Statins and PCSK9 inhibitors in patients with HCV infection.

Hossam Bahy, MD
National Heart institute

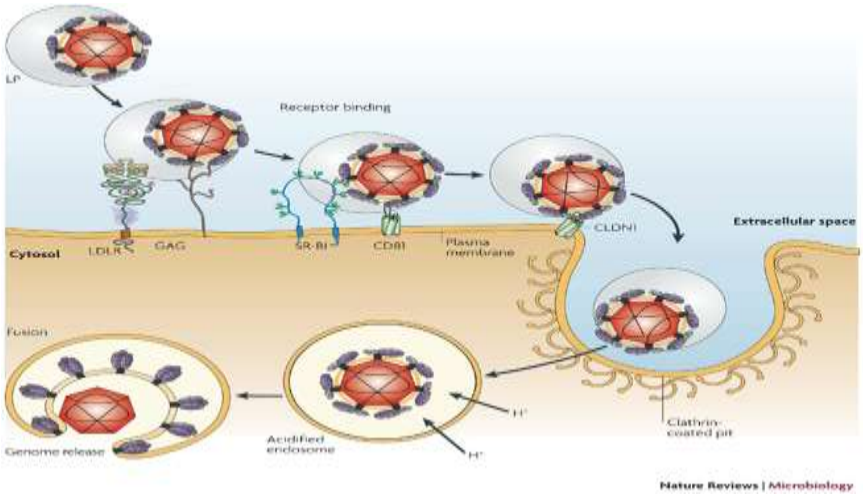
ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries

Paul Y. Kwo, MD, FACG, FAASLD[1], Stanley M. Cohen, MD, FACG, FAASLD[2] and Joseph K. Lim, MD, FACG, FAASLD[3]

Clinicians are required to assess abnormal liver chemistries on a daily basis. The most common liver chemistries ordered are serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase and bilirubin. These tests should be termed liver chemistries or liver tests. Hepatocellular injury is defined as disproportionate elevation of AST and ALT levels compared with alkaline phosphatase levels. Cholestatic injury is defined as disproportionate elevation of alkaline phosphatase level as compared with AST and ALT levels. The majority of bilirubin circulates as unconjugated bilirubin and an elevated conjugated bilirubin implies hepatocellular disease or cholestasis. Multiple studies have demonstrated that the presence of an elevated ALT has been associated with increased liver-related mortality. A true healthy normal ALT level ranges from 29 to 33 IU/l for males, 19 to 25 IU/l for females and levels above this should be assessed. The degree of elevation of ALT and or AST in the clinical setting helps guide the evaluation. The evaluation of hepatocellular injury includes testing for viral hepatitis A, B, and C, assessment for nonalcoholic fatty liver disease and alcoholic liver disease, screening for hereditary hemochromatosis, autoimmune hepatitis, Wilson's disease, and alpha-1 antitrypsin deficiency. In addition, a history of prescribed and over-the-counter medicines should be sought. For the evaluation of an alkaline phosphatase elevation determined to be of hepatic origin, testing for primary biliary cholangitis and primary sclerosing cholangitis should be undertaken. Total bilirubin elevation can occur in either cholestatic or hepatocellular diseases. Elevated total serum bilirubin levels should be fractionated to direct and indirect bilirubin fractions and an elevated serum conjugated bilirubin implies hepatocellular disease or biliary obstruction in most settings. A liver biopsy may be considered when serologic testing and imaging fails to elucidate a diagnosis, to stage a condition, or when multiple diagnoses are possible.

Am J Gastroenterol 2017; 112:18–35; doi:10.1038/ajg.2016.517; published online 20 December 2016

HCV



World Journal of Gastroenterology

World J Gastroenterol. 2015 Jul 21; 21(27): 8293–8301.
Published online 2015 Jul 21. doi: 10.3748/wjg.v21.i27.8293
PMCID: PMC4507098

Lipid dysregulation in hepatitis C virus, and impact of statin therapy upon clinical outcomes

Tracey G Simon and Adeel A Butt

Author information ▶ Article notes ▶ Copyright and License information ▶

This article has been cited by other articles in PMC.

