WCJD 世界华人消化杂志®

在线投稿: http://www.baishideng.com/wcjd/ch/index.aspx
帮助平台: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.11569/wcjd.v23.i36.5743

世界华人消化杂志 2015年12月28日; 23(36): 5743-5749
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

述评 EDITORIAL

肝纤维化诊治机遇与挑战

张 国, 胡 烨, 陆伦根

张国, 胡烨, 广西壮族自治区人民医院消化内科 广西壮族自治区南宁市 530021

陆伦根, 上海交通大学附属第一人民医院消化科 上海市 200080

张国, 主任医师, 硕士生导师, 主要从事慢性肝病, 包括病毒性肝炎、肝纤维化、肝癌的基础与临床研究.

国家自然科学基金资助项目, Nos. 81360077, 30960145, 81172260

作者贡献分布: 本文由张国与胡烨完成; 陆伦根审校.

通讯作者: 张国, 主任医师, 530021, 广西壮族自治区南宁市桃源路6号, 广西壮族自治区人民医院消化内科.
zhangguogx@hotmail.com
电话: 0771-2186545

收稿日期: 2015-09-25
修回日期: 2015-10-19
接受日期: 2015-10-26
在线出版日期: 2015-12-28

Opportunity and challenge for diagnosis and treatment of hepatic fibrosis

Guo Zhang, Ye Hu, Lun-Gen Lu

Guo Zhang, Ye Hu, Department of Gastroenterology, the People's Hospital of Guangxi Zhuang Autonomous Region, Nanning 530021, Guangxi Zhuang Autonomous Region, China

Lun-Gen Lu, Department of Gastroenterology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200080, China

Supported by: National Natural Science Foundation of China, Nos. 81360077, 30960145 and 81172260

Correspondence to: Guo Zhang, Chief Physician, Department of Gastroenterology, the People's Hospital of Guangxi Zhuang Autonomous Region, 6 Taoyuan Road, Nanning 530021, Guangxi Zhuang Autonomous Region, China. zhangguogx@hotmail.com

Received: 2015-09-25
Revised: 2015-10-19
Accepted: 2015-10-26
Published online: 2015-12-28

Abstract

Hepatic fibrosis is a wound-healing response to all kinds of chronic liver injuries, which is characterized by extracellular matrix remodeling. Hepatic fibrosis ultimately leads to cirrhosis and even hepatic cell carcinoma. Thus, diagnosis and treatment of hepatic fibrosis are important for the management of chronic liver diseases. Recently, the study of hepatic fibrogenesis has witnessed tremendous progress, with many new diagnostic and therapeutic options emerging. This article mainly discusses the opportunity and challenge for diagnosis and treatment of hepatic fibrosis.

Key Words: Hepatic fibrosis; Diagnosis; Treatment; Opportunity

Zhang G, Hu Y, Lu LG. Opportunity and challenge for diagnosis and treatment of hepatic fibrosis. Shijie Huaren Xiaohua Zazhi 2015; 23(36): 5743-5749 URL: http://www.wjgnet.com/1009-3079/23/5743.asp DOI: http://dx.doi.org/10.11569/wcjd.v23.i36.5743

摘要

肝纤维化是一种以细胞外基质重塑为特征的慢性肝损害, 随着病程进展可发展为肝硬化甚至肝癌. 因此, 肝纤维化的诊治是慢性肝病管理的关键步骤. 随着肝纤维化发生发

背景资料
肝穿刺组织学检查因创伤性、患者依从性差及难以多次重复检查应用受限, 如何发展可靠的无创肝纤维化诊断技术, 如何满足临床肝纤维化的精准诊断目标和争取特异性治疗手段的突破, 是未来肝纤维化诊治研究的重点方向.

同行评议者
杜雅菊, 教授, 哈尔滨医科大学附属第二医院消化内科

同行评价

肝纤维化是一种以细胞外基质重塑为特征的慢性肝损害, 其诊断和治疗是一项临床难题. 本文综述了肝纤维化研究的新进展, 并评价了其诊治新机遇和面临的挑战, 资料收集较全面, 论述周密, 具有重要的临床意义.

展的病理机制不断阐明, 新的诊治策略陆续涌现. 本文针对近年来肝纤维化研究的新进展及其诊治新机遇和面临的挑战进行阐述.

关键词: 肝纤维化; 诊断; 治疗; 机遇

核心提示: 近年来涌现出不少肝纤维化诊治的新方法和新手段. 然而, 面对复杂临床的需求, 这些无创诊断方法的诊断效力有亟待提高的空间. 治疗方面, 现有抗肝纤维化方法普遍缺乏特异性, 新的治疗药物也有待更多研究数据来评价.

