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Ticlopidine-associated ADAMTS13 activity deficient thrombotic thrombocytopenic purpura in 22 persons in Japan: a report from the Southern Network on Adverse Reactions (SONAR)

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Thrombotic thrombocytopenic purpura (TTP) is a life-threatening generalized disorder. The classic TTP ‘pentad’ is thrombocytopenia, microangiopathic hemolytic anemia (MAHA), renal impairment, neurological symptoms, and fever (Amorosi & Ultmann, 1966). Laboratory studies identified deficiency of plasma ADAMTS13 (a disintegrin-like and metalloprotease with thrombospondin type 1 motifs 13) activity (ADAMTS13:AC) among

some TTP patients (Furlan *et al*, 1998; Tsai & Lian, 1998). ADAMTS13 cleaves the peptide bond between Thy1605 and Met1606 in the A2 domain of von Willebrand factor (VWF) subunit. VWF is released into the plasma as unusually large VWF multimers (UL-VWFMs), which are degraded into smaller size VWF multimers by ADAMTS13. In the late 1990's, studies in the United States identified 117 cases of TTP that developed after initiation of the thienopyridine, ticlopidine; although at that time, ADAMTS13 activity levels were not widely available (Bennett *et al*, 1999; Steinhubl *et al*, 1999). A study of seven patients in the United States with ticlopidine-associated TTP found that all seven had severe deficiency of ADAMTS13 activity and five had detectable antibodies to ADAMTS13 activity (Tsai *et al*, 2000). We now report on 22 individuals from Japan with ticlopidine-induced TTP and compare these findings to those from the United States. Ticlopidine was the primary anti-platelet agent in Japan from 1989 to 2006.

Since 1998, our laboratory at Nara Medical University has been a nationwide referral centre in Japan for thrombotic microangiopathies (TMAs), including TTP (Fujimura & Matsumoto, 2010). The study protocol was approved by the Ethics Committee of Nara Medical University Hospital. TTP diagnostic criteria were: microangiopathic haemolytic anaemia (haemoglobin ≤ 120 g/l), Coombs test negative, undetectable serum haptoglobin (<1 μmol/l), more than 2 fragmented red cells (schistocytes) in a microscopic field with 9100 magnification, increased serum lactate dehydrogenase (LDH) above institutional baseline, thrombocytopenia (platelet count ≤ 100×10^9/l), absence of evidence for disseminated intravascular coagulation and no other identifiable cause of TTP. Additional information on fever ≥37°C; and central nervous system and renal function data were abstracted. Patients were included if, in addition to criteria for idiopathic TTP, the patient had received ticlopidine prior to TTP onset. Before therapeutic plasma exchange or plasma infusion was initiated, whole blood samples (five ml) were withdrawn from each patient and placed into plastic tubes containing 1/10 volume of 3.2% sodium citrate. Plasma was separated by centrifugation at 3000 g for 15 min at 4°C, kept in aliquots at −80°C until testing, and sent to our laboratory with clinical information. Until March 2005, ADAMTS13:AC was determined by classic VWF multimer (VWFM) assay with a detection limit of 3% of the normal control (Furlan *et al*, 1996; Kinoshita *et al*, 2001). Thereafter, a chromogenic ADAMTS13-act-enzyme-linked immunosorbent assay (ELISA) with a detection limit of 0-5% of the normal control was developed, and replaced the VWFM assay. Plasma ADAMTS13 inhibitor (ADAMTS13:INH) titres were analysed either by classic VWFM assay or chromogenic ADAMTS13-act-ELISA using heat-inactivated plasmas at 56°C for 30 min.

