Examining the pathological nature of Hepatitis C and current drug therapies used in an Australian general practice context

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Aim: This review aims to examine the pathological nature of Hepatitis C and review current drug therapies relevant to Australian health practitioners. **Methods:** Terms *hepatitis C, Australia, pathogenesis* and *current treatment* were searched using MEDLINE and CHINAL databases to identify research articles and systematic reviews. Constraints were used when researching drug developments to include only full-length papers, on humans published between 2009 and 2013. Literature was analysed to identify shared themes. Sixty-eight articles were analysed and fifty-two chosen based on relevance to objective, reputable data sources and current information. Two websites and five books were included upon cross referencing data to journal articles. Four Australian guideline publications were included due to relevance to topic and general practitioners. **Results:** The aetiology, clinical significance and molecular pathogenesis of hepatitis C virus were examined to provide Australian practitioners with a basis of knowledge for presentation of both acute and chronic stages of hepatitis C infection. This understanding was further linked to current drug treatments available in Australia and potential future therapeutic options. **Conclusion:** The consequences of Hepatitis C infections will burden the Australian healthcare system in the next few decades as the chronic nature of HCV infection leads to complications of liver failure, cirrhosis and hepatocellular carcinoma in many patients. Practitioners must equip themselves with knowledge of HCV pathogenesis which forms the basis of current and future treatments in order to provide best quality care at all levels of prevention and management.

Introduction

The recognition of viral hepatitis can be dated as far back as the fifth century BC to Babylonian records. [1] Our understanding of Hepatitis C gained remarkable ground when previously non-A non-B hepatitis infections were attributed to the hepatitis C virus discovered by Choo *et al.* in 1989. [1,2] Since then efforts have been made to develop drug treatments to combat the virus which progresses to chronic infection in up to 80% of patients, increasing their risk of cirrhosis, liver failure and hepatocellular carcinoma. [3,4,5] Chronic hepatitis C infection is currently the leading cause of liver transplantation in Australia. [6,7,8]

Hepatitis C is a major health concern for Australian practitioners with 260 000 Australians infected in 2010 and an estimated 12 000 new infections occurring annually. [4,7] The dominant mode of transmission of the hepatitis C virus (HCV) is parenteral exposure to infected blood and thus the epidemic of HCV infection in Australia continues to escalate predominantly through people who inject drugs (PWID). [7]

This review aims to summarise the aetiology, transmission and life cycle of HCV as well as examine the most recent literature regarding current and future drug therapies to provide the Australian general practitioner with a contemporary understanding in emerging hepatitis treatments.

Aetiology of Hepatitis C

Transmission in the Australian context

Hepatitis C is a blood-borne viral infection and is most commonly spread in Australia via shared injecting equipment (up to 80% acquiring the infection via this route). [7] Other means of transmission include unsterile tattooing, needle-stick injuries and vertical transmission

from mother-to-infants from trauma during pregnancy and/or birth. [9,10] About 5% of all cases in Australia arise from HCV contaminated blood transfusions and blood products prior to screening introduced in February 1990. [7]

Virological Structure

Hepatitis C is caused by a small, positive-stranded RNA virus of the *Flaviviridae* family. The RNA strand is enveloped by a protein capsid which is further surrounded by a lipid bilayer envelope studded with E1 and E2 heterodimer proteins. The genome contains a 5' noncoding region required for viral translation, followed by an open reading frame terminated by a 3' noncoding region necessary for replication. The open reading frame translates into a 3000 amino acid polyprotein which is cleaved into structural (core, E1, E2) and non-structural (p7, NS3, NS4A, NS4B, NS5A, and NS5B) proteins. [11-15]

