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托珠单抗治疗结缔组织病相关间质性肺病的研究进展

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摘 要

结缔组织病(Connective-Tissue Disease, CTD)常累及全身各个器官，多种CTD如类风湿关节炎(Rheumatoid Arthritis, RA)、系统性硬化症(Systemic Sclerosis, SSc)、系统性红斑狼疮(Systemic Lupus Erythematosus, SLE)等易累及肺脏，严重影响呼吸功能，具有高致死率。目前，临床上多以免疫抑制剂、支持性治疗、抗纤维化治疗及抗氧化治疗为主，但其使用时长、维持和减停标准尚无明确指南，且部分患者疗效不佳。近年来，白介素-6受体(interleukin-6 receptor, IL-6R)拮抗剂托珠单抗(tocilizumab, TCZ)开始尝试应用于多种CTD-ILD患者，但其治疗方案、使用时长还有待探讨。本文将结合近年临床指南和学科进展，对国内外现有文献进行综述，总结TCZ在常见CTD-ILD使用中的研究进展，为临床实践提供参考。

关键词

托珠单抗，肺间质病变，类风湿关节炎，系统性硬化症，系统性红斑狼疮

Research Progress on Tocilizumab in the Treatment of Connective Tissue Disease-Related Interstitial Lung Disease

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Abstract

Connective-Tissue Disease (CTD) often affects various organs throughout the body. Various CTDs such as Rheumatoid Arthritis (RA), Systemic Sclerosis (SSc), Systemic Lupus Erythematosus (SLE) and other diseases can easily affect the lungs, seriously affect respiratory function, and have a high fatality rate. At present, immunosuppressants, supportive treatments, anti-fibrosis treatments and antioxidant treatments are the main clinical treatments. However, there are no clear guidelines for the duration of use, maintenance and reduction standards, and some patients have poor efficacy. In recent years, the interleukin-6 receptor (IL-6R) antagonist tocilizumab (TCZ) has begun to be applied to a variety of CTD-ILD patients, but its treatment options and duration of use have yet to be explored. This article will review the existing literature at home and abroad based on clinical guidelines and disciplinary progress in recent years, summarize the research progress of TCZ in the use of common CTD-ILD, and provide reference for clinical practice.

Keywords

Tocilizumab, Interstitial Lung Disease, Rheumatoid Arthritis, Systemic Sclerosis, Systemic Lupus Erythematosus

1. 引言

肺间质病变(Interstitial Lung Disease, ILD)是一组异质性弥漫性炎症性疾病，主要累及肺部的间质区域，包括肺泡壁、间质和肺泡腔内的结构。这些疾病包括特发性间质性肺炎(Idiopathic Interstitial Pneumonia, IIP)、过敏性肺炎(Hypersensitivity Pneumonitis, HP)、结节病(Sarcoidosis) [1]、结缔组织病相关的肺间质性病变(Connective-Tissue Disease-Associated Interstitial lung Disease, CTD-ILD)等。结缔组织病(CTD)是一组自身免疫性疾病，主要累及结缔组织的胶原蛋白、弹性纤维、基质和细胞等。这些疾病常累及多系统、多器官，如皮肤、关节、血管、肌肉、肺脏等。常见的结缔组织病包括类风湿关节炎(Rheumatoid Arthritis, RA)、系统性红斑狼疮(Systemic Lupus Erythematosus, SLE)、系统性硬化症(Systemic Sclerosis, SSc)等。CTD-ILD 是一种高发疾病，严重威胁呼吸功能，具有高致死率。据报道，CTD-ILD 的发病率约为 12.4%至 34% [2]。CTD-ILD 患者可能会出现多种症状，包括呼吸困难、咳嗽、疲劳和胸痛等。

CTD-ILD 的治疗旨在减轻炎症、控制免疫反应、减缓纤维化进程，并改善患者的呼吸功能和生活质量[3]。治疗 CTD-ILD 的常用策略包括：一、免疫抑制剂[4]：包括糖皮质激素(如泼尼松)、免疫抑制剂(如甲氨蝶呤、硫唑嘌呤)和生物制剂[5] (如雷米刚、阿达木单抗)，这些药物可以抑制免疫反应和炎症，并减缓纤维化的进程。二、支持性治疗：包括氧疗、呼吸康复、营养支持等，以改善患者的呼吸功能和生活质量[6]。三、抗纤维化治疗：对于已经发生纤维化的患者，抗纤维化药物如胞嘧啶、尼莫地平、卡托普利等可减缓纤维化进程[3] [7]。四、抗氧化治疗：包括维生素 E、N-乙酰半胱氨酸等，可减轻氧化应激和炎症反应，对一些患者可能有益[8]。

托珠单抗(tocilizumab, TCZ)作为一种白介素-6 受体(interleukin-6 receptor, IL-6R)拮抗剂，在自身免疫性疾病中应用广泛。IL-6 是一种多效细胞因子，主要由 T 细胞、巨噬细胞、成纤维细胞、滑膜细胞、内

