the control group on day 14 and 28 ($P < .001$). All subjects in all groups had a NAb value $\geq$0.5 IU/mL on days 14 and 28. The percentages of subjects who had a NAb value $\geq$0.5 IU/mL from days 0 through 360 were not significantly different among the 3 groups.

Conclusions. After any PEP regimen, World Health Organization recommendations require a NAb value $\geq$0.5 IU/mL on days 14 and 28. The 1-week PEP regimen, therefore, appears promising. It increased immunogenicity over the 2-site intradermal schedule, and it is convenient and can be used in small clinics, because it consumes almost the entire supplied vaccine ampoule volume.

Rabies is an acute progressive fatal encephalitis. The disease is caused by RNA viruses from the family Rhabdoviridae, genus *Lyssavirus,* of 7 genotypes. There are an estimated 60,000 human rabies-related deaths worldwide each year. Most occur in Asia and Africa [1]. Rabies is almost completely preventable, provided that postexposure prophylaxis (PEP) is implemented promptly after an exposure. PEP, for people bitten by rabid mammals, consists of a combination of aggressive wound cleansing, passive immunization with rabies immune globulin, and active immunization with a tissue culture rabies vaccine using 1 of 4 World Health Organization (WHO)–approved schedules. This has proven highly effective in preventing infections and deaths [2, 3].

An antibody concentration $\geq$0.5 IU/mL on day 14 [3] that is maintained throughout days 28 or 30 [4] is generally considered adequate. Detectable neutralizing antibody levels should be present for at least 1 year.

PEP has been shown to be effective in many studies for all 4 of the WHO-recommended regimens [5–9]. The immunogenic and effective Thai Red Cross intradermal regimen (TRC-ID) represents 60%–70% vaccine saving over the Essen conventional intramuscular method, and it is now well established in several countries where canine rabies is endemic [10]. It does not reduce total PEP costs because it does not reduce transportation expenses, loss of daily wages, and time loss [10, 11]. The original TRC-ID regimen, like the original

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Failure of Rabies Postexposure Prophylaxis In Patients Presenting with Unusual Manifestations

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(See the article by Shantavasinkul et al, on pages 56–60.)

We report an atypical case of paralytic rabies presenting with trismus followed by limb weakness, areflexia, ophthalmoparesis, and bilateral ptosis. Atypical presentations and history of rabies postexposure prophylaxis led to delayed diagnosis. Nucleocapsid and glycoprotein genes of rabies viruses from the patient's and biting dog's brains were of identical sequences.

Almost all rabies-related deaths, despite administration of postexposure prophylaxis (PEP), are related to deviations from World Health Organization (WHO) guidelines [1]. Nevertheless, true failures without recognized defects in management have been reported [2, 3]. We recently encountered another treatment failure case with atypical tetanus-like presentation.

Case report. A 33-year-old Thai man presented with a 2-day history of high-grade fever, sore throat, headache, and watery diarrhea. At the first hospital encounter, he had rigidity of the masseter muscles (lockjaw) and slurred speech. He had difficulty eating and drinking and was noted to have excessive salivation. Several diagnoses, including tetanus, were considered. He was subsequently transferred to a tertiary care hospital.

He experienced dog bites on his hands and right knee on 8 January 2009, 25 days earlier. Wounds included a 1-cm laceration on his right thumb that penetrated deep into the nail bed. He also had 2 puncture wounds (width, 0.2 cm) on his left hand and bleeding scratch wounds on his right knee. The dog was owned but never vaccinated. It was seen biting other dogs. The patient was attacked while catching the dog for veterinary observation. The dog died 3 days later and was proven to be rabid by fluorescent antibody test of brain specimens at the Queen Saovabha Memorial Institute (Bangkok, Thailand).

He underwent prompt local wound care at a nearby public health center. Rabies PEP was rendered within 6 h using the WHO-approved Thai Red Cross intradermal (ID) rabies vaccination schedule (modified TRC-ID regimen; 2-site ID injections on days 0, 3, 7, and 28). The vaccine used was purified chick embryo cell vaccine (Chiron Behring; batch 1630; potency, 8.94 IU/dose; expiration date, June 2012). The entire calculated dose of human rabies immunoglobulin (HRIG; 1300 IU per 8.7 mL; Berirab P; CSL; potency, 150–300 IU/mL; expiration date, September 2010) was infiltrated into and around all wounds at the same time as the first vaccination. In spite of much pain, this was also done to the wound at the nail bed by an experienced staff. Tetanus immunization was completed 1 year previously, so booster injection was not indicated. Purified chick embryo cell vaccination was continued on days 3 and 7 as scheduled. The patient also received another dose of HRIG (1300 IU) injected into the wounds on 12 January after positive results of the fluorescent antibody test of dog brain specimens became known. He became symptomatic 24 days after being bitten.

At admission, on 3 February, the patient was fully conscious and had a temperature of 39.6°C. He did not report any prodromal symptoms as often seen in rabies [4]. He refused to drink water and avoided exposure to light and draft. No phobic spasms were observed. Brief episodes of agitation alternating with lucid calm were noted. Trismus and hypersalivation were evident. Laboratory studies were unremarkable except for leukocytosis (white blood cell count, 12,200 cells/μL, with 85% neutrophils).

Lumbar puncture revealed a pleocytosis level of 1120 cells/mm^3 (82% monocytes, 18% neutrophils), a protein level of 95 mg/dL, and a sugar level of 70 mg/dL. Examination of cerebrospinal fluid (CSF), saliva, and urine specimens and hair follicles using a previously described method [5] for the detection of rabies viral RNA yielded negative results.

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Case report

The first case report of neuroacanthocytosis in Thailand: Utilization of a peripheral blood smear technique for detecting acanthocytes

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ABSTRACT

Background: Neuroacanthocytosis (NA) is a heterogeneous group of hereditary syndromes characterized by the association of neurological abnormalities with acanthocytosis. Among those, chorea-acanthocytosis (ChAc) is the most frequent form, manifested by predominant orofacial dyskinesias associated with marked dysarthria and dysphagia.
Purpose: To describe the first known case of ChAc in Thailand.
Methods and results: A 40-year-old man presented with "core features" of NA which led to a high level of suspicion of this syndrome. An initial dry blood smear did not reveal acanthocytes but by utilizing diluted blood combined with a wet blood smear, which is accepted as the clinical gold standard when combined with an examination, acanthocytes were detected.
Conclusion: Diagnosis of NA is possible without molecular diagnostics by relying on a high degree of clinical suspicion of characteristic clinical features and a standardized wet blood smear method of peripheral blood examination for acanthocytes.

1. Introduction

The term "neuroacanthocytosis" (NA) encompasses a genetically heterogeneous group of disorders, characterized by the association of neurological abnormalities with speculated "acanthocyte" red blood cells [1]. The following three groups of disorders have been recognized: (1) the "core" NA syndromes with neurodegeneration of the basal ganglia, comprising autosomal recessive chorea-acanthocytosis (ChAc) due to the mutation of *VPS13A* and X-linked McLeod syndrome (MLS) due to the mutation of the *XK* gene on the X chromosome; (2) conditions with decreased lipoproteins, namely abetalipoproteinemia and hypobetalipoproteinemia, in which the hallmarks are peripheral neuropathy and sensory ataxia due to dorsal column degeneration; and (3) conditions in which acanthocytosis is occasionally seen, such as pantothenate-kinase-associated neurodegeneration (PKAN) and Huntington's disease-like 2 (HDL2) [2,3] (Table 1).

Despite its recognition in the medical literature, the syndrome still is a neglected group of neurodegenerative disorders due to a low standard of suspicion by clinicians when confronted with the "core features" of NA and the suboptimal utilization of the peripheral blood smear (PBS) examination for detection of acanthocytes. We have demonstrated that NA can be reliably diagnosed if physicians maintain a high degree of suspicion of the disorder in a sporadic case of chorea without autosomal dominant family history and the use of a standardized wet blood smear method of peripheral blood examination for detection of acanthocytes (Table 2).

2. Case report

A 40-year-old Thai man presented with a 3-year history of oromandibular dyskinesia, associated with severe dyarthria and dysphagia. One year prior to this presentation obsessive–compulsive behavior was noted and, in addition, he was given a three-month course of haloperidol for a diagnosis of irritable mood and anxiety. His orofacial dyskinesias continued to progress, resulting in self-mutilation of the lips, tongue biting, and difficulty swallowing.

He reported that it was difficult to hold small things. He denied any history of seizures. An older brother had a psychiatric history but details were not available. No family member was known to have an involuntary movement disorder.

The examination revealed generalized chorea and dystonia with prominent oromandibular and lingual involvement. His speech was hypophonic, slurred, and frequently interrupted by lip-biting behaviors. Phonic tics, described as intermittent grunt sounds,

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Case series

HIV-related opsoclonus–myoclonus–ataxia syndrome: Report on two cases

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ABSTRACT

Opsoclonus–myoclonus–ataxia (OMA) syndrome is a rare neurological disorder, characterized by a rapid onset of generalized myoclonus in association with chaotic multi-directional eye movements and, less frequently, cerebellar ataxia. OMA is commonly related to a paraneoplastic process, specifically neuroblastoma in children and lung or breast cancer in adults. Nevertheless, OMA may occur in association with various infectious agents, such as Coxsackie virus B3, Epstein-Barr virus, mumps, enterovirus, and streptococcus. We recently encountered two cases of HIV-related OMA syndrome. The first patient developed a sudden onset of OMA at the time of HIV seroconversion. The second patient experienced severe ataxia with a mild degree of myoclonus and opsoclonus, associated with an elevated CD4 count following the initiation of highly active antiretroviral therapy (HAART). We suggest that OMA syndrome may be another rare manifestation of HIV infection at the time of seroconversion or during an immune restoration period.