A total of 22 ticlopidine-associated TTP patients fulfilled the inclusion criteria (Table I). Age at diagnosis ranged from 41 to 89 years, with the median age of onset of 69 years. Females accounted for 45.5% of the cohort. Ticlopidine had been administered for a median of 27-5 d (range, 14–35 d) but was discontinued after a clinical diagnosis of TTP was made. Median values for hemoglobin were 83 (60–146) g/l, platelets 9–5 (3.57) × 10^9/l, and serum creatinine 132.6 (35–380) μmol/l. Abnormal neurological findings were noted in 63.6%. All of the patients had <5% ADAMTS13:AC activity and detectable inhibitors to ADAMTS13 at the time of presentation. ADAMTS13:INH titres were 0.5 to <1.0 Bethesda units (BU)/ml in 4.5% of the patients, 1.0 to <2.0 BU/ml in 13.5%, 2.0 to <5.0 BU/ml in 45.5%, 5.0 to <10 BU/ml in 18.2%, and 4.5% of the patients had ADAMTS13:INH titres of ≥ 10 BU/ml. Mortality during the acute TTP episode was 9.0%. Mortality was highest among persons 60 years of age or older (10.0% vs. 0.0%). Therapeutic plasma exchange was performed in 72.7%, at a median of 3 d after the onset of TTP (range 1–5 d), and the TTP resolved at a median of 8 d (range 3–28 d). Among four patients whose TTP cleared after 20 or more days of therapeutic plasma exchange, ADAMTS13:INH titres were 2,4.4, 17, and 20 BU/ml. Among 12 patients whose TTP resolved with therapeutic plasma exchange at <20 d, none

had ADAMTS13:INH titres >4 BU/ml. Both ticlopidine-associated TTP deaths did not receive therapeutic plasma exchange.

To our knowledge, this is the first study to report detailed characteristics of ticlopidine-associated TTP among patients outside of the United States. Our findings, from a cohort of ticlopidine-associated TTP patients in Japan, identified severe ADAMTS13 deficiency and antibodies to ADAMTS13 in 100% of these 22 individuals. A decade earlier, severe ADAMTS13 deficiency was reported in 100% of seven patients with ticlopidine-associated TTP in the United States and antibodies to ADAMTS13 in five of these patients (Bennett *et al*, 1999; Tsai *et al*, 2000). While ticlopidine-induced TTP is undoubtedly a rare disease, it is reassuring that the original observations reported from the United States have been independently replicated in Japan (Bennett *et al*, 1999; Steinhubl *et al*, 1999).

Limitations of our study should be identified. Follow-up ended at the time of hospital discharge, which prevented us from reporting on relapse rates. Ticlopidine is rarely used today, having been replaced by clopidogrel in 1999 because of safety concerns. Our research has shown that clopidogrel, unlike ticlopidine, does not lead to ADAMTS13 antibody formation and deficiency of ADAMTS13 activity and the rare cases of clopidogrel-associated TTP are not responsive to therapeutic plasma exchange. Also, very little is known about TTP associated with prasugrel (the newest thienopyridine), despite 14 cases of prasugrel-associated TTP having been reported to the Food and Drug Administration in 2009 and 2010 (Jacob *et al*, 2012). Careful pharmacovigilance to identify severe adverse drug reactions developing among small numbers of persons can serve as important warning signals for potentially serious adverse drug events internationally.

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Table I

Characteristics of ticlopidine-associated thrombotic thrombocytopenic purpura in Japan and United States.

Source	This paper	Bennett *et al* (1999)	Tsai *et al* (2000)	Steinhubl *et al* (1999)
Number of patients	22	98	7	19
Country	Japan	US	US	US
Aetiology	Ticlopidine	Ticlopidine	Ticlopidine	Ticlopidine
% female	45.50%	46.6%	70.0%	30.0%
Median age (years)	69 (41–89)	64.2 (11.1 = SD)	57 (42–89)	62 (38–75)
Platelets $<20 \times 10^9$/l	96.0% (23/24)	71.9%	100.0%	89.4%
Haemoglobin <90 g/l	72.7%	26,9%	42.3%	66.7%
Creatinine >221 μmol/l	18.1%	30.1%	NA	47.0%
Neurological abnormalities	63.6%	73.1%	70.0%	73.7%
Median days ticlopidine (range)	27.5 (14.36)	21 (7–112)	21 (14–56)	21 (14–28)
% with coronary stent	13.6%	42.3%	57.1%	100.0%
% with other Coronary artery disease indication	31.2%	0.0%	14.3%	0.0%
% stroke prevention	55.8%	57.7%	14.3%	0.0%
Survival	91.03%	84.9%	100.0%	78.9%
% Therapeutic plasma exchange (TPE)	63.6%	74.2%	100.0%	68.4%
Survival without TPE	75.0%	42.1%	—	33.3%
Survival with TPE	100.0%	81.7%	100.0%	100.0%
% with ADAMTS13 activity deficiency (<10%)	100.0%	Not available	83.3%	Not available
% with ADAMTS13 inhibitors	100.0%	Not available	100.0%	Not available