



TROMBOTİK MİKROANJİOPATİ OLGUSU

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Eylül 2011

- 20 y, kadın
- Halsizlik, ikter, alt ekstremitelerde ekimotik lezyonlar, 10 gündür devam eden mensturasyon
- Hb **7.3 g/dL**, Hct **%20.6**, trombosit **17 000/uL**
- TÜTF Acil Polikliniği

Eylül 2011

- Özgeçmiş özellik yok
- Anne HL, baba HT
- FM: vücut ısı 36.7°C,
KTA **120/dk**,
SS 10/dk,
TA: 110/70 mmHg,
ikter,
alt ekstremitelerde **ekimotik lezyonlar**

Eylül 2011

- Lökosit 5 300/uL
- Nötrofil 3 500/uL
- Hb **6.8 g/dL**
- Hct **%18.3**
- MCV 95.7 f/L
- Trombosit **8 000/uL**
- T. bilirubin **6.1 mg/dL**
- İ. bilirubin **5.6 mg/dL**
- LDH **1072 U/L**
- Düzeltilmemiş retikülosit **%16**
- Haptoglobulin **8.8 mg/dL**

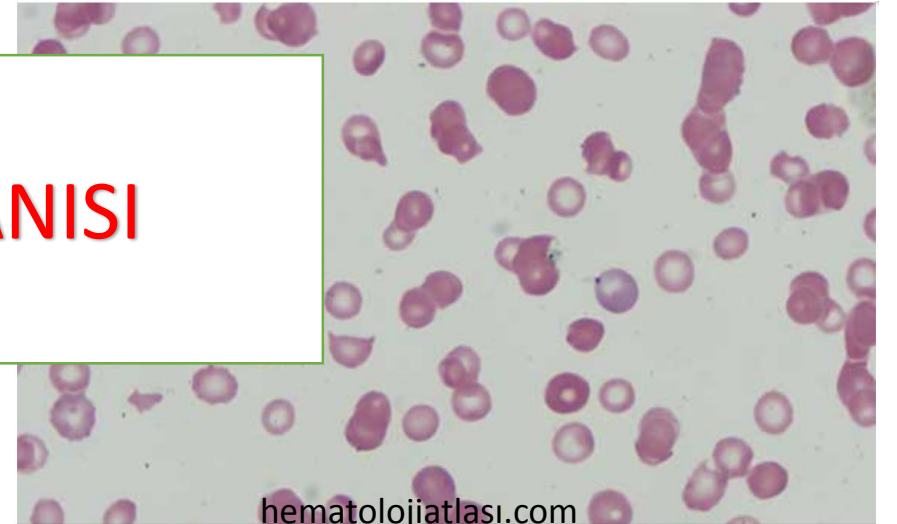
Eylül 2011

- Nutrisyonel parametreler
- Direkt ve İndirekt Coombs testleri
- Koagülasyon testleri

- Periferik yayma;

belirgin oranda şist

TMA- TTP ÖN TANISI



hematolojiatlası.com

Trombotik mikroanjiopati (TMA):

- Küçük damarlarda trombositlerden zengin trombüse bağlı mikrovasküler endotel hasarı yoluyla masif oklüzyon
- Mikroanjiopatik hemolitik anemi (MAHA, intravasküler eritrosit fragmentasyonu ile non immün hemolitik anemi)

TMA ayırıcı tanı:

- **Primer**

- ✓ Trombotik trombositopenik purpura (TTP)
- ✓ Hemolitik üremik sendrom

- **Sekonder**

- ✓ Gebelik, HELLP sendromu, eklampsi
- ✓ SLE, AFAS, skleroderma
- ✓ Hipertansiyon
- ✓ Malignite
- ✓ İlaç/radyasyon
- ✓ Sepsis, DİK
- ✓ Solid organ/ kemik iliği nakli
- ✓ Konjenital-metabolik hastalıklar

