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Pharmacogenomic Testing in the Era of Patient-Tailored HCV Treatment

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Abstract

Hepatitis C affects approximately 180 million people worldwide, with 3–4 million newly infected each year. Hepatitis C virus (HCV) has been classified into seven different genotype categories, wherein HCV genotype 1 (HCV-1) is the most prevalent. To date, there is still no vaccine available against HCV infection. Until recently, combination therapy of pegylated interferon-a (PegIFN) and ribavirin (RBV) has been the standard of care. Nevertheless, for many patients, particularly those infected with HCV genotype 1 (HCV-1), this treatment has resulted with unsatisfactory treatment response rates and high adverse drug reaction (ADR) rates. Many clinical factors, including pharmacogenetics, influence the treatment response rate. This review focuses on the association between pharmacogenetics and HCV antiviral therapy in patients infected with HCV genotype 1 and other genotypes (GT); patients reinfected with HCV after liver transplantation; and patients coinfected with HCV and human immunodeficiency virus. Data considering triple therapy in HCV-infected patients are also reviewed. Additionally, various genetic polymorphisms, with an emphasis to IL-28B, and their association with pharmacogenetic testing in HCV are discussed.

Keywords: hepatitis C virus, pharmacogenetics, pegylated interferon and ribavirin, direct-acting antiviral agents, genetic polymorphisms, IL-28B, ITPA

1. Introduction

1.1. Clinical background of HCV infection

Infection with hepatitis C virus (HCV), an enveloped single-stranded RNA virus of the *Flaviviridae* family, affects over 2% of the worldwide population and it is estimated that the number of people with a chronic HCV infection is over 180 million, representing an

important public health issue [1, 2]. Epidemiological studies have shown that 46.2% of all hepatitis C cases are caused by HCV GT1, making GT1 the most prevalent genotype [3]. Even though most of the patients initially do not experience any symptoms, about 75% are not able to spontaneously clear the virus from the organism, and develop a chronic HCV infection [4]. HCV causes progressive liver injury in those patients, which in approximately 16% progress to liver cirrhosis and ultimately in 1–5%, within two decades from acute infection, to hepatocellular carcinoma. Therefore, HCV infection is one of the most common reasons for liver failure and an indication for liver transplantation procedures worldwide [5–7]. HCV has been classified into seven different genotype categories, having nucleotide differences of greater than 30% among genotypes (GT). Due to that fact, the task to produce pan-genotypic drugs has been very demanding [8]. Accordingly, the response of HCV infection to treatment regimens and its duration can vary depending on viral genotype [9].

