◆特邀专稿◆

重症新型冠状病毒感染药物治疗的研究进展*

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摘要：新型冠状病毒引起的新型冠状病毒感染（Coronavirus Disease-2019，COVID-19）在全球流行爆发，严重威胁人类生命健康，给全球造成了巨大的医疗、经济和社会破坏。重症COVID-19患者病死率高，目前无特效治疗药物，现有的药物治疗主要是通过抑制病毒复制、抗炎及免疫调节等机制起效。对于COVID-19患者，早期使用合适、有效的治疗药物会降低住院率及死亡率，并降低医疗成本，减轻医务人员负担。本文对重症COVID-19患者治疗药物的研究进行综述，拟为临床救治COVID-19患者的药物选择提供参考。

关键词：新型冠状病毒；COVID-19；重症；治疗；药物开发

中图分类号：R186　　**文献标识码**：A　　**文章编号**：1005-9164(2023)03-0445-10
DOI：10.13656/j.cnki.gxkx.20230710.003

冠状病毒属于冠状病毒科（Coronaviridae）冠状病毒属（*Coronavirus*），是一种单股正链RNA病毒，可引起人类和蝙蝠、骆驼、狗等动物的感染，且主要为呼吸道感染[1]。于2019年12月发生并开始大流行的新型冠状病毒被命名为严重急性呼吸综合征冠状病毒2（Severe Acute Respiratory Syndrome Coronavirus 2，SARS-CoV-2），又称为2019年新型冠状病毒（2019-nCoV），该病毒导致新型冠状病毒感染（Coronavirus Disease-2019，COVID-19）的发生。COVID-19传播的方式包括动物与人、人与人之间的传播（通过气溶胶传播、院内相关感染传播和母体传播）[2]。新型冠状病毒感染动物后可引起多种疾病，人类受感染后所表现出的症状也因人而异，可能从无症状到危重症，常表现为发热、咳嗽、呼吸困难、胃肠道症状等，严重时可导致严重的肺损伤，需要住院治疗，甚至还可能导致死亡[3]。重症COVID-19患者定义为SARS-CoV-2感染者出现严重缺氧状态，SpO_2＜94%，PaO_2/FiO_2＜300 mmHg，呼吸频率＞30次/分，或肺部浸润＞50%[4]。男性、高龄和合并高血压、糖尿病、心血管疾病、恶性肿瘤等基础疾病会使重症新型冠状病毒感染的风险增加[5]。

世界卫生组织（World Health Organization，

收稿日期：2023-04-09　　修回日期：2023-05-29
*广西重点研发计划项目“新型冠状病毒感染的肺炎重症病例免疫微环境调控及ECMO新技术救治效果评价”（桂科AB20058002）资助。
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【引用本文】
韦姗汕，张剑锋.重症新型冠状病毒感染药物治疗的研究进展[J].广西科学，2023，30(3)：445-454.
WEI S S，ZHANG J F. Research Progress in Drug Treatment for Severe Coronavirus Disease-2019 [J]. Guangxi Sciences，2023，30(3)：445-454.

WHO)最新数据显示,截至 2023 年 5 月 24 日,全球累计报告确诊 COVID-19 病例 766 895 075 例,死亡 6 935 889 例,其中我国确诊病例 99 261 812 例,死亡 121 144 例[6],新型冠状病毒感染疫情给全球人口及经济带来了巨大的损失。如何有效预防及治疗重症 COVID-19 患者是一个重大挑战。世界各国在新冠疫情发生后,对新型冠状病毒感染的预防及治疗药物进行了系列研发,现将部分治疗药物研究情况列于表 1。

1 抗病毒药物

抗病毒是病毒感染的特异性治疗,我国目前关于 COVID-19 的抗病毒药物已经上市的包括 3 种国产口服药[阿兹夫定、氢溴酸氘瑞米德韦(VV-116)和先诺特韦片/利托那韦片]和 2 种进口口服药[奈玛特韦/利托那韦(Paxlovid)和莫诺拉韦(Molnupiravir)]。

