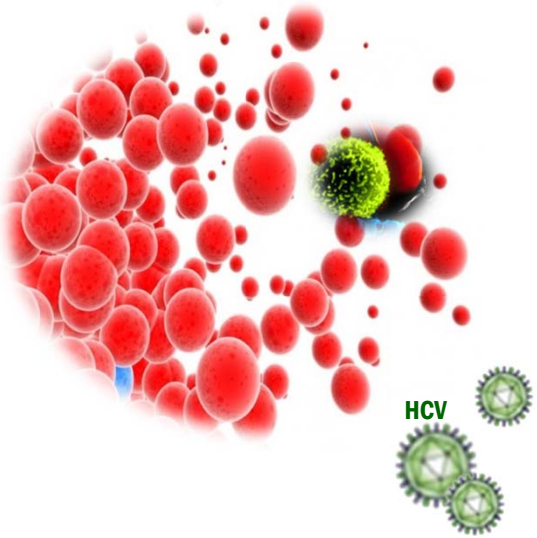

Гематологические побочные эффекты на фоне тройной терапии с ингибитором протеазы: диагностика и лечение

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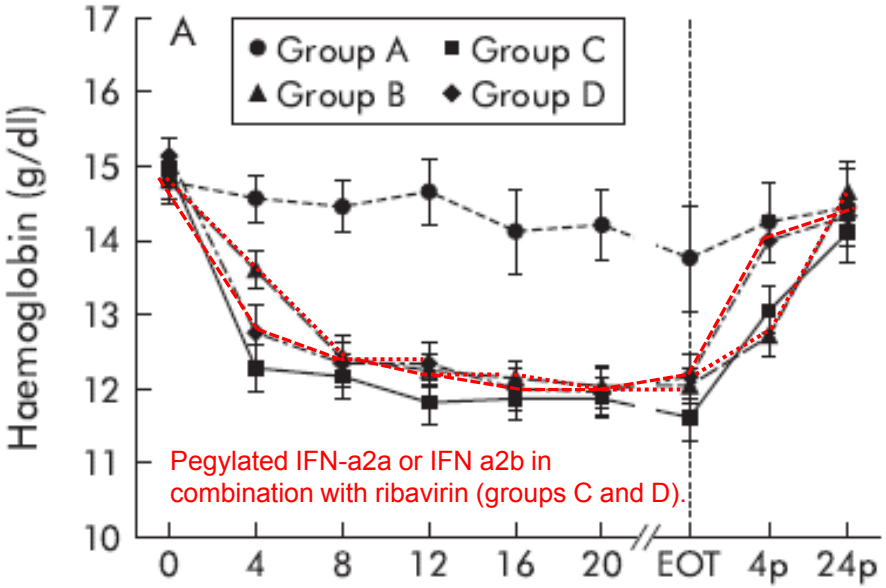
Introduction

- Addition of protease inhibitors (PIs) boceprevir (BOC) and telaprevir (TVR) to treatment regimens has led to creation of the new standard 'triple therapy' for genotype 1 patients
- The successes, failures, and new challenges of triple therapy have become well known.
- This new gold standard for treatment of genotype 1 patients presents a profile of side effects that are unique and also compound reactions seen in pegylated interferon-alfa (PEG-IFN) and ribavirin (RBV) dual therapy
- Hematologic side effects of PEG-IFN/RBV were both common and potentially problematic

Development of anemia during dual therapy

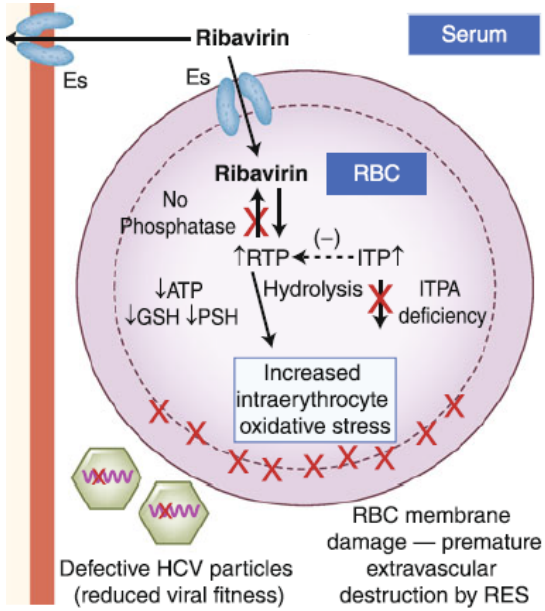


Anemia was typically seen within the first 12-20 weeks of therapy

The decrease in haemoglobin levels was more severe in patients receiving combination therapy with RBV than in those receiving IFN-a alone (group A v group B, group A v group C, group A v group D, p,0.05 at any week of therapy)

The resulting anemia was stabilized with dose reduction of RBV and resolved upon discontinuation.

