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罗沙司他在肾性贫血治疗中的作用机制及研究进展

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摘　要

肾性贫血其发生有着复杂的机制，主要与促红细胞生成素(erythropoiesis, EPO)减少有关。严重贫血可影响患者生活质量并与死亡预后相关。低氧诱导因子-1 (hypoxia inducible factor 1, HIF-1)，可与特定的低氧应答DNA元件结合，调节低氧诱导基因的转录，诱导内源性EPO的产生。近年来，多种低氧诱导因子－脯氨酸羟化酶抑制剂(hypoxia-inducible factor-prolyl hydroxylase inhibitors, HIF-PHIs)被成功开发，其中罗沙司他(Roxadustat, FG-4592)已在中国、日本获准上市，并完成了相关临床试验，已证实罗沙司他可有效提升肾性贫血患者血红蛋白、改善铁代谢及脂代谢。本文就罗沙司他在肾性贫血治疗中的作用机制及研究进展作一综述。

关键词

肾性贫血，低氧诱导因子－脯氨酸羟化酶抑制剂，罗沙司他

Mechanism of Action and Research Progress of Roxadustat in the Treatment of Renal Anemia

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Abstract

The occurrence of renal anemia has a complex mechanism, which is mainly related to the reduction of erythropoiesis (EPO). Severe anemia can affect the quality of life of patients and is associated with the prognosis of death. Hypoxia inducible factor-1 (HIF-1) can bind to specific hypoxia-responsive DNA elements, regulate the transcription of hypoxia-inducible genes, and induce the production of endogenous EPO. In recent years, a variety of hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) have been successfully developed, among which Roxadustat (FG-4592) has been approved for marketing in China and Japan, and relevant clinical trials have been completed. It has been confirmed that Roxadustat can effectively increase hemoglobin, iron metabolism and lipid metabolism in patients with renal anemia. This article reviews the mechanism of action and research progress of Roxadustat in the treatment of renal anemia.

Keywords

Renal Anemia, Hypoxia-Inducible Factor-Prolinyl Hydroxylase Inhibitor, Rosastat

1. 引言

慢性肾脏病(Chronic Kidney Disease, CKD)的常见并发症之一是贫血，与 EPO 生成不足、EPO 活性降低、铁缺乏及代谢障碍、营养不良、甲状旁腺功能亢进、炎症状态、尿毒症毒素等因素相关[1]。贫血是 CKD 的一种常见并发症，CKD 患者的贫血患病率是一般人群的两倍，且随着 CKD 的进展而增加[2]。CKD4 期或 CKD5 期患者中，贫血患病率超过 50%，而在在维持性透析的 CKD 患者中，贫血的患病率可达 90%以上[3]。患有贫血的 CKD 患者的生活质量通常低于没有贫血的患者[4]。既往，临床上治疗肾性贫血的方案以促红细胞生成刺激剂(erythropoiesis-stimulating agents, ESAs)或合并使用铁剂为主[5]。但是长期摄入高剂量 ESAs 可能引起许多不良反应，如心脑血管并发症，且微炎症状态可影响 ESAs 疗效[6] [7]。罗沙司他可抑制脯氨酸羟化酶(prolyl hydroxylase, PHD)活性，模拟低氧环境，可有效提升肾性贫血患者的血红蛋白、并改善铁代谢及脂代谢，并且在微炎症状态下可有效应答[8]。

2. 罗沙司他作用机制

2.1. 缺氧诱导因子 1 (HIF-1)

缺氧诱导因子 1 是一种 DNA 结合蛋白，由对 O_2 敏感的 HIF-1α 和稳定的 HIF-1β 构成，可在缺氧条件下激活促红细胞生成素基因转录 EPO [9] [10]。HIF-α 有分为 1α、2α、3α 三种亚型，其中 HIF-1α 是参与基因转录的主要亚基[11]。在氧气充足条件下，HIF-1α 会被泛素－蛋白酶体迅速降解[12]。脯氨酰羟化酶是其中的关键酶，具有三种亚型(PHD1, PHD2, PHD3)，泛素－蛋白酶体迅速降解依赖于脯氨酰羟化酶 PHD2 的作用[13]。在缺氧条件下，PHD 活性受到抑制，阻止 HIF-1α 的泛素化降解，从而提高 HIF-1α 蛋白水平，进入细胞核核内与 HIF-β 结合，两者形成复合物并与特定的低氧应答 DNA 元件结合，调节低氧诱导基因的转录，促使 EPO 表达[14]。

