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Cost-effectiveness of thrombotic thrombocytopenic purpura diagnosis: a retrospective analysis in the University Hospital Center of Lyon (France)

Emilie Joussetme^a, Frédéric Sobas^a, Pascale Guerre^b, Marie Simon^c and Christophe Nougier^a

The aim of the present study was to perform an economic evaluation of two alternative assays of ADAMTS13 activity (A Disintegrin And Metalloprotease with ThromboSpondin type 1 repeats, member 13) for diagnosing thrombotic thrombocytopenic purpura (TTP) in the Hospital of Lyon (France). The study approach was more economic than clinical. We retrospectively calculated the prescription costs of ADAMTS13 activity from January to December 2019 for patients depending on the assay: manual ELISA (Technozym) or automated assay (AcuStar Werfen, Instrumentation Laboratory). Then, we compared the cost of therapeutic plasma exchange (TPE) consumption awaiting ADAMTS13 activity assay results. From an economic point of view, the automated assay was more cost-effective. From a clinical one, we supposed that the faster results given by AcuStar could improve patient care by reducing the number of TPEs. Automated assay could improve patient care without increasing costs in our

Introduction

Thrombotic thrombocytopenic purpura (TTP), a form of thrombotic microangiopathy (TMA), is rare (incidence of 3–10 per million per year) and is characterized by a combination of microangiopathic haemolytic anaemia, deep thrombocytopenia, microthrombosis and, in severe cases, multiorgan failure with rapidly fatal outcome in the absence of treatment [1]. In acquired TTP (aTTP), the introduction of therapeutic plasma exchange (TPE) has resulted in a significant reduction in mortality, with more than 80% recovery [1]. Associated immunosuppressive corticosteroids and rituximab are also recommended to limit the number of TPEs and reduce disease recurrence [2,3], but have only small benefit in terms of survival [4].

Severe ADAMTS13 (A Disintegrin And Metalloprotease, with a ThromboSpondin type 1 repeats, member 13) deficiency is pathognomic for TTP when ADAMTS13 activity is undetectable (<10%) [5]. The role of this metalloprotease in plasma is to cleave von Willebrand factor (VWF). Without regulation of VWF length, spontaneous VWF-dependent platelet adhesion and aggregation occurs, leading to disseminated microvascular thrombosis [1]. aTTP through production of autoantibodies is more common than congenital deficiency (90% of cases) [6]. Recently, better understanding of the mechanisms of this disease has improved clinical care, with an innovative new drug: targeted therapy with caplacizumab

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is now recommended as first-line treatment [7,8]. This nanobody, directed against a specific VWF domain is used to prevent interaction between VWF and platelets. Caplacizumab has been shown to be effective in reducing thrombocytopenia, reducing the number of TPEs and the volume of plasma exchanged, shortening length of stay and reducing clinical recurrence and mortality. This treatment, which reverses thrombosis and haemolysis directly into the vascular microcirculation, is administered in combination with TPE and immunosuppressive therapy to resolve acquired ADAMTS13 dysfunction [7,8].

Diagnosis of TTP is challenging due to nonspecific symptoms (digestive, neurological, thrombotic and so on) in various situations (pregnancy, immune disease and so on). Biological scores, such as the French Score [9], including creatinine level ($\leq 200 \mu\text{mol/l}$) and/or platelet count ($< 30 \times 10^9/l$) and/or positive antinuclear antibodies (ANA) can be used to identify patients quickly. When one criterion is present, the positive predictive value of this score is 85.0%, negative predictive value 93.3%, sensitivity 98.8% and specificity 48.1%, but only ADAMTS13 activity less than 10% can confirm diagnosis [5]. As recommended, TPE is started before results come back. If the diagnosis is confirmed, antibody testing proves that TTP is acquired, but antibody level at the acute phase is not correlated with risk of refractory and

death [5]. If diagnosis is excluded (ADAMTS13 activity >10%), the earlier this is established, the more complications of TPE can be avoided: bleeding, catheter-associated thrombosis, infection and systemic reactions [3,4,10]. Although first-line TPE is recommended and mortality is thereby reduced, clinicians still want a biological measurement of ADAMTS13 activity in real time. This is increasingly relevant today with targeted therapy. Caplacizumab should be injected as early as possible to limit microvascular damage [8], otherwise treatments or targeted therapies for other TMAs [e.g. eculizumab in atypical haemolytic uremic syndrome (aHUS)] cannot be implemented [11]. Rapid results are also needed in emergency situations for diagnosis, prognosis and treatment options [1].