1.2. Changes in the HCV treatment goals and HCV treatment timeline development

The search for optimal hepatitis C treatment has been ongoing even before the HCV had been cloned in 1989 [10, 11]. The ultimate goal of every standard-of-care treatment from that point in history was the cure of hepatitis C, in particular, the removal of the virus from the organism and prevention of further liver damage due to HCV. A patient is considered to be cured when sustained virological response (SVR) is reached, defined as undetectable HCV RNA viral load 24 or 12 weeks post-therapy [12, 13]. Formerly, SVR had been determined 6 months (24 weeks) after completion of treatment with interferon-cased therapy. However, with direct-acting agents, that are so much more potent, it has been shown that the viral clearance can be assessed 12 weeks after therapy. Thus, SVR12 is the currently advised standard [14, 15]. At the time when interferon (IFN)-α was approved as the first anti-HCV drug in the SVR, it was only achieved in 2–7% of treated patients [16]. The addition of ribavirin (RBV) and the later change of IFN-α to its pegylated form (PegIFN (pegylated interferon-a)) in the therapeutic regimen increased the SVR marginally. Even though the dual therapy containing PegIFN-RBV showed to be a considerably effective treatment for patients who were infected with HCV GT2 or GT3, achieving SVR in up to 80% of the treated patients, the success in curing patients infected with HCV GT1 was still izbaciti R skroz below 50% despite treatment prolongation up to 72 weeks [17, 18]. Also, many treated patients suffered from severe and potentially life threatening adverse drug reactions (ADRs) such as influenza-like syndrome, anemia, leukopenia, thrombocytopenia, depression, concentration issues, gastrointestinal ADRs, etc., which often led to preterm therapy dismissal [19]. Consequently, there was a great need to develop novel targeted drugs, with higher efficacy and fewer ADRs. In order to develop such drugs, scientific progress in the fields of virology, molecular biology, and biochemistry and an understanding of the individual steps in the HCV replication cycle had to be determined. This led to the discovery of contributing viral proteins such as NS3/4A protease, NS5A polymerase, and NS5B replication complex as possible therapeutic targets [20]. The development of ciluprevir (Biln 2061), the first NS3 protease inhibitor (PI), in 2002 was the first attempt to develop direct-acting antivirals (DAA) and influence the HCV replication
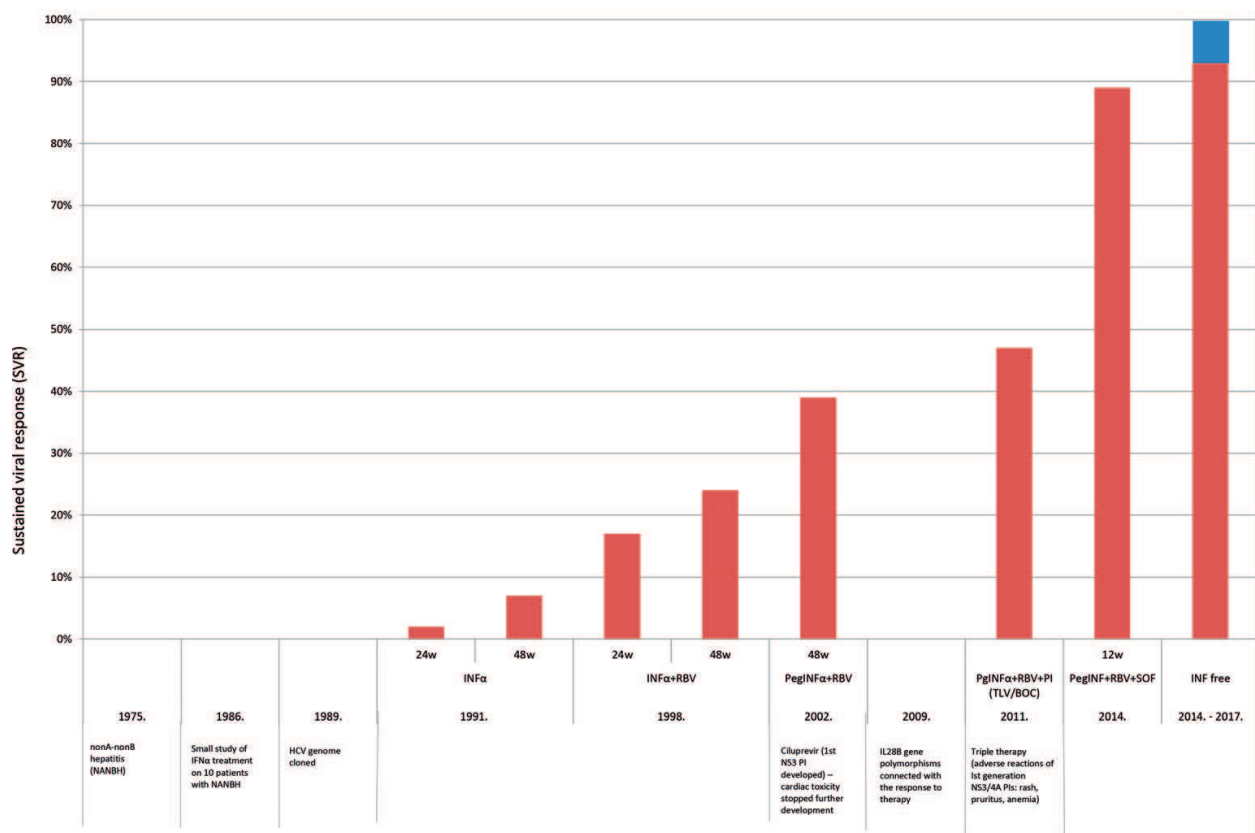
Figure 1. Timeline of discoveries in the history of HCV and the dynamics of SVR through time depending on the standard-of-care treatment. SVR rates did improve greatly since 1991, when IFN-α got approved as the first drug for patients with hepatitis C. Nowadays, the therapy with DAAs made chronic hepatitis C a curable disease with SVR rates over 93%.

