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封面故事

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文献综述 REVIEW

脂肪生成抑制剂治疗非酒精性脂肪性肝病的研究进展

杨 柳, 李锦忠, 李敏然

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Progress in research of lipogenesis inhibitors for treatment of nonalcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the main cause of chronic liver disease. At present, the main clinical treatment for NAFLD is diet adjustment, exercise, and weight loss, but the effect is poor, and there is still a lack of recognized drugs with significant efficacy in NAFLD. In recent years, with the in-depth study of the pathogenesis of NAFLD, it has been found that the core enzymes that inhibit intrahepatic *de novo* lipogenesis (DNL), including citrate/isocitrate carrier (CIC), ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), fatty acid synthase (FASN), and stearoyl-CoA desaturase 1 (SCD1), can improve hepatic steatosis and provide a new method for the treatment of NAFLD. This article reviews the research progress of five different types of lipogenesis inhibitors for treatment of NAFLD.

Key Words: Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; *De novo* lipogenesis; Lipogenesis inhibitors

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摘要

非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)是慢性肝病的主要病因, 目前临床上治疗NAFLD的主要方法是饮食调整、运动及减重, 但效果欠佳, 仍缺乏公认的对NAFLD有明显疗效的药物. 近年来随着对NAFLD发病机制的深入研究, 发现抑制肝内从头脂肪生成(de novo lipogenesis, DNL)的核心酶, 包括柠檬酸/异柠檬酸载体(citrate/isocitrate carrier, CIC)、ATP-柠檬酸裂解酶(ATP-citrate lyase, ACLY)、乙酰CoA羧化酶(acetyl-CoA carboxylase, ACC)、脂肪酸合酶(FASN)和硬脂酰辅酶A去饱和酶1(stearoyl-CoA

desaturase 1, SCD1), 能够改善肝脏脂肪变性, 为治疗NAFLD提供了一种新的方法. 目前已有几种新型合成的脂肪生成抑制剂进入了临床研究阶段, 本文对上述五种不同类型的脂肪生成抑制剂治疗NAFLD的研究进展进行综述.

关键词: 非酒精性脂肪性肝病;非酒精性脂肪性肝炎;从头脂肪生成; 脂肪生成抑制剂

核心提要: 临床上治疗非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)的主要方法是饮食调整和运动减重, 但效果欠佳, 仍缺乏有效治疗NAFLD的药物.近年来, 研究发现抑制肝内从头脂肪生成(de novo lipogenesis, DNL)的核心酶, 能够改善NAFLD患者的肝脏脂肪变性、炎症以及纤维化, 成为目前治疗NAFLD有吸引力的新靶点.

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0 引言

非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)已成为发病率最高的慢性肝病, 影响全球超过25%的人群[1], 高达30%的NAFLD患者会发生非酒精性脂肪性肝炎(nonalcoholic steatohepatitis, NASH)[2], NASH可引起肝损伤并导致进行性肝纤维化、肝硬化和肝细胞癌(hepatocellular carcinoma, HCC). 然而, NAFLD进展为NASH的发病机制相当复杂, 仍未明确. 美国食品药品监督管理局(Food and Drug Administration, FDA)尚未批准用于治疗NAFLD的药物[3], 治疗选择仅限于饮食调整、运动及减重, 临床上对NAFLD可行的治疗靶点和治疗策略的需求仍未得到满足.

肝脏脂肪变性是由肝脏脂质代谢失衡引起的, 使脂质在肝脏内储存[4], 触发肝脏炎症, 导致肝脏纤维化, 促进NAFLD进展. 长期以来, 肝脏从头脂肪生成(de novo lipogenesis, DNL)不被认为是肝脏脂肪变性的相关原因, 因为在健康人体中仅约5%的肝脏甘油三酯(triglyceride, TG)来源于DNL, 其余大部分脂肪酸来源于膳食和外周脂解[5]. 但近年来的研究证明, DNL是NAFLD发生的关键介质[6,7], 在NAFLD患者中, 20%-25%的肝脏TG来源于DNL[8], 另外, 由DNL衍生的脂质也可能促进脂肪酸代谢物的蓄积, 引起脂毒性肝细胞损伤和炎症通路上调[9]. 因此, 抑制肝脏DNL成为治疗NAFLD的一个有吸引力的治疗靶点. 目前,针对DNL过程中核心酶的抑制剂正处于临床研发阶段, 包括柠檬酸盐/异柠檬酸盐载体(citrate/isocitrate carrier, CIC)、ATP-柠檬酸裂解酶(ATP-citrate lyase, ACLY)、乙酰CoA羧化酶(acetyl-CoA carboxylase, ACC)和脂肪酸合成酶(fatty acid synthase, FASN)、硬脂酰辅酶A去饱和酶1(stearoyl-CoA desaturase 1, SCD1)抑制剂(图1), 本文就脂肪生成抑制剂治疗NAFLD的研究进展作如下阐述.

