Evidence Tables

Table 1: Rituximab used as initial treatment for acute episode of TTP

Author, year (ref)	Study design/ comparison group	Patients	TTP diagnosis/ inclusion-exclusion criteria	Rituximab dose, schedule	Additional treatments	Follow-up	Outcomes	Comments
Scully, 2011[1]	Prospective, multicenter, phase 2 study between 2006-09 with follow-up at least 12 months -Compared to historical controls (n=40) who did not receive rituximab -Historical controls matched as far as possible for sex, ethnicity, number of relapses selected from the South East England TTP Registry based on completeness of data	40; 34 first episode, 6 relapsed acute TTP -Excluded pregnant or breastfeeding, HIV, childhood TTP, HUS, transplant, cancer -86 patients screened, excluded 46 (7 deaths within 24 hours of diagnosis, 14 secondary TTP, 13 received rituximab off-trial (9 received initial rituximab >3 days after admission, 4 <18 years), 10 did not have TTP, 2 declined) -Compared to 40 controls (31 first episode TTP, 9 relapsed)	Not based on ADAMTS13 levels, but measured on admission -Median ADAMTS13 level at presentation <5% in rituximab and control groups but range of activity up to 40%	375 mg/m^2 weekly x 4, started within 3 days of admission and diagnosis -Additional rituximab x 4 given in patients with ADAMTS13 <55% or with persistently detectable inhibitors (4 patients received rituximab x 6, 2 patients received rituximab x 8)	PEX daily (intubated and ventilated patients received twice daily PEX), 38/40 (95%) patients received steroids (methylprednisolone 1 g daily x 3 days) and 4 patients received vincristine -Controls treated as per the British Committee for Standards in Haematology guidelines (Methylprednisolone 1 g daily x 3 days followed by prednisone 1 mg/kg/d or only prednisone); 35/40 (87.5%) received steroids on admission - 15 patients received: cyclosporine (7), defibrotide (5),	No median follow-up reported, rituximab patients followed at least 12 months, from Figure 4 follow-up longer in controls but time of censoring not shown for either group	<u>In rituximab group:</u> -3/40 deaths (7.5%) -4/37 relapses (11%), median time to relapse 27 months (range 17-31 months) with ADAMTS13 levels <5% at relapse in 3 patients; 1 patient persistent <5% post-rituximab, 1 patient died in relapse -Decrease in CD19 to 0.5% (0-2.78%) before 4th rituximab treatment with normalization in 75% of patients within 12 months -ADAMTS13 levels increase post-rituximab <u>In control group</u>: -2/40 deaths (5%) -21/38 relapses (55%), median time to relapse 18 months (range 3-60 months), 1 patient died in relapse <u>Rituximab vs. control</u> <u>-Relapse percentage 10% in rituximab vs. 57%in control</u> -Reduction in inpatient stay by 7 days in rituximab-treated patients compared to controls when 15 patients in the rituximab group who required ICU admission were excluded	- 6/40 (15%) rituximab patients intubated/ ventilated and received bid PEX; number of bid PEX in control group not reported -No increase in infections or adverse outcomes documented with rituximab(however no statistical test or control group)

