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Clinical Policy Bulletin:
ADAMTS13 Assay for Thrombotic Thrombocytopenic Purpura (TTP)

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Policy

Aetna considers the ADAMTS13 assay medically necessary for assessing prognosis in persons with thrombotic thrombocytopenic purpura (TTP).

Aetna considers the ADAMTS13 assay experimental and investigational for the following indications (not an all-inclusive list) because of insufficient evidence of its clinical utility for these indications:

- Diagnosis and the therapeutic monitoring of individuals with sepsis associated thrombotic microangiopathy
- Diagnosis of arterial thrombosis
- Disseminated intravascular coagulation
- Hemolytic uremic syndrome (HUS)
- Ischemic complications of malignant hypertension
- Monitoring of liver diseases
- Prediction of hepatocellular carcinoma development
- Prediction of recurrence of atrial fibrillation
- Predicting of recurrence of venous thromboembolism
- Pre-eclampsia.
Background

ADAMTS13 (A Disintegrin-like And Metalloprotease with ThromboSpondin type 1 motif) is a multi-domain protease that limits platelet thrombogenesis through the cleavage of von Willebrand factor. Retrospective studies of patients with thrombotic micro-angiopathies have shown that a deficient activity of ADAMTS13 in plasma is involved in thrombotic thrombocytopenic purpura (TTP) but not in hemolytic-uremic syndrome (HUS). It even demonstrated that patients with inherited TTP have severe ADAMTS13 deficiency. However, patients with acquired TTP present with clinical and laboratory heterogeneity, and there are unequivocal cases of acquired TTP with measurable plasma levels of ADAMTS13. This heterogeneity poses a challenge for understanding the pathogenesis of TTP and selecting appropriate therapies (Mannucci and Peyvandi, 2007). The ADAMTS13 assay has been proposed by some to distinguish chronic recurring TTP (secondary to the presence of ADAMTS13 inhibitor) and HUS.

In a multi-center prospective cohort study (n = 111), Veyradier et al (2001) reported that most patients diagnosed with HUS had normal plasma levels of ADAMTS13, even though a few of them (14 %) had reduced or even undetectable levels. However, the high diagnostic value of finding severe ADAMTS13 deficiency in TTP was subsequently challenged by other studies (Loof et al, 2001; Moore et al, 2001; Mori et al, 2002; Remuzzi et al, 2002; Coppo et al, 2004; Peyvandi et al, 2004); 2 of which involved prospectively recruited cohorts (Vesely et al, 2003; Zheng et al, 2004). Some of these studies also investigated patients with the form of HUS preceded by hemorrhagic colitis that occurs typically in children, or the atypical form that occurs more frequently in adults. Atypical HUS is sometime indistinguishable from TTP unless signs and symptoms of severe renal impairment are prominent (Mannucci and Peyvandi, 2007). The majority of these studies (Veyradier et al, 2001; Remuzzi et al, 2002; Vesely et al, 2003; Coppo et al, 2004) confirmed that ADAMTS13 is normal or only slightly decreased in typical colitis-associated HUS. However, in a few patients diagnosed with atypical HUS, ADAMTS13 was as severely deficient as in TTP (Loof et al, 2001; Veyradier et al, 2001; Remuzzi et al, 2002). Studies showing that protease activity was also reduced in plasma in an array of clinical conditions other than TTP (e.g., spanning from various thrombocytopenic disorders to disseminated intravascular coagulation, sepsis, the neonatal and post-operative period, liver cirrhosis and chronic inflammation) further challenge the paradigm that ADAMTS13 deficiency is a specific diagnostic beacon of TTP (Moore et al, 2001; Mannucci et al, 2001; Bianchi et al, 2002). In these conditions, however, ADAMTS13 deficiency was usually moderate or mild (10 % to 40 % of normal plasma value).

