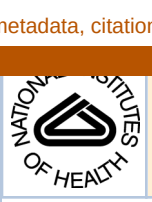

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Two Mechanistic Pathways for Thienopyridine-Associated Thrombotic Thrombocytopenic Purpura:

A Report From the SERF-TTP Research Group and the RADAR Project

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Abstract

Objectives—We sought to describe clinical and laboratory findings for a large cohort of patients with thienopyridine-associated thrombotic thrombocytopenic purpura (TTP).

Background—The thienopyridine derivatives, ticlopidine and clopidogrel, are the 2 most common drugs associated with TTP in databases maintained by the U.S. Food and Drug Administration (FDA).

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Methods—Clinical reports of TTP associated with clopidogrel and ticlopidine were identified from medical records, published case reports, and FDA case reports (n = 128). Duration of thienopyridine exposure, clinical and laboratory findings, and survival were recorded. ADAMTS13 activity (n = 39) and inhibitor (n = 30) were measured for a subset of individuals.

Results—Compared with clopidogrel-associated TTP cases (n = 35), ticlopidine-associated TTP cases (n = 93) were more likely to have received more than 2 weeks of drug (90% vs. 26%), to be severely thrombocytopenic (84% vs. 60%), and to have normal renal function (72% vs. 45%) ($p < 0.01$ for each). Compared with TTP patients with ADAMTS13 activity >15% (n = 13), TTP patients with severely deficient ADAMTS13 activity (n = 26) were more likely to have received ticlopidine (92.3% vs. 46.2%, $p < 0.003$). Among patients who developed TTP >2 weeks after thienopyridine, therapeutic plasma exchange (TPE) increased likelihood of survival (84% vs. 38%, $p < 0.05$). Among patients who developed TTP within 2 weeks of starting thienopyridines, survival was 77% with TPE and 78% without.

Conclusions—Thrombotic thrombocytopenic purpura is a rare complication of thienopyridine treatment. This drug toxicity appears to occur by 2 different mechanistic pathways, characterized primarily by time of onset before versus after 2 weeks of thienopyridine administration. If TTP occurs after 2 weeks of ticlopidine or clopidogrel therapy, therapeutic plasma exchange must be promptly instituted to enhance likelihood of survival.

Thrombotic thrombocytopenic purpura (TTP) is a severe, multisystem, thrombotic microangiopathy characterized by thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction, neurologic abnormalities, and fever (1). About one-fifth of TTP cases are associated with pharmaceuticals (2). The thienopyridine derivatives ticlopidine and clopidogrel are the 2 most commonly reported to the U.S. Food and Drug Administration (3–5) In 1998, we reported 60 cases of ticlopidine-associated TTP, identifying high survival rates after therapeutic plasma exchange (TPE) (4,6). Clopidogrel, a newer thienopyridine derivative, differs in structure from ticlopidine by one methoxycarbonyl group (7). It is now the second most commonly prescribed drug in the U.S. In 2004, we described 39 patients with TTP associated with clopidogrel use, highlighting frequent onset within 2 weeks of drug initiation and high mortality rates despite TPE (5). The manufacturer reported an incidence of one TTP case per 100,000 clopidogrel treated patients (8).

Marked advances in understanding of TTP pathophysiology have occurred recently. One area relates to proteolytic processing of plasma von Willebrand factor (VWF) and characterization of VWF-cleaving protease (VWF) and its inhibitor, an immunoglobulin (Ig)G autoantibody (9,10). In 2001, VWF-cleaving protease was identified as a metallo-protease ADAMTS13, belonging to the ADAMTS (a disintegrin-like and metalloprotease with thrombospondin type 1 motif) family (11). Among idiopathic TTP patients, many have ADAMTS13 deficiency caused by an inhibitory IgG autoantibody. ADAMTS13 activity has been measured for seven patients with ticlopidine-associated TTP, and ADAMTS13 deficiency and autoantibodies to ADAMTS13 were identified in all seven patients (12). Herein, we evaluated clinical, laboratory, and basic science findings for patients with thienopyridine-associated TTP, representing the largest cohort of individuals with this rare syndrome reported to date. Our aim is to identify clinically important differences in presentation and outcome for patients with TTP associated with shorter- versus longer-term administration of ticlopidine and clopidogrel.

