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本维莫德乳膏治疗特应性皮炎的研究进展

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摘 要

特应性皮炎(AD)是一种慢性、复发性、炎症性、瘙痒性皮肤病。其发病机制复杂，目前认为与遗传、环境、皮肤屏障异常及免疫系统紊乱有关。皮肤屏障功能障碍与丝聚蛋白(FLG)、兜甲蛋白(LOR)、内披蛋白(IVL)等的下调有关。Th2型皮肤炎症是AD的基本特征，IL4和IL-13是AD发病的重要细胞因子。本维莫德乳膏作为芳香烃受体/核因子E2相关因子(AHR/NRF2)的双重激活剂对AD的多种致病机制具有调节作用，本文就目前本维莫德乳膏治疗AD的研究进展进行综述。

关键词

特应性皮炎，本维莫德，芳香烃受体，核因子E2相关因子2

Research Progress of Benvitimod in the Treatment of Atopic Dermatitis

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Abstract

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory, pruritus skin disease. Its pathogenesis is complex, and it is currently believed to be related to heredity, environment, abnormal skin barrier and immune system disorder. Skin barrier dysfunction is associated with down regulation of Filaggrin (FLG), Loricrin (LOR), and Involucrin (IVL). Th2 skin inflammation is a basic feature of

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AD, and IL4 and IL-13 are important cytokines in AD pathogenesis. As a double activator of aryl hydrocarbon receptor/nuclear factor E2-related factor 2 (AHR/NRF2), Benvitimod cream has a regulatory effect on various pathogenic mechanisms of AD. This paper reviews the current research progress of Benvitimod in the treatment of atopic dermatitis.

Keywords

Atopic Dermatitis, Benvitimod, Aryl Hydrocarbon Receptor, Nuclear Factor E2-Related Factor 2

1. 引言

AD 是一种强烈的瘙痒性、慢性、复发性、炎症性皮肤病。AD 的病因是多因素的，遗传和环境因素、皮肤屏障功能障碍和免疫反应受损是主要因素[1] [2] [3]。频繁复发以及剧烈瘙痒会使患者生活质量明显下降，从而导致患者治疗满意度降低[4] [5] [6] [7] [8]。AD 在人群中的终身发病率达到 20% [9]。皮肤屏障功能障碍与丝聚蛋白(FLG)、兜甲蛋白(LRO)、内披蛋白(IVL)等末端分化分子的产生减少有关[10] [11]。AD 的皮肤炎症以 Th2 型炎症为主，IL4 和 IL-13 是介导 AD 发病的重要细胞因子[12]。IgE 升高以及 TH-17/Th22 炎症轴也与 AD 相关[13] [14] [15] [16]。皮肤屏障完整性异常也会导致金黄色葡萄球菌等微生物的定植增加，从而进一步加剧 Th2 型皮肤炎症[17] [18]。目前 AD 的治疗包括外用药物治疗及系统治疗[19]，外用药物主要为糖皮质激素及钙调磷酸酶抑制剂，虽然这些药物对 AD 有效，但不良反应限制了它们的长期使用[20]。本维莫德乳膏作为一种新型制剂在近期临床试验中对治疗 AD 效果明显且不良反应较少[21]，本文将从以下几方面进行综述。