					cyclophosphamide (3), splenectomy (1), vincristine (9)		-No significant decrease in median PEX treatments to remission: 16.5 (range 4-34) vs 18 (6-92); p=0.5 -No difference in median number of days admitted: 16.5 (range 5-49) vs 20 (5-62) -No difference in mortality at 3 months	
Westwood, 2013[2]	Retrospective cohort, Jan 2004-Dec 2011 -No separate comparison group but evaluated early (≤3 days) vs. later (>3 days) initial infusion of rituximab	86; 54 received initial rituximab ≤3 days from admission (31 previously reported by Scully, 2011) (38 first episode, 16 relapsed), 32 received rituximab >3 days from admission (27 first episode, 5 relapsed)	Not based on ADAMTS13 levels, but measured on admission and during follow-up -Median ADAMTS13 activity <5% in both groups but range of activity to 30% (earlier) and 40% (later)	375 mg/m^2 x 4 (maximum 8), given weekly pre-2009 (earlier n=31, later n=20); given every 3-4 days post 2009 (earlier n=21, later n=10) - 2 patients in each group that died did not receive rituximab -Additional 4 doses given if ADAMTS13 activity below normal range or continued presence of inhibitor or clinical deterioration (n=14)	PEX 1-2x/d based on clinical severity (intubated, neurologic or cardiac involvement given PEX bid), methylprednisolone 1 g/d x 3 days; other treatments not mentioned	-Median follow-up 45 months (4-100 months) -Followed weekly x 4 weeks post discharge then monthly x 3 months, then q3-6 months	- Complete remission in 82/86 (95%) patients within 14 days (4-52 days) - 4/86 deaths; 2 earlier, 2 later -Among 82 survivors, earlier rituximab administration (≤3 days, n=52) associated with faster time to remission (12 vs. 20 days, P < 0.001), fewer PEX (16 vs. 24, P = 0.03), shorter hospital stay (16 vs. 23 days, P = 0.01) compared to later rituximab administration (n=30) - No difference in median time to relapse between earlier vs. later rituximab treatment (p=0.77); 11/82 (13.4%) relapsed at median 24 months (4-49 months) - 2 deaths in previously treated	-No criteria reported for the decision to initial rituximab at ≥3 or >3 days from admission (although 31/52 survivors treated early due to Scully 2011 trial) -TTP diagnosis based on thrombocytopenia, MAHA, normal clotting screen, LDH 1-1.5 x ULN -No increase in infections (no data to support statement) -Over 50% of patients had neurologic or cardiac involvement and 1/3 required ICU admission; most patients in this study received bid PEX
Pequeno-	Case series,	3 patients, 1	1patient had	100 mg IV	PEX 2x plasma	3 patients	- All patients reached	-1 patient

Leuvano, 2013[3]	single center, January 2011-September 2012 -No comparison group	patient with HIV	ADAMTS13 measurement at diagnosis (<5% activity), 1 other patient anti-ADAMTS13 antibodies	weekly x 4, initial infusion 2-8 days after start of PEX	volume (held x 24 hours post rituximab), prednisone 1 mg/kg day x 1 week	followed 9, 12 and 18 months from treatment	remission 5-21 days after rituximab - No relapses with follow-up of 9-18 months	excluded, from this analysis who received rituximab for refractory TTP

