·HIV/AIDS 防治·讲座·

二联方案对 HIV 感染者免疫活化的影响

白若靖[1]　吕诗韵[1]　画伟[2]　吴昊[1]　代丽丽[2]

[1]首都医科大学附属北京佑安医院感染中心,北京 100069;[2]首都医科大学附属北京佑安医院感染中心旅行门诊,北京 100069

通信作者:代丽丽,Email:lilydaier@ccmu.edu.cn

【摘要】抗逆转录病毒治疗(ART)虽然能有效抑制 HIV 复制,降低 AIDS 的发病率和死亡率,但 HIV 感染者体内仍存在慢性免疫活化。近年来,随着 ART 方案的不断优化,指南推荐使用的二联方案能否与三联方案一样有效降低免疫活化的水平,是现阶段抗病毒治疗领域热点问题之一。本文总结分析了二联方案免疫活化的相关研究,并通过与三联方案的比较,阐述二联方案实现病毒学疗效后是否存在免疫活化情况。

【关键词】HIV;抗反转录病毒治疗;免疫活化;二联方案;三联方案

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Influence of dual therapy on immune activation among HIV-infected patients

Bai Ruojing[1], Lyu Shiyun[1], Hua Wei[2], Wu Hao[1], Dai Lili[2]

[1]Center for Infectious Diseases, Beijing Youan Hospital, Capital Medical University, Beijing 100069, China; [2]Travel Clinic, Center for Infectious Diseases, Beijing Youan Hospital, Capital Medical University, Beijing 100069, China

Corresponding author: Dai Lili, Email: lilydaier@ccmu.edu.cn

【Abstract】 Although antiretroviral therapy(ART) can effectively inhibit HIV replication, and reduce the morbidity and mortality of AIDS, chronic immune activation still exists in HIV-infected patients. In recent years, with the continuous optimization of ART regimen, whether the dual therapy recommended by the guidelines is as effective as the triple-drug therapy in reducing the level of immune activation has become one of the hot spots in the field of antiviral therapy. In this paper, studies relevant to the immune activation for the dual therapy are reviewed, and the immune activation after the efficacy achievement of the dual therapy comparing with triple-drug therapy is discussed.

【Key words】 HIV; Antiretroviral therapy; Immune activation; Dual therapy; Triple-drug therapy

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抗逆转录病毒治疗(ART)极大降低了艾滋病的发病率和病死率,使其成为一种慢性病。目前普遍认为,HIV 感染者体内仍存在慢性免疫活化,伴随着过度活跃的炎症状态,$CD4^+$ T 细胞不断耗竭[1-2],并与艾滋病相关性疾病(感染、肿瘤等)及非艾滋病相关性疾病(心血管疾病、骨骼疾病等)密切相关[3-7]。现阶段,由 2 种核苷类逆转录酶抑制剂(NRTIs)骨干药物和第三类药物组成的三联方案是 HIV 感染的标准治疗策略,其中第三类药物为非核苷类逆转录酶抑制剂(NNRTIs)、增强型蛋白酶抑制剂(PIs)(含利托那韦或考比司他)或者整合酶抑制剂(INSTIs)。接受三联方案的大多数 HIV 患者可实现并维持低于检测下限的病毒载量(HIV RNA<50 拷贝/mL),但仍有部分患者存在残余病毒血症,且长期 ART 用药给患者带来的不良反应以及对患者服药耐受性和治疗依从性的影响不容忽视。

近年来,大量研究发现含 INSTIs 和 PIs 的二联方案,如多替拉韦(DTG)+利匹韦林(RPV)、DTG+拉

米夫定(3TC)、达芦那韦/考比司他(DRV/c)+DTG、PIs+3TC 等，在病毒抑制方面不逊于主流的三联方案，且在药物的不良反应及成本方面均有较大优势[8-16]，因此部分二联方案被纳入国内外指南，作为 HIV 感染者的首选或备选方案[17-19]。然而，临床治疗中仍有一些问题亟需解决，例如：ART 治疗是否能够足够抑制 HIV 相关的免疫活化；二联方案与三联方案相比在抑制 HIV 相关免疫活化的效果是否等效相当，或是优于三联方案[20]。本文基于 HIV 感染免疫活化标记物的具体应用价值，通过与三联方案的比较，阐述二联方案在达到病毒学疗效后是否存在相关的免疫活化。

一、HIV 感染免疫活化标记物

研究证实，HIV 感染后，机体处于慢性免疫活化和过度活跃炎症状态，这一状态主要通过免疫活化标志物的水平来判定，目前相关标记物主要分为可溶性标志物和细胞标志物两大类[21]。

可溶性标记物被细分为炎症、凝血和微生物易位标记物。最常见的炎症标志物包括超敏 C 反应蛋白(hs-CRP)和 IL-6，两者在慢性感染期升高[22-23]，均与非艾滋病相关性疾病的发生密切相关，尤其是心血管疾病[24-27]；常见的凝血标记物为 D-二聚体，它是纤维蛋白降解产物，能促进 HIV 相关心血管疾病的发展[28-29]；微生物易位标记物包括脂多糖(LPS)和细菌 16s DNA[30]，前者与 HIV 的进展相关，后者与 HIV 预后的相关性尚不明确[31]。除此之外，可溶性标记物还包括 TNF-α、IFN-γ、线粒体 DNA(mtDNA)、β2-微球蛋白、可溶性 CD40 的配体、可溶性 CD14、可溶性 CD163[31-35]。

与可溶性标记物相比，细胞标志物在 HIV 环境中的特异性较高[21]。目前，已明确的细胞标志物包括 HLA-DR/CD38、Ki-67、膜联蛋白 V、程序性死亡因子-1(PD-1)共刺激受体，它们分别代表 T 细胞的活化[36-37]、增殖[38]、凋亡[39]和衰竭[40]。

