综述 DOI：10.13406/j.cnki.cyxb.003645

# 自身免疫脑炎的免疫治疗研究进展

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【摘　要】自身免疫性脑炎（autoimmune encephalitis，AE）是近年来发现的由自身免疫机制介导的，临床上以癫痫发作、运动障碍、行为改变、情绪障碍、认知障碍、自主神经功能障碍和意识水平改变为特征的中枢神经系统炎症性疾病。AE可依据不同的致病自身抗体分为不同的类型，大部分AE患者对免疫治疗均有反应。早期的规范免疫治疗是良好预后和防止复发的关键。近年来针对不同靶点的免疫治疗成为研究热点，成为AE患者治疗新的选择。本文拟对AE的免疫治疗研究进展进行综述。

【关键词】自身免疫性脑炎；免疫治疗；进展

【中图分类号】R741.05　　【文献标志码】A　　【收稿日期】2024-06-15

# Research progress in immunotherapy for autoimmune encephalitis

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**【Abstract】**Autoimmune encephalitis（AE）is the inflammatory disease of the central nervous system that has been found in recent years and is mediated by autoimmune mechanisms ，which is clinically characterized by seizures，movement disorders，behavioral changes，emotional disorders，cognitive disorders，autonomic dysfunction，and altered level of consciousness. AE can be classified into different types based on different pathogenic autoantibodies，and most AE patients respond to immunotherapy. Early standard immunotherapy is the key to good prognosis and prevention of recurrence.In recent years，immunotherapy targeting different targets has become a research hotspot and a new choice for the treatment of AE patients. This article aims to review the research progress of immunotherapy for AE.

**【Key words】**autoimmune encephalitis；immunotherapy；progress

自身免疫性脑炎（autoimmune encephalitis，AE）指一类由自身免疫机制介导的脑炎。AE合并相关肿瘤者，称为副肿瘤性AE[1]。自2007年抗N-甲基-D-天冬氨酸受体（N-methyl-D-aspartate receptor，NMDAR）脑炎被发现以来[2]，一系列抗神经元细胞表面或者突触蛋白的自身抗体被陆续发现，包括抗富含亮氨酸胶质蛋白1（leucine-rich glioma-inactivated protein 1，LGI1）抗体与抗γ-氨基丁酸B型受体（γ-amino butyric acid type B receptor，GABABR）抗体、抗接触蛋白相关蛋白2（contactin associated protein 2，CASPR2）抗体相关莫旺综合征（Morvan syndrome）和抗IgLON家族蛋白5（IgLON5）抗体等。这一大类新型AE，发病机制均以体液免疫为主，免疫治疗效果较好[3-4]。

多项研究表明，AE的早期诊断、规范治疗对获得良好预后非常重要。新型AE的治疗主要包括免疫治疗、对症支持治疗、对合并肿瘤者进行手术切除等抗肿瘤治疗。根据最新的2022年中华医学会神经病学分会发布了《中国自身免疫性脑炎诊治专家共识》[5]，免疫治疗分为一线免疫治疗、二线免疫治疗、长程（维持）免疫治疗、升级免疫治疗和添加免疫治疗等，本文主要对AE的免疫治疗方面进展进行阐述。

## 1　一线免疫治疗

目前，国内外指南推荐的一线免疫治疗包括糖皮质激素、静脉注射免疫球蛋白（intravenous immunoglobulin，IVIG）

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基金项目：国家自然科学基金资助项目（编号：32071054）。

优先出版：https://link.cnki.net/urlid/50.1046.R.20241210.1133.004（2024-12-10）

和血浆置换（plasma exchange，PLEX）/免疫吸附（immunoadsorption，IA）。排除感染性脑炎后，所有高度怀疑AE患者均应尽快接受一线免疫治疗[6-8]。

### 1.1 糖皮质激素

与糖皮质激素受体结合，广泛抑制细胞因子、黏附因子等多种炎症介质，非特异性诱导淋巴细胞凋亡[9]。静脉注射糖皮质激素[如静脉注射甲泼尼龙（intravenous methylprednisolone，IVMP）]是目前首选的一线免疫治疗[10]，但因糖皮质激素以诱导T淋巴细胞凋亡为主，且对抗体水平影响有限，故重症AE多联合IVIG或PLEX[11-12]，轻症患者也可直接口服糖皮质激素，激素减停过程不宜过快，过程中需要关注病情的波动与复发，一般使用6个月左右。