Mannucci and Peyvandi's (2007) reviewed the literature on ADAMTS13 and stated that it is not necessary to assay ADAMTS13 to diagnose TTP in the acute phase of the disease. Patients presenting with normal or moderately reduced ADAMTS13 can still be appropriately diagnosed with TTP. Furthermore, the authors stated, "[t]he decision to implement plasma therapy (infusion in patients with inherited disease, exchange in acquired disease) does not warrant the availability of ADAMTS13 values in real time. Clinicians need to identify patients who are more likely to relapse and develop chronic recurrent TTP. Patients who present with undetectable ADAMTS13 activity and detectable anti-ADAMTS13 during the acute episode and/or during first remission are more likely to experience other episodes. Therefore, ADAMTS13 testing appears to be more helpful as an index of relapse than as an index of short-term outcomes (remission and mortality rates), but larger confirmatory studies are warranted."
It has been posited that knowledge of the likelihood of relapse would be useful in avoiding stressors that can induce TTP. It has been observed that TTP can occur (or recur) after pregnancy, infection, pancreatitis, and surgery; acute stresses, resulting perhaps in the release of inflammatory cytokines or other prothrombotic mediators, can trigger an initial or recurrent episode, perhaps by altering the balance between levels of von Willebrand factor and ADAMTS13 activity in a susceptible patient.

van den Born et al (2008) stated that thrombotic microangiopathy (TMA) observed in malignant hypertension is similar to that of TTP, which is associated with a deficiency of ADAMTS13, a von Willebrand factor (VWF)-cleaving protease that cleaves large prothrombogenic multimers. These researchers hypothesized that ADAMTS13 is deficient in malignant hypertension and that the severity of TMA is associated with decreased ADAMTS13 activity. They included 20 patients with malignant and 20 patients with severe hypertension, and 20 matched normotensive individuals served as control subjects. Free hemoglobin, VWF, and active VWF were assessed to explore predictors of ADAMTS13 activity. Patients with malignant hypertension had lower ADAMTS13 activity (80%; interquartile range [IQR]: 53% to 130%) compared with control subjects (99% IQR: 82% to 129%; p < 0.01) but not compared with patients with severe hypertension (p = 0.14). ADAMTS13 activity negatively correlated with lactic dehydrogenase levels after logarithmic transformation (r = -0.65; p < 0.001) and was associated with platelet count (r = 0.34; p = 0.04) and the presence of schistocytes (r = -0.37; p = 0.02). Apart from the association with TMA, ADAMTS13 was inversely associated with creatinine (r = -0.42; p = 0.008). Increasing levels of VWF were associated with a decrease in ADAMTS13 activity (r = -0.34; p = 0.03). There was no significant association between ADAMTS13 activity and other parameters, including blood pressure. The authors concluded that ADAMTS13 is decreased in malignant hypertension and associated with the severity of TMA, likely because of the release of VWF after endothelium stimulation. A severe deficiency could not be demonstrated. They stated that more studies are needed to identify the role of ADAMTS13 in the TMA and ischemic complications of malignant hypertension.

Claus and colleagues (2009) measured VWF and related parameters as well as the protease activity regulating its biological activity in plasma of healthy controls and patients with different cause and severity of systemic inflammation to examine the effectiveness of the measures to detect highly prothrombotic states including TMA, one of the sequelae of sepsis. Plasma levels of VWF increased with increasing severity of systemic inflammation, probably due to activation of the endothelium. In parallel, the proteolytic activity of VWF inactivating protease, ADAMTS13, stepwise declined with the severity of inflammation, emphasizing the role of VWF-triggered platelet aggregation on the endothelium subsequently followed by development of TMA. As a consequence, the ratio of VWF antigen level and ADAMTS13 activity was significantly higher in patients with inflammation and sepsis, suggesting that this ratio might be more useful for the diagnosis of highly prothrombotic states including TMA than VWF multimer analysis alone. These findings suggested that ADAMTS13, VWF and related parameters, even in a combined approach, might be useful for the diagnosis and the therapeutic monitoring of patients with sepsis associated thrombotic microangiopathy.
In a case-control study, Molvarec et al (2009) examined if plasma ADAMTS13 activity is decreased in pre-eclampsia. A total of 67 pre-eclamptic patients, 70 healthy pregnant women and 59 healthy non-pregnant women were enrolled in this study. Plasma ADAMTS13 activity was determined with the FRETS-VWF73 assay, while VWF antigen (VWF:Ag) levels with an enzyme-linked immunosorbent assay. The multi-meric pattern of VWF was analyzed by SDS-agarose gel electrophoresis. There was no significant difference in plasma ADAMTS13 activity between the pre-eclamptic and the healthy pregnant and non-pregnant groups (median [25 to 75%]: 98.8 [76.5 to 112.8] %, 96.3 [85.6 to 116.2] % and 91.6 [78.5 to 104.4] %, respectively; p > 0.05). However, plasma VWF:Ag levels were significantly higher in pre-eclamptic patients than in healthy pregnant and non-pregnant women (187.1 [145.6 to 243.1] % versus 129.3 [105.1 to 182.8] % and 70.0 [60.2 to 87.3] %, respectively; p < 0.001). The multi-meric pattern of VWF was normal in each group. Primi-paras had lower plasma ADAMTS13 activity than multi-paras (92.6 [75.8 to 110.6] % versus 104.2 [92.1 to 120.8] %; p = 0.011). No other relationship was found between clinical characteristics, laboratory parameters and plasma ADAMTS13 activity in either study group. The authors concluded that plasma ADAMTS13 activity is normal in pre-eclampsia despite the increased VWF:Ag levels. However, further studies are needed to determine whether a decrease in plasma ADAMTS13 activity could predispose pre-eclamptic patients to develop HELLP syndrome.