M Schmid, A Kreil, W Jessner, M Homoncik, C Datz, A Gangl, P Ferenci, M Peck-Radosavljevic. Gut 2005;54:1014–1020



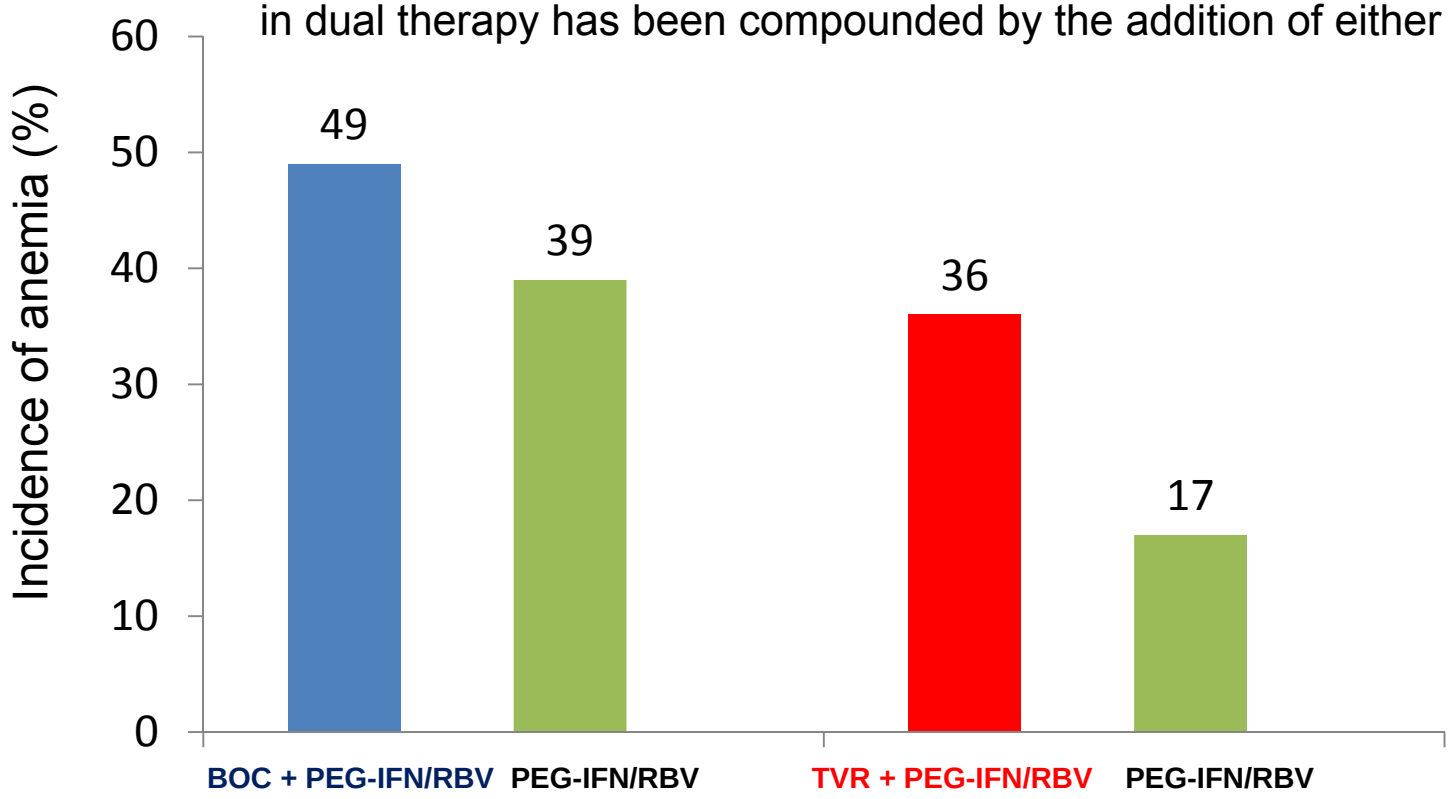
The high concentrations of RBV in erythrocytes resulting in hemolysis

RBV-associated hemolysis is compounded by suppression of erythropoesis by interferon in the bone marrow.

