**ISSN 2455–9393**

**International Journal of Gastroenterology, Hepatology, Transplant & Nutrition**

**Original Article**

# Effect of simvastatin on the transforming growth factor β1, fibroscan scores, and aspartate transaminase to platelet index ratio patients with Liver Cirrhosis

**Kusnanto P., Prabowo NA, Bambang P**

Gastroenterohepatologi, Division of Internal Medicine Department, Medical Faculty, Universitas Sebelas Maret, Indonesia

**Address for Correspondence:**
**Dr. Nurhasan Prabowo**
E-mail: dr.nurhasan@gmail.com

| Access this article online | |
|---|---|
| QR Code | Website: www.journal.pghtn.com |

## ABSTRACT

**Background:** Cirrhosis of the liver is the liver disorder marked fibrosis and abnormal liver architecture. Treatment of liver cirrhosis, among others, is to reduce fibrogenesis. Simvastatin as an anti-fibrotic among others, by a mechanism reduce the activity of hepatic stellate cell of the liver, reduce cell proliferation liver stelat, increases the production of nitric oxide and decrease vascular resistance in the liver cirrhosis.
**Aim:** This research to determine effect of simvastatin on the transforming growth factor β1, fibroscan scores, and aspartate transaminase to platelet index ratio patients with liver cirrhosis.
**Methods:** This study is a randomized experiment, a sample of 30 people, divided into a control group given a placebo and the treatment given simvastatin 20 mg / day orally for 4 weeks. Before and after treatment measured levels of TGF β1, FibroScan score, and a score of APRI. Statistical analysis using SPSS 22 for windows. Two different test mean using parametric tests (independent t test, paired t test) and if the data is normally distributed variable or non-parametric tests (Mann-Whitney / Wilcoxon Signed Rank Test). P significant if p <0.05.
**Results:** The results showed that the administration of simvastatin 20 mg for 4 weeks will reduce levels TGF β1 (20,98+7,80 µg/dl pretreatment, 16,20+5,50µg/dl post treatment; p=0,013), reduce fibroscan scores (22,29+14,65 kpa pretreatment, 13,61+4,02 kpa post treatment; p=0,049) and reduce APRI scores (40,13+41,28 pretreatment, 23,41+17,61 post treatment; p=0,002).
**Conclusion:** This study demonstrated that administration Simvastatin will be reduced levels of the transforming growth factor β1, fibroscan scores, and aspartate transaminase to platelet index ratio patients with liver cirrhosis.

***Key words:*** *Simvastatin, Transforming Growth Factor β1, Fibroscan score, Aspartate Transaminase To Platelet Index Ratio, Liver Cirrhosis*

## BACKGORUND

Liver Cirrhosis is a disease in which the micro-circulation, a large blood vessel anatomy and the entire system architecture of the liver changes become irregular and the addition of the connective tissue surrounding liver parenchyma (Guyton dan Hall, 2011). Cirrhosis of the liver was initially believed to be a reversible process, but the process is not absolutely irreversible (McCormick, 2011). After an injury to the hepatocyte cells, liver cells turn into stelat á-smooth muscle actin positive myofibroblasts which in turn will produce extracellular matrix such as collagen and non-collagen (Beyond dan Iredale, 2000). Fibrogenesis occurred with stellate cell activation by cytokines TGF (transforming growth factor) β1, PDGF (platelet derived growth factor), TNF (tumor necrozing factor) α, and IGF (insulin growth factor) 1, resulting in increased the number of cells after, there is increased synthesis of extracellular matrix composed of collagens, glycoproteins, proteoglycans and glucosaminoglycans, and a decline of matrix degradation (Kuntz, 2002).

Treatment of cirrhosis include eliminating the causes of cirrhosis, suppress hepatic inflammation, and reduces fibrogenesis. Several important pathways in fibrogenesis can be inhibited. The inhibition of the cell stelat, the use of anti-oxidants, inhibition of the cytokine receptor antagonists, and

**ISSN 2455–9393**

inhibit collagen synthesis (McCormick, 2011). Curative treatment at an advanced stage of liver cirrhosis is liver transplantation. Although liver transplantation has been widely grown lately with a number of donors is quite adequate, but the clinical condition of the patient limit this therapy. The researchers began looking for ways to stop or even reduce fibrosis care to prevent complications that arise (Benyon dan Iredale, 2000).

