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Real-World Evidence and Hepatitis C

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Contents

Abstract Direct-acting antiviral agents (DAAs) are the treatment of choice for patients with chronic hepatitis C. Their efficacy across diverse patient populations and safety among those with all stages of liver disease, including cirrhosis, have been repeatedly demonstrated in studies encompassing all classes of DAAs. Real-world evidence has confirmed that DAA therapies used in usual clinical practice achieved similar rates of sustained virological response when compared to those reported in rigorously controlled clinical trials. These data, developed from large cohort studies performed around the world, have instilled greater confidence in the management of patients with chronic hepatitis C using DAAs. Furthermore, real-world evidence contributed to better understanding the strengths and limitations of DAA treatment

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among unique populations of patients with chronic hepatitis C who were underrepresented in the original registration trials of these agents.

Keywords Hepatitis C, Observational studies, Real-world data, Real-world evidence

1 Introduction

Phase 3 clinical trials demonstrated the remarkable efficacy and safety of various classes of direct-acting antiviral agents (DAAs) for the treatment of chronic hepatitis C (CHC) [1–4]. Regardless of hepatitis C virus (HCV) genotype or level of disease severity (cirrhotic vs non-cirrhotic), all-oral DAA regimens achieve sustained virological responses in more than 90% of treated patients. These therapies were rapidly adopted, and many thousands of patients have been successfully treated since the first protease inhibitors, in combination with peginterferon and ribavirin, were approved in 2011 [5, 6]. As all-oral regimens debuted and utilization increased, additional questions arose regarding the safety and effectiveness in populations of patients that were less well studied in traditional phase 3 clinical trials. This chapter will discuss the important role played by real-world evidence in informing gaps in knowledge of safety and effectiveness across broad populations and in optimizing treatment for patients with hepatitis C in the era of direct-acting antiviral agents.

2 Identifying and Filling Knowledge Gaps for Approved HCV Therapies

Gaps in knowledge often exist between the evidence generated during clinical trials and the information needed for clinical practice, especially in the immediate period after medications are approved for general use [7–9]. Rigorous, controlled phase 3 clinical trials do provide the highest level of evidence regarding the safety and efficacy of new medications. However, these studies, specifically designed to achieve market authorization in the shortest time frame, generate clear answers to narrowly focused questions in selected populations [7–9]. Practicing clinicians, in contrast, are usually called upon to make treatment decisions in patients whose demographics or clinical status does not completely align with the patients who were enrolled in phase 3 trials. Thus, patients at the extremes of age, non-Caucasian race, those with more severe liver disease, patients in whom other medical comorbidities exist, and for which numerous concomitant medications are being administered were underrepresented or entirely excluded in the phase 3 registration trials of DAAs for HCV.

The eligibility criteria for the initial phase 3 trials of ledipasvir/sofosbuvir, for example, required participants to meet at least seven inclusion criteria, in addition to being within specified ranges for nine laboratory tests, and not meeting any of at least six exclusion criteria [2]. In usual clinical practice, the eligibility criteria of HCV treatment are many fewer: patient desire to be treated, a reasonable expectation that medications will be effective, the absence of absolute medical contraindications to the planned regimen, and access to medications. Thus, a much wider spectrum of patients are being treated for hepatitis C that is very different from the phase 3 trial populations upon which initial approval was granted.

Optimizing clinical use of new medications often requires additional information to be developed in the post-marketing period. Specific post-approval phase 4 studies could be designed to meet post-marketing requirements and expand the knowledge base around previously underrepresented populations, such as patients with cirrhosis. However, these studies are often plagued by delays in enrolling, high costs, and insufficient power to confidently answer the prespecified question and may be irrelevant by the time the studies are completed [7]. Numerous alternatives to traditional clinical trials exist and are becoming increasingly important as a source of "real-world" evidence to augment information derived from phased drug development programs.

3 FDA Commitment to Real-World Evidence

In December 2016, the 21st Century Cures Act was signed into US law with the goal of accelerating drug development by, among other things, innovating clinical trial design and clinical outcome measures. One key facet of 21st Century Cures Act required the "FDA to evaluate the use of real world evidence to help support the approval of a new indication for a previously approved drug and to help support or satisfy post-approval study requirements" [10]. Furthermore, "By no later than the end of FY 2021, FDA will publish draft guidance on how RWE can contribute to the assessment of safety and effectiveness in regulatory submissions, for example in the approval of new supplemental indications and for the fulfillment of post-marketing commitments and requirements" [10].

