

Treatment with the New Direct Acting Antivirals for Hepatitis C

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Objectives

- * Medication Administration
- * Treatment Duration
- * Side effects and Management
- * Laboratory Testing Schedule
- * Prohibited medications on treatment with Direct Acting Antivirals (DAAs)
- * Resources for Medication Access and Treatment Support

Medication Administration

Incivek (Telaprevir)

750mg (two 375mg tablets) 3 times daily

Incivek is taken 3 times daily, 7-9 hours apart

Should be taken with food, high fat snack containing 20gm of fat

Examples of foods:

- * ½ cup of nuts or trail mix
- * 3 Tablespoons of peanut butter
- * 2 oz. of cheddar cheese

Incivek must be taken with Pegylated interferon and ribavirin

Victrelis (Boceprevir)

800mg (four 200mg capsules) 3 times daily

Victrelis is taken 3 times daily, 7-9 hours apart

Should be taken with food, a meal or light snack

Victrelis must be taken with Pegylated interferon and ribavirin

Example of Dosing Schedule

- * Incivek and Victrelis must be taken on time to avoid viral resistance.
- * Incivek and Victrelis doses may not be reduced or interrupted to avoid viral resistance.
- * With a 8AM-4PM-12AM schedule the medications could be taken from 7-9AM, 3-5PM and 11PM-1AM.

Missed Dose Instructions

Incivek

- * If the missed dose is within 4 hours of the time it is usually taken, the prescribed dose is taken as soon as possible with food. The next dose is taken at the usual time.
- * If more than 4 hours have passed since the medication is usually taken, then the missed dose is not taken and the usual dosing schedule is resumed.

Victrelis

- * If a missed dose is less than 2 hours before the next dose, the missed dose should not be taken.
- * If the missed dose is more than 2 hours before the next dose, the missed dose should be taken with food. The next dose is taken at the normal time.

Treatment Duration for Incivek

Treatment Naïve and Prior Relapse Patients			
HCV-RNA	Triple Therapy: Incivek, peginterferon alfa and ribavirin	Dual therapy: peginterferon alfa and ribavirin	Total Treatment Duration
Undetectable at Weeks 4 and 12	First 12 weeks	Additional 12 weeks	24 weeks
Detectable (1000 IU/ml or less) at Weeks 4 and/or 12	First 12 weeks	Additional 36 weeks	48 weeks
Prior Partial and Null Responder Patients			
	Triple Therapy: Incivek, peginterferon alfa and ribavirin	Dual Therapy: peginterferon alfa and ribavirin	Total Treatment Duration
All Patients	First 12 weeks	Additional 36 weeks	48 weeks

Treatment Duration Victrelis

Initiate therapy with peginterferon alfa and ribavirin for 4 weeks

Add Victrelis to peginterferon alfa and ribavirin after 4 weeks of treatment

	Assessment HCV-RNA Results		Recommendation
	Treatment week 8	Treatment Week 24	
Previously Untreated Patients	Undetectable	Undetectable	Complete three-medication regimen at TW28
	Detectable	Undetectable	•Continue all three medicines and finish through TW36 •Administer peginterferon alfa and ribavirin and finish through TW48
Previous Partial Responders and Relapsers	Undetectable	Undetectable	Complete three-medicine regimen at TW36
	Detectable	Undetectable	Continue all three medicines and finish through TW36 Administer peginterferon alfa and ribavirin and finish through TW48
Compensated Cirrhosis	Complete three-medicine regimen at TW 48, 4 weeks of peginterferon alfa and ribavirin followed by 44 weeks of three medication regimen.		

Futility Rules

Incivek

If HCV RNA is >1000 at TW4 or 12, then Incivek and peginterferon and ribavirin are discontinued.

If HCV RNA is positive at TW24, then peginterferon and ribavirin are discontinued.

Victrelis

If HCV-RNA is >100 at TW12 or HCV RNA is confirmed positive at TW24 treatment is discontinued.