Methods

Investigators with the RADAR (Research on Adverse Drug Events and Reports) project identified cases of ticlopidine- and clopidogrel-associated TTP with the use of pharmaco-vigilance methods that have been described previously (3–5,13,14). Thienopyridine-

associated TTP cases were identified from 4 sources: 1) voluntary reports submitted to MedWatch, the Food and Drug Administration's Safety Information and Adverse Event Reporting System (n = 29); 2) published case series or reports from MEDLINE/PubMED, using MeSH terms ticlopidine or clopidogrel, thrombotic microangiopathy, and TTP (n = 40) (4,5,15,16); 3) direct queries of hematologists and apheresis directors in 8 large apheresis centers in geographically dispersed metropolitan areas (Charles Bennett, MD, PhD, Chicago, Illinois; Joseph Kiss, MD, Pittsburgh, Pennsylvania; Thomas Ortel MD, PhD, and Nicholas Bandarenko, MD, Raleigh-Durham, North Carolina; Josh Levy, MD, and Nurit Begani, RN, Los Angeles, California; William Bell, MD, PHD, Baltimore, Maryland; Leo J McCarthy, MD, Indianapolis, Indiana; Jean Connors, MD, Boston, Massachusetts; and Joel Moake, MD, Houston, Texas; n = 42); and 4) a national referral laboratory in Japan (Yoshihiro Fujimura; n = 17). A validated case report form was used to collect data on sociodemographic characteristics, thienopyridine use, clinical data—platelet count (per mm^3), hemoglobin level (g/dl), serum creatinine (mg/dl), neurologic findings (altered mental status, seizure, stroke, or coma)—use of TPE, and survival (4,5). Inclusion criteria were thienopyridine use before the development of thrombocytopenia (platelets <50,000/mm^3) and microangiopathic hemolytic anemia on peripheral blood smear, without the presence of any other identifiable cause, such as disseminated intravascular coagulation, cancer, or preeclampsia. Those cases that did not fulfill or report all of the required inclusion criteria were excluded from analysis.

Assaying of ADAMTS13 activity

Basic laboratory studies were conducted by investigators with the Surveillance Epidemiology and Risk Factors for TTP Study Group (17). Plasma was assayed for ADAMTS13 activity with 3 different methods. Seventeen samples from a Japanese national referral laboratory compared the classic VWF multimer assay measuring the proteolysis of purified VWF into cleaved VWF fragments by sodium dodecyl sulfate agarose gel to a novel enzyme-linked immunoassay technique using monoclonal antibodies directed against the decapeptide of the VWF-A2 domain ending with the C-terminal edge residue Y1605, a cleaved VWF byproduct, and found 100% concordance in determining severe ADAMTS13 deficiency (18). Five samples were measured by collagen binding assay, based on the preferential binding of high-molecular-weight forms of VWF to collagen (15,19). The measurement of ADAMTS13 activity in the remaining 17 plasma samples was performed by measuring proteolysis of purified VWF into VWF fragments by gel electrophoresis (20). Previous studies have reported high levels of concordance in identifying persons with severe ADAMTS13 deficiency using these methods for assaying ADAMTS13 levels (21). The inhibitory activity of the IgG autoantibody was determined by mixing TTP plasma samples at various dilutions with normal plasma and measuring the protease activity of the mixture, as previously reported and described (20).