Table 2: Rituximab used for treatment of refractory TTP

Author, year (ref)	Study design/ comparison group	Patients	TTP diagnosis/ inclusion-exclusion criteria	Rituximab dose, schedule	Additional treatments	Follow-up (months)	Outcomes	Comments
Froissart, 2012[4]	-Open label prospective, multicenter study -21 consecutive patients between 2005-08 managed on standard protocol with rituximab -Outcomes in rituximab-treated patients compared to 53 historical patients, treated between 2000-05 with same criteria for TTP (ADAMTS13 <10%) and suboptimal response to PEX, +/- vincristine +/- cyclo-phosphamide	-21 surviving adults with refractory TTP (platelets < double initial value after 4 days PEX and increased LDH) or a disease exacerbation (worsening neurologic symptoms and/or recurrent thrombocytopenia <100 x 2 days or worsening thrombocytopenia when treated with PEX) -Rituximab treated patients: 6 refractory, 16 exacerbation; 3 had previous TTP (never previously treated with rituximab) -53 surviving controls: 8 refractory, 47 had ≥ exacerbation	-ADAMTS13 <10% -Excluded patients who received rituximab for previous TTP episode. - 4 control subjects who met inclusion criteria but who died with their acute episode were excluded.	375 mg/m2 on day 1 of refractory determination (median 8.4±3.3 days after beginning PEX) and days 3, 7, 14. -1 refractory TTP patient received rituximab x 2, vincristine x 2 but died	-PEX 1.5x plasma volume x 1 then 1x plasma volume until remission, steroids 1 mg/kg/d x 3 weeks (in patients with no active infection), folic acid. -Steroid use: rituximab 15/21 (71%) Controls 42/53 (79%) -Other immune-suppressants at discretion of physician (vincristine, cyclo-phosphamide, splenectomy)	Mean 33±17.4 months (rituximab group) 2 lost to follow up, 35.3±28.5 months (controls)	-In patients treated with rituximab, time to durable remission shortened (p = .03); platelet count recovery within 35 days in the 21 survivors treated with rituximab, compared to 78% of historical controls (p < .02) -No difference in plasma volume required to achieve durable remission between groups -Mean time from rituximab to durable remission 12±6.7 days -Non-significant decreased relapse at 1 year in rituximab-treated patients, none with relapse within first year compared with 5 (9.4%) controls (p=0.34); 3 rituximab patients (15.8%) relapsed >1 year (20 months, 2 & 3 years); no difference in long-term relapse (>1 year) p=0.68 - 1 death in rituximab group (after 2 rituximab infusions) -ADAMTS13 levels higher in rituximab vs. controls after 1,3,6,9 months but not significant at 12 months; inhibitor titers similarly lower at 3,6,9 months compared to controls -B cell depletion x 9 months, not significant after 12 months	-57 historical cohort patients identified based on same criteria for TTP and suboptimal response to PEX; 3 excluded with creatinine ≥2.25 mg/dl; 4 died and excluded; among survivors, 3 vincristine + cyclo phosphamide, 17 vincristine; 42/53 (79%) received steroids; 8 refractory, 47 exacerbation -ADAMTS13 activity and inhibitors measured at diagnosis, before treatment, and after 1, 3, 6, 9 and 12 months (drawn pre-PEX in patients receiving PEX) -B-cell count evaluated before each rituximab infusion (x) and x+21 days, then 1, 3, 6, 9, and 12

								months later -Safety assessed with standard case report form
Goyal, 2013[5]	Retrospective, single center, cases between 2003-08 -No comparison group	12 included patients with first or relapsed episode who were refractory to PEX, treated with rituximab and who achieved remission	ADAMTS13 levels <5% due to inhibitor	375 mg/m^2 weekly x median 4 doses (range 1-6) -Started median 14 days post PEX initiation, range 5-28 days -Rituximab initiated at discretion of physician if deemed for refractory course	Daily PEX 1-1.5x plasma volume; 11 patients also received steroids and/or vincristine/ cyclophosphamide	Mean 73.4±6 months	-4/12 (33%) patients relapsed at mean 62±8.5 months post remission -1, 3 and 5 year relapse free survival rates: 92%, 75%, 75%	-Included only patients with ADAMTS13<5% who received PEX and rituximab - Among selected articles, the longest follow-up and also the highest relapse rate
Chemnitz, 2010[6]	Retrospective, single center, cases between 2000-08 -No comparison group	12 with first (5) or relapsed (5) episode who were, refractory to PEX (persistent TP or elevated LDH after PEX x 1 week) or who were allergic to plasma (2) 2/12 allergy to plasma. -Excluded patients with secondary TTP (BMT, CTD,	-Not based on ADAMTS13 activity, clinical assessment -2 patients had ADAMTS13 levels >75% at baseline	375 mg/m^2 weekly x 4 -Rituximab initiated at discretion of physician if patient deemed refractory or be allergic to plasma -2 patients received continuous rituximab therapy; 375 mg/m^2 every	PEX daily 1.5x plasma volume with FFP (held x 24 hours post rituximab) + steroids -4/12 patients also treated with vincristine	Median 49.6 months, range 11-97 months	-All patients achieved CR post rituximab treatment -3/12 relapsed (25%) after mean 50 months follow-up; all responded to repeated rituximab (follow up post 2nd rituximab for these patients not reported) -3/12 patients had ADAMTS13 levels <50% post-rituximab treatment at end of follow-up	-ADAMTS13 levels and inhibitors not measured on all patients at baseline (5 patients <10%; 2 patients 76% and 90%; 5 patients, ADAMTS13 activity not measured) -ADAMTS13 activity and inhibitors measured at end of follow up -No infectious