张国, 胡烨, 陆伦根. 肝纤维化诊治机遇与挑战. 世界华人消化杂志 2015; 23(36): 5743-5749 URL: http://www.wjgnet.com/1009-3079/23/5743.asp DOI: http://dx.doi.org/10.11569/wcjd.v23.i36.5743

0 引言

肝纤维化是多种病因引起的慢性肝损害, 表现为肝内细胞外基质异常沉积, 并影响肝脏的功能, 是肝脏疾病晚期并发症的基础. 随着基础和临床研究的不断开展, 我们对肝纤维化的认识也在不断完善, 从最初的“基质生物学时代”[1], 到“肝星状细胞生物学时代”[2], 再到目前的“创伤愈合整合反应新时代”[3], 见证了近年来在这一领域取得的巨大进展. 这些研究不仅为进一步阐明肝纤维化发生发展机制奠定基础, 更为其临床诊断和治疗新方法提供重要依据.

1 肝纤维化的病因及转归

肝纤维化的病因是多样复杂的, 任何长期持续损害肝脏的刺激, 都可导致肝纤维化的形成. 常见的原因有乙型肝炎病毒或丙型肝炎病毒感染、酗酒、肥胖、寄生虫感染、药物或毒物、自身免疫性肝炎、胆汁淤积、代谢性疾病、静脉阻塞及特发性肝纤维化等.

对于绝大多数慢性肝损伤患者而言, 早期肝纤维化是可逆的. 然而, 持续的刺激终可导致肝纤维化演变为肝硬化, 临床呈低蛋白血症、腹水、静脉曲张、呕血、便血、感染、电解质紊乱、肝性脑病、肝肾综合征等表现, 甚至出现癌变.

2 肝纤维化诊断机遇与挑战

肝纤维化病理改变多数发展较为缓慢, 同时, 肝脏是一个有强大代偿能力的静默器官. 大部分慢性肝炎乃至早期肝硬化患者, 并无典型临床表现, 一旦出现明显症状、体征, 多数已是失代偿期肝硬化甚至出现肝衰竭. 因此, 早期诊断肝纤维化、及时评估并发现进展期肝纤维化对慢性肝病预后评估及治疗决策有重要价值, 是慢性肝病管理的关键步骤之一.

肝穿刺组织学检查作为肝纤维化诊断的“金标准”, 因其有创性而致患者依从性差及难以重复检查, 且易因肝组织标本取样误差而导致诊断的准确性不足, 故应用受限. 因而, 发展无创肝纤维化诊断技术具有广阔的临床需求.

2.1 无创影像诊断技术 瞬时弹性成像技术(transient elastography, TE)、声脉冲辐射力成像技术(acoustic radiation force impulse, ARFI)、核磁共振弹性成像(magnetic resonance elastography, MRE)是3种最热门的肝纤维化无创影像诊断技术. Fibroscan是其中最早推出的一种TE, 应用该技术检测慢性肝炎患者肝脏硬度、评估肝纤维化进展的有效性得到临床实践证实, 已获EASL、AASLD、APASL及中国肝病学会指南推荐. Afdhal等[4]通过对2005-2008年在6家医疗中心的748例慢性乙型肝炎/丙型肝炎患者进行Fibroscan和肝活检, 对比两者在肝纤维化诊断分析中的准确性. 结果表明, Fibroscan能为慢性病毒性肝炎患者提供准确的肝纤维化评估. 这在Seo等[5]对韩国慢性病毒性肝炎患者的研究中亦得到证实. Shen等[6]研究显示, Fibroscan可用于评估胆道闭锁儿童的肝纤维化程度, 并可区分是否进展为肝硬化. 无创、快速、实时检测、操作简便、安全、重复性好是该技术的显著优点. 当然, Fibroscan也存在缺陷. 他的结果往往受操作者的主观感受影响. 因此需要经验丰富的工作人员进行操作, 且测量结果的阐释需结合患者的临床资料和其他影像学、内镜、生化结果来分析. 另一方面, Fibroscan的测定成功率受肥胖、肋间隙大小等因素的影响, 其测定值受肝脏脂肪变、炎性坏死及胆汁淤积的影响, 且不易准确区分相邻的两期肝纤维化[7]. 然而, Wong等[8]对246例非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)患者进行肝脏硬度值测定(liver stiffness measurement, LSM)和肝活检以评估TE对于NAFLD患者肝纤维化/肝硬化诊断的准确性. 他们认为, TE适用于绝大部

分NAFLD患者, TE和肝活检结果出现差异的原因主要在于肝活检标本不满意, LSM不受肝脂肪变、炎症坏死或肥胖等的影响, 并提出对于LSM>7.9 kPa的NAFLD患者才考虑肝活检. 争议提示, 影响TE测定结果准确性的因素复杂, 其是否完全适用于NAFLD患者还需进一步验证. 此外, Fibroscan采用一维超声, 操作者只能根据想象中的位置盲目取样, 增加了对局灶性病变的漏诊几率. 肝硬度值在受试者进餐后会发生改变, 这可能是由于门静脉血流增加引发肝脏微循环发生改变所致, 因此, 应注意检查前禁食. 近期国内有相类似的技术FibroTouch也已应用于临床, 并获得较满意的效果. Yuan等[9]研究显示, 与Fibroscan相比, FibroTouch对肝纤维化检测具有更好的准确性, 且与肝脏的组织学分期有良好的一致性.