The NS5B protein is a RNA-dependent RNA-polymerase which lacks proofreading function. This combined with a high replication rate (10^{12} virions/day) results in rapid mutations driving genetic diversity. [16] Thus within a host, HCV circulates as a population of extremely closely related, but not identical variants called quasispecies. [17] This feature has contributed to difficulty in developing a vaccine as well as implications for pharmacological therapies. HCV is classified into seven major genotypes which differ genetically by at least 30% with over 100 subtypes. [11,13] The prevalence of genotypes differ with geographical distribution. Genotype 1 mostly dominates Australia, the Americas, Japan and Europe with genotypes 2 and 3 also prevalent in these areas. Genotype 7 was only recently discovered in a small proportion of people in Central Africa. Disease association is largely similar across genotypes, however genotype 3 has been correlated with a higher risk of hepatic steatosis and progressive liver disease. [13,18]

Life Cycle

The main stages of the HCV replication cycle are binding and entry, uncoating, translation and replication of RNA, assembly into new particles, maturation and secretion. [11,19] Several host factors have been identified aiding entry of HCV including heparan sulphate and low-density lipoprotein receptor. Other host factors CD81, scavenger receptor B1 and tight junction proteins claudin-1 and occludin allow for clathrin-dependent endocytosis which delivers the virus to early endosomes, which become acidified causing fusion of the viral envelope, uncoating and release of the viral RNA into the cytoplasm. [12,19] HCV replication induces a membranous web concentrating

lipid-rich structures that aid the replication process. Hepatocyte -specific microRNA-122 has been shown to bind to target sites on the 5' untranslated region of the HCV genome which forms a complex that protects the HCV genome from nucleolytic degeneration and innate host immune responses. [20] Lipid droplets interact with the core and NS5A viral proteins allowing viral assembly. The newly synthesised viral proteins can then exit the cell in a manner similar to the hosts' very low-density lipoprotein (VLDL) export pathway by utilising cofactor ApoB and microsomal triglyceride transfer protein to form low-density viral particles termed lipo-viral particles. [11,12,18] ApoE is involved in HCV particle morphogenesis and infectivity. HCV particles exist in the serum as a mixture of complete low-density infectious lipo-viral particles and an excess of apoB-associated empty non-infectious particles complexed with anti-HCV envelope antibodies. [18]

The mechanism responsible for onset and progression of chronic hepatitis are not fully understood but it is currently believed that HCV establishes persistent infection by impairing host innate and adaptive immunity. [1,21] The infected hepatocytes recognise Pathogen Associated Molecular Patterns (PAMPs) through receptors known as Pattern Recognition Receptors (PRRs) which include Toll like receptors (TLRs) and RIG-1 like receptors (RLRs). Upon sensing HCV via TLR3 and RIG-1, intracellular signalling cascades result in the induction of type I and type III interferon and pro-inflammatory cytokines which establish an antiviral state in infected and neighbouring cells. [21,22] Resident antigen presenting cells, such as dendritic cells residing in the liver migrate from infected tissue to lymph nodes where they prime T and B cell activation to induce adaptive immunity. [11]

Recent studies have established multiple routes whereby HCV impairs immune functioning so as to coexist and replicate in the host. [23] NS3/4A protease cleaves intracellular pathway protein TRIF and CARDIF to impair TLR3 and RIG-1 receptors. [11] Furthermore, the HCV enveloped particle is not detected by TLR-2 and TLR-4 which also contribute to antiviral states. HCV has been shown to up regulate MHC Class I molecules on infected hepatocytes which suppresses Natural Killer cell activity. [23] Finally generation of quasispecies carry mutations to evade B and T-cell recognition as well induce hypermutation in B cell receptors to lower affinity allowing the virus to escape immune surveillance. [11]

Clinical Implications

The World Health Organisation estimates 170 million people are infected with Hepatitis C globally. [1,24] Hepatitis C is thus the leading cause of chronic liver disease worldwide and is a growing burden on healthcare systems, including within Australia. [3,25] Infection is characterised by a wide range of clinical manifestations and propensity to develop into chronicity. Up to 80% of infected patients will develop a chronic infection. [1,3] Persistent infection and chronic hepatitis are the hallmarks of HCV infection with severity varying widely from asymptomatic chronic infection with normal liver function tests to severe cases leading to cirrhosis and hepatocellular carcinoma. [2,14]