1 柠檬酸盐/异柠檬酸盐载体抑制剂

柠檬酸盐/异柠檬酸盐载体(citrate/isocitrate carrier, CIC)又称柠檬酸盐转运蛋白(citrate transport protein, CTP)、溶质载体家族25成员1(SLC25A1), 在肝脏、脂肪组织中高表达, 位于线粒体内膜内. 当底物过量(相对于细胞能量需求)导致线粒体柠檬酸盐增加时, DNL启动, 柠檬酸盐通过CIC从线粒体输出到细胞质中, 成为脂肪生成的前体, 最终转化为脂肪酸. 研究发现通过抑制在NAFLD人群肝脏中表达增加的CIC, 降低细胞质柠檬酸盐,可降低ACLY和ACC的底物可用性及变构激活来抑制DNL[10].

第一代CIC抑制剂是苯三羧酸盐(benzenetricarboxylate, BTC), 结构上与柠檬酸盐相似, 亲和力高于任何底物, 以混合竞争和非竞争方式抑制CIC[11]. 然而, BTC具有与其它柠檬酸盐结合蛋白的潜在结合性, 限制了它在治疗方面的研发. 第二代抑制剂柠檬酸盐转运蛋白抑制剂-1(citrate transport protein inhibitor-1, CTPI-1), 与柠檬酸盐无结构相似性, 可竞争性结合CIC柠檬酸盐结合位点, 亲和力略高于BTC, 但它是在酵母中发现, 与人的CIC结合欠佳,需要高剂量才能在人体内发挥活性[12]. 为了优化得到针对人类CIC的特异性抑制剂, Tan等[13]研究出了柠檬酸盐转运蛋白抑制剂-2(citrate transport protein inhibitor-2, CTPI-2), 相对于CTPI-1, 结合亲和力提高了20倍, 可在较低浓度下抑制柠檬酸转运; 并使用CTPI-2治疗NAFLD/NASH小鼠模型, 发现能够逆转肝细胞脂肪变性, 阻止向脂肪性肝炎进展, 减少肝脏中炎性巨噬细胞浸润, 对治疗NAFLD可能产生有利影响. 遗憾的是上述研究未评价CTPI-2的安全性, CTPI-2尚未进入临床试验, 仍需要进一步研究验证其有效性和安全性.

2 ATP-柠檬酸裂解酶抑制剂

ATP-柠檬酸裂解酶(ATP-citrate lyase, ACLY)是一种细胞质酶, 在脂肪组织、肝脏中高表达, 负责催化柠檬酸盐和辅酶A(coenzyme A, CoA)转化为乙酰CoA和草酰乙酸, 用于脂肪酸(fatty acid, FA)和胆固醇的从头合成[14]. ACLY通过控制葡萄糖碳流向胞质的乙酰CoA及控制TG合成, 将细胞葡萄糖分解代谢与脂质生物合成联系起来. 研