2. 本维莫德乳膏治疗 AD 的机制

本维莫德又名“本烯莫德”(英文名：Benvitimod、Tapinarof，以前被称为 GSK2894512 或 WBI-1001)是一种天然衍生的小分子，由昆虫致病线虫的细菌共生体产生[22] [23]。目前相关临床试验提示本维莫德乳膏在 AD 治疗中疗效显著[15] [19]。Susan H. Smith [24]等人的试验证明本维莫德是芳基烃受体(AHR)激动剂，并证实其疗效依赖于 AhR。除了 AhR 激动剂活性外，本维莫德的化学结构具有固有的抗氧化特性，可激活核因子 E2 相关因子 2 (NRF2)，目前已证实本维莫德是 AHR/NRF2 的双重激活剂[10]，NRF2 是一种调控细胞氧化应激反应的重要转录因子，其通路的激活可以诱导 NAD(P)：醌氧化还原酶 1 (NQO1)的表达从而减轻 CYP1A1 诱导的氧化应激[25] [26]。芳基烃受体(AHR)是一种配体依赖性转录因子[27]，其与配体结合后，与 AHR-核转位器(ARNT)二聚，并上调靶基因的转录[28] [29] [30] [31] [32]。AHR 的主要下游靶点是表皮分化复合体(EDC)，对人类表皮的末端分化非常重要[33]。EDC 包括 FLG、FLG2、LOR 和 IVL 等[34] [35]。AHR 激活可上调 FLG、IVL 和 LOR 等 EDC 蛋白[36]-[42]，这些屏障蛋白表达的上调可以抵消 AD 发病机制中关键的表皮屏障缺陷而达到治疗 AD 的目的。当受到内源性配体的刺激时，AHR 通路可减轻 AD 患者的炎症，并维持健康的皮肤屏障[43] [44]。Th2 炎症通路与 AHR 轴对皮肤屏障功能的作用相反[45]。IL-4 和 IL-13 是 AD 中主要的 Th2 细胞因子，对 LOR、IVL 和 FLG 的表达有下调作用[46] [47] [48]。其下调机制主要是通过激活 JAK1/2 和 STAT3/6 从而阻断 AHR 介导的 EDC 激活[49] [50] [51]。Van den Bogaard [10]等的研究结果显示：煤焦油可激活芳香烃受体；在未经煤焦油处理的

皮肤模型中，FLG 不存在，而在煤焦油处理的皮肤模型中 FLG 大量表达；煤焦油干扰 Th2 细胞因子介导的 STAT6 信号通路，从而抑制 TH2 型炎症反应。Tsuji [52]等的研究结果显示：1) OVOL1 调控 FLG 的表达；2) AHR 激活上调 OVOL1；3) AHR 激活通过 OVOL1 上调 FLG。Takei [53]等的研究结果显示：大豆焦油作为煤焦油的替代品，可激活 AHR，并诱导 AhR 在角质形成细胞中的核易位。大豆焦油可诱导 CYP1A1(AHR 激活的特异性标志物)呈剂量依赖性升高，还可以以 AHR 赖的方式上调 FLG 的表达；同时该研究还证实了 Th2 细胞因子对 FLG 表达的抑制作用，大豆焦油可恢复这种抑制作用。以上研究结果表明：AHR 激动剂可以减少 Th2 型炎症，恢复 FLG 的体外表达。AHR 激动剂可抑制骨髓树突状细胞中的 IL-4/STAT6，进而下调 IL-31、CCL17 和 CCL22 [54]。AHR 激动剂抑制 T 细胞扩张、Th17 分化和 IL-17 的产生[10] [55]，AHR 的激活也下调了朗格汉斯细胞中 IgE 高亲和力受体的表达[56]。NRF2 的激活对小鼠成纤维细胞中 Th2 细胞因子(IL-13，IL-33 和 IL-1β)具有抑制作用，但其机制尚不完全清楚[57]。相关研究证明 AHR 激活可影响皮肤微生物的调节，在 3D 皮肤模型中，研究表明表皮葡萄球菌定植可以通过 AHR 依赖的方式产生 IL-1α 和人 β-防御素-3 促进先天免疫信号传导，而 AHR 抑制会导致表皮葡萄球菌生长增加[58]。

综上所述，本维莫德乳膏作为 AHR/NRF2 的双重激活剂对 AD 的多种致病机制具有调节作用：1) 改善皮肤屏障功能障碍；2) 调节皮肤炎症；3) 抑制氧化应激；4) 下调 IgE；5) 调节皮肤微生物群。

3. 本维莫德乳膏治疗 AD 的临床疗效

随机、双盲、安慰剂对照的 IIA 期临床试验[23]共纳入了 37 名受试者随机分为 3 组(1%本维莫德 每日 2 次；0.5%本维莫德 每日 2 次；安慰剂 每日 2 次)，连续观察 4 周。在第 4 周，0.5%和 1.0%的本维莫德在改善 AD 方面疗效均优于安慰剂组，EASI、SCORAD、IGA 和 BSA 评分均显著降低。