Bunchorntavakul C, Reddy K.R.Curr Hepatitis Rep (2011) 10:168–178

Suppression of haematopoiesis during triple therapy

The well-recognized side effect of anemia (defined as a hemoglobin <10 g/dL) in dual therapy has been compounded by the addition of either PI

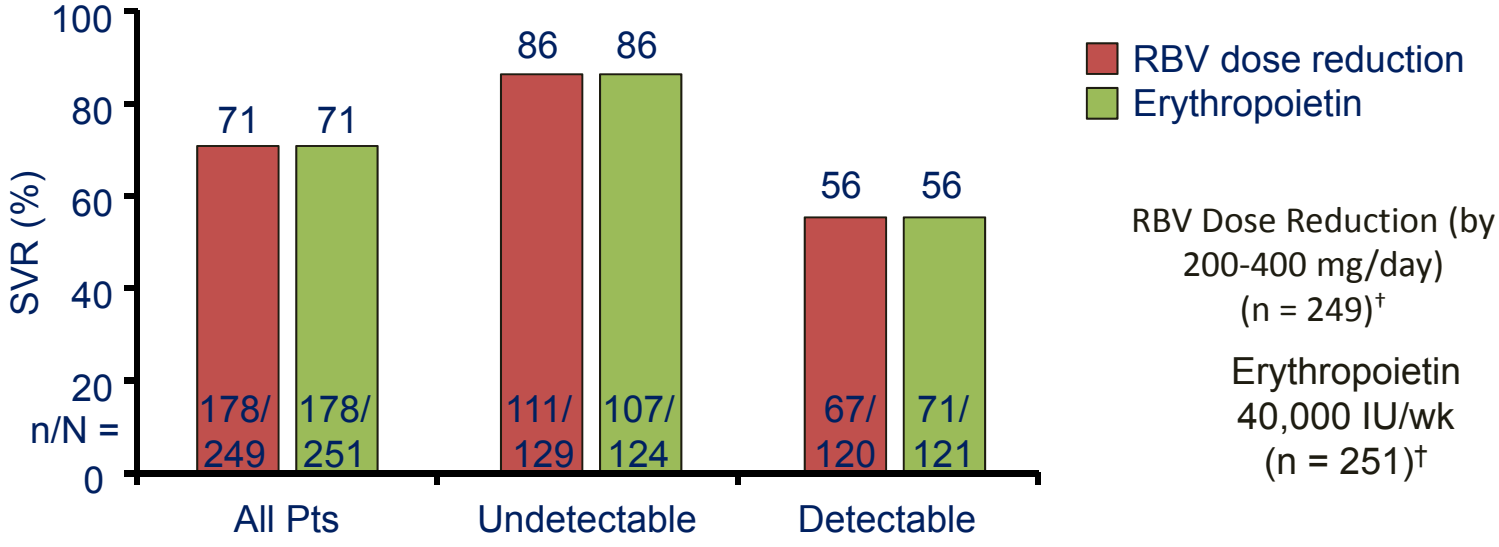


Nine percent of patients undergoing triple therapy with either BOC or TVR experienced a decline of Hb to less than 8.5 g/dL

Kwo PY et al., Lancet. 2010;376:705–16.
Poordad F et al., N Engl J Med. 2011;364:1195–206.
Jacobson IM et al., N Engl J Med. 2011;364:2405–16.

SVR Rates With RBV Dose Reduction or Erythropoietin for Anemia Management

- Similar SVR rates (71%) with both strategies[1,2]
  - Similar SVR rates regardless of timing of anemia management, number of RBV dose reductions, or lowest RBV dose received
  - Lower SVR rates if < 50% of per protocol total RBV dose received
- Higher SVR rate if anemia management initiated with undetectable HCV RNA[2]