2.2. 低氧诱导因子－脯氨酸羟化酶抑制剂——罗沙司他

罗沙司他是首款小分子低氧诱导因子脯氨酰羟化酶抑制剂(HIF-PHI)被用于治疗肾性贫血的药物，其分子量为 352.34 g/mol，化学式为 $C_{19}H_{16}N_2O_5$ [15]。罗沙司他在 2018 年首先被国家药监局批准用于治疗正在接受透析的慢性肾病患者的贫血，是全球第一款 HIF-PHI 类药物[16]。罗沙司他在促使内源性 EPO 表达增加的同时，也能使 EPO 受体以及促进铁吸收和循环的蛋白表达增加，并且药物以剂量依赖的方式稳定 HIF 水平并刺激红细胞生成[17]。

3. 罗沙司他在肾性贫血患者临床治疗中的研究进展

3.1. 罗沙司他在肾性贫血患者中的治疗疗效

2019 年，Nan Chen 等[8]首先在中国开展的一项多中心、随机对照三期临床实验证实了罗沙司他，可有效提升未接受透析的肾性贫血患者的血红蛋白。该研究在中国 29 个研究中心开展，研究者以 2:1 的比例将 154 例 CKD 患者随机分组，分别以双盲方式接受每周 3 次、为期 8 周的罗沙司他或安慰剂治疗。研究表明在第 7~9 周时的血红蛋白水平，罗沙司他组显著超过安慰剂组达到预期终点。该研究也评估罗沙司他在铁代谢及脂质代谢方面的影响，研究结果显示接受罗沙司他治疗后的 CKD 患者，其铁调素水平显著降低，转铁蛋白水平和总铁结合力则有所上升，同时总胆固醇水平相较于基线下降了 40.6 mg/dL。同时，Nan Chen 等[18]也研究了罗沙司他对长期透析患者的疗效。在这项实验中共纳入 305 例患者，以 2:1 的比例随机分组，评估在第 23~27 周的血红蛋白水平相对于基线的平均变化方面。研究发现罗沙司他治疗组的血红蛋白水平的改善情况在数值上超过 ESAs 治疗组，且增加了转铁蛋白，保持了血清铁的水平，总胆固醇及低密度脂蛋白胆固醇水平下降。一项随机、开放标签的 3 期研究比较了罗沙司他与 ESA 在 616 名非透析依赖性患者中的贫血治疗疗效和安全性。该研究表明罗沙司他可维持血红蛋白血浆水平长达 104 周，使用罗沙司他组的血红蛋白反应性不低于 ESAs 组且在第 1~36 周期间首次使用静脉铁剂的发生率较低[19]。Fishbane S 等[20]同样研究了罗沙司他治疗在非透析依赖性患者中的贫血疗效，发现罗沙司他可有效增加非透析依赖性 CKD 患者的血红蛋白并减少红细胞输血的需求。Fishbane S 等[21]也开展了另一项 3 期临床试验，评估了罗沙司他在 2133 维持性透析患者中的疗效，其中血液透析患者占比 89.1%；腹膜透析患者占比 10.8%。研究发现罗沙司他的肾性贫血疗效不劣于 ESAs，且罗沙司他组的平均每月静脉铁使用量显著低于 ESAs 组。刚开始透析的患者是高风险人群，在透析的第一年发病率和死亡率最高[22]。HIMALAYAS [23]是一项大型 RCT 研究，其评估了在美国、欧洲、南美洲和亚洲的 19 个国家中罗沙司他对治疗新透析(终末期肾脏病接受血液透析或腹膜透析 2 周至 8 周)的 1043 名 CKD 患者肾性贫血的疗效，证实罗沙司他在改善肾性贫血方面同样不劣于 ESAs。在一项涵盖了 21 项随机对照试验的荟萃分析中，研究者共纳入了中国地区的 1408 例患者。分析结果表明，与中国地区血液透析患者常用的传统红细胞生成刺激剂相比，罗沙司他在治疗贫血方面展现出了更高的有效性和安全性[24]。PYRENEES [25]研究中共纳入了 836 名欧洲地区维持性透析 CKD 患者，按 1:1 随机分配，受试者以每周 3 次的 ESAs 持续治疗 4 月后转换为罗沙司他，或继续之前的 ESAs 方案。研究表明在维持性透析且至少接受 4 个月 ESA 治疗的 CKD 贫血患者中，罗沙司他在维持血红蛋白水平方面不劣于 ESA。在中国进行的罗沙司他III期临床试验中，针对微炎症状态亚组分析结果显示，与接受促红细胞生成素刺激剂治疗的组别相比，接受罗沙司他治疗的组别血红蛋白水平升高幅度更为显著，且无需增加罗沙司他的药物剂量[8] [18]。年龄较大、罗沙司他血药谷浓度较高或基线血红蛋白水平较低的患者对罗沙司他治疗反应较好[26]。EPO 相比，罗沙司他可改善血液透析患者的左心室质量指数[27]。在尿毒症合并肿瘤的贫血患者中，一项小样本回顾性研究显示罗沙司他联合重组人促红素可有效提高血红蛋白、血清铁蛋白以及血清转铁蛋白的浓度[28]。