Eylül 2011

- Enfeksiyon serolojik testleri
- ANA, Anti ds DNA, lupus antikoagülan, β 2 glikoprotein, ANCA
- Görüntüleme
- Kemik iliği incelemeleri
- ADAMTS13 aktivite, antijen ve inhibitör düzeyleri

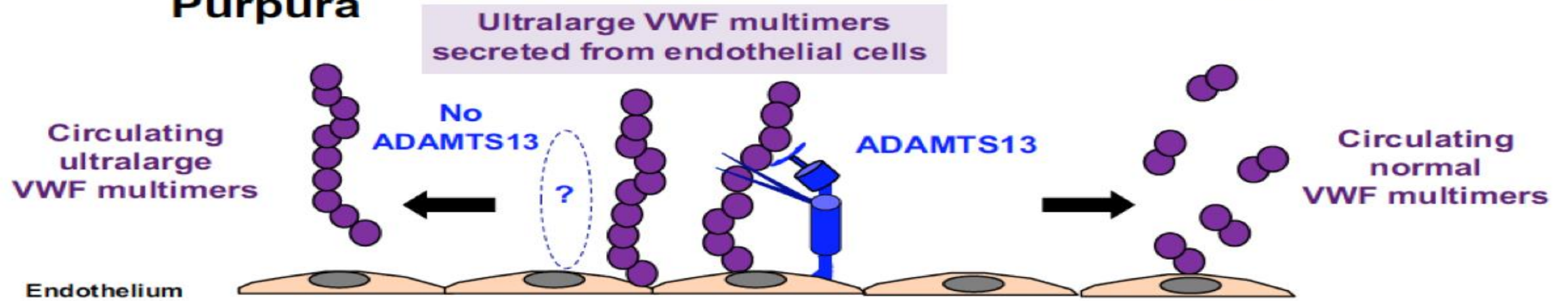
Eylül 2011

- Terapötik plazmaferéz (TPE)
- Metilprednizolon (MP)
- ADAMTS13 aktivitesi **< % 0.2**
ADAMTS13 antijen negatif
ADAMTS13 inhibitör düzeyi **87 U/mL**

İmmün aracılı, kazanılmış TTP

Thrombotic Thrombocytopenic Purpura

Physiology



The known players

Causing factors

**ADAMTS13
severe deficiency**
(autoantibodies, gene mutations,
other mechanisms)

Predisposing factors

Female gender
Black ethnicity
HLA-DRB1*11
Obesity

Precipitating factors

Conditions increasing
VWF levels
(inflammation, infections,
pregnancy...)

TTP

Protein candidates

Cell receptor / carrier protein for ADAMTS13?
Physiologic inhibitor to ADAMTS13?
Variability of VWF sensitivity to ADAMTS13
linked to VWF polymorphisms or to factor H?

Cellular candidates

Platelets?
Endothelial cells?

The unknown players

Joly et al., Blood, 2017

Table 1. Clinical features, and signs and symptoms of TTP

Clinical feature	Signs/symptoms
MAHA	Pallor, weakness, fatigue, jaundice
Thrombocytopenia	Petechiae and occasionally purpura
Bowel ischemia	Abdominal pain, nausea, vomiting, diarrhea
Cardiac ischemia	Chest pain, hypotension, heart failure
Central nervous system ischemia	Common: confusion, headache Less common: coma, encephalopathy, stroke, seizure, focal abnormalities
Renal ischemia	Hematuria, proteinuria
Fever	Fever (high fever with chills suspect other diagnosis)