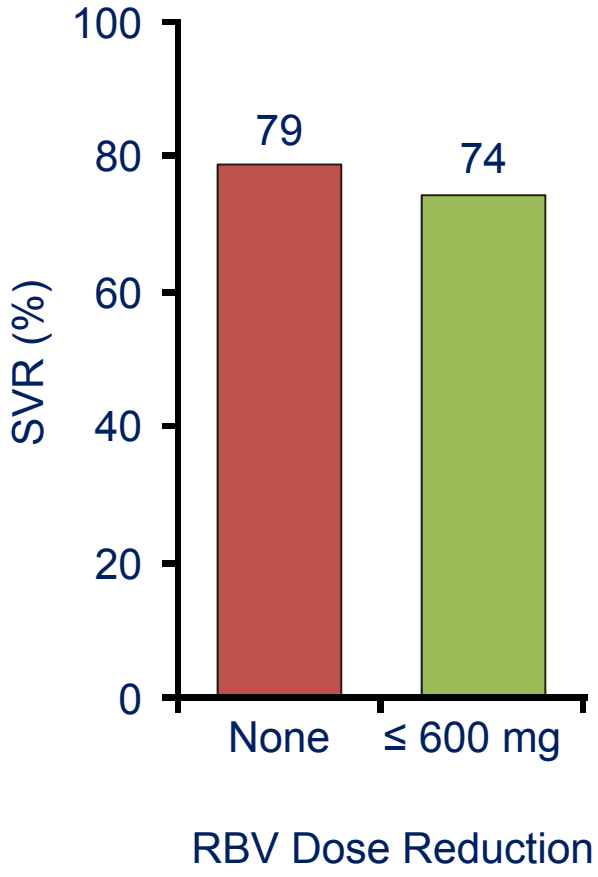


1. Poordad F, et al. EASL 2012. Abstract 1419. 2 Poordad F, et al. AASLD 2012. Abstract 154.

Impact of RBV DR for Anemia in Telaprevir Treatment–Naive Phase III Trials

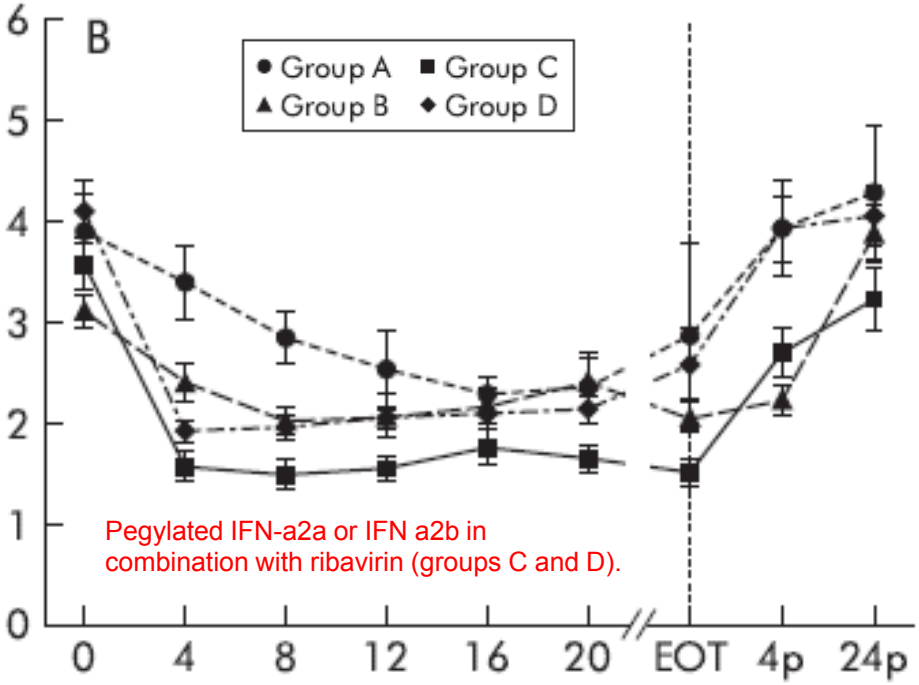
- Retrospective subanalysis
  - No erythropoiesis-stimulating agents
  - RBV dose reduction per protocol to 600 mg/day
  - T12PR arms
    - 604/885 (68%) had RBV dose reduction

Patients receiving TVR exhibited a similar pattern in the ILLUMINATE and ADVANCE phase 3 trials



Sulkowski M, et al. EASL 2012. Abstract 477.