阿兹夫定、VV-116 和 Molnupiravir 的作用靶点均为依赖 RNA 的 RNA 聚合酶(RdRp),可在宿主细胞中通过抑制 RdRp 的活性,阻断 RNA 的合成和复制。阿兹夫定、VV-116 均用于治疗轻、中症 COVID-19 成年患者,但有临床数据显示阿兹夫定也能显著缩短中、重症患者的核酸转阴时间及治疗时间。Najjar-Debbiny 等[29]的研究结果表明,Molnupiravir 可降低进展为严重 COVID-19 的风险和死亡率。瑞德西韦作用靶点也为 RdRp,一项针对非住院 COVID-19 患者的临床试验表明,瑞德西韦治疗 3 d 后的患者住院或死亡风险降低了 87%[30]。部分随机对照试验、Meta 分析结果表明瑞德西韦可降低伴有进展高风险的 COVID-19 患者的死亡率[31]。WHO 推荐对于重症、危重症患者静脉注射使用瑞德西韦。

先诺特韦片/利托那韦片和 Paxlovid 的作用靶点为冠状病毒主蛋白酶(即 3CL 蛋白酶),先诺特韦片/利托那韦片是首款国产的抗 3CL 蛋白酶的抗病毒创新药物,临床研究显示它可有效缩短症状缓解时间及核酸转阴时间;同时可显著降低病毒载量,给药 5 d 后的病毒载量下降 96.28%[32]。但先诺特韦片/利托那韦片尚缺乏降低重症以及死亡风险方面的研究。Paxlovid 可用于治疗重症 COVID-19 患者,临床研究数据显示该药可将 COVID-19 患者的住院或死亡风险降低 89%[33]。Paxlovid 也存在局限性,其对高龄、具有基础疾病等特征的高危群体有效,而对于没有基础疾病或感染超过 5 d 的高危群体治疗效果可能相对较弱。

此外,其他抗病毒药物例如洛匹那韦-利托那韦片(Kaletra)和达芦那韦比司他(Prezcobix)为蛋白酶抑制剂,是治疗艾滋病的药物,也有研究验证其对 COVID-19 患者的治疗效果。一项小型回顾性研究发现在重症 COVID-19 患者中使用 Kaletra 并不能明显改善预后[34],另一项小型单中心临床试验将轻症患者分别给予 Prezcobix 联合干扰素 α-2b 治疗或单用干扰素 α-2b 治疗,结果显示 Prezcobix 未能加速病毒的清除[35]。法匹拉韦(Favipiravir)是一种广谱抗 RNA 病毒药物,是我国第一个批准上市的、对 COVID-19 具有潜在疗效的药物。一项随机对照研究将患者随机分组给予氯喹和法匹拉韦治疗,结果显示法匹拉韦可减少患者住院时间和机械通气需求[36]。但这些抗病毒药物由于有效性不足,目前的研究纳入病例数较少或仅针对轻、中症患者有效,限制了其在 COVID-19 患者中的使用,目前我国的治疗指南均未将这些药物纳入其中。

2 Janus 激酶抑制剂

在重症 COVID-19 患者中,宿主免疫反应在驱动急性炎症过程中起着关键作用。包括白细胞介素-6 (IL-6)在内的几种细胞因子在重症 COVID-19 患者中含量水平升高,Janus 激酶(JAK)抑制剂则可抑制细胞因子风暴,并且通过阻止 AP-2 相关蛋白激酶 1(AAK1)介导的内吞作用来抑制病毒组装。因此,JAK 抑制剂被建议用作重症 COVID-19 患者的治疗药物[37]。巴瑞替尼(Baricitinib)是一种 JAK1/JAK2 抑制剂,具有抗细胞因子及抗病毒活性。Patoulias 等[38]研究表明,在住院 COVID-19 患者中使用 JAK 抑制剂(包括巴瑞替尼)治疗可降低 43%的死亡风险,以及 36%的机械通气或体外膜肺氧合风险。部分随机对照试验、Meta 分析表明巴瑞替尼可降低死亡率、重症监护病房的入院率以及对有创机械通气的需求[39,40]。上述研究结果提示,巴瑞替尼是一种有希望、有前景、安全有效的抗重症 COVID-19 药物,且生产及储存方便,但需要提供更多的数据来支持其在更广泛人群中的使用。WHO 强烈推荐重症、危重症患者使用皮质类固醇、IL-6 受体拮抗剂或者巴瑞替尼治疗,三者还可以联合使用。但由于有效性不够理想且价格不低,巴瑞替尼的使用受到了限制。

