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Review

Management of acquired, immune thrombocytopenic purpura (iTTP): beyond the acute phase

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***Abstract*:** Modern therapy for acute TTP has resulted in a dramatic improvement in outcomes, with the combination of plasma exchange, immunosuppression, and caplacizumab being associated with >90% survival rates following an acute episode. TTP is no longer associated with just the acute episode, but requires long-term follow-up. There remains significant morbidity associated with acute TTP, and many patients suffer marked neuropsychological sequelae, including impairment in cognitive functioning, affective disorders, and reduction in health-related quality of life measures. The focus of management beyond the acute phase centres on relapse prevention, *via* careful monitoring of patients and the use of either ad hoc or regular immunosuppressive therapies. The main therapy used is rituximab, but despite more limited evidence, other immunosuppressive therapies may be required to aim for normalisation of ADAMTS 13 activity. Follow-up with a reduction in ADAMTS 13 activity levels (ADAMTS 13 relapse), rituximab is central to normalisation of activity levels and prevention of a clinical relapse. Fundamental to elective therapy is the role of ADAMTS 13 activity monitoring, and impact of reduced ADAMTS13 activity on end organ damage. This review discusses monitoring and treatment strategy for long-term management of TTP, including the variety of therapies available to maintain remission, prevent relapse and a summary of a long-term treatment pathway.

Keywords: ADAMTS 13 relapse, anti CD 20 therapy, long term follow up, TTP

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare thrombotic microangiopathy (TMA) with an incidence of approximately 6 cases per million per year in the United Kingdom.[1] First described by Moschcowitz in 1924,[2] TTP was initially described as a pentad of anaemia, thrombocytopenia, renal failure, fever, and neurological symptoms; in the absence of any treatment, the disease was rapidly fatal. In later decades, there were reports of patients responding to plasma infusions, and this helped develop the idea that those affected were lacking a plasma protein. This was later found to be a von Willebrand Factor (vWF) cleaving protease,[3,4] a metalloprotease described as ADAMTS13 (*a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13)*. ADAMTS13 is essential in the cleavage of ultra-large vWF multimers; in TTP, these uncleaved ultra-large vWF multimers unfold in the microvasculature under conditions of high shear stress, resulting in the formation of platelet-rich microthrombi. Microangiopathic haemolytic anaemia (MAHA) results from the mechanical haemolysis caused by the action of microthrombi on circulating erythrocytes. Microthrombi typically occur in the brain and heart but can also affect other organs, including the kidneys. The majority (>80%) of cases of TTP are immune (termed iTTP), with the formation of anti-ADAMTS13 autoantibodies resulting in a marked reduction in ADAMTS13 activity (typically to <10% normal), either due to inhibitory action of the autoantibodies or increased clearance of the enzyme.

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A much rarer congenital form of the condition (cTTP), also known as Upshaw–Schulman syndrome, is caused by mutations in the ADAMTS13 gene, resulting in reduced production and/or functional defects of the metalloprotease.

Acute TTP and developments in treatment

Acute TTP is defined as a TMA with the presence of a MAHA and thrombocytopenia (platelets $< 150 \times 10^9$/L) associated with a severe deficiency of ADAMTS13 to <10%; although organ involvement in common, this is not a prerequisite for diagnosis. Given the brain is a primary target for TTP, neurological symptoms are the most commonly seen acutely (in approximately 70% of patients), although symptoms can be very variable. Cardiac involvement is also frequently seen (approximately 40% cases), with an elevated troponin being the commonest sign of cardiac involvement.[1]

With improved understanding of the pathophysiology of TTP, came marked improvements in therapies for acute TTP, and these have resulted in a disease which was historically universally fatal, now having much-improved outcomes. Following the initial improved survival seen with plasma infusions, came evidence of further improvement in outcomes with plasma exchange[3,4] and the use of immunosuppression with steroids. This resulted in marked improvements in acute survival and a high initial response rate (approximately 80%).[5] However, overall outcomes were affected by some patients being refractory to plasma exchange and steroids (approx. 10–20%) and the fact that some patients were quick to lose response to initial therapy (so-called exacerbation) or developed an acute relapse. Prior to the advent of newer immunosuppressive therapies, acute relapses occurred in up to 30–50% of patients who had initially attained a remission with plasma exchange and steroids, typically within a few months of the initial episode.[6]

