(54) Title: A METHOD AND SYSTEM FOR TREATING HEPATITIS C

![Diagram](image)

(57) Abstract: A method and system for treating Hepatitis C includes using an implantable pump and an outlet catheter. A proximal end of the outlet catheter is fluidly connected to an outlet port of the pump. A distal end of the outlet catheter is sized to deliver medication from the pump to a liver of a living organism, preferably a human being. By delivering medication directly to the liver the effects of the antiviral therapeutics are enhanced, and the impact of Hepatitis C infection is reduced.
Published:
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

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A METHOD AND SYSTEM FOR TREATING HEPATITIS C

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a non-provisional application which claims priority to previously filed provisional application U.S. Serial No. 60/637,477, filed December 20, 2004, entitled A Method and System for Treating Hepatitis C, the disclosure of which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a method and system for treating Hepatitis C. More particularly, the present invention relates to a method and system for treating Hepatitis C with an implantable infusion pump to deliver antiviral therapeutics directly to the liver.

2. Discussion of Related Art

The Hepatitis C virus (HCV) is one of the most important causes of chronic liver disease. Hepatitis C accounts for about 15% of acute viral hepatitis, 60 to 70% of chronic hepatitis, and up to 50% of cirrhosis, end stage liver disease, and liver cancer. Almost 4 million Americans have antibody to HCV (anti-HCV), indicating ongoing or previous infection with the virus.

Following initial acute infection, a majority of infected individuals develop chronic hepatitis because HCV replicates preferentially in hepatocytes but is not directly cytopathic. In particular, the lack of a vigorous T-lymphocyte response and the high propensity of the virus to mutate appear to promote a high rate of chronic infection. Chronic hepatitis can progress to liver fibrosis leading to cirrhosis, end-stage liver disease, and HCC (hepatocellular carcinoma), making it the leading cause of liver transplantations.

There are 6 major HCV genotypes and more than 50 subtypes, which are differently distributed geographically. HCV type 1 is the predominant genotype in Europe and the US. The extensive genetic heterogeneity of HCV has important diagnostic and
clinical implications, perhaps explaining difficulties in vaccine development and the lack of response to therapy.

Transmission of HCV can occur through contact with contaminated blood or blood products, for example following blood transfusion or intravenous drug use. The introduction of diagnostic tests used in blood screening has led to a downward trend in post-transfusion HCV incidence. However, given the slow progression to the end-stage liver disease, the existing infections will continue to present a serious medical and economic burden for decades.

Current HCV therapies are based on (pegylated) interferon-alpha (IFN-α) in combination with ribavirin. This combination therapy yields a sustained virologic response in more than 40% of patients infected by genotype 1 viruses and about 80% of those infected by genotypes 2 and 3. Besides the limited efficacy on HCV type 1, this combination therapy has significant side effects and is poorly tolerated in many patients. Major side effects include influenza-like symptoms, hematologic abnormalities, and neuropsychiatric symptoms. Hence there is a need for more effective, convenient and better tolerated treatments.

Recently, peptidomimetic HCV protease inhibitors have gained attention as clinical candidates, namely BILN-2061 disclosed in WO 00/59929 and VX-950 disclosed in WO 03/87092. A number of similar HCV protease inhibitors have also been disclosed in the academic and patent literature. It has already become apparent that the sustained administration of these agents selects HCV mutants in \textit{in vitro} HCV replicon models, which are resistant to the respective drug, so called drug escape mutants. Accordingly, additional drugs with different resistance patterns may be required to provide failing patients with treatment options, and combination therapy with multiple drugs is likely to be the norm in the future, even for first line treatment.

Experience with HIV drugs, and HIV protease inhibitors in particular, has learned that sub-optimal pharmacokinetics and complex dosing regimes often result in inadvertent compliance failures. The 24 hour trough concentration (minimum plasma concentration) of the respective drugs in an HIV regime frequently falls below the IC$_{50}$ or ED$_{50}$ threshold for large parts of the day thereby causing the emergence of drug escape mutants. The same
applies to HCV therapy. Ideally, the drug plasma concentrations of the anti-viral agent should not only be kept above such trough levels and by preference should be more or less stable without much variation. Providing anti-HCV therapy that complies with these requirements therefore is a highly desirable goal to achieve.

There is a need for new treatments of HCV, which may overcome one or more of the disadvantages of current HCV therapy such as side effects, limited efficacy, emergence of resistance, and compliance failures.

SUMMARY OF THE INVENTION

In accordance with a currently preferred exemplary embodiment, the present invention includes treating HCV by locally delivering medication directly to the liver by way of an implantable drug pump having an outlet catheter delivering medication directly to the desired location in the liver or to any body vessel outside the liver, which drains body fluid into the liver.