表 1　重症 COVID-19 患者的治疗药物研究一览表

Table 1　List of drug studies for the treatment of severe COVID-19

治疗类别 Treatment category	具体药物 Specific drug	研究类型 Research type	纳入病例的时间或检索文献的时间 Time to inclusion of cases or time of search of studies time	国家 Nation	样本量 Number of samples	纳入人群特征 Characteristics of the included population	主要结局 Main outcome	次要结局 Secondary outcome	主要安全终点 Major safety endpoint	结论 Conclusion
Antiviral drug	Remdesivir	Randomized, double-blind, placebo-controlled trial	2020.09.18－2021.04.08	US, UK, etc	562	Patients≥12 years old, with at least one risk factor for progression to severe COVID-19; or patients≥60 years old, with or without other risk factors, and non-hospitalized patients	Hospitalization or death	Complex outcome of medical treatment or death	Any adverse event	In non-hospital patients at high risk of COVID-19 progression, a 3-day course of remdesivir had an acceptable safety, with an 87% lower risk of hospitalization or death than in the placebo group[7]
	Remdesivir	Randomized, double-blind, placebo-controlled trial	2020.02.06－2020.03.12	China	237	≥18 years old	Time for clinical symptoms to improve	All-cause mortality, frequency of invasive mechanical ventilation, duration of oxygen therapy, length of hospital stay, and proportion of patients with nosocomial infections	Any adverse event	In adult patients admitted to hospital with severe COVID-19, the clinical benefit of Remdesivir did not show statistical significance[8]
	Remdesivir	Meta-analysis	2022.01.15－2022.05.05	UK, Egypt, etc	10 751	≥18 years old	Death	—	Any adverse event	Redesivir has the potential to reduce mortality in patients who need oxygen but are not yet critically ill[9]
	Nirmatrelvir/Ritonavir tablet	Retrospective study	2022.01－2022.02	Israel	180 351	Patients≥18 years old, at high risk for severe COVID-19	Severe illness or death	—	—	In the Omicron era and in real life, Paxlovid was very effective in reducing the risk of severe COVID-19 or death[10]
	Nirmatrelvir/Ritonavir tablet	Randomized, double-blind, placebo-controlled trial	2021.06.16－2021.12.09	US, UK	2 246	Patients≥18 years old, symptomatic, unvaccinated, non-hospitalized, with high risk factors for progression to severe COVID-19	Hospitalization or death	—	Any adverse event	Paxlovid treatment of symptomatic COVID-19 resulted in an 89% lower risk of progression to severe COVID-19 than placebo, with no significant safety concerns[11]
	Nirmatrelvir/Ritonavir tablet	Observational study	2022.02.26－2022.06.26	Hong Kong, China	1 074 856	≥18 years old	Inpatient and in-hospital disease progression	—	—	Early initiation of oral antivirals reduced the risk of death and nosocomial disease progression in non-hospitalized COVID-19 patients during Omicron BA.2.2 in Hong Kong, China[12]
	Molnupiravir	Randomized, double-blind, placebo-controlled trial	2021.05.06－2021.10.02	Canada, France, etc	1 433	Patients≥18 years old, non-hospitalized, unvaccinated, mild to moderate, with at least one risk factor for progression	Hospitalization or death	Progression of disease	Any adverse event	Early treatment of Molnupiravir reduced the risk of hospitalization or death in unvaccinated adults with COVID-19 who were at risk for progression[13]
	Molnupiravir	Retrospective study	2022.01－2022.02	Israel	5 322	Patients≥18 years old are at risk of progression to severe disease, with or without vaccination	Severe illness or death	—	—	In the Omicron era, treatment with Molnupiravir has the potential to reduce severe COVID-19 morbidity and mortality, especially in the elderly, women, and under-vaccinated patients[14]
JAK inhibitors	Baritinib	Randomized, double-blind, placebo-controlled trial	2020.12.23－2021.08.10	Argentina, US, etc	101	Patients≥18 years old, hospitalized under invasive mechanical ventilation or extracorporeal membrane oxygenation	All-cause mortality, ventilator-free days, length of hospital stay	—	Any adverse event	Among hospitalized patients with critically ill COVID-19, baritinib treatment reduced mortality compared with placebo (including a corticosteroid combination) [15]
	Baritinib	Randomized, controlled trials and updated meta-analyses	2021.02.02－2021.12.29	UK	8 156	≥2 years old	All-cause mortality	Combined outcome of discharge time, invasive mechanical ventilation (including extracorporeal membrane oxygenation), and death	Severe arrhythmias, thrombosis and major bleeding events and other infections	Baritinib significantly reduced the risk of death in hospitalized patients with COVID-19[16]
	Baritinib	Meta-analysis	2021.09.05	UK, US, etc	3 564	≥18 years old	All-cause mortality, disease severity	—	—	Baritinib may be a promising, safe and effective anti-COVID-19 drug[17]
Interleukin-6 (IL-6) receptor antagonist	Tocilizumab	Meta-analysis	2020.12.27－2021.03.20	US, Western Europe, etc	10 201	≥18 years old	Mortality and mechanical ventilation requirements	—	—	Tocilizumab can reduce the risk of death and the need for mechanical ventilation in COVID-19 patients, especially in critical cases[18]