Simvastatin will reduce hepatic venous pressure and increase hepatic perfusion in patients with cirrhosis (Albraldes, 2009). Anti-fibrotic mechanism of simvastatin as, among others, by lowering the activity of hepatic stellate cell of the liver (Shirin et al, 2013), reducing hepatic stellate cell proliferation and decreased collagen deposition (Rombouts et al, 2003), inhibit steatosis, fibrosis and carcinogenesis in NASH (Miyaki et al, 2011), and increase the production of nitric oxide (NO) and decrease vascular resistance in cirrhosis of the liver (Zafra et al, 2004). TGF-β is the most Fibrogenic factor in the activation of hepatic stellate cells in the mechanism of fibrogenesis (Gressnerr dan Weiskirchen, 2006). Vita et al reported that statins lower the Smad pathway activation by TGF-β. Smad pathway is the major signaling system for TGF-β. Inhibition of RhoA is intracellular mechanisms mediated by statin on the path of TGF-β. TGF - β through activation of the Smad pathway regulates many cellular responses including cell growth, cell survival, cell differentiation and extracellular matrix accumulation (Vita et al, 2008). Use of simvastatin in mice models of fibrosis showed decreased levels of TGF-β1 and decrease the degree of fibrosis (Vita et al, 2008; Wei Wang et al, 2013).

Assessment of the degree of liver cirrhosis can be done in various ways. As the gold standard in measuring the degree of liver fibrosis is by using liver biopsy and further interpreted in the Metavir score. This action is invasive, the patient will suffer pain, bleeding can occur, and rarely can cause death. With a small sample results might occur sampling error (Mona et al, 2011). Non-invasive method widely used to measure the degree of liver fibrosis. Luo reported that the diagnostic accuracy of TGF β1 in liver fibrosis patients with cirrhosis is quite good with an area under the curve of 82.5% (Luo et al, 2005). FibroScan is a non-invasive tool for measuring liver fibrosis by measuring liver stiffness. FibroScan method is painless and very good in diagnosing liver fibrosis with the area under the curve of> 90% (Mona et al, 2011). APRI is a tool for measuring liver fibrosis which is simple and easy to do. APRI sensitivity and specificity in diagnosing fibrosis was 76% and 71% (Shaheenn et al, 2007).

In previous studies in rats, simvastatin are known to have anti-fibrotic effects of hepatic better than fluvastatin (lukisvaya et al, 2007). Yang et al report simvastatin administration accompanied by protein kinase C inhibitor will reduce the activity of hepatic cells stelat, reduced collagen deposition, and decrease the degree of liver fibrosis in murine models of cirrhosis (Yang et al, 2011). But Shirin reported that atorvastatin and rosuvastatin have no anti-fibrotic effect on rat models of cirrhosis (Shirin et al, 2013). Additional experiments on rat models of cirrhosis show a benefit antifibrotik on simvatatin, tetrandrien, and candesartan (Darwin dan Aziz, 2006). Research in humans in HALT-C trial with the subject in 1050 of hepatitis C patients with ishaq score> 3, the use of simvastatin for 3.5 years will reduce the degree of liver fibrosis (Simon et al, 2015).

This research to determine effect of simvastatin on the transforming growth factor β1, fibroscan scores, and aspartat transaminase to platelet index ratio patients with liver cirrhosis.

## METHODS

This study is a randomized experiment, a sample of 30 people, divided into a control group given a placebo and the treatment given simvastatin 20 mg / day orally for 4 weeks. Inclusion criteria: Age 18 s / d 60 years, liver cirrhosis is characterized by clinical, laboratory and ultrasound liver, patients willing to participate approved informed consent. Criteria for exclusion: Pregnant Patients, Infection, Patients Encephalopathy grade II-IV, Malignancy / cancer, diabetes mellitus, chronic renal failure, heart failure, Simvastatin therapy> 3 months, Obesity, ascites permagna. Before and after treatment measured levels of TGF β1, FibroScan score, and a score of APRI. Statistical analysis using SPSS 22 for windows. Two different test mean using parametric tests (independent t test, paired t test) if the variable data is normally distributed and non-parametric tests (*Mann-Whitney / Wilcoxon Signed Rank Test)* if the data is not normally distributed. P significant if p<0,05.

## RESULT

The basic characteristics of research subjects and homogeneity can be seen in Table 1. Based on these data it appears that the basic characteristics of research subjects in the control group and the treatment group is homogeneous.

**Table 1. Characteristics of research subjects**

| Variable | Controle | | Treatment | | P |
|---|---|---|---|---|---|
| | Mean | Std Dev | Mean | Std Dev | |
| Hemoglobin (g/dL) | 11,38 | 1,68 | 11,27 | 1,08 | 0,838 |
| Trombochyte ($10^3$/µl) | 103,67 | 31,10 | 88,43 | 23,01 | 0,148 |
| Albumin (g/dL) | 3,08 | 0,51 | 3,04 | 0,65 | 0,865 |
| PT (s) | 16,67 | 4,37 | 15,87 | 1,82 | 0,530 |
| SGOT (U/L) | 77,20 | 94,62 | 80,36 | 134,59 | 0,880 |
| SGPT (U/L) | 38,40 | 51,52 | 36,93 | 79,97 | 0,652 |
| Billirubin-I (mg/dL) | 0,87 | 0,45 | 1,01 | 0,71 | 0,880 |
| Billirubin-II (mg/dL) | 0,75 | 0,49 | 0,67 | 0,40 | 0,621 |
| Billirubin Total (mg/dL) | 1,62 | 0,84 | 1,68 | 1,08 | 0,880 |
| INR | 1,42 | 0,50 | 1,35 | 0,28 | 0,780 |

