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Antiviral Therapy in HCV-Infected Decompensated Cirrhotics

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1. Introduction

What we are dealing with: Hepatitis C virus (HCV) infection is the commonest blood-borne infection, one of the commonest cause of chronic liver disease (CLD) & hepatocellular carcinoma (HCC) and one of the commonest reason for liver transplantation (LT) the world over.

What is the meaning of decompensation: Fibrosis is the histopathological hallmark of chronic hepatitis causing progressive derangement of normal liver architecture with consequent reduction in hepatic synthetic function. CLD is said to be decompensated when one or the other complication of CLD has developed - ascites, variceal bleeding (secondary to portal hypertension), impaired hepatic synthetic function (hypoalbuminemia), jaundice, and/or hepatic encephalopathy. Five years survival rate in decompensated cirrhotics is estimated to be 50%.[1]

Decompensated cirrhosis is NOT a contraindication to antiviral therapy: Decompensated cirrhosis has traditionally been considered a contraindication to interferon and ribavirin therapy. Whereas, the same may be true for advanced cirrhosis (which is only successfully amenable to LT), there are reports in the literature in which antiviral therapy was given *successfully* in selected cases of *early* hepatic decompensation with an aim to attain sustained viral clearance (SVR), halt disease progression and expect potential (though often partial) recovery of hepatic metabolic function. Antiviral therapy may also be instituted to prevent hepatitis C recurrence post-transplantation. If HCV is not eradicated pre-transplantation, reinfection with HCV occurs in *all* transplant recipients *as a rule*, with secondary cirrhosis developing in approximately 30% of cases within 5 years.[2] Pre-transplantation HCV eradication is however associated with less likelihood of reinfection and this forms the rationale for treating decompensated cirrhotics awaiting LT with antiviral therapy.[3] Initiating pre-emptive post-transplantation antiviral therapy, and treating established post-transplant HCV hepatitis are other options in LT patients. The aim of instituting pre-transplantation antiviral therapy is either to attain a sustained virological response (SVR) at transplantation, or an *on-treatment* HCV RNA clearance at transplantation. Mere reduction of viral load should *not* be the aim because, unlike HBV cirrhotics, this has not been shown to decrease the rate &/or severity of post-transplant HCV recurrence.

Thus decompensation per se is not an absolute contraindication for antiviral therapy. Although the final SVR rates attained in such patients are lower,[21,23] successful antiviral therapy is potentially lifesaving which supports the rationale for implementing HCV treatment in these patients.

In this chapter, the pros and cons of antiviral therapy in decompensated liver cirrhosis are reviewed with special emphasis on how to avoid antiviral dose reductions/ withdrawals secondary to the development of haematologic side effects by using haematopoietic growth factors (HGF's).

2. Discussion

2.1 Therapeutic options in decompensated cirrhosis

In selected cases, HCV-infected decompensated cirrhosis may be treated surgically (i.e. with LT) &/or medically (i.e. with antiviral therapy).

2.2 Surgical option

LT: How feasible is this option? LT is not a feasible option in the great majority of cirrhotics. This is not only because of the limited number of organ donors available at a given time, but also because of the age-related cardiovascular, renal, and pulmonary derangements that practically make going for this option rather *irrational* at times. Additionally, old age (≥65 years) is generally considered an exclusion criterion for LT.