Thus in one aspect, the present invention concerns a method of treating a patient infected with HCV, said method comprising locally delivering an HCV inhibitory effective amount of one or more HCV inhibitors directly to the liver by way of an implantable drug infusion pump having an outlet catheter delivering the one or more HCV inhibitors directly to the desired location in the liver or to any body vessel outside the liver, which drains body fluid into the liver.

In another aspect, the present invention concerns the use of an HCV inhibitor for the manufacture of a medicament for treating a patient infected with HCV, by locally delivering an HCV inhibitory effective amount of the HCV inhibitor directly to the liver by way of an implantable drug infusion pump having an outlet catheter delivering the HCV inhibitor directly to the desired location in the liver or to any body vessel outside the liver, which drains body fluid into the liver.

In another aspect, the present invention concerns the use of an implantable drug infusion pump having an outlet catheter delivering the HCV inhibitor directly to the
desired location in the liver or to any body vessel outside the liver, which drains body fluid into the liver, for the administration of an HCV inhibitor to a patient infected with HCV.

In still another aspect, the present invention concerns an implantable drug infusion pump loaded with an HCV inhibitor having an outlet catheter for the delivery of the HCV inhibitor directly to the liver or to at any body vessel outside the liver, which drains body fluid into the liver. The outlet catheter is connected directly to the desired location in the liver or to any body vessel outside the liver, which drains body fluid into the liver. The implantable drug pump is for treating a patient infected with HCV by locally delivering an HCV inhibitory effective amount of the HCV inhibitor directly to the liver.

BRIEF DESCRIPTION OF THE DRAWINGS

The above and still further objects, features and advantages of the present invention will become apparent upon consideration of the following detailed description of a specific embodiment thereof, especially when taken in conjunction with the accompanying drawings wherein like reference numerals in the various figures are utilized to designate like components, and wherein:

Figure 1 is a schematic view of an implantable drug pump delivering medication via a catheter to the liver.

DETAILED DESCRIPTION OF THE INVENTION

Referring now to Figure 1, a method and system for treating Hepatitis C in accordance with the present invention is illustrated. The method and system includes using an implantable pump and an outlet catheter. A proximal end of outlet catheter is fluidly connected to an outlet port of pump. A distal end of outlet catheter is sized to deliver medication from pump to a liver of living organism, preferably a human being.
As used herein delivering directly to the liver means that the medication is
delivered at a site of the liver or at any body vessel outside the liver that drains body fluid
into the liver. The medication can be, for example, delivered to the liver or upstream from
the liver vascular bed or at any other infusion location as desired by the physician. In one
embodiment, the medication is delivered to a vein of the liver, preferably the portal vein
(vena porta).

Any HCV inhibitory compound can be used in the system and method in
accordance with the present invention. HCV inhibitory agents comprise, for instance,
interferon-α (IFN-α), albumin-fused interferons, pegylated interferon-α and/or ribavirin, as
well as therapeutics based on antibodies targeted against HCV epitopes, small interfering
RNA (Si RNA) as well as vector-encoded short hairpin RNA (shRNA), ribozymes,
DNAzymes, antisense RNA, small molecule antagonists of for instance NS3 protease,
NS3 helicase and NS5B polymerase or any other HCV non structural or structural protein.

Other therapeutic agents that can be used include immunomodulatory compounds
targeting the human TOLL-like receptors (e.g. the TLR-7 and TLR-9 receptors), which
also lead to a decrease in HCV viral load. These are currently nucleic acid based and a
number of such agents have entered clinical development, and typically are delivered by
injection (Actilon, Coley Pharmaceuticals; Isatoribine, Anadys Pharmaceuticals). Some
other HCV inhibitory compounds, such as, for example, small interfering RNA (Si RNA),
have only been administered intravenously. The present inventors have discovered that
some HCV inhibitory compounds including small interfering RNA (Si RNA) can be used
in the system and method in accordance with the present invention. Si RNAs have recently
been shown to be effective in clearing HCV viral RNA from mammalian cells harboring
HCV genomes (Randall, Grakoui and Rice Proceedings of the National Academy of
Sciences, 100, 2003, pp235-24). Whether such Si RNAs will deliver therapeutic benefit in
patients will be largely dependent on their specific delivery to the target liver organ, and
the possibilities of side effects on other organs. The challenges in the delivery of nucleic
acid based therapeutics are well documented (see McHutchison and Patel, Hepatology, 36,
2002, Suppl.1 S245-S252, and Lee et al, Hepatology, 32, 2000, pp640-646) and include
the rapid breakdown of such agents by nucleases present in serum. The pharmacokinetics
and distribution of the Heptazyme HCV specific ribozyme RPI.13919 (RPI), designed to
cleave the HCV IRES sequence, have shown that it targets to the liver, but delivery to
other organs is thought to contribute to extra-hepatic toxicity in primates. While Si RNAs
have yet to be used in the clinic in HCV patients, there are many reports of their successful use in cellular models. Delivery of such nucleic acid agents direct to the liver via implantable drug pump pumps as in the system and method in accordance with the present invention may offer advantages of reduced extra-hepatic toxicity and enhanced delivery to the site of antiviral action.