Fluorescence resonance energy transfer (FRET)-VWF73, a historical method based on full-length VWF, is a reference method for the measurement of ADAMTS13 activity, but could only be performed by expert laboratories. In early 2010, commercial kits were developed, accessible to nonexpert laboratories and showing good performance [12]. One of them, a chromogenic test, Technozym ADAMTS13 ELISA (Chr-VWF73, Technoclone, Vienna, Austria), is available for diagnosis in laboratories. Although nonexpert laboratories can perform ELISA testing, it is still a manual test, requiring specific staff training, which can be time-consuming, and the assay duration is quite long (3.5 h) [13]. Many laboratories cannot measure ADAMTS13 activity continuously throughout the day, and getting a fast and reliable result is a challenge. Recently, a fully automated ADAMTS13 activity test, AcuStar (Werfen, Instrumentation Laboratory, Bedford, Massachusetts, USA), has come onto the market. This test showed high correlation with the FRET and ELISA tests, with near-zero bias on low activity (ADAMTS13 < 10%). With a turn-around time of 33 min, this automated test is also an interesting tool in emergency situations [13–15].

In our centre's haemostasis laboratory, ADAMTS13 activity is measured using the Technozym ADAMTS13 ELISA test. As mentioned in the procedure manual, results are only available every 2 weeks for optimized kits and staff. For strong suspicion of TTP, clinicians need to call the laboratory for prompt results. In this case, depending on the organization of the laboratory, results may not be available within 48 h of clinical suspicion. In case of clinical suspicion during these 48 h, TPEs are frequently performed as recommended, but sometimes unnecessarily if diagnosis is later excluded by the results for ADAMTS13 activity.

As diagnosis is crucial for patient care, we decided to evaluate ADAMTS13 activity on the AcuStar. As the laboratory already had this device, only the kits needed to be purchased. Due to the higher cost compared with ELISA kits, we decided to carry out an economic

evaluation of the two alternative diagnostic tests for TTP. As there were no available previous studies at that time, the hypothesis was that the higher item cost of AcuStar was offset by avoiding unnecessary TPEs in clinical departments and reducing technician time in the laboratory.

Materials and methods

We conducted a retrospective study of care costs for suspected TTP patients in the Lyon university hospital from January to December 2019. Timing began at the time of sampling and stopped when the results for ADAMTS13 activity were obtained. Economic comparison was based on the actual cost of patient care in 2019 resulting from the delay in obtaining the ADAMTS13 activity with the ELISA tests, with estimated cost if AcuStar tests had been used in 2019 (Fig. 1). The data comprised patient reports from the hospital database; number of tests performed and number of laboratory test series in 2019; number of fresh frozen plasma (FFP) samples consumed for TPE [information provided by the EFS (*Etablissement Français du Sang*) and regulatory cost of FFP in France (<https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000021961438&-categoryLink=id>); cost of TPEs according to the official list of medical treatments (1 January 2018) (<https://www.ameli.fr/accueil-de-la-ccam/trouver-un-acte/fiche-abregee.php>); actual cost of kits for the manual method (ELISA test) in 2019; cost of kits for AcuStar according to the supplier's estimate; and the starting salary of a laboratory technician, as given by the hospital's human resources department.