The management of relapsed/refractory cases was historically very challenging, and typically involved the use of ongoing plasma exchange and immunosuppression with steroids. Additional immunosuppressive agents were also used in these cases, including cyclosporine or vincristine, but use was frequently limited by toxicity. One of the most important developments was the introduction of anti-CD20 therapies (rituximab) which were initially used for relapse/refractory cases and found to have significant efficacy. A pivotal study showed much improved relapse-free survival in acute TTP patients, given rituximab compared to historical controls treated with plasma exchange and steroids alone.[7] Subsequently the use of rituximab has expanded, both in treatment of acute TTP cases, and preventing TTP relapse in patients in clinical remission but having low ADAMTS13 levels. Another major development in acute TTP treatment was the introduction of the anti-VWF nanobody caplacizumab. This acts by targeting the vWF A1 domain and inhibiting interaction with the platelet glycoprotein Ib-IX-V receptor, thus reducing microvascular thrombosis.[8] The use of caplacizumab has resulted in faster normalisation of platelet count and lower incidence of a composite of TTP-related death, recurrence of TTP, and thromboembolic events during the treatment period.[9,10]

The current standard of care for acute TTP comprises plasma exchange, immunosuppression, and caplacizumab.[11,12] With this approach, mortality from acute TTP is in the order of 5–10%. However, it is clear that acute TTP results in significant morbidity in survivors and limiting morbidity should be an important goal of acute therapy.

While reducing mortality and achieving remission remains the primary focus of treatment of the acute phase, maintaining remission and preventing relapse is the main challenge of managing TTP longer-term. This review will focus on the importance of monitoring and the types of therapy available to prevent TTP relapse.

TTP remission and relapse

Definitions of TTP remission have been recently updated to reflect use of newer therapies (including caplacizumab) and improved understanding of the disease itself. Remission has been redefined in new international working group (IWG) criteria into *clinical* remission and *ADAMTS13* remission, reflecting the fact that some patients attain a clinical remission without an ADAMTS13 remission.[13] These patients are given immunosuppression to try and attain an ADAMTS13 remission and therefore reduce their risk of relapse. However, there remain a subset of patients (approximately 10–20%) who do

not achieve an ADAMTS13 remission following intensive immunosuppression.[13–15]

TTP relapse was defined by an IWG (2017) as a drop in platelet count to $<150 \times 10^9$/L after attainment of clinical remission.[16] This definition was limited by not differentiating between a *clinical* relapse (with drop in platelet count) and an *ADAMTS13* relapse (where ADAMTS13 drops in the absence of thrombocytopenia); furthermore, it did not account for the fact that the effect of anti-VWF therapy (caplacizumab) on the platelet count is only transient if it is stopped before ADAMTS13 recovery has occurred.[13] A later IWG (2021) therefore re-classified TTP relapse into clinical relapse and ADAMTS13 relapse,[13] with clinical relapse needing to be confirmed by documentation of severe ADAMTS13 deficiency.[13] ADAMTS13 relapse was defined as occurring after an ADAMTS13 remission (partial or complete), with an ADAMTS13 level decrease to <20%.[13] The ADAMTS13 activity level of 20% was chosen as the threshold for defining ADAMTS13 relapse based on limited evidence that an ADAMTS13 level at or above this cut-off was felt to be protective against clinical relapse based on previous study data.[13–15,17–19]

Pavenski *et al.*[20] categorised risk factors for TTP relapse into two categories: modifiable and non-modifiable. Modifiable risk factors for TTP relapse include ADAMTS13 activity, ADAMTS13 antibody/inhibitor, ADAMTS13 antigen, exposure to triggers and a variety of investigational markers including ADAMTS13 conformation, circulating immune complexes (CICs), and immune transcripts. Non-modifiable risk factors for relapse include history of previous relapse, age, sex, non-blood group O, and HLA type (variant rs6903608).[20]

In practice, ADAMTS13 activity is the most important modifiable TTP risk factor, and the role of monitoring ADAMTS13 activity and the use of targeted treatment with immunosuppressive therapy is described below.

Role of monitoring beyond the acute phase

The main goal of monitoring TTP patients in remission is the prevention of clinical TTP relapses, through regular measurement of ADAMTS13 activity, and the timely use of immunosuppressive therapy in those having an ADAMTS13 relapse or where ADAMTS13 activity remains low following the acute episode. However, the burden of TTP extends to neuropsychological problems and long-term cardiovascular risk, both of which need to be addressed in the clinic.

Monitoring of ADAMTS13 activity and immunosuppressive therapy to prevent clinical relapse

Prevention of clinical relapses is achieved by modifying relapse risk, through monitoring ADAMTS13 activity and giving either ad hoc or continuous immunosuppressive therapy. Given the majority of patients achieve an ADAMTS13 remission shortly after a clinical remission, this entails giving ad hoc (elective) immunosuppressive therapy with anti-CD20 agents in those patients developing a drop in ADAMTS13 activity to a low level, typically <20% – this in effect means giving elective therapy to prevent a clinical relapse in those who are identified as having an ADAMTS13 relapse.