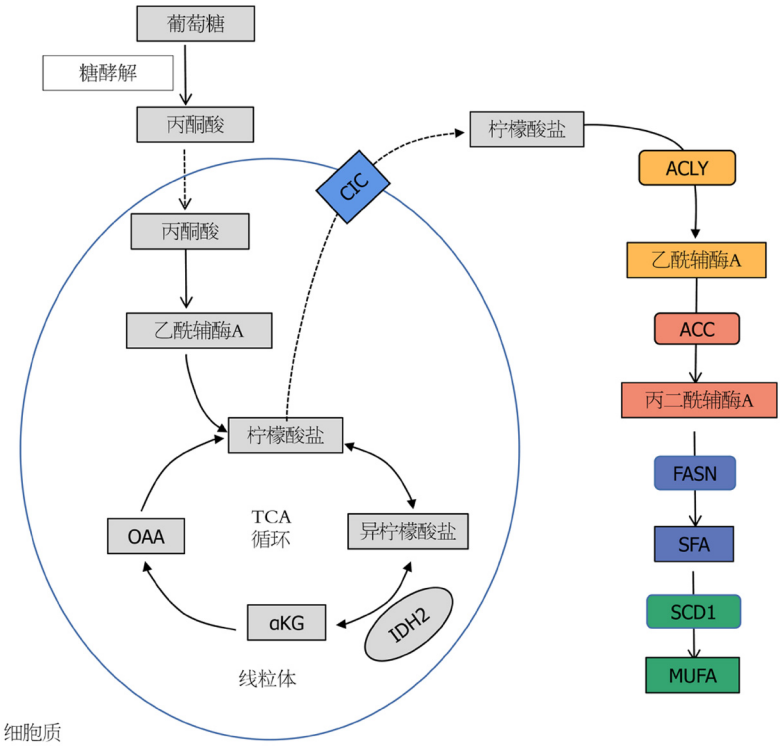

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图 1 肝脏从头脂肪生成过程及其关键酶示意图. 葡萄糖经糖酵解产生的丙酮酸在线粒体中转化为乙酰辅酶A, 乙酰辅酶A进入TCA循环产生柠檬酸盐. 在碳水化合物过量的情况下, 柠檬酸盐通过CIC输出到细胞质中, 并通过ACLY分解成乙酰辅酶A和OAA . 乙酰辅酶A随后被ACC羧化, 生成丙二酰辅酶A, 之后, 利用7个丙二酰辅酶A和1个乙酰辅酶A为引物, 由FASN催化, 经过7次缩合、还原、脱水、再还原循环, 合成SFA, 然后由SCD1催化为MUFA. TCA: 三羧酸循环; IDH2: 异柠檬酸脱氢酶2; αKG: α-酮戊二酸; CIC: 柠檬酸盐/异柠檬酸盐载体; ACLY: ATP-柠檬酸裂解酶; OAA: 草酰乙酸; ACC: 乙酰辅酶A羧化酶; FASN: 脂肪酸合成酶; SFA: 饱和脂肪; SCD1: 硬脂酰辅酶A去饱和酶1; MUFA: 单不饱和脂肪酸.

究发现NAFLD患者的ACLY mRNA量高于健康者, 刺激DNL[15,16]. 虽然ACLY不是限速酶, 但由于其在脂肪酸、胆固醇和葡萄糖代谢方面的战略地位, 使ACLY被认为是治疗脂质代谢相关疾病的有效靶点[17].

第一个被广泛研究的ACLY抑制剂是羟基柠檬酸(hydroxycitric acid, HCA), 结构与柠檬酸盐相似, 对ACLY的亲和力远大于柠檬酸盐, 能够有效竞争性抑制ACLY, 减少乙酰CoA的供应从而抑制DNL[18,21], 并具有抗肥胖、抗氧化和抗炎的潜在作用[19,20]. 除了抑制ACLY, 临床前研究发现HCA可通过调节腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)介导的信号通路减轻鸡肝细胞脂肪变性、氧化应激和炎症[22]; 还能通过激活核因子红细胞2相关因子2-抗氧化反应元件(NRF2-ARE)的抗氧化作用, 来调节脂肪生成和凋亡, 进一步改善NAFLD[23]. HCA用于治疗肥胖患者显示安全性良好, 副作用和安慰剂组相比无差异[24]. 目前HCA用于治疗NAFLD的临床研究较少, 其疗效及安全性仍需进一步研究. 首次合成的脂肪酸样ACLY抑制剂之一是化合物MEDICA16, 它与柠檬酸盐竞争性抑制ACLY, 早期研究显示MEDICA16能够抑制大鼠肝细胞中的脂肪酸和胆固醇合成[25]. 遗憾的是, MEDICA16特异性差, 也能与乙酰CoA和ATP竞争性抑制ACC[26], 近年来对它的研究较少, 且未超出临床前研究.