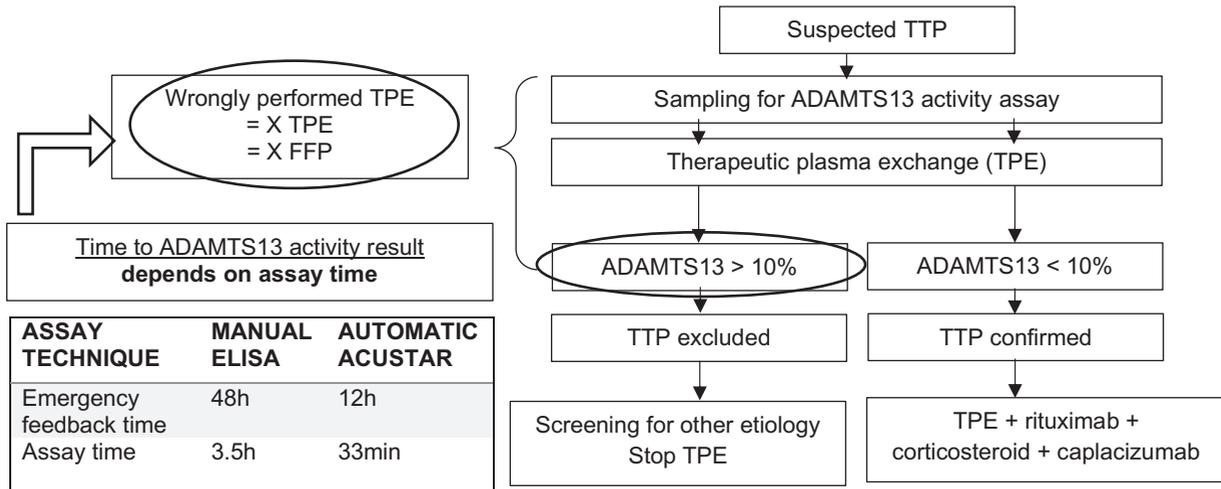
The expense items evaluated in the study were the cost of the assays (biological costs) and the cost of the TPE procedures (clinical costs). For the cost of ADAMTS13 activity measurements, we calculated the number of kits at the current price per test, and the time spent by the laboratory technician (in h to perform these tests, monetarized according to a laboratory technician's starting salary. For the cost of the TPE procedure, we calculated the number of unnecessary TPEs performed in 2019 and the cost of the procedure and the cost of FFP incorrectly, used according to the official rates.

Results

In 2019, we received 165 patient plasma samples for ADAMTS13 activity measurement from 93 patients.

Seventy-one patients did not receive TPE awaiting ADAMTS13 measurement. Ten patients were on TTP follow-up (remission or recurrence still diagnosed). Twenty-three patients had other TMA suspicion, then confirmed by biological results: nine Shiga toxin-producing *Escherichia coli* associated haemolytic uremic syndromes (STEC-HUS), 13 secondary aHUS (five malignancy aHUSs, one posttransplant aHUS, four drug-induced aHUSs, three HELLP syndromes) and one primary aHUS.

Fig. 1



Thrombotic thrombocytopenic purpura diagnosis and treatment flowchart and time to obtain results depending on ADAMTS13 activity assay used. FFP, fresh frozen plasma. TPE, therapeutic plasma exchange.

Two other patients had malignant hypertension, three had preeclampsia and 33 had other diseases.

Seventeen patients received at least one TPE awaiting ADAMTS13 activity measurement because of strong clinical suspicion of TTP, and five patients were awaiting diagnosis of recurrence (although only one of these was symptomatic) ($n = 22$). We classified these patients into four groups: wrongly treated with TPE (ADAMTS13 $> 10\%$) ($n = 9$); diagnosis of recurrent disease (ADAMTS13 $< 10\%$ with patient history) ($n = 5$); diagnosis of TTP (first time of undeterminable ADAMTS13 $< 10\%$) ($n = 5$); and no TTP but TPE nevertheless indicated (ADAMTS13 $> 10\%$) ($n = 3$) (Table 1). Using the French Score, all patients with TTP diagnosis had a positive score ($n = 5$) and seven would have been misclassified (false positive) with at least one positive criterion but normal ADAMTS13 activity (five 'wrongly treated with TPE' and two 'No TTP, but TPE justified'). Five patients were correctly classified with a negative score and negative ADAMTS13 activity (Table 2). Also, TPE other than for TTP ($n = 12$) was performed for one STEC-HUS, six secondary aHUSs (one malignancy aHUS, one posttransplant aHUS, one

drug-induced aHUS, one HELLP syndrome, one pregnancy aHUS, one autoimmune aHUS), one preeclampsia, one paroxysmal nocturnal haemoglobinuria (PNH) and three other diseases.

