

的单克隆抗体osocimab的第2阶段随机临床试验表明, osocimab预防膝关节置换术后VTE的效果优于依诺肝素^[54]; 接受膝关节置换术的患者口服Milvexian后可有效预防VTE, 且出血风险较低^[55]; 与标准剂量阿哌沙班相比, 采用Asundexian (20 mg/d或50 mg/d) 治疗的心房颤动患者出血发生率较低^[56]。另外一项临床试验表明, Asundexian、阿司匹林与P2Y12抑制剂联合用于急性心肌梗死患者二级预防时, 不会增加出血风险^[57]。

综上, 从出血风险考虑, 除FⅩⅡ外, 靶向其他凝血因子后需要止血治疗, 故FⅩⅡ可能是较FⅩⅠ更安全的抗凝靶点。但目前靶向FⅩⅠa抗凝药的研发比靶向FⅩⅡa抗凝药的研发多, 这可能与循证医学证据支持FⅩⅠ在血栓形成中的作用较FⅩⅡ更强有关。此外, 靶向FⅩⅡa时, 由TF/FⅦa复合物启动的外源性凝血系统生成的凝血酶仍会激活FⅩⅠ, 从而使抑制FⅩⅡa变得无效^[58]。总之, FⅩⅠa可能是目前研发理想抗凝药最有希望的抗凝靶点。

3 小结与前景

DOACs的问世是抗凝治疗史上的一个重要的里程碑。对于研发者, 针对凝血因子靶标研发安全、有效的抗凝药仍是当前的热点。近年来, 凝血因子功能缺失基因敲除小鼠和凝血因子先天性缺乏人群研究揭示了凝血因子对生存的重要性, 如在动物实验中, TF、FⅦ、FⅤ、FⅩ和凝血酶原缺失小鼠在胚胎发育时期或出生后不久普遍死亡^[59-63], FⅧ、FⅨ及FⅩⅢ缺失小鼠尽管能存活, 但在出血试验中存在明显的止血功能受损现象^[40, 64-65], FⅩⅠ缺失小鼠仅有轻微的止血功能受损, FⅩⅡ缺失小鼠止血功能正常^[50-51]。在人群中, FⅧ、FⅨ缺乏可导致常见的出血性疾病如血友病A和血友病B, 凝血酶原、FⅦ、FⅤ、FⅩ、FⅩⅢ缺乏患者较罕见, TF缺乏患者尚未见报道^[66]; FⅩⅠ和FⅩⅡ缺乏患者虽然罕见, 但其出血症状轻微甚至没有出血^[67-68]。

综上所述, 凝血酶和FⅩa抑制剂虽已广泛用于临床, 但适用人群有限, TF/FⅦa复合物、FⅧa及FⅨa抑制剂存在出血风险, FⅤa、FⅩⅢa、FⅩⅡa抑制剂的抗栓效果仍有待进一步评估, 而FⅩⅠa抑制剂凭借其优越的获益风险比, 可能解决抗栓与出血风险相矛盾的难题, 故FⅩⅠa可能是当前满足理想抗凝药最有希望的抗凝靶点。

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参考文献

- [1] ZHANG Z, LEI J, SHAO X, et al. Trends in hospitalization and in-hospital mortality from VTE, 2007 to 2016, in China [J]. *Chest*, 2019, 155 (2): 342-353. DOI: 10.1016/j.chest.2018.10.040.
- [2] BARCO S, VALERIO L, GALLO A, et al. Global reporting of pulmonary embolism-related deaths in the World Health Organization mortality database: vital registration data from 123 countries [J]. *Res Pract Thromb Haemost*, 2021, 5 (5): e12520. DOI: 10.1002/rth2.12520.
- [3] WOLBERG A S, ROSENDAAL F R, WEITZ J I, et al. Venous thrombosis [J]. *Nat Rev Dis Primers*, 2015, 1: 15006. DOI: 10.1038/nrdp.2015.6.
- [4] SABRA A, LAWRENCE M J, CURTIS D, et al. In vitro clot model to evaluate fibrin-thrombin effects on fractal dimension of incipient blood clot [J]. *Clin Hemorheol Microcirc*, 2019, -1: 147-153. DOI: 10.3233/CH-190615.
- [5] YIN L, QI Y, GE Z R, et al. Effects of direct oral anticoagulants dabigatran and rivaroxaban on the blood coagulation function in rabbits [J]. *Open Life Sci*, 2022, 17 (1): 1-9. DOI: 10.1515/biol-2022-0002.
- [6] MAYER A, SCHUSTER P, FINK B. A comparison of apixaban and dabigatran etexilate for thromboprophylaxis following hip and knee replacement surgery [J]. *Arch Orthop Trauma Surg*, 2017, 137 (6): 797-803. DOI: 10.1007/s00402-017-2697-8.
- [7] BERTOLETTI L, GUSTO G, KHACHATRYAN A, et al. Effectiveness and safety of oral anticoagulants in the treatment of acute venous thromboembolism: a nationwide comparative cohort study in France [J]. *Thromb Haemost*, 2022, 122 (8): 1384-1396. DOI: 10.1055/a-1731-3922.
- [8] 张广求, 张美祥, 王树平. 新型口服抗凝药物适应证及指南推荐意见 [J]. *实用心脑血管病杂志*, 2018, 26 (9): 1-5. DOI: 10.3969/j.issn.1008-5971.2018.09.001.
- [9] POLLACK C V Jr, REILLY P A, VAN RYN J, et al. Idarucizumab for dabigatran reversal - full cohort analysis [J]. *N Engl J Med*, 2017, 377 (5): 431-441. DOI: 10.1056/NEJMoa1707278.
- [10] CONNOLLY S J, CROWTHER M, EIKELBOOM J W, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors [J]. *N Engl J Med*, 2019, 380 (14): 1326-1335. DOI: 10.1056/NEJMoa1814051.
- [11] BEYER-WESTENDORF J, TITTL L, BISTERVELS I, et al. Safety of direct oral anticoagulant exposure during pregnancy: a retrospective cohort study [J]. *Lancet Haematol*, 2020, 7 (12): e884-891. DOI: 10.1016/S2352-3026(20)30327-6.
- [12] HUMBERT M, SIMONNEAU G, PITTRROW D, et al. Oral anticoagulants (NOAC and VKA) in chronic thromboembolic pulmonary hypertension [J]. *J Heart Lung Transplant*, 2022, 41 (6): 716-721. DOI: 10.1016/j.healun.2022.02.002.
- [13] CIMMINO G, CIRILLO P. Tissue factor: newer concepts in thrombosis and its role beyond thrombosis and hemostasis [J]. *Cardiovasc Diagn Ther*, 2018, 8 (5): 581-593. DOI: 10.21037/cdt.2018.10.14.
- [14] ZHU S, CHEN J, DIAMOND S L. Establishing the transient mass balance of thrombosis: from tissue factor to thrombin to fibrin under venous flow [J]. *Arterioscler Thromb Vasc Biol*, 2018, 38 (7): 1528-1536. DOI: 10.1161/ATVBAHA.118.310906.
- [15] LEE A, AGNELLI G, BÜLLER H, et al. Dose-response study of recombinant factor VIIa/tissue factor inhibitor recombinant nematode anticoagulant protein c2 in prevention of postoperative venous thromboembolism in patients undergoing total knee replacement [J]. *Circulation*, 2001, 104 (1): 74-78.