随后研究发现了一种肝脏特异性ACLY抑制剂-苯甲酸, 又称ETC1002或ESP-55016, 它在肝脏中通过酰基CoA合成酶(仅在肝脏中高度表达)转化为具有活性的ETC-1002CoA, 能够抑制ACLY和增加AMPK的活性, 从而避免了抑制肌肉和脂肪组织中ACLY导致的肌无力和脂肪代谢障碍不良反应的发生[27,28]. Sanjay等[29]研究苯甲酸在长期高脂饮食(high fat diet, HFD)诱导的NASH动物模型中的作用, 结果显示苯甲酸能够通过降低肝脏TG和总胆固醇、抑制体重增加、降低血糖、调节炎症和纤维化基因以及改善NAS评分来减轻HFD诱导的NASH. 可见苯甲酸可能是代谢综合征和NAFLD的一种潜在的治疗选择, 但目前对苯甲酸的研究未进入到临床阶段, 苯甲酸是否能有效逆转NAFLD和纤维化仍有待确定.

3 乙酰CoA羧化酶抑制剂

乙酰CoA羧化酶(acetyl-CoA carboxylase, ACC)存在于胞液中, 由生物素羧化酶(biotin carboxylase, BC)、生物素羧

基载体蛋白(biotin carboxyl carrier protein, BCCP)和羧基转移酶(carboxyl transferase, CT)3个结构域组成, 是DNL的第一个限速酶, 主要催化依赖ATP的乙酰CoA转化为丙二酰CoA(Malonyl-CoA, M-CoA). ACC有两种亚型, ACC1主要存在于脂肪生成组织(肝脏和脂肪组织)的细胞质中, 催化产生的M-CoA是脂肪酸的合成单位; ACC2主要存在于氧化组织(骨骼肌、心脏)的线粒体中, 催化生成的M-CoA是肉碱棕榈酰转移酶1(carnitine palmityl transferase 1, CPT-1)的抑制剂. 因为CPT-1是负责将长链脂肪酸酰基CoA运输到线粒体进行β-氧化的关键酶, 所以ACC2能够抑制脂肪酸的β-氧化[30]. Savage等[31]使用反义寡核苷酸抑制NAFLD大鼠模型ACC1、ACC2的表达, 抑制ACC1可减少脂肪生成, 抑制ACC2可增加线粒体脂肪酸氧化, 导致肝脏脂肪变性减少; 可见ACC1、ACC2在DNL和脂肪酸β-氧化中的核心作用, 为治疗NAFLD/NASH提供了一种有吸引力的方法.

3.1 ACC1、ACC2双重抑制剂 2003年, 国外某公司研究出了ACC抑制剂关键先导化合物CP-640186, 是一种非选择性、可逆性和ATP非竞争性的ACC1、ACC2双重抑制剂. 在乙酰基转化为丙二酰基过程中, CP-640186能够占据生物素-羧基复合物作用于CT域的位置, 阻断羧化反应的发生从而起到抑制ACC活性的作用[32]. CP-640186能降低大鼠肝脏、比目鱼肌、股四头肌和心肌M-CoA水平[半最大效应浓度EC50分别为(55、6、15、8) mg/kg], 对ACC1、ACC2的半抑制浓度相似[33], 但该公司对CP-640186的研究停留在临床前阶段. 随后, 该公司进一步研发出了PF-05221304, 是一种强效、选择性、口服生物可利用的可逆性ACC1、ACC2双重抑制剂. 由ACC1催化生成的脂肪酸对调节血小板功能和活化具有重要作用, 过度抑制DNL时, 可能导致巨核细胞分界膜形成受损, 从而导致血小板减少[34], 而PF-05221304能够优先分布于肝脏, 使肝脏DNL抑制最大化, 同时对外周组织(包括骨髓)的DNL抑制最小化[35], 从而降低抑制血小板生成的不良反应. 临床前研究表明, PF-05221304能够直接改善多种NAFLD/NASH致病因素, 包括脂肪变性、炎症和纤维化[36], 但可导致高甘油三酯血症发生[37]. Ⅰ期临床试验显示, 在健康受试者中耐受良好的PF-05221304剂量可使NASH患者的DNL正常化, 以剂量依赖性方式抑制肝脏DNL, 并且安全性良好, 在抑制肝脏DNL达到80%的剂量下, 未观察到血小板计数降低及血清TG异常升高[38]. Ⅱ期临床试验显示, PF-05221304单药治疗NAFLD患者, 当剂量≥10 mg/每天时, 肝脏脂肪呈剂量依赖性减少达到50%-65%, 同时还可降低糖化血红蛋白; 305例患者中有23例血清TG呈剂量依赖性升高, 但不良事件的总体发生率不随PF-05221304剂量增加而增加; 当PF-05221304和二酰基甘油酰基转移酶2(diacylgycerol acyltransferase 2, DGAT2)抑制剂联合给药后, ACC抑制剂介导的血清TG类化合物升高效应减轻, 两者联合给药有可能解决ACC单独抑制的一些局限性[39].