cycle (**Figure 1**). Even though ciluprevir was found to perform rapid antiviral activity, the clinical trials had to be discontinued due to cardiac toxicity and this drug was never approved for use [21–23]. Telaprevir (TLV) and boceprevir (BOC) were approved in combination with PegIFN and ribavirin (RBV) for the treatment of HCV GT1 infections by the FDA in May 2011. These were the first DAAs to reach the market [24–26]. Whereas, the so-called triple therapy, containing one of the two NS3/4A inhibitors TLV or BOC with PegIFN and RBV, markedly increased the number of patients with HCV GT1 infections achieving SVR in >70%, severe ADRs often led to discontinuation of therapy [27–29]. Indeed, since the triple therapy also involved PegIFN and RBV, some adverse effects induced by those drugs were persistent compared with the previous treatment regimen. However, the addition of NS3/4A protease inhibitor (PI) not only intensified some of the IFN-induced ADRs such as anemia, but also led to novel side effects like skin rashes, gastrointestinal disorders and dysgeusia [18, 30]. In November 2013, simeprevir (SMV), as a second generation NS3/4A inhibitor was approved by the FDA, which contrary to prior developed drugs in this class, was more convenient regarding dosing and had fewer ADRs [31, 32]. Subsequently, the first HCV NS5B polymerase inhibitor sofosbuvir (SOF) was approved. The combination of SOF with PegIFN and RBV shortened the treatment to 12 weeks and achieved SVR in 90% of the treated patients [33].

Finally, in 2014, a great step forward was made regarding pharmacotherapy of HCV-infected patients by the approval of first all-oral IFN-free regimens. The first IFN-free regimens, 3D-combination dasabuvir (DSV) plus ombitasvir (OBV) plus paritaprevir/ritonavir (PTV/r) +/− RBV (whereby OBV has been the first approved drug in the class of NS5A inhibitors), as well as ledipasvir (LDV) plus sofosbuvir (SOF were marketed in 2014 [34, 35]. Moreover, in July 2015, daclatasvir (DCL) and the fixed combination of OBV plus paritaprevir plus ritonavir became FDA approved, followed by elbasvir plus grazoprevir as well as velpatasvir plus sofosbuvir in 2016 [36–39]. Presently, as a result of IFN-free DAA treatment regimens, 92–100% of treatment naïve patients infected with HCV GT1 achieve SVR [40]. Provided that with IFN-free treatments shortage of therapy duration, improvements in efficacy and fewer ADRs are possible, the prospect of HCV eradication became a real opportunity rather than an unachievable goal [41]. However, the extremely high costs of IFN-free regimens combined with limited healthcare resources hinder accessibility of this valuable therapy worldwide.

2. Pharmacogenetic testing

During the past decades, much effort has been applied toward improvement of the safety and efficiency of drugs used for the treatment of many diseases, including hepatitis C. Adverse drug reactions (ADRs) are a significant cause of morbidity and mortality in patients. However, existing evidence considering individualization of pharmacotherapeutic regimens based on the patient genetic information indicate that ADRs could be at least partially overcome by the application of pharmacogenetics and pharmacogenomics. Pharmacogenetics is a scientific field for studying differences in drug response and the occurrence of adverse drug reactions due to the genetic impact of variations in individual genes, whereas pharmacogenomics studies the impact of the whole genome on drug response, nowadays using genome-wide association studies (GWAS) as successful tools [42–44].

