·综述·

# 肿瘤坏死因子抑制剂致风湿免疫性疾病患者结核病风险增加的研究进展

时翠林[1] 肖玉梅[1] 曾令武[1] 陆静[1] 刘佳[1] 唐佩军[1] 魏巍[2] 吴妹英[1]
[1]苏州大学附属传染病医院（苏州市第五人民医院）肺科，苏州 215131；[2]南京中医药大学常熟附属医院脾胃科，苏州 215131
通信作者：吴妹英，Email: wu_my@126.com

【摘要】 肿瘤坏死因子（TNF-α）抑制剂是治疗风湿免疫性疾病的常用药物，其使用与结核病风险增加有关。结核高风险患者考虑接受 TNF-α 抑制剂治疗时，推荐使用如依那西普等融合蛋白类 TNF-α 抑制剂，其次考虑单克隆抗体类 TNF-α 抑制剂，如英夫利西单克隆抗体和阿达木单克隆抗体等。在开始 TNF-α 抑制剂治疗前，应对患者进行潜伏性结核感染筛查，在治疗过程中应监测结核病的症状和体征。本文对抗 TNF-α 治疗致风湿免疫疾病患者结核病风险增加的流行病学、致病机制、筛查及治疗策略等进行综述。

【关键词】肿瘤坏死因子 α；风湿免疫性疾病；结核潜伏感染
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**Recent advances in the use of tumor necrosis factor inhibitors to increase the risk of tuberculosis among patients with rheumatic immune diseases**

*Shi Cuilin[1], Xiao Yumei[1], Zeng Lingwu[1], Lu Jing[1], Liu Jia[1], Tang Peijun[1], Wei Wei[2], Wu Meiying[1]*
*[1]Department of Pulmonary, the Affiliated Infectious Diseases Hospital of Soochow University (The Fifth People's Hospital of Suzhou); [2]Department of Spleen and Stomach, Changshu Hospital Affiliated to Nanjing University of Chinese Medicine*
*Corresponding author: Wu Meiying, Email: wu_my@126.com*

【**Abstract**】 Tumor necrosis factor (TNF-α) inhibitors are common agents to treat rheumatic immune diseases, and their application is associated with an increased risk of tuberculosis. Therefore, when patients at high risk of tuberculosis are considered for the treatment with TNF-α inhibitors, fusion protein-based TNF-α inhibitors such as etanercept are recommended, followed by monoclonal antibody-based TNF-α inhibitors such as infliximab and adalimumab. Before starting TNF-α inhibitor therapy, patients should be screened for latent tuberculosis infection and be monitored for signs and symptoms of tuberculosis. In this article, the epidemiology, pathogenesis, screening and treatment strategies of the increased risk of tuberculosis caused by TNF-α inhibitors in patients with rheumatic immune diseases are reviewed.

【**Key words**】Tumor necrosis factor-alpha; Rheumatic immune disease; Tuberculosis latent infection
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风湿免疫性疾病主要是指包括类风湿关节炎（RA）、系统性红斑狼疮、系统性硬化症、多发性肌炎/皮肌炎和干燥综合征等一大类以自身免疫反应导致自身机体器官功能障碍为主要发病机制的疾病，主要治疗手段有糖皮质激素、免疫抑制剂及生物制剂等。近年研究发现，风湿免疫性疾病合并结核的风险较高，肿瘤坏死因子-α（TNF-α）抑制剂是用于治疗风湿性疾病的首批免疫生物学药物，其使用与结核病风险增加有关，本文对使用 TNF-α 抑制剂治疗的风湿免疫性疾病患者的风险因素、检测、治疗等最新研究进行综述。

## 一、抗 TNF-α 治疗致结核病风险增加的流行病学研究

与普通人群相比，暴露于 TNF 的个体患活动性肺结核的风险明显增加。Noguera-Julian 等[1]纳入使用抗TNF 免疫相关

疾病的患儿 19 例，发现从开始抗 TNF-α 治疗到诊断结核病的中位间隔为 13.1（IQR:7.1~20.3）个月,14 例为粟粒性结核,抗结核治疗的中位持续时间为 50(IQR:46~66)周。完成结核病治疗的 15 例患者中有 5 例患有长期后遗症。Chung 等[2]研究发现 RA 患者较非特异性背痛患者患结核病的风险高 2.53 倍(*HR*=2.53,95%*CI*:1.29~4.94),TNF-α 抑制剂的使用和既往结核病史等是结核发病的危险因素。在非 HIV 患者中,TNF-α 抑制剂的使用与结核相关的免疫重建炎症综合症有关(TB-IRIS)。Hachisu 等[3]通过回顾分析发现过敏史和血清高钙血症可能是 TB-IRIS 的独立预测因子。Chiu和 Chen[4]的临床荟萃分析结果提示,接受生物制剂(包括 TNF-α 抑制剂和非 TNF-α 抑制剂或靶向合成药物)治疗的炎性关节炎患者的细菌和分枝杆菌感染的风险增加,其中接受 TNF-α 抑制剂治疗患者分枝杆菌感染的风险最高。基于此,英国于 2019 年发布了炎性关节炎患者使用生物制剂安全指南[5]。