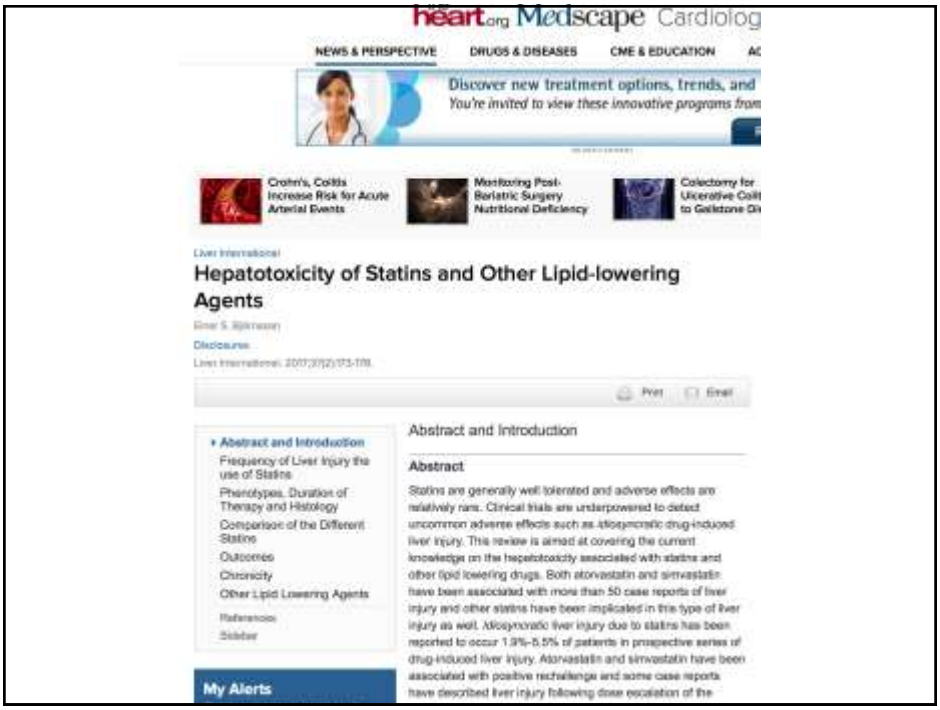
Abstract

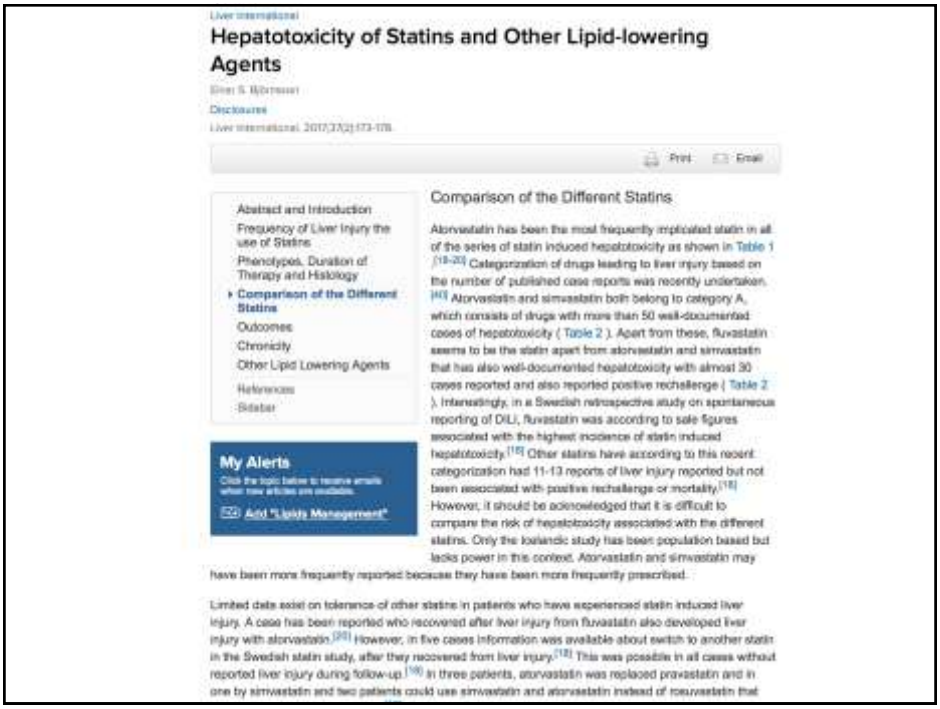
Go to ▾

The hepatitis C virus (HCV) is one of the most common causes of chronic liver disease and the leading indication for liver transplantation worldwide. Every aspect of the HCV life cycle is closely tied to human lipid metabolism. The virus circulates as a lipid-rich particle, utilizing lipoprotein cell receptors to gain entry into the hepatocyte. It has also been shown to upregulate lipid biosynthesis and impair lipid degradation, resulting in significant intracellular lipid accumulation and circulating hypocholesterolemia. Patients with chronic hepatitis C (CHC) are at increased risk of hepatic steatosis, fibrosis, and cardiovascular disease including accelerated atherosclerosis. HMG-CoA Reductase inhibitors, or statins, have been shown to play an important role in the modulation of hepatic steatosis and fibrosis, and recent attention has focused upon their potential therapeutic role in CHC. This article reviews the hepatitis C viral life cycle as it impacts host lipoproteins and lipid metabolism. It then describes the pathogenesis of HCV-related hepatic steatosis, hypocholesterolemia and atherosclerosis, and finally describes the promising anti-viral and anti-fibrotic effects of statins, for the treatment of CHC.

Keywords: Hepatitis C virus, Lipid profiles, Cholesterol, Statin, Fibrosis, Cirrhosis

Core tip: This article reviews the complex relationship between hepatitis C virus (HCV) infection and human lipid metabolism. It discusses the aspects of the hepatitis C viral life cycle that are entwined with cholesterol homeostasis, as well as the clinical implications of HCV-mediated changes in human lipid profiles. Finally, it describes the current state of knowledge regarding the impact of statin medications on histological, virological and clinical outcomes, among patients with chronic hepatitis C.