Most Common Side Effects for Incivek

Side effects that occurred at least 5% more often when treated with Incivek in Phase 3 clinical trials		
Side effect	Incivek combination treatment	Peginterferon and ribavirin alone
Rash	56%	34%
Fatigue	56%	50%
Pruritus	47%	28%
Nausea	39%	28%
Anemia (Hgb <10)	36%	17%
Diarrhea	26%	17%
Vomiting	13%	8%
Hemorrhoids	12%	3%
Anorectal discomfort	11%	3%
Dysgeusia	10%	3%
Anal Pruritis	6%	1%

ADVANCE: Adverse Events

% of Patients with	T12PR N=363	T8PR N=364	PR (control) N=361
Any Adverse Event*	99	99	98
Fatigue	57	58	57
Pruritus	50	45	36
Headache	41	43	39
Nausea	43	40	31
Rash	37	35	24
Anemia	37	39	19
Insomnia	32	32	31
Diarrhea	28	32	22
Influenza-like illness	28	29	28
Pyrexia	26	30	24

- Reported in $\geq 25\%$ of patients regardless of severity in any treatment arm, events occurring at $\geq 10\%$ points in any T group vs PR (shaded in grey)

ADVANCE: Discontinuation for Adverse Events

D/C	T12PR	T8PR	PR
TVR/Placebo only	11%	7%	1%
All therapy (overall study)	10%	10%	7%

Jacobson IM, et al. EASL 2011; March 30-April 3, 2011; LB1369.

Rash Events During Telaprevir/ Placebo Phase

% of Patients with	T12PR N=363	T8PR N=364	PR (control) N=361
Rash Events	56	53	37
Severe Rash Events	6	3	1
Discontinuation of telaprevir/ placebo only	7	5	1
Discontinuation of all study drugs	1	1	0

Jacobson IM, et al. EASL 2011; March 30-April 3, 2011; LB1369.

Rash Associated With Telaprevir

- * Primarily eczematous and resolved upon cessation of therapy
- * Moderate and severe rash were managed by sequentially discontinuing telaprevir, followed by RBV and, if indicated, PEG-IFN for continued progression

Rash Management for Incivek

Rash occurred in 56% of patients, 4% were severe. Serious rash occurred in less than 1% of patients.

Rash is most frequent in the first 4 weeks of treatment

Practice Good Skin Care including:

- * Apply moisturizer
- * Avoid hot showers and use a mild soap such as Cetaphil
- * Drink plenty of water
- * Use mild laundry detergent
- * Limit exposure to the sun and wear sunscreen with a high SPF
- * In the event of a rash, oral antihistamines and topical corticosteroid creams may be used.
- * Report any signs of rash to your provider so it can be managed properly.

