L'infettivologia del 3° millennio:

AIDS ed altro

VI Convegno Nazionale

Paestum, 15- 16 -17 maggio 2014

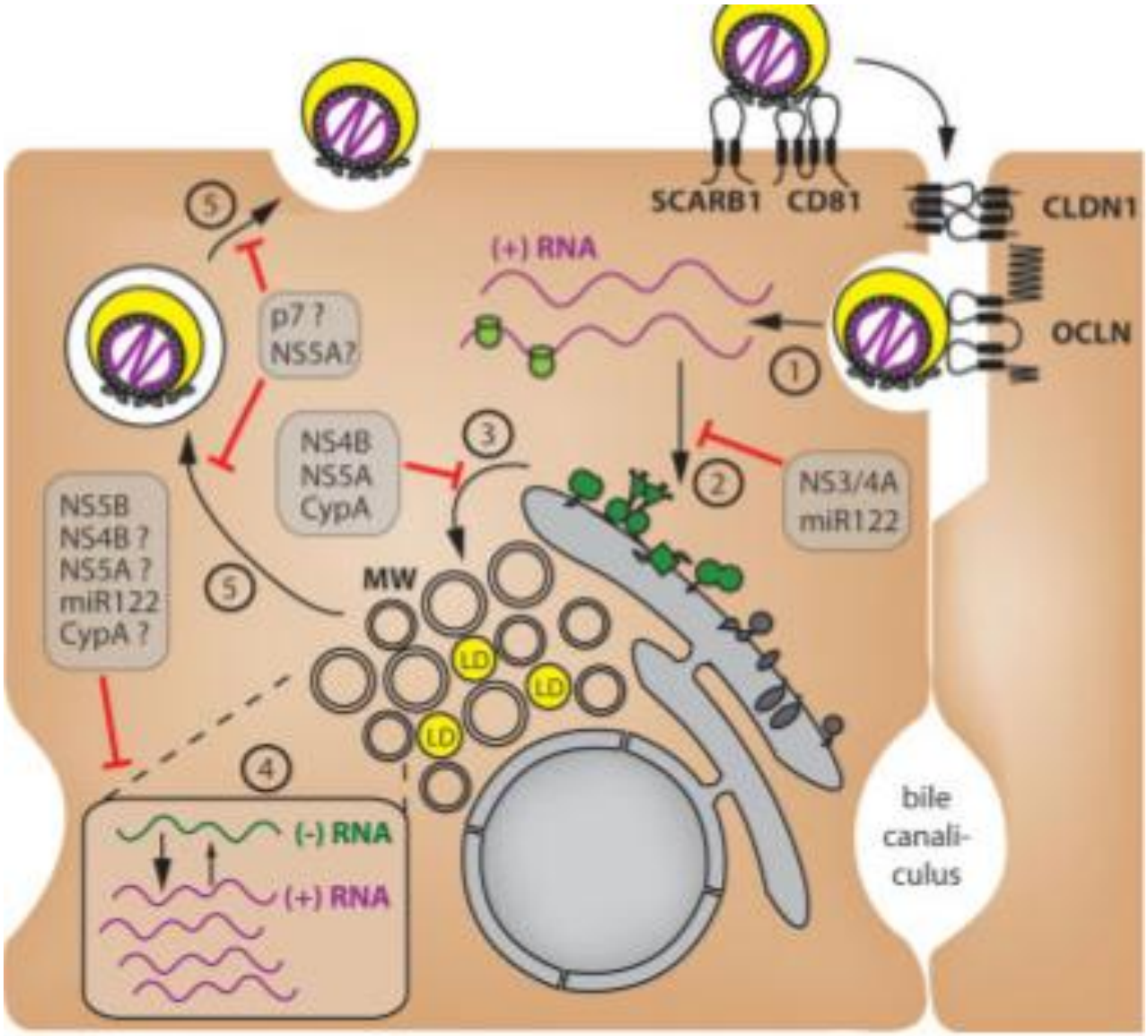
DAA: caratteristiche e gestione della safety e delle interazioni farmacologiche

Amelia Filippelli MD, PhD

Professore Ordinario di Farmacologia, Facoltà di Farmacia e Medicina, Dipartimento di Medicina e Chirurgia, Università degli Studi di Salerno

Direttore Servizio Farmacologia Clinica - AOU S. Giovanni di Dio e Ruggi d'Aragona

afilippelli@unisa.it


SCARB1
CD81
CLDN1
OCLN
(+) RNA
p7 ?
NS5A?
NS4B
NS5A
CypA
NS3/4A
miR122
NS5B
NS4B ?
NS5A ?
miR122
CypA ?
MW
LD
LD
LD
(-) RNA
(+) RNA
bile
canali-
culus
1
2
3
4
5
5

HCV DAAs and HTAs in clinical development (January 2014)

NS3-4A protease inhibitors

1st-wave, 1st-generation

Telaprevir (Janssen) – approved
Boceprevir (Merck) – approved

2nd-wave, 1st-generation

Simeprevir (Janssen) – approved
Faldaprevir (BI) – phase III
Asunaprevir (BMS) – phase III
ABT-450/r (Abbvie) – phase III
Vedroprevir (Gilead) – phase II
IDX-320 (Idenix) – phase II
Sovaprevir (Achillion) – clinical hold
Danoprevir/r (Roche) – phase II
Vaniprevir (Merck) – phase II

2nd-generation

MK-5172 (Merck) – phase II
ACH-2684 (Achillion) – phase II

Nucleoside/nucleotide analogue RdRp inhibitors

Sofosbuvir (Gilead) – approved
VX-135 (Vertex) – partial clinical hold

Non-nucleoside RdRp inhibitors

Thumb-1

BMS-791325 (BMS) – phase II
TMC-647055 (Janssen) – phase II

Thumb-2

Lomibuvir (Vertex) – phase II
GS-9669 (Gilead) – phase II

Palm-1

ABT-333 (Abbvie) – phase III
ABT-072 (Abbvie) – phase II
Setrobuvir (Roche) – phase II

NS5A inhibitors

1st-generation

Daclatasvir (BMS) – phase III
Ledipasvir (Gilead) – phase III
ABT-267 (Abbvie) – phase III
PPI-668 (Presidio) – phase II
ACH-2928 (Achillion) – phase II
GSK2336805 (GSK) – phase II
BMS824393 (BMS) – phase II
Samatasvir (Idenix) – phase II

2nd-generation

MK-8742 (Merck) – phase II
ACH-3102 (Achillion) – phase II
GS-5816 (Gilead) – phase II

Cyclophilin A inhibitors

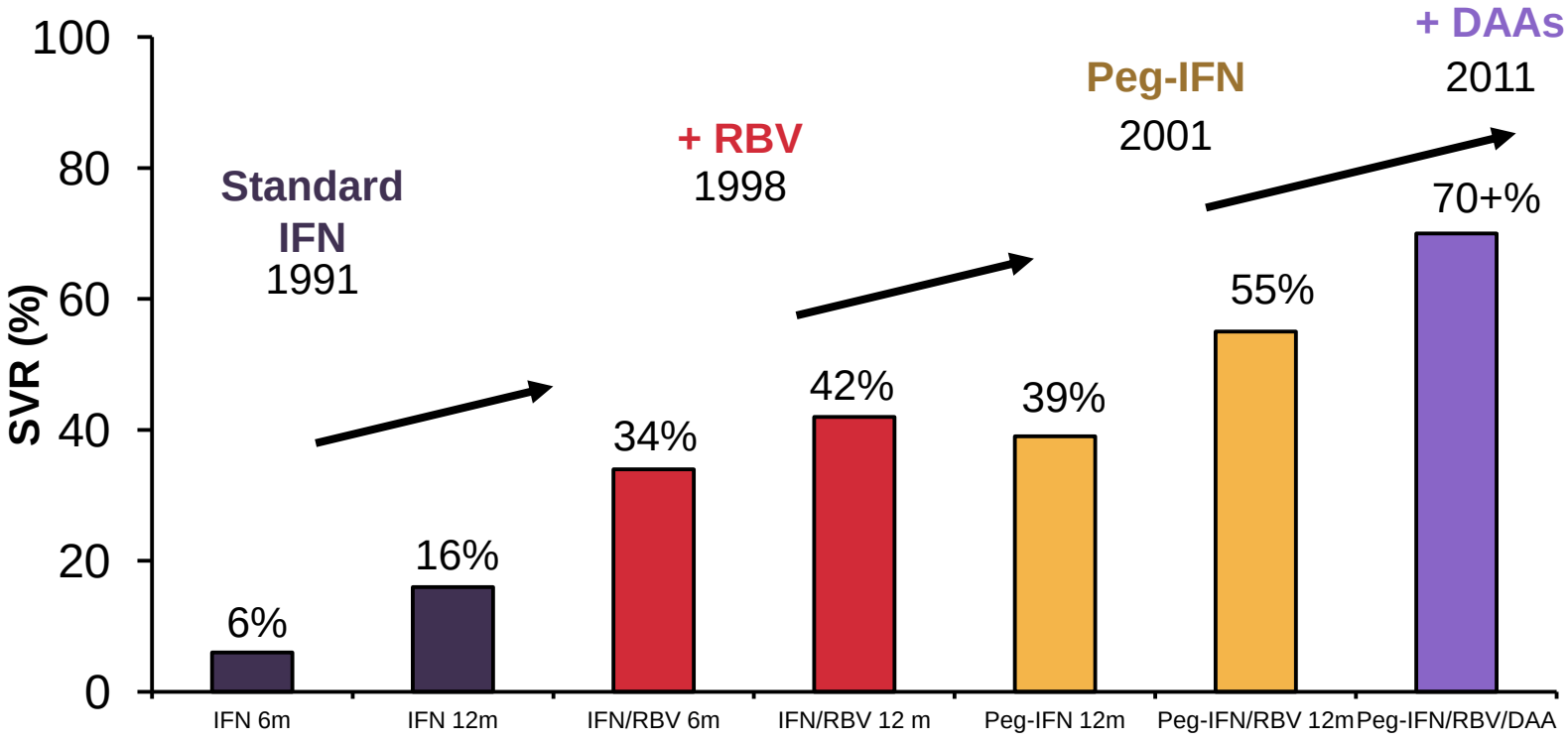
Alisporivir (Novartis) – phase II
SCY-635 (Scynexis) – phase II