不同于TE, ARFI采用二维超声成像, 该技术可嵌入到常规的超声扫描仪中, 实现对肝实质的检测, 可任意选点多点、多次取样, 适用于弥漫性、不均匀性、局灶性病变, 且有多普勒、声学造影和穿刺功能. Bota等[10]通过META分析研究接受了同一部位ARFI检测和肝活检的132例慢性丙型肝炎患者情况, 结果显示ARFI诊断进展期肝纤维化的阳性预测值为93.2%, 用于排除代偿期肝硬化的阴性预测值为97.8%. Liu等[11]对ARFI用于检测NAFLD患者肝纤维化诊断价值的系统评价显示, ARFI在NAFLD患者肝纤维化检测准确性好. 近期, Park等[12]报道105例慢性乙型肝炎患者的ARFI检测和肝活检结果的符合率, 指出对高级别的肝纤维化(F3-4)两者的诊断符合率最好, 其中体质量指数(body mass index, BMI)乃影响ARFI检测准确性的重要负性因素.

另一热门技术MRE可以定量测定和直观显示通过肝组织的剪切声波, 因可用于检测评估整个肝脏, 避免了取样误差而有望成为新的“金标准”. Batheja等[13]的研究表明, MRE对于检测和评估肝纤维化是可行和有效的, 特别是用于鉴别F0-2级和F3-4级.

尽管已有这些可喜的进展, 但仍然有许多问题需要解决, 如上述无创诊断方法的诊断效力、肝纤维化程度分级的界点和阈值、诊断成本以及广泛推广的可行性等.

2.2 血清生物学标志物

2.2.1 血清生物学标志物数学模型: 以往诊断肝纤维化常用的血清生物学标志物组合有APRI、TPRI等. 目前已上市或临床验证有效用于评价细胞外基质更新的数学模型, 包括: FibroMeter、FibroTest-ActiTest、HCV FibroSure、HepaScore、Fibrosis-4指数、增强肝纤维化试验、Hui index、上海肝纤维化模型[S指数: 1000×GGT/(PLT×ALB^2)]等[14-17]. 这些模型均由一系列能够预测肝纤维化进展或程度的指标组成, 他们有较好的临床适用性和可重复性, 反复检测这些标志物可以评价肝纤维化生成的病理生理过程, 进而预测临床结局, 有助于病情监测和预后判断, 因此正逐渐被大家所接受. Wong等[14]的前瞻性队列研究显示Hui index可用于预测慢性乙型肝炎患者病情变化, 高指数等级预示着发生肝硬化各种并发症、肝癌及相关死亡事件的可能性增加. 通过对386例慢性乙型肝炎病毒携带者进行肝活检和常规实验室检测以评估其肝纤维化程度, 我们的研究结果显示, S指数用于预测慢性乙型肝炎病毒感染者的显著肝纤维化和肝硬化程度有较高的准确性[17]. 而Boursier等[18]研究表明这些模型用于判断慢性丙型肝炎患者的预后比肝活检更准确, 他们之间的组合可以优化其预后评估. 尽管如此, 这些血清学标志物的特异性和敏感性还有待进一步提高, 且这些数学模型大多来源于慢性乙型/丙型肝炎研究, 对于其他病因所致的肝纤维化诊断价值如何以及其确切的临床意义还有待更大样本的验证, 才能在临床推广应用.

2.2.2 新生表位生化标志物: 近年来, 检测血清或血浆中新生表位生化标志物受到越来越多的关注. 新生表位标志物指的是在蛋白质水解剪切过程中产生的一种特定蛋白印记片段, 这种标志物可以反映纤维组织自身的转化过程, 且与诊断、预后及疗效评价相关[19]. 以Ⅰ型胶原纤维为例, 在不同的蛋白酶作用下可产生PINP、CTX1、ICTP、C1M等不同的新生表位, 他们提供着不同的诊断信息[19]. Leeming等[20]对大鼠的研究结果表明, 这些新生表位标志物可以为临床评估肝纤维化提供有价值的诊断信息. 目前可用于评估细胞外基质变化的标志物有: P1NP、P4NP 7S、PⅢNP、HA等[21]. 这些标志物能定量分析细胞外基质的转化过程, 可用于监测肝纤维化的动态发展, 甚至早期无症状患者亦适用, 价格实惠, 操作简

易省时, 易于被患者接受. Leeming等[22]研究结果显示, P4NP 7S与肝纤维化及其程度高度相关, 检测P4NP 7S可提高肝纤维化定量分析. 但同样, 这种检测也存在特异性低的缺点. 近期我们对40例慢性乙型肝炎患者肝纤维化病灶血清标本采用多肽组学检测技术(PF2D/ICAT LC-MS)检测, 质谱数据经过Profile Analysis软件分析得出差异多肽. 应用该软件的MS-T-Test模型分析LC-MS/MS数据, 共筛检出重度纤维化组血清和轻度纤维化组血清之间存在显著差异多肽峰21个. 选取86例乙型肝炎患者和20例健康体检血清标本行验证MS-MRM研究, 仅显著差异多肽m/z 520.3的离子对存在统计学差异(P<0.05). 我们建立了6个m/z 520.3离子对诊断模型: 176.1、353.7、459.8、503.3、351.3、593.1, 以差异多肽m/z 520.3离子对的SPAR值建模, AUROC诊断显著肝纤维化(≥S2期)在0.871-0.915; 诊断严重肝纤维化(≥S3期)在0.804-0.924. 该多肽鉴定结果是二羟基丙酮酸激酶, 下一步我们将开发其用于临床诊断[23].