However, 10–20% of patients do not achieve an ADAMTS13 remission following the acute phase, and in these patients, the strategy to prevent clinical relapse involves the use of other immunosuppressive therapies; this may include continuous immunosuppression with mycophenolate mofetil (MMF) or the use of alternative anti-CD 20 therapy (including ofatumumab or obinutuzumab). It is also important to note that low ADAMTS13 levels can be potentially associated with morbidity without a clinical TTP relapse, and there is some evidence to suggest a higher risk of ischaemic stroke in this group.[21] On this basis, every effort should be made to achieve ADAMTS13 recovery in all patients, despite the fact this is not possible in all cases.

Given the importance of ADAMTS13 activity level as a predictor of relapse, the frequency of monitoring ADAMTS13 activity should be determined by whether or not an ADAMTS13 remission has been achieved and the ADAMTS13 activity level itself. In practice, this will mean that most patients will require monitoring every 3–6 months, as long as ADAMTS13 activity remains in the normal range. In those patients developing a drop in ADAMTS13 activity, the frequency of monitoring should be adjusted to reflect this. In cases where there is a marked

reduction in ADAMTS13 activity to a level consistent with an ADAMTS13 relapse (ie <20%), then the ADAMTS13 activity level should be repeated within 1–2 weeks with a view to starting elective anti-CD20 therapy. Where an ADAMTS13 relapse is identified (or felt imminent, based on reducing ADAMTS13 activity), it is essential to ensure the patient's platelet count is monitored carefully, and a clinical assessment of the patient is also made. Some patients may become symptomatic, such as increased headaches, visual auras, lethargy, in association with an ADAMTS13 relapse.

In those patients not attaining an ADAMTS13 remission following the acute episode, it is important that monitoring be more frequent. In practice, patients are monitored in the longer term at least every 3 months, assuming that there has been no evidence of a clinical relapse during the early period (typically first few months) post the initial acute phase. Given the higher relapse risk in this group, it is essential that patients present promptly on developing any new symptoms, and urgent assessment is carried out on suspicion that a clinical relapse is occurring. While there are no specific symptoms of a TTP relapse, patients should be encouraged to report any new symptoms, including any new neurology (Figure 1).

Use of elective immunosuppressive therapy to prevent TTP relapses

For patients identified through monitoring to have a new drop in ADAMTS13 activity to <20%, ad hoc elective anti-CD20 therapy is typically given in the form of rituximab. More recently, newer anti-CD20 therapies such as ofatumumab and obinutuzumab have also been used in this setting, usually in patients who have previously developed complications (include severe reactions) precluding further rituximab use.

For patients in clinical remission, with persistently low ADAMTS13 activity levels despite initial (and/or repeated) use of anti-CD20 therapy, long-term oral immunosuppressive agents can be given, such as MMF.[22] The use of anti-CD20 therapy can also be employed in this group, guided by anti-ADAMTS13 IgG antibody levels (and/or ADAMTS13 antigen levels); a rise in anti-ADAMTS13 antibodies and/or a decline in ADAMTS13 antigen level can indicate that additional immunosuppressive therapy may be useful.[23,24]

In some cases where patients do not have an adequate response to anti-CD20 therapy or MMF, other immunosuppressive therapies can be considered. These include anti-CD38 therapy (such as bortezomib)[25] or other agents such as cyclosporine[26] or cyclophosphamide;[27] the use of these latter agents is frequently limited by toxicity.

Rituximab

Rituximab (Mabthera; Roche Pharmaceuticals) is a humanised anti-CD 20 monoclonal antibody. This was initially used in patients with relapsed or refractory acute TTP and was found to be effective both in terms of improving remission and reducing relapse rates.[28,29] It was subsequently found to be associated with prolonged disease-free survival when used in patients with acute TTP as an adjunct, when compared to historical patients treated with plasma exchange and steroids alone.[7] More recently it has proved efficacious when given on a prophylactic/elective basis in patients at risk of relapse. Although there are no prospective clinical trials evaluating the use of rituximab on a prophylactic/elective basis, rituximab use has been reported in several individual cases and case series[30–36] and larger retrospective reviews,[14,17–19] as well as forming part of a systematic review/meta-analysis.[37]

Hie *et al.*[19] performed a cross-sectional analysis of 48 patients from the French Thrombotic Microangiopathies Reference Centre (all having ADAMTS13 activity <10% in remission) and compared those given rituximab (375 mg/m^2, 1–4 doses per course, weekly) on a pre-emptive basis in remission ($n = 30$) with those not given rituximab ($n = 18$). ADAMTS13 activity in the treatment group had increased to 46% by 3 months post infusion [interquartile range (IQR): 30–68%]. After a median of 17 months post-rituximab, the relapse incidence in the pre-emptive rituximab group had decreased from 0.57 episodes/year to 0 episodes/year ($p < 0.01$). The relapse rate in the untreated group was significantly higher at 0.5 episodes/year ($p < 0.01$) and pre-emptive rituximab group had a longer relapse-free survival ($p = 0.049$).[19]