续表

Continued table

治疗类别 Treatment category	具体药物 Specific drug	研究类型 Research type	纳入病例的时间或检索文献的时间 Time to inclusion of cases or time of search of studies time	国家 Nation	样本量 Number of samples	纳入人群特征 Characteristics of the included population	主要结局 Main outcome	次要结局 Secondary outcome	主要安全终点 Major safety endpoint	结论 Conclusion
	Tocilizumab	International，multi-factor，adaptive platform trials	2019.12－2020.11	UK，US，etc	803	Critically ill patients ≥18 years old	Number of days without organ support such as ventilators	90-day survival time，ICU occupancy，and discharge time	Any adverse event	Treatment with tocilizumab and saliuzumab in critically ill patients with COVID-19 improves outcomes，including survival[19]
	Tocilizumab	Randomized，Controlled trials	2020.04.23－2021.01.24	UK	21 550	≥18 years old	All-cause mortality	Time to discharge，mortality rate	—	In hospitalized COVID－19 patients with hypoxia and systemic inflammation，tocilizumab improves survival and other clinical outcomes[20]
Corticosteroids	Corticosteroids	Randomized，Controlled trials	2019.12－2020.06.08	UK	6 425	≥18 years old	All-cause mortality	Time of discharge，or time of death	Any adverse event	In hospitalized patients with COVID-19，the use of dexamethasone reduced 28-day mortality in patients randomized to invasive mechanical ventilation or oxygen alone，but the effect was not significant in patients not receiving respiratory support[21]
	Corticosteroids	Retrospective study	2020.03.01－2020.05.31	US	184	Critically ill patients≥18 years old	Mortality，number of days out of ICU	Other organ support is needed	—	High-dose corticosteroids have a survival benefit in critically ill patients with COVID-19. In terms of mortality，high-dose corticosteroids are superior to pulse-dose corticosteroids[22]
	Corticosteroids	Meta-analysis	2020.02.26－2020.06.09	UK，China，etc	1 703	≥18 years old	All-cause mortality	Serious adverse event	—	For critically ill patients，the use of systemic corticosteroids was associated with a lower 28-day all-cause mortality compared to conventional treatment or placebo[23]
Anticoagulant therapy	Anticoagulant therapy	Meta-analysis	2021.06.01－2021.07.15	US，Italy	5 154	≥18 years old	All-cause mortality	—	Excessive bleeding	Routine use of prophylactic anticoagulant therapy in hospitalized patients with COVID-19 is not supported[24]
Convalescent plasma therapy	Convalescent plasma therapy	Open，extended trials	2020.04.04－2020.06.04	US	35 322	≥18 years old	Death	—	Any adverse event	Earlier transfusion time and increased antibody infusion levels reduce mortality[25]
	Convalescent plasma therapy	Retrospective study	Enrollment ends to 2020.06.04	US	3 082	Patients≥18 years old，who had been severely ill or were at high risk of developing severe or life-threatening disease	Death	—	Any adverse event	In hospitalized COVID－19 patients who did not receive mechanical ventilation，plasma transfused with higher levels of anti-SARS-CoV-2 IgG antibodies was associated with a lower risk of death than plasma transfused with lower levels of antibodies[26]
Traditional Chinese medicine	Traditional Chinese medicine	Systematic review	Literature search up to 2021.06.21	China	15 520	≥18 years old	Severe illness or death	Clinical symptom improvement rate，clinical cure rate，discharge rate and length of stay	—	Chinese medicine treatment can reduce the proportion of patients with severe disease progression by 55%，and the mortality rate of patients with severe or critical disease by 49%[27]
	Traditional Chinese medicine	Systematic review and Meta-analysis	2020.01.01－2021.01.30	China	1 789	Patients diagnosed with COVID-19，regardless of age，gender，etc	Effective rate (e.g. improvement of clinical symptoms)	Improvement in adverse events	—	The combined treatment of Chinese and Western medicine has certain therapeutic efficacy and safety for COVID－19，especially for patients with mild and moderate symptoms[28]

