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·论　著·

基于美国 FDA 不良事件报告系统数据库的度普利尤单抗不良事件信号挖掘及分析

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［摘要］ **目的**　利用美国 FDA 不良事件报告系统（FAERS）对度普利尤单抗（dupilumab）的药物安全性进行研究，挖掘潜在的不良事件信号，为临床合理用药提供参考。**方法**　通过检索 FAERS 数据库 2017 年第 2 季度到 2020 年第 2 季度数据，将度普利尤单抗进行药名标准化后以“主要怀疑药物”作为限制条件，获得与度普利尤单抗有关的不良事件记录。通过不相称测定分析法中的报告比值法（ROR）和信息成分法（IC）挖掘潜在不良事件信号，并通过 MedDRA 23.0 软件对不良事件信号挖掘结果进行系统分类。**结果**　在 16 684 618 条数据记录中获得 97 205 条与度普利尤单抗有关的不良事件记录。根据 2 种不良事件信号挖掘方法所得结果，以 ROR 值 95% *CI* 下限＞1 或 IC 值 95% *CI* 下限＞0 为限制条件，共得到 365 个不良事件信号。通过对非不良事件的去除和同义合并，最终获得 82 个有较大临床意义的不良事件信号，度普利尤单抗的不良事件主要为眼部疾病、皮肤及皮下组织类疾病、感染及传染性疾病。引起严重不良事件结局的不良事件信号主要包括可能由该药物引起的眼部疾病、感染和炎症、是否存在加速皮肤 T 细胞淋巴瘤恶化、免疫系统的超敏反应、呼吸系统的支气管炎、骨骼系统的关节痛，以及全身性疾病及给药部位各种反应的病情恶化等。在合并用药总不良事件和严重不良事件中，合并使用的最常发生不良事件的药物前 5 名均为泼尼松、环孢素、曲前列环素、泼尼松龙、甲氨蝶呤。**结论**　度普利尤单抗不良事件除轻中度的浅角膜受损和结膜炎外，角膜变性、溃疡性角膜炎等较为严重的眼部检出信号应引起临床医师注意，并建议在指导患者用药的过程中及时联合眼科医师进行病情评估，对原有眼部问题的患者用药更需提高警惕。其他系统检出不良反应信号仍有待真实世界的药物不良反应长期监测加以证实。此外，度普利尤单抗的严重不良事件结局和对应的检出信号及最常发生不良事件的合并用药应引起重视。

［关键词］ 度普利尤单抗；不良事件报告系统；不良事件信号挖掘；药物警戒性
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Data mining and analysis for adverse event signals of dupilumab based on U. S. Food and Drug Administration Adverse Event Reporting System database

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［**Abstract**］ **Objective**　To study the safety profile of dupilumab using the U. S. Food and Drug Administration Adverse Event Reporting System (FAERS) database and to mine the potential adverse event signals, so as to provide reference for rational clinical drug use. **Methods**　The dupilumab-related adverse event records were selected by searching the FAERS database from the second quarter of 2017 to the second quarter of 2020 and standardizing dupilumab's drug name, with the primary suspected drug as a restriction. Potential adverse event signals were mined using the disproportionality analysis, including reporting odds ratio (ROR) and information component (IC), and MedDRA 23.0 was used to systematically classify

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the results. **Results** A total of 97 205 dupilumab-related adverse event records out of 16 684 618 data records were obtained. According to the results of 2 adverse event signal mining methods, 365 adverse event signals were obtained under the restricted conditions of the lower limit of the ROR value 95% confidence interval (*CI*) ＞1 or the lower limit of the IC value 95% *CI* ＞0. Finally, 82 adverse event signals with greater clinical significance were obtained through the removal of non-adverse events and the merger of the same name, and the adverse events of dupilumab were mainly eye, skin and subcutaneous diseases, infections and infestations. The adverse event signals leading to serious adverse event outcomes mainly included eye diseases, infections and inflammations that may be caused by the drug, accelerated deterioration of cutaneous T-cell lymphoma, hypersensitivity of immune system, bronchitis of respiratory system, arthralgia and systemic diseases of skeletal system, and deterioration of various reactions at the site of administration. The top 5 drugs were prednisone, cyclosporine, treprostinil, prednisolone and methotrexate among the total adverse events and serious adverse events of drug combination. **Conclusion** In addition to the mild and moderate shallow corneal damage and conjunctivitis, clinicians should pay attention to the more serious eye detection signals such as corneal degeneration and ulcerative keratitis. It is also recommended to conduct a medical assessment with the ophthalmologist to instruct patients on medication. Doctors need to be more vigilant in medicine for patients with original eye problems. The adverse reaction signals detected by other systems still require long-term monitoring of adverse drug reactions of real-world medications. The outcome of serious adverse events of dupilumab and the corresponding detection signals, as well as the medications in combination with the most adverse events are worthy of attention.

