

乌帕替尼缓释片治疗难治性中重度特应性皮炎 72周之临床观察一例

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摘 要

特应性皮炎, 是一种慢性复发性、瘙痒性、炎症性皮肤病。该文报道四川首例使用乌帕替尼缓释片患者, 该患者为59岁男性, 因全身反复泛发对称性红色斑丘疹、结节伴瘙痒10+年就诊。近10年经过常规治疗、选择性JAK抑制剂、生物制剂等治疗后效果欠佳, 症状反复发作。患者使用乌帕替尼缓释片治疗1天后全身瘙痒症状缓解, 7天后瘙痒症状完全消失, 皮损面积减少、严重程度降低, 生活质量提高。随访72周, 患者全身皮损消退, 未见明显新发皮损。该例提示使用乌帕替尼缓释片作为选择性JAK1抑制剂治疗常规治疗无效或效果不佳的难治性、中重度AD患者是可以迅速且持久获益的。

关键词

特应性皮炎, 乌帕替尼缓释片, 瘙痒

A Case of Refractory Moderate-to-Severe Atopic Dermatitis Treated with Upadacitinib Sustained-Release Tablets for 72 Weeks: A Clinical Observation

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Abstract

Atopic dermatitis is a chronic recurrent, pruritus, inflammatory skin disease. This article reports on the first patient in Sichuan to use Upadacitinib sustained-release tablets. The patient is a 59-year-old male with a history of recurrent symmetric red papules and nodules accompanied by itching all over the body for over 10 years. Over the past decade, various treatments such as conventional therapy, selective JAK inhibitors, and biologics were administered with suboptimal efficacy, and symptoms recurred. The patient experienced relief from itching throughout the body and a reduction in the area and severity of skin lesions within one day of initiating Upadacitinib treatment. Complete resolution of itching was observed after 7 days, leading to an improvement in the quality of life. During the 72-week follow-up, the patient's systemic skin lesions subsided and no significant new skin lesions were observed. This case suggests that the use of Upadacitinib sustained-release tablets as a selective JAK1 inhibitor in the treatment of refractory, moderate-to-severe AD patients who have failed or failed to respond to conventional therapy may be of rapid and lasting benefit.

Keywords

Atopic Dermatitis, Upadacitinib Sustained-Release Tablets, Pruritus

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1. 前言

特应性皮炎(Atopic Dermatitis, AD)是一种慢性、炎症性和瘙痒性皮肤病,多形性皮损及剧烈瘙痒的自觉症状严重影响患者日常生活及工作,极大程度上降低生活质量。近年来,特应性皮炎的患病率呈上升趋势,全球儿童患病率为15%~30%,成人2%~10% [1]。AD发病机制复杂,与遗传和环境因素密切相关,目前尚无法根治。AD的西医治疗常采用抗组胺药、免疫抑制剂、生物制剂,外用糖皮质激素、钙调磷酸酶抑制剂等[2],但对于部分患者副作用较大,不易耐受,临床治疗效果较不理想。近年来,随着对AD发病机制的深入研究,Janus 激酶信号转导和转录激活因子(JAK-STAT)通路在AD发展中的关键作用逐渐被揭示[3],这一发现为AD的治疗提供了新的思路。乌帕替尼(Upadacitinib)是一种高效、有选择性的第二代JAK1抑制剂,研究表明[4],乌帕替尼缓释片能够显著改善AD患者的皮损及瘙痒症状,提高生活质量。乌帕替尼缓释片作为一种新型的治疗药物,为特应性皮炎患者提供了新的治疗选择。本文回顾分析了我院1例中重度特应性皮炎患者的临床资料,为该疾病的临床诊治提供一定程度上的参考。

2. 病例资料

2.1. 病史和体格检查

患者男,59岁,因“全身反复泛发对称性红色斑丘疹、结节伴瘙痒10+年”于成都中医药大学附属医院就诊。10+年前患者无明显诱因出现全身泛发对称性红斑、丘疹,伴明显瘙痒,搔抓后局部渗液,发病1年后全身出现散在结节,前后就诊于多家医院,诊断为“湿疹”。既往使用“中药、雷公藤片、沙利度胺片、环孢素、倍他米松、巴瑞替尼、托法替布、度普利尤单抗”等药物治疗,疗效欠佳,期间皮损反复发作。患者既往有高血压病史、过敏性鼻炎史,否认家族史。本院首次就诊时情况:全身皮肤干燥,大片