Statistical analysis

Bivariate analysis of factors associated with administration of ticlopidine versus clopidogrel, and shorter- versus longer-term thienopyridine administration, were evaluated with a nonparametric exact methodology called optimal discriminant analysis. Used to analyze binary attributes, optimal discriminant analysis yields results isomorphic with the Fisher exact test and, when used to analyze ordinal attributes, optimal discriminant analysis identifies a threshold value that explicitly maximizes classification accuracy (22). A cut point of 2 weeks or less was determined a priori to define short-term thienopyridine administration based on findings reported previously (3–5). For the subset of patients for whom ADAMTS13 activity levels were measured, optimal discriminant analysis was used to evaluate clinical and laboratory findings associated with severe ADAMTS13 deficiency, characterized as activity levels <15% of normal human plasma as in prior studies (23).

However, our findings were qualitatively similar if a cut point of 5% was used, a threshold that was used in some studies (23). A multivariate nonlinear model for predicting survival from TTP was obtained via hierarchically optimal classification tree analysis (21,24). Finally, survival analysis was conducted with Cox proportional hazards survival analysis, with log-rank statistics used to test for differences in the survival outcomes, and Kaplan-Meier analysis for plotting survival curves.

Results

Between 1998 and 2005, 93 ticlopidine- and 35 clopidogrel-associated TTP cases were identified (Table 1). Patients with ticlopidine- and clopidogrel-associated TTP were similar in age (mean 64.2 vs. 58.1 years) and gender (male 53.4% vs. 54.3%) but differed significantly in duration of thienopyridine exposure prior to development of TTP ($p \leq 0.002$) (Fig. 1A). In comparison with patients with clopidogrel-associated TTP, those with ticlopidine-associated TTP were more likely to have received more than 2 weeks of a thienopyridine before TTP (90.3% vs. 25.7%, $p < 0.0001$) and to present with severe thrombocytopenia (platelet count $<20 \times 10^9$/l) (83.9% vs. 60.0%, $p < 0.005$) but less likely to have renal insufficiency (27.8% vs. 55.2%, $p < 0.02$) (Table 1).

We evaluated clinical findings, outcomes, and plasma ADAMTS13 activity for 39 thienopyridine-associated TTP patients (Table 1). In comparison with TTP patients with ADAMTS13 activity >15%, those with severely deficient ADAMTS13 activity were more likely to have received ticlopidine (92.3% vs. 46.2%, $p \leq 0.003$) and to be severely thrombocytopenic (96.2% vs. 38.5%, $p < 0.001$) (Table 1) and had a trend toward developing TTP after longer periods of drug exposure (Fig. 1B). Among 30 patients with thienopyridine-associated TTP and plasma available for assays of autoantibody to ADAMTS13, none with normal ADAMTS13 activity had detectable levels of inhibitor, whereas every patient with severe ADAMTS13 deficiency had IgG autoantibodies that inhibited ADAMTS13 activity ($p < 0.0001$). Survival was greater among thienopyridine-associated TTP patients with deficient ADAMTS13 activity levels who underwent TPE compared with those who did not (90.9% vs. 50.0%, $p < 0.05$). Among six ticlopidine-associated and seven clopidogrel-associated TTP patients whose ADAMTS13 levels were >15%, 12 underwent TPE, and only 7 (58.3%) survived.

Overall, the mortality rate for patients with thienopyridine-associated TTP was 25.8%. Univariate associations identified several characteristics significantly associated with an increased mortality risk for the total sample, including abnormal neurologic status ($p < 0.02$), serum creatinine >2.5 mg/dl ($p < 0.04$), and not receiving TPE ($p < 0.0006$). Among patients who developed TTP after >2 weeks of thienopyridine exposure, survival was 2.2-fold greater when treated with TPE (84% vs. 38%, $p < 0.05$). Among patients who developed TTP within 2 weeks of starting thienopyridines, survival was 77% with TPE and 78% without. A multivariate classification tree analysis model revealed that among thienopyridine-associated TTP patients who received TPE, those patients with ADAMTS13 activity levels >15% at the time of diagnosis of TTP were 4-fold more likely to die (41.9% vs. 9.1%, $p < 0.036$).