Klasik pentad: Trombositopeni

MAHA

Nörolojik değişiklikler

Böbrek yetmezliği

Ateş

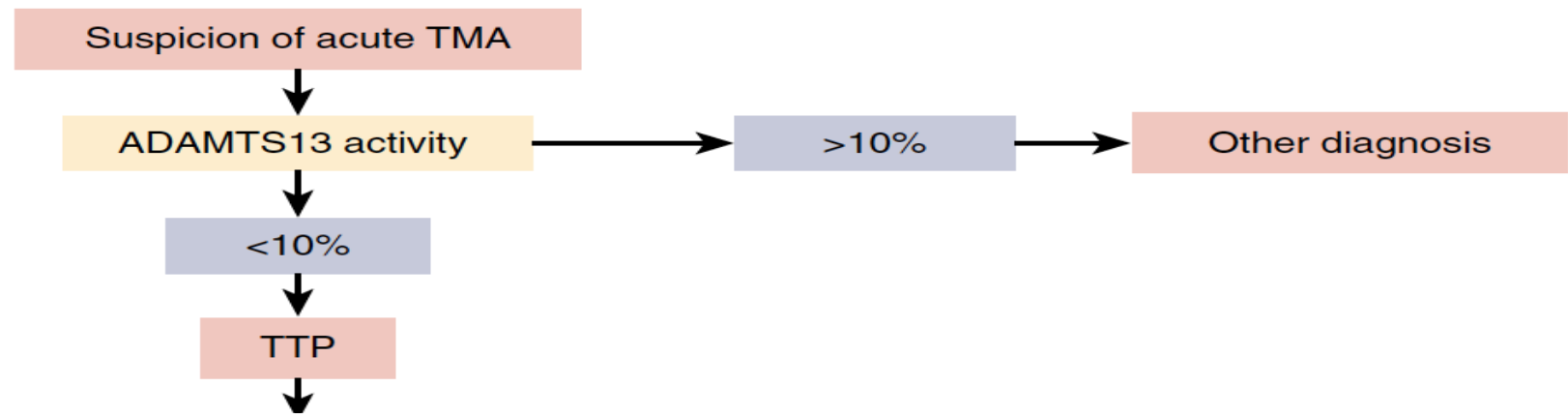
Sayani et al., Blood, 2015

Table 2. Laboratory findings suggestive of acquired TTP

Laboratory data		Results
Platelet count, $\times 10^3/\mu\text{L}$		<30
Hemoglobin, g/dL		<10
Lactate dehydrogenase		Elevated
Haptoglobin		Decreased
Reticulocyte count		Increased
Indirect bilirubin		Increased
Peripheral blood smear		Increased schistocytes, nucleated red blood cells*
Creatinine		Mildly increased (<1.5 mg/dL)
Troponin T		May be increased
INR, PTT, fibrinogen		Normal

INR, international normalized ratio; PTT, partial thromboplastin time.

*Consider a bone marrow biopsy in the presence of numerous nucleated red blood cells to rule out an alternative etiology, for example, occult systemic malignancy.⁹⁻¹²



*The PLASMIC Score for TTP Prediction	
Component	Point
Platelet count $<30 \times 10^9$ per L	1
HemoLysis (indirect bilirubin $>2 \text{ mg dL}^{-1}$, uncorrected reticulocyte $> 2.5\%$, OR undetectable haptoglobin)	1
No Active cancer in previous year	1
No history of Solid-organ or stem-cell transplant	1
MCV $<90 \text{ fL}$	1
INR <1.5	1
Creatinine $<2.0 \text{ mg dL}^{-1}$	1

HASTANIN
SKORU:

- 6

0-4 puan: düşük risk, 5 puan: orta risk, 6-7 puan: yüksek risk

Bendapudi et al., Lancet Haematol 2017;

THROMBOTIC MICROANGIOPATHY, THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

Incidence: <1/100,000/yr

Procedure

Recommendation

Category

TPE

Grade 1A

I

Volume treated: 1-1.5 TPV

Frequency: Daily

Replacement fluid: Plasma or Plasma/Albumin

ASFA, 2019

ADULT-ONSET ACQUIRED TTP

Standard treatment of acute TTP

Daily therapeutic plasma exchange (TPE) (\pm steroids) in emergency until remission