4 Sources of Real-World Evidence

Real-world data (RWD) can be derived from a wide range of sources, including information gathered from medical and pharmacy claims, electronic health records, pharmacy data, electronic health devices, social media, and prospective observational registry data [11]. Real-world evidence (RWE) is the clinical evidence derived from the analysis of RWD [11]. RWE can contribute to all phases of drug development by defining the natural history of disease, identifying medical comorbid

conditions that could impact a product profile, characterizing current practice patterns, and quantifying risks and benefits in certain subpopulations [7, 11]. In the post-marketing period, real-world evidence has provided important insights into the safety of new drugs in diverse populations and has supported new indications for previously approved medications [11].

5 HCV-TARGET and Other Real-World Cohorts

Multiple prospective, longitudinal observational registries were initiated shortly after the approvals of the first oral protease inhibitors, circa 2011. Nearly every continent has contributed important real-world evidence demonstrating the safety and effectiveness of DAAs for the treatment of hepatitis C across diverse populations (Fig. 1). To date, these registries have cumulatively enrolled tens of thousands of patients whose insights have had a substantial impact on optimal management for patients with hepatitis C.

HCV-TARGET (Hepatitis C Therapeutic Registry and Research Network) was established as an academic collaboration between the University of Florida (David R. Nelson, PI) and University of North Carolina (Michael W. Fried, PI) to better understand the impact of new therapies on the management and long-term outcomes of patients with hepatitis C. It was evident that there were many unanswered questions as these new classes of drugs were increasingly utilized in populations that were different from those studied in phase 3 registration trials. Thus, patients with cirrhosis (compensated and decompensated), African American race, elderly populations, and those with many comorbid medical conditions were being treated with DAA regimens despite a paucity of clinical data regarding safety and effectiveness in these populations.

Fig. 1 Real-world cohorts from around the globe have provided RWE regarding the safety and effectiveness of DAAs

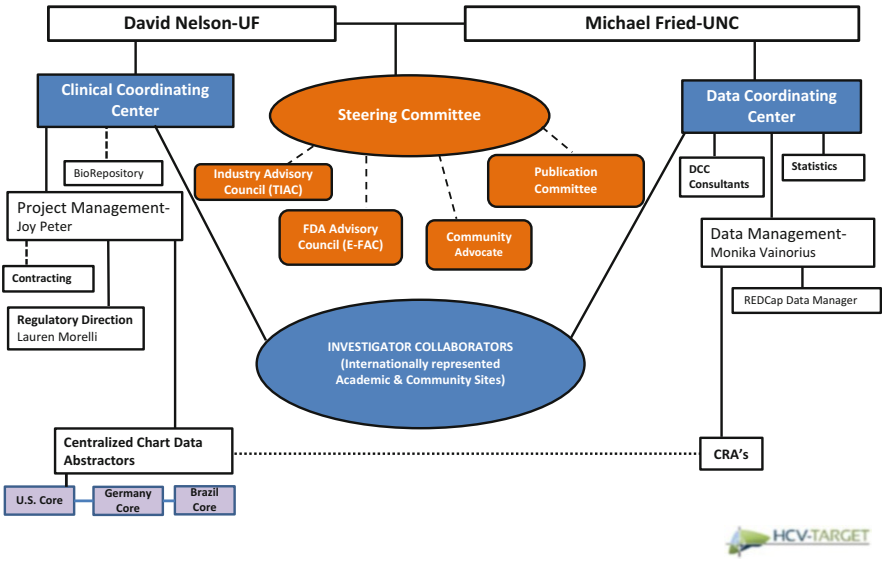

Fig. 2 Organizational structure of HCV-TARGET

HCV-TARGET is a unique collaboration between academia, industry, and community working together to fill in knowledge gaps about the rapidly evolving HCV treatment landscape (Fig. 2). A memo of understanding with the FDA (MOU 225-13-0012) was executed in 2013 which allowed members of the Division of Antiviral Products to participate in HCV-TARGET steering committee meetings, query the database, and exchange scientific insights with the network [12]. HCV-TARGET is led by an academic steering committee composed of global experts in viral hepatitis (Fig. 2). The steering committee works closely with the industry advisory board to establish the research agenda, implement policies, and plan for abstracts, presentations, and manuscripts that served to disseminate important clinical findings to the scientific community.