Pharmacogenomics is a rapidly emerging and promising scientific field, used to improve drug safety by avoiding specific drugs to susceptible individuals who are likely to develop ADRs [45]. Although there are still challenges remaining, with the improvement of study designs and the establishment of international cooperation pharmacogenomic study results could be validated and pharmacogenetic testing could become a clinical reality [45, 46]. Additional studies with even more participants are likely to yield results in the near future, which could enhance the number of clinical implementations of pharmacogenetic test results and make another step toward personalized medicine [46]. The cost-effectiveness of drugs is likely to improve by the implementation of pharmacogenomic tests, since the drugs should be used only to treat patients expected to experience a satisfactory therapeutic effect, with minimal risk for morbidity and mortality [47–50]. Furthermore, it is of enormous significance to educate clinicians on data interpretation of pharmacogenetic test results, so that they could gain the required knowledge to accurately stratify patients into high risk or low risk groups regarding drug toxicity. Consequently, therapeutic outcome would be improved without putting susceptible patients at risk of predictable life threatening ADRs. Therefore, new user-friendly and up-to-date guidelines should be made for clinicians, which could help the future implementation of pharmacogenomic study results into the clinical daily routine [45, 51–53].

3. HCV pharmacogenetic testing in the IFN era

As previously mentioned, combination of PegIFN and RBV had been the standard-of-care for patients with chronic hepatitis C for more than a decade [9]. Notwithstanding, many patients still did not respond to therapy and could not achieve SVR or developed adverse events [54]. It has been noticed that many clinical factors, including pharmacogenetics, could influence the treatment response rate [9]. Both virological factors (such as HCV genotype, quasispecies diversity, and baseline viremia) and host factors (age, gender, race-ethnicity, fibrosis stage, obesity, hepatic steatosis, low-density lipoprotein cholesterol, insulin resistance, and genetic variances) played an important role in predicting the natural course of hepatitis C and IFN response to therapy [7, 55–57]. Pharmacogenetic testing could play very important role in optimizing HCV therapy by identifying variations in response to treatment, considering ethnic variations in response to therapy, enlightening the molecular mechanism of current and future therapies, and advancement of innovative genetic tools that will enable physicians to individualize drug therapy, adjust dosages, and reduce the possibility of adverse drug reactions and therapeutic costs (**Table 1**) [54, 58]. Over 40 genes have been linked to modulation of anti-HCV therapy affecting either adverse drug events or response to treatment [59, 60].

Genetic polymorphism	Mechanism of action	Favorable genotypes	Use in predicting treatment outcomes	Use in predicting adverse drug events
IL28B rs8099917 IL28B rs12979860	Triggers JAK-STAT pathway and activates ISG	rs8099917 TT rs12979860 CC	HCV 1, HCV 4 infection, liver transplantation, HIV-HCV coinfection	NO
ITPA rs1127354 ITPA rs7270101	Reduced ITPA activity advances the accumulation of ITP in erythrocytes, reduces ATP depletion and protects against hemolytic anemia caused by RBV	rs1127354 AA/AC rs7270101 CC/CA	NO	HCV 1 infection, HIV-HCV coinfection
G protein b3 unit (GNB3) C825T	Transmits signals via the G protein-coupled receptors, consequently advancing immune response	rs5443 TT	HIV-HCV coinfection	NO
LDLR rs14158	Decreases HCV entry into hepatocytes	rs14158 CC rs12979860 CC	HCV-1 infection, HIV-HCV coinfection	NO
CTLA4 A49G	Decreases suppression of T-cell proliferation, adjusts the threshold of T-cell activation	rs231775 GG	HCV-1 infection, HIV-HCV coinfection	NO
IL 6* C174G	Involved in liver regeneration and in protection against hepatic injury	rs1800795 GG	HCV-1 infection, HIV-HCV coinfection	NO

Abbreviations: IL28B, interleukin 28B; ITPA, inosinetriphosphatase; LDLR, low-density lipoprotein receptor; CTLA, cytotoxic lymphocyte antigen 4; IL 6, interleukin 6.

Note: Data for IL28B from Kamal [54], for ITPA, G protein b3 unit, LDLR, CTLA4 and for IL 6 from Kawaguchi-Suzuki and Fyre [9].