Acute Hepatitis

Acute HCV infection is often asymptomatic due to a mild immune response and reversible cellular injury seen at the microscopic level. [9] Where symptoms occur they tend to be minimal involving jaundice and flu-like malaise. [5] Strong immune responses during the acute infection are associated with clearance of the virus however in the majority of cases milder initial infections lead to chronic viral persistence. [5,26]

Chronic Hepatitis

Cirrhosis develops in as many as 20% of chronic HCV patients and is associated with hepatocellular failure. Patients may present with portal hypertension manifested as splenomegaly, variceal bleeding or ascites. [9,26] Primary hepatocellular carcinoma is thought to result from the continual division of infected hepatocytes attempting to regenerate in the presence of injury. [5] Once cirrhosis has established, patients have a 5% annual risk of developing hepatocellular carcinoma. [27] Extra-hepatic diseases such as mixed cryoglobulinemia and glomerulonephritis are also believed to be caused by HCV induced antibody complex depositions in small vessels causing vasculitis, however the pathogenesis of this is not fully understood providing an area for investigation in the future. [28,29]

Current drug therapies

Current standard of care treatment of HCV genotype 1 is triple therapy with pegylated interferon-α (cytokine), ribavirin (antiviral) and a direct acting antiviral (NS3/4A protease inhibitor) - either telaprevir or boceprevir. [2,8,30] The combination of pegylated interferon (PEG-IFN) and ribavirin remain the recommended treatment for HCV infection with genotypes 2, 3, 4, 5 and 6. [19] The aim of treatment is a sustained virological response (SVR), defined as the absence of detectable HCV RNA for 6 months after treatment cessation. [31] SVR is associated with crucial end points, particularly survival and protection from the complications of chronic hepatitis C such as cirrhosis and hepatocellular carcinoma. [19,30]

For reasons that remain elusive, interferon-based therapies result in a SVR of 80% in genotype 2 and 3 infections but only 45% in genotype 1 and 4 infections. [4,13] With the approval of boceprevir and telaprevir in 2011 by the US Food and Drug Administration, triple therapy has enabled the SVR to increase in patients with genotype 1 from 45% in 2010 to ~66% in 2011 and is expected to be >75% by 2014. [4,26]

The SVR is also influenced by a myriad of host factors such as ethnicity, gender, age and insulin resistance. [13,32] Furthermore, new biomarkers such as serum IP10 levels and genetic tests to determine polymorphisms in the gene encoding IFNL3 (formerly known as IL28B or IFN-λ3) and recently discovered IFNL4 show strong value with respect to interferon-based therapy as predictors of treatment outcome. [1,13,30]

In Australia, hepatitis C treatment is available for all eligible patients over 18 years of age who have chronic HCV infection with compensated liver disease and are using effective forms of contraception. Treatment is subsidised by the government under the Highly Specialised Drugs (HSD) program, section 100 (S100) of the *National Health Act 1953* (Cwlth). [8]

Pegylated Interferon-α

Interferons are naturally produced by immunological cells in response to tumour or infectious organism. They are glycoproteins with antiviral, anti-proliferative and immunomodulatory functions. [31]

Upon administration of IFN- α, the type I interferon binds to IFNAR-1 and IFNAR-2 receptors on cell surfaces initiating a complex intracellular signalling pathway resulting in activation of genes coding for proteins which inhibit intracellular viral replication. Proteins include RNA-dependant protein kinase (PKR) which inhibits RNA translation and oligoadenylate synthetase (OAS) which mediates RNA degradation. IFN- α also stimulates T_H1 cell production while reducing suppressor T_H2 cells as part of its immunomodulation. [31,33]

Pathogenesis of HCV occurs as a result of the virus' ability to prevent host cells from responding to natural levels of interferon. As previously discussed, HCV blocks TLR3 and RIG-1 receptors reducing type I IFN production. [5,11] Thus overwhelming host cells with high levels of injected IFN allow normal cellular mechanisms to control the virus. [5,13] Replacement of standard interferon with pegylated interferon (interferon-α conjugated to polyethylene glycol) improves pharmacokinetics and efficacy and has allowed its administration as a once weekly subcutaneous injection. [30]