Note：inclusion criteria for treatment studies：(1) The treatment of COVID-19 recognized by the China′s Health Commission or World Health Organization；(2) Sample size>100.

3 IL-6 受体拮抗剂

紧急感染或组织损伤诱导 IL-6 快速产生，并通过增强包括 C 反应蛋白、纤维蛋白原和血小板生成素等在内的急性期蛋白和免疫反应来激活宿主防御。但 IL-6 过度产生可导致过多的 IL-6 受体信号传导，从而导致免疫反应性疾病[41]。IL-6 直接影响血管内皮细胞，而血管内皮细胞可产生几种类型的细胞因子和趋化因子并激活凝血级联反应。以凝血异常和血管渗漏为特征的内皮细胞失调是细胞因子风暴的常见并发症[42]。托珠单抗（Tocilizumab）是一种阻断 IL-6 受体的单克隆抗体，已被批准用于接受全身性皮质类固醇治疗且需要辅助供氧、机械通气或体外膜肺氧合的住院 COVID-19 成年患者[43]。针对托珠单抗治疗重症 COVID-19 患者的部分随机对照试验结果表明，使用托珠单抗治疗重症 COVID-19 患者的死亡率有所降低[44]，但有几项试验结果并未显示出明显的临床获益[45,46]，可能与病例数不足有关，需要更多的回顾性或前瞻性研究来验证其对重症 COVID-19 患者的治疗效果。WHO 推荐重症、危重症患者可使用 IL-6 受体拮抗剂（托珠单抗）治疗。