Results of testing the mean difference two control and treatment groups for variable TGF β1, FibroScan score, and a score of APRI to a prior administration of simvastatin treatment shows the test results were not significant at the 5 percent significance level (p> 0.05). Thus the variable TGF β1, FibroScan score, and APRI score in the control group and the treatment of conditions

**ISSN 2455–9393**

before administration of simvastatin did not differ conclusively (Table 2).

**Table 2. Comparison of TGFβ1, Scores FibroScan, and APRI Score on control and treatment groups in Condition Before Treatment**

| Variable | Control | | Treatment | | P value |
|---|---|---|---|---|---|
| | Mean | Std Deviasi | Mean | Std Deviasi | |
| TGF β1 (µg/dL) | 21,74 | 9,71 | 20,98 | 7,80 | 0,817 |
| Fibroscan score (kpa) | 17,85 | 5,32 | 22,29 | 14,65 | 0,477 |
| APRI score | 24,74 | 19,99 | 40,13 | 41,28 | 0,591 |

Results of testing the mean difference two control and treatment groups for variable TGF β1 and score FibroScan on the condition after treatment administration of of simvastatin showed significant assay results for the variable TGF β1, and variable FibroScan score with 5 percent significance level ($p < 0.05$). But for the variable APRI score shows the test results were not significant at the 5 percent significance level ($p > 0.05$) (Table 3).

**Table 3. Comparison of TGFβ1, Scores FibroScan, and APRI score between Control group and Treating Condition After Treatment**

| Variable | Control | | Treatment | | P |
|---|---|---|---|---|---|
| | Mean | Std Dev | Mean | Std Dev | |
| TGFβ1 (µg/dL) | 25,60 | 11,71 | 16,20 | 5,50 | 0,011* |
| *Fibroscan* (kpa) score | 23,62 | 15,56 | 13,61 | 4,02 | 0,027* |
| APRI score | 26,70 | 24,63 | 23,41 | 17,61 | 0,747 |

Results of testing the mean different 2 t test for paired samples to variable TGF β1 and FibroScan scores before and after treatment in the group treated samples show significant results of the testing on the degree of significance of 5 percent ($p < 0.05$) for both variables. It may mean that after getting treatment administration of simvastatin, variable TGF β1 and score FibroScan change convincingly. Variable TGF β1 and FibroScan score after treatment decreased to change convincingly, as well as variables change APRI score decreased significantly (Table 4).

**Table 4. Comparison of TGF-β1, FibroScan Scores and APRI score before and after treatment in treatment group**

| Variable | Pre-test | | Post test | | P |
|---|---|---|---|---|---|
| | Mean | Std Dev | Mean | Std Dev | |
| TGF β1 (µg/dL) | 21,74 | 9,71 | 25,60 | 11,71 | 0,013* |
| Fibroscan score (kpa) | 17,85 | 5,32 | 23,62 | 15,56 | 0,049* |
| APRI score | 24,74 | 19,99 | 26,70 | 24,63 | 0,002** |

The result of the calculation different 2 mean by Mann Whitney test between variables delta-TGF β1, delta-FibroScan, and delta-APRI showed that the three variables that change (delta-TGF β1, delta_Fibroscan and delta_APRI) differs convincingly on the degree of significance of 5 percent ($p < 0.05$) (Table 5).

**Table 5. Comparison of TGF-β1, and APRI Score FibroScan Before and After Treatment**

| Variable | Control | | Treatment | | P |
|---|---|---|---|---|---|
| | Mean | Std Dev | Mean | Std Dev | |
| *Delta*-TGF β1 (µg/dL) | -3,86 | 5,18 | 4,77 | 6,22 | 0,001** |
| *Delta-Fibroscan* (kpa) | -5,77 | 11.06 | 8,68 | 14,95 | 0,001** |
| *Delta*-APRI | -1,96 | 15,79 | 16,72 | 26,55 | 0,010* |

Simvastatin therapy would reduce levels of TGF β1, FibroScan score, and APRI score in patients with liver cirrhosis. It can be seen from the administration of simvastatin 20 mg for 4 weeks will reduce levels of TGF β1, FibroScan score, and APRI score in patients with liver cirrhosis.