Ribavirin

Unlike pegylated interferon-α, whose function was unravelled due to developments in cell culture models, the mechanism of action

of ribavirin against HCV is unknown. [33] Ribavirin was originally synthesised as a guanosine analogue that could inhibit viral polymerases by chain termination. The process by which this is thought to occur is when the polymerase incorporates the nucleotide but cannot add more after inserting the analogue, hence preventing viral replication and transcription. [5]

However there is much debate about the mechanism of ribavirin activity in chronic hepatitis C. Despite showing in vitro activity against some RNA and DNA molecules, studies conducted with ribavirin as a monotherapy against HCV reflect no effect on HCV RNA levels or improvement of hepatic histology following 12 months of therapy. [33] Yet analysis of the current literature shows multiple studies where combination therapy of IFN- α and ribavirin is significantly more effective then IFN- α alone. [34-36] Furthermore, the anti-HCV activity of ribavirin occurs at much lower doses then expected for the chain termination theory to occur. [5] This suggests other mechanisms of action are at work.

Greenblatt presents two possibilities. [5] One involves ribavirin as depleting the cell's reservoir of normal guanosine to interfere with viral RNA synthesis. Secondly she proposes a mutagenic theory in which ribavirin incorporation into viral genomes renders them funtionless. [5] Other theories propose that ribavirin induces IFN-stimulated genes or may have immunomodulatory functions which like IFN- α, push patient cytokine profiles towards T_H1 types which are more effective against viral infections then type 2 Helper T cells. [13,31]

Telaprevir and Boceprevir

Telaprevir and boceprevir are first generation peptidomimetic, reversible inhibitors of NS3/4A protease. [30] The HCV NS3/4A serine protease is essential for viral replication by cleaving polyproteins into mature non-structural proteins. [13] Thus by inhibiting this protease, telaprevir and boceprevir are the first direct-acting antivirals (DAAs) approved for use against HCV genotype 1.

Despite both drugs having similar mechanisms of action and thus sharing most clinically relevant strengths and weaknesses, there are discrepancies between telaprevir-based regimens and boceprevir-based regimens. [1,30] These differences are in the timing and duration of combined therapy. Typically, telaprevir is given in triple therapy with PEG-IFN and ribavirin for the first 12 weeks of therapy, PEG-IFN and ribavirin are then continued for the remainder of treatment (either 24 or 48 weeks) without the protease inhibitor. Duration of treatment is dependent on virological response (response-guided therapy). Boceprevir, however is started 4 weeks after commencement with PEG-IFN and ribavirin and is continued for the remaining treatment duration of 28 or 48 weeks depending on response. [19] Telaprevir-based regimen is stopped in patients with a HCV RNA level greater than 1000 IU/ml at week 4 or 12 and all three drugs should be discontinued. For the boceprevir-based regimen, patients with HCV RNA levels greater than 100 IU/ml at week 12 should discontinue treatment. For both treatments, if HCV RNA is detectable at 24 weeks of therapy, all three drugs should be stopped. [19]

Side effects profile – pegylated interferon-α and ribavirin

These can be quite distressing and contribute to low tolerance and compliance in patients. The major effects of interferon include depression, constant flu-like symptoms, thrombocytopenia, leucopenia, thyroid dysfunction, retinopathy and alopecia. [25,37] Ribavirin is highly teratogenic and can lead to haemolytic anaemia and autoimmune disorders. [37]

Psychiatric status as well as full blood count, kidney and liver function tests should be monitored continuously throughout therapy. Furthermore, precautions should be taken with patients with depressive histories, thyroid dysfunctions, diabetes, autoimmune disorders and renal impairment. [38] Finally pregnancy in female patients or the partners of male patients must be avoided during treatment, and owing to the long half life of ribavirin, also 6 months after cessation of treatment. [39]