［**Key words**］ dupilumab; Adverse Event Reporting System; adverse event signal mining; pharmacovigilance

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特应性皮炎是一种慢性、复发性、炎性皮肤病，通常表现为明显瘙痒、红斑、表皮脱落和浆液性渗出等，且常伴随哮喘、鼻窦炎、食物过敏等过敏性共病，严重影响患者生活质量和身心健康。自 21 世纪以来，全球每年有高达 17.1% 的成年人和 22.6% 的儿童被诊断为特应性皮炎，每年有高达 9.6% 的儿童新发病例，各国之间发病率存在一定差异[1]。特应性皮炎发病的确切机制目前尚未明确，但在皮肤炎症、屏障功能障碍、引发瘙痒的介质或因子等方面的基础研究取得了一定进展[2]，并助益于新药的研发。

特应性皮炎被认为是 2 型辅助性 T 细胞（type 2 helper T cell, Th2）驱动的炎症反应，而度普利尤单抗（dupilumab）是一种针对 IL-4 受体 α 亚单位的全人类单克隆抗体，可与该受体 α 亚单位结合以抑制在 Th2 介导途径中发挥关键作用的 2 种细胞因子 IL-4 和 IL-13 的下游信号转导，进而减轻炎症反应，发挥治疗作用[3-4]。2017 年美国 FDA 批准度普利尤单抗用于治疗成年人或青少年（12 岁以上）中重度特应性皮炎，在局部治疗控制不良或其他疗法不可取的情况下使用[5]。作为第 1 个用于治疗成年人特应性皮炎的靶向生物制药[6]，其正作为取代包括皮质类固醇、钙调神经磷酸酶抑制剂和全身免疫抑制剂的“新范式”[7]，在早期临床试验中显示出较好的疗效和安全性，但由于临床试验的用药人群规模的局限性，有关度普利尤单抗的药物安全性评价尚不全面，且该药物通常被长期应用于控制特应性皮炎的不良症状，长期的药物不良事件监测非常必要。度普利尤单抗常见的药物不良反应为注射部位反应、头痛、结膜炎等[8]，说明书中记录的不良反应为注射部位反应、结膜炎、睑缘炎、口腔疱疹、角膜炎、眼瘙痒、其他单纯疱疹病毒感染和干眼。随着有关度普利尤单抗的不良事件可疑个案报告逐渐增多，其药物安全性的现状及更新值得挖掘与探索。美国 FDA 不良事件报告系统（U. S. Food and Drug Administration Adverse Event Reporting System, FAERS）提供了大量真实世界药物安全性数据[9]，通过检测早期定量安全性信号并评估潜在药物安全性问题的方法进行药物潜在不良事件信号挖掘，可为临床医师合理用药提供参考。

1 资料和方法

1.1 *数据来源* 选取 FAERS 数据库 2017 年第 2 季度到 2020 年第 2 季度报告的关于度普利尤单抗安全性的数据[10]，经过去重后得到以“主要怀疑药物”为限制条件的初始数据。首先对 FAERS 数据库中重复上报数据去重及药物名称标准化，检索数据库中“DUPILUMAB”“BLINDED DUPILUMAB”“DUPILUMAB（DUPILUMAB 150 MG/ML INJ, SYR, 2 ML）”“DUPILUMAB