Jestin *et al.*[14] reported on long-term outcome data for the French group, but with a larger patient

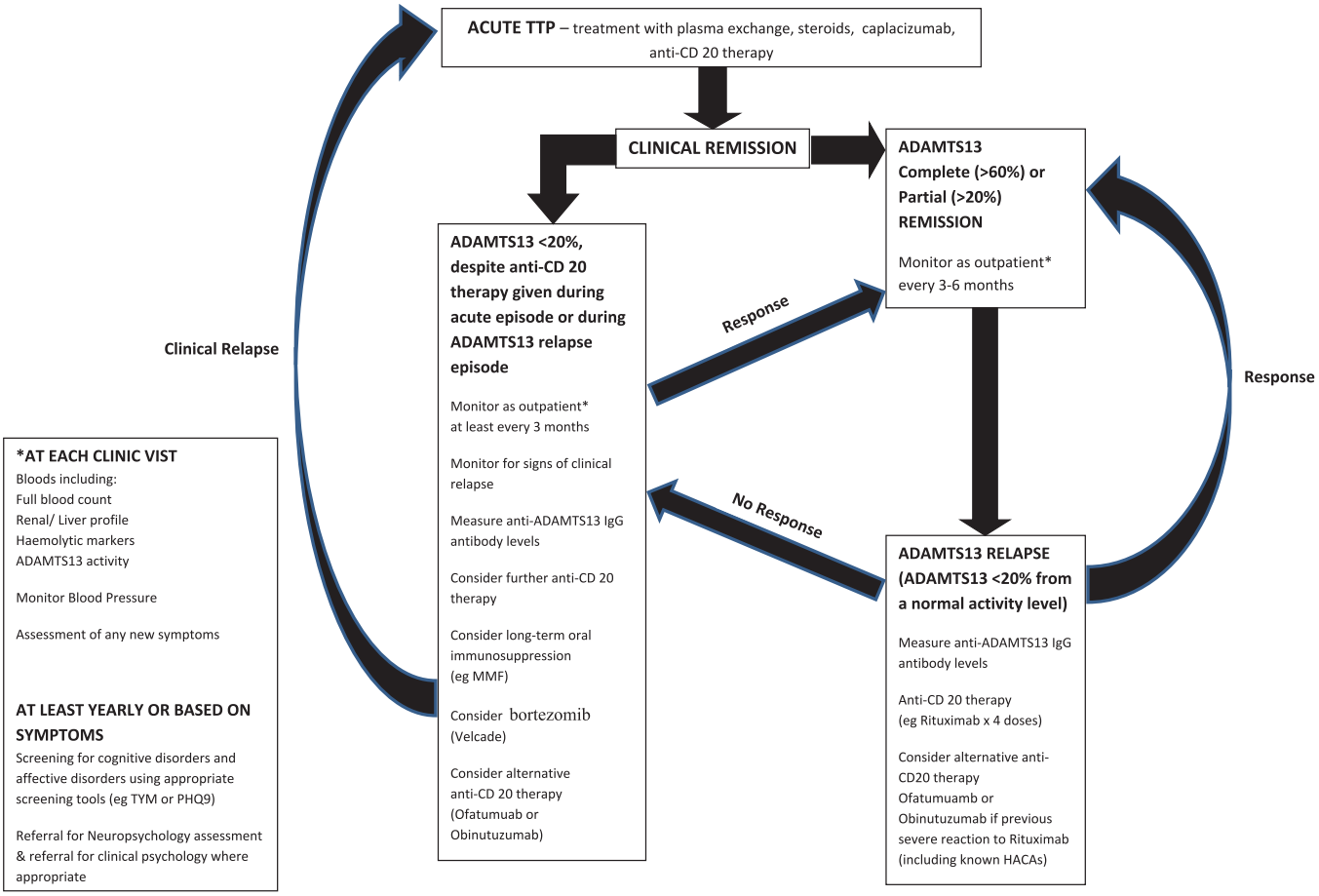

Figure 1. Flow sheet of follow-up following acute TTP.

