Best Practice & Research Clinical Gastroenterology 26 (2012) 413–427

Contents lists available at SciVerse ScienceDirect

Best Practice & Research Clinical Gastroenterology

5

The role of viral and host genetics in natural history and treatment of chronic HCV infection

Joseph S. Doyle, MBBS BA(Hons) MSc FRACP, Infectious Diseases Physician and NHMRC Research Scholar [a,b,c,*], Margaret E. Hellard, MBBS PhD FRACP FAFPHM, Professor [a,b,c,1], Alexander J. Thompson, MBBS PhD FRACP, Hepatologist and Senior Research Fellow [d,e,f,2]

[a] *Centre for Population Health, Burnet Institute, 85 Commercial Road, Melbourne, VIC 3004, Australia*
[b] *Infectious Diseases Unit, The Alfred Hospital, Melbourne, VIC, Australia*
[c] *Department of Epidemiology and Preventative Medicine, Monash University, Melbourne, VIC, Australia*
[d] *Department of Gastroenterology and Hepatology, St Vincent's Hospital, 41 Victoria Parade, Melbourne, VIC 3065, Australia*
[e] *Victorian Infectious Diseases Reference Laboratory, Melbourne, VIC, Australia*
[f] *Duke Clinical Research Institute and Department of Gastroenterology, Duke University Medical Center, Durham, NC, USA*

Keywords:
Hepatitis C virus
Genetics
Genome-wide association
Natural history
Treatment
IL28B
Single nucleotide polymorphism

A B S T R A C T

Understanding of the natural history and treatment responsiveness of chronic hepatitis C virus (HCV) infection has evolved rapidly in recent years. Advances in HCV molecular virology and host genetics can now better predict spontaneous clearance and treatment outcomes. HCV genotype is the most important viral factor predicting interferon-α treatment responsiveness; HCV-1 subtype is emerging as a key determinant of the efficacy of direct acting antiviral therapy. Genome-wide association studies have recently identified several clinically important host determinants of the outcomes of peginterferon-α and ribavirin treatment outcome: *IL28B* polymorphism is associated with spontaneous clearance and treatment responsiveness; *ITPA* polymorphism protects against ribavirin-induced anaemia and dose reductions; genetic determinants of liver fibrosis progression rate have been proposed. In this review, we evaluate the role of viral

* Corresponding author. Centre for Population Health, Burnet Institute, 85 Commercial Road, Melbourne, VIC 3004, Australia. Tel.: +61 3 8506 2324; fax: +61 3 9282 2100.
E-mail addresses: j.doyle@burnet.edu.au (J.S. Doyle), hellard@burnet.edu.au (M.E. Hellard), alexander.thompson@svhm.org.au (A.J. Thompson).
[1] Tel.: +61 3 8506 2306; fax: +61 3 9282 2100.
[2] Tel.: +61 3 9288 3580; fax: +61 3 9288 3590.

1521-6918/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bpg.2012.09.004

and host genetics in the natural history and treatment outcomes of chronic HCV infection, and consider how this knowledge might help individualize clinical management in the era of DAA therapy.
© 2012 Elsevier Ltd. All rights reserved.

Background

Between 130 and 170 million people are infected with hepatitis C virus (HCV), and it is the leading cause of liver transplantation globally [1]. The long term sequelae of chronic HCV include chronic liver disease, hepatocellular carcinoma and death, with HCV the second most common cause of liver cancer worldwide [2]. Despite receiving less attention than other blood borne viruses, HCV recently surpassed human immunodeficiency virus (HIV) in terms of attributable deaths in the United States [3].

20–30% of individuals acutely infected with HCV will spontaneously clear the virus, with the remaining 70–80% developing persistent HCV infection [4]. Complex host–viral interactions largely determine the outcome of acute HCV infection [5,6]. HCV infection can be treated in the acute stage with good success, and 70–90% of adherent patients treated with pegylated interferon-alpha (PEG-IFN) monotherapy will achieve a sustained virological response (SVR) [7]. Unfortunately acute HCV is often asymptomatic and diagnosis is more often delayed until chronic infection is established, and treatment response rates are lower.

PEG-IFN and ribavirin (RBV) had been standard of care therapy for chronic HCV infection for the past decade. PEG-IFN and RBV will cure at best 50% of patients infected with genotype-1 HCV, the predominant HCV strain in Europe and the North America. PEG-IFN and RBV therapy is also associated with considerable toxicity, including neuropsychiatric morbidity, influenza-like symptoms, cytopenias, and rash, and mandating careful patient selection and monitoring [7–10]. The newly licenced directly acting antiviral agents (DAAs), telaprevir and boceprevir, both used in combination with PEG-IFN and RBV can dramatically improve effectiveness and can cure up to 75% of patients chronically infected with genotype-1 HCV. Whilst this represents a significant advance, tolerability remains a clinical issue, due to the ongoing need for PEG-IFN combination, as well as DAA-specific adverse events.

The limited efficacy of PEG-IFN and RBV therapy, combined with the cost and unfavourable toxicity profile, generated much interest in identifying viral and host factors that would predict HCV outcomes. The critical role of HCV sequence was recognized early, and HCV genotype is the strongest predictor of PEG-IFN and RBV response. More recently, advances in sequencing technology have allowed comprehensive interrogation of host determinants of HCV outcome, and genome-wide association studies (GWAS) have identified associations between *IL28B* polymorphism and viral clearance, as well as *ITPA* polymorphism and RBV-anaemia. HCV genotyping is a routine clinical test, and assessment of host IL-28B genotype is increasingly used among HCV genotype-1 infected patients to inform clinical decision making [11,12].

In this review we consider the available literature concerning host and viral determinants of HCV treatment outcome and natural history, and their implications for HCV current clinical practice. We will also consider these biomarkers in the context of the transformative role DAAs will play in shaping HCV treatment algorithms over the next five years.

Genetic influences on treatment response

Several factors have been associated with HCV treatment-mediated clearance. Important predictors of PEG-IFN and RBV response include age, pre-treatment HCV viral load, liver fibrosis and insulin resistance, ethnicity and viral and host genetics [13–15].

Viral genetic factors

HCV genotype and subgroup

HCV viral genotype is a major predictor of HCV treatment response. In treatment naïve individuals, PEG-IFN/RBV results in SVR rates of 40–50% in HCV genotype-1 infection, compared to 75% in

Download English Version:

https://daneshyari.com/en/article/3254194

Download Persian Version:

https://daneshyari.com/article/3254194

Daneshyari.com