PRE-FILLED SYRINGE”“DUPIXENT”“DUPLIXET”“Dupilumab”“Dupilumab pre-filled syringe”“SAR231893”“dupilumab”10 个药物名称（英文字母区分大小写）并标准化为“dupilumab”，选取 ROLE_COD 标签为“PS”（primary suspect drug，主要怀疑药物），得到目标药物度普利尤单抗为“主要怀疑药物”的不良事件记录。

1.2　*数据处理和统计学分析*　FAERS 数据库中不良事件采用国际医学用语词典（medical dictionary for drug regulatory activities, MedDRA）的首选语（preferred term, PT）进行编码。采用 SAS 9.4 软件进行数据处理与分析，采用中英文版本 MedDRA 23.0[11] 对照不良事件信号。采用药物不良事件信号挖掘的报告比值法（reporting odds ratio, ROR）和信息成分法（information component, IC）进行不相称测定分析[12-13]，并通过压缩估计方法减少例数较低的罕见事件造成的虚假关联[14]。对药品不良事件记录数不低于 3 的药物不良事件进行分析，在保证较高灵敏度的要求下，满足 ROR 值 95% *CI* 下限值＞1 或 IC 值 95% *CI* 下限值＞0 即纳入不良事件信号。ROR 值与 IC 值大小代表目标药物与对应不良事件之间的统计学关联强度，数值越大表示统计关联越强，最终按照 ROR 值大小对不同系统器官分类（system organ classification, SOC）中的重要不良事件信号进行描述。

2　结　果

2.1　*基线资料*　在 16 684 618 条数据记录中获得 97 205 条与度普利尤单抗有关的不良事件记录。在度普利尤单抗为主要怀疑药物的不良事件记录中，男性（56.96%）多于女性（33.85%），不良事件报告数量逐年增多，16.70% 的不良事件为严重不良事件，其中以“其他严重不良事件”（9.51%）比例最高。由于度普利尤单抗在其他国家和地区上市时间较晚，应用尚不广泛，有 96.82% 的不良事件报告来自美国，其次为日本（0.72%）。见表 1。

2.2　*信号挖掘结果*　根据不良事件信号检出条件，共获得 365 个度普利尤单抗不良事件信号。按照 MedDRA 23.0 软件将 365 个潜在不良事件信号对应于其 SOC，对于对应多个 SOC 名称的 PT 统一选择主要 SOC 进行归类，结果如表 2 所示。限于篇幅原因，仅列出最终同义合并后 82 个具有较大临床意义的不良事件信号，其中度普利尤单抗的眼部潜在不良事件信号数目最多，其次为皮肤及皮下组织类疾病和感染及传染性疾病，其他系统中也有部分信号检出。各个系统器官分类中的最终不良事件检出信号及其 ROR 值、IC 值如表 3 所示。

表 1　度普利尤单抗不良事件的基线资料

Tab 1　Baseline of adverse events for dupilumab

N＝97 205, *n* (%)

Characteristic	Data
Gender	
Male	55 371 (56.96)
Female	32 905 (33.85)
Missing	8 929 (9.19)
Age/year	
＜18	5 268 (5.42)
18-＜65	52 246 (53.75)
≥65	12 158 (12.51)
Missing	27 533 (28.32)
Year	
2017 (1st and 2nd quarter)	2 181 (2.24)
2018	19 355 (19.91)
2019	43 311 (44.56)
2020 (1st and 2nd quarter)	32 358 (33.29)
Outcome	
Death	384 (0.40)
Life-threatening	354 (0.36)
Disability	686 (0.71)
Hospitalization	5 563 (5.72)
Congenital anomaly	4 (0.00)
Other serious events (important medical events)	9 240 (9.51)
Required intervention to prevent permanent impairment/damage	1 (0.00)
Non-serious adverse events and missing	80 973 (83.30)
Report country or region	
United States	94 116 (96.82)
Japan	699 (0.72)
Germany	617 (0.63)
Britain	440 (0.45)
Others	1 322 (1.36)
Missing	11 (0.00)

