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Acute HCV Treatment: What Should We Do in the DAA Era?

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Abstract

Purpose of Review Acute hepatitis C infection is a growing concern in the USA, especially in light of the opioid epidemic. Prior treatment data consisted of trials in patients receiving interferon-based regimens. There is now emerging evidence regarding the safety and efficacy of direct-acting antivirals for the treatment of acute hepatitis C. This review summarizes the current evidence on the treatment of acute HCV in the DAA era.

Recent Findings Certain populations, such as people who inject drugs, or HIV-positive men who have sex with men, may benefit from early treatment of acute HCV. As compared with chronic hepatitis C, shorter durations of treatment appear highly effective in acute infection, resulting in reduced viral transmission, as well as potentially reduced overall costs of care related to this disease.

Summary Further studies are needed to clarify the optimal drug combinations and treatment durations to achieve sustained virologic response in these patients.

Keywords Acute hepatitis C · Recent hepatitis C · Direct-acting antivirals

Introduction

Epidemiology

Acute hepatitis C virus (HCV) infection represents a growing health threat even as highly effective interferon-free direct-acting antiviral (DAA) therapies become available. The worldwide burden of HCV seroprevalence is estimated at 2.5% of the global population, or about 177.5 million people, with a viremia rate of 67%, or 118.9 million people [1]. Compared with the period ranging from 1990 to 2005, this represents a decrease in the overall HCV burden of disease (from 2.8% global prevalence) [2]. However, with the limited data available on trends in de novo infections, acute HCV appears to be on the rise in the USA. There were an estimated 29,700 new cases in 2013, representing a 180% increase over cases in 2011 [3]. The estimated incidence of new HCV infections in 2016 is even higher, at 41,200 [4]. Young (aged < 30) people who inject drugs (PWID) are at particular risk, especially in predominantly rural areas east of the Mississippi (Fig. 1) [6, 7]. Furthermore, up to three-fourths of PWID with acute HCV in one study reported concomitant prescription opioid abuse, highlighting the impact of the ongoing opioid abuse epidemic [6].

Aside from injection drug use, other routes of blood exposure account for the remaining sources of new HCV infections: nosocomial acquisition or unsafe healthcare procedures (mostly in the developing world), accidental exposures in healthcare workers (such as needlestick injuries), sexual exposure (especially in HIV-positive men who have sex with men, or MSM), and transmission of HCV in the setting of organ transplantation.

Diagnosis

Acute HCV infection is variably defined, with seroconversion (HCV antibody detected in a patient with a previously negative antibody within the prior 4–6 months) and nucleic acid test (NAT) for HCV RNA positive in a patient with a negative HCV antibody (seronegative window period), being the most accepted scenarios indicative of acute HCV [8]. In regard to seroconversion, it must be kept in mind that some

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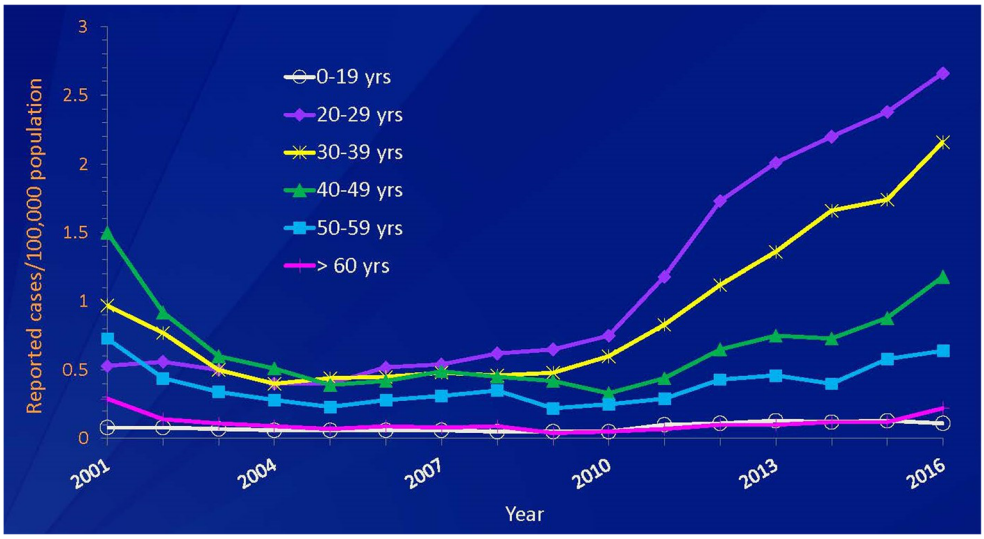