COMPLETE RESPONSE
Full clinical recovery
AND recovery of a normal
platelet count ($>150 \times 10^9/L$)
for at least 2 days

UNRESPONSIVE TTP
Platelet count $<$ double the
initial, after 4 days of
standard intensive treatment
AND persistently elevated
LDH levels

TTP EXACERBATION
Worsening clinical manifestations
AND/OR recurrent thrombocytopenia
($<100 \times 10^9/L$ for at least 2 days) AND/OR
worsening thrombocytopenia (platelet count
decrease $>$ one-third the highest count, for at
least 2 days) with no other identifiable cause



Eylül 2011

- Kötüleşme; TPE 2X1
- Yanıt; TPE 1X1
- Toplam 22 seans TPE

- MP azaltılarak kesilmesi
- Remisyonda izlem

Ağustos 2015

- Bilateral alt ekstremitelerde ekimotik lezyonlar
- 2014 yılında C/S ile doğum
- Lökosit 7 630/uL,
- Hb **11.6 g/dL**, Hct **%33.2**, MCV 95.7 f/L,
- Trombosit **22 000/uL**,
- T. bilirubin **1.4 mg/dL**, İ. bilirubin **1 mg/dL**,
- LDH **619 U/L**

Ağustos 2015

- Renal fonksiyon testleri
- Haptoglobulin 32 mg/dL
- Koagülasyon testleri
- Enfeksiyon parametreleri
- Periferik yaymada >%1 oranında şistosit

Relaps TTP

Ağustos 2015

- TPE, MP
- ADAMTS 13 aktivitesi **<%0.4**
- ADAMTS 13 inhibitör **67 U/mL**
- ADAMTS 13 antijen negatif
- Toplam 6 seans TPE
- MP azaltılarak kesilmesi
- Remisyonda izlem

Ocak 2018

- Bilateral alt ekstremitelerde ekimotik lezyonlar
- Lökosit 11 600/uL,
- Hb 12.6 g/dL, Hct %36.4,
- Trombosit **26 000/uL**,
- T. bilirubin 1.2 mg/dL, İ. bilirubin 0.9 mg/dL,
- LDH **674 U/L**

Ocak 2018

- Haptoglobulin 30 mg/dL
- Renal fonksiyon testleri
- Coombs testleri negatif
- Koagülasyon testleri
- Enfeksiyon parametreleri
- Periferik yaymada >%1 oranında şistosit

2. Relaps TTP

Ocak 2018

- TPE, MP
- ADAMTS 13 aktivitesi **<%0.3**
- ADAMTS 13 inhibitör **75 U/mL**
- ADAMTS 13 antijen negatif
- Toplam 7 seans TPE

Refrakter- Relaps

- Rituximab
- Splenektomi
- Azatiopirin
- Siklosporin
- Siklofosfamid
- Vinkristin
- Yeni ajanlar;

Bortezomib

NAC

Rekombinant ADAMTS 13

Anti vWF tedavi (ALX- 0681; caplacizumab)