Table 1. Most important host genetic polymorphisms associated with HCV pharmacogenetic testing in the IFN era.

3.1. IL 28B polymorphisms in prediction of HCV infection treatment outcome

IL 28B gene belongs to the type III IFN family named IFN-λ located on the human chromosome 19, and corresponds to IFN-λ3 [7]. Viral infection induces the corresponding cytokines and their antiviral activity is mediated by triggering JAK–STAT pathway [61–63]. ISGs (interferon stimulated genes), which are known to cause apoptosis, growth inhibition, and inhibition of viral replication, are activated by JAK–STAT pathway [64].

3.1.1. IL 28B polymorphisms and HCV1 infection

Several GWAS have demonstrated the role of SNPs near the interleukin 28B (IL 28B) gene in predicting PegIFN/RBV treatment outcome and spontaneous clearance of HCV infection [7, 55]. Two bi-allelic SNPs were most strongly associated with favorable response in HCV genotype 1 (HCV-1) infected patients: rs8099917 located 8 kb downstream of the IL28B gene (favorable response TT genotype, and unfavorable GT/GG genotypes) and rs12979860 located 3 kb upstream of the IL28B gene (favorable response CC genotype, and unfavorable CT/TT genotypes) [7]. Other SNPs of IL28B (rs8105790, rs11881222, rs28416813, rs4803219, and rs7248668) have been also identified in HCV genotype 1-infected patients, but they have not yet been strongly associated with the treatment outcome [55]. It has been shown that unfavorable IL28B genotypes expressed higher baseline ISGs levels compared with the favorable genotype, which could indicate an exhaustion of innate immunity prior to treatment in patients with unfavorable IL28B genotype [65–67]. In contrast, rs12979860 CC and rs8099917 TT genotypes were associated with low ISG expression at baseline, which led to greater ISG expression upon IFN treatment and better treatment responses [68]. Differences in the SVR rates were large and clinically significant with a ~2-fold increase in SVR (70–80% vs. 40%) observed in patients carrying the favorable IL28B rs12979860 CC genotype [9]. Independent studies confirmed the association of the IL28B genotype with SVR in various populations from Asia, Europe, and Latin America [9]. The IL28B favorable genotype also indicates an increased likelihood of achieving SVR among a pediatric population [69]. These treatment response findings were confirmed in different populations: HCV GT1 patients, HCV GT4 patients, patients with a recent HCV infection, adults and children with a spontaneous HCV clearance, HCV/HIV co-infected patients and patients with a recurrent HCV infection after orthotopic liver transplantation [7].

3.1.2. IL28B polymorphisms and HCV2/3 infection

Studies have shown different results which relate to association of IL28B SNP and HCV 2/3 genotype infection. Mangia et al. showed that IL28B SNP rs12979860 was significantly associated with SVR to PEG-IFN/ribavirin therapy in chronic HCV genotype 2/3 [70]. Other studies demonstrated that the difference in the SVR rates between the IL28B genotypes was generally smaller in HCV-2/3 infections than in genotype 1 infection, which could indicate that IL28B has less value in predicting SVR in genotype 2 and 3 infections [9]. It is also possible that some studies did not achieve statistical significance because the SVR rates were generally high among patients infected with HCV-2/3 [9].

3.1.3. IL28B polymorphisms and liver transplantation

HCV reinfection after liver transplantation can occur in most patients and had represented the primary reason for death and graft loss in the pre-DAA era [71]. The cause of the reinfection of the new liver is residual HCV, and IL28B genotype was shown to be an important predictor of SVR for liver transplant recipients reinfected with HCV [9]. The rs12979860 CC and rs8099917 TT genotypes of the recipient were notably associated with higher SVR rates, and the same trend was detected with the donor genotype [72]. Although, both donor and recipient IL28B genotypes have been associated with treatment response, it has not yet been confirmed which genotype is the better indicator of SVR, but it is clear that having both genotypes would be most informative [9]. Most of the study participants were infected with HCV-1, with scarce evidence for HCV non-genotype 1 infections [9]. Considering that this is a complicated patient population, other clinical factors should not be ignored while therapeutic decisions are made [9].