红色斑丘疹及散在结节，部分皮损高出皮肤表面，伴明显抓痕、渗液、结痂，自觉瘙痒剧烈。

专科检查：皮损总面积约 2000 cm²，渗液面积约 800 cm²；湿疹面积和严重程度指数(eczema area and severity index, **EASI**)评分 47.5 分，皮损占体表面积体表受累面积(body surface area, **BSA**)评分 11.8%，特应性皮炎严重程度(scoring atopic dermatitis, **SCORAD**)评分 60 分，瘙痒数值分级量表(itch numeric rating scale, **NRS**)评分 9 分。

2.2. 实验室及辅助检查

血常规 EOS 0.31 × 10⁹/L、IgE 125 IU/ml、血生化、肿瘤标志物、胸片结果正常，乙肝、丙肝、梅毒、艾滋结果阴性，结核 T-spot 结果阴性，右侧大腿皮肤组织病理学活检可见：表皮角化过度，可见痂液渗出，局灶表皮缺损，可见炎性坏死组织，真皮浅层毛细血管周围见组织细胞、淋巴细胞及个别嗜酸性粒细胞浸润(图 1)。

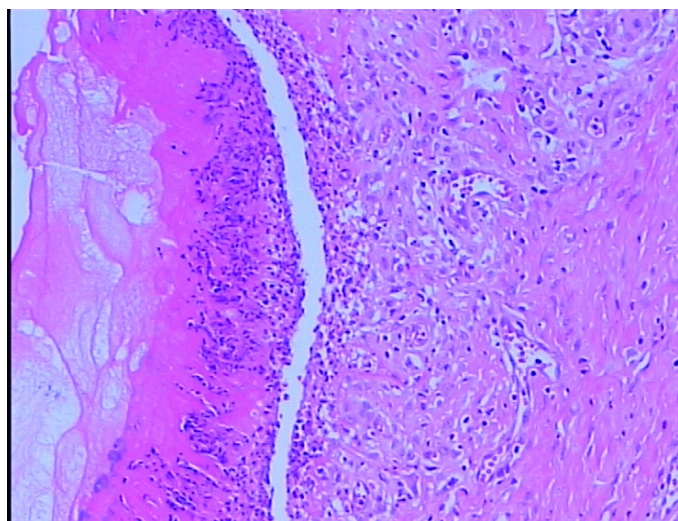


Figure 1. Skin histopathology shows epidermal hyperkeratosis with crust formation and focal epidermal loss with inflammatory necrotic tissue. Perivascular infiltration of histiocytes, lymphocytes, and occasional eosinophils is observed in the superficial dermal layer around capillaries (HE × 10)

图 1. 皮肤组织病理示：表皮角化过度，可见痂液渗出，局灶表皮缺损，可见炎性坏死组织，真皮浅层毛细血管周围见组织细胞、淋巴细胞及个别嗜酸性粒细胞浸润(HE × 10)

2.3. 诊断及治疗

诊断：重度特应性皮炎[1] [2]。

治疗经过：与患者签署知情同意后，予乌帕替尼缓释片口服治疗，具体方案为 15 mg 每日一次，口服，不受进餐影响。治疗 1 天后瘙痒明显减轻，睡眠好转；7 天后瘙痒完全消失，皮损较前减少，颜色由鲜红色变为淡红色，局部渗液、血痂减少(见图 2(b))；15 天后皮损较前明显减少，皮损颜色基本恢复正常(见图 2(c))。治疗后特应性皮炎相关评价指标均有显著改善(见表 1)。随访 72 周，患者全身未见明显红斑、丘疹、结节(见图 3)，否认瘙痒、疼痛等自觉症状，复查实验室检查示：血常规 EOS 0.08 × 10⁹/L、IgE 53 IU/ml、血生化 ALT 24.8 U/L、AST 27.6 U/L、肌酐 67.2 μmol/L。至撰稿日仍在继续随访中，无明显不良反应。



2a: 1 天后，瘙痒明显减轻，睡眠改善；2b: 7 天后，瘙痒完全消失，皮损较前减轻，颜色由鲜红变为淡红，局部渗出和血痂减少；2c: 15 天后，皮损较前明显减轻，颜色基本恢复正常。

Figure 2. Skin manifestations of the patient
图 2. 患者皮肤表现



随访观察 72 周后，患者的全身皮损完全消退，全身未见明显红斑、丘疹、结节。

Figure 3. Skin manifestations of the patient
图 3. 患者皮肤表现

Table 1. Assessment of atopic dermatitis-related evaluation parameters**表 1.** 治疗前后特应性皮炎相关评价指标评价

Rate	Baseline	Day 7	Day 15	12 weeks	24 weeks	48 weeks	60 weeks	72 weeks
EASI	47.5	8.7	1	0	0	0	0	0
BSA	11.8	6	1	1	0	0	0	0
SCORAD	60	27.4	2	1	0	0	0	0
NRS	9	0	0	0	0	0	0	0