2.3 Medical option

Historical reasons for reluctance to institute medical therapy in decompensated cirrhotics: Historically, despite the known theoretical benefits of antiviral therapy (improvement in liver histology, partial reversal of established cirrhosis, and prevention of life-threatening complications), most decompensated cirrhotics have not been offered antiviral therapy. Primarily, this has been due to the concerns regarding the therapeutic efficacy and safety of antiviral therapy in such cases. Peginterferon-ribavirin combination therapy is known to have *limited efficacy* in decompensated cirrhotics.[4,5] Also, compared to non-cirrhotics, such patients are more prone to develop *hematologic side effects* (neutropenia, thrombocytopenia & anemia) with antiviral therapy.[6] In fact, patients who already have severe neutropenia or thrombocytopenia (neutrophil count <1500/mm^3 or platelets count <75,000/mm^3) are highly prone to develop life-threatening infections after starting antiviral therapy, particularly if they have Child–Pugh class C disease.[7,8] Also, it is generally thought that age-related derangements in cardiovascular and pulmonary functions make the cirrhotic patients less tolerant to ribavirin-induced hemolytic anemia. Finally, there are concerns that decompensation may worsen with antiviral therapy as is the case with decompensated chronic hepatitis B cases.[9]

Do the reasons for reluctance evidence-based: Current literature reviews shows that because of the unstandardized dosage schedules being administered over variable periods of time in the past studies, we may have actually under/ overestimated the potential benefits and risks of antiviral therapy respectively in decompensated cirrhotics. There are now several reports in the literature in which antiviral therapy was relatively well tolerated

by decompensated cirrhotics with reasonable rates of attainment of end-of-treatment response (ETR) & sustained virological response (SVR):[4,7,10,11]

1. In one study,[7] 39% of the patients receiving low, accelerating regimen of non-pegylated interferon plus ribavirin experienced clearance of HCV-RNA, & 21% attained an SVR. Results with pegylated interferon are even better. In the first study[12] *proving* the benefits of antiviral therapy in cirrhotics with signs of portal hypertension, 51 cirrhotics received 1mg/kg/wk of pegylated-interferon alpha-2b plus oral ribavirin at a fixed dose of 800mg/d for 52 wks. By intention-to-treat analysis, SVR was achieved in 21.6% patients. As otherwise, patients with genotypes 2 & 3 showed better results (83.3%) than genotype 1 cases (13.3%). Although antiviral therapy was stopped in 5 of the patients because of neutrophil counts falling below 0.75×10^3/dL, none of them developed superadded infections. The disease deteriorated in only 6% of those who attained SVR compared to 38% of the non-responders.
2. In another study,[10] Peg-IFN alpha-2b (1.0 mg/kg/wk) plus standard dose of ribavirin were administered to all patients for 24 wks *regardless of the genotype*. The overall SVR rate attained even with this *suboptimal dose* regimen was 19.7%. Except patients with very advanced liver disease (CTP score >10), none experienced life-threatening complications. Peg-IFN and ribavirin in the standard dosage (Peg-IFN alpha-2b 1.5mg/kg & ribavirin 800-1000mg for genotypes 2 and 3, and 1000-1200mg for genotypes 1 and 4) for the standard duration of time (48 & 24 wks for genotype 1 & non-1, respectively) has also been tried.
3. In another study,[13] 35% of end-stage cirrhotics cleared the HCV infection (16% genotype 1 & 4, and 59% genotype 2 & 3 cases). 60% of all patients tolerated the antiviral therapy without any major untoward effects; treatment was discontinued in 19.1% of the patients with 4 among those ending up having severe superadded infections.
4. In yet another study[14] a 48 week course was planned for patients who demonstrated EVR with a standard regimen of PEG-IFN alfa-2a (135µg, once a week) plus ribavirin (1000-1200 mg/day). Results showed 60% patients completing the course with ETR & SVR achieved in 45% & 35% cases, respectively.
5. In a recent study[15] aimed to evaluate both the prevention of post-transplantation HCV recurrence & the risk of bacterial infections during therapy, 47% patients achieved HCV RNA negativity *during* treatment, 29% were HCV RNA negative *at the time of transplantation* (drop outs *n*=3, deaths *n*=4, viral relapse *n*=2) and 20% achieved an SVR *post-transplantation*. Importantly, none of the patients who achieved SVR pre-transplantation developed a recurrence post-transplantation.