4 皮质类固醇

新型冠状病毒可能会诱导过度的免疫应答，导致促炎介质过量产生，从而导致急性呼吸窘迫综合征（ARDS）、弥散性血管内凝血和多器官衰竭。因此，减轻 COVID-19 引起的过激炎症也至关重要[47]。皮质类固醇具有强大的抗炎作用，是治疗 COVID-19 引起的过激炎症的理想药物。Karakoc 等[48]进行了一项大剂量皮质类固醇冲击治疗重症 COVID-19 患者的回顾性研究，结果显示在给予大剂量皮质类固醇后，77.8％重症患者的实验室指标及临床症状均有所改善。Sterne 等[49]所做的 Meta 分析结果显示，对危重 COVID-19 患者给予全身性皮质类固醇治疗，可降低 28 天全因死亡率。但关于全身性皮质类固醇治疗重症 COVID-19 患者最有效的类型、剂量或时机的证据仍不成熟，缺乏多中心、样本量充足的大型研究，且对儿童的影响尚不清楚。美国国立卫生研究院（National Institutes of Health，NIH）所发布的指南建议，对于重症患者的治疗为每日给予 1 次地塞米松治疗，剂量为 6 mg，持续 10 d，这也是目前美国医院治疗重症 COVID-19 患者的方案[50]。WHO 也强烈推荐使用皮质类固醇治疗重症、危重症 COVID-19 患者。

5 抗凝药物

COVID-19 可能与凝血功能异常有关，包括 D-二聚体、凝血酶原时间、部分凝血活酶时间等指标[51]。Zhou 等[52]研究报道 COVID-19 患者相关凝血功能障碍与不良预后（包括死亡率、重症监护病房入住率、需要通气支持）相关。COVID-19 患者可能因过激炎症反应、内皮功能障碍和血流淤滞而易发生血栓并发症。由于 COVID-19 住院患者（尤其是重症患者）发生静脉血栓风险增加，目前推荐使用低分子肝素或普通肝素进行血栓预防[53]。一项对照试验显示，给予治疗剂量的抗凝治疗可显著增加无器官支持天数，增加生存的可能性[54]。一项纳入 11 项随机临床试验和 17 项观察性研究的 Meta 分析结果表明，COVID-19 患者的治疗性抗凝治疗和预防性抗凝治疗的死亡率并无显著差异；对于非危重症 COVID-19 患者，预防性抗凝治疗优于治疗性抗凝治疗；而观察性研究分析结果表明，危重症 COVID-19 患者进行治疗性抗凝治疗是必要的[55]。NIH 指南建议对于无治疗性抗凝指征的患者，除非有禁忌证，均应给予预防性抗凝治疗，且预防性剂量的肝素也适用于孕妇；对于在非 ICU 病房中开始服用治疗剂量的肝素然后转到 ICU 病房的患者，建议改用预防性剂量的肝素。由于血栓并发症可能会增加 COVID-19 患者的死亡风险，预防性或治疗性抗凝至关重要，住院患者排除禁忌证后应给予普通肝素或低分子肝素抗凝治疗，并且与 COVID-19 相关的静脉血栓栓塞应抗凝治疗至少 3 个月。

6 恢复期血浆

恢复期血浆是中和抗体的来源，由于其含有足够浓度的中和抗体，在早期疾病治疗时效果最好[56]。恢复期血浆治疗是指采集 COVID-19 痊愈患者的血浆成分，输注给目前重症 COVID-19 患者，对危重症患者有一定疗效。Joyner 等[25]研究分析了美国 2 807 家急症护理机构的住院患者使用恢复期血浆的情况，结果显示在诊断 COVID-19 后 3 d 内输血的患者的 7 天死亡率为 8.7％，在诊断后 4 d 或更长时间内输血的患者的 7 天死亡率为 11.9％，30 天死亡率的结果类似（21.6％ vs 26.7％）；对于接受高 IgG、中等 IgG、低 IgG 血浆的患者，其 7 天死亡率分别为 8.9％、11.6％、13.7％，而且 30 天死亡率的结果也类