TTP treatment

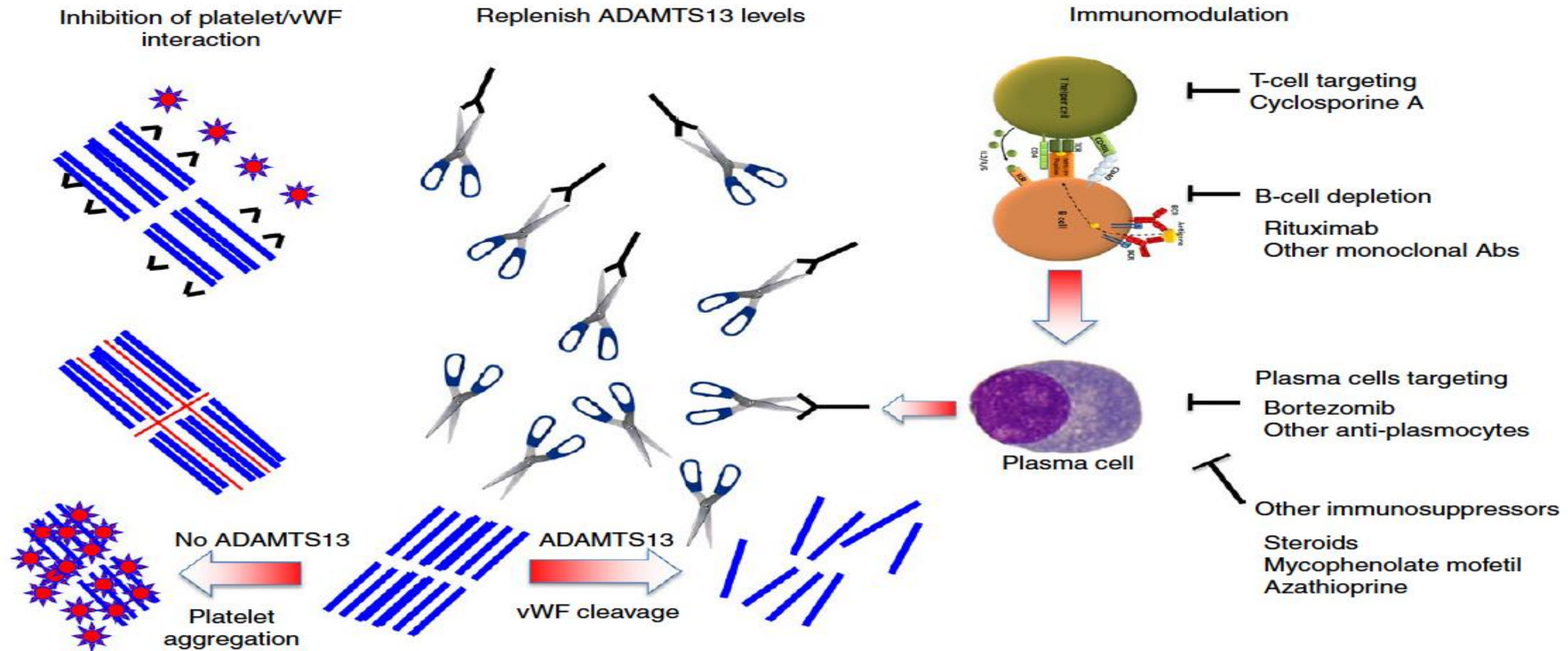


FIGURE 1 The three strategies of immune thrombotic thrombocytopenic purpura treatment. Abs, antibodies; vWF, von Willebrand factor. ✂, ADAMTS13; ★, platelets; //, von Willebrand factor; Y, anti-ADAMTS13 antibodies; <, anti-vWF nanobody (caplacizumab); ✂, N-acetylcysteine

TABLE 1 Novel therapies in TTP

Novel therapies for TTP	Mechanism	Evidence
Caplacizumab	VWF A1 antagonist - blocks VWF and platelet interaction	Phase II showed decrease time to recover from acute episodes and lower exacerbation rate, Phase III completed
Anfibatide	Platelet Gplb antagonist - block VWF and platelet interaction	Inhibits adhesion and thrombus formation in murine models
rADAMTS13	Restoration of ADAMTS13 function	Phase I in cTTP have shown good safety and tolerability
N-acetylcysteine	Reduce the ULVWF	Pre-clinical studies showing mechanism. Case reports with mixed results.
Bortezumib	Eliminates plasma cells, thereby decreases the production of autoantibodies against ADAMTS13	Case reports and case series showing clinical improvement for refractory TTP
Splenectomy	Reduce the autoimmune response/Eliminate B-cell reservoir	Case reports and Case series for its use in prevention of relapses
Rituximab	Aim at decreasing the production of anti-ADAMTS13 autoantibodies by B-cell depletion	Cohort and Case control studies for its use as first line therapy (with fewer and later relapses than PEX and steroids alone) and also for prevention of relapses.