Uemura et al (2010) stated that ADAMTS13 is a metalloproteinase, produced exclusively in hepatic stellate cells, and specifically cleaves highly multi-meric VWF, which plays a pivotal role in hemostasis and thrombosis, and its function is dependent on its multimeric state. Deficiency of ADAMTS13 results in accumulation of unusually large VWF multimers (UL-VWFM) in plasma, in turn induces platelet clumping or thrombi under high shear stress, followed by microcirculatory disturbances. Considering that UL-VWFM, the substrate of ADAMTS13, is produced in transformed vascular endothelial cells at sites of liver injury, decreased ADAMTS13 activity may be involved in not only sinusoidal microcirculatory disturbances, but also subsequent progression of liver injuries, eventually leading to multi-organ failure. This concept can be applied to the development or aggravation of liver diseases, including liver cirrhosis, alcoholic hepatitis, veno-occlusive disease, and adverse events after liver transplantation. These results promise to bring further understanding of the pathophysiology of liver diseases, and offer new insight for development of therapeutic strategies.

Okano et al (2010) evaluated changes of plasma ADAMTS13 activity and its clinical relevance in patients with hepatectomy. Plasma ADAMTS13 activity and its related parameters were sequentially determined after hepatectomy in 70 patients. ADAMTS13 activity significantly decreased from pre-operative 67.0 +/- 30.6 % to 48.1 +/- 24.6 % after hepatectomy (p < 0.0001). Pringle's maneuver for longer than 45 mins (p = 0.0007) and major hepatectomy (p = 0.0002) were significantly associated with the decrease of ADAMTS13 activity to less than 40 %. The decreased ADAMTS13 activity reflected post-operative thrombocytopenia (p = 0.0028) and hyper-bilirubinemia (p < 0.05). The authors concluded that plasma ADAMTS13 activity significantly decreased after hepatectomy due to ischemic injury together with liver mass reduction, reflecting a post-operative liver dysfunction. They stated that monitoring of ADAMTS13 activity may be useful to prevent further development of the liver failure after hepatectomy. Well-designed studies are needed to ascertain the clinical value of ADAMTS13 in monitoring liver diseases.
Choi et al (2011) examined ADAMTS13 activity as well as the ADAMTS13 gene mutation in children with hemolytic uremic syndrome (HUS). A total of 18 patients, including 6 diarrhea-negative (D-HUS) and 12 diarrhea-associated HUS (D+HUS) patients, were evaluated. The extent of VWF degradation was assayed by multimer analysis, and all exons of the ADAMTS13 gene were PCR-amplified using Taq DNA polymerase. The median and range for plasma activity of ADAMTS13 in 6 D-HUS and 12 D+HUS patients were 71.8 % (22.8 to 94.1 %) and 84.9 % (37.9 to 119.9 %), respectively, which were not statistically significantly different from the control group (86.4 %, 34.2 to 112.3 %) (p > 0.05). Five ADAMTS13 gene mutations, including 2 novel mutations [1584+2T>A, 3941C>T (S1314L)] and 3 polymorphisms (Q448E, P475S, S903L), were found in 2 D-HUS and 1 D+HUS patients, which were not associated with deficiency of ADAMTS13 activity. Whether these mutations without reduced ADAMTS13 activity are innocent bystanders or predisposing factors in HUS remains unanswered.