Discussion

Our study identifies distinct clinical, laboratory, and outcome differences between ticlopidine- and clopidogrel-associated TTP. More than 90% of the ticlopidine-associated TTP cases develop after more than 2 weeks of thienopyridine use. Among these patients, severe thrombocytopenia and preserved renal function at diagnosis is common, ADAMTS13 activity levels are frequently <15%, and survival is 86% if TPE is administered versus 46%

if TPE is not used. These findings are similar to those reported previously for idiopathic TTP cases with severely deficient ADAMTS13 activity levels (16,23,25). In contrast, three-quarters of the clopidogrel-associated TTP cases develop after 2 weeks or less of thienopyridine use. These patients are characterized by mild thrombocytopenia and renal insufficiency at diagnosis, ADAMTS13 activity levels >15%, and survival rates that are similar with versus without TPE (72.4% and 66.7%), findings that are similar to those reported previously for TTP cases with ADAMTS13 activity levels >25%. Our findings suggest 2 mechanistic pathways for thienopyridine-associated TTP, an immunologic pathway associated with more than 2 weeks of thienopyridine use and a nonimmunologic pathway associated with 2 weeks or less of thienopyridine use. In interpreting our study, several factors should be considered.

The results for patients with severe ADAMTS13 deficiency and thienopyridine-associated TTP reinforce previous observations for patients with ticlopidine-associated TTP. Tsai et al. (12) reported 7 ticlopidine-associated TTP patients who had severe ADAMTS13 deficiency and inhibitors to ADAMTS13 at diagnosis, all of whom responded rapidly to TPE. The use of TPE in these patients may result in removal of ADAMTS13 inhibitors and ultra-large VWF multimers, replenishment of ADAMTS13 and VWF, and reduction of cytokines that induce endothelial cell damage and platelet activation (26). Our study also describes cases of thienopyridine-associated TTP cases who do not have severe ADAMTS13 deficiency and whose survival was not influenced by TPE. Preservation of ADAMTS13 activity has been described in patients with post-transplantation thrombotic microangiopathy (27,28) who frequently present with renal insufficiency, moderate thrombocytopenia, and high mortality rates despite TPE. Others have described TTP-like findings among persons with factor V Leiden mutation (29).

Our study has implications for patient safety. First, for the rare individual with a drug-eluting coronary artery stent who develops TTP after the administration of clopidogrel and for whom discontinuation of thienopyridine-therapy could be catastrophic, ticlopidine challenge can be considered. For most patients with clopidogrel-associated TTP, our findings suggest that the toxicity is unlikely to be immunologic in etiology. Patel et al. (30) recently described a case report of a patient with a history of clopidogrel-associated TTP who successfully received ticlopidine therapy following implantation of a drug eluting coronary artery stent. Two years had elapsed between the development of clopidogrel-associated TTP and ticlopidine initiation. Second, the RADAR program has developed new approaches to drug safety that build on close collaborations with referral centers that have developed novel assays (13). We identified a large part of our cohort by querying hematologists or medical directors of TPE centers who were collaborating in a prospective case-control epidemiologic study or who sent plasma samples for possible TTP cases to a referral center for measurement of ADAMTS13 activity. Similar collaborations with a referral center that developed novel assays for detecting antierythropoietin-associated antibodies facilitated the identification of another drug-associated toxicity, erythropoietin-associated pure red cell aplasia (31).

Study limitations

The limitations of our study should be identified. First, thienopyridine-associated TTP is undoubtedly a rare diagnosis, limiting our ability to obtain plasma from large numbers of patients. Second, although clinical information on most of the cases reported herein have been reported previously, these studies did not directly compare TTP cases according to drug (ticlopidine vs. clopidogrel) or the duration of thienopyridine administration (4,5). Also, previous studies included information on ADAMTS13 activity levels and ADAMTS13 inhibitors for only 10 patients with thienopyrindine-associated TTP. Third, the demographic characteristics of the TTP patients in this study differ from those reported in

case series of TTP patients. In particular, in comparison with thienopyridine-associated TTP patients, patients in the study of Vesely et al. (24) were younger (mean 35 to 50 vs. 60 to 65 years) and more likely to be female (80% vs. 45%) (16,17,25) and, therefore, there continues to be uncertainty about causal mechanisms for clopidogrel, primarily because clopidogrel-associated TTP occurs markedly less often than ticlopidine-associated TTP (32–35).