heart.org Medscape Cardiolog
NEWS & PERSPECTIVE
DRUGS & DISEASES
CME & EDUCATION
Discover new treatment options, trends, and
You're invited to view these innovative programs from
Crohn's, Colitis Increase Risk for Acute Arterial Events
Monitoring Post-Bariatric Surgery Nutritional Deficiency
Colectomy for Ulcerative Coli to Gallstone Di
Liver International
Hepatotoxicity of Statins and Other Lipid-lowering Agents
Disclosures
Print
Email
Abstract and Introduction
Frequency of Liver Injury the use of Statins
Phenotypes, Duration of Therapy and Histology
Comparison of the Different Statins
Outcomes
Chronicity
Other Lipid Lowering Agents
References
Sidebar
Abstract and Introduction
Abstract
Statins are generally well tolerated and adverse effects are relatively rare. Clinical trials are underpowered to detect uncommon adverse effects such as idiosyncratic drug-induced liver injury. This review is aimed at covering the current knowledge on the hepatotoxicity associated with statins and other lipid lowering drugs. Both atorvastatin and simvastatin have been associated with more than 50 case reports of liver injury and other statins have been implicated in this type of liver injury as well. Idiosyncratic liver injury due to statins has been reported to occur 1.9%–5.5% of patients in prospective series of drug-induced liver injury. Atorvastatin and simvastatin have been associated with positive rechallenge and some case reports have described liver injury following dose escalation of the
My Alerts