3.1.4. IL28B polymorphisms and HIV-HCV coinfection

Several studies have confirmed the association between IL28B genotypes and treatment response in HIV/HCV coinfected patients [9]. rs12979860 CC genotype and rs8099917 TT genotype have been demonstrated as strong predictors of SVR in HIV/HCV coinfection [9, 68]. This association was observed in patients infected with genotype 1 and 4, but less obvious in patients with genotype 2 and 3 [9, 54, 68, 73]. SVR rates were generally higher among HCV-2 or 3-infected patients than those with HCV-1 or 4. Therefore, HCV2/3 genotype itself indicated good response to treatment [9]. Favorable rs12979860 CC genotype was associated with a higher SVR rate in a study of patients coinfected with HIV/HCV-1 or 4, even if patients were previous nonresponders to PegIFN/RBV therapy [73]. IL28B genotypes remained a good indicator of SVR, but they were not proven to affect HIV outcomes [73]. Consequently, IL28B genotypes should be interpreted only for the HCV outcomes, focusing on IFN-based treatment of patients coinfected with HIV/HCV-1 or 4.

3.2. ITPA in prediction of adverse drug reactions

Hemolytic anemia is a very common side effect of RBV-based HCV therapy [9, 55]. In clinical trials, 30% of treatment-naïve patients experienced anemia on PegIFN/RBV therapy, and most likely the major cause of anemia is ribavirin-induced hemolysis [68, 74]. Furthermore, in more than 15% of cases it is a cause of RBV dose reduction or premature discontinuation of RBV therapy, which may have had a deleterious impact on SVR [74, 75]. RBV depletes guanosine triphosphate (GTP) and causes a relative deficiency of ATP in human erythrocytes consequently inhibiting the ATP-dependent oxidative metabolism [7]. Depletion of erythrocyte ATP content leads to oxidative damage to the erythrocyte membranes, consequently causing extravascular hemolysis by the reticuloendothelial system [76–78]. ITPA gene encodes inosine-triphosphatase which is a protein that hydrolyses inosine triphosphate (ITP). A reduced ITPA activity advances the accumulation of ITP in erythrocytes allowing substitution of ITP

for GTP in ATP biosynthesis which reduces ATP depletion and protects against hemolytic anemia [79–82]. Two functional SNPs (rs1127354 and rs7270101) in the ITPA gene, responsible for ITPA deficiency, were identified in two large GWAS [83, 84]. Consequently, the AA/AC$_{rs1127354}$ (for rs1127354, the wild-type and variant alleles are the C and A alleles) protective genotypes, as well as the CC/CA$_{rs7270101}$ (for rs7270101, the A allele is the wild type, and the C allele is the variant) protective genotypes, led to a decrease in hemolytic side effects from RBV therapy of HCV-1 infection [7]. Additionally, various studies showed an association between SNP ITPA and lower rates of clinically significant hemoglobin reduction among HIV/HCV coinfected patients [85–88]. Nevertheless, SNP ITPA does not predict SVR and was not associated to treatment outcomes [89]. However, considering that anemia is one of the main ADRs leading to premature withdrawal of therapy, any marker able to predict the risk of severe anemia before treatment would be of extreme importance [7]. For this purpose, two studies have designed predictions models incorporating *ITPA* genotype along with creatinine clearance, baseline hemoglobin and quantitative hemoglobin decline at week 2 of treatment [90, 91]. Further validation before entering these algorithms into clinical practice is necessary [7].

4. HCV pharmacogenetic testing in the IFN-free era

Since pharmacogenomics played a very important role in the era of IFN-based therapy, questions arose as to whether pharmacogenomic markers would still have a meaningful place in IFN-free treatment regimens involving DAA +/− ribavirin. Even though some studies suggested that HCV patients with the IL28B TT genotype had reduced therapeutic efficacy of some DAA regimens, IL28B genotyping did lose importance in the IFN-free era [15, 29, 92]. Furthermore, in African-American patients infected with HCV GT1a, ribavirin is recommended to be added to ombitasvir plus paritaprevir/ritonavir or dasabuvir treatment regimens to improve cure rates [93]. Even though IL28B is not as important for IFN-free treatments as it was before, genotyping is still being routinely performed in some countries in order to identify patients likely to be cured with older drugs at significantly lower cost.