3. 讨论

特应性皮炎(atopic dermatitis, AD), 也称特应性湿疹, 是一种以慢性反复发作的瘙痒和多形性炎症性皮肤病为特征的皮肤病, 不可治愈。AD 最突出的表现为长期慢性瘙痒[5][6]。瘙痒引起的先天性搔抓反应破坏皮肤屏障, 导致外界刺激更易侵入皮肤, 加重局部炎症, 从而刺激神经继续形成瘙痒症状[7]。Simpson 等[8]调查了 380 例 AD 患者, 其报告显示 85.8% 的患者瘙痒每天发作, 68.2% 的患者瘙痒发作后导致睡眠障碍, 41% 的患者每天瘙痒发作时间超过 18 小时。AD 瘙痒的发生涉及 IL-4、IL-13、IL-22、IL-31、TSLP 等下游信号通路的细胞因子, 这些细胞因子与神经元受体结合, 受体通过细胞内 JAKs 传递信号激活痒觉动作电位, 因此 JAK 成为控制瘙痒的治疗靶点[9]-[11]。由于 JAK 信号通路的过度激活和上述多种炎症因子在 AD 皮损中表达上调, 通过痒觉神经元上的受体直接引发瘙痒, 瘙痒的加重会进一步破坏皮肤屏障, 形成“瘙痒-搔抓-瘙痒”的恶性循环, 进而引起严重的睡眠障碍和多维负担[12]-[15]。JAKs 是一个由四种酪氨酸受体激酶[JAK1、JAK2、JAK3 和酪氨酸激酶 2 (Tyk2)]组成的家族, 在细胞因子受体信号传导中起着关键作用[16]。《中国特应性皮炎诊疗指南(2020 版)》[17]提出, 外用药(如外用糖皮质激素、钙调神经磷酸酶抑制剂等)、系统药物(如口服抗组胺药、免疫抑制剂、糖皮质激素等)治疗是 AD 治疗的主要手段。然而临床发现, 上述治疗针对中重度 AD 存在疗效欠佳可能。欧洲 EADV/ETFAAD 指南[18]明确指出 JAK1 覆盖 AD 病理生理过程中涉及的多种细胞因子, 包括 IL4、IL-13、IL-22、IL-31、和 TSLP。因此, 在传统治疗和生物制剂临床效果不佳的情况下, 高选择性的 JAK1 抑制剂可能是更优选择。

乌帕替尼是一种高选择性的 JAK1 抑制剂, 同时可减少对其他 JAK 亚基生理功能(如造血、免疫功能)的影响[19]。在生化分析结果中, 乌帕替尼对 JAK1 的选择性分别是 JAK2、JAK3、TKY2 的 2、46、104 倍(JAK1、JAK2、JAK3 和 TKY2 分别为 0.045、0.109、2.1、4.7 $\mu\text{mol/L}$); 在工程细胞系测定结果中, 乌帕替尼对 JAK1 的选择性分别是 JAK2、JAK3、TKY2 的 42、133、194 倍(JAK1、JAK2、JAK3 和 TKY2 的 IC50 分别为 0.014、0.593、1.860、2.715 $\mu\text{mol/L}$) [20]。其III期临床试验包含 3 项全球性的随机对照试验, 3 项实验中 16 周最严重瘙痒症数字评分表(Worst Pruritus Numerical Rating Scale, WP-NRS)改善 ≥ 4 应答率结果显著优于安慰剂, 且均达到次要终点, 且乌帕替尼 15 mg 治疗最快 2 天后即可观察到 WP-NRS 改善 ≥ 4 应答率显著提高, 连续治疗 52 周后, WP-NRS 改善 ≥ 4 应答率仍能持续提高达 64.8%, 故乌帕替尼缓解瘙痒症状疗效快速、持久[21]。

瘙痒是 AD 的主要症状, 控制瘙痒是 AD 管理的关键环节。在本次病例中, 患者经乌帕替尼治疗后, 瘙痒迅速缓解, 皮损逐渐控制, 睡眠及生活质量显著提高, 随访 72 周仍未复发。患者乌帕替尼缓释片未减量持续口服至今, 随访 12 周、24 周、48 周、60 周、72 周后复查血常规、肝肾功能, 均未见明显异常。基于本例病例报告及文献复习, 乌帕替尼具有可观的皮损清除率和瘙痒缓解疗效, 且由于其为高选择性 JAK 抑制剂, 安全性相对较高。说明使用乌帕替尼作为选择性 JAK1 抑制剂治疗常规治疗无效或效果不佳的中重度 AD 患者是可以迅速且持久获益的。但由于乌帕替尼在中国临床使用时间较短, 治疗中重度

特应性皮炎中缺少大样本量的数据来评估其效价，期待更多的临床数据提供更全面的证据支撑。

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