如果说上述影像学诊断技术是静态捕捉疾病的某一现状, 那么血清生物学标志物的不断创新就为动态检测疾病进展、评估疗效、预测临床结局提供了更优的条件. 因此, 影像诊断技术和血清学标志物联合检测将为肝纤维化诊断提供更好的依据, 这不仅解决了动态监测疾病的困境, 更提高了疾病诊断的特异性和准确性, 并有助于明确临床试验的终点指标. Crisan等[24]对446例慢丙型肝炎患者进行APRI、Forns、Fib-4、Hepascore、FibroTest和Fibrometer检测, 联合TE评估肝纤维化进展, 并与肝活检对比, 研究结果显示, 血清学联合影像学同步检测可提高无创诊断技术对肝纤维化进展评估的准确性.

3 肝纤维化治疗的进展与挑战

当今肝纤维化药物治疗发展的最大障碍在于缺乏理想的药物临床试验动态评价指标. 总体上, 特异性抗纤维化治疗的药物研发还处于初始阶段. 病因治疗、减轻炎症刺激、下调肝星状细胞(hepatic stellate cell, HSC)活化、促进HSC凋亡、增加细胞外基质降解等仍是目前抗纤维化治疗的主要策略.

病因治疗方面, 抗病毒治疗、酒精性肝病患者戒酒、清除Wilson病患者体内过量沉积的铜、抗寄生虫治疗、解除胆道梗阻、帮助非酒精性脂肪系肝炎患者体质量控制等对于延缓肝纤维化发展的意义毋庸置疑. 4006试验随访10年数据证实: 拉米夫定长期治疗组织学明显改善[25]. 抗炎保肝方面, 磷脂酰胆碱、马洛替酯、熊去氧胆酸、水飞蓟宾、γ-干扰素、转化生长因子β拮抗剂、皮质类固醇激素等, 均可用于抗纤维化治疗, 但都缺乏特异性. 中医中药治疗方面值得一提的是, 作为中药制剂的扶正化瘀片/胶囊治疗肝纤维化有较好的临床疗效[26]. 近期美国II期临床试验报告表明, 扶正化瘀片治疗难治性慢性丙型肝纤维化患者有良好的安全性和药物耐受性, 显示减轻肝组织纤维化程度的可喜作用. 这为推广中药制剂治疗肝纤维化, 尤其是通过优化组方, 考虑联合应用抗病毒治疗措施以提高疗效提供了参考和机遇.

针对HSC为靶标的治疗策略中, 新近的研究表明, 肝纤维化的发生发展与细胞自噬密切相关, 这为肝纤维化治疗提供了新思路. Hernández-Gea等[27]研究显示, 细胞自噬通过自噬相关脂质代谢方式参与肝HSC激活. Hidvegi等[28]研究表明, 卡马西平通过细胞自噬方式促进α1胰蛋白酶变异体降解, 减少肝纤维化发生.

阻碍以上各种治疗策略实施的主要屏障是, 激活HSC的病因复杂, 无论是病毒感染、免疫损伤, 还是毒物作用、淤胆刺激, 往往难以彻底或快速消除; 通过针对转化生长因子TGF-β1/Smad等关键性信号靶点以控制HSC纤维化激活仍无实质性突破, 而体内HSC一旦激活常通过自分泌途径持续活化, 很难被逆转; 降解细胞外基质的治疗也因不良反应过大受到制约.

近期有一些肝纤维化治疗新药及小分子物质已获批准开展临床试验. 首先, 既往报道氯沙坦[29]、罗格列酮[30]、吡格列酮[31,32]、奥贝胆酸[33,34]、腺苷蛋氨酸[35-37]、维生素E[38,39]等对于非酒精性脂肪性肝炎治疗有效, 他们进一步用到了改善肝纤维化的临床试验观察; 其次, PPARγ激动剂ZYH-1[40]、细胞凋亡信号Caspase广谱抑制物IDN-6556[41,42]、组织蛋白酶B抑制剂VBY-376[43]、线粒体抗氧化剂MitoQ[44,45]及FXR激动剂PX20606[43]等新型化合物用于治疗非酒精性脂肪性肝病、肝纤维化的临床试验也在开展当中. 此外, F-351是

一种非甾体类小分子抗纤维化药物, 动物实验显示其能显著减少肝纤维化, 目前正在进行Ⅰb/Ⅱ期临床试验[43]. 还有以CCR5[46,47]、CCR2[48,49]、RHO激酶[50-52]等肝纤维化通路中分子为靶点的小分子物质用于与改善肝纤维化的研究. 迄今为止, 部分这些在研新药对改善肝功能, 预防纤维化进展甚至逆转肝脏组织疤痕结构, 以及受试者良好耐受性等方面展示良好表现, 非常值得期待. 当然, 其治疗效果的特异性也有待更多数据和研究澄清.