cohort of 92 patients, all having ADAMTS13 activity <10% and followed up for at least 12 months post-rituximab. Prior to pre-emptive rituximab, 37 patients had had >1 episode of acute TTP, with a median cumulative relapse incidence of 0.33 episodes/year (IQR 0.23–0.66). Rituximab was given at a dose of 375 mg/m^2 in 79 patients and 500 mg/m^2 in 13 patients (1–4 doses per course, weekly). Post pre-emptive rituximab, ADAMTS13 recovery was sustained in 34 patients (37%) over a median follow-up of 31.5 months (IQR 18–65), with severe ADAMTS13 deficiency (defined as <10%) recurring in 45 patients (49%) after an initial response. The median cumulative relapse incidence in the treated group decreased to 0 episodes/year (IQR 0–1.32, $p < 0.001$). Overall, 14 patients (15%) had a clinical relapse, over a median follow-up of 37.8 months (IQR 20–57). This relapse rate was much lower than that reported in 23 historical patients with persistently undetectable ADAMTS13 activity of 74% after a 7-year follow-up (IQR 5–11).[14]

Our own group has reported on pre-emptive rituximab use initially in 21 patient episodes in remission (15 patients); in 17 of these cases, patients had low ADAMTS13 levels <15%, and in four cases, rituximab was given to enable patients to come off long-term immunosuppressive therapy with ciclosporin/tacrolimus. All but two patients were given 375 mg/m^2 once weekly for 4 weeks, with the other two receiving 100 mg/m^2 once weekly for 4 weeks. In the 17 cases where pre-emptive rituximab was given to patients with low ADAMTS13 levels, recovery of ADAMTS13 into the normal range was seen in 16/17 patient episodes, with no acute relapses in this group over a median follow-up of 23 months (range 1–89 months). Four patients required further

rituximab courses (four doses each course) over a total of six episodes following a drop in their ADAMTS13 activity levels occurring at a median of 13 months (range 10–26 months).[17]

We have subsequently published a larger retrospective review as part of the UK TTP Registry, encompassing 76 pre-emptive rituximab treatment episodes in 45 patients.[18] All patients were in clinical remission but deemed to be at high risk of relapse with median ADAMTS13 activity levels of 5% (range <5–17%). Patients received different dosing regimens, allowing a comparison across groups. In 24 treatment episodes 375 mg/m^2 rituximab (standard dose) was given weekly for 4 weeks; in 19 episodes, a fixed dose of 200 mg (low dose) was given weekly for 4 weeks; in 17 episodes, a fixed dose of 500 mg (intermediate dose) was given weekly for 4 weeks; in the remaining 16 episodes, patients received doses of 100–1000 mg rituximab in 1–5 doses. Normalisation of ADAMTS13 occurred in 78.9% patients (ADAMTS13 $\geqslant$ 60%), with at least 92.1% having a partial response (ADAMTS13 $\geqslant$ 30%). There were only three TTP relapses (two of these sub-acute) all occurring in the low-dose group. Re-treatment with rituximab occurred in 50% patient episodes at a median of 17.5 months (range 9–112 months) after initial pre-emptive treatment; in 35/38 (92.1%) re-treatment episodes occurred following a recurrent drop in ADAMTS13 to $\leqslant$15%. A significantly higher rate of re-treatment was seen in the reduced dose (200 mg) *vs* the standard dose (375 mg/m^2) group, with 0.38 *vs* 0.17 re-treatment episodes/year respectively, $p = 0.039$. Overall, 20/45 (44.4%) patients received pre-emptive rituximab on two or more occasions: 12 patients on two occasions, 5 patients on three occasions, 2 patients on four occasions, and 1 patient on five occasions. Of eight patients treated on three or more occasions, there was no apparent reduced efficacy of rituximab, with no reduction in treatment-free survival after second and third treatment episodes compared to first episode. To date, the optimal dose of pre-emptive rituximab is not known.

Although generally well tolerated, toxicity associated with rituximab is an important consideration. In Jestin *et al.*'s[14] study, 19 patients (20.7%) were reported as experiencing benign adverse effects, and all were deemed benign. In 12 patients, these were described as moderate intolerance reactions during or within 3 days following infusion. Two patients experienced headache or diarrhoea. Serum sickness was reported in four patients, occurring 1–2 weeks after the rituximab infusion, these were treated with steroids. No severe infections were reported. There were no cases of hypogammaglobulinaemia or multifocal leukoencephalopathy.[14] In our own cohort, adverse events were recorded in 23/76 (30.3%) patient episodes, with 15/23 (65.2%) being infusional reactions. In two treatment episodes (same patient, both given 375 mg/m^2 dose), reactions were reported as severe, including a severe allergic reaction with syncope and the second an allergic reaction with tongue swelling. Of the 8/23 non-infusional reactions, one was considered severe: the patient developed acute serum sickness the day following the second rituximab infusion, necessitating treatment with steroids. Other reactions included joint pain (three episodes), mild neutropenia (one episode), and mild flu-like symptoms (three episodes). There were no episodes of hepatitis B reactivations or abnormal liver function. There was no evidence of hypogammaglobulinaemia or increase in infections, including in those re-treated with rituximab.[18] Vendramin *et al.*[38] reported on 64 TTP patients given rituximab, of which seven developed serum sickness (three acute at a median of 10.5 h post-infusion and four delayed at a median of 7 days post-infusion. In four of these cases, patients had been given rituximab on a pre-emptive basis. Human antichimeric antibodies (HACAs) to rituximab were detected in the three acute serum sickness patients. All of these three patients were subsequently given alternative anti-CD20 therapy ofatumumab, with a good response and ADAMTS13 levels recovering into the normal range. One patient, having had delayed serum sickness and negative anti-rituximab antibodies, was given further rituximab at a later date with no further reaction.[38]