1. Introduction

Opsoclonus–myoclonus–ataxia syndrome (OMA) is a rare neurological disorder characterized by multi-directional chaotic saccadic eye movements, accompanied by myoclonus and, less frequently, cerebellar ataxia [1]. Although the evidence for this is limited, in most cases this syndrome is paraneoplastic or idiopathic; however some are reported as a post-infectious mechanism related to a dysfunction of the humoral and cell-mediated immune mechanism [2–5]. The identification of the specific microorganism is very rare but OMA has been reported as occurring after infection with Epstein-Barr virus, Coxsackie virus B2 and B3, mumps, enterovirus, West Nile Virus, *Borrelia Burgdorferi* or streptococcus [6–11]. More recently, HIV-associated OMA has been described as a consequence of a deranged immune system when the CD4/CD8 ratio is reduced [12]. In this report we describe two HIV-infected cases presenting with OMA in different clinical settings: one at the time of probable seroconversion and the other as part of a possible immune reconstitution syndrome.

2. Case report

2.1. Patient 1

A previously healthy 25-year-old man developed a sudden onset of gait unsteadiness and body jerks following a two-week history of low-grade fever and malaise. During the subsequent week his symptoms gradually worsened to include unsteadiness, tremors, vomiting, vertigo and diplopia. A physical examination revealed opsoclonus and coarse bilateral hand tremor. He was totally bed-bound with marked truncal ataxia and myoclonic jerks of the face, head, trunk and all extremities to such an extent that he could not sit up in bed. The remainder of the general examination was otherwise unremarkable. The full blood count, chemistry, chest radiograph and MRI of the brain were all normal. Cerebrospinal fluid (CSF) analysis disclosed 26 cells/mm^3 with lymphocytic predominance, protein 97 mg/dl, and glucose 53 mg/dl. CSF polymerase chain reactions (PCR) for herpes simplex virus (HSV), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), pan-enterovirus, adenovirus and tuberculosis (TB) were all negative. The HIV ELISA Test, performed 24 h after admission, indicated that the patient was antibody positive in a low titer with a CD4 count of 952 cells/μL and a viral load of 30,200 copies/ml. The patient's symptoms improved with diazepam 5 mg/day and were almost resolved after three weeks. An examination, performed six months after the onset, revealed very mild opsoclonus and mild bilateral action tremor.

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Pharmacokinetics of low-dose protease inhibitors and efavirenz in low- and middle-income countries

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Purpose of review

The costs associated with antiretroviral therapy are becoming a major concern for the treatment of HIV-infected patients in resource-limited countries. Potential risk for the increase in toxicity due to higher drug exposure among Asians is also a concern. In this article, we discuss the studies performed using low-dose antiretroviral therapy as an effective and well tolerated strategy.

Recent findings

The studies reviewed demonstrate that dose reduction of antiretroviral therapy provides adequate plasma concentrations and effective immunological and virological responses in, mainly, a Thai population compared with whites. The differences in these pharmacokinetic parameters could possibly be due to differences in body weight and composition, drug–food interactions, metabolism, environmental factors and genetic background. Moreover, dose reduction can possibly decrease toxicity and save costs for patients in low- and middle-income countries.

Summary

Although the use of low-dose antiretroviral drugs showed adequate plasma levels in an Asian population, in particular, careful attention has to be given to pharmacokinetic, safety and efficacy data to avoid problems of subtherapeutic levels and drug resistance. Large, phase III studies are warranted.

Keywords

low-dose antiretroviral therapy, pharmacokinetics, resource limited, Thailand

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Introduction

According to the 2008 Report on the global AIDS epidemic, in 2007, there were an estimated 33 million people living with HIV, of whom 67% are from sub-Saharan Africa [1]. Despite the fact that sub-Saharan Africa remains the heavily affected region, HIV treatment trials were primarily investigated in Europe and the USA [2,3] and, therefore, the doses are more appropriate for whites. Moreover, the genetic differences in different population groups play a major role in antiretroviral drug pharmacokinetics [4•,5,6] and toxicity. In phase II studies, pharmaceutical companies often select relatively high doses of antiretroviral drugs to avoid subtherapeutic levels and drug resistance, as long as such a dose is tolerated well. However, for Asians, in whom the average body weight is lower than whites, they are more likely to experience antiretroviral drug-related toxicities [7,8]. Hence, it is rational to investigate the low-dose antiretroviral drugs in Asians to minimize toxicity while maintaining the antiviral efficacy. Likewise, for low- and middle-income countries, where access to antiretroviral drug is quite restricted, the lower doses in combination with generic formulations are more likely to save costs and increase access to antiretroviral therapy.

Pharmacokinetic and efficacy data on low-dose antiretroviral therapy

The accumulating information on pharmacokinetic data from various studies in low- and middle-income countries, mostly from Thailand, is presented below, using low-dose antiretroviral agents.

Low-dose indinavir

Indinavir (IDV) was one of the first protease inhibitors approved for use in HIV-infected patients. At present, the recommended dose of IDV with low-dose ritonavir in developed countries is 800/100 mg twice daily (b.i.d.). However, this protease inhibitor is not a preferable option for developed countries where other more favorable protease inhibitors are available. Despite the fact that IDV has a high incidence of renal toxicity, it remains one of the first priority protease inhibitors in some low- and middle-income countries. In Thailand, the major concern of IDV is the low body weight-related toxicities. Thus, the use of low-dose IDV is of special interest.

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Brief report

Urinary type IV collagen excretion predicts subsequent declining renal function in type 2 diabetic patients with proteinuria

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ABSTRACT

Baseline urinary type IV collagen excretion was negatively correlated with the subsequent GFR change ($r_s = -0.39$, $p = 0.04$) in our cohort of 30 type 2 diabetic patients with proteinuria. Therefore, it could be used to predict subsequent declining renal function in type 2 diabetic patients with proteinuria.

1. Introduction

Identifying diabetic patients who are at risk to have rapid renal progression would help us tailor appropriate treatment: more aggressive intervention for the 'progressor' and less toxic therapy for the 'non-progressor'. Urine type IV collagen is a specific marker for diabetic kidney injury [1–3]. It correlates with level of albuminuria, decreased renal function, and severity of diabetic renal pathology [3–7]. Therefore, urine type IV collagen is a potential biomarker for predicting the renal function decline in diabetic kidney disease. The objective of this study was to examine the correlation between urinary type IV collagen excretion and subsequent declining renal function in type 2 diabetic patients with proteinuria.

2. Materials and methods

The studied cohort consisted of 30 type 2 diabetic patients (age 43–86 years) with proteinuria (2.06 ± 1.48 g/gCr) enrolled from the outpatient clinic, King Chulalongkorn Memorial Hospital, between January and December 2003. Sixteen patients (53%) were female. Duration of diabetes was 13.7 ± 6.1 years.

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REVIEW

Nonalcoholic Fatty Liver Disease and the Coronary Artery Disease

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Abstract
Background Nonalcoholic fatty liver disease (NAFLD) is increasingly prevalent and is recognized as part of the metabolic syndrome (MetS). Patients with NAFLD have a lower life expectancy compared to the general population, with coronary artery disease (CAD) as the leading cause of death.
Aims We aim to address the epidemiological data of CAD, the possible pathogenesis or linkage mechanisms of NAFLD and atherosclerosis and the strategies to reduce the CAD risk in NAFLD patients.
Methods We reviewed data from a Medline and PubMed search which was performed to identify relevant literature using search terms "NAFLD," "metabolic syndrome" and "coronary artery disease."
Results Patients with steatohepatitis, a part of the spectrum of NAFLD, have more cardiovascular events than patients without steatohepatitis. However, the association between liver histological progression and the risk of CAD events is not linear. A multidisciplinary approach to NAFLD patients based on controlling related risk factors and monitoring for CAD risks and liver complications is necessary. The combination of lifestyle modification with pharmacological treatment tailored to each individual's risk factors needs to be considered. There is a need for more research on primary prevention for CAD in NAFLD patients and interventional studies for determining the nature of the relationship between NAFLD and CAD.
Conclusions NAFLD is recognized as part of the MetS and increases cardiovascular risks. Therefore, a multidisciplinary approach to these patients of controlling the related risk factors and monitoring for cardiovascular and liver complications must be done.

Keywords Coronary artery disease · Management · Nonalcoholic fatty liver disease

Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CAD	Coronary artery disease
DM	Diabetes mellitus
FRS	Framingham risk score
HDL-C	High density lipoprotein cholesterol
MetS	Metabolic syndrome
IR	Insulin resistance
NAFLD	Non-alcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis

Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in Western countries and is becoming more prevalent worldwide. The

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ORIGINAL ARTICLE

Concurrent bilateral pheochromocytoma and thoracic paraganglioma during pregnancy

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Abstract Although hypertension occurring during pregnancies is not uncommon and its prognosis is generally excellent, some of its unusual causes can lead to catastrophic consequences, especially in undiagnosed cases. Here, we report a pregnant woman who presented with hypertension in her early pregnancy. It was subsequently found to be caused by bilateral pheochromocytoma. After removal of both tumors, catecholamine levels unexpectedly and unexplainably remained elevated. At 23 weeks of gestation, the fetus was found dead in utero. After the fetal death, additional studies were performed and revealed a thoracic paraganglioma. To our knowledge, this is the first report of a case of three catecholamine-producing tumors occurring concurrently during a pregnancy. Genetic analysis helped identify this unprecedented condition; the patient harbored a heterozygous missense mutation c.482G>A in exon 3 of the *VHL* gene, indicating von Hippel-Lindau syndrome. Physicians who care for hypertensive pregnant patients should be aware of this condition as its diagnosis would probably lead to a better outcome.