3. Evidence-based pharmacotherapy of HCV infection in decompensated cirrhotics

Child–Pugh (sometimes called Child-Turcotte-Pugh [CTP]) scoring – see table 1 - helps determine the need and utility of instituting antiviral therapy:

1. The ideal candidate for antiviral therapy remains a patient with Child–Pugh class A disease in whom the risk of drug-induced side effects is almost identical to that of the controls. Nonetheless, all cirrhotic patients with a CTP score ≤9 and a decompensated event that abated with routine management may be considered for antiviral therapy.

2. Whether or not to institute antiviral therapy in Child–Pugh class B patients should be individualized on case-to-case basis giving due consideration to factors like genotype (2 & 3 better than 1) & pre-treatment viral loads (< 800,000 IU/mL better than higher loads). In all such cases, antiviral therapy probably should be discontinued after 4 or 12 weeks if there is no virological response.
3. Patients with Child–Pugh class C (CTP score ≥10 or MELD score 18 [table 2]) disease are not considered appropriate candidates to institute antiviral therapy.

Measure	**1 point**	**2 points**	**3 points**
Total bilirubin, µmol/l (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/l	>35	28-35	<28
INR	<1.7	1.71-2.20	> 2.20
Ascites	None	Mild	Severe
Hepatic encephalopathy	None	Grade I-II	Grade III-IV

Table 1. Child–Pugh Score

Points	**Class**	**One year survival**	**Two year survival**
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Table 1.a Interpretation of Child–Pugh Score

MELD = 3.78[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.57[Ln serum creatinine (mg/dL)] + 6.43

NB:

1. If the patient has had dialysis at least twice in the past week, then the value for serum creatinine used should be 4.0
2. Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8, a value of 1.0 is used). This helps prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any value below 1 would yield a negative result).

Ln = natural logarithm

Table 2. MELD Score (Model For End-Stage Liver Disease) (12 and older):

MELD Score:	3 month mortality:
≥40	71.3%
30–39	52.6%
20–29	19.6%
10–19	6.0%
≤9	1.9%

Table 2.a Interpretation MELD Score

Peginterferon-ribavirin combination therapy (table 3) is now considered the standard drug regimen in cases of HCV infection. In peginterferon, an inert polyethylene glycol moiety is inserted into the interferon molecule. This causes a decrease in renal clearance and thus an increase in the plasma half life (80 hrs) of the peginterferon molecule. Because of the prolonged half life, whereas the non-pegylated interferons need to be administered thrice weekly, pegylated interferons are administered once weekly. The two formulations of peginterferon currently available are peginterferon alpha-2a and 2b. They differ in the size and configuration of the polyethylene glycol moiety attached to the interferon molecule. Although the two peginterferon formulations have not yet been compared head-to-head in the published controlled trails, they are generally believed to be equivalent therapies and thus can be used interchangeably.

Drug:	**Recommended Dosage:**
Peginterferon alfa-2a (40 kD)† (Inj Pegasys 180 µg)	180 µg SQ once weekly regardless of the weight
Peginterferon alfa-2b (12 kD) (Inj Peg-Intron 50/80/100/120/180 µg)	1.5 µg/kg SQ once weekly
Ribavirin∂	*Genotype 1*: Higher weight-adjusted dosage has shown better response rates (1000mg if ≤75kg∆ orally in two divided doses; 1200mg if >75kg)∞. *Genotype 2&3*: Higher dosage has not been shown in published studies to be consistently associated with better response rates. Therefore, 800mg/day orally in two divided doses is the current dosage of choice regardless of the weight.⌂

Abbreviations: kD, kilodaltons; µg, micrograms; SQ, subcutaneously; kg, kilograms; mg, milligrams.
† Peginterferons are therapeutically superior to non-pegylated interferons.
∂ Peginterferon-ribavirin combination therapy is therapeutically superior to peginterferon monotherapy as well as non-pegylated interferon-ribavirin combination therapy.
∆ More studies are needed to ascertain whether or not the treatment outcomes with 1000mg and 800mg ribavirin in patient's ≤75kg weight are comparable.
∞ It is not yet clear whether or not patients heavier than 88 kg will have better outcomes on 1400mg of ribavirin than 1200mg.
⌂ More studies are needed to ascertain that whether or not heavier patients yield better results with >800mg of ribavirin dose in genotypes 2 & 3 cases.