Pleiotrofik effect mechanism of statin associated with inhibition of the synthesis of mevalonate pathway of isoprenoid intermediates such as isopentenyl adenosine, farnesylpyrophosphate and geranyl-geranyl pyrophosphate. Intermediate serves as a hook protein to lipid in the cell membrane (lipid anchors) for post-translational modification of a number of proteins involved in intracellular signal transduction pathways, including heterotrimeric G-proteins and small guanosine triphosphate (GTP) -binding proteins, such as Ras, Rho and Rac1 (Tamargo et al., 2007). Small molecular weight G-proteins are involved in cell proliferation, differentiation, apoptosis, migration, contraction and regulation of gene transcription (McFarlane et al, 2002). Small molecular weight G-proteins are involved in cell proliferation, differentiation, apoptosis, migration, contraction and regulation of gene transcription (Sadowitz et al., 2010).

Rac, activating Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in Smooth Muscle Cell (SMC) and endothelium, is a major source of ROS in the vascular wall. Increased ROS production will result in endothelial dysfunction and progression of atherosclerosis. Wassmann et al reported that atorvastatin lowers the production of ROS induced by angiotensin II and endothelial growth factor (EGF). Further explained that atorvastatin lowered Rac in the membrane and increase in cytoplasmic resulting in a decrease in NADPH oxidase activity (Paul 2003).

Activation of Angiotensin receptor 1 (AT1) angiotensin angiotensin II in the cells of the blood vessels is one of the most prominent mechanism of ROS production in vitro and in vivo. AT1 receptor expression levels following and influenced by up or down-regulation of the activity of the renin angiotensin system (RAAS). It has been shown that statins inhibit

**ISSN 2455–9393**

posttranslational isoprenylation small GTP-binding protein in the vascular smooth muscle cells. Rac1 GTPase allegedly essential for the activation of NADPH oxidase and the release of free radicals. Rac1 is posttranslational geranylgeranylated. Giving statins lowers the membrane translocation of Rac1 under basal conditions and actually prevent angiotensin II-mediated increased expression of Rac1 in cell membranes (Wassmann S et al, 2001).

Nucleus Factor kappa Beta (NFκb) had a seminal role in immunity, because it activates genes encoding proinflammatory. It is activated by phosphorylation, ubiquitination and subsequent proteolytic degradation of the inhibitor of kappa B kinase (IKK). NFκb liberated translocate to the nucleus and bind as a transcription factor kappa B motif (kb) in the target gene promoter, leading to transcription. Antioxidants can inhibit the activation of nucleus factor κβ (NFκb) (Guntur 2008).

Statins have antioxidant capabilities so that they can as antioxidants act as inhibitors against κβ kinase inhibitor (IKK) so that activation of nucleus factor κβ (NFκβ) inhibited resulting in a decrease in the number of pro-inflammatory cytokines including IL-6 and TNF-α. Excessive TNF-α would lead to oxidative stress (Guntur, 2008). So will decrease the degree of fibrosis in patients with liver cirrhosis.

Previous studies in rats, simvastatin are known to have anti-fibrotic effects of hepatic better than fluvastatin (lukisvaya et al, 2007). This study uses a rat model of liver fibrosis induced by administration of tioacetamid 200 mg / kg 2 times a week for 12 weeks. The study compared the effectiveness of simvastatin 5 mg / kg, simvastatin 10 mg / kg, and fluvastatin 10 mg / kg orally for 2 months after 12 weeks of administration of tioacetinamide. The degree of liver fibrosis was measured by histological examination of the liver with mallory azan staining hydroxiproline, and measurement of mRNA levels of procollagen 1, MMP 13 and TIMP 1. The results showed that simvastatin had moderate anti-fibrotic, while fluvastatin does not have anti-fibrotic. This is evidenced by improvement of liver histology and increased mRNA levels of MMP 13 in rats given a dose of 10 mg simvastatin (lukisvaya et al, 2007).

Yang et al reported the administration of simvastatin with protein kinase C inhibitor will reduce the activity of hepatic cells stelat, reduced collagen deposition, and decrease the degree of liver fibrosis in murine models of cirrhosis (Yang et al, 2011). The study by Yang et al use a mouse model of liver fibrosis induced by intraperitoneal injection of carbon tetrachloride for 6 weeks, then given pravastatin and enzasnaurin (inhibitor of protein kinase C) for 5 weeks. Assessment of liver fibrosis using liver histology using masson trichome staining and immunohistochemical examination of α-smooth muscle actin to show HSC activation. Results showed statins would improve liver histological and lower activation of HSC, this effect will be increased by administering a combination of satin and enzasnaurin (inhibitor of protein kinase C) (Yang et al, 2011).