Keywords *VHL* · Pregnancy · Bilateral pheochromocytoma · Paraganglioma

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Introduction

Pheochromocytoma and paraganglioma are catecholamine-producing tumors that are derived from the neural crest. Tumors that arise within the adrenal medulla are called pheochromocytoma while tumors that arise in sympathetic ganglia outside the adrenal gland are defined as extra-adrenal pheochromocytoma or paraganglioma [1]. The sympathetic or functioning paraganglioma are mainly located in abdomen and thorax. The term "paraganglioma" also include the tumors originated from parasympathetic ganglia, which are mainly in head and neck region and usually nonfunctioning [2]. Association of pheochromocytoma or paraganglioma with pregnancy are exceeding rare, with about 300 cases having been reported [3]. The simultaneous occurrence of both forms during pregnancy is even less common.

Pheochromocytoma or paraganglioma can occur as a sporadic case or as autosomal dominant inherited syndromes including von Hippel-Lindau (VHL) caused by germline mutations in the *VHL* gene; multiple endocrine neoplasia (MEN) type 2 caused by mutations in the *RET* gene; neurofibromatosis type 1 (NF-1) caused by mutations in the *NF1* gene; and the familial paraganglioma syndromes (PGL) caused by mutations in the *SDHB*, *SDHC,* or

compared with adults (Rheims et al., 2008). Several factors may explain this discrepancy. Our work analyzed trials with five AEDs assessed in both adults and children with partial epilepsy, whereas Beyenburg et al. compared the pooled effect of 14 AEDs in adults with that of only 5 AEDs studied in children with different epilepsy syndromes. In addition, we assessed responder rates in an intention-to-treat (ITT) analysis over the whole treatment period, whereas Beyenburg et al. in Figure 2 seem to have used in many trials a modified ITT or a per-protocol analysis. Beyenburg et al. used risk differences, whereas we used relative risk, which provides more robust estimates than absolute measures (Deeks, 2002). In fact, the heterogeneity between the same five pediatric trials was greater in the model of Beyenburg et al. (I^2 = 62%) than in our model (I^2 = 31%), which might indicate inadequate model fit (Deeks, 2002).

Overall, we believe that meta-analyses should be performed on datasets comparable in terms of effective (or most effective) doses, seizure type, and efficacy endpoints. Efficacy data should ideally focus on completers to avoid the bias deriving from LOCF analysis, and editorial policies should be standardized to ensure that authors disclose in their publications those datasets that are most meaningful clinically.

Disclosure

We have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Sylvain Rheims has received speaker fees from Pfizer.

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HLA-B 1502* screening: Time to clinical practice

To the Editors:

Association between *HLA-B*1502* and carbamazepine (CBZ)–induced Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) has recently been reported in certain Asian populations (Han Chinese, Thai, and Malay) (Chung et al., 2004; Hung et al., 2006; Man et al., 2007; Chang et al., 2008; Locharernkul et al., 2008; Tassaneeyakul et al., 2010). Summation of the linkage from all documents showed an odds ratio (OR) of 84.75 [95% confidence interval (CI) 42.53–168.91; p = 8.96*10E-15], the strongest HLA correlation ever been found in human disorders, with 98% negative predictive value, 92% sensitivity, and 4.2–19% false positivity. The association was not found in studies of Caucasian and Japanese patients (Alfirevic et al., 2006, Lonjou et al., 2006; Kaniwa et al., 2008; Ikeda et al., 2009), making *HLA-B*1502* a genetic biomarker for CBZ-induced SJS/TEN with ethnic preponderance. These Asian studies are from the region having high *HLA-B*1502* allele frequency (10–15% in Asians vs. 1–2% in Caucasians) and high incidence of SJS/TEN (17–25: 10,000 in Thailand and Taiwan vs. 1–6: 10,000 in Caucasians) (Tennis & Stern, 1997; Mockenhaupt et al., 2005, Hung et al., 2006; Locharernkul et al., 2008).

To prevent susceptible individuals from life-threatening SJS/TEN, it is time to implement *HLA-B*1502* screening before prescribing CBZ (FDA 2007, FDA 2008). The ethnic preponderance of the association helps to guide determinations of which populations should be screened. The benefit is most obvious in ethnic groups showing strong association (eastern China, Taiwan, Thailand, and Malaysia). The biomarker testing may also be useful in those carrying high *HLA-B*1502* allele (Singapore, Vietnam, Indonesia, the Philippines, southwestern India) as well as in people of Asian ancestry in other continents (FDA 2007). The yield is apparently low in populations showing no genetic susceptibility (Japanese and some Caucasians). However, no estimation of the screening advantages can be made in those for which *HLA-B*1502* prevalence and the genetic susceptibility are unknown.

Most of the allergic reactions develop within the first 2 months after starting CBZ (Tennis & Stern, 1997). Those who use CBZ for more than 3 months without allergy are

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CARDIOVASCULAR FLASHLIGHT

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Rare angiographic and echocardiographic findings of an aortic arch interruption in a patient with differential cyanosis

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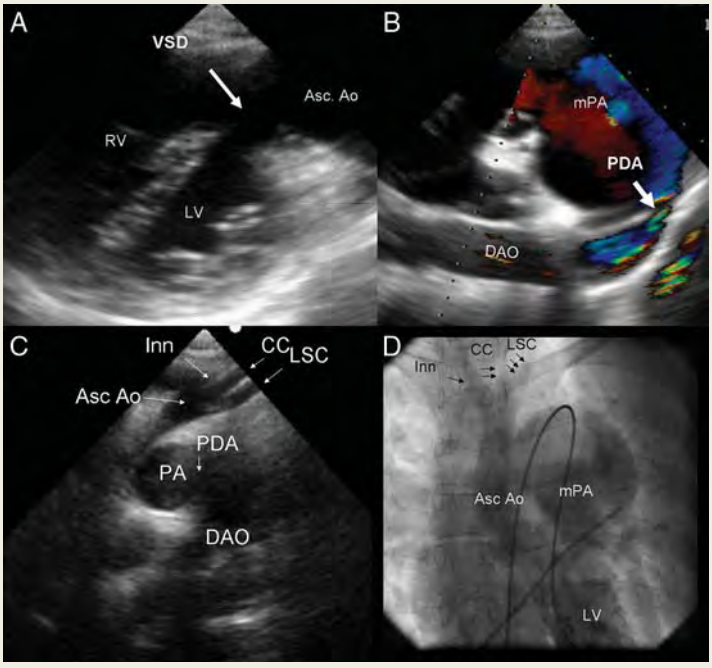

A 23-year-old lady with a 3-year history of undiagnosed murmur and progressive dyspnoea was referred to our institution for a percutaneous patent ductus arteriosus (PDA) closure. Physical examination revealed differential cyanosis with an oxygen saturation in the upper and lower extremity of 95 and 86%, respectively. A loud P2 with a grade 3/6 systolic murmur was audible at the second left intercostal space with radiation to the back. An echocardiogram revealed a non-restrictive ventricular septal defect (*Panel A*, arrow) with an overriding aorta and a large PDA (*Panel B*, arrow) with a diminished diastolic flow. A suprasternal view demonstrated an aortic arch interruption (type A) (*Panel C*) and aortic discontinuity distal to the left subclavian artery. A left ventriculography confirmed an interrupted aortic arch with a clear separation between three branches of aortic arch and the descending aorta (*Panel D*). A right heart catheterization revealed severe fixed pulmonary hypertension with a mean pulmonary artery pressure of 92 mmHg and pulmonary vascular resistance of 11 Woods units. Since the patient had fixed pulmonary hypertension, the surgical correction was unfortunately not performed. The patient was then referred to heart and lung transplantation.

This case highlights the essence of left heart or aortic obstruction, i.e. interrupted aortic arch or coarctation of the aorta, when PDA is discovered. Failure to identify aortic arch interruption in this case of attempted PDA closure will lead to catastrophic lower-half ischaemia.

Panels A–D. Asc Ao, ascending aorta; CC, left common carotid artery; DAO, descending aorta; LV, left ventricle; LSC, left subclavian artery; mPA, main pulmonary artery; PDA; patent ductus arteriosus; Inn, innominate artery, VSD, ventricular septal defect; RV, right ventricle.

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Review

Venous thromboembolism in multiple myeloma: Current perspectives in pathogenesis

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ABSTRACT

Patients with multiple myeloma are at increased risk of venous thromboembolism (VTE) compared to the general population. The introduction of immunomodulatory agents, such as thalidomide and lenalidomide, substantially increases the incidence of VTE in multiple myeloma patients, especially when used in combination with high-dose dexamethasone and/or anthracycline-based chemotherapy. Thromboprophylaxis is recommended for reducing VTE in patients receiving immunomodulatory agent-based regimens. On the other hand, bortezomib, a proteasome inhibitor, is not associated with an increased risk of VTE, as observed by a very low incidence of thrombotic complications in the absence of thromboprophylaxis. Currently, the mechanisms underlying the impact of these agents on VTE are not well-understood. Further studies to investigate the pathogenesis of VTE in multiple myeloma are warranted. These studies may not only yield greater insight into the pathogenesis of disease but may also define novel targets for the prevention and treatment of thromboembolic events in patients with multiple myeloma.

1. Introduction

Multiple myeloma is a clonal plasma cell neoplasm accounting for 15% of haematologic malignancies and 1% of all cancers. There are approximately 20,000 new cases and 10,000 estimated deaths per year in the United States.[1,2] Multiple myeloma remains an incurable disease, but the advent of novel agents, such as immunomodulatory drugs (IMiDs) and proteasome inhibitors, has significantly improved clinical outcomes including survival.[3] However, IMiD administration has been associated with a remarkable rise in the incidence of thromboembolic events.[4,5] Although a recent retrospective study demonstrated that venous thromboembolism (VTE) development in patients with multiple myeloma who received lenalidomide and high-dose dexamethasone did not affect overall survival and time to progression, this may be explained by the favourable impact of lenalidomide on survival.[6] Furthermore, despite the absence of data that VTE impacts survival in multiple myeloma, it could certainly have an impact on the quality of life and the cost of treatment.