		active cancer)		4 weeks; 1 for 3 months, 1 continuous				complications reported but unclear reporting/ collection of adverse events
de la Rubia, 2010[7]	Retrospective, multicenter between 2003-08 -No comparison group -Survey sent to participating centers to complete case report form; 15/33 (45%) centers used rituximab and responded to survey	24 with refractory TTP; 14 first episode 10 relapse. - Excluded secondary TTP (infection, pregnancy, drugs, CTD, malignancy, BMT)	Not based on ADAMTS13 activity; clinical assessment	375 mg/m^2 weekly x 4 (range 1-8) -Started at median 13 days (range 2-57 days) after diagnosis -Rituximab initiated at discretion of physician if patient deemed refractory (TP <50 after PEX x 7 days or new clinical symptoms)	Daily PEX + prednisolone 1-2 mg/kg/day IV -Previous treatment with vincristine (n=12) and splenectomy (n=3)	-Median 30 months (range 7.5-64 months)	-21/24 (87.4%) patients achieved CR at median 2 weeks (range 1-5) - Median follow-up 30 months (range 7.5-74 months), In patients with first episode: - Median 16 PEX prior to rituximab -13/14 (93%) patients achieved CR -1/14 deaths -13 patients in remission; 1 relapse at 29 months post-rituximab In patients with a relapsed episode: Median 11 PEX prior to rituximab -8/10(80%) patients achieved CR -2/10 deaths -8 patients in remission and 2 relapsed at 7 and 29 months post rituximab	-Diagnosis not based on ADAMTS13 levels -Measured ADAMTS13 in 3 patients, noted <5% with inhibitors detected prior to rituximab; activity increased and inhibitors decreased post-rituximab (data not supplied) -Mild side effects in 4 (17%) patients with chills, erythema, pruritis
Ling, 2009[8]	Retrospective, single center, cases between 2001-07 -No comparison group	13; 6 first episode TTP,, 7 relapsed episode -5 patients had additional disorders ((SLE, HIV, MCTD, CTD, myositis)	Based on clinical assessment, not ADAMTS13 activity. 12 patients had ADAMTS13 <10%, 1	375 mg/m^2 weekly x 4, -Started after 12-39 PEX -Rituximab initiated at discretion of physician if patient	PEX daily 1.5x volume and FFP, 11/13 received steroids (5/6 first episode, 6/7 relapsed), 3/13 (1 first episode, 2 relapsed) received cytotoxic	-Median 24 months (range 13-84 months) -Followed monthly x 6 months then yearly	-12/13 (92%) achieved CR (6/6 first episode; 6/7 relapsed) -No subsequent relapses occurred with median follow-up of 24 months (range, 13-84 months) -12/13 patients with ADAMTS13 activity <10% with detectable inhibitor levels prior	-ADAMTS drawn prior to PEX and 3-6 months as outpatient - 4 patients had an additional diagnosis of CTD; 1 patient had HIV infection. 4