Table 2. Treatment with rituximab in the acute phase of autoimmune TTP, in reports involving 10 or more patients

Series (year)	N	Age (yr), median (range), mean±SD	%F	%R	Number of rituximab infusion, median (range)	CR (%)	Days to CR, median (range), mean ± SD
Scully et al (2007) ⁹⁴	25	43 (17-67)	76	44	4 (2-8)	100	11
Jasti et al (2008) ⁹⁰	12	43 (19-59)	83	8	(1-13)	83	18 (14-41)
Ling et al (2009) ⁹¹	13	42 (23-71)	69	54	NA	92	NA
de la Rubia et al (2010) ⁹²	24	(24-72)	71	42	4 (1-8)	87.5	14 (7-35)
Scully et al (2011) ⁸⁹	40	42 (21-76)	65	15	4 (2-8)	82.5	12
Froissart et al (2012) ⁸²	22	36.8 ± 11	67	14	4	82	12 ± 6.7
Page et al (2016) ⁹³	16	41 (20-79)	75	0	4 (1-4)	100	21* (5-76)

CR, complete remission (durable treatment response at least 30 d after discontinuation of TPE; F, female; N, number of patients; NA, data not available; R, relapsing patients (recurrent disease ≥ 30 d after reaching treatment response); yr, year.

*Days from first to last TPE.

Joly et al., Blood, 2017

Table 3. Clinical relapses and adverse events after treatment with rituximab in the acute phase of autoimmune TTP, in reports involving 10 or more patients

Series (year)	Clinical relapse (%)	Time to relapse, median (range)	Clinical RFS* (months), median (range)	Serious adverse events
Scully et al (2007) ⁹⁴	0	—	10 (1-33 mo)	1 fatal pneumonia, 1 morbilliform rash
Jasti et al (2008) ⁹⁰	8	23 mo	48.5 (1-79 mo)	1 VZV transverse myelitis and encephalitis
Ling et al (2009) ⁹¹	0	—	<div>Rituximab 375 mg/m² /hafta 4 kurs</div>	
de la Rubia et al (2010) ⁹²	12.5	29 mo (7-40)		
Scully et al (2011) ⁸⁹	10	27 mo (1-40)		
Froissart et al (2012) ⁸²	14	24 mo (2-40)		
Page et al (2016) ⁹³	12.5*	2.5 and 12 mo		

RFS, relapse-free survival; VZV, varicella zoster virus.

*Two relapses.

Temmuz 2019

- Bulantı, kusma, halsizlik, tüm vücutta yaygın purpurik lezyonlar, ikter
- 6 gün önce C/S ile doğum
- Lökosit 7 200/uL
- Hb **6.3 g/dL**, Hct %**18.6**, MCV 77. 2 f/L
- Trombosit **5 000/uL**
- T. bilirubin **2.5 mg/dL**, İ. bilirubin **2.02 mg/dL**
- LDH **2699 U/L**

Temmuz 2019

- Karaciğer fonksiyon testleri
- Haptoglobulin **8 mg/dL**
- Üre 63 mg/dL, kreatinin 1.05 mg/dL,
- Coombs testleri
- Koagülasyon testleri
- Enfeksiyon parametreleri
- Periferik yaymada belirgin oranda şistosit (her alanda >10)

Temmuz 2019

- TPE, MP
- ADAMTS 13 aktivitesi **<%0.2**
- ADAMTS 13 inhibitör **19.53 U/mL**
- ADAMTS 13 antijen negatif

Gebelik ile indüklenen/ immün aracılı TTP

- Toplam 9 seans TPE
 - MP azaltılarak kesilmesi
 - Remisyonunda izlem
-
- Lökosit 5 600/uL
 - Hb 12.1 g/dL, Hct % 37, MCV 86. 2 f/L
 - Trombosit 245 000/uL



Sabrınız için teşekkürler...