Previously, thromboembolic events were less emphasised than bleeding complications in patients with haematologic malignancy. However, a recent large population-based study demonstrated that patients with haematologic malignancy, especially multiple myeloma, carry the highest risk of VTE – up to 28-fold compared to persons without malignancy

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EXPERT REVIEWS

Ante- and post-mortem diagnosis of rabies using nucleic acid-amplification tests

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Sensitivity, specificity and short turn-around time nucleic acid-amplification tests (NATs) have been steadily improving. NATs have been employed in the diagnosis of rabies to distinct different strains, as well as to identify new lyssaviruses. NATs have advantages over traditional methods, such as the direct fluorescence antibody test. They can be applied to fluid samples and brain tissue that is substantially decomposed. NATs can be used as an alternative method for confirmation or exclusion of the diagnosis in a suspected rabies patient. Real-time PCR methods are more favored than conventional reverse-transcription PCR methods by several laboratories. Second-round PCR, either nested or heminested, has been used for ante-mortem diagnosis to detect low levels of RNA. This review the details obstacles in making a diagnosis, how to properly utilize NATs (sample preparation, nucleic amplification techniques, amplification targets and primer design); and interprets the results obtained in recent studies.

Keywords: ante-mortem • detection • diagnosis • nucleic acid amplification • PCR • post-mortem • rabies • real-time PCR

Rabies remains a neglected disease. This is true especially in canine rabies-endemic regions of Asia and Africa. It has been estimated by the WHO that 55,000 individuals (~30,000 in India alone) die of rabies each year [1]. The actual number of human deaths must be higher than what the WHO estimates since several rabies-endemic regions have not submitted any reports [101]. This under-reporting can be readily explained by the fact that rabies is not classified as a notifiable disease in many countries especially those where reliable diagnostic facilities are lacking [2,3]. Rabies in large parts of the world is diagnosed based on clinical grounds alone, which are not reliable. This poses problems in prioritizing the importance of this disease and results in judgment errors by policy makers.

It has been increasingly known that rabies in humans presents in different clinical forms. The classic forms are furious and paralytic rabies. Although the latter has been recognized for many decades, misdiagnoses still occur leading to transplantation of tissues or organs [4,5]. Paralytic rabies is usually confused with Guillain–Barre syndrome and poliomyelitis-like illness from arboviruses [6]. Even in the case of furious rabies, cardinal manifestations, such as phobic spasms, may not be present [7]. Stages of the disease (early or comatose), nature of viral genotype and nature of virus variant (dog or bat despite belonging to the same genotype 1), inadequate history taking, lack of bite exposure history and disease ignorance can cloud judgments of physicians confronted by a rabies patient [7]. In addition, atypical forms have been reported in association with bat and dog variants.

Post-mortem diagnosis of rabies is essential to formulate control programs, epidemiologic surveys and prophylactic measures. Post-mortem examination using the direct fluorescence antibody (DFA) test on brain impression smears is the gold standard [8], with direct rapid immunohistochemical test (dRIT) as an optional test [9], and the rabies tissue culture infection test (RTCIT), the mouse inoculation test (MIT) or ELISA technique [10] as confirmatory methods. The sensitivity of these methods can be reduced, especially when the brain tissues submitted for testing are decomposed. In such cases, the nucleic acid-amplification tests (NATs) are preferable, as they have a higher sensitivity compared with DFA/MIT. NATs are as specific as DFA and can be completed faster than MIT or RTCIT with superior sensitivity [11,12]. They can

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The Predictors of the Presence of Varices in Patients with Primary Sclerosing Cholangitis

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The predictors for developing varices in patients with primary sclerosing cholangitis (PSC) have not been well studied prospectively. We sought to define the predictors for the presence of varices at baseline and for newly developing varices in patients with PSC. We used prospectively collected data from a multicenter randomized trial of high dose ursodeoxycholic acid for PSC. All 150 patients enrolled were reviewed for predictors of varices and we excluded 26 patients who had esophageal varices at baseline so that predictors of newly developing varices could be determined. Clinical examination, blood tests, and upper endoscopy were done before randomization, at 2 years and after 5 years. Liver biopsy was performed at entry and at 5 years. The median age (interquartile range) of patients was 45.9 years (35.8, 54.9). In a multivariable logistic regression, a higher Mayo risk score (≥0.87) or a higher aspartate/alanine aminotransferase (AST/ALT) ratio (≥1.12) were significantly associated with the presence of varices at initial endoscopy (odds ratio = 1.9 and 3.9). By the end of the study, 25 patients had new varices (20.2%). In a Cox model, after adjustment for baseline variables lower platelet count and higher total bilirubin at 2 years were significantly associated with the presence of new varices. The platelet count of 205 ($\times 10^9$/L) and the total bilirubin level of 1.7 mg/dL were the best cutoff values for the detection of new varices. *Conclusion:* A higher Mayo risk score and higher AST/ALT ratio were significantly associated with the presence of varices at initial endoscopy. Lower platelet count and higher total bilirubin at 2 years were significantly associated with an increased risk of developing new varices in patients with PSC. (HEPATOLOGY 2010;51:1302-1310.)

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown etiology characterized by fibrosing inflammation and destruction of the extrahepatic and/or intrahepatic bile ducts. No effective medical therapy exists for patients with PSC.[1] The diseases progresses slowly and usually leads to biliary cirrhosis, portal hypertension, and liver failure over 10-15 years with significantly shorter survival than people of similar age and sex.[2] A previous study showed that 36% of patients with PSC had esophageal varices (EV) at the time

Abbreviations: ALP, alkaline phosphatase; ATL, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; CI, confidence interval; EV, esophageal varices; OR, odds ratio; NPV, negative predictive value; PPV, positive predictive value; PSC, primary sclerosing cholangitis; ROC, receiver operating characteristic; TB, total bilirubin; UDCA, ursodeoxycholic acid.

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Potential conflict of interest: Dr. McCashland is on the speakers' bureau of Roche.

Additional Supporting Information may be found in the online version of this article.

INTERNAL MEDICINE

□ PICTURES IN CLINICAL MEDICINE □

Craniofacial Fibrous Dysplasia

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Key words: fibrous dysplasia, craniofacial

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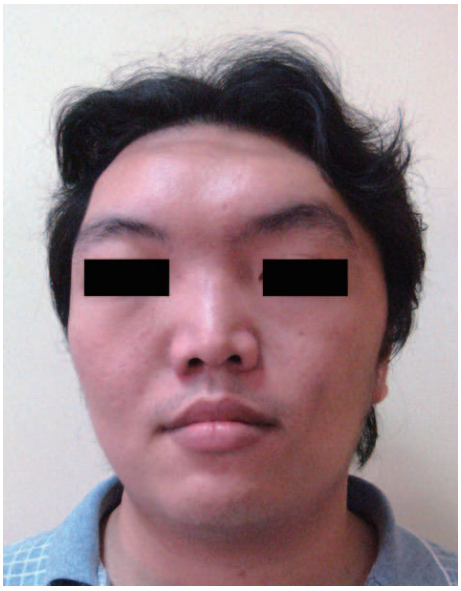
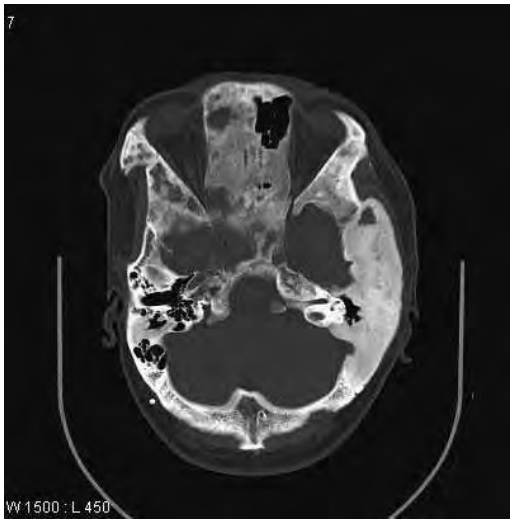


Picture 1. **Preoperative view of the patient. Note the *leontiasis ossea* or "lion face" with asymmetrical facial features.**



Picture 2. **A CT scan (axial view) in the bone window. An expansile lesion with a heterogenous pattern including lucent zones plus areas of ground-glass opacity involving multiple craniofacial bones was revealed.**

A 25-year-old man with a slowly progressive facial asymmetry presented with hearing impairment and severe headache, especially over the deformed bones, during the past year. Physical examination revealed asymmetrical facial features (Picture 1) with complete occlusion of the left ear canal. Fibrous dysplasia (FD) was diagnosed by radiological (Picture 2) and histopathological (Picture 3) findings. He underwent frontal bone cranioplasty with uneventful outcome. His bone pain was dramatically improved. Extensive bone scans as well as endocrine assessments were unremarkable.

FD is a benign and progressive osseous disorder in which normal medullary bones are replaced and expanded by abnormal fibro-osseous tissue (1). It may affect one (monostotic) or multiple bones (polyostotic) and may represent part of McCune-Albright syndrome (polyostotic FD, café-au-lait spots and endocrinopathy). It is caused by an activating somatic mutation of the *GNAS1* gene, resulting in a substitution of cysteine or histidine with arginine in a position 201 in the $G_{s\alpha}$ protein.