Ikeda et al (2011) noted that chronic liver injury evokes a wound healing response, promoting fibrosis and finally hepatocellular carcinoma (HCC), in which hepatic stellate cells play an important role. Although a blood marker of hepatic stellate cells is not known, those cells importantly contribute to the regulation of plasma ADAMTS13 activity. In this study, plasma ADAMTS13 activity was used to predict development of HCC in patients with chronic hepatitis B and C. Plasma ADAMTS13 was evaluated in chronic hepatitis B or C patients with or without HCC. Plasma ADAMTS13 activity significantly correlated with serum aspartate aminotransferase and alanine aminotransferase, liver stiffness value, and aspartate aminotransferase-to-platelet ratio index, irrespective of the presence of HCC, suggesting that it may reflect hepatocellular damage and subsequent wound healing and fibrosis as a result of hepatic stellate cell action. During the 3-year follow-up period for patients without HCC, it developed in 10 among 81 patients. Plasma ADAMTS13 activity was significantly higher in patients with HCC development than in those without and was a significant risk for HCC development by uni-variate and multi-variate analyses. Furthermore, during the 1-year follow-up period for patients with HCC treated with radiofrequency ablation, HCC recurred in 55 among 107 patients. Plasma ADAMTS13 activity or antigen level was significantly higher in patients with HCC recurrence than in those without and was retained as a significant risk for HCC recurrence by multi-variate analysis. The authors concluded that higher plasma ADAMTS13 activity and antigen level was a risk of HCC development in chronic liver disease. They stated that plasma ADAMTS13 as a potential marker of hepatic stellate cells may be useful in the prediction of hepatocarcinogenesis.

In an observational study, Freynhofer et al (2011) investigated the alterations of plasma VWF and ADAMTS13 following cardioversion (CV) and evaluated the predictive value of these parameters for recurrence of atrial fibrillation (AF). These researchers determined plasma levels of VWF and ADAMTS13 in 77 patients before and immediately after CV, as well as 24 hours and 6 weeks thereafter, by means of commercially available assays. The VWF/ADAMTS13-ratio was significantly elevated immediately after CV (p = 0.02) and 24 hours after CV (p = 0.002) as compared to baseline levels. ADAMTS13, 24 hours after CV, exhibited a significant association with recurrence of AF (hazard ratio [HR]: 0.97; p = 0.037). Accordingly, tertiles of ADAMTS13 showed a step-wise inverse correlation...
with the risk of recurrent AF (HR: 0.50; p = 0.009). After adjustment for confounders, ADAMTS13 remained significant as an independent predictor of recurrent AF (HR: 0.61; p = 0.047). Similarly, the VWF/ADAMTS13-ratio, 24 hours after CV, was associated with rhythm stability and remained an independent predictor of recurrent AF (HR: 1.88; p = 0.028). The regulation of VWF and its cleaving protease ADAMTS13 after CV might play a critical role in producing a pro-thrombotic milieu immediately following CV for AF. The authors concluded that since ADAMTS13 plasma concentration as well as the VWF/ADAMTS13-ratio are independently associated with rhythm stability, these indexes might be used for prediction of recurrence of AF. These findings need to be validated by well-designed studies.

Habe and co-workers (2012) noted that ADAMTS13, endothelial VWF and related proteins are involved in the pathogenesis of some life-threatening systemic thrombotic coagulopathies. Changes of plasma ADAMTS13 activity in TTP is well-known but is also involved in septic disseminated intravascular coagulation (DIC). These researchers investigated the ADAMTS13 activity, VWF and VWF pro-peptide (VWFpp) antigens in 69 patients with DIC, 143 with non-DIC, 21 with TTP and 23 with atypical HUS (aHUS) for diagnosis of DIC. The plasma ADAMTS13 activity was significantly low in patients with DIC, and the plasma levels of VWF and VWFpp antigens, were the highest in these patients, but there were no significant differences in the plasma VWFpp levels between the patients with DIC and those with aHUS. The difference in the plasma ADAMTS13 activity, the VWF and VWFpp antigens between DIC and non-DIC cases was significant in those with infectious and malignant diseases, but the difference in the VWFpp/VWF ratio were significant only in subjects with infectious diseases. As an indicator for prognosis, the plasma levels of VWFpp were significantly higher in non-survivors than in survivors. Then, VWFpp/VWF ratio and VWFpp/ADAMTS13 ratio will be potent informative indicators in DIC. The authors concluded that these findings suggested that ADAMTS13/VWF profiles may have important roles in the pathogenesis of DIC, and that ADAMTS13 and VWFpp are useful indicators for the diagnosis and prognosis of DIC. These findings need to be validated by well-designed studies.