Table 3. Peginterferon-Ribavirin Combination Dosage Regimen: The Current Standard

After starting antiviral therapy, HCV RNA assay needs to be repeated at specific intervals to determine the treatment responses. Depending upon the results of the repeat HCV RNA assays, different treatment responses have been defined (table 4).

Rapid virologic response (RVR)	Qualitative HCV RNA assay done at 4 weeks comes back to be negative (<50IU/mL)
Early virologic response (EVR)	Quantitative HCV RNA assay done at 12 weeks: • Comes back to be negative – called early virologic clearance (EVC) or aviremic response • Shows a decline in the HCV RNA titre (compared with the pre-treatment assay) of ≥ 2 log – called partial virologic response (PVR) or viremic response
Nonresponders	Quantitative HCV RNA assay done at 12 weeks showing either no decline in the HCV RNA titre (compared with the pre-treatment assay) or a decline of < 2 log
End of treatment response (ETR)	Qualitative HCV RNA assay done on completion of the recommended duration of the treatment course comes back to be negative
Sustained virologic response (SVR)*	Qualitative HCV RNA assay done 24 weeks after completion of the recommended duration of the treatment course comes back to be negative
Relapsers	Qualitative HCV RNA assay done on completion of the recommended duration of the treatment course was negative (ETR achieved), but 24 weeks later it becomes positive again (SVR not achieved). .

*Achievement of SVR is generally considered as the marker of eradication of HCV infection. Almost all such patients show EVC or PVR on 12 weeks assay.

Table 4. Definitions of Treatment Responses

Positive and negative predictors of therapeutic response:

1. *Positive predictors:* As otherwise, attainment of a rapid/ early virological response and genotypes 2 & 3 are the most robust predictors of viral clearance with antiviral therapy.[10,12] Child–Pugh class A and lower pre-transplantation viral loads (< 800,000 IU/mL) are other positive predictors.
2. *Negative predictors:* A reduction in the viral load of ≤2 l $\log^{10}$ between baseline & week 4, Child–Pugh class C or MELD >18 have a strong negative predictive value. In the absence of a ≥2 $\log^{10}$ reduction in HCV RNA at week 4, probably the best approach to reduce the risk of complications is to stop antiviral therapy at this point.

The exact treatment protocol instituted in a given patient depends upon the genotype. Genotypes 2&3 are more responsive to interferon therapy than genotype 1 and therefore the recommended duration of antiviral therapy in former is 06 months as compared to one year in the latter. Although more data and experience is needed to establish definite protocols in genotypes 4, 5 & 6 cases, current evidence suggests treating them as genotype 1 cases.[23] Tables 5 & 6 summarize the current standards of treatment depending upon the genotype.

HCV RNA Assay:	**Recommendations according to the PCR results:**
Week 4 qualitative HCV RNA assay:†	
Negative assay (<50IU/mL) i.e. a case of RVR	Shorten the standard treatment course of 24 weeks to 12-16 weeks. Ribavirin is given at higher weight-adjusted dosage in the short courses (1000mg if ≤75 kg orally in two divided doses; 1200mg if >75 kg)‡,∂
Positive assay	Give treatment for the standard duration of 24 weeks$^{\Delta}$ (may be 36-48 weeks)
Week 24 qualitative HCV RNA assay:	
Negative assay i.e. a case of ETR	Successful therapy. Needs a repeat qualitative HCV RNA assay at week 48 (24 weeks after ETR) to establish SVR
Positive assay	Treatment failed
Week 48 qualitative HCV RNA assay:	
Negative assay i.e. a case of SVR	HCV infection eradicated
Positive assay i.e. a case of relapse	*Previously treated with non-pegylated interferon:* Treat with peginterferon and ribavirin. If EVR is not achieved at week 12, stop the treatment *Previously treated with pegylated interferon:* Retreatment is not indicated even if a different type of peginterferon is administered. Consensus interferon has shown to improve responses in such cases, but it is too premature to recommend it.