似。这些结果表明,早期输注高抗体水平恢复期血浆可降低重症患者的死亡率。Joyner 等[57]的一项回顾性分析表明,在未接受机械通气的 COVID-19 住院患者中,输注较高 IgG 抗体水平的血浆比输注抗体水平较低的血浆的死亡风险更低。但 Alemany 等[58]进行的一项研究报道认为,恢复期血浆未能防止轻症 COVID-19 患者进展为重症,也未能有效降低门诊患者的病毒载量。综上,目前恢复期血浆治疗 COVID-19 患者的有效性证据不足。虽然美国食品药品监督管理局(Food and Drug Administration,FDA)已授权使用康复期患者的血浆来治疗重症患者,但是目前美国对院内患者不常规使用,对免疫抑制患者(例如器官抑制患者)才使用恢复期血浆。WHO 均不推荐普通型、重型患者使用恢复期血浆。我国《新型冠状病毒感染诊疗方案(试行第十版)》指出,恢复期血浆可在病程早期用于伴有重症高风险、病毒载量高、病情进展快的患者。

7 中药

目前有关中药治疗对 COVID-19 的有效性也有深入研究,多项临床研究表明,中西医联合治疗可以提高 COVID-19 患者的治愈率,缩短平均住院时间[59]。中药联合常规治疗对重症患者有保护作用,清肺排毒汤联合西医常规治疗的研究表明该治疗措施可改善重症患者的症状[60]。中药治疗重症 COVID-19 患者的可能机制有:(1)直接抑制病毒——富含类黄酮化合物的中药具有抗病毒作用;(2)抑制炎症,调节免疫功能;(3)抑制血栓形成,抑制血小板的黏附和聚集;(4)抑制氧化应激反应,例如甘草酸可以抗氧化应激,且能抑制炎症反应[61,62]。我国《新型冠状病毒感染诊疗方案(试行第十版)》推荐,参照指南合理使用中药辅助治疗 COVID-19 患者。

8 正在申请上市或正在研究的药物

普克鲁胺是一种雄激素受体拮抗剂,可以下调血管紧张素转化酶 2(ACE2)和跨膜丝氨酸蛋白酶 2(TM-PRSS2)的活性,这两种酶是 SARS-CoV-2 侵入宿主细胞的关键蛋白,因此普克鲁胺可以抑制病毒进入宿主细胞,目前已在巴拉圭获批用于紧急治疗 COVID-19 患者。2021 年 12 月,美国治疗轻、中症非住院 COVID-19 患者的Ⅲ期临床试验中期数据显示,普克鲁胺的有效性无统计学意义[63]。2022 年 4 月,普克鲁胺的全球多中心Ⅲ期临床试验数据显示,普克鲁胺可有效降低 COVID-19 患者的住院或死亡率,尤其是用药超过 7 d 的患者,普克鲁胺的保护率可达 100%[64]。目前苏州开拓药业股份有限公司已就该药物向我国国家药品监督管理局申请上市,尚在审评中。

度维利塞胶囊(Duvelisib)是一种磷脂酰肌醇-3 激酶(PI3K)的小分子抑制剂,是多种肿瘤的口服治疗药物。Duvelisib 可能会通过抑制 PI3K 来抑制先天性免疫系统的异常过度激活,优先极化巨噬细胞,减少肺部炎症,并减弱病毒持久性,从而改善患者的预后。一项研究探讨了 Duvelisib 对重症 COVID-19 患者的作用,共纳入 28 名重症成年患者,结果显示使用 Duvelisib 治疗组患者的 6 个月内的全因死亡率为 40%,而使用安慰剂组为 61.54%。

Ensitrelvir (S-217622)作用靶点是 3CL 蛋白酶,作用机制与 Paxlovid 相同。2022 年 2 月,日本盐野义制药公布 S-217622 的Ⅱ/Ⅲ期临床试验部分数据,结果显示 S-217622 组病毒滴度和病毒 RNA 迅速下降[65]。此外,研究者正计划向中、美两国递交 3CL 蛋白酶抑制剂 ASC11 和 RdRp 抑制剂 ASC10 的临床研究申请,还有上海君实生物医药科技股份有限公司的 3CL 蛋白酶抑制剂 VV993、广东众生药业股份有限公司的 3CL 蛋白酶抑制剂 RAY003,以及科兴生物制药股份有限公司的 RdRp 抑制剂 SHEN26 等多种治疗药物处于临床前研发阶段[66]。这些正在申请上市或正在研究中的药物同时也需要进一步多中心和大样本量数据来证实它们在 COVID-19 治疗中的有效性和安全性。