Similarly, ISIS-14803 is an antisense oligonucleotide that entered clinical development for treatment of HCV infected patients, but has since been halted because of limited efficacy and adverse effects. The system and method of the present invention may allow using these agents in HCV therapy.

Of interest are protease inhibitors such as BILN-2061 disclosed in WO 00/59929 and Vertex’ VX-950 disclosed in WO 03/87092. Other protease inhibitors are GS 9132, also known as ACH-806. (Gilead/Achillion) and SCH-503034 (Schering). Further agents that can be used are those disclosed in WO-98/17679, WO-00/056331 (Vertex); WO 98/22496 (Roche); WO 99/07734, (Boehringer Ingelheim ), WO 2005/073216 WO2005073195 (Medivir) and structurally similar agents. Other agents that can be used are the imino sugar derivative, UT231B (United Therapeutics) that appears to block the activity of the p7 HCV protein and the NS5B polymerase inhibitor NM283 (Valopicitabine; Idenix/Novartis), an oral prodrug of 2’-C-methyl-cytidine. Other agents that can be used are the non-nucleoside polymerase inhibitors (NNIs) such as JTK-109 and JTK-003 (Japan Tobacco), and R803 (Rigel), HCV-371, HCV-086 and HCV-796 (ViroPharma/Wyeth) Further agents that can be used are nucleoside analogues with the potential to complement or replace ribavirin such as viramidine (Valeant Pharmaceuticals), a less toxic pro-drug of ribavirin, and levovirin, an L-isomer of ribavirin, merimepodib (Vertex), an IMPDH inhibitor.

Also combinations of HCV inhibitory agents may be used for purposes of combination therapy. The term “combination therapy” relates to the administration of more than one anti-HCV compound, which may be administered as a combined preparation for simultaneous administration, or for separate or sequential administration. Current standard of care of HCV comprises combination therapy with pegylated interferon-α and ribavirin. Other combinations comprise any of the above mentioned nucleosides with pegylated interferon.
By delivering medication directly to the liver the effects of Hepatitis C are more effectively reduced. Additionally, the side effects, as compared to conventional methods of treatment are also reduced. Conventional methods comprise the systemic administration of HCV inhibitory agents thereby causing the spread of these agents at various parts of the body where their presence is not necessary and may cause side effects. The method and system of the present invention allows a more targeted administration of the HCV agents in that these are directly delivered to the liver, which is the site where the Hepatitis C virus exerts its negative effects.

Moreover, this mode of administration is less prone to pharmacokinetical problems, which in particular in case of oral administration can reduce the effectiveness of the active ingredient. A more targeted administration as in the system and method of the present invention allow lower doses of the active ingredient to be administered for the drug to be effective, thereby reducing the risk of undesired side effects. In instances where the drug is less effective or the diagnosis of the disease requires the system and method of the invention allow the administration of increased doses of the drug with limited risk of side effects.

Additionally, the method and system of the invention allow for a better control of the drug plasma concentrations of the anti-viral agent in that these levels not only can be kept in the safe area above the minimum plasma levels (‘trough’ levels) below which the virus is able to mutate. The method and system furthermore allow the keeping of the plasma levels stable without much variation, thereby avoiding undesired side effects.

The HCV inhibitors for use in the system and method of the invention preferably are formulated into liquid formulations that are suited for parenteral administration. In these formulations, the carrier will usually comprise sterile water, while other ingredients, for example, to aid solubility, may be included. The carrier may comprise saline solution, glucose solution or a mixture of saline and glucose solution. The carrier may further comprise appropriate liquid carriers, suspending agents and the like. This type of formulation is desired because in preferred embodiments, the pump is refilled by injection through the skin into an appropriate inlet into the pump’s drug reservoir.
Various types of drug administration pumps can be used with the system and method of the present invention. In one embodiment use is made of the Archimedes™ implantable pump and another type is the Codman 3000™ pump, both of which are commercially available from Codman & Shurtleff of Raynham, Mass. Other implantable pumps, whether constant flow pumps or programmable variable flow pumps, that may be available in the future may be used as well. Additionally, peristaltic type implantable pumps may also be used with the present invention.

Having described the presently preferred exemplary embodiment of a method and system for treating Hepatitis C in accordance with the present invention, it is believed that other modifications, variations and changes will be suggested to those skilled in the art in view of the teachings set forth herein. Substitutions of elements from one described embodiment to another are also fully intended and contemplated. It is also to be understood that the drawing is not necessarily drawn to scale, but that it is merely conceptual in nature. It is, therefore, to be understood that all such modifications, variations, and changes are believed to fall within the scope of the present invention as defined by the appended claims.