Mazetto et al (2012) stated that increased levels of inflammatory markers and clotting factors have been related to the pathogenesis and prognosis of venous thromboembolism (VTE). In particular, the imbalance between VWF and ADAMTS13 has been described in patients with arterial thrombosis. In this study, a total of 77 patients with previous VTE and 77 matched controls were selected for the evaluation of the inflammatory markers, FVW, ADAMTS 13, and D-dimer. The presence of post-thrombotic syndrome (PTS) and residual vein obstruction (RVO) were also assessed in patients. Serum levels of tumor necrosis factor-alpha and interleukin-6 were significantly increased in patients compared to controls (median = 2.25 versus 1.59 pg/ml, p ≤ 0.001; 1.16 versus 0.98 pg/ml, p = 0.013, respectively). Plasma levels and activity of VWF (median = 150.25 versus 95.39 U/dL, p ≤ 0.001; 145.26 % versus 92.39 %, p ≤ 0.001) and ADAMTS 13 (median = 1088.84 versus 950.80 ng/ml, p ≤ 0.001; 96.03 versus 83.64 %, p ≤ 0.001) were also higher in patients. These investigators further analyzed the subgroups of patients with higher risk for VTE recurrence or VTE sequelae, defined as the presence of high D-dimer levels, RVO or PTS. All inflammatory markers were significantly higher in patients with increased D-dimer. The presence of PTS or
RVO was not associated with higher inflammatory or coagulation parameters. The increased levels of inflammatory markers and VWF may suggest that there is a persistence of inflammatory activity in patients even at long periods after the VTE episode. In this context, it may be postulated that increased levels of ADAMTS13 could represent a compensatory mechanism against persistently increased levels of VWF. Moreover, increased inflammatory activity was associated with increased D-dimer levels, thus it is possible that this inflammatory activity may also be related to the risk of VTE recurrence.

Sonneveld et al (2014) stated that VWF plays an important role in hemostasis by mediating platelet adhesion and aggregation. Ultra-large VWF multimers are cleaved by ADAMTS13 in smaller, less pro-coagulant forms. An association between high VWF levels and cardiovascular disease has frequently been reported, and more recently also an association has been observed between low ADAMTS13 levels and arterial thrombosis. These investigators reviewed the current literature and performed meta-analyses on the relationship between both VWF and ADAMTS13 with arterial thrombosis. Most studies showed an association between high VWF levels and arterial thrombosis. It remains unclear whether ADAMTS13 is a causal independent risk factor because the association between low ADAMTS13 and arterial thrombosis is so far only shown in case-control studies. The authors concluded that prospective studies are awaited; a causal role for ADAMTS13 is supported by mice studies of cerebral infarction where the infusion of recombinant human ADAMTS13 reduced the infarct size.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met:

85397

ICD-9 codes covered if selection criteria are met:

446.6 Thrombotic microangiopathy [thrombotic thrombocytopenic purpura]

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

155.0 Malignant neoplasm of liver, primary
283.11 Hemolytic-uremic syndrome
401.0 Malignant essential hypertension
402.00 - 402.01 Malignant hypertensive heart disease
403.00 - 403.01 Malignant hypertensive chronic heart disease
404.00 - Malignant hypertensive heart and chronic kidney disease
404.03

405.00 - Malignant secondary hypertension
405.09

411.81 - Acute coronary occlusion without myocardial infarction

427.31 - Atrial fibrillation

453.0 - 453.9 - Other venous embolism and thrombosis [for prediction of recurrence of venous thromboembolism]

570 - Acute and subacute necrosis of liver

571.0 - 571.9 - Chronic liver disease and cirrhosis

572.0 - 572.8 - Liver abscess and sequelae of chronic liver disease

573.0 - 573.9 - Other disorders of liver

642.40 - Pre-eclampsia or eclampsia
642.94

995.90 - Systemic inflammatory response syndrome (SIRS) [sepsis
995.94 - associated with thrombotic microangiopathy]
[reported with
446.6]

The above policy is based on the following references:


hepatectomy, reflecting a postoperative liver dysfunction. 
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factor (VWF) and VWF propeptide profiles in patients with DIC and related 
29. Mazetto BM, Orsi FL, Barnabe A, et al. Increased ADAMTS13 activity in 
30. Aref S, Goda H. Increased VWF antigen levels and decreased ADAMTS13 
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