miR-122 antagonist

Miravirsen (Santaris) – phase II

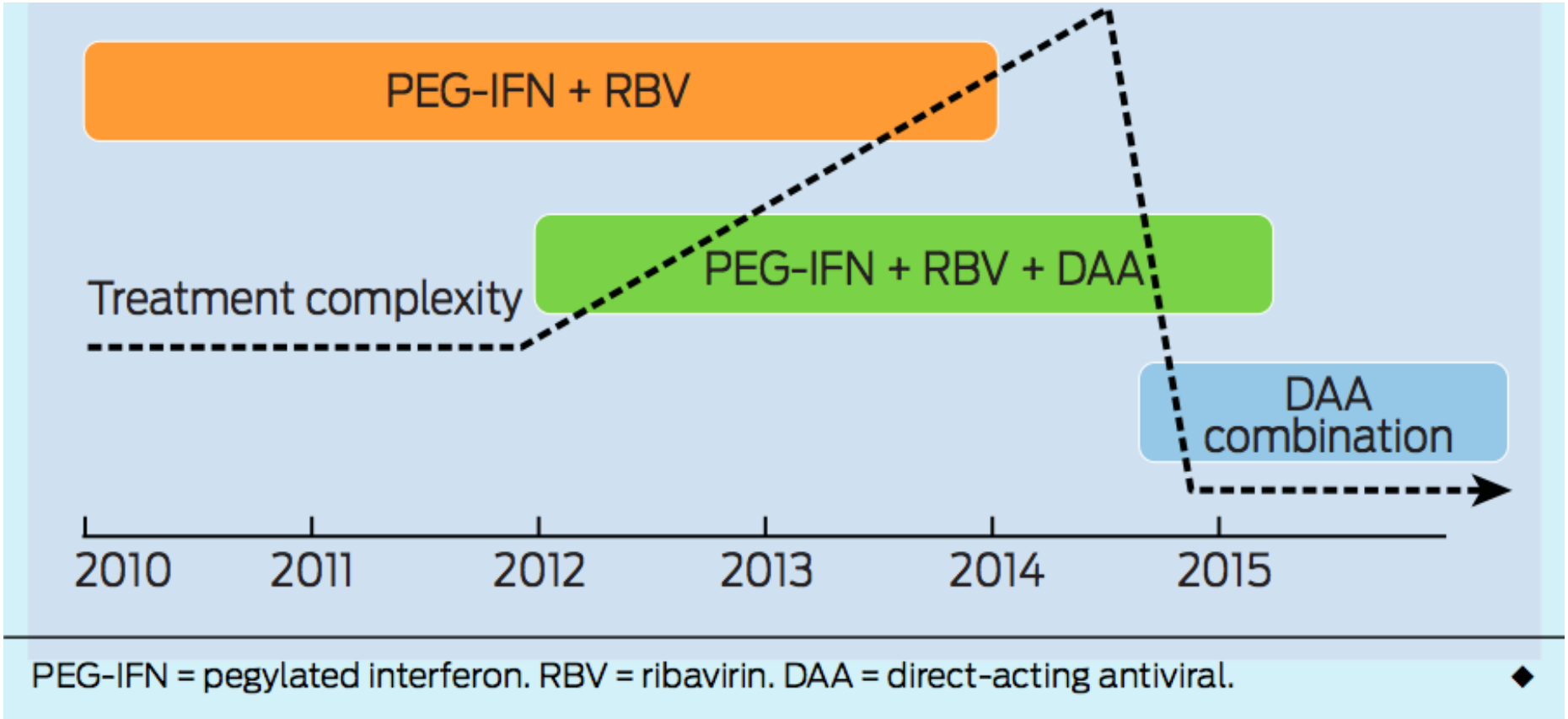
Pawlotsky JM. New Hepatitis C Virus (HCV) Drugs and the Hope for a Cure: Concepts in Anti-HCV Drug Development. Semin Liver Dis. 2014 Feb;34(1):22-9..

Milestones in Therapy of CHC: Average SVR Rates from Clinical Trials



Adapted from US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring MD.

Changing HCV treatment landscape



Dore G. The changing therapeutic landscape for hepatitis C. J Med J Aust. 2012 Jun 4;196(10):629-32.

Hepatitis C direct-acting antiviral (DAA) agents

- Boceprevir (BOC) and Telaprevir (TVR) represent a new era of therapy, as they are the first commercially available hepatitis C direct-acting antiviral (DAA) agents, which directly inhibit viral replication.
- In clinical trials of HCV genotype 1-infected patients receiving PegIFN and RBV, combined with BOC or TVR, SVR was achieved in 63-75% of treatment-naïve patients, in 69-88% of PegIFN and RBV relapsers, and in up to 33% of PegIFN and RBV nonresponders.
- Triple therapy is associated with more side effects and requires closer patient follow-up than treatment with PegIFN and RBV alone.
- Increased hematological toxicity from triple therapy may lead to increased utilization of growth factors, which will further strain medical resources in healthcare systems.
- Additionally, BOC and TVR carry the risk of inducing HCV resistance mutations, and it is likely that cross-resistance to future generations of PIs will develop in some patients who do not achieve SVR.

Boceprevir and Telaprevir Clinical Trials

- **Boceprevir plus pegIFN/RBV**
  - **SPRINT-2**: treatment-naive patients[1]
  - **RESPOND-2:** treatment-experienced patients[2]

- **Telaprevir plus pegIFN/RBV**
  - **ADVANCE:** treatment-naive patients[3]
  - **ILLUMINATE:** treatment-naive patients[4]
  - **REALIZE:** treatment-experienced patients[5]

[1] Poordad F, et al. N Engl J Med. 2011;364:1195-1206.
[2] Bacon BR, et al. N Engl J Med. 2011;364:1207-1217.
[3] Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416.
[4] Sherman KE, et al. N Engl J Med. 2011 Sep 15;365:1014-24.
[5] Zeuzem S, et al. N Engl J Med. 2011;364:2417-2428.

Boceprevir/Telaprevir in Combination with PEG-IFN/RBV: Limitations of Current Therapy

- Telaprevir and boceprevir only approved for Genotype 1
- Interferon backbone required
- TID dosing for telaprevir/boceprevir
- Response guided therapy (both) and lead-in (boceprevir) complicated
- 24-48 week treatment
- Limited efficacy in difficult to cure patients (e.g., patients with cirrhosis, prior null responders, African-Americans)
- Hematologic (both) and rash/dermatological (telaprevir) adverse events: (management plan)
- Drug-drug interactions

Boceprevir-Related Adverse Events in Clinical Trials

- Most notable adverse events occurring more frequently with boceprevir plus pegIFN/RBV vs pegIFN/RBV alone
  - Anemia, neutropenia, and dysgeusia

Adverse Event, %	Boceprevir + PegIFN/RBV	PegIFN/RBV
Treatment-naive patients	(n = 1225)	(n = 467)
▪ Anemia*	50	30
▪ Neutropenia	25	19
▪ Dysgeusia	35	16
Treatment-experienced patients	(n = 323)	(n = 80)
▪ Anemia	45	20
▪ Dysgeusia	44	11

*Anemia was managed with RBV reduction and/or epoetin alfa (43% of BOC + PR and 24% of PR).