			patient 36%.	deemed refractory (>1 week PEX)	agents (vincristine or cyclophosphamide). I patient had splenectomy (first episode)		to rituximab; post-rituximab 7/8 patients (3/3 first episode; 4/5 relapsed)had increased ADAMTS levels with resolution of inhibitor; 1 relapsed patient with no response and died of bleeding	patients had concurrent treatment with cyclophosphamide or splenectomy.
Jasti, 2008[9]	Retrospective, single center, cases between January 2001-February 2007 -No comparison group	12 ; 11 first episode 1 relapsed episode -Excluded TTP due to drugs, transplant, pregnancy, CTD -1 patient with pancreatitis, 1 with HIV	6/12 patients with ADAMTS13 <5% with inhibitor; no measurements in 6 patients	-375 mg/m^2 every 3-7 days in most patients x 1-13 doses -100 mg/m^2 x12 doses in 1 patient -Started 2-19 days from presentation (text; table 2-16 days) -Dose, timing, frequency at physician discretion	-PEX 1-1.5x plasma volume daily, held day post-rituximab -Median number of PEX 19 (range 13-41) -Steroids in 'most of patients at varying doses'	Median 57 months (range 1-79 months) -2 patients lost to follow-up; 1 and 8 months	-10/12 (83%) responded after median 10 days (5-32) after rituximab, 2 patients died -Median time to CR 18 days (14-41) among 10 survivors,. -1/10 relapsed twice after rituximab at 24 and 22 months	-1 patient (also reported by Montoya below in prophylaxis section) with herpes zoster transverse myelitis with paraplegia and, encephalitis after 2nd course of rituximab, also on steroids; she slowly regained strength and normal mental status. She received re-treatment with rituximab and PEX on relapse (no steroids, received prophylactic antivirals) with no complications
Scully, 2006[10]	Prospective, multicenter (3 UK tertiary referral centers) -No comparison group	25; 14 first episode, 11 relapsed episode (failed to achieve normal platelet count after PEX x 7 days or deterioration of clinical symptoms),	Included only patients with an inhibitor or IgG antibodies to ADAMTS13 at presentation. 21 patients with ADAMTS13	375 mg/m^2 weekly x 4 following PEX -4 patients with ADAMTS13 levels below normal range or	-PEX 1-1.5 x plasma volume daily and methylprednisolone IV daily x 3 -PEX daily until platelets >150 x 10^9/L for minimum 48 hours, then every	-Median follow up 10 months (range 1-33 months) -Followed monthly x 3 months, then q3 months x 12 months, then q6	-All patients (25/25) reached CR in median 11 days after rituximab -6 patients with persistently low ADAMTS13 post-rituximab (below normal value of 66%; for 6 median 31%, <5% - 55%) -1 death from pneumonia after remission -No relapses reported within	No increase in infections or side effects from rituximab -1 patient had widespread mobilliform pruritic rash, with eosinophilia, 1 week after 4

		-Excluded TTP due to HIV, drugs, bone marrow transplant, cancer, pregnancy	activity <5%; 3 with ADAMTS13 activity 11-23%.; 1 no baseline ADAMTS13 activity, transferred to participating center after 6 weeks PEX – ADAMTS13 activity 64%	inhibitors received additional rituximab weekly to maximum 8 treatments -1 patient only weekly x 2	other day -Vincristine 1 mg IV q3-4 days x 4 in 12 patients, defibrotide in 3 patients, cyclosporin (4), cyclophosphamide (1)	months	follow-up period	rituximab treatments; resolved over 4 weeks with steroid creams and antihistamines -After acute treatment, 1 patient also received rituximab prophylaxis (ADAMTS13 <10% occurring 2 years after previous rituximab)

Table 3: Rituximab prophylaxis in asymptomatic patients following recovery from TTP with severe ADAMTS13 deficiency