Liver International
Hepatotoxicity of Statins and Other Lipid-lowering Agents
Disclosures
Print
Email
Abstract and Introduction
Frequency of Liver Injury the use of Statins
Phenotypes, Duration of Therapy and Histology
Comparison of the Different Statins
Outcomes
Chronicity
Other Lipid Lowering Agents
References
Sidebar
My Alerts
Add "Lipids Management"
Comparison of the Different Statins
Atorvastatin has been the most frequently implicated statin in all of the series of statin induced hepatotoxicity as shown in Table 1 .[13-20] Categorization of drugs leading to liver injury based on the number of published case reports was recently undertaken. [40] Atorvastatin and simvastatin both belong to category A, which consists of drugs with more than 50 well-documented cases of hepatotoxicity (Table 2). Apart from these, fluvastatin seems to be the statin apart from atorvastatin and simvastatin that has also well-documented hepatotoxicity with almost 30 cases reported and also reported positive rechallenge (Table 2). Interestingly, in a Swedish retrospective study on spontaneous reporting of DILI, fluvastatin was according to sale figures associated with the highest incidence of statin induced hepatotoxicity.[18] Other statins have according to this recent categorization had 11-13 reports of liver injury reported but not been associated with positive rechallenge or mortality.[18] However, it should be acknowledged that it is difficult to compare the risk of hepatotoxicity associated with the different statins. Only the Icelandic study has been population based but lacks power in this context. Atorvastatin and simvastatin may have been more frequently reported because they have been more frequently prescribed.
Limited data exist on tolerance of other statins in patients who have experienced statin induced liver injury. A case has been reported who recovered after liver injury from fluvastatin also developed liver injury with atorvastatin.[20] However, in five cases information was available about switch to another statin in the Swedish statin study, after they recovered from liver injury.[18] This was possible in all cases without reported liver injury during follow-up.[18] In three patients, atorvastatin was replaced pravastatin and in one by simvastatin and two patients could use simvastatin and atorvastatin instead of rosuvastatin that

Liver International

Hepatotoxicity of Statins and Other Lipid-lowering Agents

Einar S. Björnsson

Disclosures

Liver International. 2017;37(2):173-178.

Print Email

Table 2. Number of case reports of DILI with different statins and whether cases of positive rechallenge and fatality from the liver injury has been reported (modified from reference)[48]

	Number of cases reported	Positive rechallenge	Fatal liver injury reported (yes/no)
Simvastatin	69	yes	yes
Atorvastatin	65	yes	yes
Fluvastatin	28	yes	no
Rosuvastatin	13	no	no
Lovastatin	12	no	no
Pravastatin	11	no	no

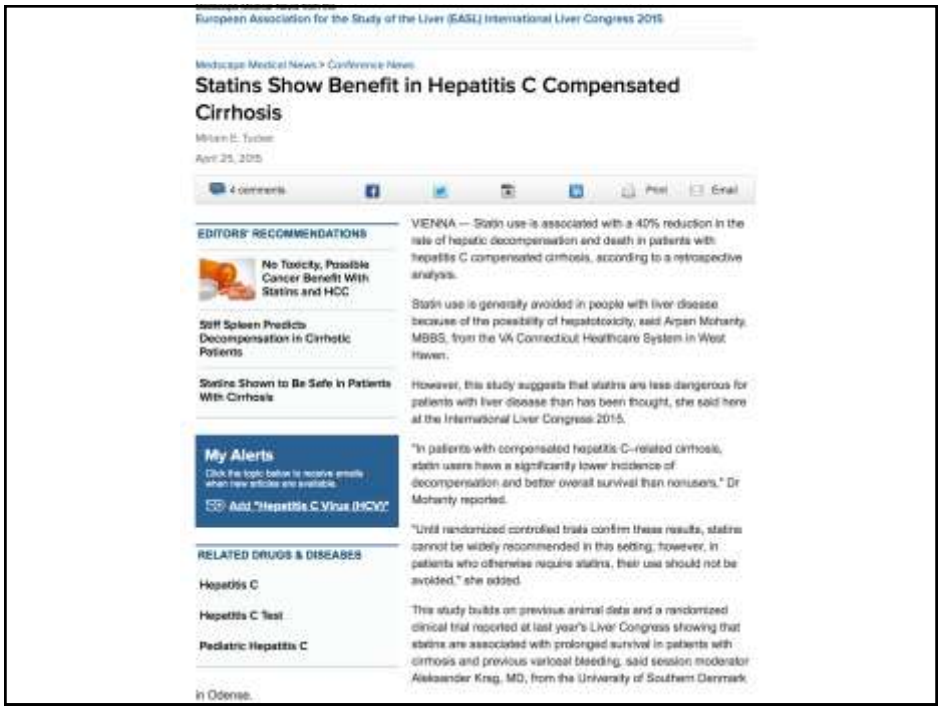
Add "Lipids Management"

statin in all
n in Table 1
based on
ndertaken
jory A,
nented
fluvastatin
rvastatin
most 30
e (Table 2
pontaneous
juries
ed
s recent
ed but not
g.[16]

However, it should be acknowledged that it is difficult to compare the risk of hepatotoxicity associated with the different statins. Only the Icelandic study has been population based but lacks power in this context. Atorvastatin and simvastatin may have been more frequently reported because they have been more frequently prescribed.