In these 22 patients, ADAMTS13 results immediately impacted patient management; turn-around time for ADAMTS13 activity measurement was shortest for the 'TTP Diagnosis' group (49 h), less than that in the 'Wrongly treated' group (67 h) (Table 1).

In our cohort, we retrospectively calculated the laboratory and clinical procedure cost of potential TTP patient care in 2019 (Table 3). For all 165 plasma samples, the laboratory consumed eight ELISA kits (€8179.2) and 129.5 technician hours (€2235.17), for a total €10414.37. From a clinical point of view, as the aim of the study was to address costs wrongly incurred, we analysed only the clinical data of the nine patients in whom TPEs were unnecessary. Eighteen TPEs were performed in the ICUs [one ($n = 4$), two ($n = 2$), three ($n = 1$), four sessions ($n = 1$)], using 277 FFPs. The clinical cost was €31 287.31: €3412.80 for the TPE procedure and €27 974.51 for the FFPs. Thus, in 2019, with the

Table 1 Classification of patients for clinical suspicion of thrombotic thrombocytopenic purpura

ADAMTS13 activity results: ELISA measurement

Number of patients	Groups	Average time to obtain results ^a	Number of TPEs performed	Number of FFPs used
9	Wrongly treated by TPE	68 h	18	277
5	Diagnosis of recurrence	186 h	6	56
5	Diagnosis of TTP	49 h	9	153
3	No TTP, but TPE justified	90 h	4	95

Classification of patients who received Therapeutic Plasma Exchange (TPE) in 2019 in the University Hospital of Lyon for clinical suspicion of Thrombotic Thrombocytopenic Purpura (TTP). FFP, fresh frozen plasma. ^aAverage time: time between sampling and biological validation.

Table 2 Contingency table of French Score according to final first diagnosis of thrombotic thrombocytopenic purpura in the group of patients who received therapeutic plasma exchange other than for relapse (n = 17)

French score	TTP first diagnosis based on ADAMTS13 activity measurement (<10%)	
	Present (n = 5)	Absent (n = 12)
Positive = At least one criterion	Five patients 'Diagnosis of TTP'	Five patients 'Wrongly treated by TPE' Two patients 'No TTP, but TPE justified'
Negative	0 patients	Four patients 'Wrongly treated by TPE' One patient 'No TTP, but TPE justified'

Using the French Score, all five patients with diagnosis of TTP had positive scores, seven patients would have been misclassified (false positive) and five with unnecessary TPEs, and five patients were correctly excluded.

ELISA test, the total cost was €41 707.68. Regarding these nine patients, and using the French Score to improve therapeutic management, five patients would have been misclassified with unjustified TPEs ('Wrongly treated by TPE') (Table 2). These patients can be considered as needing results in emergency to allow TPE to be discontinued. Awaiting ADAMTS13 measurement, they received 13 TPEs, using 208 FFPs (Table 3). With the ELISA test and the French Score, clinical cost can be retrospectively calculated at €23 395.84 for a total cost of €33 810.21.

For the same population in 2019, we estimated the hypothetical biological and clinical costs if the AcuStar test had been used in our hospital. Although AcuStar is an automated test with 33-min turn-around, we estimated that technicians would need 10 min to manage AcuStar analyser. For the activity recorded in 2019, technician time would be 8 h (€138.08) for 10 kits consumed (€30 240). Regarding clinical cost, as clinical results can be obtained in real time, no TPEs should be

performed incorrectly and no unnecessary FFPs should be used. Thus, for 2019, with the AcuStar test, costs should be purely biological, at €30 378.08.