3.2. 罗沙司他与其他药物之间的相互作用

CKD 患者常伴随电解质及内分泌代谢紊乱、胃肠道和营养异常，需要服用其他药物来治疗这种疾病的许多并发症[29]。在抗凝、血小板及质子泵抑制剂等相关药物方面，奥美拉唑、氯吡格雷、口服铁剂、碳吸附剂和华法林对罗沙司他药代动力学没有显著影响[30]-[33]。在磷结合剂方面，碳酸镧在对罗沙司他的药代动力学没有临床相关影响[34]。而司维拉姆或醋酸钙与罗沙司他同时服用可形成不溶性的螯合物从而降低罗沙司他的吸收和利用程度，但服用磷酸盐结合剂与口服罗沙司他间隔超过 1 小时，这种效果会减弱[35]。在降脂药物方面，罗沙司他与他汀类药物同用会增加他汀类药物血药浓度[36]。

4. 罗沙司他的安全性

Jonathan Barratt [37]汇总分析了四项 3 期研究的罗沙司他在 CKD 患者中的疗效和心血管安全性，研究显示罗沙司他与 ESAs 相比，CKD 患者心血管事件或死亡率风险并无显著差异。在临床试验中，罗沙司他不良反应报道主要是腹泻、恶心、头晕、鼻咽炎、高钾血症等[18] [19] [21] [38]。有病案报道表明罗沙司他可能会引起甲状腺功能减退[39]-[42]。随后有回顾性研究及队列研究显示罗沙司他会引起甲状腺功能减退，其机制可能是罗沙司他与甲状腺激素受体相互作用，抑制垂体中促甲状腺激素分泌的负反馈，导致甲状腺激素分泌减少[43]-[45]。

5. 总结

罗沙司他可有效改善 CKD 患者的贫血，并可调节铁调素水平，增加铁的利用，降低总胆固醇水平。在安全性方面，与 ESAs 相比罗沙司他是一种相对安全有效的治疗 CKD 患者贫血的药物。

6. 展望

尽管罗沙司他作为治疗肾性贫血的首个口服小分子 HIF-PHI，在中国和日本的 III 期临床试验中显示出显著疗效，例如在治疗第 27 周时，罗沙司他组平均 Hb 升高值高于 ESAs 组，且有效率接近 93%，但治疗期间仍需警惕严重不良反应。因此，进一步的研究是必要的，以优化其治疗方案并确保患者安全。罗沙司他在治疗肾性贫血方面显示出潜力，但目前尚缺乏前瞻性研究证实其对甲状腺功能的长期影响，如罗沙司他导致甲状腺功能减退的案例所示，因此需要进一步开展相关临床试验。另外，罗沙司他在骨髓增生异常综合征等血液疾病中的潜在治疗效果也值得进一步探究。罗沙司他的出现为肾性贫血的治疗开辟了新途径，其独特的作用机制和良好的疗效使其具有广阔的应用前景。未来，随着研究的深入和临床经验的积累，罗沙司他可能成为肾性贫血治疗的一线选择，进一步改善患者的生活质量和临床预后。

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