4 结论

目前肝纤维化的诊断与治疗取得了令人鼓舞的进展, 但距离肝纤维化的精准诊断目标和特异性治疗手段的突破, 仍有很长的路要走.

5 参考文献

1 Bissell DM, Friedman SL, Maher JJ, Roll FJ. Connective tissue biology and hepatic fibrosis: report of a conference. *Hepatology* 1990; 11: 488-498 [PMID: 2179098 DOI: 10.1002/hep.1840110322]

2 Friedman SL, Maher JJ, Bissell DM. Mechanisms and therapy of hepatic fibrosis: report of the AASLD Single Topic Basic Research Conference. *Hepatology* 2000; 32: 1403-1408 [PMID: 11093750 DOI: 10.1053/jhep.2000.20243]

3 刘成海, 吕靖. 美国肝病学会肝纤维化专题会议报道. 肝脏 2007; 2: 138

4 Afdhal NH, Bacon BR, Patel K, Lawitz EJ, Gordon SC, Nelson DR, Challies TL, Nasser I, Garg J, Wei LJ, McHutchison JG. Accuracy of fibroscan, compared with histology, in analysis of liver fibrosis in patients with hepatitis B or C: a United States multicenter study. *Clin Gastroenterol Hepatol* 2015; 13: 772-779.e1-e3 [PMID: 25528010]

5 Seo YS, Kim MY, Kim SU, Hyun BS, Jang JY, Lee JW, Lee JI, Suh SJ, Park SY, Park H, Jung EU, Kim BS, Kim IH, Lee TH, Um SH, Han KH, Kim SG, Paik SK, Choi JY, Jeong SW, Jin YJ, Lee KS, Yim HJ, Tak WY, Hwang SG, Lee YJ, Lee CH, Kim DG, Kang YW, Kim YS. Accuracy of transient elastography in assessing liver fibrosis in chronic viral hepatitis: A multicentre, retrospective study. *Liver Int* 2015; 35: 2246-2255 [PMID: 25682719]

6 Shen QL, Chen YJ, Wang ZM, Zhang TC, Pang WB, Shu J, Peng CH. Assessment of liver fibrosis by Fibroscan as compared to liver biopsy in biliary atresia. *World J Gastroenterol* 2015; 21: 6931-6936 [PMID: 26078570]

7 贾继东, 李兰娟. 慢性乙型肝炎防治指南(2010年版). 胃肠病学和肝脏病学杂志 2011; 2: 421-431

8 Wong VW, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, Choi PC, Kowo M, Chan AW, Merrouche W, Sung JJ, de Lédinghen V. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. *Hepatology* 2010; 51: 454-462 [PMID: 20101745 DOI: 10.1002/hep.23312]

9 Yuan L, Shao J, Hao M, Li C, Wang G, Wang T, Luo J, Bai J, Ma A. [Correlation between liver hardness testing results obtained by FibroTouch and FibroScan and liver pathological stage]. *Zhonghua Ganzangbing Zazhi* 2014; 22: 425-429 [PMID: 25203705]

10 Bota S, Sporea I, Sirli R, Popescu A, Gradinaru-Tascau O. How useful are ARFI elastography cut-off values proposed by meta-analysis for predicting the significant fibrosis and compensated liver cirrhosis? *Med Ultrason* 2015; 17: 200-205 [PMID: 26052571]

11 Liu H, Fu J, Hong R, Liu L, Li F. Acoustic Radiation Force Impulse Elastography for the Non-Invasive Evaluation of Hepatic Fibrosis in Non-Alcoholic Fatty Liver Disease Patients: A Systematic Review & Meta-Analysis. *PLoS One* 2015; 10: e0127782 [PMID: 26131717 DOI: 10.1371/journal.pone.0127782]

12 Park MS, Kim SW, Yoon KT, Kim SU, Park SY, Tak WY, Kweon YO, Cho M, Kim BK, Park JY, Kim DY, Ahn SH, Han KH. Factors Influencing the Diagnostic Accuracy of Acoustic Radiation Force Impulse Elastography in Patients with Chronic Hepatitis B. *Gut Liver* 2015 Jun 19. *[Epub ahead of print]* [PMID: 26087790 DOI: 10.5009/gnl14391]

13 Batheja M, Vargas H, Silva AM, Walker F, Chang YH, De Petris G, Silva AC. Magnetic resonance elastography (MRE) in assessing hepatic fibrosis: performance in a cohort of patients with histological data. *Abdom Imaging* 2015; 40: 760-765 [PMID: 25542217 DOI: 10.1007/s00261-014-0321-8]