随机、双盲、安慰剂对照的 II 期临床试验[59]评估了本维莫德治疗 AD 的有效性和安全性。研究共纳入了 247 例 AD 患者，以相同比例随机分为 6 组(1%本维莫德 每日 2 次；1%本维莫德 每日 1 次；0.5%本维莫德 每日 2 次；0.5%本维莫德 每日 1 次；安慰剂 每日 2 次；安慰剂 每日 1 次)。连续用药 12 周，1%本维莫德每日 2 次治疗成功率(53%)显著高于安慰剂每日 2 次治疗成功率(24%)；每日 2 次涂抹的应答率(53%)高于每日 1 次涂抹的应答率(46%)；1%浓度治疗组的有效率比 0.5%浓度治疗组的有效率高；EASI75 的比例在 1%本维莫德治疗组最高(60% [1%每日 2 次]和 51% [1%每日 1 次])，本维莫德治疗组 EASI75 患者比例高于安慰剂组(每日 2 次和每日 1 次 0.5%本维莫德治疗组分别为 51%和 39%，每日 2 次和每日 1 次安慰剂组分别为 26%和 25%)。

随机、双盲、安慰剂对照的 IIb 期临床试验[60]在上述 II 期试验基础上进一步评估了本维莫德治疗 AD 的有效性、安全性以及治疗后四周的疗效评估。在第 12 周，IGA 及 EASI75 结果与上述 II 期临床试验相符；除 0.5%每日 2 次组外，本维莫德组的 EASI90 显著高于安慰剂组；瘙痒数字评分(NRS)改善≥3 分的患者比例本维莫德组显著高于安慰剂组；除每日 2 次 0.5%本维莫德组外，其余本维莫德组体表面积(BSA)的平均变化百分比较基线显著降低；此次试验结果包含了患者对 AD 症状严重程度改善的评价，与用安慰剂治疗的患者相比，使用本维莫德乳膏治疗的患者将 AD 症状的严重程度评价为非常或中度改善的比例明显更高。同时试验证实了患者治疗效果可维持至少四周。

4. 本维莫德乳膏治疗 AD 的安全性及不良反应

在非盲、双队列的 I 期临床试验中[61]，没有任何受试者死亡或严重不良事件的报告。在两个队列中，头痛是最常见的不良事件，2 名使用 2%本维莫德乳膏的受试者(40%)和 3 名使用 1%本维莫德的受试者(50%)出现毛囊炎，这是使用本维莫德时典型的不良事件。

随机、双盲、安慰剂对照的 2A 期临床试验[60]结果提示本维莫德乳膏(WBI-1001)在为期四周的 AD 治疗中最常见的不良反应为轻度丘疹，未发生其余不良反应，受试者对 0.5%和 1%本维莫德乳膏耐受性均良好。

随机、双盲、安慰剂对照的 II 期临床试验[60]结果提示本维莫德治疗 AD 最常见的不良事件为鼻咽炎，其余常见不良事件为毛囊炎、AD (AD 恶化或发作)、上呼吸道感染、头痛、痤疮和脓疱疮。无系统不良反应发生，所有治疗组中，无论给药剂量如何，免疫球蛋白水平(IgA、IgG 和 IgM)均未见明显临床变化。

综上所述，目前国外相关临床研究结果表明本维莫德乳膏治疗 AD 患者耐受性良好，头痛、毛囊炎及鼻咽炎为其常见的不良反应，无系统不良反应发生，但目前临床试验周期均未超过 12 周，且目前临床试验仅处于 2b 期，远期使用安全性有待考量。

5. 总结及展望

目前 AD 的局部治疗方法，即局部外用皮质类固醇和局部外用钙调磷酸酶抑制剂均存在使用限制以及潜在的局部和全身不良反应。尽管目前有 crisaborole 和 dupilumab 等药物的出现，但仍需要寻找其他有效的治疗方法。本维莫德乳膏可以从 AD 的多个致病环节发挥其治疗作用。根据目前临床试验结果，本维莫德乳膏治疗 AD 的疗效显著，患者耐受性好，不良反应较少，临床使用安全性较高，且其独特的作用机制明确地将该药物与目前可用的 AD 治疗方法区别开来。本维莫德乳膏代表了 AD 局部药物开发的一个重要进展，值得在三期临床试验中进一步研究以进一步明确其在治疗 AD 中的安全性及有效性。

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