While new, effective, and well-tolerated drugs with fewer ADRs and minimal monitoring requirements are on the market, the high treatment price is reducing accessibility, leading to compromises in the price-effectiveness area. The high cost of IFN-free treatment regimens leads to a resource-guided therapy assessment in countries with a lower national affordability for expensive DAAs [94]. The reason for further IL28B genotype determination in the era of available IFN-free treatments lies in the fact that patients with the interferon-favorable CC allele combination achieve SVR in 70–80% when treated with PegIFN plus ribavirin, which makes this treatment regimen only a relatively acceptable alternative for those patients in countries with deficient resources for new and expensive treatments [9, 94]. While in high-income countries like the USA as well as in most Northern and Western European countries, IFN-free treatments became first-line therapy for all patients with

chronic HCV infections, in lower- or middle-income countries, which represent around 85% of the HCV related global health burden. This is still inaccessible for socioeconomic reasons [95–97]. In resource-limited countries, treatment naïve patients with IL28B CC allele, a viral load below 400,000–800,000 IU/ml and a low stage liver fibrosis (F1 and F2), are considered as good responders to a 24-week IFN-based therapy with SVR rates up to 80%with PegIFN plus ribavirin treatment [94, 95, 97]. However, even though patients with IL28B non-CC allele or a higher viral load are not considered easy-to-cure, the initial therapy in Croatia is PegIFN plus ribavirin for patients suffering from low stage liver fibrosis (F1 or F2), with a treatment duration of 24–48 weeks if rapid virological response (RVR, defined as not detectable HCV RNA 4 weeks after treatment start) is achieved [98, 99]. In patients where RVR is not achieved, simeprevir or sofosbuvir are added to the treatment [98]. However, priority for obtaining IFN-free treatment for treatment naïve patients is accessed by evaluation of the liver fibrosis stage according to Metavir classification (whereas, F3 and F4 stages as well as decompensated liver cirrhosis, where contraindications for IFN-based regimens exist, are being prioritized for DAA treatments). Also, patients with greater risk for disease progression, with the existence of extrahepatic manifestations of the HCV infection, those who are at higher risk of viral transmission, with a presence of HIV-HCV coinfection or in the case of prior liver transplantation should be receive priority [98, 100]. However, for socioeconomic reasons, patients with liver fibrosis stages F1, F2, or F3 with relapse or only partial response to previous therapy are being treated with PegIFN plus ribavirin plus sofosbuvir/simeprevir in Croatia [98].

5. Conclusion

We have witnessed remarkable improvement in HCV therapy options, resulting from cutting-edge discoveries. Treatment of HCV infection has been challenging since 1989, when HCV was first discovered and published [101]. After approval of interferon in 1992, great progress has been made. Consequently, many drugs have been introduced to clinical practice for HCV therapy [101]. In the late 2000s, another class of drugs, DAAs, was approved for use in combination therapy [101]. DAAs have been shown to be very effective HCV therapy, with high SVR rates and enhanced treatment safety. Nevertheless, barriers still remain in making these therapies accessible worldwide. Drug pricing, screening and disease assessment, and public health prioritization represent the biggest issues associated with DAAs treatment accessibility [102, 103]. Development of pharmacogenetic testing in the IFN-ribavirin era has been remarkable, leading to the discovery of various genetic polymorphisms associated with treatment outcome predictions. Although application of pharmacogenetic testing in IFN-free DAA era has been doubtful, it could play an important role in concept of "resource-guided therapy," where peginterferon/ribavirin might be applied for easy-to-treat interferon-eligible patients in resource-constrained areas [94]. Although treatment efficacy of HCV infection has increased dramatically, the goal of making the therapy available to everyone in need remains a major challenge.

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