Craniofacial FD typically manifests before the fourth decade of life. Most patients have functional and cosmetic complaints such as facial swelling or asymmetry, facial pain and paresthesias as well as compressive symptoms namely nasal obstruction, sinusitis, hearing loss and visual disturbances (2). The mixture of fibrous and osseous elements in FD causes the characteristic homogenous "ground glass" appearance with ill-defined borders by radiographic study. The affected bone is sometimes widened, and it may appear scle-

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ORIGINAL ARTICLE

Glutathione as an oral whitening agent: A randomized, double-blind, placebo-controlled study

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Abstract

Objective: To determine whether orally administered glutathione, 500 mg per day for 4 weeks, affects the skin melanin index, when compared with placebo. *Methods*: This randomized, double-blind, two-arm, placebo-controlled study was set in the King Chulalongkorn Memorial Hospital, Bangkok, Thailand, a teaching hospital affiliated with a medical school. Sixty otherwise healthy medical students were randomized to receive either glutathione capsules, 500 mg/day in two divided doses, or placebo for 4 weeks. The main outcome was mean reduction of melanin indices measured at six different sites. Several secondary outcomes, including UV spots, were recorded by VISIA™. Efficacies of glutathione and placebo were compared by ANCOVA with baseline values as co-variates. *Results*: Sixty participants enrolled and completed the study. At 4 weeks, the melanin indices decreased consistently at all six sites in subjects who received glutathione. The reductions were statistically significantly greater than those receiving placebo at two sites, namely the right side of the face and the sun-exposed left forearm (p-values = 0.021 and 0.036, respectively). This was similarly reflected in the changes in the number of UV spots, as measured by VISIA. Both glutathione and placebo were very well tolerated. *Conclusion*: Oral glutathione administration results in a lightening of skin color in a small number of subjects. However, long-term safety has not been established and warrants more extensive clinical trials.

Key words: *glutathione, melanin, melanin index, melanogenesis, whitening*

Introduction

The grass is always greener on the other side of the fence. Many fair-skinned individuals do all they can just to be tanned, while people with skin of color are continually in search of a miracle whitening or lightening agent.

Topical, oral and even intravenous 'whitening' agents of various natures and mechanisms of action are widely available. Numerous topical agents acting on various steps before, during or after melanin biosynthesis (1) and sunscreening agents are widely used for facial lightening purposes.

Because total-body skin lightning is often desired, oral agents have also been widely popular. One such agent used in many parts of Asia, especially Japan, is tranexamic acid. However, the safety of long-term use of this plasmin inhibitor has never been adequately demonstrated. Another interesting agent is glutathione, a cysteine-glycine-glutamate tri-peptide, which exerts several effects on melanogenesis through different mechanisms involving the functions and cellular transport of tyrosinase, the rate-limiting step enzyme in melanin formation (2). Importantly, it is well-known that when glutathione or cysteine is added to melanocytes or melanoma cell lines, the melanogenetic pathway is shifted from eumelanin towards pheomelanin formation.

After oral dosing, glutathione is not well absorbed from the gastrointestinal tract and intravenous administration has thus been used in many counties, especially in southeast Asia. Recently, there has been a

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Pimecrolimus for Idiopathic Guttate Hypomelanosis

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ABSTRACT

Idiopathic guttate hypomelanosis (IGH) is a very common skin disorder, although the precise prevalence of which is unknown. There are no universally safe and efficacious treatments for this condition. The authors report the success of 1% pimecrolimus cream in inducing repigmentation is this hypomelanotic disorder.

INTRODUCTION

Several studies have documented the role of topical calcineurin inhibitors, namely pimecrolimus[1,2] and tacrolimus[3-5] for the treatment of vitiligo. For the treatment of other leukodermas, including idiopathic guttate hypomelanosis (IGH), their roles are less well studied.

Although IGH is a harmless condition, patients affected often seek treatments, which, in most cases, are of no clinical benefit. Several treatments—including cryotherapy, topical retinoids and superficial dermabrasion—have been reported with variable success rates. The authors report the promising results of topical pimecrolimus in the treatment of IGH.

Report of Four Cases

Four female patients all of skin type IV, whose ages ranged from 45–73 years, were seen at the dermatology clinic of King Chulalongkorn Memorial Hospital (Bangkok, Thailand) for small hypopigmented macules on sun-exposed areas of the forearms, for which no treatments had been previously given. Patients were advised to apply pimecrolimus 1% cream (Elidel, Novartis Pharmaceuticals, East Hanover, NJ) twice daily to the lesions on one forearm, while the contralateral forearm was left untreated. Topical applications of moisturizers and sunscreens were allowed, given that these agents were applied to both forearms. Patients' assessment and digital photography took place every four weeks for 16 weeks. The clinical response was graded as follows: no improvements, 1–25% improvement, 26–50% improvement, 51–75%, improvement and 76–100% improvement. A blinded evaluator graded the clinical response from digital images, using the same scoring system, at the end of the study.

Compliance was excellent in all subjects. The lesions improved by 25–75%, as judged by the patients and physician, in three patients, who were very satisfied with the results. The improvement was first noticeable within eight weeks of treatment. The typical response is shown in Figures 1 and 2. In one patient, no clinically apparent improvement was seen. In this particular patient the lesions were better circumscribed and more depigmented than were those in other patients. No stinging sensation or other adverse effects were observed.

DISCUSSION

Calcineurin inhibitors exert their effects primarily through immunomodulatory pathways, however, other mechanisms may also be involved. Recently, Grimes and co-workers demonstrated that there are certain cytokine changes following topical application of calcineurin inhibitor to vitiliginous lesions, such as decrease in TNF alpha expression.[5] Moreover, it was reported that the supernatant from tacrolimus (FK-506)-treated keratinocyte cultures had direct stimulatory effects on melanocytes and melanoblasts, probably via the creation of a favorable milieu for cell growth and differentiation.[6] Most recently, tacrolimus

FIGURE 1. Patient at baseline.

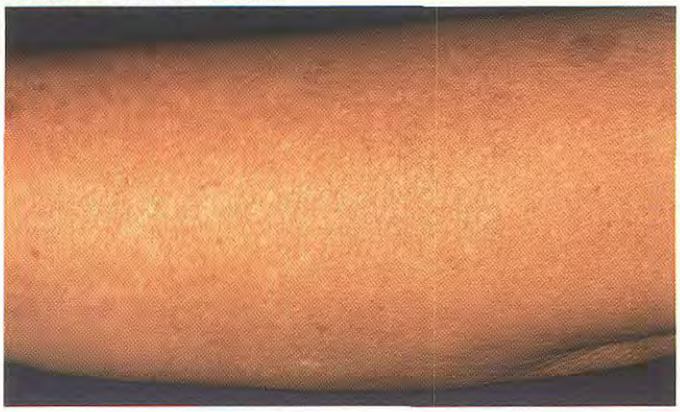
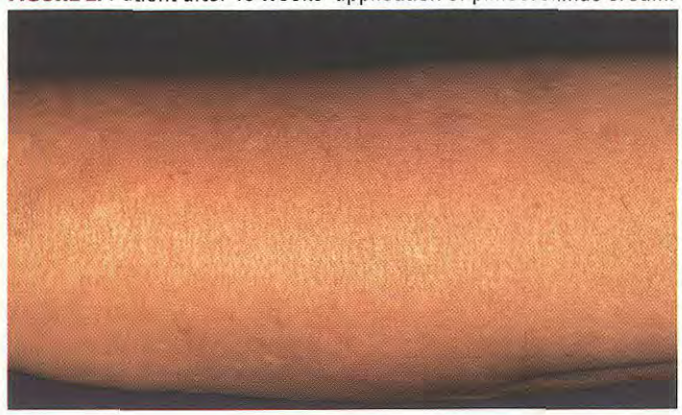


FIGURE 2. Patient after 16 weeks' application of pimecrolimus cream.



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HEPATOLOGY

A comparison of diagnostic efficacies among different reagent strips and automated cell count in spontaneous bacterial peritonitis

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Key words
automated cell count, diagnosis, reagent strip, spontaneous bacterial peritonitis.

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Abstract

Background: Currently, decision to give antibiotics in spontaneous bacterial peritonitis (SBP) suspected patient depends mainly on the result of manual cell count, which requires significant waiting period. Recently, many reports on the efficacies of reagent strips and a few reports of automated cell count are available but there has been no direct comparison study.

Aims: This prospective study was to assess the diagnostic efficacies of different reagent strips (Aution, Multistix, Combur) and automated cell count.

Methods and Results: A total of 250 paracenteses were performed. There were 40 specimens obtained from patients with clinical suspicion for SBP, the rest were obtained from non SBP suspected patients. Thirty specimens from 250 samples (12%) were diagnosed as SBP by manual cell count. Automated system provided higher value for SBP diagnosis in all parameters (sensitivity, specificity, PPV, NPV, and accuracy; 87.5–99.1%) whereas the strip tests provided lower number in all parameters (80–98.6%). Multistix provided the lowest sensitivity (80%). The false negative rates by Aution, Multistix, Combur tests and automated cell count were 10%, 20%, 10% and 3.3%, respectively. By lowering the cut off for SBP diagnosis with the automated system to 200 cells/mm^3, there was no false negative.

Conclusions: Comparing to reagent strips, automated cell count is a better screening tool for SBP diagnosis because it provides higher validity scores and a lower false negative rate. However, the discrepancy of cell count reading may occur, we suggest using a lower cut off for SBP diagnosis by the automated system.