Limited data exist on tolerance of other statins in patients who have experienced statin induced liver injury. A case has been reported who recovered after liver injury from fluvastatin also developed liver injury with atorvastatin.[20] However, in five cases information was available about switch to another statin in the Swedish statin study, after they recovered from liver injury.[16] This was possible in all cases without reported liver injury during follow-up.[16] In three patients, atorvastatin was replaced pravastatin and in one by simvastatin and two patients could use simvastatin and atorvastatin instead of rosuvastatin that

BUT



European Association for the Study of the Liver (EASL) International Liver Congress 2015

Medscape Medical News > Conference News

Statins Show Benefit in Hepatitis C Compensated Cirrhosis

Miriam E. Tucker

April 25, 2015

4 comments | Print | Email

EDITORS' RECOMMENDATIONS

No Toxicity, Possible Cancer Benefit With Statins and HCC

Stiff Spleen Predicts Decompensation in Cirrhotic Patients

Statins Shown to Be Safe in Patients With Cirrhosis

My Alerts

Click the topic below to receive emails when new articles are available.

Add "Hepatitis C Virus (HCV)"

RELATED DRUGS & DISEASES

Hepatitis C

Hepatitis C Test

Pediatric Hepatitis C

VIENNA — Statin use is associated with a 40% reduction in the rate of hepatic decompensation and death in patients with hepatitis C compensated cirrhosis, according to a retrospective analysis.

Statin use is generally avoided in people with liver disease because of the possibility of hepatotoxicity, said Arpan Mohanty, MBBS, from the VA Connecticut Healthcare System in West Haven.

However, this study suggests that statins are less dangerous for patients with liver disease than has been thought, she said here at the International Liver Congress 2015.

"In patients with compensated hepatitis C–related cirrhosis, statin users have a significantly lower incidence of decompensation and better overall survival than nonusers," Dr Mohanty reported.

"Until randomized controlled trials confirm these results, statins cannot be widely recommended in this setting; however, in patients who otherwise require statins, their use should not be avoided," she added.

This study builds on previous animal data and a randomized clinical trial reported at last year's Liver Congress showing that statins are associated with prolonged survival in patients with cirrhosis and previous variceal bleeding, said session moderator Aleksander Krag, MD, from the University of Southern Denmark in Odense.

Statin Drugs Decrease Progression to Cirrhosis in HIV/Hepatitis C Virus Coinfected Individuals

Nora T. Oliver; Christine M. Hartman; Jennifer R. Kramer; Elizabeth Y. Chiao

Disclosures

AIDS. 2016;30(15):2469-2476

Wolters Kluwer | Wilkins

Print | Email

- Abstract and Introduction
- Methods
- Results
- Discussion
- References

My Alerts

Click the topic below to receive emails when new articles are available.

Add "HIV Infection"

Abstract and Introduction

Abstract

Introduction: Chronic HIV/hepatitis C virus (HCV) coinfection carries increased risk of cirrhosis, hepatocellular carcinoma, and death. Due to anti-inflammatory properties, 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) inhibitors (statins) may be useful adjunctive therapy to reduce liver disease progression.

Methods: Clinical information was extracted from the Veterans Affairs HIV and HCV Clinical Case Registries (1998–2010). HIV-related variables included combination antiretroviral therapy era of diagnosis, CD4+ cell count, and percentage time with undetectable HIV viral load. Metabolic variables included diabetes, low high-density lipoprotein (HDL), and hypertension. Statin use was measured as percentage time with active prescription (time-updated throughout the follow-up period). Cox proportional hazards analysis was used to determine risk factors for cirrhosis (International Classification of Diseases-9 or aminotransferase-to-platelet ratio index >2) overall and in groups stratified by alanine aminotransferase (ALT) level above and below 40 IU/l.