Side effects profile – telaprevir and boceprevir

Although triple therapy is more efficacious in HCV genotype 1 infections, there are additional side effects compared to traditional dual therapy and thus management of hepatitis C patients has become more complex. Common side effects of telaprevir include rash and anorectal discomfort while dysgeusia (altered taste sensation) and neutropaenia are associated with boceprevir. The most challenging side effect of both drugs is marked anaemia (haemoglobin level < 10 g per decilitre) occurring in 36-50% of patients. [19,30] Erythrocyte-stimulating agents have some success in managing this complication however are not approved for routine use in chronic hepatitis C patients due to serious side effects and cost. Some studies have shown that reduction in the dose of ribavirin can effectively manage anaemia in this setting and this is the current recommended first line approach. [19]

Due to the highly variable nature of HCV with the error-prone RNA polymerase, drug resistance is also an issue with these protease inhibitors and can develop as early as day 4 upon use in monotherapy. Consequently, these drugs are not to be used in isolation. Because of the similar mechanism of action, resistance to one protease inhibitor can result in other drugs within the same class to be ineffective. Once the drug is stopped, the frequency of resistance-associated variants within the quasispecies slowly decreases until they disappear, most likely because they do not replicate as effectively as the wild-type virus. [19,30] General practitioners can play a crucial role in patient education to ensure adherence to the prescribed regimen in order to limit the development of resistance-associated variants.

The third major consideration with these new drugs is the issue of drug-drug interactions. Both telaprevir and boceprevir are inhibitors of the cytochrome P450 3A (CYP3A). CYP3A enzymes are involved in the metabolism of numerous drugs such as statins, antidepressants, antiarrhythmics, anticonvulsants, analgesics and sedatives. [19] As such, these are all contraindicated in patients undergoing treatment with telaprevir and boceprevir. This has important implications for general practitioners who are frontline prescribers of such agents. Efforts are being made to make such complex information widely available to the medical community through platforms such as the 'Hepatitis Drug Interactions' website from the University of Liverpool, UK. [30,40]

The future of hepatitis C

With the exponential increase in knowledge of life cycle and replication of HCV due to breakthroughs in cell culture systems in 2005, there is fierce competition to develop medicines that will replace PEG-IFN, ribavirin and first generation protease inhibitors. [30] About two-thirds of agents in Phase II and III trials are directed against the NS3/4A and NS5B viral proteins called second generation protease inhibitors and polymerase inhibitors respectively. [19,30] The current challenges in drug development are decreasing side effects and drug interactions, exploring combinations for genotypes 2-6, exploring individualised drugs to specific genetic polymorphisms, and eradicating the need for interferon and ribavirin in treatment.

A number of drugs are currently being developed for genotypes 2-6. A preliminary phase 2a study in New Zealand involved combining sofosbuvir, an oral nucleotide inhibitor of HCV polymerase, and ribavirin in various interferon and interferon-sparing regimens for 12 weeks. [41] Patients with HCV genotype 1, 2 and 3 were investigated. In this early trial sofosbuvir showed a promising result with 100% rate of SVR among patients with genotype 2 or 3 infection. [19,26,41] However phase 3 studies of sofosbuvir fall short of the results produced by the phase 2a study. [42,43,44] One noninferiority trial looked at sofosbuvir plus ribavirin compared to standard peginterferon alfa-2a plus ribavirin in 499 patients with HCV genotype 2 or 3 infection. The results revealed the same SVR rate of 67% in both the sofosbuvir-ribavirin and peginterferon-ribavirin group at 12 weeks after cessation