2.3　*不良事件结局*　度普利尤单抗相关严重不良事件中仅有 1 例为由结膜炎引起的“需要干预以防永久性损伤”事件，其他已检出不良事件信号对应的严重不良事件结局分析结果如表 4 所示，可能引起死亡、残疾、住院、危及生命及其他严重事件（重大医疗事件）的不良事件信号主要包括可能由该药物引起的眼部疾病、感染和炎症、加速皮肤 T 细胞淋巴瘤恶化、免疫系统的超敏反应、呼吸系统的支气管炎、骨骼系统的关节痛，以及全身性疾病和给药部位各种反应的病情恶化等。

表 2　度普利尤单抗不良事件信号按照 SOC 的分布

Tab 2　Adverse event signal distribution of dupilumab according to SOC

N=365, *n* (%)

SOC	Data	SOC	Data
Eye disorders	71 (19.45)	Reproductive system and breast disorders	6 (1.64)
Skin and subcutaneous tissue disorders	62 (16.99)	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (1.64)
Infections and infestations	50 (13.70)		
General disorders and administration site conditions	46 (12.60)	Musculoskeletal and connective tissue disorders	5 (1.37)
Injury, poisoning and procedural complications	28 (7.67)	Blood and lymphatic system disorders	5 (1.37)
Surgical and medical procedures	22 (6.03)	Product issues	3 (0.82)
Gastrointestinal disorders	18 (4.93)	Congenital, familial and genetic disorders	2 (0.55)
Respiratory, thoracic and mediastinal disorders	16 (4.38)	Psychiatric disorders	2 (0.55)
Immune system disorders	7 (1.92)	Metabolism and nutrition disorders	1 (0.27)
Nervous system disorders	7 (1.92)	Renal and urinary disorders	1 (0.27)
Investigations	7 (1.92)	Total adverse event signals	365 (100.00)

SOC: System organ classification; incl: Including.

表 3　度普利尤单抗主要不良事件信号的 ROR 值、IC 值及 95% *CI*

Tab 3　ROR value, IC value and 95% *CI* of main adverse event signals of dupilumab

SOC and PT	Record	ROR (95% *CI*)	IC (95% *CI*)	Mentioned in instructions
Eye disorders				
Blepharitis	210	41.88 (35.95, 48.79)	5.08 (4.85, 5.31)	Yes
Keratitis	93	20.52 (16.52, 25.48)	4.20 (3.86, 4.55)	Yes
Keratoconus	19	19.54 (11.88, 32.13)	4.14 (3.36, 4.92)	No
Periorbital inflammation	10	15.67 (7.64, 32.16)	3.85 (2.75, 4.96)	No
Ectropion	18	14.46 (8.84, 23.66)	3.75 (2.94, 4.55)	No
Atopic keratoconjunctivitis	6	12.85 (1.55, 106.74)	3.59 (2.10, 5.07)	Yes
Chalazion	12	8.91 (4.95, 16.04)	3.09 (2.09, 4.09)	No
Eye ulcer	13	8.34 (4.75, 14.62)	3.00 (2.04, 3.96)	No
Conjunctival irritation	5	7.61 (3.00, 19.34)	2.87 (1.22, 4.53)	No
Ocular rosacea	5	7.55 (2.98, 19.15)	2.86 (1.21, 4.52)	No
Xerophthalmia	9	7.29 (3.71, 14.31)	2.81 (1.64, 3.99)	No
Dacryostenosis acquired	13	6.81 (3.90, 11.89)	2.72 (1.76, 3.68)	No
Punctate keratitis	10	6.75 (3.57, 12.77)	2.71 (1.60, 3.81)	No
Giant papillary conjunctivitis	3	6.61 (1.58, 27.67)	2.68 (0.39, 4.97)	Yes
Vernal keratoconjunctivitis	3	6.40 (1.70, 24.12)	2.63 (0.34, 4.92)	No
Corneal erosion	6	5.68 (2.50, 12.92)	2.47 (0.98, 3.95)	No
Corneal irritation	3	5.37 (1.62, 17.73)	2.39 (0.10, 4.68)	No
Corneal degeneration	3	4.38 (1.37, 14.04)	2.10 (0.19, 4.39)	No
Ulcerative keratitis	18	3.97 (2.49, 6.34)	1.96 (1.16, 2.77)	Yes
Corneal scar	4	3.80 (1.40, 10.28)	1.90 (0.00, 3.80)	No
Visual impairment	492	2.30 (2.11, 2.52)	1.19 (1.04, 1.34)	No
Myopia	8	2.29 (1.14, 4.60)	1.18 (0.07, 2.44)	No
Skin and subcutaneous tissue disorders				
Neurodermatitis	27	15.42 (10.34, 23.00)	3.83 (3.18, 4.48)	No
Alopecia areata	29	8.88 (6.10, 12.91)	3.08 (2.46, 3.71)	No
Pruritus	3 679	7.22 (6.98, 7.47)	2.76 (2.70, 2.81)	Yes
Sebaceous gland disorder	4	6.03 (2.16, 16.82)	2.55 (0.65, 4.45)	No
Alopecia totalis	4	5.32 (1.93, 14.65)	2.38 (0.48, 4.28)	No
Skin erosion	24	3.85 (2.57, 5.77)	1.92 (1.23, 2.61)	No
Vitiligo	12	3.02 (1.70, 5.34)	1.58 (0.57, 2.58)	No