Author, year (ref)	Study design/ comparison group	Patients	TTP diagnosis/ inclusion-exclusion criteria	Rituximab dose, schedule	Additional treatments	Follow-up	Outcomes	Comments
Hie, 2014[11]	Cross sectional analysis of 12 year follow-up data (Oct 2000- Jan 2012) from the French TMA Reference Center comparing relapse incidence with and without rituximab	48; 30 (group 1); received preemptive rituximab and other treatments), 18 (group 2); no treatment, these patients were managed prior to the era of rituximab or centers where prophylactic rituximab was not standard of care); all patients had ≥1 episode of TTP followed by ADAMTS13 <10% during remission. 33% (10/30) in group 1 and 67% (12/18) in group 2 had persistent undetectable ADAMTS13 activity after TTP ep isode (p=.0248).	Selected surviving patients from French registry who were in durable clinical remission (no thrombocytopenia, renal failure or clinical worsening >30 consecutive days from 1st day of platelet recovery) with ADAMTS13 activity <10% and follow-up ≥1 year	375 mg/m^2 weekly x 1-4 infusions at discretion of physician, started after detection of ADAMTS13 deficiency (activity and antibodies measured before rituximab, 1 and 3 months after rituximab then q3 x 2 years)	-Acute phase TTP treatment based on protocol implemented in Oct 2000; PEX 1.5x volume daily until remission then maintenance x 3 weeks + steroids 1 mg/kg/d x 3 weeks (if no active infection) + folic acid -10/30 (33%) patients in group 1 and 5/18 (28%) in group 2 received rituximab during acute TTP episode. -Treatment during remission: 9/30 patients received 1-10 additional courses of rituximab; 1 patient received continuing rituximab every 6 months; 4 of these 9 patients + 1 other patient	Median follow-up after initial rituximab infusion, 36 months (IQR 24-65 months) Follow-up after completion of all treatments not reported. Median follow-up of control patients, 60 months (IQR 30-72 mo)	- Decrease in relapse incidence from 0.57 episodes/year (IQR, 0.46-0.7) to 0 episodes/year (IQR, 0-0.81) (P<0.01) after median 17 months (IQR 11-29) post rituximab, compared to 0.5 relapses/year (IQR 0.12-0.5;p<0.01) in group 2 - Relapse-free survival longer in group 1 vs group 2 (P=0 .049) <u>Rituximab treated patients (group 1)</u> -16/30 (53%) had >1 episode TTP before rituximab with median 2 (IQR 1-3) episodes within 54 months (IQR 33-63)=0.57 episodes/year (IQR 0.46-0.7) -3/30 (10%) relapsed at 14, 18, 43 months = 0 episodes/year (0-0.81) -9/30 (30%) patients required additional rituximab for levels <10% during follow up; 4 of these patients had received rituximab in acute phase -No durable increase in ADAMTS13 activity in 5 patients who then received additional treatments; <u>Control patients (group 2)</u> -14/18 (78%) had >1 episode	Control group may not be well matched in terms of time or duration of ADAMTS13 deficiency in remission. Increased relapse-free survival in treated group marginal. Decreased frequency of relapse in treated group may be related to continuing treatment and shorter follow-up. Only 16 of the 30 patients who relapsed were used to estimate baseline relapse rate in treated patients which may overestimate actual baseline relapse rate; also relapse rate assumed to be constant over