of therapy. [43] Two further phase 3 trials (POSITRON and FUSION studies) investigated sofosbuvir-ribavirin therapy in patients for whom peginterferon treatment was not an option (due to pre-existing psychiatric or autoimmune disorders) and in those who did not have a response to previous interferon treatment. The POSITRON trial was a randomized, blinded, placebo-controlled study that compared 12 weeks of sofosbuvir-ribavirin treatment with matching placebo in patients who had previously discontinued interferon therapy due to adverse events or concurrent medical condition. In this group, 78% had a SVR at 12 weeks after treatment compared to 0% in the placebo group. [42] The FUSION study looked at patients who had failed a sustained response to interferon-based therapy and compared 12 and 16 week regimens of sofosbuvir-ribavirin therapy. Results showed that four additional weeks of therapy made a difference with an increase in the SVR from 86% to 94% in patients with genotype 2 infection and from 30% to 63% in genotype 3 infections. [42,44] All three phase 3 studies with sofosbuvir-ribavirin showed better SVR rates in genotype 2 infections compared to genotype 3 infections. [42,43,44]

Nonstructural 5A (NS5A) protein is also a target of recent drug development. [45] The functions of the NS5A protein are not yet fully understood with in vitro studies suggesting is has a role in viral replication and assembly and release of infectious particles. [45] Daclatasvir is a potent NS5A inhibitor which has shown early promising results for use in interferon-free combinations with rapid decline of extracellular HCV titres upon administration. [45] In a phase 2a trial, patients who had not had a response to previous therapy received daclatasvir and a protease inhibitor (asunaprevir) for 24 weeks. [46] Four out of eleven patients had a SVR at 12 and 24 weeks after treatment ended, suggesting a cure may be possible with an all-oral interferon-ribavirin free treatment. [45,46]

Another group of host targeting antiviral agents are arising. Miravirsen is a drug undergoing development which targets miR-122. Liver specific miR-122, as discussed previously is a microRNA which all strains of HCV use to survive and replicate in liver cells. [11,12] A recent phase 2a study by Janssen et al, dose-dependent reductions in HCV RNA levels were found without viral resistance. [20] The study was limited by a small sample of 36 patients and only moderate levels HCV RNA reduction which rebounded once miravirsen was stopped in patients who had not begun interferon and ribavirin. [20,47] Normally miR-122 is involved in controlling cholesterol levels independent of its effect on HCV. In the study, there was a sustained decrease of serum cholesterol levels by ~25% which lasted 14 weeks after the final injection. [47] Given statins are contraindicated in the current triple therapy treatment of HCV genotype 1 infections, there is potential in the future to develop liver-targeting nucleic acid drugs which can be used intermittently for both HCV treatment and other co-morbid conditions.

Furthermore, the future of HCV treatment is trending towards highly individualised regimens which consider not only the viral genotypes but also the patient's genetic polymorphisms. For instance, easy-to-treat patients have been identified as treatment-naïve, IL28B CC. [30] Patients with a favourable interlukin-28B genotype (CC variant as opposed to CT or TT) have shown sustained virologic responses up to 80%. [19] It is theorised that these patients could receive PEG-IFN and ribavirin first, minimising the adverse effects of triple therapy. [19] Although testing for the IL28B genotype is not currently the approved standard of care, in the future Australian general practitioners may be managing care of these 'easy-to-treat' patients while more complex cases, such as patients with IL28B TT with decompensated cirrhosis are managed at tertiary centres using a cocktail of tailor made drug regimens. [30]

Implications for Australian health practitioners

Accessing and treating hepatitis C infection in PWID – the role of the general practitioner