续表

SOC and PT	Record	ROR (95% *CI*)	IC (95% *CI*)	Mentioned in instructions
Infections and infestations				
Conjunctivitis	1 659	74.82 (70.59, 79.30)	5.69 (5.61, 5.77)	Yes
Hordeolum	104	17.60 (14.37, 21.55)	4.00 (3.68, 4.33)	No
Molluscum contagiosum	19	15.31 (9.47, 24.77)	3.82 (3.04, 4.60)	No
Conjunctivitis bacterial	15	12.01 (7.04, 20.47)	3.50 (2.61, 4.38)	No
Herpes ophthalmic	28	11.28 (7.67, 16.58)	3.41 (2.77, 4.05)	No
Eye infection bacterial	8	6.27 (3.08, 12.78)	2.60 (1.35, 3.86)	No
Staphylococcal impetigo	3	6.14 (1.73, 21.75)	2.57 (0.28, 4.87)	No
Blastocystis infection	3	6.07 (1.73, 21.32)	2.56 (0.27, 4.85)	No
Eye infection staphylococcal	4	4.76 (1.74, 13.01)	2.22 (0.32, 4.12)	No
Pertussis	9	4.61 (2.37, 8.97)	2.18 (1.00, 3.35)	No
Meningitis viral	11	4.01 (2.20, 7.30)	1.98 (0.93, 3.03)	No
Helminthic infection	3	3.75 (1.18, 11.89)	1.88 (0.41, 4.17)	No
Ophthalmic herpes simplex	5	3.71 (1.52, 9.02)	1.87 (0.21, 3.52)	Yes
Herpes virus infection	30	3.07 (2.14, 4.41)	1.60 (0.99, 2.22)	Yes
Genital herpes	7	2.43 (1.15, 5.13)	1.27 (0.09, 2.63)	Yes
Folliculitis	19	2.42 (1.54, 3.81)	1.26 (0.48, 2.05)	No
Staphylococcal infection	91	1.91 (1.56, 2.35)	0.93 (0.58, 1.28)	Yes
Herpes zoster	169	1.60 (1.38, 1.86)	0.67 (0.42, 0.93)	No
Injury, poisoning and procedural complications				
Conjunctival scar	3	5.51 (1.66, 18.36)	2.43 (0.14, 4.72)	No
Traumatic fracture	4	2.77 (1.03, 7.45)	1.45 (0.45, 3.35)	No
General disorders and administration site conditions				
Injection site exfoliation	31	26.84 (18.05, 39.91)	4.54 (3.94, 5.15)	No
Injection site rash	384	11.79 (10.63, 13.08)	3.47 (3.30, 3.64)	No
Injection site irritation	92	11.34 (9.18, 14.01)	3.42 (3.07, 3.76)	No
Injection site paraesthesia	19	7.56 (4.76, 11.99)	2.86 (2.08, 3.64)	No
Injection site swelling	616	7.37 (6.80, 7.99)	2.82 (2.69, 2.95)	No
Injection site erythema	806	6.54 (6.09, 7.01)	2.65 (2.54, 2.77)	No
Injection site urticaria	148	5.68 (4.82, 6.69)	2.46 (2.19, 2.74)	No
Injection site ulcer	6	3.73 (1.66, 8.40)	1.88 (0.39, 3.36)	No
Gastrointestinal disorders				
Enterovesical fistula	4	2.78 (1.03, 7.48)	1.46 (0.44, 3.36)	No
Respiratory, thoracic and mediastinal disorders				
Upper-airway cough syndrome	49	3.06 (2.30, 4.05)	1.59 (1.12, 2.07)	No
Bronchitis	187	1.21 (1.05, 1.40)	0.28 (0.03, 0.52)	No
Immune system disorders				
Serum sickness-like reaction	20	15.39 (9.64, 24.58)	3.83 (3.07, 4.59)	Yes
Serum sickness	43	12.58 (9.21, 17.17)	3.56 (3.05, 4.07)	Yes
Eosinophilic granulomatosis with polyangiitis	21	6.60 (4.26, 10.21)	2.68 (1.93, 3.42)	Yes
Hypersensitivity	477	1.50 (1.37, 1.64)	0.58 (0.43, 0.73)	Yes
Nervous system disorders				
Tunnel vision	7	2.34 (1.11, 4.93)	1.21 (0.14, 2.57)	No
Investigations				
Eosinophil count increased	85	6.57 (5.29, 8.16)	2.67 (2.31, 3.03)	No
Peak expiratory flow rate decreased	4	2.87 (1.07, 7.74)	1.51 (0.39, 3.41)	No
Reproductive system and breast disorders				
Scrotal inflammation	3	5.32 (1.61, 17.53)	2.37 (0.08, 4.67)	No
Prostatic haemorrhage	4	3.91 (1.44, 10.61)	1.94 (0.04, 3.84)	No
Infertility	5	2.44 (1.01, 5.91)	1.28 (0.38, 2.93)	No
Menstrual disorder	21	1.76 (1.15, 2.71)	0.81 (0.07, 1.55)	No