					also received additional treatments: (cyclophosphamide, cyclosporine, mycophenolate, bortezomib, splenectomy)		TTP with 7 patients (39%) having median 1 (IQR 1-3) episode/year within 5 year follow up (IQR 30-72 months) = 0.5 relapses/year (IQR 0.12-0.5)	time, which is unlikely. Additional treatments given in prophylaxis group during follow-up (benefit of a single course of rituximab unknown)
Westwood, 2013[2]	Retrospective cohort, Jan 2004-Dec 2011 -No comparison group	14 patients (19 episodes) who previously had TTP and were in clinical remission with ADAMTS13 levels <14%. Two patients who were treated to allow withdrawal from cyclosporine or tacrolimus were not analyzed here.	Based on ADAMTS13 levels of <5-14%	-375 mg/m^2 x 4 (maximum 6), given weekly (n=12 patients); -100 mg/m^2 x 4 (n=3 patients) more recently	-12/14 patients received additional treatment (excluding PEX, steroids) -8/14 patients received rituximab previously -3 vincritine, 4 defibrotide, 6 cyclosporine	-Follow-up median 23 months (1-89 months) -Followed weekly x 4 weeks post discharge then monthly x 3 months, then q3-6 months (median, 15 months)	-18/19 episodes treated with rituximab resulted in normalization of ADAMTS13 levels within 3 months -4 patients (5 episodes) given additional rituximab (375 mg/m^2 in 4; 100 mg/m^2 in 1 weekly x 4) [f]or subsequent drop in ADAMTS13 levels, median time to decrease in ADAMTS13 levels of 13 months (10-26 months) -1 patient relapsed at 70 months	Interpretation uncertain because of no comparison group. ADAMTS13 levels <5% or <15% (deemed at high risk for relapsed based on previous presentation) in remission
Montoya, 2012[12]	Case report -No comparison group	1 patient with 5 previous relapses	No ADAMTS13 measurement for diagnosis	375 mg/m^2 weekly x 4 started when ADAMTS13 level 11% and inhibitor 1.8 IU, patient asymptomatic in clinical remission	-1st relapse treated with PEX, steroids -Received rituximab during treatment of 2nd relapse due to non-response to PEX and steroids, 3rd, 4th and 5th relapses treated	See Outcomes	- ADAMTS13 level increased to 59% 1 week post 1st treatment and increased >95% 4 weeks after 4th infusion - Follow-up 6 months - Patient previously treated with rituximab for four relapses, and then treated in remission with a low ADAMTS13 activity following her fifth relapse. Duration of remission after 4th relapse, 22	This patient (also reported by Jasti above) had herpes zoster transverse myelitis with paraplegia and, encephalitis after 2nd course of rituximab, also on steroids; she slowly regained strength and

					with PEX ± steroids and rituximab -Received rituximab weekly x 8 following relapse 3, 4 and 5		months; duration of follow-up after 5th relapse 18 months until ADAMTS13 11% with no clinical evidence of TTP. -Rituximab given with subsequent follow-up of 14 months.	normal mental status. She received re-treatment with rituximab and PEX on relapse (no steroids, received prophylactic antivirals) with no complications
Jayabose 2011[13]	Case report -No comparison group	1, 2 relapses after first TTP, each in approximately 1 year	ADAMTS13 <5%	375 mg/m^2 weekly x 4 started when ADAMTS13 levels <4% and inhibitor detected	-After 2rd relapse and clinical remission, treated with vincristine, prednisone and one dose of rituximab with increase in ADAMTS13 99% but decreased <5% with detectable inhibitor, while in clinical remission one year later. Given rituximab	124 weeks (~2.4 years) from 2nd relapse; 60 weeks following prophylactic rituximab	-ADAMTS13 levels >100% at 9 weeks, and 108% at 60 weeks -Patient in remission for 60 months at time of publication	-Patient initially presented at age 10 -ADAMTS13 levels <5% for 20-47 weeks prior to 2 clinical relapses
Bresin, 2009[14]	Retrospective registry data from 154 centers in Italy and 11 additional countries -No comparison group	5, 4 with relapsed TTP, 1 following first episode (Patient #1 previously reported by Galbusera and Fakhouri)	ADAMTS13 <6% for inclusion during a clinical remission -ADAMTS13 activity and inhibitors measured q3 months	375 mg/m^2 weekly x 4, timing of start variable but all patients in clinical remission -Two patients treated with 2 courses while in remission then 1	-All patients previously treated with PEX or plasma infusions, steroids; 4 received IVIG, 3 ASA, 3 vincristine/ vinblastine, 2 cyclosporine, 2 cyclophosphamide, 1 defibrotide, 1 azathioprine, 1 splenectomy, -2 patients received rituximab	Follow-up of 4 patients 6-32 months (median, 28 months)	- Disappearance of inhibitors after 3 months in all patients - ADAMTS13 activity>20% without inhibitors at 6 months in all patients - Disease-free in 4 patients after, 29, 24 and 6 months - Relapses in 2 patients during follow-up; 1 patient treated with rituximab 19 months apart and relapsed at 51 months; second patient treated with rituximab, vincristine, vinblastine at relapse and given rituximab	- Adults with at least 1 episode TTP in current clinical remission >30 days from last PEX with <6% ADAMTS13 activity -ADAMTS13 activity 15- 75% at 3months post rituximab