Shirin et al reported that atorvastatin and rosuvastatin have no anti-fibrotic effect on rat models of cirrhosis (Shirin et al, 2013). This study uses a rat model of liver fibrosis with induction tioacetamide for 12 weeks and using drugs artovastatin dose of 1, 10, and 20 mg / kg, rosuvastatin doses of 1, 2.5, 5, 10, and 20 mg / kg. Assessment of the degree of fibrosis using histological examinations, measurement of hisroksiprolin, levels of malondialdehyde, measurement HSC. The results showed that rosuvastatin artovastatin and not have the effect of improvement in liver fibrosis. However, this study shows that both artovastatin and rosuvastatin safe, has no side effects, do not add to mortality, and well tolerated in mice models of fibrosis, it is shown by the levels of transaminase enzymes, levels of malondialdehyde, levels hydroxiprolline, and histology were not increased bad in rats receiving statins (Shirin et al, 2013). Additional experiments on rat models of cirrhosis show a benefit antifibrotik on simvatatin, tetrandrien, and candesartan (Darwin dan Aziz, 2006).

Research in humans, the HALT-C trial is a cohort study that examined effect simvastatin in subjects with chronic hepatitis C with the use of simvastatin for 3.5 years will reduce the degree of liver fibrosis (Simon et al, 2015). The study involved 1050 subjects in the Finnish study and were followed for 3.5 years. Assessment of the degree of liver fibrosis using the Ishak score. The results showed that the subjects who used statins hepatitis C will decrease the degree of liver fibrosis with an average of 0.34, whereas in subjects who did not use statins ishak an increase in the average score of 0.42 with a Hazard Ratio of 0.31 (95 % CI 0.1 to 0.97). The weakness of this study do not mention a dose of simvastatin (Simon et al, 2015).

Assessment of the degree of liver cirrhosis can be done in various ways. As the gold standard in measuring the degree of liver fibrosis is by using liver biopsy and further interpreted in Metavir score. This action is invasive, the patient will suffer pain, bleeding can occur, and rarely can cause death. With a small sample results might occur sampling error (Mona et al, 2011). Non-invasive method widely used to measure the degree of liver fibrosis. Luo reported that the diagnostic accuracy of TGF β1 in liver fibrosis patients with cirrhosis is quite good with an area under the curve of 82.5% (Luo et al, 2005). FibroScan is a non-invasive tool for measuring liver fibrosis by measuring liver stiffness. Meniumbulkan FibroScan method is not painful and very good in diagnosing liver fibrosis with the area under the curve of> 90% (Mona et al, 2011). AST to platelet index ratio (APRI) is a tool for measuring liver fibrosis which is simple and easy to do. APRI sensitivity and specificity in diagnosing fibrosis was 76% and 71% (Shaheenn et al, 2007).

This study uses TGF β1, FibroScan score, and APRI score as a marker of liver fibrosis. Previous research simvastatin as an anti-fibrotic liver has not been done using markers TGF β1, FibroScan score, and APRI score as a marker of liver fibrosis. This study shows the alignment of with other studies that simvastatin has anti-fibrotic effect on liver cirrhosis in which the research is demonstrated by decreased levels of TGF β1, FibroScan score, and APRI score in patients with liver cirrhosis in administration of simvastatin 20 mg for 4 weeks.

## CONCLUSION

1. Simvastatin therapy lowered levels of TGF-β1 in patients with liver cirrhosis

**ISSN 2455–9393**

2. Simvastatin therapy lowered FibroScan scores in patients with liver cirrhosis
3. simvastatin theraphy lowered the APRI score in patients with liver cirrhosis