HCV-TARGET has focused on data quality with a REDCAP-based data platform that was compliant with 21CFR part 11 standards for electronic data capture, met CDISC standards compatible for data exchange, and incorporated industry recognized WhoDrug coding for concomitant medications and MEDDRA for classifying adverse events. Furthermore, HCV-TARGET utilizes a novel data capture process whereby sites upload the entire redacted health record (structured and unstructured data, lab and x-ray reports, telephone messages, biopsy results) from consented patients which is then abstracted and entered into the database by a team of trained abstractors. This centralized method minimized the burden to sites and allowed for greater consistency of data entry than traditional distributive models that relies on individual sites and variably experienced study staff completing case report forms. HCV-TARGET also employed an independent monitoring core that compared source documents with database entries using a risk-based strategy for key outcome variables.

The HCV-TARGET consortium includes over 60 sites throughout the United States, Germany, and Israel and enrolled over 12,000 patients treated with every generation of DAA medications. The unique rolling design allowed for rapid acquisition of data as new medications were approved and began to be utilized in usual clinical practice. Evidence generated from HCV-TARGET informed treatment guidelines for AASLD, EASL, and the World Health Organization [13, 14].

Other important RWD cohorts include

1. the French cohort ANRS C022 HEPATHER, a national 32-center prospective observational cohort that included up to 15,000 HCV-infected patients and was established to identify prognosis factors, including response to treatment and long-term impact of viral clearance. Demographic and history of liver disease were collected at entry into the cohort. Clinical, adverse events, and virological data were collected throughout treatment and posttreatment follow-up [15].
2. The Veterans Affairs Healthcare System, which includes 167 medical centers and 875 ambulatory care and community outpatient clinics throughout the United States [16]. It is the largest integrated healthcare provider for HCV-infected patients in the United States, with over 175,000 pts diagnosed with HCV infection in VA care in 2014. The VA utilizes electronic medical records and electronic clinical data, and HCV treatment regimens are collected into the VA Corporate Data Warehouse, a national repository of data from VA's computerized patient records. Data extracted includes all pt pharmacy prescriptions, demographic characteristics, inpatient and outpatient visits, problem lists, procedures vital signs, diagnostic tests, and laboratory tests.
3. German Hepatitis C Cohort (GECCO), which is a multicenter prospective database from 9 German HCV treatment centers [17];
4. TRIO Health Cohort, which comprises patients treated in approximately 500 community and academic practices affiliated with the TRIO Health Innovation Platform [18]. Baseline information as well as outcomes data are collected through both specialty pharmacies and clinicians, allowing the evaluation of concomitant medications and the evaluation of compliance using pharmacy dispense data; however no safety data are collected; and
5. United Kingdom cohort, comprising 10,184 patents with a history of HCV infection enrolled through attendance at one of 56 UK HCV clinics between 2012 and 2013 [19].

6 Real-World Evidence Finds an Important Safety Signal in Patients with Cirrhosis

The approval of the first-generation HCV protease inhibitors, telaprevir and boceprevir in combination with peginterferon and ribavirin, began the transformation of HCV therapies and served as an important interim step toward the development of all-oral regimens. The registration trial treated 363 patients with 12 weeks of peginterferon, ribavirin, and telaprevir and yielded a remarkable 75% sustained

virological response, compared to only 44% in those treated with peginterferon and ribavirin alone [20]. However, there was evidence of an altered safety profile in patients treated with triple therapies. Most evident was the increased frequency of anemia in patients treated in the triple therapy arm compared to peginterferon/ribavirin, 37% vs 19%, respectively, with 5% of patients requiring blood transfusion. Of note, only 6% of patients enrolled in the registration trial had evidence of cirrhosis [20].

Perhaps the earliest demonstration of the importance of real-world evidence to inform HCV therapy was the French CUPIC study, an open-label, real-world early access protocol that enrolled over 600 cirrhotic patients treated with triple therapy (telaprevir or boceprevir) [21]. Among the patients treated with telaprevir-based therapy, 23% discontinued treatment due to adverse events. Thirty-one percent of patients developed treatment-emergent anemia (hemoglobin <9.0 mg/dL), including 54% who received RBC growth factors and 16% blood transfusions. Thus, the safety signal of anemia was greatly amplified in patients with cirrhosis, leading to immediate changes in clinical practice with more vigilant monitoring as well as early and rapid dose reductions in ribavirin to mitigate development of anemia [21].