				treated with continuous rituximab every 3 months			prophylaxis after ADAMTS13 activity low ~17 months after initial rituximab dose another pre-emptive course of rituximab 13 months later with relapse 11 months later, for one year one dose of rituximab every 3 months -Both relapsed patients treated with additional rituximab	
Schleinitz, 2007[15]	Case report -No comparison group	1, patient with 2 relapses; first TTP developed during pregnancy	ADAMTS13 activity undetectable, inhibitor detected	375 mg/m^2 weekly x 4	-first episode treated with PEX with clinical remission -Relapsed after delivery, treated with PEX x 7 with clinical remission. Second -relapse 22 mo later treated with PEX x 31, vincristine, steroids with increase in ADAMTS13 activity to 58% and disappearance of inhibitor; ADAMTS13 activity decreased to 5% 15 months later	- 9 months after prophylactic rituximab	-15 months follow-up from last relapse found ADAMTS13 activity 5% with recurrence of inhibitor -Post-rituximab ADAMTS13 activity levels increased to normal and inhibitor eradicated -9 months post treatment ADAMTS13 activity 128%	-Follow-up duration may be insufficient to determine risk for relapse.
Benetatos, 2006[16]	Case report - No comparison group	1, patient with 6 relapses	No measurement of ADAMTS13 activity	375 mg/m^2 weekly x 8 started 1 month after last PEX while in clinical remission	-Previous treatments with PEX, FFP infusion, steroids, Ig, antiplatelet agents	-23 months post rituximab	-No relapse reported at 23 months post-rituximab therapy	- No measurement of ADAMTS13 activity or antibodies

Fakhouri, 2005[17]	Prospective, open label, multicenter between Feb 2004-Jan 2005 -No comparison group	5 with ≥2 previous TTP episodes, failed ≥1 treatment other than plasma (vincristine, IVIG, splenec-tomy) in current clinical remission -Excluded patients with immune deficiencies , active viral infections (hepatitis, HIV)	ADAMTS13 <5% with a demonstrable inhibitor	375 mg/m^2 weekly x 4 - Patients in remission for 1-19 months at study inclusion	-Previous treatments with PEX, vincristine (n=4), splenectomy (4), IVIG (2), cyclosporine (1), rituximab (2) -Patients treated with rituximab received it 17 and 20 months prior to inclusion	Followed q3 months clinically and ADAMTS and inhibitor measurement -Range 6-11 months	- No clinical relapse occurred with 6-11 months follow-up -2 patients recovered ADAMTS13 activity (21% and 45%)) with disappearance of inhibitor; 11 months later inhibitor detectable and ADAMTS13 levels decreased; rituximab restarted in 1 patient with no clinical relapse in both - Anti-ADAMTS13 antibodies disappeared, plasma ADAMTS13 activity 29%-75% noted 7-24 weeks after last rituximab infusion -1 patient with ADAMTS13 activity <5% noted at 3 month follow-up with detectable inhibitor, increased activity to 75% with negative inhibitor at 6 months and not seen at 9 month follow-up	Follow-up duration may be insufficient to determine risk for relapse. -Included age >18 years with ≥2 previous TTP episodes, ≥1 extra-hematologic symptoms during previous relapses, failure to ≥1 treatment in addition to PEX, current remission, ADAMTS13 <5% due to inhibitor -B-cell depletion in all patients with recovery by 9 months (but missing data for 3 patients)

Legend: CTD, connective tissue disease; HIV, human immunodeficiency virus; HUS, hemolytic uremic syndrome; IVIG, intravenous immune globulin; IQR, interquartile range; LDH, lactate dehydrogenase; MAHA, microangiopathic hemolytic anemia; MCTD, mixed connective tissue disease; PEX, plasma exchange; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura; ULN, upper limit of normal

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