Suppression of leucopoiesis during dual therapy



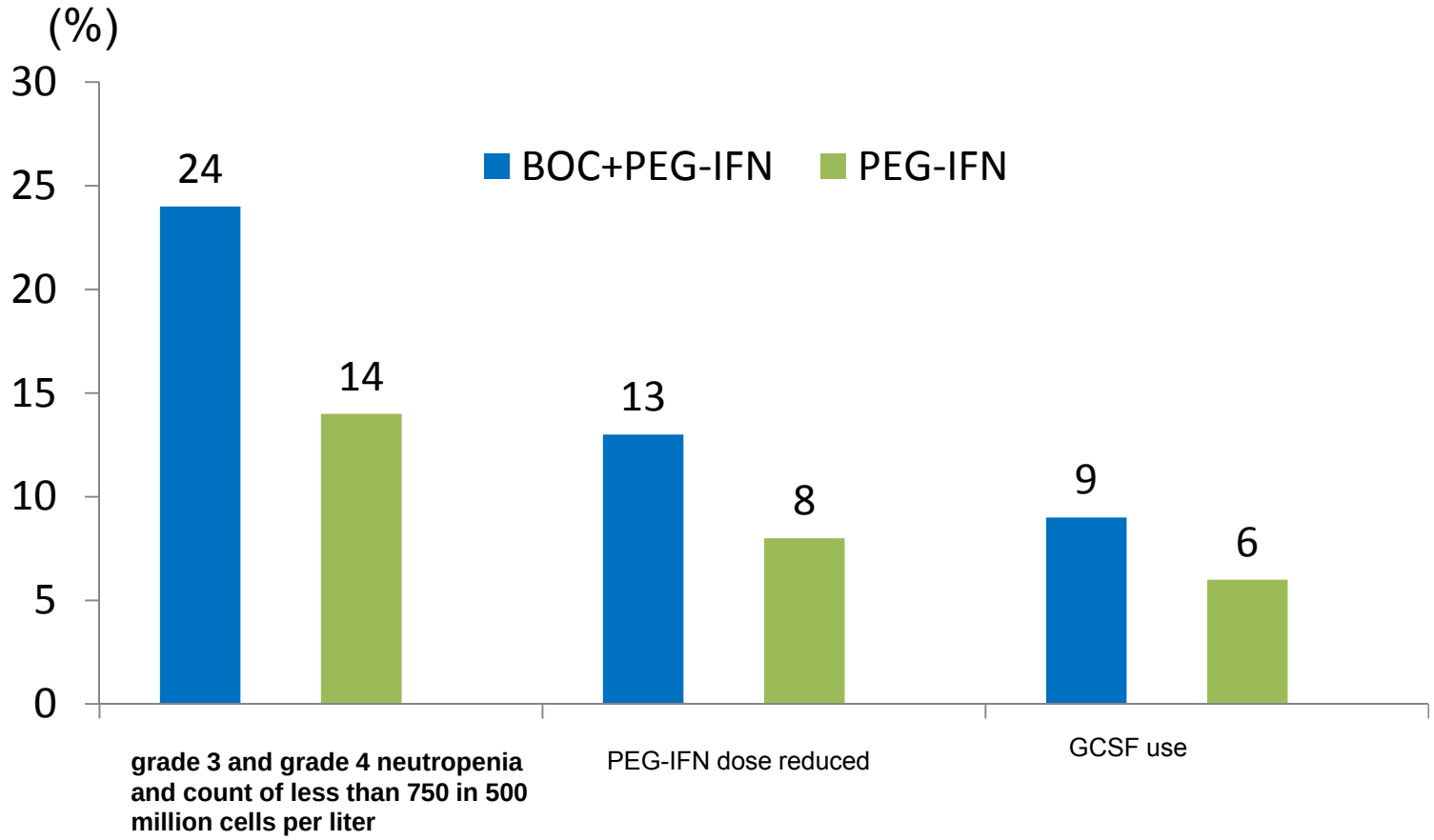
Both pegylated IFNs exerted a stronger suppressive effect on leucopoiesis compared with monotherapy with conventional IFN, but compared with group B, only group C showed a significantly stronger suppression of WBC.

The decrease in neutrophil counts was comparable between groups A, B, and D, showing significant differences only at the beginning of therapy (group A v group B, group A v group D, p,0.05 for weeks 4 and 8, NS for any other week of treatment; group B v group D, NS for any week of therapy).

