Patent documents

[0006]

Patent Document 1: Japanese Patent No. 4021327

Patent Document 2: Japanese Patent No. 5094384

Patent Document 3: Japanese Examined Patent Application Publication No. 2015-52162

Non-Patent Documents

[0007]

Non-Patent Document 1: AMER. J. Hypertension, 18, 720-730 (2005)

Non-Patent Document 2: Current Hypertension Report, 10, 261-267 (2008)

Non-Patent Document 3: BMC Res Notes; 2: 70 (2009)

Non-Patent Document 4: Hepatology, 34, 745-750 (2001)

Non-Patent Document 5: Hepatol Res, 27, 51-56 (2003)

Non-Patent Document 6: Journal of Gastroenterology, DOI: 10.1007/s00535-015-1104-x, pp. 1-11, first online: 21 July 2015

Non-Patent Document 7: Journal of Lipid Research, 45, 132-138 (2004)

Summary

[0007a]

In one aspect of the present disclosure, there is provided a combination pharmaceutical agent, comprising as active ingredients a farnesoid X receptor agonist (FXR agonist) or a pharmaceutically acceptable salt thereof and an angiotensin II receptor blocker (ARB) or a pharmaceutically acceptable salt thereof.

[0007b]

In another aspect of the present disclosure, there is provided a pharmaceutical agent of disclosed herein for use in treating non-alcoholic steatohepatitis (NASH).

[0007c]

In a further aspect of the present disclosure, there is provided a combination of a farnesoid X receptor agonist (FXR agonist) or a pharmaceutically acceptable salt thereof and an angiotensin II receptor blocker (ARB) or a pharmaceutically acceptable salt thereof for use in the treatment of non-alcoholic steatohepatitis (NASH).

[0007d]

In another aspect of the present disclosure, there is provided a kit for the treatment of non-alcoholic steatohepatitis (NASH), comprising:

1) a pharmaceutical agent comprising a farnesoid X receptor agonist (FXR agonist) or a pharmaceutically acceptable salt thereof;

2) a pharmaceutical agent comprising an angiotensin II receptor blocker (ARB) or a pharmaceutically acceptable salt thereof; and

3) instructions for administration of a combination of 1) and 2) above.

[0007e]

In a further aspect of the present disclosure, there is provided a combination pharmaceutical agent disclosed herein for use in inhibiting hepatic fibrosis in liver disease, wherein the liver disease is selected from hepatitis B; hepatitis C; parasitic liver disease; post-transplant bacterial infections, post-transplant viral infections, or post-transplant fungal infections; alcoholic liver disease (ALD); non-alcoholic fatty liver disease (NAFLD); methotrexate-induced liver disease, isoniazid-induced liver disease, oxyphenistatin-induced liver disease, methyldopa-induced liver disease, chlorpromazine-induced liver disease, tolbutamide-induced liver disease, or amiodarone-induced liver disease; autoimmune hepatitis; sarcoidosis; Wilson's disease; hemochromatosis; Gaucher's disease; glycogen storage disease type III, glycogen storage disease type IV, glycogen storage disease type VI, glycogen storage disease type IX, or glycogen storage disease type X; α-1 antitrypsin deficiency; Zellweger syndrome; tyrosinemia; levulosemia; galactosemia; Budd-Chiari syndrome-related angiopathy, veno-occlusive disease-related angiopathy, or portal vein thrombosis-related angiopathy; or congenital hepatic fibrosis.

[0007f]

In another aspect of the present disclosure, there is provided a use of a pharmaceutical agent disclosed herein in the manufacture of a medicament for treating non-alcoholic steatohepatitis (NASH).

[0007g]

In a further aspect of the present disclosure, there is provided a use of a combination of a farnesoid X receptor agonist (FXR agonist) or a pharmaceutically acceptable salt thereof and an angiotensin II receptor blocker (ARB) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating non-alcoholic steatohepatitis (NASH).