Boceprevir-Related Adverse Events in Clinical

ADVERSE EVENTS	PREVIOUSLY UNTREATED (SPRINT-1 AND SPRINT-2)		PREVIOUS TREATMENT FAILURES (RESPOND-2)	
BODY SYSTEM ORGAN CLASS	VICTRELIS + PEGINTRON + REBETOL (N=1225)	PEGINTRON +REBETOL (N=467)	VICTRELIS + PEGINTRON + REBETOL (N=323)	PEGINTRON +REBETOL (N=80)
Median Exposure (days)	**197**	**216**	**253**	**104**
Blood and Lymphatic System Disorders				
Anemia	50	30	45	20
Neutropenia	25	19	14	10
Gastrointestinal Disorders				
Nausea	46	42	43	38
Dysgeusia	35	16	44	11
Diarrhea	25	22	24	16
Vomiting	20	13	15	8
Dry Mouth	11	10	15	9
General Disorders and Administration Site Conditions				
Fatigue	58	59	55	50
Chills	34	29	33	30
Asthenia	15	18	21	16
Metabolism and Nutrition Disorders				
Decreased Appetite	25	24	26	16
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	19	19	23	16
Nervous System Disorders				
Dizziness	19	16	16	10
Psychiatric Disorders				
Insomnia	34	34	30	24
Irritability	22	23	21	13
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea Exertional	8	8	11	5
Skin and Subcutaneous Tissue Disorders				
Alopecia	27	27	22	16
Dry Skin	18	18	22	9
Rash	17	19	16	6

Boceprevir-Related Adverse Events in Clinical Trials

Se[illegible]s

HEMATOLOGICAL PARAMETERS	PREVIOUSLY UNTREATED (SPRINT-1 AND SPRINT-2)		PREVIOUS TREATMENT FAILURES (RESPOND-2)	
	VICTRELIS + PEGINTRON +REBETOL (N=1225)	PEGINTRON + REBETOL (N=467)	VICTRELIS + PEGINTRON +REBETOL (N=323)	PEGINTRON + REBETOL (N=80)
Hemoglobin (g/dL)				
< 10	49	29	49	25
< 8.5	6	3	10	1
Neutrophils (x 10^9/L)				
< 0.75	31	18	26	13
< 0.5	8	4	7	4
Platelets (x 10^9/L)				
< 50	3	1	4	0
< 25	< 1	0	0	0

Telaprevir-Related Adverse Events in Clinical Trials

- Most notable adverse events occurring more frequently with telaprevir vs pegIFN/RBV alone
  - Rash, anemia, and anorectal symptoms

Adverse Event, %	Telaprevir + PegIFN/RBV (n = 1797)	PegIFN/RBV (n = 493)
Rash	56	34
Anemia*	36	17
Anorectal symptoms	29	7

*Anemia was managed with RBV reduction and/or epoetin alfa (43% of BOC + PR and 24% of PR).

- In most subjects, rash was mild to moderate
  - ✓ Severe rash in 4%; discontinuation due to rash in 6% of subjects
    - Occurred early, usually first 4 wks, but can occur at any time during TVR exposure
    - < 1% had SJS or DRESS (11 cases DRESS and 3 cases SJS)

Sofosbuvir-Related Adverse Events in Clinical Trials

- Fatigue (59%), headache (36%), nausea (34%) and insomnia (25%).
- 20% of patients developed a hemoglobin level of <10 g/dL and 2% developed a hemoglobin level of <8.5 g/dL.
- Neutropenia developed in approximately 20% of cases and thrombocytopenia in <1% of cases.

Simeprevir-Related Adverse Events in Clinical Trials

- Photosensitivity (28%), pruritus (22%), nausea (22%), dyspnea (12%), and hyperbilirubinemia (49%).

RETE NAZIONALE DI FARMACOVIGILANZA

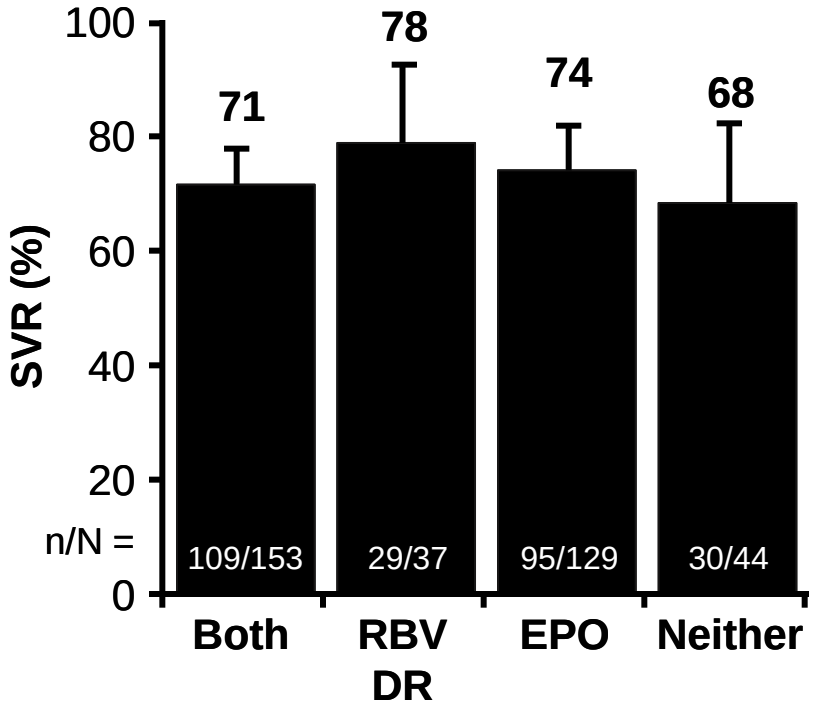
	Classe Terapeutica	Decessi	Gravi	Non Gravi	Non Indicato	Totale	Perc
J05AR	ANTIVIRALI PER IL TRATTAMENTO DELLE INFEZIONI DA HIV, ASSOC.	0	29	128	0	157	(13.9%)
J05AB	Nucleosidi e nucleotidi escl. inibitori della transcriptasi inversa	3	217	315	10	545	(48.2%)
J05AE	Inibitori della proteasi	2	188	333	8	531	(47%)
J05AG	Inibitori della transcriptasi inversa, non nucleosidi	0	26	109	1	136	(12%)
J05AF	Inibitori della transcriptasi inversa, nucleosidi	1	24	53	1	79	(7%)
J05AX	Altri antivirali	0	8	21	2	31	(2.7%)
J05AD	Derivati dell'acido fosfonico	1	0	3	0	4	(0.4%)
	TOTALE	6 (0.5%)	366 (32.4%)	739 (65.4%)	19 (1.7%)	1130	100%

RETE NAZIONALE DI FARMACOVIGILANZA

P.A. Sospetti	Decessi	Gravi	Non Gravi	Non Indicato	Totale	Perc
DARUNAVIR	0	9	29	0	38	(7.2%)
RITONAVIR	0	17	38	1	56	(10.5%)
ATAZANAVIR SOLFATO	0	25	41	2	68	(12.8%)
BOCEPREVIR	1	42	74	3	120	(22.6%)
LOPINAVIR/RITONAVIR	0	2	17	0	19	(3.6%)
TELAPREVIR	1	105	163	3	272	(51.2%)
FOSAMPRENAVIR	0	2	3	0	5	(0.9%)
TOTALE	2 (0.4%)	188 (35.4%)	333 (62.7%)	8 (1.5%)	531	100%

Boceprevir-Related Adverse Events: Management of Anemia

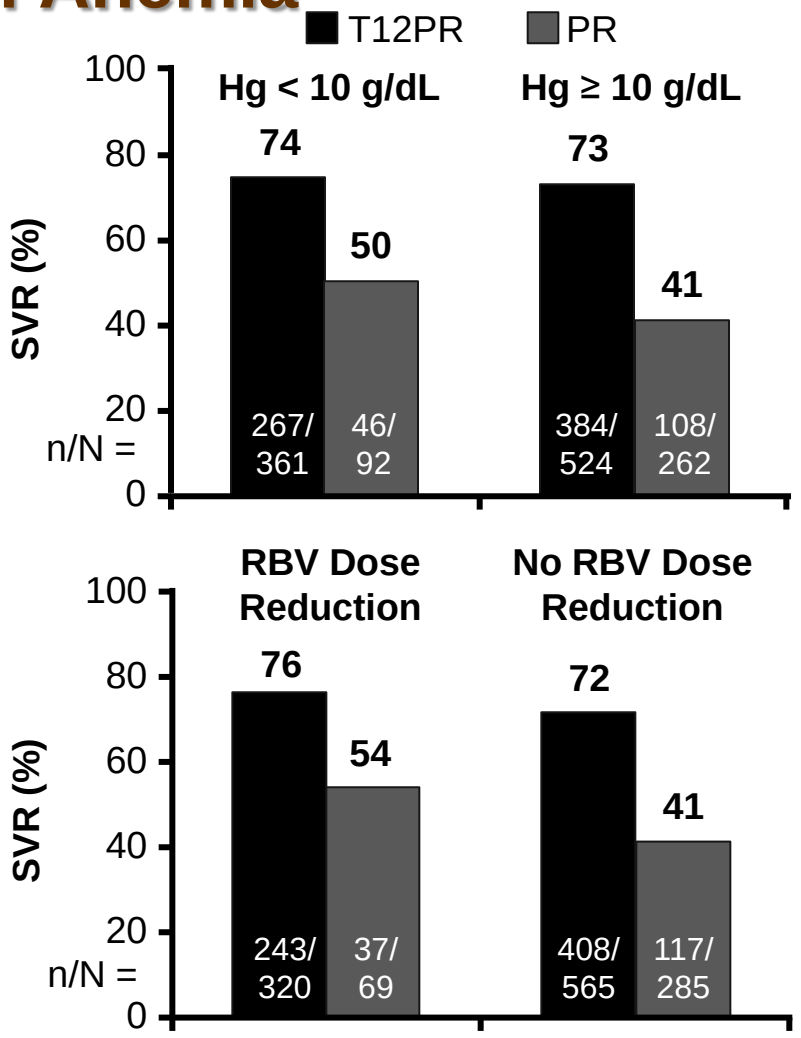
- **In clinical trials, anemia managed with RBV dose reduction and/or erythropoietin**
  - ✓ 43% of boceprevir-treated patients took erythropoietin
  - ✓ 3% required blood transfusion
- **SVR rates with boceprevir higher among anemic vs nonanemic patients**
  - ✓ RBV dose reduction does not impair boceprevir efficacy



Sulkowski M, et al. (SPRINT-2), Hepatology, 2013.
.