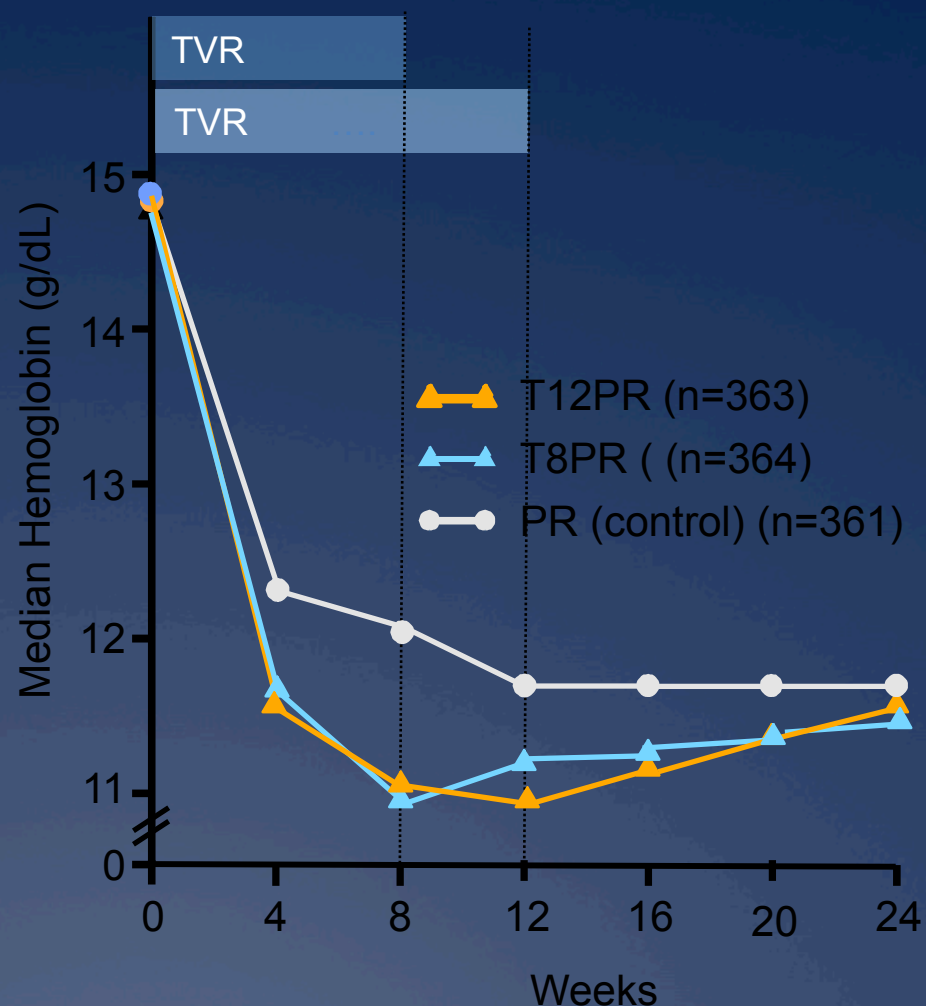
Nadir Hemoglobin, Discontinuation for Anemia, and Median Hemoglobin Levels

Hemoglobin nadir during TVR/Pbo Phase

% of Patients with	T12PR N=363	T8PR N=364	PR N=361
Hemoglobin <10 g/dL	36	40	14
Hemoglobin <8.5 g/dL	9	9	2

- Per protocol, anemia was to be managed with RBV dose modifications and ESAs were not allowed
- 1%, 3% and 1% of patients in T12PR, T8PR and PR, respectively discontinued all drugs due to anemia events
- 4%, 2% and 0% of patients in T12PR, T8PR and PR, respectively discontinued telaprevir/placebo only

Median Hemoglobin



Management of Anemia on Incivek

- * Decrease in hemoglobin (Hgb) occurs during the first 4 weeks with the lowest value occurring at the end of Incivek dosing.
- * Hgb will gradually return to pre-treatment levels after treatment is completed.
- * Close monitoring of hemoglobin will be necessary.
- * Anemia will be managed with ribavirin dose reduction if indicated.

Anorectal Side effects on Incivek

- * These side effects can be relieved with topical medications to relieve itching.
- * Antihistamines can be given at bedtime.
- * Control of diarrhea if present is helpful.

Side effects of Victrelis

Most commonly reported side effects (greater than 35% of subjects) in clinical trials in adult subjects that received Victrelis with peginterferon and ribavirin are listed below.

- * Fatigue
- * Anemia
- * Dysguesia (taste change)
- * Nausea
- * Headache

Neutropenia (low white count) and Low platelets were increased in subjects who took Victrelis containing regimens.