续表

SOC and PT	Record	ROR (95% *CI*)	IC (95% *CI*)	Mentioned in instructions
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Cutaneous T-cell lymphoma	20	11.42 (7.23, 18.05)	3.43 (2.67, 4.19)	No
Cutaneous T-cell lymphoma stage Ⅳ	3	6.76 (1.36, 33.51)	2.71 (0.42, 5.00)	No
Skin papilloma	33	4.19 (2.97, 5.92)	2.04 (1.46, 2.63)	No
Musculoskeletal and connective tissue disorders				
Seronegative arthritis	5	2.47 (1.02, 5.99)	1.29 (0.36, 2.95)	No
Enthesopathy	9	2.13 (1.10, 4.12)	1.08 (0.09, 2.26)	No
Arthralgia	1 218	1.93 (1.82, 2.04)	0.93 (0.84, 1.03)	Yes
Joint stiffness	61	1.36 (1.06, 1.75)	0.44 (0.02, 0.87)	No
Blood and lymphatic system disorders				
Eosinophilia	48	1.75 (1.32, 2.33)	0.80 (0.32, 1.29)	Yes
Congenital, familial and genetic disorders				
Ichthyosis	3	4.26 (1.33, 13.61)	2.06 (0.23, 4.35)	No
Corneal dystrophy	3	3.28 (1.04, 10.34)	1.69 (0.60, 3.98)	No
Psychiatric disorders				
Sleep disorder	651	6.25 (5.78, 6.76)	2.59 (2.46, 2.72)	No

ROR: Reporting odds ratio; IC: Information component; *CI*: Confidence interval; SOC: System organ classification; PT: Preferred term; incl: Including.