Comparison between ELISA and AcuStar showed that the new test had higher biological cost but, overall, costs associated with the manual test were higher from the institution's perspective, due to significant clinical costs and mean differences between the two alternative diagnostic tests was €11 323.60. This difference was always in favour of the AcuStar test (€3432.13) when using the French Score to improve identification of TTP patients.

Discussion

The results of the present study showed that, in our centre, diagnosis could be improved, as the average time to diagnose a new case of TTP is 49 h, although the laboratory time for an ADAMTS13 activity result is less than 48 h in emergency cases. Patient identification time associated with the time to obtain biological results may contribute to patient death [4]. The purpose of the study

Table 3 Retrospective costs depending on the assay used for ADAMTS13 activity

2019		Expenditure	ELISA Real cost (€)	ELISA Real cost (€) using the French Score	ACUSTAR Estimated cost (€)	
BIOLOGICAL	Assay: 165 plasma samples	Cost of one kit	1022.40	1022.40	3024	
		Number of ADAMTS13 activity assays	165	165	165	
		Number of kits for the number of plasma samples in 2019	8	8	10	
	Laboratory technician	Annual cost	8179.20	8179.20	30 240	
		Starting salary per hour	17.26	17.26	17.26	
		Number of hours spent on ADAMTS13 activity measurement in 1 year	129.5	129.5	8	
		Annual cost	2235.17	2235.17	138.08	
	<i>Biological costs</i>			10 414.37	10 414.37	10 414.37
	Number of patients wrongly treated		Nine patients	Five patients	0 patient	
	CLINICAL	Number of TPEs	Cost of one TPE session	189.60	189.60	189.60
Number of TPEs wrongly performed			18	13	0	
Cost of sessions			3412.80	2464.80	0	
Number of FFPs		Cost of one FFP	100.63	100.63	100.63	
		Number of FFPs wrongly used	277	208	0	
		Cost of FFPs	27 874.51	20 931.04	0	
<i>Clinical Costs</i>			31 287.31	23 395.84	31 287.31	
All costs			41 701.68	33 810.21	30 378.08	
Difference (AcuStar-ELISA)				-11 323.60		
Difference (AcuStar-ELISA using French Score)				- 3432.13		

Retrospective costs for laboratory and clinical procedures in suspected TTP in 2019 in the University Hospital of Lyon depending on the assay used for ADAMTS13 activity: manual ELISA or automated AcuStar. In 2019, 165 measurements were performed and nine patients wrongly received therapeutic plasma exchange (TPE) awaiting assay results. Using French Score classification, five patients would have been misclassified. FFP, fresh frozen plasma.

was to conduct an economic evaluation of the automated test (AcuStar) compared with the classical ELISA: the results indicated that AcuStar is more cost-effective than ELISA because of the clinical consideration of avoiding unnecessary TPE even when using the French Score to improve patient classification. However, we probably underestimated the actual clinical costs, such as nursing care time, medical devices and ICU beds, and this would doubtless be to the benefit of the AcuStar approach. This type of evaluation requires a micro-costing study of the time spent by each professional, which cannot be done in a retrospective study. The time spent in clinical departments is also difficult to estimate as patients sometimes suffer from many other illnesses. Otherwise, we assumed that early diagnosis should improve patient care, not only for patients who had unnecessary TPE but also for all patients in the hospital: the bed and the FFPs used for suspected TTP could be allocated to those patients who really need it.

This study demonstrated significant cost-savings in suspected TPP through rapid diagnosis and targeted treatment, reducing length of stay and unnecessary TPEs. However, a longer-term, multicentre, prospective, cost-effectiveness study should be conducted to validate these initial results.

Conclusion

In the Lyon University Hospital Center, automated measurement of ADAMTS13 activity could enable better patient care without increasing costs from the institution's point of view. This new technology provides immediate benefit to the hospital through a biological and evidence-based approach to patient treatment.

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Dr. Jousselme E., Dr. Sobas F., Dr. Nougier C., Mme Guerre P. contributed to the study conception and design. Jousselme E. performed material preparation, data collection and analysis, wrote the first draft of the

manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

No ethical approval was needed, as the study was retrospective and no contact with the participants was involved.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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