SPRINT-2: Most Common Treatment-Related Adverse Events

Adverse Event	Arm 1 (PR48) n = 363 (%)	Arm 2 (BOC RGT) n = 368 (%)	Arm 3 (BOC/PR48) n = 366 (%)
Fatigue	59	52	57
Headache	42	45	43
Nausea	40	46	42
Anemia	29	49	49
Dysgeusia	18	37	43
Chills	28	36	33
Pyrexia	32	33	30
Insomnia	32	31	32
Alopecia	27	20	28
Decreased appetite	25	26	24
Pruritis	26	23	25
Neutropenia	21	25	25
Influenza-like illness	25	23	22
Myalgia	26	21	24
Rash	22	24	23
Irritability	24	22	22
Depression	21	23	19
Diarrhea	19	19	23
Dry skin	18	18	22
Dyspnea	16	18	22
Dizziness	15	21	17

*Reported in >20% of patients in any treatment arm and listed by decreasing overall frequency

Poordad F et al. NEJM 2011;364:1195-1206

Safety Profile Over Entire Course of Therapy

	48 PR n = 363	BOC RGT n = 368	BOC/PR48 n = 366
Median treatment duration, days	203	197	335
Deaths	n = 4	n = 1	n = 1
Serious AEs	9%	11%	12%
Discontinued due to AEs	16%	12%	16%
Dose modification due to AEs	26%	40%	35%
Hematologic parameters			
Neutrophil count (<750 to $500/\text{mm}^3$ / $<500/\text{mm}^3$)	14% / 4%	24% / 6%	25% / 8%
Hemoglobin (<10 to 8.5 g/dL / <8.5 g/dL)	26% / 4%	45% / 5%	41% / 9%
Discontinuation due to anemia	1%	2%	2%
Dose reductions due to anemia	13%	20%	21%
Erythropoietin use	24%	43%	43%
Mean (median) days of use	121 (109)	94 (85)	156 (149)

Management of Adverse Events With Protease Inhibitors

* Anemia

- * Occurs with both drugs, mean increment in hemoglobin decline ~ 1.0-1.5 gm/dl
- * Mechanism not clear
- * Duration of incremental anemia depends on time of drug administration, i.e. longer with boceprevir
- * Reassuring that RBV dose reduction does not seem to affect SVR with either basis
- * Await additional data from ongoing trial of epo vs RBV dose reduction
- * Epo can be used on individualized basis

Management of Anemia, Neutropenia and Thrombocytopenia on Victrelis

- * Increased frequency of monitoring of complete blood count may be required.
- * A peginterferon alfa dose reduction may be indicated to manage neutropenia and thrombocytopenia.
- * A ribavirin dose reduction may be indicated to manage anemia.

Laboratory Testing Schedule on Triple Therapy

Incivek

- * Laboratory assessment for hematology and chemistry evaluation is recommended at TW 2,4,8 and 12
- * HCV RNA assessment is done at TW4 and 12

Victrelis

- * Hematology assessment at TW 4,8,12 and as clinically indicated
- * HCV-RNA levels assessed at TW4,8,12 and 24

Prohibited Medications on Treatment

While on treatment with Incivek or Victrelis do not initiate any prescription, over the counter medications or herbal products without consulting with your HCV provider.

List of common medications that are prohibited for both Incivek and Victrelis

- * Atorvastatin (Incivek), lovastatin, simvastatin
- * Sildenafil (Revatio) for pulmonary artery hypertension. Same medication as Viagra and may be allowed in low dose for erectile dysfunction, speak with your provider
- * Ergot derivatives- used for migraine headaches
- * St. John's Wart

Resources for Medication Access and Treatment support

- * Incivek medication Access information can be found at <http://www.incivek.com>
- * Victrelis medication access information can be found at <http://www.victrelis.com>
- * Hepatitis C support groups can be found at the American Liver Foundation website.
<http://www.liverfoundation.org/chapters/greaterny/>

References

Incivek (treatment management guide). Boston, MA: Vertex Pharmaceuticals Incorporated; 2011

Victralis (product information). Whitehouse Station, NJ: Schering Corporation a subsidiary of Merck & Co., Inc.; 2011