全球不同地区接受 TNF-α 抑制剂治疗的人群中,罹患结核的风险有所不同。在低结核病发病率国家,接受抗 TNF 治疗个体的结核病风险比一般人群高 8~12 倍，在高结核病发病率的国家高达 24~40 倍[6]。Sartori 等[7]纳入全球 52 项研究,发现用 TNF-α 抑制剂治疗风湿病患者的结核病发病率为 9.62/1 000。与北美和欧洲相比,南美和亚洲的结核病发病率更高,分别为 11.75/1 000 和 13.47/1 000,多数病例发生在使用后的 18.05 个月,且以肺部疾病为主。Pettipher 等[8]发现南非地区风湿性疾病生物制剂使用者的结核发病率为 12.4/1 000，因此需要对此类人群进行潜伏结核感染(LTBI)筛查。

## 二、TNF-α 抑制剂治疗增加结核病风险的机制

TNF-α 作为一种细胞因子,在宿主抗结核分枝杆菌感染中起着重要作用,通过其在巨噬细胞活化和细胞持续招募中的作用,维持肉芽肿的结构[9]。TNF-α 及其受体的相互作用可以激活关键信号通路,如核因子 κB(NF-κB)通路、NF-κB 受体活化因子配体(RANKL)信号通路、细胞外信号调节激酶信号通路以及促凋亡信号转导通路等,TNF-α 抑制剂可通过阻断上述信号通路的信号转导而阻止炎症细胞聚集,从而快速缓解患者症状。TNF-α 抑制剂生物疗法的出现极大地促进了风湿性疾病的治疗,但可能会增加结核感染风险或导致结核复燃,其主要机制包括:①TNF-α 抑制剂可抑制吞噬体的成熟,影响细胞凋亡、补体依赖性细胞毒性反应和抗体依赖细胞介导的细胞毒性作用等机制，抑制 T 细胞的杀伤效应;②TNF-α 抑制剂可以削弱 IFN-γ 反应，促进 IL-10 分泌;③TNF 被抗体中和、或 T 细胞的耗竭,导致肉芽肿结构溶解,残存细菌复活并播散感染[10]。

## 三、应用不同 TNF-α 抑制剂治疗的结核病患病风险不同

现常使用的 TNF-α 抑制剂有 5 种，依那西普为重组人 TNF-α 二聚体受体融合蛋白,阿达木单克隆抗体、英夫利昔单克隆抗体、戈利木单克隆抗体和赛妥珠单克隆抗体为单克隆抗体。抗 TNF-α 单克隆抗体与可溶性 TNF-α 受体治疗相比,存在较高的结核病患病风险[11-16]。美国食品和药物管理局数据显示,英夫利昔单克隆抗体治疗者中结核年发病率约为 144/10 万,是依那西普(35/10 万)的 4 倍以上[17]。法国一项前瞻性研究发现，使用 TNF-α 抑制剂如英夫利昔单克隆抗体、阿达木单克隆抗体和依那西普治疗的患者标准化结核病发生率与普通人群的比值分别为18.6（95% *CI*:13.4~25.8)、29.3 (95% *CI*:20.3~42.4)和 1.8(95% *CI*: 0.7~4.3)[18]。Koo 等[19]对接受了 TNF-α 抑制剂的 12 246 名的强直性脊柱炎患者进行回顾性分析,肺结核年发生率为 4.90/1 000,其中英夫利昔单克隆抗体的结核病风险是依那西普的 9.05 倍。新型抗 TNF-α 单克隆抗体如戈利木单克隆抗体和赛妥珠单克隆抗体的结核病风险暂未见增加,但仍需长期随访研究验证[20-21]。