Telaprevir-Related Adverse Events: Management of Anemia

- **In clinical trials, erythropoietin use was prohibited; anemia managed through RBV dose reduction**
  - ✓ Among anemic patients (Hg < 10 g/dL), more blood transfusions required in telaprevir (12%) vs control (5%) arm
- **Neither anemia nor RBV dose modification associated with lower SVR in telaprevir-treated patients**
  - ✓ Lower SVR rates with both in pegIFN/RBV-treated patients



Boceprevir/Telaprevir-Related Adverse Events: Management of Anemia

Table 5. General guidelines for PegIFN–RBV dose reduction or discontinuation (32,33,57,58)

	PegIFN dose recommendation[a]
WBC	
<1.5×10⁹/l	PegIFN alfa-2b: reduce dose to 1 mcg/kg per week, then to 0.5 mcg/kg per week if needed
<1.0×10⁹/l	Discontinue PegIFN alfa-2b until resolution
ANC[b]	
<0.75×10⁹/l	PegIFN alfa-2a: reduce dose to 135 mcg per week PegIFN alfa-2b: reduce dose to 1 mcg/kg per week, then to 0.5 mcg/kg per week if needed
<0.50×10⁹/l	Discontinue PegIFN until resolution
Platelets[c]	
<50 k/mm³	PegIFN alfa-2a: reduce dose to 90 mcg per week PegIFN alfa-2b: reduce dose to 1 mcg/kg per week, then to 0.5 mcg/kg per week if needed
<25 k/mm³	Discontinue PegIFN until resolution

	RBV dose recommendation
Hb	
<11.0, but >10 g/dl	No change in RBV dose if patient has minimal symptoms In a symptomatic patient, consider RBV dose reduction
<10.0, but >8.5 g/dl	Decrease RBV, consider starting an erythropoietic growth factor In patients with a cardiac history, reduce RBV dose and reduce PegIFN alfa-2b dose by 50%
<8.5 g/dl	Discontinue RBV until resolution If RBV is stopped for ≥7 days or discontinued in patients who are concomitantly receiving BOC or TVR, then BOC or TVR must be permanently discontinued

ANC, absolute neutrophil count; BOC, boceprevir; GCSF, granulocyte colony-stimulating factor; Hb, hemoglobin; HCV, hepatitis C virus; PegIFN, peginterferon; RBV, ribavirin; TVR, telaprevir; WBC, white blood cell counts.

[a]Manufacturer package insert recommendations.

[b]If dose is maintained outside of manufacturer recommendations, monitor ANC more frequently, and counsel patient on neutropenic precautions. In post-liver transplantation or HIV/HCV-coinfected patients who remain neutropenic despite dose reduction, consider starting GCSF until resolution.

[c]If dose is maintained outside of manufacturer recommendations, monitor platelet counts, and signs or symptoms of unusual bleeding or bruising more frequently.

Yee HS et al. ***Update on the management and treatment of hepatitis C virus infection: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office.*** Am J Gastroenterol. 2012 May;107(5):669-89.

Boceprevir/Telaprevir-Related Adverse Events: Management of Anemia

- Ribavirin dose reduction
- Erythropoietin alpha (EPO)
- Peg-INF reduction
- PI discontinuation

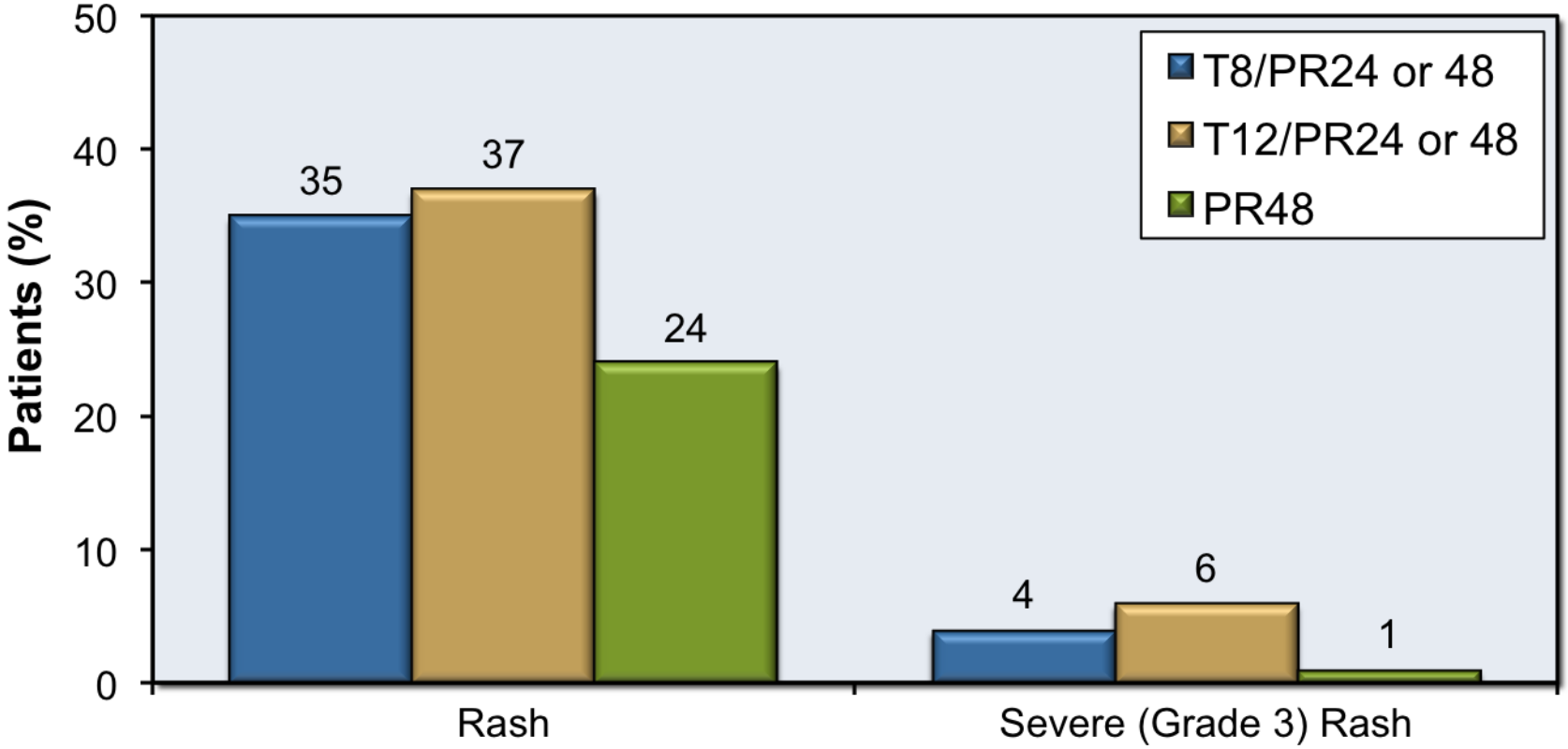
NEVER REDUCE THE DOSE OF PROTEASE INHIBITOR

Telaprevir-Related Adverse Events: Management of Rash

- **Telaprevir-related rash**
  - Primarily eczematous
  - Resolves with discontinuation of therapy
  - Typically observed within first 4 wks of treatment but can occur at any time during therapy

Rash Severity	Definition
Grade 1	Mild, localized skin eruption
Grade 2	Diffuse skin eruption involving ≤ 50% of body surface area
Grade 3	Severe, generalized skin eruption involving > 50% of body surface area, or rash with substantial systemic signs/symptoms

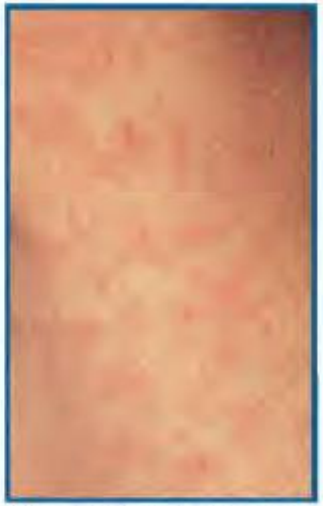
Telaprevir-Related Adverse Events: Percentage of Patients with Rash