Introduction

Cirrhotic with ascites is prone to develop spontaneous bacterial peritonitis (SBP). The overall prevalence of SBP in cirrhotics presenting to hospital varies from 10–30%.[1–3] In addition, the prevalence of SBP in asymptomatic cirrhotics undergoing a routine large volume paracentesis is also significant (3.5%).[4] The standard criteria for SBP diagnosis are an ascitic fluid polymorphonuclear (PMN) cell count of equal to or greater than 250/mm^3 with or without a positive ascitic fluid bacterial culture.[5] The available guideline from the International Ascites Club has suggested that all patients with ascites who got admitted should undergo for paracentesis.[6] In addition, empirical antibiotic treatment for SBP should be started when there is an elevated ascites PMN count. However, a prompt result of ascitic fluid cell count is not possible in practical setting. On the other hand, ascitic fluid culture result always takes day to week thus it can not be used as a screening tool. In addition, majority of patients with positive culture without PMN elevation (bacterascites) generally recover without a need for treatment.[7]

In search for rapid SBP diagnostic tests that based on PMN cell count, the only two techniques showing promising results are regent strip test and automated cell count. With difference in colorimetric scales, many reagent strips showed various acceptable results in efficacies.[8–13] Likewise, automated cell count provides almost perfect validity scores and is rapidly available when manual cell count is referred as a gold standard.[14,15] In the earlier year, many studies had shown the excellent efficacy of reagent strips in diagnosing SBP.[8–13] However, recent data have been accumulated and raised a word of caution on the use of these devices due to a high risk of false negative results.[16] To date, there has been no report on direct comparison of these two techniques for rapid diagnosis of SBP. The aim of this prospective study was to assess the diagnostic accuracies of different reagent strips (Aution,

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HEPATOLOGY

Ursodeoxycholic acid and artesunate in the treatment of severe falciparum malaria patients with jaundice

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Key words
artesunate, falciparum malaria, jaundice, ursodeoxycholic acid.

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Abstract

Background and Aims: *Plasmodium falciparum* (PF) infection can lead to severe complications. Ursodeoxycholic acid (UDCA) is increasingly used for the treatment of cholestatic liver diseases. The present study aims to determine the effects of combined UDCA and artesunate compared to placebo and artesunate on the improvement of liver tests in severe PF jaundiced patients.

Methods: All severe PF jaundiced patients, aged ≥ 15 years and diagnosed as having severe malaria according to WHO 2000 criteria, were enrolled. Patients with evidence of biliary obstruction, other cholestatic liver diseases and those who were pregnant were excluded. Patients were randomized to receive either oral UDCA or placebo for 2 weeks in additional to artesunate. All patients were admitted for at least 14 days to monitor the result of the treatment.

Results: Seventy-four severe PF malaria patients with jaundice were enrolled. Both groups had similar demographic and laboratory tests, with the exception being more males in the UDCA group than in the placebo group ($P = 0.04$). The median of percentage change of total bilirubin and aminotransferase levels at the end of weeks 1, 2, 3 and 4 showed no difference between the two groups. Only the median of percentage change of alkaline phosphatase at the end of week one compared with the baseline values showed less increment in the UDCA group than in the placebo group ($P = 0.04$). No serious adverse events were seen during the 4 weeks of follow up.

Conclusions: In severe PF malaria patients with jaundice, combined therapy with UDCA and artesunate is safe, but does not significantly improve liver tests compared to placebo and artesunate.

Introduction

Plasmodium falciparum (PF) infection causes severe complications, including acute renal failure (ARF), pulmonary edema and jaundice.[1] The standard antimalarial treatment in Thailand and South-East Asia are artemisinin derivatives; for example, artesunate[2,3] or quinine. Intravenous artesunate is an effective antimalarial therapy and has been shown to be significantly more effective than quinine in the treatment of severe malaria.[4,5] The proportions of patients with severe PF malaria with jaundice have been reported to be 20%–32% of PF malarial infection.[6,7] The liver histology of malarial hepatitis is characterized by the presence of Kupffer cell hyperplasia and the deposition of malarial pigment, as observed in 46% of PF malarial patients with jaundice.[8] The pathophysiology of malarial hepatitis has been linked to two mechanisms: hemolysis and injured hepatocytes.[9] The mean serum total bilirubin (TB) was 10.4–12.7 mg/dL with the range of TB varying from 3 to 64 mg/dL.[6–8,10] The presence of intrahepatic cholestasis can persist for several weeks.[7,11] Jaundice and hepatomegaly in PF malarial patients were significantly associated with ARF.[12] These findings were confirmed by subsequent studies and concluded that concomitant jaundice indicates a more severe illness with higher incidence of complications and higher mortality rate.[11–14]

Dash *et al*. reported nine patients who had acute PF malaria with severe hyperbilirubinemia and ARF. All of them had evidence of intrahepatic cholestasis and needed hemodialysis for several weeks.[11] The course of cholestasis, the intrahepatic accumulation of hydrophobic bile acids, is thought to induce liver damage.[15] Currently, ursodeoxycholic acid (UDCA) is increasingly used for the treatment of cholestatic liver diseases. Its mechanisms can be related to the protection of cholangiocytes against cytotoxicity of hydrophobic bile acids, stimulation of hepatobiliary secretion into the canalicular membrane of the hepatocyte and the protection of hepatocytes against bile acid-induced apoptosis.[16] UDCA has been

Pharmacokinetics of mycophenolic acid in severe lupus nephritis

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Mycophenolic acid (MPA) is an effective treatment for active lupus nephritis despite its variable efficacy in different ethnic groups. Here we tested whether pharmacokinetic monitoring may help to optimize dosing of MPA in an Asian population. Patients with biopsy-proven class III or IV lupus nephritis (ISN/RPS category) were treated with mycophenolate mofetil or enteric-coated mycophenolate sodium. One month after initiating treatment we measured plasma MPA levels in eight samples taken over a 12-h period after drug administration. The mean area under the time-dependent curve for MPA of responding patients was significantly higher than those not responding. Successful treatment was seen in patients with areas >45 mg h/l. The dosage of the drug was not related to MPA pharmacokinetics. In the mycophenolate mofetil group, however, MPA-area under the curve was positively, and significantly, correlated with trough or 1 h after dose concentrations and associated with a therapeutic response. Thus, our study shows that MPA pharmacokinetics were positively correlated with therapeutic responses of mycophenolate, suggesting that controlling the concentrations may improve its therapeutic efficacy in lupus nephritis. As the absorption and pharmacokinetic peak of enteric-coated tablets is slower, it is important to take different formulations into account when determining optimal MPA concentrations.

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KEYWORDS: glomerulonephritis; immunosuppression; lupus nephritis; mycophenolate mofetil; pharmacokinetics

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Proliferative lupus nephritis (International Society of Nephrology/Renal Pathology Society class III/IV categorization) is the most common and serious complications of systemic lupus erythematosus (SLE). Without the appropriate treatment, this complication can turn into an end-stage kidney disease within a few months. The standard of care for lupus nephritis is cyclophosphamide and steroids, even though it has many drug-related adverse events.[1] The most common causes of death for SLE patients are fatal infections acquired in consequence of using immunosuppressive therapy.[2] Therefore, a more effective and safer treatment for lupus nephritis is needed.

Recently, the first-line treatment for proliferative lupus nephritis cyclophosphamide was replaced by mycophenolate mofetil (MMF), because its efficacy was comparable and less toxic.[3–10] Furthermore, results from a recent multicenter, randomized-controlled study showed that African Americans responded poorly to cyclophosphamide.[6] In contrast, the results from the Aspreva Lupus Management Study showed that Asians responded equally well to both MMF and cyclophosphamide, even though there were more deaths reported in the MMF group.[11] It should be noted that the Aspreva Lupus Management Study trial was the largest multinational study in lupus nephritis, which increased target MMF dose to 3 g per day. Although most studies used 2 g per day of MMF,[1,3,4] the high-targeted MMF dose in this Aspreva Lupus Management Study trial may be too much, particularly for Asians. It has been pointed out that ethnicity may partly explain the different pharmacokinetic profiles seen in MMF and variation in the treatment responses.[6,11] Therefore, therapeutic drug monitoring (TDM) study may help to optimize dosing of MMF in different ethnicities.

It has been shown that TDM of mycophenolic acid (MPA) can improve clinical outcomes in organ transplant recipients.[12] Acute rejection rate was reduced in kidney allograft recipients, who had achieved MPA therapeutic levels consistently and early after transplantation. Similar to that observed in organ transplant recipients, severe lupus nephritis also requires early and maximal therapeutic efficacy to stop the inflammation process. As MMF became the mainstay immunosuppressive drug with steroid minimization, thus we determined the correlation

The Au Article Reviewed

Extranodal NK/T-cell Lymphoma: Basic Questions Remain

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Extranodal natural killer/T-cell lymphoma (ENKTL), nasal type, is a distinct entity of non-Hodgkin lymphoma with interesting unique biologic and clinicopathologic features. The tumor is characterized by ethnic preponderance, a consistent association with Epstein-Barr virus (EBV) infection, peculiar histopathologic findings, and a predilection to affect primarily the upper aerodigestive tract, inclusive anatomically of the nasal cavity, nasopharynx, paranasal sinuses, oral cavity, hypopharynx, and larynx. The characteristic clinical features are nasal stuffiness, relentless, nonhealing ulcers, or symptoms due to obstruction of the aforementioned areas. Distant metastasis at time of diagnosis is uncommon. However, 10% of patients may present with "extranasal" diseases with inconspicuous upper aerodigestive tract symptoms. Based on a clinicopathologic study of 136 patients, the recent International Peripheral T-cell Lymphoma Project found that the outcome of patients with extranasal disease is much worse than for those with nasal disease, with a median overall survival of 0.36 vs 1.6 years ($P < .001$).[1]

The Revised European-American Classification of Lymphoid Neoplasms (REAL), invented by a group of expert hematopathologists in 1994, has stimulated investigators around the globe to look into ENKTL as a distinct separate entity of lymphoma. Since then, considerable progress has been made in the understanding of the biology of ENKTL, particularly with regard to the role of EBV in malignant transformation. In contrast, little progress has been made regarding the optimal strategy of treatment, so that in 2010 there remains a lack of consensus on treatment of ENKTL and no therapy is considered standard. Almost all of the published reports have been limited by small sample sizes, and nonrandomized studies have included a heterogeneous patient population or patients treated with a wide range of treatment modalities.