In the US cohort, HCV-TARGET similarly demonstrated that patients treated with these first-generation protease inhibitors had high rates of advanced disease (38%), had lower SVR rates, and were more likely to experience significant adverse events compared to patients in registrational trials [22]. The lower SVR rates in HCV-TARGET were likely explained by the high proportion of patients with cirrhosis and African American race, factors that have been associated with a lower SVR with interferon-based therapies [12, 22].

7 RWE Contributes to the Approval of the First All-Oral DAA Regimen Commonly Prescribed

The near simultaneous approval in 2013 of two triple therapy regimens (sofosbuvir + peginterferon/ribavirin and simeprevir + peginterferon/ribavirin) set the stage for the first commercially available, but unapproved, all-oral regimen for the treatment of hepatitis C [23, 24]. Simeprevir, a first-generation protease inhibitor with once daily administration and a better safety profile than earlier HCV protease inhibitors, was immediately an attractive candidate to be combined with the nucleoside analogue, sofosbuvir. Indeed, a small phase 2 study treated 167 patients with the combination of simeprevir and sofosbuvir yielding SVR in over 90% of patients with negligible side effects [25]. These encouraging results provided reassurance that combining two classes of DAAs and shedding peginterferon and ribavirin was a viable alternative to triple therapy regimens, and simeprevir plus sofosbuvir became the first commonly used all-oral regimen.

This seismic shift in HCV treatment paradigms was immediately captured across multiple ongoing real-world cohorts, and evidence was rapidly developed regarding the safety and effectiveness of this treatment regimen that was routinely being utilized in an “off-label” manner. Between 2014 and 2015, HCV-TARGET enrolled

~1,400 patients treated with simeprevir/sofosbuvir. Sulkowski and colleagues reported the final results of more than 800 genotype 1 patients treated in the HCV-TARGET prospective observational study [26]. The study included treatment-naïve or treatment-experienced, cirrhotic and non-cirrhotic patients. Overall SVR was 88% and was higher in non-cirrhotic vs cirrhotic patients (94% vs 84%, respectively). The regimen was also demonstrated to be safe with only 2% discontinuing treatment prematurely due to adverse events [26]. Several other real-world cohorts provided additional evidence regarding the effectiveness of simeprevir and sofosbuvir [27].

When the manufacturer of simeprevir submitted an efficacy supplement to the FDA to support the use of this combination based on the prior phase 2 results, the sponsor also included a robust dossier of safety and effectiveness data from HCV-TARGET in support of this application, which was ultimately approved [12]. Interestingly, the HCV-TARGET results that had been generated in real-world settings were comparable to subsequent phase 3 confirmatory trials generated by the sponsor to fulfill specific post-marketing commitments [12, 28, 29].

8 RWE Confirms Safety and Effectiveness of DAA Regimens

In late 2014, a single tablet regimen, ledipasvir/sofosbuvir, was approved for treatment of HCV based on the remarkable results of several phase 3 trials. In treatment-naïve patients, SVR rates ranged from 97–99% to 94–99% in treatment-experienced patients [1, 2]. Moreover, efficacy was demonstrated across a wide spectrum of patients who previously had lower response rates with interferon-based medications, such as those with cirrhosis and African American patients. With nearly 1,300 patients enrolled, confidence intervals for most subpopulations were quite small with rare exceptions. However, only 181 patients with cirrhosis were included which comprised approximately 14% of the study population (in contrast to a 40–50% prevalence of cirrhosis in patients being treated in real-world cohorts) [1, 2].

Numerous real-world cohorts quickly augmented, and largely confirmed, the results of these phase 3 clinical trials (Table 1). Sustained virological response rates in a per protocol analysis for patients with cirrhosis treated with ledipasvir/sofosbuvir were 94% in the HCV-TARGET study ($n = 677$) and 92% in the TRIO cohort [18, 39]. Similar results were obtained from the Veterans Administration cohort and a large number of international cohorts [30, 40]. In an ongoing study from the German Hepatitis C Registry, 93/96 patients (97%) treated with glecaprevir/pibrentasvir, one of the newest DAA regimens, achieved SVR without any virological failures reinforcing the real-world effectiveness of this regimen [41].