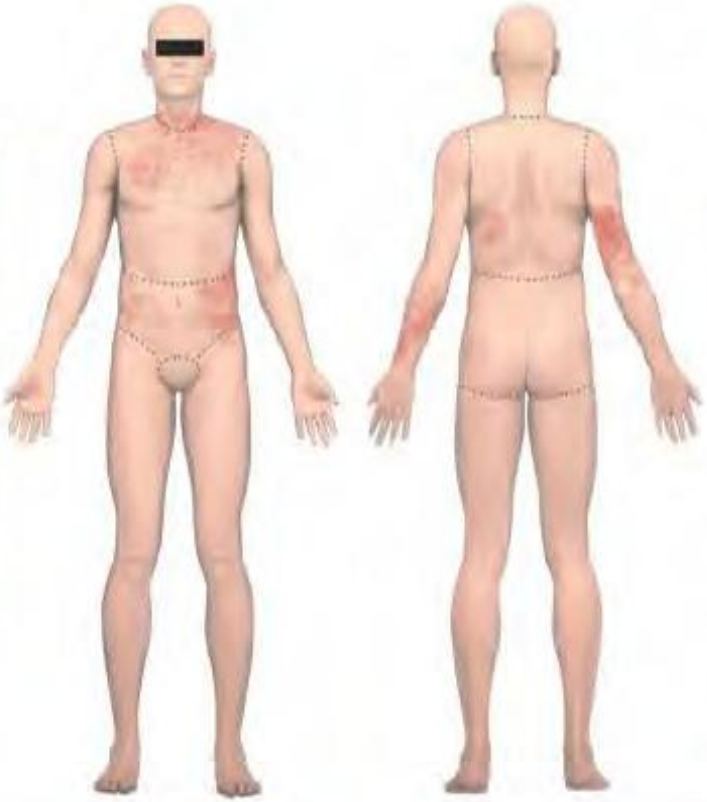
Jacobson IM, et. al. N Engl J Med. 2011;364:2405-16.

Telaprevir-Related Adverse Events: Mild Rash Identification and Management

Mild Rash



Images are for illustrative purposes only.



Assessment

- Localized rash and/or a rash with limited distribution
- With or without associated pruritus

Management

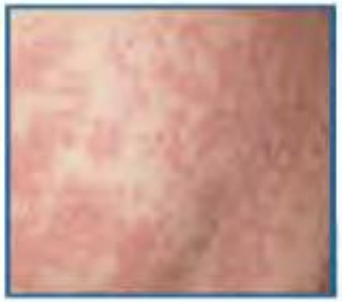
Continue all drugs

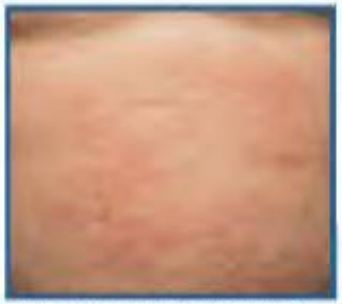
- **Monitor** for signs of progression or development of systemic symptoms
- INCIVEK dose should not be reduced or interrupted
- Consider good skin care practices
- Consider oral antihistamines (sedating and/or non-sedating*)
- Consider topical corticosteroids (systemic corticosteroids are not recommended)

If progression or systemic symptoms are observed, re-assess severity and proceed accordingly

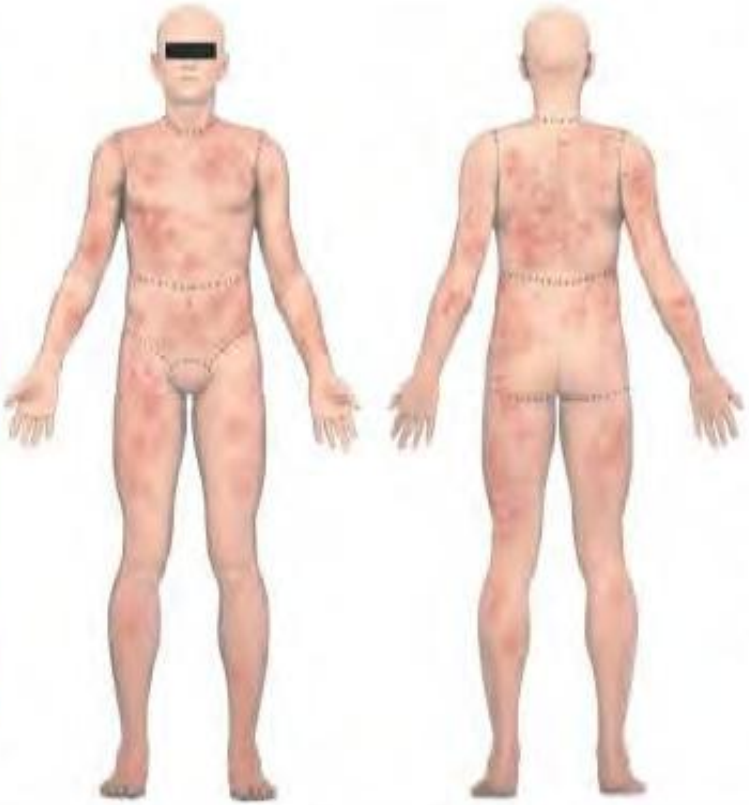
Telaprevir-Related Adverse Events: Moderate Rash Identification and Management

Moderate Rash





Images are for illustrative purposes only.



Assessment

- Diffuse rash
- With or without superficial skin peeling, pruritus, or mucous membrane involvement with no ulceration

Management

Continue all drugs

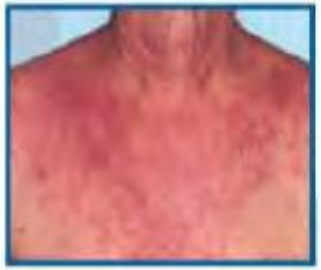
- **Monitor** for signs of progression or development of systemic symptoms
- INCIVEK dose should not be reduced or interrupted
- Consider good skin care practices
- Consider oral antihistamines (sedating and/or non-sedating*)
- Consider topical corticosteroids (systemic corticosteroids are not recommended)

If progression or systemic symptoms are observed, re-assess severity and proceed accordingly

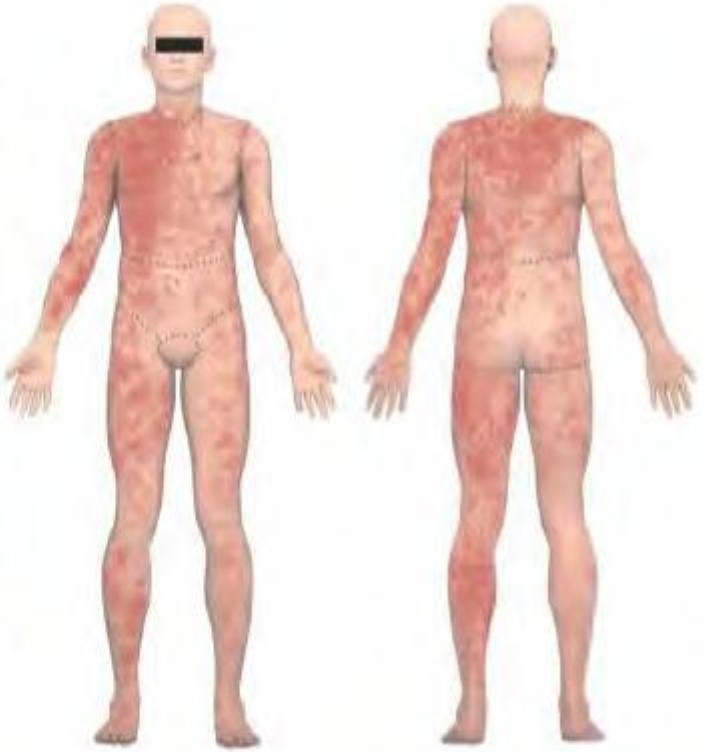
*If sedating antihistamines are prescribed, advise patients of appropriate precautions (eg, avoid operating heavy machinery, etc).

Telaprevir-Related Adverse Events: Severe Rash Identification and Management

Severe Rash



Images are for illustrative purposes only.



Assessment

- Generalized rash with or without pruritus

OR

- Rash with vesicles, bullae, or ulcerations (other than SJS)

Management

Discontinue INCIVEK

May continue Peg-IFN-RBV

- Closely monitor for signs of progression
- **If rash does not improve within 7 days of INCIVEK discontinuation (or earlier if worsening rash), consider interruption or discontinuation of RBV and/or Peg-IFN**
- Earlier interruption or discontinuation of RBV and/or Peg-IFN/RBV may be needed if medically indicated
- Consider utility of good skin care practices
- Consider oral antihistamines (sedating and/or non-sedating*)
- Consider topical corticosteroids (systemic corticosteroids are not recommended)
- INCIVEK must not be restarted after discontinuation
- Consider dermatology consult

If systemic symptoms develop, see Serious Skin Reaction management

*If sedating antihistamines are prescribed, advise patients of appropriate precautions (eg, avoid operating heavy machinery, etc).

Peg-IFN = peginterferon alfa; RBV = ribavirin.