Compared with groups A, B, and D, neutrophil count was lower in group C throughout the whole therapy (group A v group C, group B v group C, group C v group D, p,0.01 for any week of therapy)

M Schmid, A Kreil, W Jessner, M Homoncik, C Datz, A Gangl, P Ferenci, M Peck-Radosavljevic. Gut 2005;54:1014–1020

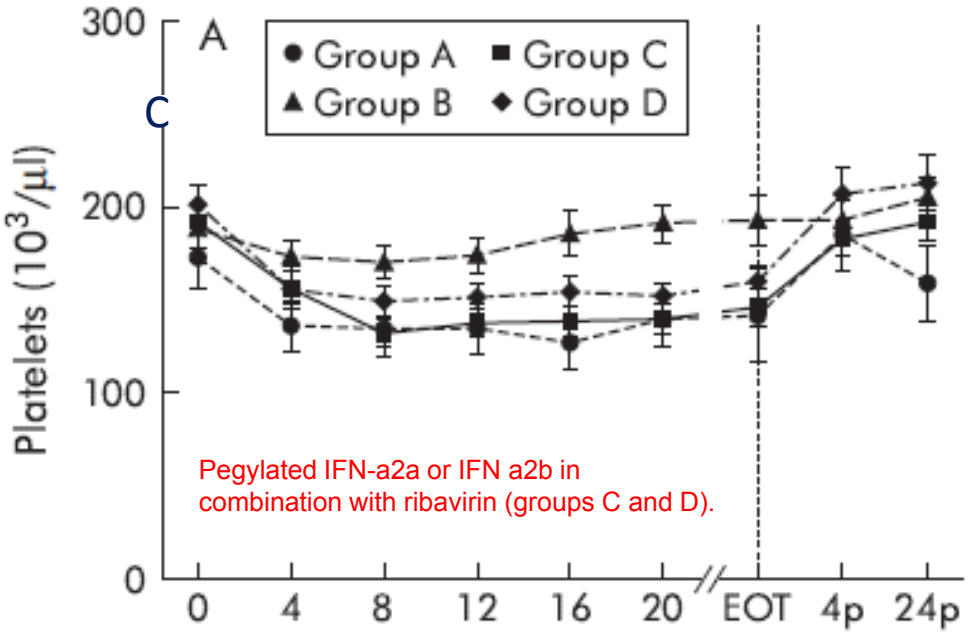
Suppression of leucopoiesis during triple therapy



TVR-based triple therapy did not have an increased incidence of neutropenia, as compared with dual therapy. However, 14 %–17 % of patients still experience neutropenia in TVR-based therapy

FDA. Transcript for the meeting of the Antiviral Drugs Advisory Committee. April 27, 2011 Accessed 8/31/12 at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/ drugs/antiviraldrugsadvisorycommittee/UCM257464.pdf

Suppression of thrombocytoiesis during dual therapy



At week 4 of therapy, peripheral platelet count (PPC) decreased in all groups (median decrease in group A, 25%; group B, 8%; group C, 21%; group D, 23%; p,0.05 for all groups)

PPC remained decreased throughout therapy, with a nadir of 34% in group A at week 16, 36% in group C at week 8, and 24% in group D at week 12. Platelets returned to baseline levels within four weeks after discontinuation of therapy in these groups

- PPC was significantly reduced in all groups after four weeks of treatment.
- The significant increase in TPO levels paralleling the decrease in platelet count indicates a true reduction in platelet number
- The decrease in PPC by IFN-a is caused by diminished pro-duction of platelets through suppression of megakaryocyte progenitor cell proliferation and differentiation in bone marrow

M Schmid, A Kreil, W Jessner, M Homoncik, C Datz, A Gangl, P Ferenci, M Peck-Radosavljevic. Gut 2005;54:1014–1020

Suppression of thrombocytopoesis during dual therapy

- Adverse event reporting in phase III trials evaluating the addition of PIs with pegIFN/RBV therapy

	Platelet Count < 50,000/mm^3, %	
	PI Regimen	pegIFN/RBV
Boceprevir[1] (previously untreated)	3	1
Boceprevir[1] (previous treatment failures)	4	0
Telaprevir[2]	3	1

1. Boceprevir [package insert]. July 2012.
2. Telaprevir [package insert]. October 2012.

Impact of Thrombocytopenia on Clinical Practice During Treatment of Chronic HCV

- AASLD guidelines: platelet count should be ≥ 75,000/mm^3 (with compensated liver disease) to initiate treatment[1]
  - ? cirrhosis

Platelet Count	Strategy	
	PegIFN alfa-2a[2]	PegIFN alfa-2b[3]
< 50,000/mm^3	Dose reduce to 90 µg	First DR to 1 µg/kg/wk Second DR to 0.5 µg/kg/wk (if needed)
< 25,000/mm^3	Discontinue treatment	Discontinue treatment

1. Ghany M, et al. AASLD practice guidelines. April 2009. 2. PegIFN alfa-2a [package insert]. September 2011. 3. PegIFN alfa-2b [package insert]. October 2012.