Advances made in the development of better tolerated interferon free HCV treatment will remain negligible as long as access to therapy cannot be expanded to the most affected and underserved risk groups. [48,49,50] People who inject drugs act as a virus reservoir, as the burden of HCV-related liver disease in this group is increasing but treatment uptake remains low. [49,50] There are a number of barriers to accessing care at the level of the patient, practitioner and system. [48,50,51] New guidelines have been published with recommendations for the management of HCV infection among PWID which aim to overcome these barriers by providing evidence-based treatment recommendations.[50] Analysis of the literature revealed a common theme supported by high quality evidence which was the use of multidisciplinary care teams in enhancing treatment uptake in PWID. [49,50] General practitioners can play a crucial role in co-ordinating multidisciplinary care between specialists, drug and alcohol support services, psychiatric services, social work and other social supports such as peer-based groups. [49] In an Australian community-based study, hepatitis C positive patients who had seen a general practitioner about HCV in the last 6 months were four times more likely to be assessed for therapy by a specialist. [50] Furthermore, a prospective cohort study using telehealth technology in supporting and training GPs was compared to HCV treatment provided at a tertiary centre. Similar rates of treatment success were achieved in both groups. [49,51] From these studies, it was seen that general practitioners not only co-ordinated care but provided a more patient-centred approach necessary in dealing with the complex psychiatric and substance abuse co-morbidities which required individualised models of care. Enhanced personal contact provides an ideal environment for pre-therapeutic assessment of housing, education, cultural and social issues, supports, finances, nutrition, drug and alcohol use and psychiatric evaluation. [50] Merging different disciplines into one general practice model may be a simple and effective model in the future for a sub-population of PWID with HCV but will require commitment by motivated and

Table 1. *Hepatitis C and the role of the General Practitioner. [8,26,50,52].*

Primary Measures
History – ask about risk factors. People who have never been tested before and: • Ever injected drugs • Ever been in a correctional facility • Received a blood transfusion in Australia prior to 1990 • Received blood products overseas • Born in a country of high prevalence of hepatitis C • Mother with hepatitis C • Ever had a tattoo or body piercing • Multiple sexual partners • Partner with hepatitis C • Needle stick injury Investigations • Test blood for HCV-specific antibodies and HCV RNA • Full blood count, liver function tests and thyroid function • Screen for HBV and HIV co-infection in patients with risk factors Counsel patients with detectable levels of HCV RNA to eliminate transmission-prone practices Counsel patients and partners with regards to effective contraception forms prior to initiating treatment
Secondary Measures
Vaccinate for hepatitis A and B virus Education and support to reduce / eliminate drug and alcohol use Education regarding safe injecting and needle sharing practices Treat with antivirals – referral to liver clinic Management and continued follow up of adverse effects Surveillance of drug interactions Long term follow up and multidisciplinary care in conjunction with liver clinic

supported GPs who have undergone further training in addiction and HCV medicine. [49]

The role of general practitioners in assessment and management of HCV infection

As stated previously, hepatitis C may be present in patients unknowingly for decades before symptoms of liver failure prompt a seeking of treatment. At this stage of irreversible cellular damage, treatment options are limited, often associated with distressing side effects and yield less efficient results in certain genotypes. The onus is on health practitioners, armed with an understanding of the pathogenesis of HCV, to identify high risk patients and test for anti-HCV antibodies and HCV RNA levels as a secondary preventative strategy to provide early detection and referral. There are a number of useful international guidelines which can assist general practitioners in managing newly diagnosed hepatitis C patients in regards to indications for treatment as well as first-line treatment recommendations. [3,24] Furthermore, primary prevention strategies whereby educating the public about transmission, symptoms and progression of the disease can be effectively implemented in a consultation setting.

In regards to treating chronic hepatitis C patients, this review aims to equip the general practitioner with an up-to-date understanding of the molecular and immunological aspects of HCV pathogenesis to aid in diagnostic tools as well as provide a platform of knowledge for future pharmaceuticals. We are entering an exciting new era of hepatitis C treatment where interferon-free therapies are likely to dominate the therapeutic landscape within the next 5 years [19] and so an understanding of their mechanism of action in hepatitis C is crucial for continuing treatment and management.

Conclusion

From the ancient observations to the discovery of hepatitis C virus 24 years ago, up until recent advances in cell model systems, our understanding of the pathological nature of hepatitis C has grown exponentially. With this growth have come parallel developments in treatment, both in understanding mechanisms behind current drug therapies but also providing a platform for future pharmaceuticals to target aspects of HCV pathogenicity. These developments come at a timely point, as the burden of an escalating epidemic of hepatitis C in Australia will have major impacts on our healthcare system within the next few decades as the chronic nature of the disease will come into play.

Conflict of interest

None declared.

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