Every issued patent, pending patent application, publication, journal article, book or any other reference cited herein is each incorporated by reference in their entirety.
CLAIMS

What is claimed is:

5. A method of treating a patient infected with Hepatitis C, said method comprising the steps of:
   filling an implantable drug infusion pump with at least one HCV inhibitor
   locally delivering an HCV inhibitory effective amount of at least one HCV inhibitor directly to the liver by way of an implantable drug infusion pump having an outlet catheter delivering the at least one HCV inhibitor directly to the desired location in the liver or to any body vessel outside the liver that drains body fluid into the liver.

2. The method of claim 1, wherein the catheter delivers the at least one HCV inhibitor directly to the portal vein.

3. The method of claim 1, wherein the at least one HCV inhibitor includes small interfering RNA (Si RNA).

4. The method of claim 1, wherein the infusion pump is a bellows reservoir pump.

5. The method of claim 1, wherein the infusion pump is a peristaltic pump.

6. A method for treating Hepatitis C by use of an implantable pump and an outlet catheter having a proximal end and a distal end, said method comprising the steps of:
   surgically implanting the implantable pump in a body of a patient;
   fluidly connecting the proximal end of the outlet catheter to the pump;
   fluidly connecting the distal end of the outlet catheter to the desired location in the patient’s liver or to any body vessel outside the patient’s liver, draining body fluid into the liver
   operating the pump to deliver medication by way of the outlet catheter to the liver;

and
whereby the effects of Hepatitis C are reduced.

7. The method of claim 6, wherein the catheter delivers the at least one HCV inhibitor directly to the portal vein.

8. The method of claim 6, wherein the at least one HCV inhibitor is a nucleic acid based therapeutic.

9. The method of claim 6, wherein the at least one HCV inhibitor includes small interfering RNA (Si RNA).

10. The method of claim 6, wherein the infusion pump is a bellows reservoir pump.

11. The method of claim 6, wherein the infusion pump is a peristaltic pump.

12. A system for treating Hepatitis C comprising:

   an implantable pump having an outlet port;

   an outlet catheter having a proximal end and a distal end, said proximal end being fluidly connected to said outlet port, said distal end of said outlet catheter being sized to deliver medication from said pump to a liver of living organism.

13. The system according to claim 12, wherein said living organism is a human being.

14. The system of claim 12, wherein the infusion pump is a bellows reservoir pump.

15. The method of claim 12, wherein the infusion pump is a peristaltic pump.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

**INV. A61M5/142**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practical, search terms used)

EPO-Internal, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>X</td>
<td>US 6 638 263 B1 (THEEUWES FELIX ET AL) 28 October 2003 (2003-10-28) column 1, lines 6-23 column 2, lines 16-22 column 5, lines 18-28 column 5, line 36 column 5, line 61 - column 6, line 25 column 13, line 62 - column 14, line 3 column 14, lines 27-35 claims 1, 8, 20, 23, 28, 31, 36</td>
<td>12-15</td>
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* Further documents are listed in the continuation of Box C.

* Document published prior to the international filing date

*Document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

*Document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

*Document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

*Document member of the same patent family

**Date of the actual completion of the International search**

28 April 2006

**Date of mailing of the International search report**

10/05/2006

Name and mailing address of the ISA/

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Authorized officer

Nielsen, M

Form PCT/ISA/210 (second sheet) (April 2006)
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<td>US 5 319 519 A (WILK ET AL) 7 June 1994 (1994-06-07) abstract column 4, lines 20-29; figures 1,2</td>
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<tr>
<td>Y</td>
<td>WO 00/59929 A (BOEHRINGER INGELHEIM LTD; TSANTRIZOS, YOULA, S; CAMERON, DALE, R; FAU) 12 October 2000 (2000-10-12) cited in the application abstract page 1, line 10 - page 2, line 13 page 16, line 12 - page 17, line 21</td>
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<td>A</td>
<td>WO 03/087092 A (VERTEX PHARMACEUTICALS, INC; PITLIK, JANOS; COTTRELL, KEVIN, M; FARMER) 23 October 2003 (2003-10-23) cited in the application abstract page 114, line 3 - page 115, line 28</td>
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INTERNATIONAL SEARCH REPORT

Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This international Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claims Nos.: 1-11 because they relate to subject matter not required to be searched by this Authority, namely:
   
   Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

2. □ Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful international Search can be carried out, specifically:

3. □ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This international Searching Authority found multiple inventions in this international application, as follows:

1. □ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. □ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. □ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

□ The additional search fees were accompanied by the applicant's protest.

□ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
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