French multicentre CUPIC study

Events	Telaprevir (n=292)	Boceprevir (n=205)
Anemia (%)		
Grade 2 (8.0 - < 9,0 g/dl)	18.8	23.4
Grade 3/4 (< 8.0 g/dl)	11.6	3.4
EPO use	53.8	46.3
Blood transfusion	16.1	6.3
RBV dose reduction or discontinuation	17.1	14.6
Neutropenia (%)		
Grade 3 (500 - < 750/mm^3)	2.0	1.0
Grade 4 (< 500/mm^3)	0.7	3.4
G-CSF use	2.4	4.4
Thrombocytopenia (%)		
Grade 3 (20 000 - < 50 000)	9.6	4.9
Grade 4 (< 20 000)	3.1	1.5
Thrombopoietin use	1.4	1.0
PEG-IFN dose reduction or discont.	30.5	34.6

Gezode C et al., J Hepatol. 2013 May 10. pii: S0168-8278(13)00290-0. doi: 10.1016/j.jhep.2013.04.035. [Epub ahead of print]

Hematologic Safety of Direct-Acting Antiviral Therapies in US Veterans With Chronic Hepatitis C

Hematologic characteristic	Boceprevir (n=661)	Telaprevir (n=198)	P value
Anemia (%)			
Grade 2-4	50	49	0.89
Grade 3-4	7	13	0.01
RBV dose reduction	44	38	0.13
ESA use	25	26	0,93
Blood transfusion	5	8	0,08
Neutropenia (%)			
Grade 2 ≥ 750	68	77	0.03
Grade 3-4 (749 - < 500/mm^3)	32	21	0.008
G-CSF use	9	2	<0.001
Thrombocytopenia (%)			
Grade 3 (25 000 - < 50 000)	13	14	
Grade 3-4 (< 25 000)	16	18	0.46
Platelet transfusion	0.3	1.0	0.20

Belperio PS et al., Clin Gastroenterol Hepatol. 2013 Mar 21. pii: S1542-3565(13)00385-6. doi: 10.1016/j.cgh.2013.03.006. [Epub ahead of print]

Заключение 1 (анемия)

- Хорошо известный эффект терапии ПЕГ ИФН в комбинации с рибавирином на развитие анемии увеличивался при добавлении к стандартной терапии любого ингибитора протеаз. И распространенность, и выраженность анемии увеличивалась при терапии тремя препаратами
- Механизмы развития анемии при использовании тройной терапии множественны, каждый из трех препаратов является причинным фактором
- Стратегии терапии на первом этапе включают уменьшение дозы рибавирина. Если анемия персистирует, используются переливание крови и эритропоэтины
- У пациентов с циррозом печени (CUPIC study) уровень анемии был выше, чем у больных без цирроза печени в регистрационных исследованиях. В когорте больных с ЦП эритропоэтин использовался в 53,8 % случаев (ТЕЛ) и 46,3% случаев (БОЦ)

Заключение 2 (нейтропения и тромбоцитопения)

- Нейтропения увеличивается при включении в стандартную терапию БОЦ (24% vs 14%). Терапия с включением ТЕЛ не увеличивает нейтропению в сравнении со стандартной терапией, однако но является присущей 14-17% пациентов
- Стратегии терапии включают использование гранулоцитарного колониестимулирующего фактора (G-CSF)
- Распространенность тромбоцитопении среди пациентов, получавших тройную терапию в регистрационных исследованиях небольшая (3% при использовании БОЦ в сравнении с 1% пациентов, получавших традиционную терапию). Никаких серьезных нежелательных явлений не зарегистрировано
- У пациентов с циррозом печени (CUPIC study) G-CSF использовался у 2,4% (ТЕЛ) and 4,4% случаев (БОЦ), тромбопоэтин в 1,4% и 1,1% случаев, соответственно