皮细胞及胶质细胞产生，在炎症介导的神经损伤中发挥重要作用[9]。IL-6R 以可溶性和跨膜性受体 2 种形式存在，IL-6 与 2 种受体结合，并与 gp130 结合磷酸化，共同作用触发下游信号转导和基因表达，发挥正常生理功能。大部分细胞表面缺乏跨膜性 IL-6R，而 gp130 几乎存在于所有细胞，血清中存在大量可溶性 IL-6R，因此 IL-6 在体内可发挥广泛作用。TCZ 通过竞争性结合 IL-6R，阻断 IL-6 与 IL-6R 结合，减轻 IL-6 所致的炎性反应[10]。国外文献报道及国内专家共识均推荐 TCZ 治疗 CTD-ILD，近年来 TCZ 在 CTD-ILD 的应用逐渐增加，本文就 TCZ 在 CTD-ILD 中的应用进展进行综述。

2. RA

RA 是一种自身免疫性疾病，主要表现为多发对称性小关节炎，其致残率较高，需要进行长期治疗以实现长期缓解。ILD 是 RA 常见的表现之一[11]，一旦发生，将影响患者生存质量、药物选择以及导致感染并发症而死亡[12] [13] [14]。研究显示，RA-ILD 的患病率约为 20%，占所有 RA 患者死亡率的 10%~20%，平均生存期为 5~8 年[14] [15]。导致 RA-ILD 的危险因素较多，包括性别、年龄、类风湿因子(rheumatoid factor, RF)、骨侵蚀、高疾病活动度等[16] [17] [18]。近年来研究还发现，血清抗 CarP 抗体、MUC5B 启动子变异等在 RA-ILD 的发病中起到一定作用[19] [20]。

目前，糖皮质激素联合免疫治疗(如环孢素)仍然是 RA-ILD 的首要治疗方法。近期研究显示，甲氨蝶呤(MTX)和来氟米特(LEF)与 ILD 的发病无明显相关性[21] [22] [23]，然而，临床使用仍需谨慎。RA-ILD 的治疗一般优先选择阿巴西普(Abatacept)和利妥昔单抗(RTX) [24] [25]。近年来，一些新型的靶向药物[26]如肿瘤坏死因子抑制剂、B 细胞抑制剂和 JAK 抑制剂等也被用于治疗 RA-ILD，并取得了一定的疗效。

2018 年，Manfredi 等人[27]报告了 4 例接受 TCZ 单药治疗的 RA-ILD 患者，其中 RA 缓解，ILD 稳定或改善。随后，Otsuji 等人[28]研究发现，12 例 RA-ILD 患者给予 TCZ 治疗，可显著改善 RA 的疾病活动性，不会导致 ILD 进展。该研究结果表明，在 RA 和 ILD 患者中，TCZ 可以安全使用，且不会加重 ILD。Manfredi 等[29]招募了 28 名接受至少一剂 TCZ 治疗的 RA-ILD 患者，对每位患者的疾病活动性和血清学数据进行评估，并分析了高分辨率计算机断层扫描(High-Resolution Computed Tomography, HRCT)和肺功能测试，包括用力肺活量(FVC)和肺一氧化碳弥散能力(DLCO)。随访 30 个月结束后，针对 FVC 和 DLCO，14 例(56%)患者保持稳定，5 例(20%)改善，6 例(24%)恶化。3 例患者 DLCO 和 FVC 呈相反趋势。大多数病例(25 例)的 HRCT 表现保持稳定，2 例寻常型间质性肺炎患者的 HRCT 表现恶化，只有 1 例非特异性间质性肺炎患者的 HRCT 表现改善。该回顾性研究表明，TCZ 在 RA-ILD 患者中表现出良好的安全性，并对稳定肺部有潜在作用。

3. SSc

SSc 是一种罕见的自身免疫性疾病，其主要特征是皮肤和内脏器官的纤维化和血管异常[30] [31]。SSc 常累及肺，ILD 是常见的表现[32]，可发生于 35%~52%的 SSc 患者[33]，占 SSc 死亡人数的 15%~33% [34]。与 SSc 患者进展性 ILD 相关的危险因素包括：弥漫性皮肤 SSc、男性、非裔美国人种族和抗 SCL-70 抗体(也称为抗拓扑异构酶 I 抗体或 ATA)的存在[35] [36]。目前临床上评估 SSc-ILD 的严重程度相关的其他指标包括疾病进展的影像学评估以及肺功能测试中 DLCO (预测百分比)和 FVC (预测百分比)的下降[37] [38]。

目前已经研究了许多治疗 SSc-ILD 的方法，包括免疫抑制疗法、抗纤维化药物、免疫调节剂、单克隆抗体、造血干细胞移植(Hematopoietic stem cell transplantation, HSCT)和肺移植。自上一个指南发布以来，其他药物，如托珠单抗，已被批准用于减缓 SSc-ILD 患者肺功能下降的速度(美国标签) [39]。