### 1.2 IVIG

有免疫替代和免疫调节双重治疗作用，可以中和抗体同时抑制B细胞产生致病抗体。一般情况下，IVIG多与糖皮质激素或二线免疫药物联合使用，但当患者不能耐受激素或表现为抗谷氨酸脱羧酶65（glutamic acid decarboxylase 65，GAD65）脑炎相关的僵人综合征时，IVIG也可单独作为首选治疗[13-14]。IVIG可使用单轮，重症或难治性AE也可考虑多轮IVIG为基础的强化一线治疗[15]。IVIG的使用时机暂无定论，目前国内外相关共识推荐确诊AE或合理怀疑AE时，建议在使用IVMP治疗的同时或之后3~7 d内使用IVIG或PLEX[13,16]。IVIG目前在AE治疗中应用广泛，在抗NMDAR脑炎中疗效确切[7]，在IG4类脑炎（如抗LGI1和抗CASPR2脑炎）中的应用效果有限[17]，但IVIG治疗AE的RCT研究结果表明在IVIG可使抗LGI1和抗CASPR2脑炎癫痫发作降低50%[18]。

### 1.3 PLEX

PLEX可以快速降低血浆中的抗体滴度，对脑脊液中的抗体滴度产生影响，同时影响其他炎症因子的释放，因此对于重症或难治性AE可考虑使用血浆置换[19]。PLEX治疗AE不作为首选治疗，一般与激素联合使用[20-21]，目前建议在使用IVMP治疗的同时或之后使用IVIG或PLEX，目前仍无研究比较IVIG和血浆置换的疗效差异，IVIG和血浆置换的选择多取决于患者的自身状况以及医生的临床实践经验。PLEX也可与IVIG联合使用，因血浆置换能够清除血浆中的免疫球蛋白，故建议在PLEX后使用IVIG。

### 1.4 IA

IA是一种特殊的治疗性血浆置换技术，能够通过吸附柱较为特异地吸附并清除血液中的致病性抗体，IA作为PLEX的替代治疗相较于PLEX，更有针对性地去除蛋白质，可避免PLEX的缺点（如感染或发生过敏反应及对凝血的影响等）。IA最常见的并发症是低血压和纤维蛋白原减少[22-24]。关于IA和PLEX治疗AE的疗效比较，目前研究提示IA与PLEX相比临床疗效无明显差异，安全性更高[25-26]。

## 2 二线免疫治疗

利妥昔单抗与静脉注射用环磷酰胺最为常用，主要用于一线免疫治疗效果不佳的重症患者。

### 2.1 利妥昔单抗（rituximab，RTX）

RTX是靶向B细胞表面CD20分子的部分人源化单克隆嵌合抗体，最初被批准用于非霍奇金淋巴瘤，但现已广泛应用于血小板减少性紫癜、系统性红斑狼疮、视神经脊髓炎等多种中枢及外周自身免疫性疾病[27]。利妥昔单抗可耗竭外周血内$CD20^+$B淋巴细胞，且在治疗后的6~8个月后B细胞水平均低于检测值，治疗有效，同时可减少疾病复发[27]。多项研究均证实了利妥昔单抗治疗抗NMDAR脑炎安全有效[7,28]。利妥昔单抗在IG4相关疾病中的治疗具有高效性[17,29]，在以IG4亚类抗体为主的抗LGI1脑炎、抗CASPR2脑炎、抗IgLON5脑炎中已广泛应用[17,28-30]。目前暂无利妥昔单抗作为AE早期治疗与其他一线免疫治疗效果的对比研究。中国自身免疫性脑炎诊治专家共识推荐若使用2种或以上一线免疫治疗，2周后病情无明显好转，应及时启动静脉注射利妥昔单抗治疗[31]。利妥昔单抗使用期间，建议酌情监测外周血$CD3^-CD19^+/CD20^+$B淋巴细胞，同时注意感染、乙型肝炎等慢性病毒重新激活、进行性多灶性白质脑病等罕见并发症[32-33]。

### 2.2 环磷酰胺（cyclophosphamide，CTX）

CTX是一种抑制细胞增殖的烷化剂，可直接作用于T、B淋巴细胞，多作为恶性肿瘤化疗药物或严重风湿性及肾脏疾病的免疫抑制剂使用[34-35]。环磷酰胺的临床使用经验成熟，价格低廉，但因其潜在的严重不良反应（骨髓抑制、不孕症、出血性膀胱炎和恶性肿瘤风险增加等），在AE二线治疗中优先使用的级别降低，仅当利妥昔单抗无法获得或存在药物禁忌证时，可考虑静脉注射环磷酰胺药物[5,36]。

## 3 AE的长程维持免疫治疗

经过规范一线及二线免疫治疗，部分AE患者仍未达到完全临床缓解，因此急性期后为进一步缓解病情，并且预防AE复发，部分AE患者应考虑加用AE长程维持免疫治疗。目前国内专家共识推荐所有复发AE患者在规范的一线或二线免疫治疗后均应加用长程免疫治疗，强化一线或二线免疫治疗无效的首发AE也可考虑加用长程维持免疫治疗[5,37]。

AE的长程免疫治疗方案包括吗替麦考酚酯、硫唑嘌呤和重复利妥昔单抗等[6,38-41]。吗替麦考酚酯和硫唑嘌呤口服制剂使用方便但起效较慢，使用时需要与皮质类固醇重叠3~6个月。利妥昔单抗作为急性期二线治疗的主要药物，具有起效快，致癌潜力小等优势。目前暂无吗替麦考酚酯、硫唑嘌呤和重复利妥昔单抗作为AE维持免疫治疗的对比研