## 四、使用 TNF-α 抑制剂治疗前的患者 LTBI 筛查方法

鉴于使用 TNF-α 抑制剂的患者发生结核病再激活的风险增加，在开始 TNF-α 抑制剂治疗前进行 LTBI 筛查可以显著降低结核病的发病率。西班牙风湿病学会的研究证实,LTBI 筛查后进行预防治疗再使用生物制剂患者的活动性结核发病率下降 78%(*HR*=0.22,95%*CI*:0.03~0.88)[22]。关于 LTBI 筛查方法的使用,从只推荐结核菌素试验(TST)或IFN-γ 体外释放试验(IGRA)到使用 TST 和 IGRA 的组合[23-25],不同专业组织和不同国家的建议并不一致。LTBI 筛查测试的性能受到免疫介导的炎症性疾病和患者免疫抑制治疗的影响,在接种卡介苗(BCG)的患者中,IGRA 的特异性高于 TST,在免疫抑制的患者中 IGRA 比 TST 的灵敏度更高[26],患者的 IGRA 和 TST 检测结果的不一致性较差,从 64%到 89.5%不等[27-29]。Arias-Guillén 等[30]开展了一项共纳入 393 例风湿性疾病患者的前瞻性单中心研究,发现合并使用甲氨蝶呤(MTX)患者较未使用的患者 TST 阳性风险增加 2 倍,而与 IGRA 阳性率无相关性，建议对接受 MTX 的患者优先使用 IGRA 检测。Lee 等[31]开展了一项对结核高流行地区患者使用生物疗法治疗期间 LTBI 情况 3 年随访研究，发现 108 例患者中 IGRA 阳转且 IGRA 持续高水平的受试者结核病再激活或发展为活动性结核病的风险增高,因此对于此类特殊人群,需动态监测检查活动性结核病。

## 五、LTBI 治疗及抗 TNF-α 治疗过程中活动性结核治疗策略

依据我国《肿瘤坏死因子拮抗剂应用中结核病预防与管

理专家共识》[25]，若 IGRAs 阳性或(和)TST 硬结≥10 mm，无结核中毒症状、胸片正常的患者考虑为 LTBI 人群，需予以预防性抗结核治疗。对于既往有或无结核病史，胸部 X 线片、胸部 CT 等检查证实为陈旧性结核病但从未经过抗结核治疗的患者，使用 TNF-α 抑制剂前也应考虑预防性抗结核治疗。接受预防性抗结核治疗至少 4 周后可开始使用 TNF-α 抑制剂，对于存在陈旧性病灶的患者或其他高风险人群优先选择融合蛋白类 TNF-α 抑制剂。韩国的一项研究比较了 408 例接受 TNF-α 抑制剂治疗的患者中不同 LTBI 治疗方案的完成率和不良事件，发现接受 3 个月异烟肼-利福平治疗患者的治疗完成率最高(94.2%)，接受 9 个月异烟肼、4 个月利福平或 3 个月异烟肼-利福平治疗患者的药物不良反应相似[32]。

所有接受 TNF-α 抑制剂治疗的患者都应该监测结核病的症状和体征，至少到停止治疗后 6 个月[33]。美国 CDC[23]和美国风湿病学会[34]建议对继续接受 TNF-α 抑制剂治疗时结核感染风险增加的个体进行年度结核病筛查。对于基线时 TST 或 IGRA 为阳性的患者，重点应该是评估是否有新的暴露于结核病的风险，并监测活动性结核病的临床症状和表现。如果出现发热、盗汗、乏力、食欲不振和体重下降，即使没有肺部症状，也要考虑结核病。一旦怀疑有结核病的临床诊断，就需要立即开始抗结核治疗，即使患者以前对 LTBI 检测阴性或有 LTBI 治疗史[35]。大多数共识建议在诊断为结核病时暂停抗 TNF-α 治疗，而重启 TNF-α 抑制剂治疗的最佳时机尚不清楚[36-37]。使用 TNF-α 抑制剂的患者是否需要延长抗结核治疗，目前尚不清楚。

## 六、结语

使用 TNF-α 抑制剂与结核病的风险增加有关，不同 TNF-α 抑制剂相关的结核病风险差异很大，相对风险最高的是阿达木单抗和英夫利昔单抗。因此应在接受 TNF-α 抑制剂治疗前进行 LTBI 的筛查和治疗可有效降低结核发病率，LTBI 筛查项目推荐结合危险因素评估、TST、IGRA 三种方法。所有接受抗 TNF-α 治疗的患者都应该监测结核病的症状和体征，TNF-α 抑制剂治疗期间合并结核病的患者需要立即开始抗结核治疗，并且暂停抗 TNF-α 治疗。

**利益冲突**　所有作者均声明不存在利益冲突

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