† The newly recommended week 4 qualitative HCV RNA assay helps modify the duration of the therapy based on viral kinetics. On one hand, this approach helps maximize the SVR rates and on the other hand, limits the toxicities and cost associated with the extended treatment courses. Achievement of RVR means that we can consider shortening the treatment course.
‡ With the shortened treatment courses in subjects who show RVR, SVR rates of 80-100% have been reported in genotype 2 cases and 77-85% in genotype 3 cases.
∂ In case of relapse, retreatment with the standard 24 weeks course is recommended.
Δ SVR rates achieved in this subgroup are poor, particularly in genotype 3 cases – 41-58%. In genotype 2 cases, the results are relatively better - 50-89%. Because of the poor SVR rates, prolonged therapy (>24 weeks) may be considered in this subgroup, although more evidence is needed at this time for a definite recommendation.

Table 5. Summary of Current Standards in the Management of Genotypes 2&3 Cases:

HCV RNA Assay:	**Recommendations as per the PCR results:**
Week 4 qualitative HCV RNA assay:	
Negative assay (<50IU/mL) i.e. a case of RVR	*Predictors of poor response absent:*† Shorten the treatment duration to a total of 24 weeks‡,∂ *Predictors of poor response present:* Give treatment for the standard duration of 48 weeks
Positive assay	Continue treatment and repeat HCV RNA at 12 weeks
Week 12 qualitative HCV RNA assay:	
Negative assay i.e. a case of EVC	Continue treatment for a total of 48 weeks
HCV RNA fall by ≥ 2 logs i.e. a case of PVR	Continue treatment & repeat qualitative HCV RNA at 24 weeks.
HCV RNA fall by < 2 logs i.e. a case of non-responder	Stop treatment
Week 24 qualitative HCV RNA assay (only done in cases which show PVR at week 12 assay):	
Negative assay (this subgroup is called 'slow responders')	Continue treatment for a total of 48-72 weeks. 72 weeks therapy has generally shown superior results as compared to 48 weeks therapy in slow responders.
Positive assay	Stop treatment as probability of attaining SVR is negligible
Week 48 qualitative HCV RNA assay:	
Negative assay i.e. a case of ETR	Successful therapy. Needs a repeat qualitative HCV RNA assay at week 72 (24 weeks after ETR) to establish SVR
Positive assay	Treatment failed
Week 72 qualitative HCV RNA assay:	
Negative assay i.e. a case of SVR	HCV infection got eradicated
Positive assay i.e. a case of relapse	*Previously treated with non-pegylated interferon:* Treat with peginterferon and ribavirin. If EVR is not achieved at week 12, stop the treatment *Previously treated with pegylated interferon:* Retreatment is not indicated even if a different type of peginterferon is administered. Consensus interferon has shown to improve responses in such cases, but it is too premature to recommend it.

† Old age (>50yrs); male gender; African American race; obesity; alcoholism; HIV confection or immunosuppression; more-than-portal fibrosis on liver biopsy (Metavir ≥2 or Ishak ≥ 3); a pretreatment viral load of >800,000IU/mL.

‡ SVR rates of 80-89% can be achieved in this subgroup.

∂ In case of relapse, retreatment with the standard 48 weeks course is recommended.

Table 6. Summary of Current Standards in the Management of Genotype 1 Cases

Monitoring the antiviral therapy not only involves asking repeat HCV RNA assays at specific intervals to determine therapeutic response, but also a battery of other blood tests to rule out the development of any adverse effects (see table 7).