In addition to safety and efficacy, RWE has subsequently shown improved clinical outcomes from DAA therapy in cirrhotic HCV-infected patients. In a comparison between 6,460 patients who received DAA vs 2,835 who did not receive a DAA, DAA use was associated with a decrease in deaths (HR 0.65; more pronounced for liver-related deaths) and no increased risk of HCC and hepatic

Table 1 Efficacy of DAA regimens in real-world cohorts (from [30])

Cohort (ref)	Regimen	No. of patients (treatment-naive/ treatment-experienced/ cirrhosis)	SVR treatment naïve (%)	SVR treatment experienced (%)	SVR cirrhosis (%)
Genotype 1 patients					
Target [31]					
	LDV/SOF 8 weeks	154/–/–	97	NR	NR
	LDV/SOF 12 weeks	627/–/239	97	NA	96
Trio [32, 33]					
	LDV/SOF 8 weeks	263/–/–	95	NR	NR
	LDV/SOF 12 weeks	632/–/121	95	NA	84
	LDV/SOF 24 weeks	–/–/329	NA	NA	92
VA [7]					
	LDV/SOF 8 weeks	2,027/–/–	94	NR	NR
	LDV/SOF 12 weeks	2,899/933/925	95	96	92
	LDV/SOF 24 weeks	141/479/473	92	95	93
Hepather [34]					
	SOF/ DCV ± RBV 12 weeks	66/82/118	89	91	90
	SOF/ DCV ± RBV 24 weeks	59/349/442	88	97	96
HCV Research UK Registry/Expended Access Program [12]					
	SOF/DCV/ RBV 12 weeks	–/–/30	NA	NA	88
	LOV/ SOF + RBV 12 weeks	–/–/136	NA	NA	91
Israel Cohort [35]					
	PrOD ± RBV	–/–/253	NA	NA	99
German Cohort Register [36]					
	PrOD ± RBV	208/322/252	96	97	95
Genotype 2 or 3 patients					
Target G2 [37]					
	SOF/RBV 12–16 weeks	198/97/80	89	84	80

(continued)

Table 1 (continued)

Cohort (ref)	Regimen	No. of patients (treatment-naive/ treatment-experienced/ cirrhosis)	SVR treatment naïve (%)	SVR treatment experienced (%)	SVR cirrhosis (%)
VA G2 [7]					
	SOF/RBV 12 weeks	1,910	88	80	77
VA G3 [7]					
	SOF/RBV 24 weeks	630	75	61	62
	LDV/ SOF + RBV 12 weeks	344	78	77	65
French multicenter compassionate use program G3 [38]					
	SOF/ DCV ± RBV 12 weeks	–/–/37	NA	NA	73
	SOF/ DCV ± RBV 24 weeks	–/–/183	NA	NA	85
HCV Research UK Registry/Expended Access Program genotype 3 [12]					
	SOF/ DCV + RBV 12 weeks	–/–/75	NA	NA	71
	LDV/ SOF + RBV 12 weeks	–/–/37	NA	NA	65

decompensation [42]. The US Veterans Affairs Healthcare System analysis of 62,354 patients who initiated antiviral therapy found that SVR was associated with significantly decreased HCC risk in multivariable models, irrespective as to whether the antiviral treatment was IFN-based (HR 0.32) or IFN-free (HR 0.29) [43].

9 RWE Reassures and Refines Criteria for Shortened Treatment Duration

The ION-3 trial of ledipasvir/sofosbuvir randomized treatment-naïve, non-cirrhotic patients to either standard 12 weeks of treatment or an abbreviated 8-week regimen [44]. SVR rates were similar for both groups 93% with 8 weeks of treatment and 95% with 12 weeks of treatment [44]. Post hoc analysis completed by FDA and study sponsors demonstrated that the relapse rate varied by the pretreatment level of HCV RNA. Among those with HCV RNA <6 million IU, the relapse rate was 2% in

both the 12-week and 8-week treatment arms. However, for patients with HCV RNA >6 million IU at the start of treatment, the relapse rate was 1% for those treated with 12 weeks duration but increased substantially to 10% for those treated with the shortened 8-week regimen [12]. Thus, the initial label for ledipasvir/sofosbuvir included the following language: "LDV/SOF for 8 weeks can be ***considered*** in treatment-naïve genotype 1 patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL."