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Role of Radiation

As radiation was the principal therapy when the disease was formerly known as lethal midline granuloma, radiotherapy is, for the past 20 years, the mainstay of treatment for patients with limited-stage ENKTL, nasal type. Experience from most large series studies showed that the overall response rate was over 80% with a complete remission rate of 70% when radiation was given as a sole therapy to patients with limited-stage disease.[2,3] However, only 30% to 40% of these patients enjoyed long-term survival, as relapses—both local and systemic—were reported in up to 25% to 50%. The use of chemotherapy or a combination of chemotherapy and radiation to ameliorate the rate of relapse therefore deserves further exploration.

Given that standard treatment for patients with early-stage, diffuse large-cell lymphoma is chemotherapy followed by involved-field radiation, it is not surprising that several centers advocated this treatment strategy for patients with limited-stage ENKTL, nasal type. Using a brief course of anthracycline-based chemotherapy followed by radiation, the 5-year overall survival rate was only 50% for patients with localized ENKTL.[4,5] However, studies using upfront radiation followed by chemotherapy reported a far better outcome, with a complete response rate greater than 80% and a 5-year overall survival rate of 67% to 77%.[3,6] Studies of anthracycline-based chemotherapy without radiation are disappointing because of high rates of refractory disease. A mechanism postulated for a high failure rate after chemotherapy is high p-glycoprotein (P-gp) expression in NK lymphoma cells, which results in drug efflux and intracellular decrease of cytotoxic agents—in particular, vincristine and doxorubicin, the two main components in the CHOP regimen (which also includes cyclophosphamide and prednisone).

Systemic Chemotherapy

Systemic chemotherapy is essential in patients with stage III/IV extranasal or relapsed/refractory ENKTL. To overcome the intrinsic multidrug resistance (MDR)-mediated chemotherapy resistance of ENKTL, investigators proposed novel chemotherapy regimens including non–P-gp efflux medications and etoposide, which is effective for EBV-associated lymphoproliferative diseases. Experiences with SMILE (steroid dexamethasone, methotrexate, ifosfamide, asparaginase [Elspar], etoposide) or the other asparaginase-based regimen showed complete response rates of about 50% and an overall response rate of 70% in patients with advanced or relapsed/refractory ENKTL.[7,8]

Another approach is to apply the concept of concurrent chemoradiotherapy, which has been established as a standard therapy for several types of solid tumors. Yamaguchi et al and Kim et al treated newly diagnosed ENKTL, stage IE/IIE with concurrent chemoradiotherapy and reported complete response rates of 77% and 83% with manageable toxicities.[9,10]The 2- to 3-year progression-free survival rates were 67% and 85%. The definitive roles

Continued on page 362.

serotype coverage for the PCV 13-valent vaccine (72%; 95% CI: 67.0–76.6) compared with PCV7 (58.4%; 95% CI: 53.1–63.6) and to PCV 10-valent (59.3%; 95% CI: 54.0–64.5) vaccines. Coverage by PNSp was 77.1% for both, PCV7 and PCV10, and 83.1% for PCV13. Results for 141 PNSp isolates tested with antimicrobials other than PEN show high rates of resistance to SXT (Table, Supplemental Digital Content 1, http://links.lww.com/INF/A296). MDR was found in 24.8% of the isolates. A total of 63.6% of NTPn were MDR. All serotypes were susceptible to levofloxacin and vancomycin. The median of the MIC values to PEN was higher for nonsusceptible erythromycin isolates when compared with susceptible erythromycin isolates. The comparison between 178 PNSp and 508 PSSp isolates, found that significant factors independently associated with the risk of carrying PNSp were age ≤23 months (28.1% vs. 18.1%; OR: 1.79; 95% CI: 1.19–2.70), hospitalization during the previous 3 months (9.6% vs. 4.1%; OR: 2.19; 95% CI: 1.10–4.35), and recurrent acute otitis media (6.2% vs. 2.6%; OR: 2.89; 95% CI: 1.24–6.67). Having older siblings was identified as a protective factor for carriage of PNSp (59% vs. 67.9%; OR: 0.66; 95% CI: 0.46–0.95).

DISCUSSION

To our knowledge, this is the first published survey of pneumococcal NP carriage in Brazilian DCCs that sampled large enough numbers of attendees to represent the entire population, instead of a convenient sample of 1 or a few centers.

Our data suggest that recurrent otitis media (3 episodes diagnosed in 6 months) may favor NP colonization by PNSp. Because DCCs may be a significant distribution site of antibiotic-resistant pneumococci to the community, we wonder if attendees with a history of recurrent acute otitis media might contribute in the spread of PNSp strains to the community.

It is interesting to note that 35 (10.5%) of 332 serotyped isolates could not be assigned a capsular type by Quellung reaction as well as the multibead assay. This percentage of NTPn carriage was higher than those observed in children in The Gambia (2.4%)[8] and in previous studies in Brazil.[4] The levels of MDR NTPn (63%) were higher than those observed in attendees in Portugal[9] and in children of Israel.[10] Little is known about the genetic, epidemiology, and the true role of NTPn in NP carriage.[9] In a recent study of 40 NTPn isolates from Gambian children, *cpsA* gene was found only in 31 isolates.[8] Our preliminary studies suggest that most NTPn have *cpsA* gene and some even have *cps14H* gene, which is specific for serotype 14 capsule gene locus. Thus, the NTPn isolates with *cps14H* gene presumably have nonfunctional serotype 14 capsule gene locus.

The PEN resistance was slightly higher in this study than the levels we have previously detected in carriage isolates in healthy children and in children at the time of hospital admission.[4] The high rate resistance to both, PEN and SXT, as well the low rate of resistance to erythromycin are in accordance with previous studies in Brazil.[11] PNSp serotype 14 was the major type isolated in our study and has been the most common serotype associated with erythromycin resistance in several reports, including Brazil.

Serotype 19A, which is an important serotype causing invasive pneumococcal disease in Brazil,[12] was among the top 3 ranked serotypes and fifth PNSp serotype in our study. In a recent pneumococcal carriage in our country, serotype 19A also appeared as a prevalent serotype.[4] These findings deserve consideration as a baseline data before the introduction of the PCV into the Brazilian universal immunization program. As expected, serotypes 1 and 5, as well 3 and 7, were not isolated in nasopharynx of children, but they are among the most common invasive pneumococcal disease serotypes in Brazil.[12] Our data showed that 58% of the serotypes colonizing the nasopharynx of children were those present in the PCV7, but a significantly greater proportion of 72% would be covered by the PCV13, mainly because of the high prevalence of non-PCV7 serotypes 6A and 19A. Therefore, investigational vaccines containing these serotypes would increase significantly the coverage of NP carriage serotypes in our country.

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THERAPEUTIC DRUG MONITORING OF LOPINAVIR IN HUMAN IMMUNODEFICIENCY VIRUS-INFECTED CHILDREN RECEIVING ADULT TABLETS

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Abstract: Because of the lack of a lopinavir/ritonavir (LPV/r) pediatric formulation, 54 HIV-infected children were given generic LPV/r adult tablets. Of 54 children, 21 took cut pills to get the appropriate dose. The median (interquartile range) LPV trough serum concentration (C_{trough}) was 6.7 (5.0–9.9) mg/L. All the children had C_{trough} >1.0 mg/L and 96% had values >4.0 mg/L. LPV/r adult tablets can be used in children when it is necessary.

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Outcome of second interventions for occluded metallic stents in patients with malignant biliary obstruction

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Abstract
Background Although self-expandable metallic stent (SEMS) has a longer patency than plastic stent (PS) for malignant biliary obstruction, stent occlusion can occur and drainage has to be reestablished in a patient with expected long survival. However, the choices are still controversial among restenting with SEMS, PS, and percutaneous transhepatic biliary drainage (PTBD). This study was designed to determine the efficacy and outcome of PS, SEMS, and PTBD for patients with occluded SEMS.
Methods A total of 154 ERCPs with SEMS insertion were performed at the Endoscopy Unit of Chulalongkorn University. The causes of obstructive jaundice were cholangiocarcinoma ($n = 110$), pancreatic cancer ($n = 41$), and metastatic carcinoma ($n = 3$). Thirty-two patients (20.9%) with occluded SEMS (uncovered SEMS = 22 and covered SEMS = 10) were identified. PS, SEMS, and PTBD were used to reestablish drainage in 11, 14, and 7 patients, respectively. The second stent was inserted as stent-in-stent. Patients with less advanced disease were preferably opted to have a second SEMS.
Results The median stent patency of second SEMS (100 days) was significantly longer than PS (60 days) and PTBD (75 days; $p < 0.05$). The median survival time for patients with second SEMS (230 days) was significantly longer than patients with PS (130 days) and PTBD (150 days; $p < 0.05$). Subgroup analysis in hilar obstructions showed no statistical difference in second stent patency and survival between PS and SEMS. Pain that required oral narcotic developed in 71% (5/7) of PTBD patients.
Conclusions In general, a second SEMS insertion in occluded SEMS provides a significant longer patency time than PS and PTBD. However, the benefit of SEMS as a second intervention in hilar obstructed patients is still doubtful.

Keywords Malignant biliary obstruction · Self-expandable metallic stent · Occlusion · Intervention · Endoscopic retrograde cholangiopancreatography

The insertion of biliary stent(s)—endoscopically or percutaneously—is accepted as a palliative management in patients with unresectable malignant biliary obstruction [1, 2]. Plastic stent (PS) insertion has been previously used as a standard mode for endoscopic biliary drainage. However, it requires periodic stent exchange at interval of 3–4 months because of stent clogging with biliary sludge [2]. During the past two decades, self-expandable metallic stent (SEMS) has been developed [3]. With a larger diameter, it has proven to provide a longer patency time than plastic stents [4–9]. However, tumor ingrowth, overgrowth, biliary sludge, and mucosal hyperplasia induced by chronic inflammation can occur and cause stent occlusion. To date, the proper management for an occluded SEMS has not been well-established. The current approaches include insertion of a second stent (plastic or metallic) as stent-in-stent,

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ELSEVIER

Endothelial Progenitor Cells in Asian Kidney Transplant Patients

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ABSTRACT

Background. Endothelial progenitor cells (EPC) involved in endothelial repair and maintenance are restored following renal transplantation. There are scarce data regarding EPC in Asian kidney allograft patients.