Fortnightly:	CBC at weeks 1, 2, 4, 6, 8 and then monthly
Week 4:	Qualitative HCV RNA assay at week 4 in both genotype 1 and 2&3 cases to assess for RVR
Every month:	Pregnancy assay in a sexually-active female of child bearing age
Week 12:	Quantitative HCV RNA test at week 12 in genotype 1 cases only to assess for EVR
Every 3 months:	LFTs, INR, albumin, creatinine, urinalysis, glucose and TSH
Week 24:	• Qualitative HCV RNA assay at week 24 in only those genotype 1 cases who attained EVR at week 12 • Qualitative HCV RNA assay at week 24 in genotype 2&3 cases to determine ETR
Week 48	• Qualitative HCV RNA assay at week 48 in genotype 2&3 cases to determine SVR • Qualitative HCV RNA assay at week 48 in genotype 1 cases to determine ETR
Week 72	• Qualitative HCV RNA assay at week 72 in genotype 1 cases to determine SVR

Table 7. Monitoring of Anti-viral Therapy

4. Pharmacotherapy of side effects

As a general rule, decompensated cirrhotics are more prone to develop drug-induced side-effects compared to patients with compensated disease. Important side effects in decompensated cirrhotics include:[16]

1. Drug-induced hematological side effects: neutropenia (50–60%), thrombocytopenia (30–50%), hemolytic anemia (30–50%).
2. Superadded infections: spontaneous bacterial peritonitis (SBP), spontaneous bacteraemia/ septicaemia/ septic shock (due to Gram-negative bacilli) etc (4–13%).
3. Worsening of hepatic decompensation with therapy (11–20%).

4.1 Drug-induced hematological side effects

4.1.1 Ribavirin-induced hemolytic anemia

The minimum effective dose of ribavirin appears to be 10.6 mg/kg/day. In case hemolytic anemia develops, it is recommended to first reduce the dose of ribavirin to the minimum

effective level. If no or little improvement in hemoglobin (Hb) level occurs, initiating concomitant erythropoietin (EPO) therapy may be considered.[17,18]

Possible indications:	1. Fall in Hb level by >4 g/dL. 2. Hb levels of <8g/dL. 3. Development of symptoms and signs attributable to anemia (palpitations, dyspnea, easy fatigability, pallor).[21,22]
Dosage regimens:	1. 20,000-40,000IU/week given in three divided doses subcutaneously (max. 60,000IU/week) with an aim to achieve & maintain Hb level of ≥10g/dL (return to the pretreatment level is NOT the aim).[23] 2. Another study suggested starting EPO therapy at a lower dose of 4,000IU subcutaneously thrice weekly (12,000IU/week) and then increasing the dose depending upon the response.[24]

Table 8. Erythropoietin (EPO) therapy

Monitoring EPO therapy: The first evidence of response to the thrice weekly EPO administration is an increase in the reticulocyte count within 10 days.[25] Since erythroid progenitors take several days to mature, a clinically significant increase in hematocrit is usually not observed in less than 2 weeks and may require up to 6 weeks in some patients.[26] If the rate of rise of hemoglobin is greater than 1 g/dL over 2 weeks, it generally warrants decreasing EPO dose. This is because a greater than 1 g/dL rise in *any* 2 weeks during the course of the therapy has been associated with an increased risk of thromboembolic phenomenon, predisposing to myocardial infarction, stoke and even death.[27] Also, according to manufacturer's recommendations, a Hb level of greater than 12g/dL should not be aimed, the reason being potentially increased risk of thromboembolic phenomenon.[28] Once adequate Hb level (≥10g/dL) is achieved, ribavirin dose can be increased to the optimum level.[20] Once started, adjunct EPO therapy may be required until the end of the treatment. In one study,[24] the median duration of EPO treatment was 24 weeks (range 6–39).