Telaprevir-Related Adverse Events: Good Skin Care for Telaprevir-Associated Rash

- Apply skin moisturizers at least twice a day
- Avoid perfumes and other scented skin care products
- Use hypoallergenic products
- Keep hydrated
- Wear loose-fitted clothing
- Avoid scratching
- Use unscented and mild laundry detergent
- Avoid using dryer sheets with clothes in dryer
- Limit sun exposure and use sun screen when out in sun
- Avoid hot showers and hot baths
- Consider using a nonsoap cleanser
- Apply skin moisturizers after bathing (before drying off)

Source: Vertex Pharmaceuticals

Telaprevir-Related Adverse Events: Treatment and prophylactic measures for rash

PROPHYLACTIC MEASURES

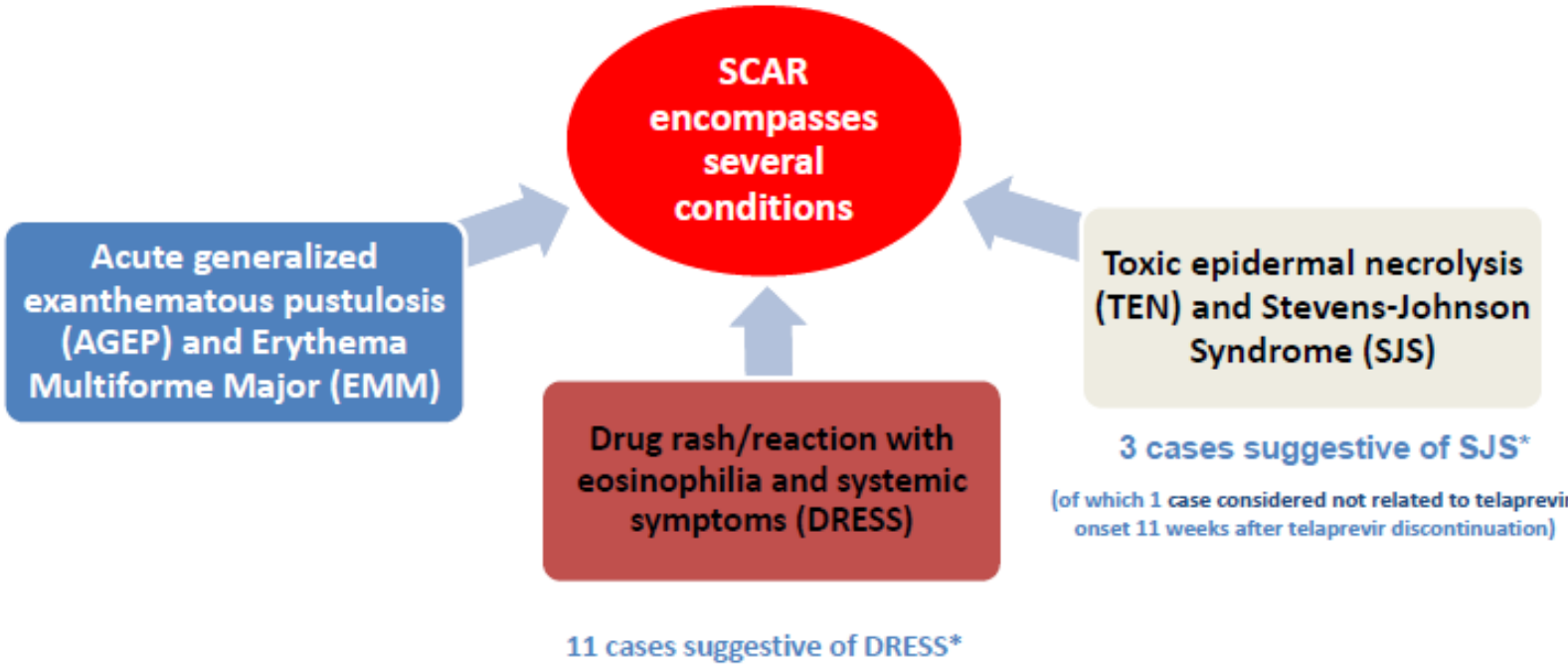
- Limit exposure to sun/heat
- Use sunscreen (SPF 15 or more)
- Wear light clothes, preferably cotton
- Bathing with moisturizing soap

TREATMENT

- Emollient creams, rather than lotions or ointments, may be effective for relieving eczematous reactions
- Systemic antihistamine drugs (desloratadine 5mg/day) may be used for the treatment of pruritus.
- Rash can primarily be treated with topical corticosteroids (dexametasone or 1% clobetazol)
- Calamine and Pramoxine HCl (Caladryl ®)

Telaprevir [package insert]. May 2011.

Telaprevir-Related Adverse Events: SCAR (Severe Cutaneous Adverse Reactions)



*In placebo-controlled Phase II/III trials, 0.4% of patients had suspected DRESS; in telaprevir clinical experience, less than 0.1% of patients had SJS

INCIVO (telaprevir) EU SmPC
http://www.fda.gov/downloads/AdvisoryCommittees/Committees/MeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM252562.pdf

Telaprevir-Related Adverse Events: SCAR (Severe Cutaneous Adverse Reactions)

When suspect DRESS *

*DRESS: Drug Reaction (or rash) with Eosinophilia and Systemic Symptoms.

- **Warning Signs:**
  Beggining between 6-10 weeks after 1st. dose
  Rash progresses fast
  Prolonged fever (> 38.5 ° C)
  Facial edema

What to do?

- **Check confirmatory signs**
  Enlarged lymph nodes (at least 2 locations)
  Eosinophilia (≥ 700/µL or ≥ 10%)
  atypical lymphocytes
  Involves other organs
  Liver: ALT ≥ 2x ULN FA
  Kidney: creatinine ≥ 150% of baseline

- **If confirmed:**
  Stopped all drugs
  Hospitalize the patient
  Consult with a dermatologist

Cacoub P, et al. J Hepatol 2012;56:455–463

Telaprevir-Related Adverse Events: SCAR (Severe Cutaneous Adverse Reactions)

When suspected SJS / TEN *

SJS: *Stevens Johnson Syndrom* / **TEN:** *toxic epidermic necrosis*

- Rash rapidly progressive
  Cutaneous pain
  Involvement of mucous membranes (≥ 2 sites)
  Blistering or peeling of the epidermis
  Target lesions (typical / atypical)

What to do?