Fig. 1 Incidence of acute HCV in the USA by age group, 2001–2016 (Source CDC) [5]

immunocompromised patients, such as those with HIV, may have persistently negative HCV antibody after exposure (in up to 5% at 1 year) [9]. Re-infection may be seen in patients with prior chronic or acute HCV that was treated or spontaneously cleared with subsequent re-exposure; these patients will have long-term positive HCV antibody, with HCV NAT positivity after prior documented clearance. Finding a different HCV genotype further supports the diagnosis of re-infection. Although ALT and symptoms may be used to aid in the diagnosis of acute HCV, these are both imperfect markers as intermittently normal ALT may be seen in those with fluctuating viremia after acute infection, and most patients with acute HCV are asymptomatic [10, 11].

Natural History

Whereas spontaneous clearance of established chronic HCV is rare, acute infection may clear without antiviral treatment. Estimated rates of spontaneous clearance of acute infection are variable, with reported percentages ranging from 10 to 50%. One systematic review of 31 studies found a spontaneous clearance rate of 26%, and a more recent multicenter, multinational cohort study of 632 acute HCV cases found a rate of 25% [12•, 13]. The median time to clearance in the cohort study was 16.5 weeks, but interestingly, only 67% and 83% of patients that spontaneously cleared the virus had done so by 6 and 12 months, respectively, with approximately 3% of these patients clearing after 24 months. Factors predictive of spontaneous clearance include female sex, acute clinical hepatitis, interleukin-28B CC genotype of the patient (now renamed interferon lambda-3 or IFNL3), and HCV genotype 1 [12•, 13]. In patients with HIV, the presence of hepatitis B surface antigen appears to confer an increased rate of spontaneous clearance, compared with those without hepatitis B (43% vs 21%), likely due to the phenomenon of "viral interference" [14]. In a multicenter Italian study of mono-infected patients with acute HCV, jaundice and IFNL3 CC genotype were both independent predictors of spontaneous clearance [15]. In fact, in patients without this genotype and without jaundice, the spontaneous clearance rate was only 2%, indicating that such patients would be good candidates for treatment. Furthermore, delaying treatment (which consisted of interferon ± ribavirin) in this group of patients to beyond 48 weeks after diagnosis reduced the sustained virologic response (SVR) rate from 90–100% to 27% [15]. Based on a retrospective cohort of patients in Austria, scores to predict spontaneous clearance of acute HCV have been developed, which combine patient age, peak bilirubin, presence of IFNL3 CC genotype, rate of HCV RNA decline in 4 weeks, levels of serum interferon-gamma inducible protein 10 (IP-10), and presence of CD4+ TH1 cells [16]. The sensitivity and specificity of these scores is quite good, with AUROC up to 0.97. However, the limited availability of some of these diagnostic tests precludes widespread use of such prediction models.

How to Approach Acute HCV

Once acute HCV is diagnosed, the decision of whether or not to treat the infection must be made. If treatment is pursued, then the appropriate regimen and duration must be chosen.

When to Treat Acute HCV

Most arguments to treat acute HCV rest on the concept of immediately linking afflicted patients with care and thus increasing SVR rates, decreasing endemic transmission of HCV (treatment as prevention), and improving cost-effectiveness of treatment.

Earlier data demonstrated that early treatment (i.e., within 12 weeks) of acute HCV with interferon-based regimens tends to achieve improved SVR rates and less loss to follow-up compared with delayed treatment [17, 18]. In the DAA era, SVR rates are excellent for both acute and chronic HCV, but the issue of loss to follow-up remains. Patients who can be expected to reliably take antiviral medications for a relatively short period of time, but who otherwise are expected to have poor long-term follow-up with the healthcare system, should be considered for treatment. A microsimulation model of genotype 1 acute HCV shows that immediate treatment with 6 weeks of ledipasvir/sofosbuvir compared with 8 weeks of therapy after waiting 6 months, assuming a 25% spontaneous clearance rate, is cost-effective in patients not at risk of transmitting HCV, and actually cost-saving in patients at risk of transmitting the infection [19••]. These effects are magnified with shorter durations of treatment for acute HCV, longer durations of treatment for chronic HCV, and higher rates of transmission of infection. Therefore, treatment should be considered in PWID and HIV-positive MSM diagnosed with acute HCV. When treating acute HCV, the AASLD recommends waiting 12–16 weeks after diagnosis to allow time for potential spontaneous clearance [20].