While it appears that rituximab in the setting of pre-emptive treatment for TTP is generally well tolerated, with mild infusional reactions being the most common, alternative anti-CD20 should be considered in those having more severe reactions – including those with a history of serum sickness following rituximab.

Ofatumumab and obinutuzumab

The fully humanised type-1 anti-CD 20 monoclonal antibody ofatumumab has been reported

in a TTP patient who developed anaphylaxis following pre-emptive treatment with rituximab and was found to develop HACAs. Although there was an initial partial recovery of ADAMTS13 activity following rituximab, there was a further drop in ADAMTS13 activity to <5%, and no response with MMF. The patient was therefore treated with ofatumumab, and given three weekly doses (300 mg, 1 g, 1 g) without any reaction or anaphylaxis. ADAMTS13 levels recovered to 64%.[39] Ofatumumab has also been successfully used in the setting of acute TTP in a patient who previously developed a hypersensitivity reaction to rituximab.[40]

The type 2 anti-CD20 monoclonal antibody obinutuzumab has also been used to treat TTP. Robertz *et al.*[41] has reported obinutuzumab use in 2 TTP patients, both who had developed serum sickness with pre-emptive rituximab treatment. One patient was treated pre-emptively with in Obinutuzumab remission with low ADAMTS13 levels, and the other was treated during a subacute relapse (platelets dropping to 125 and the presence of neurological symptoms). Both patients were given three weekly doses of 1000 mg obinutuzumab (the first dose being split into 100 mg and 900 mg in consecutive daily doses); ADAMTS13 normalised in both cases.[41]

More recently, Ofatumumab and Obinutuzumab use has been reported by Doyle *et al.*,[42] with treatment of 15 patients in 26 treatment episodes, ofatumumab ($n=18$) and obinutuzumab ($n=8$). In 21/26 cases, these agents were given as pre-emptive therapy to prevent a TTP relapse; in 12/15 cases, patients had previously developed serum sickness associated with rituximab. All patients achieved a remission, with 24/26 episodes associated with normalisation of ADAMTS13 activity to ⩾60%; the median time to remission was 15 days (IQR 11.5–32.5 days). These agents were generally well tolerated, with 4/26 (15%) episodes of adverse events, comprising two infections and two atopic episodes.[42]

Other immunosuppressive agents

MMF. MMF is an immunosuppressive agent that works by reducing B and T lymphocyte proliferation and antibody production. Use of MMF in TTP has been reported predominantly in treatment of acute TTP episodes, where it has been used successfully typically in conjunction with anti-CD 20 therapy. These include cases where patients have had coexistent systemic lupus erythematosis (SLE), including a 35-year-old patient where MMF was used with steroids as part of acute therapy,[43] a 20-year-old patient where MMF was used in conjunction with rituximab where the patient was not responsive to steroids and cyclophosphamide,[40] and a 30-year-old patient[44] and a child.[45] MMF has also been reported in a 60-year-old patient where MMF and rituximab was used to successfully maintain remission following relapse,[46] and in a case of post-partum TTP where MMF was also used with rituximab.[47] While there is little evidence supporting the use of MMF to prevent relapse in TTP, we have used MMF in patients having persistently low ADAMTS13 levels despite initial (and/or repeated) use of anti-CD20 therapy. Anecdotally, this can be associated with reducing relapse risk, and in some cases, eventual recovery of ADAMTS13 activity into the normal range.

Anti CD38 therapy. Anti CD38 therapy can be used in patient having ongoing ADAMTS13 activity <10 iu/dL and detectable anti-ADAMTS 13 antibodies, despite having received anti-CD20 therapy. The theoretical advantage of these agents relates to the fact that they target plasma cells directly, and plasma cells are not affected by anti-CD20 therapy. Of the two anti-CD38 agents reported, the proteasome inhibitor bortezomib has been used in the majority of cases. The use has been reported in case reports and case series, with remission in 16/18 cases of acute TTP,[25,48–53] although these data may be limited by the fact that bortezomib was used in conjunction with a number of other immunosuppressive agents. Intravenous or subcutaneous treatment can be used at doses of 1–1.3 mg/m^2 for between 2–4 doses, although up to 13 have been given in published data.