另一公司研究出了与BC结构域结合, 阻断ACC二聚化, 从而抑制ACC酶活性的强效ACC1、ACC2非选择性抑制剂GS-0976(又称ND-630、NDI 010976、Firsocostat). 由于它被设计为对肝脏具有组织特异性的有机阴离子转运肽的底物, 从而具有肝脏特异性. 临床前研究表明, GS-0976可减少肝脏DNL并增加氧化, 从而减少肝脏脂肪变性和胰岛素抵抗[40]. 一项NASH患者的II期随机安慰剂对照试验中评价了GS-0976的安全性和疗效, 将126例肝脏脂肪变性高于8%且肝脏硬度至少为2.5 kPa的患者随机分配至GS-0976 20 mg(n = 49)、GS-0976 5mg(n = 51)及安慰剂组(n = 26)治疗12 wk, 结果显示GS-0976 20mg组患者的DNL相对于基线中位水平下降了22%, 纤维化标志物组织金属蛋白酶抑制剂1(tissue metalloproteinase inhibitors 1, TIMP-1)显著降低; 三组中达到磁共振成像估计的质子密度脂肪分数(magnetic resonance imaging estimates of proton density fat fraction, MRI-PDFF)缓解(相对基线下降至30%)的患者比例分别48%、23%和15%; 三组间磁共振弹性成像测量的硬度变化无差异; 安全性良好, 未观察到对血小板计数或出血风险的影响, 但在接受GS-0976 20 mg及5 mg治疗的患者观察到血清TG水平升高, 中位相对增幅分别为11%和13%. 对于血清TG异常升高的原因, 可能是ACC抑制剂过度抑制DNL导致的, 因此监测血清TG水平可能对ACC抑制剂的研究至关重要[41]. 另两项临床研究同样表明GS-0976可抑制肝脏DNL, 以及能够改善MRI-PDFF、磁共振弹性成像和肝纤维化标志物[42,43]. 上述研究虽然存在治疗时间短、未包括肝硬化患者等局限性, 但研究结果在一程度上支持了未来研究GS-0976靶向抑制ACC治疗NASH患者的安全性和有效性.

3.2 选择性ACC1抑制剂 早期研究提出在NAFLD患者肝脏中是ACC1表达上调而非ACC2[44], 单独抑制ACC1可能有改善肝脏脂肪变性和纤维化的潜力, 并避免ACC1、ACC2双重抑制剂过度抑制ACC活性诱导的不良反应, 如血浆TG升高. 2018年Mizojiri等[45]研究出一种新型人选择性ACC1抑制剂, 对ACC1的选择性是ACC2的17000倍以上, 体外抑制ACC1和ACC2的IC50值分别为0.58 nM和>10000 nM. 随后Tamura等[46]进一步在临床前NASH模型研究该种选择性ACC1抑制剂(化合物-1)的疗效, 结果显示化合物-1抑制实验小鼠ACC1和ACC2的IC50值分别为1.9 nM和>10000 nM, 呈剂量依赖性降低实验小鼠肝脏M-CoA含量, 30 mg/kg时疗效最大, 比对照组