14 Wong GL, Chan HL, Yu Z, Wong CK, Leung C, Ho PP, Chan CY, Chung VC, Chan ZC, Tse YK, Chim AM, Lau TK, Chan HY, Tse CH, Wong VW. Noninvasive assessments of liver fibrosis with transient elastography and Hui index predict survival in patients with chronic hepatitis B. *J Gastroenterol Hepatol* 2015; 30: 582-590 [PMID: 25252074 DOI: 10.1111/jgh.12779]

15 Zhou K, Lu LG. Assessment of fibrosis in chronic liver diseases. *J Dig Dis* 2009; 10: 7-14 [PMID: 19236541 DOI: 10.1111/j.1751-2980.2008.00356.x]

16 Zeng MD, Lu LG, Mao YM, Qiu DK, Li JQ, Wan MB, Chen CW, Wang JY, Cai X, Gao CF, Zhou XQ. Prediction of significant fibrosis in HBeAg-positive patients with chronic hepatitis B by a noninvasive model. *Hepatology* 2005; 42: 1437-1445 [PMID: 16317674 DOI: 10.1002/hep.20960]

17 Zhou K, Gao CF, Zhao YP, Liu HL, Zheng RD, Xian JC, Xu HT, Mao YM, Zeng MD, Lu LG. Simpler score of routine laboratory tests predicts liver fibrosis in patients with chronic hepatitis B. *J Gastroenterol Hepatol* 2010; 25: 1569-1577 [PMID: 20796157 DOI: 10.1111/j.1440-1746.2010.06383.x]

18 Boursier J, Brochard C, Bertrais S, Michalak S, Gallois Y, Fouchard-Hubert I, Oberti F, Rousselet MC, Calès P. Combination of blood tests for significant fibrosis and cirrhosis improves the assessment of liver-prognosis in chronic hepatitis C. *Aliment Pharmacol Ther* 2014; 40: 178-188 [PMID: 24889599 DOI: 10.1111/apt.12813]

19 Karsdal MA, Krarup H, Sand JM, Christensen PB, Gerstoft J, Leeming DJ, Weis N, Schaffalitzky de Muckadell OB, Krag A. Review article: the efficacy of biomarkers in chronic fibroproliferative diseases - early diagnosis and prognosis, with liver fibrosis