Despite the remarkable effectiveness in both arms of the study and the relapse rate that could be mitigated by stratifying by viral load, clinicians remained concerned that the body of evidence was insufficient and that some patients would be disadvantaged by a shorter treatment duration. Payers, already balking at the high cost of this medication at the time of its introduction, usually *mandated* that patients who met the above criteria be treated for 8 weeks rather than 12 weeks as a cost-saving measure [12]. Clinicians countered that in the absence of any compelling safety signal shortening treatment duration was unnecessary. These competing interests, cost vs perceived optimized patient care, created great tension and clinicians regularly appealed denials for 12 weeks duration of therapy (M. Fried, personal communication).

Real-world evidence helped to reassure clinicians that patients could be considered for 8 weeks of treatment without sacrificing outcomes. Terrault and colleagues in HCV-TARGET analyzed patients who met the criteria for 8 weeks of treatment but received either 8 or 12 weeks based on patient choice, physician choice, or payer factors. Among 586 patients who *qualified* for 8 weeks of therapy (treatment-naïve, non-cirrhotic, with baseline HCV RNA <6 million IU) but *actually received either* 8 weeks or 12 weeks of treatment, SVR was 96% and 98%, respectively, further instilling confidence in the abbreviated regimen [39]. A similar analysis in the TRIO cohort demonstrated that 98% (95% CI 96.8–99.1) of patients treated with 8 weeks of ledipasvir/sofosbuvir achieved SVR, which was further supported by an accompanying meta-analysis.

The VA cohort further refined the criteria for shortening therapy with the ledipasvir/sofosbuvir regimen. Overall sustained virological response rates for patients treated with a variety of all-oral DDA regimens generally paralleled those in registration trials [40]. Furthermore, no significant difference was found between white and black patients treated with these regimens [45]. However, African American patients treated for 8 weeks with LDV/SOF had lower SVR (93%) compared to whites with the same baseline characteristics (96%). This suggestion that African American patients may be disadvantaged by a shorter duration of therapy was adopted by the HCVguidelines.org who recommended against the abbreviated regimen for African American patients.

10 RWE Characterizes Impact of Proton Pump Inhibitors on Outcomes

Phase 1 studies of ledipasvir indicated that bioavailability was reduced during coadministration with H2 blockers and proton pump inhibitors (ledipasvir has a pH-dependent solubility whereby it is essentially insoluble when pH $\geq$ 4) and original US labeling for ledipasvir/sofosbuvir suggested limiting exposure to concurrent acid-reducing agents during the course of therapy [46]. It was unknown whether this interaction was a clinically significant effect in light of the stellar cure rates in most patients treated with these agents in phase 3 trials where exposure to acid-reducing medications had been limited. Terrault and colleagues performed the most detailed investigation of this issue in over 1,700 patients treated with LDV/SOF regimen. The unadjusted SVR was modestly lower in patients who took PPIs (94%) compared to those who did not take PPIs (97%) [39]. It was recognized that numerous factors besides PPI use could impact SVR in this nonrandomized real-world cohort and, therefore, a rigorous secondary analysis incorporating inverse probability weighting was performed. Despite very few overall failures, any PPI use, PPI use at beginning of therapy, PPI use >20 mg daily, as well as twice daily PPI use remained significantly associated with treatment failure [39]. A similar analysis in the TRIO cohort confirmed that high-dose PPI was associated with lower SVR, although lower doses of PPI did not impact treatment response [47].

11 RWE Contributes to Safety and Efficacy Profile of DAAs in Unique Populations

As reported in multiple phase 3 clinical trials, DAAs have outstanding safety profiles, highlighted by treatment discontinuation rate for adverse events below 1% for non-cirrhotic populations [1, 2, 4, 48]. Given this favorable safety profile of DAAs, there has been dramatic expansion of HCV treatment into populations of patients that have been historically underserved by previous interferon-based regimens: chronic kidney disease, liver/kidney transplant, decompensated cirrhosis, and HCV/HIV co-infected patients.