## REFERENCES


1. Abenavoli L. 2007. Elastrography in hepatology. Can J gastroenterol; 21 (12): 839–42.
2. Abraldes JG, Rodriguez-Vilarrupla A, Graupera M, et al. 2007. Simvastatin treatment improves liver sinusoidal endothelial dysfunction in CCl4 cirrhotic rats. J Hepatol. 46: 1040–1046.
3. Anand, B.S. 2002. Cirrhosis of Liver. Western Journal of Medicine, 171: 110-115.
4. Bader T. 2010. The Myth of Statin-Induced Hepatotoxicity. Am J Gastroenterol; 105: 978–980.
5. Bansal MB and Friedman SL. 2011. Hepatic Fibrogenesis. In : Dooley JS, Lok ASF, Burroughs AK, Heathcote EJ (Editors). Sherlock's Diseases of the Liver and Biliary System. 12th Edition. West Sussex: Blackwell Publishing Ltd. 94-102.
6. Bataler R, Brenner DA. 2005. Liver Fibrosis. J. Clin. Invest. 115: 209–218.
7. Bataller R Brenner DA. 2009. Miscellaneous, Overview of liver fibrosis, Textbook of Gastroenterology, fifth Edition. Blackwell Publishing. 658–79.
8. Beddosa P, Poynard T. 1996. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative study Group. Hepatology.; 24: 289–93.
9. Bemion D, Arthur MJP. 2001. ekstracelluler matrix degradation and the role of stellata cells. Semin Liv Dis 21: 373–84.
10. Benyon RC dan Iredale JP. 200. Is liver fibrosis reversible? gut.46.4.44346: 443-446 G
11. Bergkamen HS. 2007. Hepatocyte apoptosis and necrosis. Textbook of Hepatology From Basic Science to Clinical Practice, Third Edition. Blackwell Publishing; 335-347.
12. Czeczot H, Scibior D, Skrzycki M, Podsiad M. 2006. Glutathione and GSH-dependent enzymes in patients with liver cirrhosis and hepatocellular carcinoma. Acta Biochim Pol 53: 237–242.
13. Cobbold JFL. 2007. Transient elastrography for assessement of chronic liver disease: ready for clinic.World J Gastroenterology. 4791–97.
14. Dahlan M.S. 2009. Menggunakan rumus besar sampel secara benar. Dalam : Dewi J (editor). Besar sampel dan cara pengambilan sampel dalam penelitian kedokteran dan kesehatan. Salemba Medika. Jakarta. Edisi 2. 33-78.
15. Darwin IE dan Aziz HK. 2006. Role of simvastatin, tetrandrine and candesartan in experimental induced liver fibrosis in rats. Alexandria Journal of Medicine; 42: 27-31.
16. Ekong U, Zeng S, Dun H, Feirt N, Guo J, Ippagunta N, et al. 2006. Blockade of the receptor for advanced glycation end products attenuates acetaminophen-induced hepatotoxicity in mice. J Gastroenterol Hepatol 21: 682–688.
17. Franchis R. Evolving. 2005. Consensus In Portal Hypertension Report Of The Baveno IV Consensus Workshop On Methodology Of Diagnosis And Therapy In Portal Hypertension. J Hepatol .43: 167–176.
18. Ferri FF. 2015. Cirrhosis. In : Ferri FF (editor). Ferri's Clinical Advisor. Alpert : Elsevier. 297-8.
19. Friedman SL. 2007. Cellular and molecular pathobiology of liver fibrosis and its pharmacological intervention. Hepatology; 590-599
20. Goodman and Gilman. 2008. Drug Therapy for Hypercholesterolemia and Dyslipidemia. In Brunton L, Parker K, Blumental D and Buxton I (editors). Goodman & Gilman's Manual of Pharmacology and Therapeutics. Mc Graw-Hill Companies. USA, 611-15.
21. Gressner AM, Weiskirchen R. Modern pathogenik concepts of liver fibrosis suggest stellate cells and TGF-β as mayor player and therapeutic targets. J. cell. Mol. Med. 2006; 10: 76–99.
22. Grigorescu M. 2006. Noninvasiv biochemical marker of liver fibrosis. J gastrointestin Liver Dis.; 149-159.
23. Grunhage F,lammert F. 2003. Assessement of hepatic fibrosis in chronic viral hepatitis. Hepatology- A clinical textbook. New York : McGraw Hill. 291–300.
24. Guntur HA, 2008. SIRS, sepsis dan syok septik imunologi, Diagnosis dan Penatalaksanaan). Dalam : Guntur (editor). Perspektif masa depan imunologi-infeksi. Sebelas Maret University Press. Surakarta. 35-37.
25. Guyton A and Hall J. 2011. Liver. In : Guyton A, Hall J. (editors). Textbook of Medical Physiology. 12edition. Philadelphia : Saunders Elsevier. 967-85.
26. Hadi, Sujono. 2002 . Gastroenterologi . Bandung : PT Alumni. Hal : 613–651.
27. Hyogo H, Yamagishi S. 2008. Advanced glycation end products (AGEs) and their involvement in liver disease. Curr Pharm Des 14: 969–972.
28. Iredale JP. 2007. Models of liver fibrosis: exploring the dynamic nature of inflammation and repair in a solid organ. J. Clin. Invest. 117: 539–548.
29. Josan K, Majumdar SR, McAlister FA. 2008. The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials. CMAJ;178(5). 576-584.
30. Judajana. 2005. Simposium Pelaksanaan Pembuatan Proposal Penelitian. FK-UNAIR.
31. Khimji A, Shao R, Rockey D. 2008. Divergent Transforming Growth Factor-β Signaling in Hepatic Stellate Cells after Liver Injury. Am J Pathol. 173(3): 716–727.
32. Kirkham P. 2007. Oxidative stress and macrophage function: a failure to resolve the inflammatory response. Biochem Soc Trans 35: 284–287.
33. Knopp RH. 1999. Drug Treatment of Lipid Disorders. NEJM, 341(7): 498-508.
34. Kumar S, Grace ND, Qamar AA. 2012. Statin Therapy Decreases the Risk of Hepatic Decompensation in Cirrhosis. Gastroenterology 142 (5) 1: 919-920.
35. Kuntz E, Kunt HD. 2008. Liver Cirrhosis. In: Kuntz E, Kunt HD. (editors). Hepatology, Textbook and Atlas. 3rd Edition. Chapter 35: 738-772.
36. Kusumobroto HO. 2007. Dalam : Lesmana, Sulaiman, Akbar, Noer. Editors. Buku Ajar Ilmu Penyakit Hati. Jakarta: Jayabadi. Hal: 335-45.