表 4　度普利尤单抗不良事件信号对应的严重不良事件结局

Tab 4　Adverse event signals corresponding to serious adverse event outcomes of dupilumab

Serious adverse event outcome	The top 3 adverse event signals (number of cases)
Death	Drug ineffective (6), bronchitis (3), cutaneous T-cell lymphoma stage Ⅳ (2)
Disability	Arthralgia (17), worsening symptoms (16), dry eye (10)
Hospitalization	Arthralgia (67), conjunctivitis (37), hypersensitivity (35)
Life-threatening	Conjunctivitis (6), staphylococcal infection (4), enterovesical fistula (3)
Other serious events (important medical events)	Pruritus (210), conjunctivitis (154), worsening symptoms (141)

2.4　合并用药　度普利尤单抗的主要合并药物如表 5 所示，在合并用药总不良事件和严重不良事件中，合并使用的最常发生不良事件的药物前 5 名排序完全一致，依次为泼尼松、环孢素、曲前列环素、泼尼松龙、甲氨蝶呤。合并药物的不良反应主要为胃肠道反应，眼部不良反应较少。肠膀胱瘘也是引起严重不良事件结局的不良事件信号（表 5），但并未在说明书中列出，且目前并无相关的个案报道，其信号检出可能与合并用药有关，提示利用度普利尤单抗作为“主要怀疑药物”的该胃肠毒性新信号值得注意。

表 5　度普利尤单抗总不良事件和严重不良事件中的主要合并用药

Tab 5　Total adverse events and serious adverse events of main drug combination with dupilumab

n (%)

Drug combination	Common adverse reaction	Total adverse event *N*=2 226	Serious adverse event *N*=1 120
Prednisone	Headache, obesity, vomiting	233 (10.47)	116 (10.36)
Cyclosporine	Nausea, vomiting, gum hyperplasia, hyperuricemia, high blood pressure	97 (4.36)	56 (5.00)
Treprostinil	Headache, diarrhea, nausea, flushing	52 (2.34)	52 (4.64)
Prednisolone	Muscle weakness, headache, dizziness, heartburn, indigestion	41 (1.84)	41 (3.66)
Methotrexate	Stomatitis, lip ulcers, pharyngitis, nausea, vomiting, leukopenia	39 (1.75)	31 (2.77)

3　讨　论

本研究基于 FAERS 数据库，利用 ROR 和 IC 方法对度普利尤单抗潜在不良信号进行挖掘。ROR 与 IC 分别属于频数法和贝叶斯法。ROR 通过四格表进行计算，利用目标药品的目标不良事件报告数、目标药品的其他不良事件报告数、目标药品外其余药品的目标不良事件报告数和目标

药品外其余药品的其他不良事件报告数 4 个频数，求得 ROR 值及其 95% *CI*，因对药物和不良事件的关联进行比值比较，故采用 95% *CI* 下限＞1 的限定条件。IC 方法基于先验信息，利用样本数据进行总体参数的统计推断，IC 值反映相关性的强弱，故采用 0 作为 IC 值 95% *CI* 下限界值。两种方法建立在不同的统计思想上，能够快速、灵活、定量反映目标药物与目标不良事件的关联度。本研究利用 ROR 和 IC 方法挖掘不良信号，除了证实度普利尤单抗说明书中提示的不良反应外，还检出眼部与其他系统新的不良事件信号。

3.1　眼部疾病　本研究发现，眼部是度普利尤单抗不良信号数目最多的器官，角膜糜烂、圆锥形角膜等在说明书中均未提及。有研究者报道，1 例有过角膜手术史但无角膜溃疡史的患者接受度普利尤单抗治疗后，出现可能严重影响视力的角膜浸润、溃疡和变薄症状，最终中止用药[15]；1 例接受度普利尤单抗治疗的患者由获得性泪管狭窄发展为点状梗阻和瘢痕性睑外翻[16]。上述病例报告提示使用度普利尤单抗可能产生角膜变性、溃疡性角膜炎等较严重的眼部不良反应。因此，临床医师应注意与度普利尤单抗治疗相关的严重眼部炎症风险，除了轻中度的表浅角膜受损等可逆损伤，对于眼器官可能造成的不可逆性损害需引起格外注意。对于患有严重、长期特应性皮炎尤其是伴随既往眼病患者使用度普利尤单抗治疗时应提高警惕，注意及时联合眼科医师进行眼科病情评估。新近研究发现使用度普利尤单抗对 IL-13 信号转导的阻断可能导致眼部黏蛋白的缺乏，进而表现出一系列眼部炎症反应，该结果为探讨眼部不良反应病因提供了思路，但限于样本量小且未考虑患者用药初始黏蛋白含量，仍需扩大病例样本进一步分析黏蛋白水平与整体用药人群或特殊用药人群眼部不良反应的关系[17]。不同类别的眼部不良事件发生机制仍需进一步研究。