Other groups that would benefit from early treatment include certain healthcare workers that would have a non-trivial risk of transmission of HCV to their patients, such as surgeons or other proceduralists, and patients with decompensated cirrhosis of another etiology with superimposed acute HCV. In both cases, rapid elimination of HCV is warranted to minimize transmission risk in the former group, and reduce the risk of developing acute-on-chronic liver failure in the latter.

There are no reported cases of extrahepatic manifestations of acute HCV necessitating early treatment. However, acute HCV can be symptomatic, and treatment could be considered in those with particularly debilitating symptoms. Acute HCV causing acute liver failure is extremely rare, and due to the rapidity of progression of disease, the role of DAAs is likely to be very limited. No data exist on the use of DAAs in preventing liver transplant in "fulminant" hepatitis C. However, liver transplantation could be a salvage treatment, followed by initiation of antiviral therapy soon after transplant [21, 22].

A related situation is the intentional transmission of hepatitis C, and therefore induction of acute HCV, in certain HCV-negative patients after solid organ transplantation with HCV-positive organs. In efforts to reduce waitlist mortality and expand the donor pool for patients awaiting transplant, heretofore discarded organs from donors with HCV viremia (HCV NAT positive) are now increasingly being used in patients with otherwise limited access to organs [23]. A full exploration of this topic is beyond the scope of this review, but these patients would certainly be candidates for early treatment after their transplant.

Table 1 summarizes the populations of patients that would benefit from treatment of acute HCV.

When Not to Treat Acute HCV

Clearly, treating every single case of acute HCV is unnecessary. According to AASLD HCV guidance, pre-exposure prophylaxis or immediate post-exposure prophylaxis with antiviral treatment is not recommended [20]. Similarly, EASL guidelines recommend against post-exposure prophylaxis due to the relatively low rate of transmission after most parenteral exposures and the high efficacy of DAA therapy [24]. For patients diagnosed with acute HCV with expected good follow-up and access to the healthcare system, it is reasonable to wait at least 4–6 months to allow time for potential spontaneous clearance. If after 6 months, HCV viremia persists, the patient may be diagnosed with chronic HCV, and treated according to the usual recommendations.

Treatment Regimens and Duration

As of now, data on the use of DAAs for acute HCV are limited. However, given the spectacular success of DAAs in chronic infection, and preliminary data showing that shorter courses of

Table 1 Patients that would benefit from treatment of acute HCV

Category	Notes
People who inject drugs	Assess risk of medication non-adherence prior to starting therapy; provide linkage to mental healthcare and substance abuse/addiction resources
Men who have sex with men, especially if HIV positive	Provide counseling regarding transmission risk; consult with patient's HIV provider regarding drug-drug interactions
Healthcare workers at risk of transmitting HCV to patients	Provide counseling regarding transmission risk
Cirrhotics suffering from or at risk of decompensation	Rule out other causes of hepatic decompensation; use treatment regimens approved for cirrhotics
Acute HCV after organ transplant	Utilize a standardized pre-transplant informed consent process within the framework of a research protocol; determine in advance if insurance will cover antiviral therapy

therapy can be very effective in treating acute HCV, these medications are promising options.

A pilot study of PWID in Brooklyn showed a greater than 90% SVR-20 rate achieved by both simeprevir/sofosbuvir for 8 weeks, as well as ledipasvir/sofosbuvir for just 4 weeks [25]. A German study of 20 patients with genotype 1 acute HCV showed 100% SVR-12 rate with 6 weeks of ledipasvir/sofosbuvir, with no drug-related serious side effects, even in patients with jaundice [26••]. In this trial, mean time to initiation of treatment after diagnosis was 33 days. Importantly, active systemic drug use was a contraindication to inclusion in the study, and only 5 patients had a screening or baseline HCV RNA greater than or equal to 1,000,000 IU/mL.

