Drug Resistance Updates 16 (2013) 60–67

Contents lists available at ScienceDirect

Drug Resistance Updates

journal homepage: www.elsevier.com/locate/drup

Review

Containing "The Great Houdini" of viruses: Combining direct acting antivirals with the host immune response for the treatment of chronic hepatitis C

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ARTICLE INFO

Article history:
Received 10 January 2013
Accepted 6 March 2013

Keywords:
Therapeutic vaccine
HCV
DNA vaccine
Electroporation
T cell

ABSTRACT

Presently the development of new therapies for hepatitis C virus (HCV) is rapidly moving forward. Almost every week new data appear on how direct acting antivirals (DAAs) succeed or fail in clinical trials. Despite the potency of many of the DAA combinations, the effect exerted by ribavirin (RBV) is still needed for an effective therapy in many new DAA combinations. Due to the strong antiviral effect of DAAs, it is likely that a major complementary therapeutic effect exerted by RBV is immune modulation resulting in an increased barrier to development of resistance. For HCV genotype 1a infections elimination of pegylated interferon, is not possible in many DAA combinations without jeopardizing the results. The host immune response is thus likely to play a key role even during DAA-based therapies. Hence, T cells may recognize and eliminate viral variants with resistance to the DAAs. We herein show several examples where this may be the case, supporting the rationale of including the host response also in the new therapeutic regimens. This review will describe the potential benefits of combining various DAAs with means to activate the specific immune response against HCV.

Contents

1. Introduction

The development of therapies for chronic infections caused by the hepatitis C virus (HCV) has exploded in the past five years with the introduction of direct acting antiviral (DAA) compounds

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1368-7646/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.drup.2013.06.001

(Hofmann and Zeuzem, 2011; Welsch et al., 2012). Pegylated interferon alpha 2a, or 2b (IFN) and ribavirin (RBV) is presently still used as a backbone when combined with the 1st generations protease inhibitors (PIs) against HCV (McHutchison et al., 2009). The efficiency of the combination is dependent on the host IL-28B genotype (CC, CT, or TT), the viral genotype (gt) 1–6, and the viral load (Ge et al., 2009). The IL-28B genotype also predicts the chance to achieve spontaneous resolution of an acute HCV infection (Thomas et al., 2009). By using baseline factors a prediction of sustained viral response (SVR) can be done with moderate accuracy. In addition, the kinetics of the early viral kinetics during therapy has been found very useful for the prediction of SVR and has generated stopping rules during therapy when a low probability for eventual final cure is at hand (Sherman et al., 2011). This reduces overtreatment and unnecessary treatment and reduces the cost and adverse events in patients who will have a low chance to achieve SVR and hence be taken off therapy.

IFN/RBV treatment does not cause emergence of viral resistance and the mechanisms for non-response to IFN/RBV is poorly understood. Viral strains which do not respond to IFN therapy with an at least 2 log decline during the initial 12 weeks treatment could be defined as resistant to IFN/RBV and are defined as null responders (Wedemeyer et al., 2012a). No specific mutations have been associated with such resistance. However, identification of an interferon sensitivity-determining region (ISDR) has been published in Japanese patients (Enomoto et al., 1996). With respect to RBV no specific viral genotype or phenotype resistance has been identified.

This strongly contrasts to what is seen with the direct acting antivirals (DAAs; Fig. 1), where resistance mutations are readily detected in the target protein, which explain the lack of efficacy once they occur (Welsch et al., 2012). Identification of viral resistance mutations, hence, can be expected to play a role during monitoring of treatment with new DAA-based combination therapies. New treatment strategies with combination of several DAA compounds targeting different regions of HCV will be used to overcome emergence of resistance if such combinations will be sufficient or if addition of immune modulating therapies will be needed in difficult to treat patients remains to be explored (Figs. 2 and 3).

1.1. The mechanisms of action of IFN and RBV

After having acknowledged that the combination of IFN and RBV can cure around 50% of the patients with chronic genotype 1 (gt1) HCV infection and some 80% of genotype non-1 infections, the question arises how these drugs act on the infected cell. With respect to IFNα, it is well known that it binds to the IFNα/β receptor (IFNAR), which is composed of the two subunits IFNAR1 and IFNAR2, constitutively expressed on the surface of many cells including hepatocytes. The binding of IFNα to its receptor results in the activation of the Janus kinases Jak1 and Tyk2, which phosphorylate signal transducer and activator of transcription (STAT) 1 and 2. STAT1 and 2 form a complex with the IFN-regulatory factor 9 (IRF9), which binds to IFN-stimulated response elements (ISRE) on DNA leading to the expression of several hundred genes named IFN-stimulated genes (ISGs). These ISGs have a variety of antiviral, antiproliferative and immunomodulatory effects. Some of them such as the protein kinase R (PKR) or the 2′–5′oligoadenylate synthetase (OAS) directly inhibit viral transcription and translation and, thus, reduce virus replication, and others act by strengthening the antiviral immune response. Hence, IFNα is known to be involved in the induction of T cell proliferation, the activation of NK cells, the maturation of dendritic cells and the prevention of T cell apoptosis (Pitha and Kunzi, 2007).