9 药物开发

治疗 COVID-19 患者的其他药物正在开发,例如通过多靶点防止病毒进入宿主细胞或通过抑制主要蛋白酶来抑制复制和转录复合物的形成。研究报道靶向 S 蛋白肽可阻止病毒进入宿主细胞,如 Curreli 等[67]构建的吻合肽 NYBSP-4 作用靶向于 S1 刺突蛋白中的受体结合域,但未在体内模型进行研究;Karoyan 等[68]设计的人血管紧张素转换酶 2 肽模拟物的 3 种肽(P8、P9 和 P10),但也未进行体内研究。Bestle 等[69]研究表明,TMPRSS2 肽模拟抑制剂 MI-432、MI-1900 均可抑制 SARS-CoV-2 复制。另外,与靶向 S 蛋白肽的 S1/S2 切割位点结合并阻止宿主蛋白酶分解的治疗药物还需进一步研究。抑制病毒进入宿主细胞和抑制复制、转录复合物形成的治疗策略

正在开发并不断取得进展。

在重症 COVID-19 患者中,高炎症综合征和细胞因子风暴与不良预后相关。对患者已使用抗炎药和免疫调节剂,但未能成功规避重症患者的免疫应答加剧,可能是由于细胞因子相互作用的复杂性以及炎症途径的多样性,使得药物对其中一个或几个分子的抑制不足,难以逆转炎症风暴;也可能是这些药物存在生物利用度差、稳定性差和药代动力学不良的缘故[70]。因此,开发合适的药物输送系统也至关重要。药物输送系统可用于承载常规抗炎药或免疫调节剂等,特别是生物利用度差和不稳定的药物,可安全有效地将药物输送到治疗靶点。

10 展望

目前 COVID-19 仍然存在。重症 COVID-19 患者病死率高,目前暂无特效药,接种疫苗仍是最有效的疫情防控手段,可有效降低重症发生率和死亡率。感染 SARS-CoV-2 后,病程的第 1 阶段是病毒复制期,因此抑制病毒复制的治疗在疾病早期更有效,应尽早使用抗病毒治疗。病程的第 2、3 阶段处于免疫因子风暴期,此时抗病毒治疗已作用不大,主要为抗炎、抑制免疫治疗。临床医生必须综合患者的临床表现及辅助检查来判断疾病的严重程度,这对治疗药物的选择有重要意义。NIH 建立了"加速 COVID-19 治疗干预和疫苗(ACTIV)"联盟,旨在开发 COVID-19 治疗药物[71]。目前关于多种单克隆抗体、免疫调节剂、抗凝剂和其他治疗药物的临床研究正在 ACTIV 联盟内进行,大多数药物现在都处于Ⅲ期试验中,相信在不久的将来会有更多更安全有效的治疗 COVID-19 的药物面市。

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Research Progress in Drug Treatment for Severe Coronavirus Disease-2019

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Abstract:Coronavirus Disease-2019 (COVID-19,referred to a novel coronavirus pneumonia) caused by the novel coronavirus infection has broken out in the world,which seriously threatens human life and health,and has caused huge medical,economic and social damage to the world. The fatality rate of patients with severe COVID-19 is high. At present,there is no specific therapeutic drug. The existing drug treatment mainly works by inhibiting viral replication,anti-inflammatory and immunomodulatory mechanisms. For patients with COVID-19,early use of appropriate and effective therapeutic drugs will reduce hospitalization rates and mortality,reduce medical costs,and reduce the burden on medical staff. This article reviews the research on therapeutic drugs for patients with severe COVID-19,and intends to provide a reference for the selection of drugs for clinical treatment of patients with COVID-19.

Key words:novel coronavirus;COVID-19;severe cases;treatment;drug development

责任编辑:米慧芝