4.1.2 Interferon-induced neutropenia/ thrombocytopenia

The minimum effective dose of pegylated interferon appears to be 1 µg/kg/wk. It is recommended to reduce IFN dose to the minimum effective level if neutrophil count falls to $<0.5x10^9$/L, and discontinue it if it falls to $<0.3x10^9$/L.[17] Regarding platelet count, IFN dose should be reduced to the minimum effective level if platelet count falls to $<30x10^9$/L, and discontinued if it falls to $<20x10^9$/L.[17] If no or little improvement in neutrophil/ platelet counts occur, initiating concomitant granulocyte-colony-stimulating-factor (G-CSF) or granulocyte-monocyte-colony-stimulating-factor (GM-CSF) therapy may be considered[19,20] with an aim to avoid using the suboptimal drug doses.

Possible indications:	1.	Neutrophil count <0.5x10^9/L.
	2.	Platelet count <30x10^9/L
Dosage regimens:	3.	30MU subcutaneously once weekly and then adjusting the dose as per the response/ requirement.

Table 9. Granulocyte-colony-stimulating-factor (G-CSF) therapy

Monitoring G-CSF therapy: Complete blood counts should be requested twice or thrice weekly and response to therapy judged. Once adequate neutrophil count is achieved, IFN dose can be *increased* to the optimum level.[21] Once started, adjunct G-CSF therapy may be required till the end of the treatment. In one study,[24] the median duration of G-CSF therapy was 20 weeks (range 9–45).

4.2 Pharmacotherapy of superadded infections

Norfloxacin prophylaxis has been shown to reduce the incidence of superadded infections.[15,16] In cases of established nosocomial SBP (often caused by bacteria resistant to 3rd-generation cephalosporins and/or amoxicillin-clavulanic acid), broad-spectrum antibiotics like carbapenems or glycopeptides should be prescribed.

Although it is not yet clear how much survival benefit antiviral therapy confers, a standardized mortality rate analysis in one study reported a lower liver-related mortality among cirrhotics with SVR (0.6: CI: 0.0-3.1) compared to untreated patients.[29] In post-liver transplant cases, avoidance of allograft failure due to recurrence of HCV infection has also been reported in the literature although it needs further studies and validation.[30]

5. Conclusion

One thing that has become increasingly clear from the existing trials data is that cirrhotic patients who are treated with antiviral therapy and who achieve SVR are less likely to develop liver-related complications as compared to the non-responders. Despite the many encouraging studies on this subject, data on the long-term disease progression, avoidance of transplantation, and most importantly, improvement of life expectancy is however still sparse. Although liver functions have clearly been shown to improve with antiviral therapy (as indicated by significant reductions in CTP and MELD scores), the same are more likely to deteriorate within a few years in patients with advanced cirrhosis thus explaining the need to accumulate data on the possible survival benefit conferred by antiviral therapy in cirrhotic patients.

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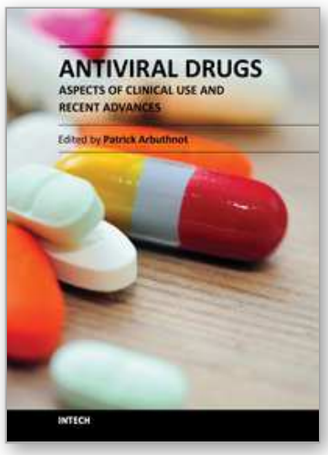

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The articles that appear in Antiviral Drugs - Aspects of Clinical Use and Recent Advances cover several topics that reflect the varied mechanisms of viral disease pathogenesis and treatment. Clinical management and new developments in the treatment of virus-related diseases are the two main sections of the book. The first part reviews the treatment of hepatitis C virus infection, the management of virus-related acute retinal necrosis, the use of leflunomide therapy in renal transplant patients, and mathematical modeling of HIV-1 treatment responses. Basic research topics are dealt with in the second half of the book. New developments in the treatment of the influenza virus, the use of animal models for HIV-1 drug development, the use of single chain camelid antibodies against negative strand RNA viruses, countering norovirus infection, and the use of plant extracts to treat herpes simplex virus infection are described. The content of the book is not intended to be comprehensive, but aims to provide the reader with insights into selected aspects of established and new viral therapies.

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