低62%; 分别以3 mg/kg、10 mg/kg和30 mg/kg的化合物-1给药实验组小鼠, 每日1次, 连续8 wk, 与对照组相比, 肝脏总重量分别降低了9.1%、23.8%和57.1% , 此外, 化合物-1能显著降低炎症标志物(MCP-1、F4/80)及肝脏纤维化活性标志物(Col1a1、Col1a2、αSMA、TGF-β1)的基因表达水平; 研究结果表明化合物-1能够改善肝脂肪变性和肝纤维化, 且安全性良好, 未显著升高血浆TG浓度. 该研究首次表明选择性ACC1抑制剂在临床前模型中具有足够的疗效, 从而为治疗NAFLD/NASH提供了一种可行的方法.

4 脂肪酸合成酶抑制剂

脂肪酸合成酶(fatty acid synthase, FASN)位于细胞质中, 在肝脏、脂肪组织中高表达, 将乙酰辅酶a和丙二酰辅酶a转化为棕榈酸酯. 棕榈酸酯在肝脏产生过量脂肪及生成某些脂毒性分子中起主要作用, 在实验模型中可直接引起肝损伤和NASH[47]. NAFLD患者的FASN基因表达水平升高[48], 临床前研究表明在FASN基因敲除小鼠模型中, DNL减少和M-CoA增加[49]. 初步临床试验显示, 在代谢综合征患者中, 抑制FASN可抑制DNL, 且不使循环TG升高[50]; 针对ACC和FASN抑制剂对循环TG的不同影响, 可以用二者对肝脏M-CoA浓度的相反作用解释, M-CoA是合成多不饱和脂肪酸(polyunsaturated fatty acids, PUFA)所必需的中间体,抑制ACC可降低M-CoA水平, 可能影响PUFA的合成, 进而导致LXR/SREBP1c靶基因表达增加, 随后刺激VLDL分泌和血浆TG浓度升高[51], 而抑制FASN则使M-CoA水平升高. 因此, 抑制FASN成为一种有吸引力的治疗NAFLD的方法.

TVB-2640是第一个进入临床试验的FASN抑制剂, 具有高效(IC50: 0.05 μM)、选择性和可逆性特点, 通过靶向β-酮酰基还原酶结构域抑制FASN. Syed-Abdul等[50]研究中首次检测该药物对DNL通路作用, 12例代谢综合征受试者接受TVB-2640(剂量范围50 mg/d-150 mg/d)治疗10 d, DNL呈剂量依赖性降低, 降低程度高达90%, 但需要进一步的研究来确定长期使用的适当剂量和效果. 随后, 一项随机、安慰剂对照2期临床研究评估TVB-2640的安全性并检测对NASH患者肝脏脂肪及肝脏代谢标志物的影响, 结果显示经TVB-2640口服治疗12 wk后肝脏脂肪含量显著呈剂量依赖性降低, 50 mg/d治疗时, 肝脏脂肪平均减少了28.1%; 61%的受试者达到了MRI-PDFF缓解, 纤维化血清生物标志物蛋白C3和TIMP-1显著降低; 且安全性良好, 不会导致TG升高. 但该研究的局限性在于样本量相对较小和给药持续时间较短, 可能混淆对患者血浆中纤维化生物标志物的评估, 因此需要进一步的研究来直接评估TVB-2640对肝组织学的影响[52].

另一个靶向β-酮酰基还原酶结构域的FASN抑制剂是FT-4101, 它是一种强效(IC50: 23 nM)、选择性、口服生物可利用的小分子化合物. Beysen等[53]在健康受试者中研究FT-4101单次口服给药对肝脏DNL抑制的剂量反应, 结果示FT-4101呈剂量依赖性抑制DNL, 最高剂9 mg下的抑制率为68%. 随后进一步纳入了NAFLD受试者随机(2:1)接受3 mg FT-4101(n = 9)或安慰剂(n = 5)间歇性治疗12 wk(3 wk、6 wk、9 wk和12 wk暂停给药), 评价FT-4101对肝脏脂肪变性的安全性、耐受性和疗效, 结果显示能够改善肝脏脂肪变性并抑制了肝脏DNL, 22%的受试者达到相对MRI-PDFF降低≥30%, 安全性良好, 未发现皮肤干燥、脱发及TG升高. 但该研究的局限性在于未纳入确诊NASH或肝纤维化受试者, 不能得出FT-4101对NASH缓解和纤维化改善有效性的结论, 需要进一步的研究来评价更高剂量和延长治疗时间的疗效和安全性.