Aim. We determined the EPC numbers in Thai renal allograft patients to compare with various other parameters.

Patients and Methods. The EPC numbers which were verified as CD 133+/VEGFR-2 cells in peripheral blood of 38 renal transplant recipients were measured by flow cytometry, and by a cell culture assay using acetylated low-density lipoprotein and *Ulex europaeus* agglutinin-1 immunofluorescence. Renal function calculated as estimated glomerular filtration rate (eGFR) was obtained by the abbreviated Modification of Diet in Renal Disease (MDRD) formula.

Results. Renal allograft patients had lower EPC numbers than normal controls ($P < .05$). The EPC numbers showed a significant correlation with renal allograft function ($P < .05$). Recipients with stable eGFR at 12 months of follow-up displayed significantly greater EPC numbers at baseline compared with those subjects who experienced a decline in eGFR ($P < .05$). Recipients using angiotensin receptor blockers had greater EPC numbers at baseline and better 12-month renal allograft function ($P < .05$).

Conclusion. EPC numbers may influence the fate of renal allograft function. Enhancing EPC numbers may be a new strategy to improve long term renal allograft function.

CHRONIC ALLOGRAFT DYSFUNCTION (CAD), a major cause of long-term renal allograft loss, is pathologically characterized by neointimal hyperplasia that can induce vascular occlusion. Several patient- as well as treatment-related factors can induce or potentiate CAD.[1,2] Bone marrow–derived endothelial progenitor cells (EPC) play a crucial role in the re-endothelialization repair process by ameliorating neointima formation and maintaining the patency of intrarenal arteries.[3]

There are few studies regarding EPC among kidney transplant patients. Most of these reports utilized CD34 as one of the vital markers to identify EPC.[4–6] Recently, CD34− cells bearing CD133+/VEGFR-2+, which have been reported to be precursors of CD34+ EPC, have been shown to display more potent re-endothelialization activity.[7] As such, the numbers of EPC reported in earlier studies may not accurately represent the actual numbers of EPC that have vascular repair properties.[4–6] This observation may also explain the discrepancies in the results among EPC-related studies. Heretofore, there are scarce data regarding EPC in Asian kidney transplant recipients. The present study was performed to determine the role of EPC, which were verified to be CD133+/VEGFR-2+ cells, among oriental kidney transplant recipients.

PATIENTS AND METHODS

This study was approved by our ethical committee. Each patient gave informed consent. The numbers of EPC by flow cytometry and cell culture were determined in 38 kidney transplant patients who were actively followed up during July and December 2007. The EPC numbers were also assessed by flow cytometry in 15 healthy subjects.

The EPC numbers were measured by flow cytometry for CD133, VEGFR-2 phenotype. The peripheral blood mononuclear cells were separated from acid citrate dextrose

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Neutralizing antibody response after intradermal rabies vaccination in hemodialysis patients

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ABSTRACT

Abnormal immune function in chronic hemodialysis (HD) patients could impair immunologic responsiveness to various vaccinations. Such inadequate response makes the HD patients to be at risk of certain fatal but preventable diseases including rabies. Although the effectiveness of rabies vaccination has been established in healthy subjects, the responsiveness of the current rabies vaccination has never been examined in HD patients. The effectiveness of post-exposure rabies vaccine was assessed in 20 stable thrice-a-week chronic HD patients who received adequate dialysis and did not have history of rabies vaccination during the last 20 years. All participants received the standard intradermal Thai Red Cross post-exposure rabies vaccination. Blood samples were obtained for determination of rabies neutralizing antibody (Nab) before the first dose (day 0) and on days 14 and 90 after vaccination. Prior to simulated vaccination, six of twenty patients already had Nab titers above the protective levels of 0.5 IU/mL while the remaining fourteen patients showed undetectable Nab. All subjects reached Nab titers above 0.5 IU/mL(acceptable level for rabies protection) by days 14 after vaccination. The geometric mean titers (GMTs) on days 14 after vaccination were 3.2 + 3.1 IU/mL (range 0.81–9.17 IU/mL). At day 90 after vaccination, 13 of 14 patients had Nab titers above the protective levels, resulting in the response rate of 92.8%. The GMTs of Nab on day 90 after vaccination were 5.09 + 1.79 IU/mL (0.42–25.0 IU/mL). There were no correlations between Nab titers and patient characteristics. No serious adverse reactions were detected. In conclusion, chronic HD patients receiving adequate dialysis have excellent protective immunological response after intradermal post-exposure rabies vaccination as WHO recommendation.

1. Introduction

Patients with end stage renal disease (ESRD) exhibit defects in various host defense mechanisms including phagocytosis, complements, humoral mediated immune response, and cell mediated immune response (CMIR). Clinical evidence demonstrating impaired CMIR in ESRD patients comprises cutaneous anergy, higher carrier state following hepatitis B viral infection, greater incidence of malignancy than normal, and decreased immune response to vaccination. In this regard, chronic hemodialysis (HD) patients have been shown to express suboptimal immune responses to hepatitis B, influenza, pneumococcal, tetanus, and diphtheria vaccination [1–6]. Intradermal injection and increasing dosage as well as frequency of vaccination in HD patients have been recommended and shown to enhance the seroconversion rate [1,2,7].

Rabies is a zoonotic disease that produces acute, progressive, and fatal encephalitis in humans and most other mammals. The World Health Organization (WHO) estimates that approximately 50,000 rabies deaths are currently reported every year. In Asia, Africa, and other areas where animal control programs are not developed extensively, humans acquire rabies primarily from rabid dogs. Annually, more than 10 million people, mostly in Asia, receive post-exposure vaccination against rabies. Post-exposure prophylaxis (PEP) is a very effective method of preventing the development of rabies in an exposed individual, on the condition that it is done

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Short communication

A preliminary study of chemo- and cytokine responses in rabies vaccine recipients of intradermal and intramuscular regimens

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ABSTRACT

Plasma from 10 patients who had received rabies vaccine either intradermally (ID) or intramuscularly (IM) was examined for 20 chemo- and cytokines. Plasma samples were withdrawn on days 0, 3 and 7 after vaccination. These chemo- and cytokines and sampling days were chosen based on data collected from a protein array analysis of 122 cytokines conducted on one recipient of vaccine administered IM and one recipient of vaccine administered ID. Although eotaxin, interleukin (IL)-5 in the ID and IL-1 beta in the IM group were the only chemo- and cytokines that reached statistical significance ($p < 0.05$), the overall trends may suggest bias on Th1 or Th2 according to vaccination routes. IL-1 alpha, -2, and -6, hemofiltrate cysteine–cysteine chemokine (HCC-4), glucocorticoid induced tumor necrosis factor receptor (GITR), tumor necrosis factor (TNF) related apoptosis inducing ligand-receptor (TRAIL-R3) had some degree of elevation in the ID group. TNF-alpha, gamma-interferon, granulocytes/macrophages – colony stimulating factor (GM-CSF), transforming growth factor (TGF)-beta, lymphotactin and pulmonary and activation-regulated chemokine (PARC) were elevated, although not to a significant level, in the IM group. IL-12, interferon-inducible T cell alpha chemoattractrant (I-TAC) and sertoli cell factor (SCF) were not significantly elevated in both groups whereas IL-4 and -10 were unchanged. Further studies are required to determine whether the presence of specific chemokines, such as eotaxin, is responsible for the production of high levels of rabies virus neutralizing antibody after administration of the dose-sparing ID regimen.

1. Introduction

The intradermal (ID) route for rabies post-exposure prophylaxis (PEP) was introduced in 1985 in Thailand [1]. By 1988, ID regimens for PEP completely replaced the use of 14–21 subcutaneous injections of the nervous tissue derived vaccine produced in sheep (Semple) and suckling mouse brain (Fuenzalida) vaccines in Thailand. These nervous tissue derived rabies vaccines induced an unacceptable rate of neurological complications and were of unreliable immunogenicity [2–4]. The World Health Organization (WHO) subsequently endorsed and approved the use of ID for PEP in 1992 [5]. Since the introduction of the economical ID PEP strategy, rabies deaths in Thailand have declined from 185 (in 1990) to 68 (in 1999) and 19 (in 2004) [6]. In 2009, 24 deaths were reported (data of ministry of public health, Thailand, unpublished).

The most widely used ID regimen for rabies PEP is the Thai Red Cross (TRC) regimen. The TRC regimen consists of injecting 0.1 ml of WHO approved tissue culture rabies vaccine intradermally at two different lymphatic drainage sites on the left and right upper arm on days 0, 3, 7 and 28 [7]. The amount of vaccine required for PEP can be significantly reduced when the TRC ID regimen is used. For example, the Essen IM PEP regimen requires 5 vials (one vial is administered on each of days 0, 3, 7, 14, 28) whereas the TRC ID regimen requires only 1 or 2 vials, depending upon the volume of the IM dose of rabies vaccine [0.5 and 1.0 ml preparation of purified Vero cell and purified chick embryo vaccine (PCECV) respectively]. The immunogenicity and efficacy of the TRC ID regimen have been proven in several clinical trials [8–10]. The long term antibody persistence and confirmation of an anamnestic response after vaccination with a tissue culture rabies vaccine have also been confirmed for both IM and ID vaccination. In one study, conducted in Vietnam, patients vaccinated 5 years previously responded with an anamnestic response to one booster dose of vaccine [11]. Long lasting immunity was also confirmed in a clinical trial conducted in 118 Thai patients that received pre-exposure vaccination (PreP)

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