In a different trial of 26 HIV coinfected patients with genotype 1 or 4 acute HCV treated with 6 weeks of ledipasvir/sofosbuvir, the SVR rate was less impressive at 77% [27•]. Of the six treatment failures, two were lost to follow-up at 12 weeks post-treatment, but had undetectable virus at 4 weeks after treatment, one was re-infected with a different genotype, while the three patients who had documented relapse had baseline HCV RNA greater than 9,000,000 IU/mL. This study highlights the importance of optimal treatment duration in coinfected patients with elevated baseline HCV RNA levels.

Table 2 Recommended treatment regimens for acute HCV mono-infection in non-cirrhotics

Genotype	Treatment regimen	Duration (weeks)
1a	Ledipasvir/sofosbuvir* Paritaprevir/ritonavir/ombitasvir + dasabuvir + ribavirin	8
	Sofosbuvir/velpatasvir	
	Glecaprevir/pibrentasvir	
1b	Ledipasvir/sofosbuvir* Paritaprevir/ritonavir/ombitasvir + dasabuvir	8
	Sofosbuvir/velpatasvir	
	Elbasvir/grazoprevir	
	Glecaprevir/pibrentasvir	
2	Sofosbuvir/velpatasvir Glecaprevir/pibrentasvir	8
3	Sofosbuvir/velpatasvir Glecaprevir/pibrentasvir	8
4	Ledipasvir/sofosbuvir Elbasvir/grazoprevir	8
	Glecaprevir/pibrentasvir	
5	Ledipasvir/sofosbuvir Sofosbuvir/velpatasvir	8
	Glecaprevir/pibrentasvir	
6	Ledipasvir/sofosbuvir Sofosbuvir/velpatasvir	8
	Glecaprevir/pibrentasvir	

*Consider 6 weeks duration if baseline HCV RNA < 1,000,000 IU/mL

In a study of 30 patients with or without HIV coinfection and genotype 1 recently acquired HCV, an 8-week regimen of paritaprevir/ritonavir/ombitasvir and dasabuvir (with weight-based ribavirin in 29 patients) yielded a 97% SVR-12 rate [28••]. The patient who did not receive ribavirin had genotype 1b HCV. Treatment failure occurred in one patient who discontinued therapy at 2 weeks due to an unrelated hospitalization and subsequently withdrew from the study. In this trial, elevated baseline HCV RNA levels of > 1,000,000 IU/mL or even > 10,000,000 IU/mL did not adversely impact SVR. Of note, recent infection was defined as HCV acquired within the preceding 12 months, with 43% of trial participants meeting criteria for acute HCV, defined as acquisition of infection within 24 weeks of screening.

These studies form the basis for the current EASL guidelines: 8 weeks of ledipasvir/sofosbuvir for genotypes 1, 4, 5, and 6, or 8 weeks of paritaprevir/ritonavir/ombitasvir and dasabuvir for genotype 1b; due to lack of data, a weaker recommendation is given for 8 weeks each of sofosbuvir/velpatasvir for all genotypes, glecaprevir/pibrentasvir for all genotypes, or elbasvir/grazoprevir for genotypes 1b and 4 [25]. Table 2 summarizes our recommended treatment regimens for acute HCV mono-infected patients without preexisting cirrhosis.

Conclusion

Despite remarkable advances in HCV antiviral treatment, acute HCV is emerging as a growing health threat in certain segments of the population. PWID and HIV-positive MSM are at particular risk of transmitting and acquiring HCV. Aside from preventative measures, targeted efforts to diagnose and treat infection in these populations will be crucial in curtailing viral transmission rates and eventually eradicating hepatitis C. Fortunately, with the advent of DAAs, multiple safe treatment options with unprecedentedly short regimen durations now exist to aid in this effort. In the coming years, more data will undoubtedly become available to guide us in selecting the optimal agents and duration of treatment.

Compliance with Ethical Standards

Conflict of Interest Robert S. Brown, Jr., reports grants and personal fees from Gilead, grants and personal fees from Abbvie, grants and personal fees from Merck, and grants and personal fees from BMS, outside the submitted work. Zurabi Lominadze declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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