More recently, Daratumumab use has been reported in two cases where it was successfully used in two cases refractory to rituximab.[54]

Cyclosporine. Cyclosporine is an immunomodulatory agent that suppresses cytokine production involved in T-cell activation. It has been used in refractory and relapsing TTP with improvement of ADAMTS13 activity levels.[55,56] Cataland *et al.*[56] reported on 19 TTP patients treated with cyclosporine (at a dose of 2–3mg/kg in divided doses) for 6 months; of these, 17/19 completed 6 months in remission, with 10/19 maintaining

remission at a median of 21 months after stopping cyclosporine. More recently, the same group have presented a randomised controlled study comparing cyclosporine with steroids; the study was stopped because of no improved exacerbation/relapse rate and improved ADAMTS 13 recovery in the steroid group.[26]

Other agents

Azathioprine use has been reported in a few cases of TTP and can be useful in the setting where other agents are not suitable due to pregnancy or breast feeding.[57,58] Cyclophosphamide has also been used in the setting of relapsed/refractory TTP, although its use has been reduced following the availability of ritxumab.[27] Vincristine has been used both in acute and relapsed/refractory TTP cases, but use is very limited due to toxicity.[59–61]

Splenectomy has also been reported in relapsed/refractory cases,[62–64] with one group reporting 33 patients treated with splenectomy (24 relapsed cases, 9 cases refractory to PEX); over a median follow-up of 109 months (range 28–230 months) the relapse rate post-splenectomy was 0.09 relapses/patient year.[63]

Cardiovascular disease and mortality in survivors

While reducing mortality associated with acute TTP has been the primary focus for many years, it is clear that higher mortality risk extends well beyond the acute episode. A recent multicentre cohort study of 222 TTP survivors from Ohio State University and John Hopkins TTP Registry found a 1.8 × higher mortality in TTP survivors compared to an age/sex/race-adjusted population followed up for a median of 4.5 years.[65] This study highlighted that higher mortality was also seen in other cohort studies of TTP survivors, including an Oklahoma study of 77 TTP survivors,[66] and a French cohort study finding a 3x higher mortality in TTP survivors compared to an age-matched general population.[67] Cardiovascular death was reported as the joint leading cause of mortality in TTP survivors in the Ohio/John Hopkins study, with cardiovascular disease and TTP relapse cited as a cause of death in 27.6% survivors, respectively.[65] Cardiovascular death was also the leading cause of death in the Oklahoma cohort at in 37.5% patients, and indeed higher than TTP recurrence as a cause of death in 12.5% patients.[66]

The explanation for higher rates of cardiovascular disease is unclear; Sukumar *et al.*[65] highlight studies showing higher rates of cardiovascular risk factors (including hypertension and obesity) in TTP patients[68,69] but also the possible association of reduced ADAMTS13 levels as a risk factor. Their study showed a non-significant trend towards higher all-cause mortality and cardiovascular mortality in patients having lower ADAMTS13 activity in remission.[65] Cerebrovascular disease also appears to be associated with reduced ADAMTS13 activity in TTP survivors.[21] In the non-TTP population, reduced ADAMTS13 levels appear to be associated with higher all-cause and cardiovascular mortality,[70] and are a risk factor for cardiovascular disease[71] and ischaemic stroke.[72]

While targeting ADAMTS13 may have an important impact on cardiovascular risk, the apparent higher risk of cardiovascular disease (and related mortality) in TTP survivors indicates that modification of risk factors should form a key part of monitoring in remission. We would therefore advocate regular monitoring of blood pressure and modification of this, and other cardiovascular risk factors, where appropriate.

Neuropsychological effects related to TTP

Given the brain is one of the main target organs affected by acute TTP, it is not surprising that survivors of acute TTP can have several neuropsychological sequelae. A number of studies, largely based on TTP registry cohorts, have examined cognitive function, psychological effects, and health-related quality of life (HRQOL) in TTP patients.

Kennedy *et al.*[73] evaluated a range of cognitive functions in 24 TTP patients in remission, at a median of 4 years post the acute TTP episode (range 0.1–10.6 years). TTP patients performed worse in 4 out of 11 domains examined compared to standardised data ($p < 0.05$), including complex attention/concentration, information processing speed, rapid language generation, and rote memorisation; furthermore, 88% patients tested performed below expectation in at least 1 of the 11 domains. There was no clear relationship found between these results and patient age, degree of neurological injury related to TTP, patients having multiple TTP episodes and time interval from the acute TTP episode. However,

investigators proposed that TTP patients may have persistent cognitive abnormalities, characteristic of diffuse subcortical microvascular disease.[73]