**ISSN 2455–9393**


37. Liu Y, Dai B, Xu C, Fu L, Hua Z, Mei C. 2011. Rosiglitazone Inhibits Transforming Growth Factor-b1 Mediated Fibrogenesis in ADPKD Cyst-Lining Epithelial Cells. PLoS ONE 6(12): e28915
38. Lukivskaya O, Popov Y, Zaks J, Schuppan D, Buko V. 2007. Comprarison of two statins efficacy on a reversibility of experimental rat liver fibrosis. EASL; 11-14:4.
39. Luo R, Yang S, Xie J, Zhao Z, He Y, Yao J. 2001, Diagnostic value of five serum markers for liver fibrosis. Zhonghua Gan Zang Bing Za Zhi; 9(3): 148-5.
40. Mahassadi AK. 2010. Diagnostic accuracy of biochemic markers of fibrosis in black African patients with chronic hepatitis B. NEJM. 12(12): 1413-1420.
41. McCormick PA. 2011. Hepatic Cirrhotic. In : Dooley JS, Lok ASF, Burroughs AK, Heathcote EJ. (Editors). Sherlock's Diseases of the Liver and Biliary System. 12th Edition. West Sussex : Blackwell Publishing Ltd. 103-20.
42. McFarlane SI, Muniyappa R, Francisco R, Sowers JR. 2002. Pleiotropic Effects Of Statins: Lipid Reduction And Beyond. J Clin Endocrinol Metab 87(4): 1451–1458.
43. Miyaki T, Nojiri S, Shinkai N, Kusakabe A, Matsuura K, Iio E, et al. Pitavastatin inhibits hepatic steatosis and fibrosis in non-alcoholic steatohepatitis model rats. Hepatol Res 2011; 41: 375-385.
44. Mona HM, Pinzani M. 2011. Reversal of hepatic fibrosis: pathophysiological basis of antifibrotic therapies. Hepat Med; 3: 69–80.
45. Nayak, NC. 2011. End Stage Chronic Liver Disease , Yesterday, Today and Tomorrow. In : Michelli, L Miranda. (editors). Hepatology Research And Clinical Development Liver Cirrhorsis: Causes, Diagnosis And Treatment. New York : Nova Biomedical Books. 59–83.
46. Nurdjanah, S. Sirosis Hati. Dalam : Sudoyo AW, Setiohadi B, Alwi I, Simadibrata M, Setiati S, Syam AF. Buku Ajar Ilmu Penyakit Dalam Edisi 6 Jilid I. Jakarta: Interna publishing. Hal 668-73.
47. Paul DP, Gahtan V. 2003. Noncholesterol-Lowering Effect of Statins. Vasc Endovasc Surg, 37: 301-13.
48. Rifa'i M. 2009. Signal Transduksi Dan Sistem Pertahanan Tubuh. Malang : Galaxy Science. Hal: 245-67.
49. Rombouts K, Kisanga E, Hellemans K, Wielant A, Schuppan D, Geerts A. Effect of HMG-CoA reductase inhibitors on proliferation and protein synthesis by rat hepatic stellate cells. J Hepatol 2003; 38: 564-572.
50. Sadowitz B, Maier KG, Gahtan V. 2010. The pleiotropic effects of statins in cardiovascular disease. Vasc Endovascular Surg 44(4): 241-251.
51. Sage PB. 2007. Liver and biliary tract histology. Textbook of Hepatology From Basic Science to Clinical Practice, Third Edition. London : Blackwell Publishing; 9-19.
52. Santjaka A. 2011. Teknik sampling. dalam : Sigit H, Abay F (editors). Statistik untuk penelitian kesehatan. Yogyakarta : Nuha Medika. Edisi I. 50-66.
53. Sebekova KV, Kupcova R, Schinzel A, Heidland J. 2002. Markedly elevated levels of plasma advanced glycation end products in patients with liver cirrhosis — amelioration by liver transplantation. J Hepatol 36: 66–71.
54. Shaheen AA, Myers RP. 2007. Diagnostic accuracy of the Aspartate aminotransferase- to – Platelet Rasio Index for the prediction of hepatitis C – related fibrosis : A systematic review. Hepatology; 912–20.
55. Shirin H, Sharvit E, Aeed H, Gavish D, Bruck R. 2013. Atorvastatin and rosuvastatin do not prevent thioacetamide induced liver cirrhosis in rats. World J Gastroenterol; 19(2): 241-248.
56. Silbernagl S.,Lang F. 2003. Fibrosis dan sirosis hati. Teks dan Atlas berwarna; Patofisiologi. Jakarta : EGC. 172-73.
57. Simon TG, King LY, Zheng H, Chung RT. 2015. Statin Use is associated with a reduced risk of fibrosis progression in chronic hepatitis C. J Hepatol. 62 j: 18–23.
58. Stancu C, Sima A. 2001. Statins: Mechanism Of Action And Effects. J Cell Mol Med (5) 4: 378-387.
59. Tamargo J, Caballero R, Gómez R, Núñez L, Vaquero M, Delpón E. 2007. Lipid Lowering Therapy With Statins, A New Approach To Antiarrhythmic Therapy. Pharmacology & Therapeutics 114: 107–126.
60. Tarantino G , Conca P, Riccio A, Tarantino M, Di Minno M, Chianese D, et al. 2008. Enhanced serum concentrations of transforming growth factor-beta1 in simple fatty liver: is it really benign? Journal of Translational Medicine, 6: 72.
61. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. 2007. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 39: 44–84.
62. Videla LA. 2009. Oxidative stress signaling underlying liver disease and hepatoprotective mechanisms. World J Hepatol 31: 72–78.
63. Vita RJ, Galán E, Santamaría B, López S, Díez R, Colio LM, et al. 2008. Essential role of TGF-beta/Smad pathway on statin dependent vascular smooth muscle cell regulation. PLoS One; 3(12): e3959.
64. Wai CT, Greenson JK, Fontana RJ. 2003. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology; 38: 518–26.
65. Wassmann S, Laufs U, Baumer AT, Muller K, Konkol C, Sauer H, et al. 2000. Inhibition of Geranylgeranylation Reduces Angiotensin II Mediated Free Radical Production in Vascular Smooth Muscle Cells: Involvement of Angiotensin AT1 Receptor Expression and Rac1 GTPase. Mol Pharmacol (59): 646–654.
66. Wei Wang, Zhao C, Zhou J, Zhen Z, Wang Y, Shen S. 2013. Simvastatin Ameliorates Liver Fibrosis via Mediating Nitric Oxide Synthase in Rats with Non-Alcoholic Steatohepatitis-Related Liver Fibrosis. PLoS One.; 8(10): e76538.
67. Wolfrum S, Jensen KS, Liao JK. 2003. Endothelium-Dependent Effects of Statins. Arterioscler Thromb Vasc Biol 23: 729-736.
68. Wu SD. 2008. Staging of liver fibrosis in chronic hepatitis B patients with a composite predictive model: A comparative study. World J. Gastroenterology 28; 16: 501-507.
69. Xu R, Zhang Z,Wang FS. 2012. Liver fibrosis: mechanisms of immune-mediated liver injury. Cellular & Molecular Immunolog; 9: 296–301.
70. Yagmur E, Tacke F, Weiss C, Lahme B, Manns MP, Kiefer P, et al. 2006. Elevation of Nε-(carboxymethyl) lysine-