[0007h]

In another aspect of the present disclosure, there is provided a use of the combination pharmaceutical agent disclosed herein in the manufacture of a medicament for inhibiting hepatic fibrosis in liver disease, wherein the liver disease is selected from hepatitis B; hepatitis C; parasitic liver disease; post-transplant bacterial infections, post-transplant viral infections, or post-transplant fungal infections; alcoholic liver disease (ALD); non-alcoholic fatty liver disease (NAFLD); methotrexate-induced liver disease, isoniazid-induced liver disease, oxyphenistatin-induced liver disease, methyldopa-induced liver disease, chlorpromazine-induced liver disease, tolbutamide-induced liver disease, or amiodarone-induced liver disease; autoimmune hepatitis; sarcoidosis; Wilson's disease; hemochromatosis; Gaucher's disease; glycogen storage disease type III, glycogen storage disease type IV, glycogen storage disease type VI, glycogen storage disease type IX, or glycogen storage disease type X; α-1 antitrypsin deficiency; Zellweger syndrome; tyrosinemia; levulosemia; galactosemia; Budd-Chiari syndrome-related angiopathy, veno-occlusive disease-related angiopathy, or portal vein thrombosis-related angiopathy; or congenital hepatic fibrosis.

Object of the invention

[0008]

The object of the present invention is to provide an agent which is useful for the prevention and/or treatment of NASH, more particularly the prevention, treatment, or improvement of hepatic fibrosis in NASH, containing as its active ingredients an FXR agonist or a pharmaceutically acceptable salt thereof and an ARB or a pharmaceutically acceptable salt thereof.

Means for achieving object

[0009]

In an effort to achieve the above object, the inventors of the present invention, taking into account in particular that NASH constitutes a complex pathology involving a variety of interconnected factors, conducted various studies in an attempt to provide effective treatment using various combinations of multiple drugs having different mechanisms of action, and as a result of extensive research, discovered that administration of a combination of an FXR agonist or a pharmaceutically acceptable salt thereof, particularly obeticholic acid or a pharmaceutically acceptable salt thereof, and an ARB or a pharmaceutically acceptable salt thereof markedly inhibited hepatic fibrosis in a model of non-alcoholic steatohepatitis (NASH) in rats, thus arriving at the present invention. More particularly, the inventors discovered that the combination of these drugs produced a

Claims

[Claim 1]

A combination pharmaceutical agent, comprising as active ingredients a farnesoid X receptor agonist (FXR agonist) or a pharmaceutically acceptable salt thereof and an angiotensin II receptor blocker (ARB) or a pharmaceutically acceptable salt thereof.

[Claim 2]

The pharmaceutical agent of claim 1, in which the FXR agonist is obeticholic acid, chenodeoxycholic acid, INT-767, LY-2562175, Px-104 or LJN-452.

[Claim 3]

The pharmaceutical agent of claim 1 or 2, in which the FXR agonist is obeticholic acid.

[Claim 4]

The pharmaceutical agent of any one of claims 1-3, in which the ARB is losartan, candesartan, telmisartan, valsartan, olmesartan, irbesartan or azilsartan.

[Claim 5]

The pharmaceutical agent of any one of claims 1-4, in which the ARB is losartan.

[Claim 6]

The pharmaceutical agent of any one of claims 1-5 for use in treating non-alcoholic steatohepatitis (NASH).

[Claim 7]

The pharmaceutical agent for use of claim 6, characterized in that the FXR agonist or a pharmaceutically acceptable salt thereof and the ARB or a pharmaceutically acceptable salt thereof are to be administered simultaneously or separately at different times.

[Claim 8]

A combination of a farnesoid X receptor agonist (FXR agonist) or a pharmaceutically acceptable salt thereof and an angiotensin II receptor blocker (ARB) or a pharmaceutically acceptable salt thereof for use in the treatment of non-alcoholic steatohepatitis (NASH).

[Claim 9]

The combination for use of claim 8, in which the FXR agonist is obeticholic acid, chenodeoxycholic acid, INT-767, LY-2562175, Px-104 or LJN-452.

[Claim 10]

The combination for use of claim 8 or 9, in which the FXR agonist is obeticholic acid.

[Claim 11]

The combination for use of any one of claims 8-10, in which the ARB is losartan, candesartan, telmisartan, valsartan, olmesartan, irbesartan or azilsartan.

[Claim 12]

The combination for use of any one of claims 8-11, in which the ARB is losartan.