Defects in cognitive functioning have also been reported in other studies. Cataland *et al.*[56] studied 27 patients with a history of acute TTP across two centres and performed mgnetic resonance imaging (MRI) brain scans as well as neurocognitive testing and measures of HRQOL. About 9/23 (29%) patients had abnormal MRI scans; 17/23 (63%) had evidence of neurocognitive impairment, particularly in visual learning and memory; HRQOL scores were significantly lower than age and gender-matched normal controls.[74] Alwan *et al.*[75] studied 131 patients with acute TTP having severe headache or neurological symptoms at presentation. MRI brain scans demonstrated 56% of these patients had abnormalities, with abnormal MRI findings being seen more commonly in patients with neurological symptoms rather than headache alone. When assessed in remission, 35/131 (27%) patients reported persistent cognitive symptoms, including impaired memory (66%), difficulty concentrating (26%), and word finding difficulties not related to an acute stroke (26%). There was a significant association between abnormal MRI results and lower median verbal IQ (85 *vs* 99, $p=0.02$) and lower performance IQ (83 *vs* 100, $p=0.02$). The frontal lobe was disproportionately affected in those having neurological impairment. Furthermore, 65% patients had evidence of depression and 55% anxiety, although this was not related to the presence of neurological symptoms at presentation.[74]

Riva *et al.*[76] assessed 35 patients with immune TTP in remission (at least 3 months post the acute TTP event) and assessed memory, attentional function, and emotional well-being. About 17/35 (49%) patients had persisting subjective neurological impairment, reporting at least one symptom during the remission phase. Patients had lower scores on neuropsychological testing, including direct/indirect and deferred memory. An increased frequency of memory problems was seen in those with neurological involvement at presentation. Only 7/35 (20%) patients were found to have evidence of anxiety and 15/35 (43%) of depression. Patients also had lower HRQOL scores than the general population.[76] An increased incidence of depression and lower HRQOL scores have been found in other studies. Han *et al.*,[77] assessed 61 TTP patients in remission and performed at least one (median of 4) evaluation for depression using a Beck Depression Inventory-II tool. Of the 52 patients who had at least one evaluation, 31/52 (59%) screened positive for depression on at least one occasion, with 15/52 (29%) having severe depression at least once. Eight of nine patients who underwent a psychiatric interview were categorised as having a major depressive disorder. There was no association with depression and number of TTP episodes or low ADAMTS13 levels (<10%) in remission. As a group, the TTP patients were found to have significant cognitive impairment using the Montreal Cognitive Assessment tool and RBANS tool.[77]

Based on the severity of possible neuropsychological effects of TTP, reflected by the results of TTP survivors and the profound effects of TTP on their HRQOL, it is essential that patients undergo screening for cognitive and affective disorders both early post the acute phase, and regularly during long-term monitoring, to ensure appropriate interventions are made. We would recommend the use of standardised assessment tools in TTP patients; for example the Patient Health Questionnaire-9 (PHQ-9)[78] to screen for depressive disorders, and the 'Test Your Memory' (TYM) cognitive screening test[79] to screen for cognitive impairment. Although these tools have not been specifically validated for use in TTP patients, they have been found to be useful screening tools for depression and cognitive impairment. In our practice, we use the TYM tool to identify patients who may benefit from referral for formal neuropsychological assessment, and the PHQ-9 tool to identify patients who may require referral for assessment by a clinical psychologist or counselling service. Despite the presence of registry studies demonstrating the neuropsychological burden of TTP on patients, there is to date a lack of interventional studies available in this group, and this should form part of future research.

Conclusion

For a disease that historically was associated with a very high mortality, modern combination therapy for acute TTP (including plasma exchange, immunosuppression, and caplacizumab) has resulted in excellent survival rates of >90%. However, it is clear that there is significant morbidity associated with acute TTP episodes,

including a variety of neuropsychological affects, which can have a marked impact on quality of life in survivors. Management of TTP beyond the acute phase should focus on identifying morbidity (particularly psychological) associated with the acute episode and targeting the most important modifiable risk factor in preventing relapse, namely ADAMTS13 activity. Monitoring of patients is essential, and frequency should be guided by ADAMTS13 activity levels, with those patients not achieving an ADAMTS13 remission requiring most frequent monitoring. Achieving ADAMTS13 recovery should be a goal for all patients, with the use of ad hoc anti-CD20 therapies such as rituximab, and/or longer-term regular oral immunosuppression in patients, where anti-CD20 therapy has not resulted in an ADAMTS13 remission. Given the risk of late relapses, lifelong monitoring following the acute phase should be undertaken in all patients.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
John Paul Westwood: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Resources; Writing – original draft.

Marie Scully: Conceptualisation; Data curation; Formal analysis; Resources; Writing – review & editing.

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