二、三联方案的残余免疫活化

大多数接受三联方案的 HIV 感染者可实现快速病毒学抑制及免疫活化水平的显著降低[41]，但长期 ART 并不能完全恢复机体的炎症状态，即机体仍存在残留免疫活化[42]，残余免疫活化水平的高低尚不明确[43-44]。最近的一项研究比较了 NNRTIs、PIs、INSTIs+替诺福韦(TDF)/恩曲他滨(FTC)三种治疗方案下的血清免疫活化标记物，发现与 INSTIs 和 NNRTI 相比，PIs 与更高水平的促炎因子有关，如 IL-1Ra、IL-12p70、TNF-α、IL-8 和巨噬细胞炎性蛋白 1β[45]。另一项研究发现，INSTIs 比 NNRTIs 更能减轻炎症，但与 PIs 相比，INSTIs 是疗效更加尚不明确[46]，仍需对初治患者进一步研究。

目前，三联方案的残余免疫活化的发生机制和临床意义尚不清楚。研究推测体内残余免疫活化可能来源于持续的病毒复制[47]，病毒潜伏在解剖学的病毒储存库内，如脾脏、淋巴结和胃肠道等，不受 ART 药物的影响而持续复制。同时，持续的 HIV-1 复制与淋巴组织中 ART 药物浓度较低有关。此外，三联方案的残余免疫活化还与持续的微生物易位以及 HBV 等病毒的合并感染相关[48-49]。研究发现，接受三联方案的 HIV 患者以及精英控制者的非艾滋病相关性疾病的发病率较高，尤其是心血管疾病，其临床意义不容小觑[3-5]。

三、二联方案的免疫活化

近年来，国际上有研究发现部分二联方案在病毒抑制方面不劣于三联方案，同时在控制药物不良反应及药物成本方面均存在较大优势，因此根据患者的个体情况，制定适合患者的二联方案逐步成为当前国际上抗病毒治疗的主流方向。

目前，关于二联方案的已注册的大型临床试验主要围绕“DTG+RPV”治疗策略展开，其中 SWORD-1&2 研究表明：DTG+RPV 在初治患者中的病毒学疗效并不逊于三联方案[50]，该研究还简单阐述了两组患者的炎症和心血管标记物的动态变化，从基线到治疗后的第 48 周，两组患者免疫活化标志物如 IL-6、hs-CRP、可溶性 CD14、可溶性 CD163 和 D-二聚体的水平相近。有研究发现，DTG+RPV 在经治患者中的病毒学疗效并不逊于三联方案，但二联方案患者血清中 IL-6 水平的下降幅度明显较小[9]；另有研究认为，DTG+RPV 在初治患者中的病毒学疗效并不逊于基于 INSTIs 的三联方案[15]，但该研究并没

有呈现二联方案免疫活化的相关数据。以上研究显示二联方案的抗病毒疗效与三联方案相当,但关于免疫活化集中在部分可溶性标志物的动态变化,有待开展更多的临床研究进一步挖掘其治疗价值。

除上述已注册的临床试验外,一些未注册的临床试验也探讨了二联方案的免疫活化情况。Romero-Sánchez 等[51]发现,58 例 HIV 感染者在至少 6 个月的时间内未检测到病毒载量,随后转换到二联方案 PIs +马拉韦罗,随访 24 周(±12 周)后,β2-微球蛋白、可溶性 CD40 配体和 hs-CRP 基线水平较高的患者这些指标显著下降。Belmonti 等[52]比较了二联方案和三联方案中的 IL-6、hs-CRP、可溶性 LPS 受体和 D-二聚体从基线到 48 周的动态变化,并未发现上述标记物的显著变化,且接受二联方案和三联方案两组患者的标记物水平也未有差异。Vallejo 等[53]进行了一项对三联方案治疗 HIV 患者的研究,评估转换为二联方案与继续三联方案后免疫活化标志物的水平,结果显示与三联方案相比,二联方案患者中 IL-6 和可溶性 LPS 受体水平较低,IFN-γ、诱导蛋白 10、hs-CRP、D-二聚体和 TNF-α 等标记物没有差异。可见,从三联方案到二联方案的转换后,可溶性标志物未表现出明显波动。

值得关注的是,最近的一项旨在评估二联方案免疫活化的 Immunadapt 前瞻性研究表明,从三联方案转换为二联方案后,IP-10(38.3 pg/mL vs. 22.8 pg/mL)和 sCD14 水平降低 (3.6 pg/mL vs. 3.0 pg/mL),但 sCD163 水平增加(371.9 ng/mL vs. 416.0 ng/mL)。该结果提示,更换为二联方案的患者体内存在免疫活化的风险,且与单核细胞/巨噬细胞的激活密切相关[54]。但该研究为单臂研究,样本量较少,缺少对单核细胞/巨噬细胞激活的细胞标志物的检测,因此,"二联方案可能与单核细胞/巨噬细胞活化增加有关"这一结论仍需进一步验证。

四、问题与展望

综上所述,部分二联方案经初步研究,其病毒学疗效并不逊于三联方案,但关于抑制 HIV 相关免疫活化的疗效尚无充分的证据。此外,从三联方案转换为二联方案后,单核细胞/巨噬细胞活化是否增加仍需进一步的研究。因此,二联疗法在真实世界中能否降低 ART 治疗的不良反应,同时抑制免疫活化水平,尚有待更多高质量的研究来评估,以阐明二联方案"风平浪静"的病毒学疗效表面之下是否存在"暗潮汹涌"的免疫活化。

利益冲突　所有作者均声明不存在利益冲突

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