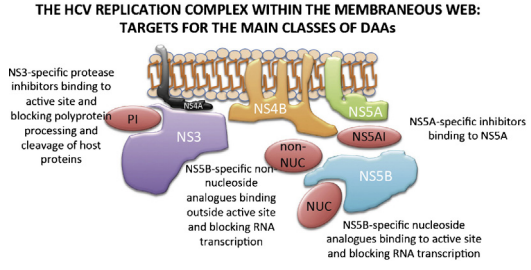

Fig. 1. Description of the functions of the non-structural HCV proteins and how the different classes of DAAs interacts with these.

Successful IFNα treatment is characterized by two phases (Neumann et al., 1998). In the first phase, a rapid decline of the viral load is believed to be caused by a direct antiviral effect exerted by IFN (Neumann et al., 1998). The antiviral effect is mediated by ISGs such as the PKR or the 2′–5′ OAS, which reduce the viral replication by directly inhibiting viral transcription and translation. The second, and slower viral decline phase is thought to be immune mediated by the IFN/RBV stimulation of innate and adaptive immune system. IFNα is e.g. known to be involved in the induction of T cell proliferation and cytotoxicity (Le Bon et al., 2006a,b), the activation of NK cells (Trinchieri and Santoli, 1978), the maturation of dendritic cells (Le Bon et al., 2001) and the augmentation of B cell responses (Le Bon et al., 2001; Badr et al., 2010).

RBV on the other hand has a much less well characterized effect on the infected cell. Several direct or indirect mechanisms have been proposed. RBV is well known to deplete the cell of the guanosine tri-phosphate (GTP) necessary for viral RNA synthesis by blocking the enzyme inosine-5′-monophosphate dehydrogenase (IMPDH) (Malinoski and Stollar, 1981). Furthermore, RBV has been proposed to act as an inhibitor of the RNA-dependent RNA polymerase (Maag et al., 2001), and as a mutagen causing an error catastrophe (Crotty et al., 2000). The high concentrations needed for RBV to act as a direct antiviral agent causes major adverse events and cannot be used in practice, and are difficult to reach in vivo (Zoulim et al., 1998). Hence, the effect of ribavirin during HCV therapy is likely to be immune modulatory e.g. by altering the Th1/Th2 balance towards an antiviral Th1 response (Hultgren et al., 1998; Ning et al., 1998), or by inducing the expression of ISGs (Liu et al., 2007; Zhang et al., 2003). Even today when using new highly potent DAA drugs RBV seems to be needed as a complement to increase the efficacy via a presumed immune modulatory effect which is not provided by the current DAAs.

It is important to note that the most refractory patients to IFN/RBV combination therapy are those with ISG already switched on (Sarasin-Filipowicz et al., 2008). The continuous activation of ISGs by intracellular HCV RNA in these patients is not sufficient to clear the virus but results in an upregulation of negative regulators in the Jak-STAT pathway such as protein inhibitor of activated STAT (PIAS) 1 and suppressor of cytokine signalling (SOCS) 3 causing a decrease in the sensitivity to IFNα. Patients lacking an ongoing IFN response before therapy, who do not have upregulated ISGs, will have a strong ISG induction and activation of an intrahepatic IFN necessary for the treatment to be effective.

An important finding linking the host immune response to treatment outcome was the identification of the IL-28B (IFNλ3) single nucleotide polymorphisms (SNPs) (Ge et al., 2009; Suppiah et al., 2009; Tanaka et al., 2009). It was shown that patients with genotype (rs12979860 CC or rs8099917 TT) had much higher SVR rates than patients lacking this polymorphism. Interestingly, hepatic ISG expression before treatment was initiated was found to be significantly lower in patients with the favourable IL28B genotype (Honda et al., 2010). IFN/RBV combination therapy in these patients resulted in a strong ISG induction and a better treatment response with higher SVR rates.