Chronic Kidney Disease The large registration trials of DAAs for HCV infection have generally excluded patients with significant renal impairment, with the exception of glecaprevir-pibrentasvir [49, 50]. Nevertheless, the available evidence suggests that patients with renal impairment can expect a virological response rate to a given regimen similar to that observed in the general population, as long as the regimen is tolerated. In an international cohort study of patients treated with DAA-based regimens in real-world settings, SVR rates were similar, among patients across all eGFR spectrums (<30, 31–45, 46–60, and >60 mL/min per 1.73 m^2) [51]. In an observational VA cohort study of almost 14,000 persons treated with a

ledipasvir-sofosbuvir regimen, SVR for those with stage 3 CKD who completed treatment was 97%, while those with stage 4–5 was 94% [52].

Transplantation HCV is a common comorbidity in patients who have undergone kidney and/or liver transplantation and is associated with increased morbidity and mortality compared with recipients who do not have chronic HCV infection. Recent reports in the literature from clinical trials and real-world cohorts demonstrate that direct-acting antiviral therapies effectively cured HCV liver and kidney transplant recipients (>95%); the majority were treated with sofosbuvir-based regimens [53]. Smaller numbers of transplant recipients have been treated with paritaprevir-ritonavir, ombitasvir and dasabuvir, elbasvir-grazoprevir, or glecaprevir-pibrentasvir with excellent success [54, 55]. DAA therapies were well tolerated and did not increase the rate of acute rejection. For example, the HCV-TARGET cohort study evaluated 347 liver, 60 kidney, and 36 dual liver kidney transplant recipients [56]. Among the 279 participants treated with ledipasvir/sofosbuvir for 12 weeks or 24 weeks, the SVR rates were 97% for those also taking ribavirin and 95% for patients not taking ribavirin. The rate of therapy discontinuation due to an adverse event was 1.3%, highlighting the safety of the drug combination. Acute graft rejection occurred in only 1.4% of patients and serve to remind clinicians of the need to monitor immunosuppressive agent levels during DAA therapy [56].

Decompensated Cirrhosis Clinical trial data indicate that persons with decompensated cirrhosis who receive DAAs have high rates of SVR and that SVR can lead to improvement in clinical and biochemical indicators of liver disease, including patients with CTP class C cirrhosis [57–59]. Both the UK and HCV-TARGET observational cohorts evaluated decompensated cirrhotic patients treated with sofosbuvir/ledipasvir +/− ribavirin and showed high SVR (86–90%) and relatively low rates of treatment-related adverse events [39, 60, 61]. Furthermore, the predictors of improvement or decline in liver disease are now being evaluated in observational cohorts, though patients with Model for End-Stage Liver Disease (MELD) score of >20 or severe portal HTN complications (ascites, encephalopathy) may be less likely to improve and are potentially better served by transplantation than HCV treatment [54, 61].

HIV Coinfection The introduction of DAAs has changed the landscape of therapy for persons with HCV and HIV coinfection. Several studies using DAA-based therapy have demonstrated SVR rates among individuals with HCV-HIV coinfection that are comparable to those with HCV monoinfection, providing convincing evidence that persons with HCV-HIV coinfection no longer require the designation of a "special" population. It should be noted that these trial participants in registration trials included primarily individuals without cirrhosis and those with CD4 counts usually well above 200 cells/mm^3 [62, 63]. Several observational cohort studies have shown comparable clinical efficacy in more heterogeneous cohorts of persons with HCV and HIV coinfection, including those with lower CD4 cell counts [64, 65].

12 Summary

Direct-acting antiviral agents have demonstrated remarkable rates of cure of hepatitis C infection across all patient populations studied in phase 3 clinical trials. Real-world evidence derived from global cohorts evaluating the safety and effectiveness of DAAs in usual clinical practice generally paralleled those impressive results. RWE contributed to optimizing treatment paradigms when gaps in knowledge existed and in expanding utilization to populations underrepresented in registrational trials.

Compliance with Ethical Standards

Conflict of Interest: MWF received research grants to his institution from AbbVie, BMS, Gilead, Merck. He serves as unpaid consultant to AbbVie, BMS, Merck, and TARGET PharmaSolutions. Stock in TARGET PharmaSolutions is held in an independent blind trust.

DRN received research support from AbbVie, BMS, Gilead, and Merck paid to his institution and is a stockholder of TARGET PharmaSolutions.

Ethical Approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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