Results: The cohort included 5985 HIV/HCV coinfected veterans. The majority was black race, and the mean age at index date was 45 years. Statin use was significantly protective of cirrhosis for patients with ALT 40 IU/l or less; for every 30% increase in time on statin, there was a 32% decreased risk of developing cirrhosis (hazard ratio 0.68, 95% confidence interval 0.47–0.98). Diabetes and low HDL were significantly associated with cirrhosis in patients with ALT greater than 40 IU/l (hazard ratio 1.15, $P < 0.04$ and hazard ratio 1.3, $P < 0.0001$).

Conclusion: Statin drug use is beneficial in mitigating the risk of liver disease progression for HIV/HCV coinfected patients without advanced liver disease. Low HDL and diabetes in coinfected patients with abnormal ALT have greater risk of cirrhosis development.

As long as there is NO DILI

you should not withdraw statins and they should be used in people who have the right indications for them.

What if

What if liver enzymes become raised in a person taking lipid-lowering drugs?

If <3×ULN:

- Continue therapy
- Recheck liver enzymes in 4–6 weeks

If values rise to ≥3×ULN:

- Stop statin or reduce dose, recheck liver enzymes within 4–6 weeks
- Cautious reintroduction of therapy may be considered after ALT has returned to normal

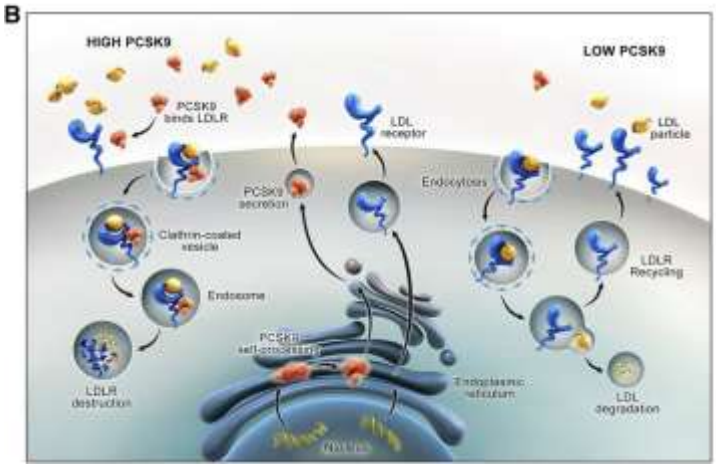
Drug interaction

NO drug interactions have been

Common medications checked in combination with Sovaldi (sofosbuvir)

- amlodipine
- clonazepam
- cyclobenzaprine
- Daklinza (daclatasvir)
- gabapentin
- Harvoni (ledipasvir / sofosbuvir)
- hydrochlorothiazide
- levothyroxine
- metformin
- Olysio (simeprevir)
- omeprazole
- Pegasys (peginterferon alfa-2a)
- prednisone
- Protonix (pantoprazole)
- RibaPak (ribavirin)
- Ribasphere (ribavirin)
- ribavirin
- tramadol
- trazodone
- Vitamin D3 (cholecalciferol)

PCSK 9



PCSK9 inhibitors

A new class of lipid-lowering medications that are administered as monthly or bimonthly subcutaneous injections. They are monoclonal antibodies to PCSK9