[Claim 13]

A kit for the treatment of non-alcoholic steatohepatitis (NASH), comprising:

1) a pharmaceutical agent comprising a farnesoid X receptor agonist (FXR agonist) or a pharmaceutically acceptable salt thereof;

2) a pharmaceutical agent comprising an angiotensin II receptor blocker (ARB) or a pharmaceutically acceptable salt thereof; and

3) instructions for administration of a combination of 1) and 2) above.

[Claim 14]

The kit of claim 13, in which the FXR agonist is obeticholic acid, chenodeoxycholic acid, INT-767, LY-2562175, Px-104 or LJN-452 and

ARB is losartan, candesartan, telmisartan, valsartan, olmesartan, irbesartan or azilsartan.

[Claim 15]

The combination pharmaceutical agent of any one of claims 1-5 for use in inhibiting hepatic fibrosis in liver disease, wherein the liver disease is selected from hepatitis B; hepatitis C; parasitic liver disease; post-transplant bacterial infections, post-transplant viral infections, or post-transplant fungal infections; alcoholic liver disease (ALD); non-alcoholic fatty liver disease (NAFLD); methotrexate-induced liver disease, isoniazid-induced liver disease, oxyphenistatin-induced liver disease, methyldopa-induced liver disease, chlorpromazine-induced liver disease, tolbutamide-induced liver disease, or amiodarone-induced liver disease; autoimmune hepatitis; sarcoidosis; Wilson's disease; hemochromatosis; Gaucher's disease; glycogen storage disease type III, glycogen storage disease type IV, glycogen storage disease type VI, glycogen storage disease type IX, or glycogen storage disease type X; α-1 antitrypsin deficiency; Zellweger syndrome; tyrosinemia; levulosemia; galactosemia; Budd-Chiari syndrome-related angiopathy, veno-occlusive disease-related angiopathy, or portal vein thrombosis-related angiopathy; or congenital hepatic fibrosis.

[Claim 16]

Use of the pharmaceutical agent of any one of claims 1-5 in the manufacture of a medicament for treating non-alcoholic steatohepatitis (NASH).

[Claim 17]

The use of claim 16, wherein the FXR agonist or a pharmaceutically acceptable salt thereof and the ARB or a pharmaceutically acceptable salt thereof are to be administered simultaneously or separately at different times.

[Claim 18]

Use of a combination of a farnesoid X receptor agonist (FXR agonist) or a pharmaceutically acceptable salt thereof and an angiotensin II receptor blocker (ARB) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating non-alcoholic steatohepatitis (NASH).

[Claim 19]

The use of claim 18, in which the FXR agonist is obeticholic acid, chenodeoxycholic acid, INT-767, LY-2562175, Px-104 or LJN-452.

[Claim 20]

The use of claim 18 or 19, in which the FXR agonist is obeticholic acid.

[Claim 21]

The use of any one of claims 18-20, in which the ARB is losartan, candesartan, telmisartan, valsartan, olmesartan, irbesartan or azilsartan.

[Claim 22]

The use of any one of claims 18-21, in which the ARB is losartan.

[Claim 23]

Use of the combination pharmaceutical agent of any one of claims 1-5 in the manufacture of a medicament for inhibiting hepatic fibrosis in liver disease, wherein the liver disease is selected from hepatitis B; hepatitis C; parasitic liver disease; post-transplant bacterial infections, post-transplant viral infections, or post-transplant fungal infections; alcoholic liver disease (ALD); non-alcoholic fatty liver disease (NAFLD); methotrexate-induced liver disease, isoniazid-induced liver disease, oxyphenistatin-induced liver disease, methyldopa-induced liver disease, chlorpromazine-induced liver disease, tolbutamide-induced liver disease, or amiodarone-induced liver disease; autoimmune hepatitis; sarcoidosis; Wilson's disease; hemochromatosis; Gaucher's disease; glycogen storage disease type III, glycogen storage disease type IV, glycogen storage disease type VI, glycogen storage disease type IX, or glycogen storage disease type X; α-1 antitrypsin deficiency; Zellweger syndrome; tyrosinemia; levulosemia; galactosemia; Budd-Chiari syndrome-related angiopathy, veno-occlusive disease-related angiopathy, or portal vein thrombosis-related angiopathy; or congenital hepatic fibrosis.