5 SCD1抑制剂

硬脂酰辅酶A去饱和酶1(stearoyl-CoA desaturase 1, SCD1)是一种内质网结合的微粒体酶, 主要在脂肪组织和肝脏中表达, 是催化饱和脂肪酸向单不饱和脂肪酸转化的关键限速酶, 在DNL的最后阶段发挥关键作用[54]. 研究已证明[55]SCD1是脂质代谢和体重控制的关键因素, SCD1过表达可使脂肪酸合成增加, 脂肪酸β氧化降低, 导致肝脏脂质蓄积, 可能与NAFLD的发生和进展有关[56,57]. 因此, 抑制SCD1可能成为治疗NAFLD的新方法 . 由于在SCD1缺陷的小鼠研究中报告了皮肤异常和眼裂狭窄不良反应, 因此, 强效全身分布的SCD1抑制剂可能导致基于机制的不良反应发生[58], 为了提高SCD1抑制剂安全性, Iida等[59]开发了一种强效肝脏选择性SCD1抑制剂, 即噻唑-4-乙酸类似物48, 它在肝脂肪变性动物模型中呈剂量依赖性降低肝脏TG, 并有足够的安全剂量范围(10-81-fold, AUC水平), 安全性良好, 治疗期间无显著的不良事件发生, 具有治疗NAFLD潜在价值.

3β-花生四烯酸酰胺胆酸(Aramchol)是另一种肝脏靶向的SCD1部分抑制剂, 在体外模型中, Aramchol对SCD1活性的抑制率达到70%-83%. 在动物模型中可部分抑制肝脏SCD1蛋白表达并降低肝脏TG和纤维化[60]. 一项NASH患者的Ⅱb期随机安慰剂对照试验研究了Aramchol的疗效和安全性[61], 纳入的247例患者随机分为Aramchol 400 mg(n = 101)、600 mg(n = 98)、安慰剂组(n = 48), 结果显示Aramchol 600 mg和安慰剂组分别有16.7%和5%的受试者达到 NASH 缓解不伴纤维化恶化(OR = 4.74, 95%CI: 0.1-22.7), 分别有29.5%和17.5%达到纤维化改善≥1期不伴NASH恶化(OR = 1.88, 95%CI: 0.7-5.0); Aramchol 600 mg组的肝脏甘油三酯(通过MRS测量)

与安慰剂组相比降低, 但无明显差异; Aramchol安全且耐受性良好, 因AE提前终止的发生率<5%. 虽然该研究种aramchol 600 mg组的肝脏脂肪减少未达到显著性水平, 但其安全性以及肝脏组织学变化为SCD1抑制剂作为治疗NAFLD/NASH提供了依据, 还需要进一步在III期临床实验中进行相关评价.

6 总结与展望

目前通过治疗性生活方式改变来减重仍是NAFLD/NASH的一线治疗方法, 尚无FDA批准的药物用于治疗该患者人群. 近年来, 通过探索DNL在NAFLD/NASH疾病发生、发展过程中的作用机制, 开发出了数种用于治疗NAFLD/NASH的DNL抑制剂, 并取得了一定的进展. 虽然CIC和ACLY抑制剂大部分停留在临床前研究阶段, 但ACC抑制剂GS-0976、FASN抑制剂TVB-2640和SCD1抑制剂Aramchol的II期临床试验结果显示的疗效令人鼓舞. 然而, 抑制DNL可能导致循环TG的增加、血小板减少以及皮肤和眼睛等不良反应发生, 因此, 提高疗效的同时保证安全性对DNL抑制剂的研究亦至关重要. DNL抑制剂的疗效和安全性是否足以用作单药治疗或与其他疗法联合使用以增强疗效或减轻不良反应, 以阻止NAFLD/NASH进展为肝硬化, 仍需进一步临床研究.

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