3.2　感染及传染性疾病　结膜炎是度普利尤单抗治疗较为常见的不良反应，且多为表浅的轻症炎症，无须停用药物并在治疗结束时可得到缓解[18]。既往临床研究中推测结膜炎的风险因素为严重特应性皮炎、结膜炎史和某些生物标志物[19]，Uchida 等[20]认为胸腺和活化调节趋化因子（thymus and activation-regulated chemokine, TARC）与 IgE 的血清水平可以更准确地反映中重度特应性皮炎患者结膜炎易感性的差异。除结膜炎外，用药后还可能出现传染性软疣播散[21]、单纯疱疹病毒葡萄膜炎和水痘－带状疱疹病毒脑膜炎[18]等感染，严重者需要入院治疗并中止使用度普利尤单抗。

3.3　其他系统疾病　度普利尤单抗治疗后可能出现红斑、瘙痒和脱皮等皮肤相关不良反应，大多数持续时间短暂，多表现为与药物注射剂量相关的不良反应，但也有用药后产生无法解释的面部红斑及严重瘙痒，有研究认为这可能是度普利尤单抗抑制 Th2 通路后引起的药物性狼疮的皮肤表现[22]。度普利尤单抗治疗后可能导致患者的临床疾病范围扩大，有病例报告显示用药后皮肤活检病理组织学特征与皮肤 T 细胞淋巴瘤一致，度普利尤单抗可能并非导致皮肤 T 细胞淋巴瘤产生的原因，但其与免疫系统之间的相互作用可能加速皮肤 T 细胞淋巴瘤的进展，两者之间的免疫学联系仍有待探索[23]。度普利尤单抗可能造成全身性关节痛，停药后关节疼痛长期存在，而关节痛在严重不良反应事件的残疾与住院中均为最主要的不良事件，提示应注意与度普利尤单抗有关的关节痛症状。关节痛可能是由于度普利尤单抗通过抑制 IL-4 和 IL-13 增强了 IL-17 介导的周围型脊椎关节炎 / 银屑病关节炎模式的炎性关节炎 / 附着点炎，从而诱发血清阴性关节炎[24]，具体发病机制仍需研究。度普利尤单抗在生殖系统、呼吸系统的不良事件报道较少，对于支气管炎、前列腺出血、不育等新信号有待进一步确认。

本研究存在一定的局限性。一方面，由于 FAERS 数据库可能存在少报漏报等问题，且药物应用时间较短，应用人群范围较窄，某些不良事件例数较少，可能存在一定偏倚；另一方面，ROR、IC 方法仅能得到目标药物与目标不良事件的统计学关联，无法获得确定的因果关系。初筛不良反应信号作为利用真实世界数据的结论补充，仍需要长期的药物不良反应监测和科学设计的前瞻性试验加以验证。

度普利尤单抗作为治疗特应性皮炎的崭新方向，了解规避不良反应并充分发挥治疗优势是用药的根本目的，对于度普利尤单抗的安全性评价及不良反应发生机制研究也将持续更新。根据本研究结果，临床医师应在药物使用前对患者眼部、皮肤等情况进行更为深入的评估，预防感染并注意胃肠、生殖、骨关节、免疫、呼吸等系统不良事件发生的可能，为安全合理用药提供保障。度普利尤单抗在我国上市以后，其在亚洲人群的药物毒性有无新特点同样值得探究。

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