- Stopped all drugs
- Hospitalize the patient
- Consult with a dermatologist

Cacoub P, et al. J Hepatol 2012;56:455–463

Telaprevir-Related Adverse Events: Anorectal Symptoms

- **Anal pruritus, anorectal discomfort , hemorrhoids or rectal burning**

  Usually beginning in the first 2 weeks of treatment

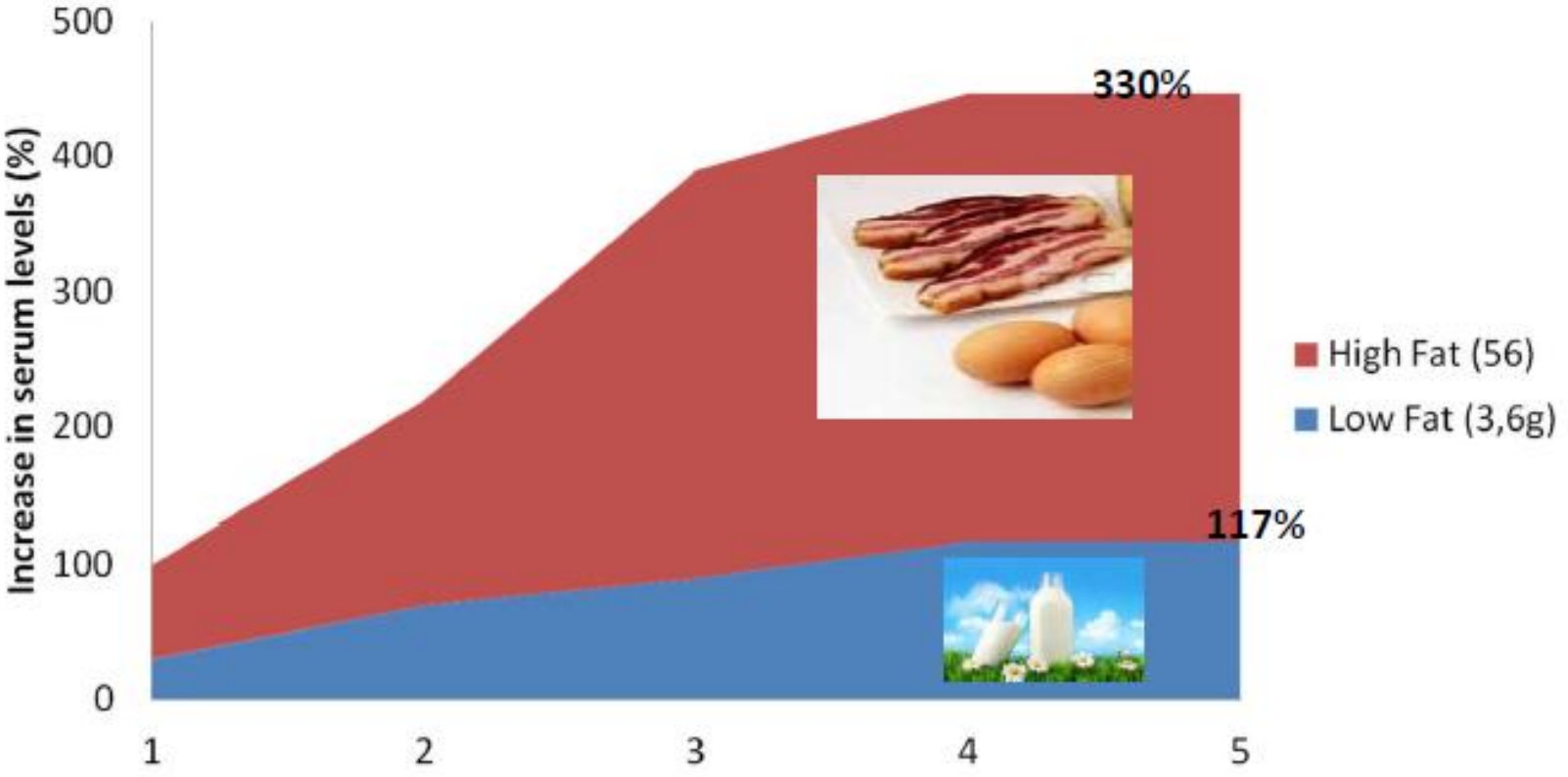
  - **Mechanism unknown**

    Telaprevir primarily excreted in feces
    Without specific rectal findings
    Unrelated rash or itchy skin

  - **Treatment**

    Check for Diet
    Hygiene anal - douche with water
    Fiber, loperamide, hydrocortisone, and pramoxine topical cream

Effect of Dietary Fat on Serum Levels of Telaprevir



Panel Recommendations: Managing Adverse Events With PI-Based Therapy

- Modest RBV dose reduction is a good approach for managing anemia
  - ✓ Some clinicians may choose to use erythropoietin
- Preventing blood transfusion is a primary goal of anemia management
- Anemia management is critical for avoiding discontinuation of the PI
  - ✓ Once a PI has been stopped, it should not be restarted
  - ✓ PIs cannot be dose reduced
- Patients should be educated prior to treatment initiation regarding the signs and symptoms so rash can be quickly identified and managed
  - ✓ Topical steroids and antihistamines are primary management; systemic steroids should be avoided
- Practices should use a "go-to" dermatologist for identification and management of telaprevir-associated rash
- Suggestions for anorectal symptom management include administration of any of the following: fiber, loperamide, hydrocortisone, or pramoxine topical cream

Drug-Drug Interactions
Boceprevir

- **Potential for Boceprevir to Affect Other Medications**
  - ✓ Boceprevir is strong inhibitor of CYP3A4/5 enzyme
  - ✓ Boceprevir is potential inhibitor of p-glycoprotein (P-gp)

- **Potential for Other Medications to Affect Boceprevir**
  - ✓ Boceprevir primarily metabolized by aldo-ketoreductase (AKR)
  - ✓ Boceprevir may be co-administered with aldo-ketoreductase inhibitors
  - ✓ Partially metabolized by CYP3A4/5
  - ✓ Potential for interactions with drugs that inhibit or reduce CYP3A4/5

Drug-Drug Interactions
Boceprevir

Boceprevir and Interactions with HIV Antiretroviral Medications		
Medication	**Effect on Boceprevir or Concomitant Drug**	**Recommendation**
HIV NNRTIs: efavirenz	↓ Boceprevir	Plasma trough concentrations of boceprevir were decreased when boceprevir was coadministered with efavirenz, which may result in loss of therapeutic effect. Avoid combination
HIV PIs: ritonavir	↓ Boceprevir ↑ or ↓ HIV protease inhibitors	Boceprevir concentrations decreased with ritonavir; the effect of ritonavir-boosted HIV protease inhibitors on boceprevir exposure is unknown. The effect of boceprevir on HIV protease inhibitor concentrations is unknown.

Drug-Drug Interactions PIs

- HCV PIs are CYP3A4 inhibitors
  - ~ One half of FDA-approved drugs are metabolized by CYP3A4
- Until the drug is specifically studied, magnitude of the impact of PI on its level is not known
- HCV PI metabolism differs
  - Boceprevir: primarily aldo-ketoreductase and partially CYP3A4/5
  - Telaprevir: CYP3A4
- Exercise caution with ALL coadministered medications

Drug-Drug Interactions

Several drugs contraindicated; many more require dose adjustment or caution (studies of drug–drug interactions incomplete)

Drug Class	Contraindicated With BOC[1]	Contraindicated With TVR[2]
Alpha 1-adrenoreceptor antagonist	Alfuzosin	Alfuzosin
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin	N/A
Antimycobacterials	Rifampin	Rifampin
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agents	Cisapride	Cisapride
Herbal products	*Hypericum perforatum* (St John's wort)	*Hypericum perforatum*
HMG CoA reductase inhibitors	Lovastatin, simvastatin	Lovastatin, simvastatin
Oral contraceptives	Drospirenone	N/A
Neuroleptic	Pimozide	Pimozide
PDE5 inhibitor	Sildenafil or tadalafil when used for tx of pulmonary arterial hypertension	Sildenafil or tadalafil when used for tx of pulmonary arterial hypertension
Sedatives/hypnotics	Triazolam; orally administered midazolam	Orally administered midazolam, triazolam

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

Drug-Drug Interactions

TABLE 1. Drugs Absolutely Contraindicated With the Prescription of Telaprevir or Boceprevir Because of Potentially Serious Adverse Events

Drug Class	Examples	Potentially Serious or Life-Threatening Adverse Events
CYP3A substrates/inhibitors		
Alpha-1-adrenoreceptor antagonists	Alfuzosin	Hypotension, dizziness
Ergot derivatives	Dihydroergotamine Ergonovine Ergotamine Methylergonovine	Peripheral vasospasm or ischemia
Gastrointestinal motility agents	Cisapride	Cardiac arrhythmia, QT prolongation
3-Hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins)	Atorvastatin* Lovastatin Simvastatin	Myopathy, rhabdomyolysis
Neuroleptics	Pimozide	Cardiac arrhythmia
Oral contraceptives†	Drospirenone	Hyperkalemia
Phosphodiesterase type 5 enzyme inhibitors‡	Sildenafil Tadalafil	Visual abnormalities, hypotension, prolonged erection, syncope
Sedatives	Midazolam Triazolam	Prolonged sedation, respiratory depression
CYP3A inducers		
Anticonvulsants†	Carbamazepine Phenobarbital Phenytoin	Reduced DAA levels with potentially reduced antiviral efficacy and increased drug resistance
Antimycobacterials	Rifampin	
Herbal products	St. John's wort	

The information in this table was obtained from package inserts for boceprevir and telaprevir (February 2012).[8,9]

*For telaprevir only.
†For boceprevir only.

Rangnekar and Fontana Clinical Liver Disease 2012

Drug-Drug Interactions

TABLE 2. Selected Drugs That Should Be Used With Caution in Subjects Receiving Boceprevir or Telaprevir Because of Altered Metabolism

Drug Class	Examples	Potential Impact
CYP3A substrates		
Antiarrhythmics	Amiodarone Digoxin Lidocaine Quinidine	Increased arrhythmia
Antidepressants	Escitalopram*	Decreased efficacy of antidepressant
Antidepressants	Desipramine Trazodone	Increased sedation, dry mouth
Azole antifungals	Itraconazole Ketoconazole Posaconazole	Increased vomiting, diarrhea, hypertension
Antigout agents	Colchicine	Increased diarrhea
Calcium channel blockers	Amlodipine Diltiazem Nifedipine Verapamil	Increased hypotension, bradycardia
Corticosteroids	Budesonide Fluticasone Methylprednisolone Prednisone	Increased hyperglycemia, osteoporosis, insomnia, acne
HIV protease inhibitors†	Atazanavir	Increased vomiting, diarrhea
HIV reverse transcriptase inhibitors	Tenofovir	Increased nephrotoxicity
Hormonal contraceptives	Ethinyl estradiol	Decreased efficacy
Immunosuppressants	Cyclosporine Sirolimus Tacrolimus	Increased nephrotoxicity, hypertension, neurotoxicity
Inhaled beta-agonists	Salmeterol	Increased tachycardia
Macrolide antibiotics	Clarithromycin Erythromycin Telithromycin	Increased diarrhea, QT prolongation
CYP3A inducers		
HIV protease inhibitors†	Atazanavir Darunavir Fosamprenavir Lopinavir	Reduced DAA levels with potentially reduced antiviral efficacy and increased drug resistance
HIV reverse transcriptase inhibitors	Efavirenz	
Narcotic analgesics	Methadone	
Sedatives	Zolpidem	

Drug-Drug Interactions

TABLE 3. Drugs That Can Alter Serum Boceprevir and Telaprevir Levels

Drug Class	Examples	Impact on DAA Level	Potential Manifestation of Altered DAA Metabolism
CYP3A substrates			
Azole antifungals	Itraconazole Ketoconazole Posaconazole Voriconazole	Increase	Increased number of adverse events such as rash, myelotoxicity, and gastrointestinal side effects (telaprevir) or anemia and dysgeusia (boceprevir)
HIV protease inhibitors	Atazanavir Darunavir Fosamprenavir Lopinavir	Increase	
CYP3A inducers			
Anticonvulsants	Carbamazepine Phenobarbital Phenytoin	Decrease	Decreased antiviral efficacy with potential increase in drug-resistant variants
Antimycobacterials	Rifabutin	Decrease	
Corticosteroids	Dexamethasone	Decrease	
HIV reverse-transcriptase inhibitors	Efavirenz	Decrease	
HIV protease inhibitors*	Atazanavir Darunavir Fosamprenavir Lopinavir	Decrease	

The information in this table was obtained from package inserts for boceprevir and telaprevir (February 2012).[8,9]

*When coadministered with ritonavir.