**ISSN 2455–9393**

modified advanced glycation end products in chronic liver disease is an indicator of liver cirrhosis. Clin Biochem 39: 39–45.

71. Yanez RM, Dávalos A, Castillo J. 2008. Withdrawal From Statins: Implications For Secondary Stroke Prevention And Acute Treatment. Int J Stroke 3(2): 85-87.
72. Yang JI, Yoon JH, Bang YJ, Lee SH, Lee SM, Byun HJ, et al. 2010. Synergistic antifibrotic efficacy of statin and protein kinase C inhibitor in hepatic fibrosis. Am J Physiol Gastrointest Liver Physiol 298: G126–G132.
73. Zafra C, Abraldes JG, Turnes J, Berzigotti A, Fernández M, Garca-Pagán JC, et al. . enhances hepatic nitric oxide production and decreases the hepatic vascular tone in patients with cirrhosis. Gastroenterology; 126: 749-755.
74. Sebastian G, Alberti A. 2006. Noninvasiv fibrosis biomarkers reduce but not subtitute the need for liver biopsy. World J Gastroenterol 12; 3682-3694 Humana Press Inc, Totowa, New Jersey, pp 236-57.
75. Widlansky ME, Gokce N, Keaney JF, and Vita JA. 2003. The Clinical Implications of Endothelial Dysfunction. JACC, 42(7): 1149-60.
76. Wolfrum S, Kristin S and Liao JK. 2003. Endothelium-Dependent Effect of Statin. Arterioscler Thromb Vasc Biol, 23: 729-36.
77. Yanez MR, Agulla J, Gonzalez RR, Sobrino T and Castillo J. 2008. Review: Statin and Stroke. Therapeutic Advances in Cardiovascular Disease, 2(3): 157-66.
78. Zoccai GG, Abbate A, Liuzzo G and Biasucci LM. 2003. Atherothrombosis, Inflammation and Diabetes. JACC, 41(7): 1071-77.