as an exemplar. *Aliment Pharmacol Ther* 2014; 40: 233-249 [PMID: 24909260 DOI: 10.1111/apt.12820]
20 Leeming DJ, Byrjalsen I, Jiménez W, Christiansen C, Karsdal MA. Protein fingerprinting of the extracellular matrix remodelling in a rat model of liver fibrosis--a serological evaluation. *Liver Int* 2013; 33: 439-447 [PMID: 23279004 DOI: 10.1111/liv.12044]
21 Karsdal MA, Nielsen MJ, Sand JM, Henriksen K, Genovese F, Bay-Jensen AC, Smith V, Adamkewicz JI, Christiansen C, Leeming DJ. Extracellular matrix remodeling: the common denominator in connective tissue diseases. Possibilities for evaluation and current understanding of the matrix as more than a passive architecture, but a key player in tissue failure. *Assay Drug Dev Technol* 2013; 11: 70-92 [PMID: 23046407 DOI: 10.1089/adt.2012.474]
22 Leeming DJ, Nielsen MJ, Dai Y, Veidal SS, Vassiliadis E, Zhang C, He Y, Vainer B, Zheng Q, Karsdal MA. Enzyme-linked immunosorbent serum assay specific for the 7S domain of Collagen Type IV (P4NP 7S): A marker related to the extracellular matrix remodeling during liver fibrogenesis. *Hepatol Res* 2012; 42: 482-493 [PMID: 22221767 DOI: 10.1111/j.1872-034X.2011.00946.x]
23 Xu MY, Jia XF, Qu Y, Zheng RD, Yuan ZH, Weng HL, Dooley S, Wang XP, Zhang LJ, Lu LG. Serum dihydroxyacetone kinase peptide m/z 520.3 as predictor of disease severity in patients with compensated chronic hepatitis B. *J Transl Med* 2013; 11: 234 [PMID: 24289155 DOI: 10.1186/1479-5876-11-234]
24 Crisan D, Radu C, Lupsor M, Sparchez Z, Grigorescu MD, Grigorescu M. Two or more synchronous combination of noninvasive tests to increase accuracy of liver fibrosis assessement in chronic hepatitis C; results from a cohort of 446 patients. *Hepat Mon* 2012; 12: 177-184 [PMID: 22550525 DOI: 10.5812/hepatmon.5106]
25 许蓓, 徐国光, 郭清, 庄焱, 刘芸野, 王晖, 周霞秋, 巫善明, 谢青. 拉米夫定在重度肝纤维化慢乙型肝炎患者中的长期应用疗效-NUCB4006十年随访研究. 中国传染病杂志 2010; 11: 656-661
26 王寿明, 何长伦, 于乐成, 李鑫, 郝坤艳, 汪茂荣. 两种常用抗肝纤维化中成药临床疗效的比较. 肝脏 2014; 5: 332-334
27 Hernández-Gea V, Ghiassi-Nejad Z, Rozenfeld R, Gordon R, Fiel MI, Yue Z, Czaja MJ, Friedman SL. Autophagy releases lipid that promotes fibrogenesis by activated hepatic stellate cells in mice and in human tissues. *Gastroenterology* 2012; 142: 938-946 [PMID: 22240484 DOI: 10.1053/j.gastro.2011.12.044]
28 Hidvegi T, Ewing M, Hale P, Dippold C, Beckett C, Kemp C, Maurice N, Mukherjee A, Goldbach C, Watkins S, Michalopoulos G, Perlmutter DH. An autophagy-enhancing drug promotes degradation of mutant alpha1-antitrypsin Z and reduces hepatic fibrosis. *Science* 2010; 329: 229-232 [PMID: 20522742 DOI: 10.1126/science.1190354]
29 Orlic L, Mikolasevic I, Lukenda V, Anic K, Jelic I, Racki S. Nonalcoholic fatty liver disease and the renin-angiotensin system blockers in the patients with chronic kidney disease. *Wien Klin Wochenschr* 2015; 127: 355-362 [PMID: 25412597 DOI: 10.1007/s00508-014-0661-y]
30 Samah M, El-Aidy Ael-R, Tawfik MK, Ewais MM. Evaluation of the antifibrotic effect of fenofibrate and rosiglitazone on bleomycin-induced pulmonary fibrosis in rats. *Eur J Pharmacol* 2012; 689: 186-193 [PMID: 22659583 DOI: 10.1016/j.ejphar.2012.05.026]
31 Boettcher E, Csako G, Pucino F, Wesley R, Loomba R. Meta-analysis: pioglitazone improves liver histology and fibrosis in patients with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2012; 35: 66-75 [PMID: 22050199 DOI: 10.1111/j.1365-2036.2011.04912.x]
32 Arab JP, Candia R, Zapata R, Muñoz C, Arancibia JP, Poniachik J, Soza A, Fuster F, Brahm J, Sanhueza E, Contreras J, Cuellar MC, Arrese M, Riquelme A. Management of nonalcoholic fatty liver disease: an evidence-based clinical practice review. *World J Gastroenterol* 2014; 20: 12182-12201 [PMID: 25232252 DOI: 10.3748/wjg.v20.i34.12182]
33 Mudaliar S, Henry RR, Sanyal AJ, Morrow L, Marschall HU, Kipnes M, Adorini L, Sciacca CI, Clopton P, Castelloe E, Dillon P, Pruzanski M, Shapiro D. Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease. *Gastroenterology* 2013; 145: 574-582.e1 [PMID: 23727264 DOI: 10.1053/j.gastro.2013.05.042]
34 Gitto S, Vitale G, Villa E, Andreone P. Treatment of nonalcoholic steatohepatitis in adults: present and future. *Gastroenterol Res Pract* 2015; 2015: 732870 [PMID: 25866507 DOI: 10.1155/2015/732870]
35 Basaranoglu M, Basaranoglu G, Sentürk H. From fatty liver to fibrosis: a tale of "second hit". *World J Gastroenterol* 2013; 19: 1158-1165 [PMID: 23483818 DOI: 10.3748/wjg.v19.i8.1158]
36 Lieber CS, Leo MA, Cao Q, Mak KM, Ren C, Ponomarenko A, Wang X, Decarli LM. The Combination of S-adenosylmethionine and Dilinoleoylphosphatidylcholine Attenuates Non-alcoholic Steatohepatitis Produced in Rats by a High-Fat Diet. *Nutr Res* 2007; 27: 565-573 [PMID: 18769506 DOI: 10.1016/j.nutres.2007.07.005]
37 Ramani K, Yang H, Kuhlenkamp J, Tomasi L, Tsukamoto H, Mato JM, Lu SC. Changes in the expression of methionine adenosyltransferase genes and S-adenosylmethionine homeostasis during hepatic stellate cell activation. *Hepatology* 2010; 51: 986-995 [PMID: 20043323]
38 Marquardt D, Williams JA, Kučerka N, Atkinson J, Wassall SR, Katsaras J, Harroun TA. Tocopherol activity correlates with its location in a membrane: a new perspective on the antioxidant vitamin E. *J Am Chem Soc* 2013; 135: 7523-7533 [PMID: 23581571 DOI: 10.1021/ja312665r]
39 Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, Neuschwander-Tetri BA, Lavine JE, Tonascia J, Unalp A, Van Natta M, Clark J, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010; 362: 1675-1685 [PMID: 20427778 DOI: 10.1056/NEJMoa0907929]
40 Jani RH, Kansagra K, Jain MR, Patel H. Pharmacokinetics, safety, and tolerability of saroglitazar (ZYH1), a predominantly PPARα