2020 年，Mihai 等人[40]报告了一例 SSc-ILD 并发 COVID-19 的患者，使用 TCZ 治疗，每 4 周静脉

注射 8 mg/kg，关节和 SSc-ILD 得到良好控制，肌肉骨骼和呼吸症状，肺功能和高分辨率 CT 成像逐渐改善。在 2020 年 1 月的最后一次年度评估中，她的 FVC 和 DLCO 分别为各自预测值的 92%和 70%，随后继续进行TCZ治疗，直至痊愈。该病例结果表明，对SSc-ILD进行IL-6阻断治疗可以预防严重的COVID-19的发展。Khanna D 等人[41]招募了患有弥漫性皮肤 SSc 60 个月且急性期反应物升高的成人，包括 ILD 患者，在 48 周双盲期间每周接受安慰剂或 TCZ 162 mg 皮下注射，在 48 周至 96 周接受开放标签 TCZ (安慰剂-TCZ；连续-TCZ)，从基线到 96 周，安慰剂-TCZ 组改良罗南皮肤评分的平均变化为−8.4，连续-TCZ 组为−9.6。安慰剂-TCZ 组的 FVC 平均变化为−3.3，连续 TCZ 组的 FVC 平均变化为−0.5，在随机分析中，弥漫性 ILD 的 FVC 平均变化分别为−4.1 和−0.6。从 48 周到 96 周，安慰剂-TCZ 组的严重不良事件发生率为 14.8 每 100 患者年，连续-TCZ 组为 15.8。该结果证实，TCZ 保护了 SSc 患者(包括 ILD 患者)的肺功能，减缓了 FVC 的下降，长期安全性与 TCZ 的已知安全性一致。近期，Kudsi M 等人[42]进行了一项研究，发现 SSc-ILD 患者罗德曼的得分为 18 分，皮下注射 TCZ 162 mg，每 2 周 1 次，4 周后，观察到罗德曼评分下降。并且在 6 个月后停止 TCZ 治疗，没有任何副作用。该研究证实了 TCZ 可能有效且相当安全，进一步的探索有望推进 SSc-ILD 治疗的新进展。

4. SLE

SLE 是一种机体免疫系统异常激活的自身免疫性疾病，导致多个器官和系统受损，包括皮肤、关节、肾脏、心脏、肺部和中枢神经系统等，临床表现多样化，包括疲劳、关节痛、皮疹、肾炎等。相比其他 CTD，SLE 伴发 ILD 概率较低(8%~10%) [43] [44]。

目前，SLE 的治疗仍然存在挑战，因为传统的免疫抑制剂和激素治疗可能会导致严重的副作用，并且对于部分患者疗效不佳。近年来，一些新的治疗方法和药物也被引入 SLE 的治疗中。早期，Gabor G Illei 等人[44]在一项开放标签 I 期剂量递增研究中发现，15 例患者中，有 8 例患者的(Systemic Lupus Erythematosus Disease Activity Index, SLEDAI)评分降低了 4 分或更多。7 例基线时有关节炎的患者其关节炎均有所改善，其中 4 例缓解。这项研究表明，TCZ 对于 SLE 患者的皮肤损害和炎症反应具有显著的改善作用。另一项研究提示[45]，TCZ 治疗后，75%的患者病情得到改善。改良罗德曼皮肤评分平均降低 11 分，75%和 80%的患者肌肉骨骼和关节受累得到改善，46%的患者肺功能得到改善。近期，Ma Chaoyi 等人[46]报告了两例持续高热合并 SLE 患者，这两例患者的发烧及其他症状对广谱抗生素、抗真菌药物、抗病毒药物和糖皮质激素反应不佳，但是接受 TCZ 治疗后，体温恢复正常，关节痛等症状逐渐好转，并且通过随访得知，其病情至今保持稳定。该研究表明，TCZ 可能是对初始抗生素和大剂量糖皮质激素无效的 SLE 合并持续性高热患者的替代治疗方法。陈建锋等研究发现，TCZ 可以显著改善 SLE 患者的整体症状和生活质量，减轻关节炎和皮疹等症状[47]。此外，TCZ 治疗组的疾病活动度和免疫炎症反应水平较对照组明显降低。同时，Shirota 研究表明 TCZ 可以减少 SLE 患者的内脏器官损伤风险，特别是肾炎和心脏病变[44]。

5. 小结与展望

综上所述，尽管 TCZ 在 CTD-ILD 治疗中的潜力已经得到初步证实，但仍需要进一步的研究来确定其最佳用药方案、剂量和疗程。此外，还需要开展更多的临床试验以扩大样本量，并进行多中心研究，以验证 TCZ 在 CTD-ILD 治疗中的疗效和安全性。展望未来，随着对 CTD-ILD 病理机制的深入研究，我们对于 TCZ 在 CTD-ILD 治疗中的应用可能会有更多的认识。同时，与其他治疗药物的联合应用、个体化治疗和精准医学的发展，也将为 CTD-ILD 患者提供更多的治疗选择和更好的生活质量。

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