Conclusions

Thrombotic thrombocytopenic purpura is a rare complication of thienopyridine treatment. This drug toxicity appears to occur by 2 different mechanistic pathways, characterized primarily by time of onset of > versus <2 weeks of thienopyridine administration. If TTP occurs after 2 weeks of ticlopidine or clopidogrel therapy, TPE must be promptly instituted to enhance the likelihood of survival.

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Abbreviations and Acronyms

TPE	therapeutic plasma exchange
TTP	thrombotic thrombocytopenic purpura
VWF	von Willebrand factor

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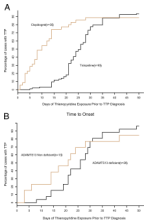

Figure 1. Duration of Thienopyridine Exposure Prior to TTP Onset

(A) Thienopyridine-associated thrombotic thrombocytopenic purpura (TTP) onset: ticlopidine versus clopidogrel ($p = 0.0016$). **(B)** Thienopyridine-associated TTP onset: ADAMTS13 deficient versus ADAMTS13 nondeficient ($p > 0.05$).

Table 1

Characteristics of Thienopyridine-Associated TTP Cases

	All Patients (n = 128)	Thienopyridine Rx ≤14 Days (n = 35)	Thienopyridine Rx >14 Days (n = 93)	Ticlopidine (n = 93)	Clopidogrel (n = 35)	ADAMTS13 Deficient (n = 26)	ADAMTS13 Nondeficient (n = 13)
Mean age, yrs (SD)	62.4 (13.9)	59.8 (13.2)	63.4 (14.1)	64.2 (12.9)	58.1 (15.3)	67.1 (12.0)	60.3 (20.2)
Male	53.7%	57.1%	52.3%	53.4%	54.3%	46.2%	61.5%
Thienopyridine Rx ≤14 days	27.3%	—	—	9.7%*	74.3%*	15.4%	38.5%
Thienopyridine Rx >14 days	72.7%	—	—	90.3%	25.7%	84.6%	61.6%
ADAMTS13 deficient	66.7%	44.4%	73.3%	80%*	22.2%*		
Platelet count <20,000/mm^3	77.3%	65.7%†	81.7%†	83.9%*	60.0%*	96.2%*	38.5%*
Creatinine >2.5 mg/dl	35.6%	41.9%	32.9%	27.8%*	55.2%*	26.9%	46.2%
Abnormal neurologic findings	29.1%	33.3%	27.3%	27.8%	32.3%	19.2%	15.4%
Received TPE	76.6%	74.3%	77.4%	74.2%	82.9%	84.6%	92.3%
Survival	74.2%	77.1%	73.1%	75.3%	71.4%	84.6%	61.5%

*$p < 0.05$;

†$p < 0.07$.

Rx = treatment; TPE = therapeutic plasma exchange; TTP = thrombotic thrombocytopenic purpura.

Table 2

Outcomes for Ticlopidine- and Clopidogrel-Associated TTP Cases

	Survival With TPE, %	Survival Without TPE, %
All patients (n= 128)*	81.6	50.0
Ticlopidine (N = 93) *	85.5	45.8
Ticlopidine Rx ≤ 14 days (n = 9)	100.0	100.0
Ticlopidine Rx >14 days (n = 84)	84.1*	38.1*
Clopidogrel (N = 35)	72.4	66.7
Clopidogrel Rx ≤14 days (n = 26)	70.0	66.7
Clopidogrel Rx >14 days (n = 9)	77.8	—
Thienopyridine Rx ≤ 14 days (n = 35)	76.9	77.8
Thienopyridine Rx >14 days (n = 93)	83.3*	38.1*

* $p < 0.05$ (for comparison of survival with TPE vs. without TPE).

Abbreviations as in Table 1.