Drug-Drug Interactions

www.hep-druginteractions.org

Interaction Charts | News & Archive | Interaction Query Service | About Us | Pharmacology Resources | Links | Meetings | Feedback

Cookies policy. You will see this message only once.
We use cookies to ensure that we give you the best experience on our website. If you continue without changing your settings, we'll assume that you're happy to receive all cookies on this site. However, if you would like to, you can **change your cookie settings** at any time. Find out more.

Continue.

LATEST ARTICLES

Meeting Report - EASL, London, 2014

Meeting Report - 2014 CROI, Boston

Drug Interactions - Boceprevir or telaprevir with maraviroc.

Meeting Report - HEP DART, 2013

FDA & EMA News - Simeprevir and Sofosbuvir

Case Report - Boceprevir and α-1 adrenergic antagonists and/or quetiapine.

Click here for previous news items

SITE UPDATES

Sofosbuvir

Sofosbuvir, the recently approved directly acting antiviral for HCV, has been added to the intera...

>>more

A few more comedications

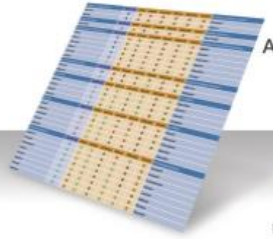
The following comedications have been added to the web and app versions of the interaction charts...

>>more

Further Comedications Added
New comedications have been added to the interaction charts which takes the total number of comedica...

>>more

DRUG INTERACTION CHARTS



Access our comprehensive, user-friendly, free, drug interaction charts

CLICK HERE

Providing clinically useful, reliable, up-to-date, evidence-based information

TELAPREVIR INTERACTION QUERY SERVICE

Telaprevir Interaction Query Service

Q&A

A service for healthcare professional for queries relating to drug-drug interactions with telaprevir which the hospital pharmacy or medicines information unit are unable to answer.

To see what other people have asked or to submit a question, click here.

CLINICAL PHARMACOLOGY OF HIV & HEPATITIS THERAPY WORKSHOP

HIV Hepatitis

15th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy
Washington DC, 19-21 May 2014

Deadline dates are approaching for this workshop:
Late Registration - 1 May.

UNIVERSITY OF LIVERPOOL

ASSOCIATED SITES

www.hiv-druginteractions.org
A comprehensive HIV drug-drug interaction resource, freely available to healthcare workers, patients and researchers. The site is also available in a low graphics version - www.hiv-druginteractionslite.org.

BRITISH SOCIETY FOR NANOMEDICINE
Website of the British Society of Nanomedicine with sections for scientists, the general public and teachers.

EXTERNAL LINKS

Viral Hepatitis Congress
9-11 October, 2014

3rd World Congress on Controversies in the Management of Viral Hepatitis (C-Hep)

German Liver Foundation

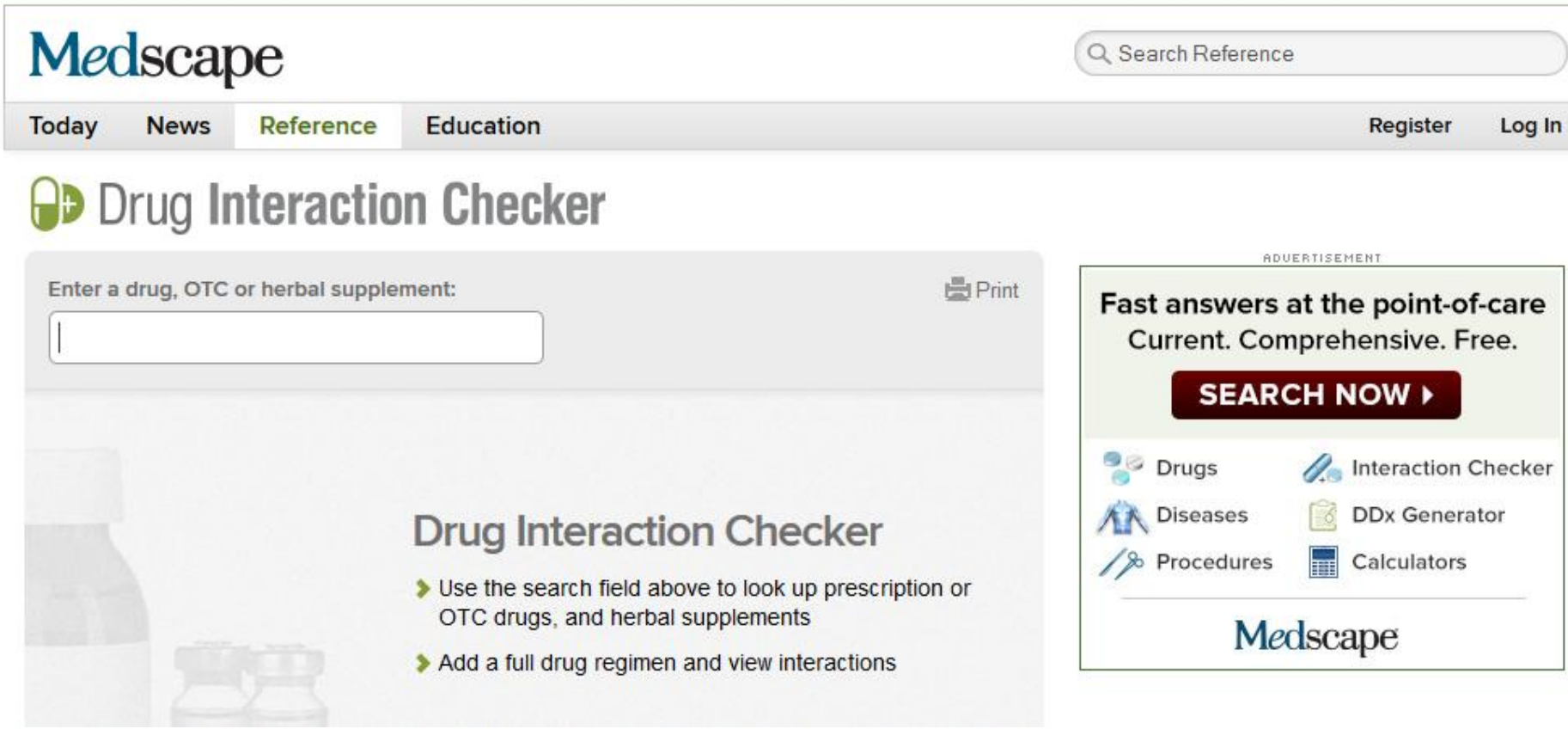
Deutschen Leberstiftung

FOLLOW US ON TWITTER

For the latest additions and updates to the site, click the button to follow

Drug-Drug Interactions

http://reference.medscape.com/drug-interactionchecker



Article in Press

Effectiveness of Telaprevir or Boceprevir in Treatment-experienced Patients with HCV Genotype 1 Infection and Cirrhosis

Christophe Hezode, Helene Fontaine - Gastroenterology 2014

Background & Aims

We investigated the effectiveness of the protease inhibitors peginterferon and ribavirin in treatment-experienced patients with hepatitis C virus (HCV) genotype 1 infection and cirrhosis.

.....

Conclusions

Relatively high percentages of real-life, treatment-experienced, patients with HCV genotype 1 infection and cirrhosis respond to the combination of peginterferon and ribavirin with telaprevir or boceprevir. However, side effects are frequent and often severe side. Baseline levels of albumin and platelet counts can be used to guide treatment decisions. ClinicalTrials.gov number, NCT01514890.

Several Patient Populations With Continued Need in Current Era

- Contraindication or poor tolerance to pegIFN or RBV
- Safety and efficacy of boceprevir and telaprevir not fully established
  - ✓ Organ transplant recipients
  - ✓ Patients with end-stage liver disease
  - ✓ Patients with HIV and/or HBV coinfection
  - ✓ Pediatric patients
- Patients with decompensated cirrhosis or moderate to severe hepatic impairment
- Although pegIFN/RBV effective for non–genotype 1, comes with all of the issues related to the use of IFN
- Patients with poor IFN responsiveness
- Patients unable to adhere to complex, lengthy regimens

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

Remaining challenges

- Unclear how to use in special patient populations with highest risk of disease progression
- Need for defining stopping rules to prevent resistance emergence
- High compliance requirement
- Drug-drug interactions
- In whom to start and in whom to wait