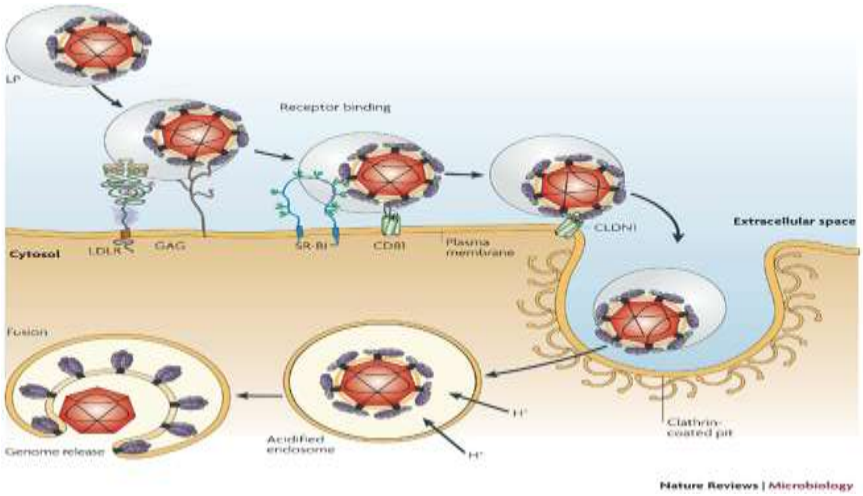
PCSK9 inhibitors

The PCSK9 Inhibitors have been shown to markedly lower LDL-C in phase 3 trials.
The ODYSSEY COMBO II trial randomly assigned patients at high cardiovascular risk and elevated LDL-C despite maximal doses of statin to alirocumab or ezetimibe (on a background of statin therapy).
At week 24, the alirocumab group had 50.6% reduction in LDL-C compared with 20.7% for the ezetimibe group.

PCSK9 inhibitors

In the GAUSS-2 trial, patients at high cardiovascular risk who were statin intolerant were randomly assigned to either evolocumab (140 mg every 2 weeks or 420 mg monthly) or ezetimibe. After 12 weeks, LDL-C lowering in the evolocumab groups ranged between 53% and 56% compared with 37%-39% for ezetimibe.

HCV



Alirocumab, a Therapeutic Human Antibody to PCSK9, Does Not Affect CD81 Levels or Hepatitis C Virus Entry and Replication into Hepatocytes

Aarti Ramanathan[¤], Viktoria Gusarova, Neil Stahl, Anne Gurnett-Bander, Christos A. Kyratsous*

Regeneron Pharmaceuticals, Inc., Tarrytown, NY, United States of America

¤ Current address: Department of Microbiology and Immunology, Drexel College of Medicine, Philadelphia, PA, United States of America
* christos.kyratsous@regeneron.com

OPEN ACCESS

Citation: Ramanathan A, Gusarova V, Stahl N, Gurnett-Bander A, Kyratsous CA (2016) Alirocumab, a Therapeutic Human Antibody to PCSK9, Does Not Affect CD81 Levels or Hepatitis C Virus Entry and Replication into Hepatocytes. PLoS ONE 11(4): e0154498. doi:10.1371/journal.pone.0154498

Editor: Eve-Isabelle PECHEUR, UMR Inserm U1052 / CNRS 5286, FRANCE

Received: November 25, 2015

Accepted: April 14, 2016

Published: April 28, 2016

Abstract

Background

Proprotein convertase subtilisin/kexin type 9 (PSCK9) is secreted mainly from the liver and binds to the low-density lipoprotein receptor (LDLR), reducing LDLR availability and thus resulting in an increase in LDL-cholesterol. While the LDLR has been implicated in the cell entry process of the hepatitis C virus (HCV), overexpression of an artificial non-secreted, cell membrane-bound form of PCSK9 has also been shown to reduce surface expression of CD81, a major component of the HCV entry complex, leading to concerns that pharmacological inhibition of PCSK9 may increase susceptibility to HCV infection by increasing either CD81 or LDLR availability. Here, we evaluated effects of PCSK9 and PCSK9 blockade on CD81 levels and HCV entry with a physiologically relevant model using native secreted PCSK9 and a monoclonal antibody to PCSK9, alirocumab.

Drug	Indication	Administration and Dosage	Annual Cost	Monitoring
Alirocumab (Praluent®)	Adjunct to: -Diet -Maximally tolerated statin therapy for the treatment of adults with HeFH or clinical atherosclerotic CVD who require additional lowering of LDL-C	Subcutaneous injection Starting dose: 75 mg once every 2 weeks If response inadequate, increase to 150 mg once every 2 weeks	$13,440	Measure levels of LDL-C within 4-8 weeks of initiating therapy
Evolocumab (Repatha™)	Adjunct to: -Diet -Maximally tolerated statin therapy for treatment of adults with HeFH or clinical atherosclerotic CVD who require additional lowering of LDL-C -Other LDL-lowering therapies in patients with HoFH who require additional lowering of LDL-C	Subcutaneous injection HeFH: 140 mg every 2 weeks or420 mg once monthly HoFH: 420 mg once monthly	$13,015	Measure levels of LDL-C within 4-8 weeks of initiating therapy

CVD = cardiovascular disease; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol
Sources: The Medical Letter on Drugs and Therapeutics; package inserts

Thank You