agonist with moderate PPARγ agonist activity in healthy human subjects. *Clin Drug Investig* 2013; 33: 809-816 [PMID: 24062180 DOI: 10.1007/s40261-013-0128-3]
41 Elpek GÖ. Cellular and molecular mechanisms in the pathogenesis of liver fibrosis: An update. *World J Gastroenterol* 2014; 20: 7260-7276 [PMID: 24966597 DOI: 10.3748/wjg.v20.i23.7260]
42 Linton SD, Aja T, Armstrong RA, Bai X, Chen LS, Chen N, Ching B, Contreras P, Diaz JL, Fisher CD, Fritz LC, Gladstone P, Groessl T, Gu X, Herrmann J, Hirakawa BP, Hoglen NC, Jahangiri KG, Kalish VJ, Karanewsky DS, Kodandapani L, Krebs J, McQuiston J, Meduna SP, Nalley K, Robinson ED, Sayers RO, Sebring K, Spada AP, Ternansky RJ, Tomaselli KJ, Ullman BR, Valentino KL, Weeks S, Winn D, Wu JC, Yeo P, Zhang CZ. First-in-class pan caspase inhibitor developed for the treatment of liver disease. *J Med Chem* 2005; 48: 6779-6782 [PMID: 16250635 DOI: 10.1021/jm050307e]
43 Nanthakumar CB, Hatley RJ, Lemma S, Gauldie J, Marshall RP, Macdonald SJ. Dissecting fibrosis: therapeutic insights from the small-molecule toolbox. *Nat Rev Drug Discov* 2015; 14: 693-720 [PMID: 26338155 DOI: 10.1038/nrd4592]
44 Chacko BK, Reily C, Srivastava A, Johnson MS, Ye Y, Ulasova E, Agarwal A, Zinn KR, Murphy MP, Kalyanaraman B, Darley-Usmar V. Prevention of diabetic nephropathy in Ins2(+/-)(AkitaJ) mice by the mitochondria-targeted therapy MitoQ. *Biochem J* 2010; 432: 9-19 [PMID: 20825366 DOI: 10.1042/BJ20100308]
45 Chacko BK, Srivastava A, Johnson MS, Benavides GA, Chang MJ, Ye Y, Jhala N, Murphy MP, Kalyanaraman B, Darley-Usmar VM. Mitochondria-targeted ubiquinone (MitoQ) decreases ethanol-dependent micro and macro hepatosteatosis. *Hepatology* 2011; 54: 153-163 [PMID: 21520201 DOI: 10.1002/hep.24377]
46 Ochoa-Callejero L, Pérez-Martínez L, Rubio-Mediavilla S, Oteo JA, Martínez A, Blanco JR. Maraviroc, a CCR5 antagonist, prevents development of hepatocellular carcinoma in a mouse model. *PLoS One* 2013; 8: e53992 [PMID: 23326556 DOI: 10.1371/journal.pone.0053992]
47 Pérez-Martínez L, Pérez-Matute P, Aguilera-Lizarraga J, Rubio-Mediavilla S, Narro J, Recio E, Ochoa-Callejero L, Oteo JA, Blanco JR. Maraviroc, a CCR5 antagonist, ameliorates the development of hepatic steatosis in a mouse model of non-alcoholic fatty liver disease (NAFLD). *J Antimicrob Chemother* 2014; 69: 1903-1910 [PMID: 24651825 DOI: 10.1093/jac/dku071]
48 Seki E, de Minicis S, Inokuchi S, Taura K, Miyai K, van Rooijen N, Schwabe RF, Brenner DA. CCR2 promotes hepatic fibrosis in mice. *Hepatology* 2009; 50: 185-197 [PMID: 19441102 DOI: 10.1002/hep.22952]
49 Miura K, Yang L, van Rooijen N, Ohnishi H, Seki E. Hepatic recruitment of macrophages promotes nonalcoholic steatohepatitis through CCR2. *Am J Physiol Gastrointest Liver Physiol* 2012; 302: G1310-G1321 [PMID: 22442158 DOI: 10.1152/ajpgi.00365.2011]
50 Chou HC, Huang LT, Yeh TF, Chen CM. Rho-kinase inhibitor Y-27632 attenuates pulmonary hypertension in hyperoxia-exposed newborn rats. *Acta Pharmacol Sin* 2013; 34: 1310-1316 [PMID: 23974518 DOI: 10.1038/aps.2013.93]
51 Pigati PA, Righetti RF, Possa SS, Romanholo BS, Rodrigues AP, dos Santos AS, Xisto DG, Antunes MA, Prado CM, Leick EA, Martins Mde A, Rocco PR, Tibério Ide F. Y-27632 is associated with corticosteroid-potentiated control of pulmonary remodeling and inflammation in guinea pigs with chronic allergic inflammation. *BMC Pulm Med* 2015; 15: 85 [PMID: 26264367 DOI: 10.1186/s12890-015-0073-4]
52 Tada S, Iwamoto H, Nakamuta M, Sugimoto R, Enjoji M, Nakashima Y, Nawata H. A selective ROCK inhibitor, Y27632, prevents dimethylnitrosamine-induced hepatic fibrosis in rats. *J Hepatol* 2001; 34: 529-536 [PMID: 11394652 DOI: 10.1016/S0168-8278(00)00059-3]

编辑: 于明茜 电编: 闫晋利