究。长程维持免疫治疗疗程一般为12~24个月，治疗疗程受抗体类型、疾病严重程度、复发次数等多种因素影响。

## 4 难治性AE的治疗

一线免疫治疗2周仍疗效欠佳的AE定义为难治性AE[31]。AE患者经过规范的一线和二线免疫治疗，大部分患者临床改善明显，但仍有部分患者无明显临床改善，这类患者则需要进一步的单克隆抗体或直接输注免疫介质等治疗[5]。

二线治疗的失败原因可能与AE的发病机制有关，主要考虑以下2个方向：①二线免疫代表药物利妥昔单抗针对CD20+细胞，对CD20-的长寿浆细胞无靶向作用，长寿浆细胞可持续产生致病性抗体，抗体无法清除，导致长期慢性炎症或复发。②自身免疫性脑炎如抗NMDAR脑炎的B细胞鞘内增殖分化已被证实，也能产生致病性抗体，而二线治疗药物如利妥昔单抗无法通过血脑屏障，这也可能是导致二线治疗失败的原因。

针对难治性AE的治疗目前产生了很多新兴抗体和药物，主要分为5个方向：①针对细胞因子药物：主要以托珠单抗和低剂量IL-2为代表；②浆细胞消耗剂；③靶向B细胞的新兴抗体；④针对鞘内免疫细胞；⑤针对其他靶位药物。

### 4.1 针对细胞因子药物

4.1.1 针对白细胞介素6（interleukin-6，IL-6）受体的单克隆抗体 代表药物如托珠单抗（tocilizumab，TCZ）、萨特丽珠单抗（satralizumab）是一类针对IL-6受体的单克隆抗体。IL-6是一种多效细胞因子，发挥抑制B细胞的增殖、分化，调节T细胞分化、破坏血脑屏障等多种效应，在炎症介导的神经损伤中发挥重要作用[42-43]。有研究发现，AE患者血清及脑脊液中IL-6水平增高[44]。近年来TCZ在各种类型AE中应用广泛。目前多项托珠单抗成功治疗难治性抗NMDAR脑炎[45-46]、抗CASPR2抗体脑炎[47-48]、抗GAD脑炎[49-50]、血清阴性AE[50-51]的病例被报道。Lee WJ等[52]进行了RTX及TCZ治疗难治性AE的队列研究，结果提示加用TCZ比重复使用RTX更加安全有效，但此项研究因纳入病例多为血清阴性AE，故结果有待进一步研究证实。目前托珠单抗的应用时间及剂量尚无统一专家意见，Lee WJ等[45]对抗NMDAR脑炎患者进行队列研究提示发病早期（1个月内）加用托珠单抗治疗效果更好，而2021年的国际抗NMDAR脑炎指南推荐一二线免疫治疗无效的儿童AE患者，1~3个月后应加用TCZ治疗[53]。托珠单抗总体应用安全性较高，不良反应轻，使用过程中应注意肝功能、血小板计数、中性粒细胞绝对计数等指标。萨特丽珠单抗目前主要用于视神经脊髓炎的治疗，在AE暂无应用临床病例。

4.1.2 低剂量IL-2 IL-2是调节T细胞分化、生存和功能的关键调节因子，在自身免疫耐受方面发挥作用[54-55]。因为IL-2对调节性T细胞的激活阈值低于效应T细胞，低剂量IL-2可以选择性地激活调节性T细胞[56-57]，从而用于丙型肝炎、系统性红斑狼疮等疾病的治疗[58-59]。目前低剂量IL-2在脑炎中研究较少，Lim JA等[60]对10例难治性AE患者给予低剂量IL-2，结果提示有治疗作用。

### 4.2 浆细胞消耗剂

硼替佐米是一种靶向长寿浆细胞的蛋白酶体抑制剂，最初被批准用于治疗骨髓瘤[61]。长寿浆细胞为CD20-B细胞，可在使用利妥昔单抗等B细胞耗竭剂后仍持续性产生致病性抗体，从而导致难治性AE，这也是硼替佐米治疗难治性AE的基础[62]。已有较多病例报道了硼替佐米治疗难治性抗NMDAR脑炎、抗CASPR2抗体脑炎的良好疗效及安全性[63-66]。然而在1项治疗重症难治性抗NMDAR脑炎的前瞻性研究结果提示硼替佐米治疗效果与自然病程并无明显差异[66]，这可能与硼替佐米血脑屏障渗透率较低有关[67]，因此有必要进一步开展硼替佐米在AE的应用研究。急性肺损伤和硼替佐米相关神经病变仅在少数病例中被报道[63,68]。另外1项临床前研究表明，硼替佐米可以影响睾丸功能[69]，因此使用过程应关注男性儿童的生殖健康。

### 4.3 靶向B细胞的新型单克隆抗体

4.3.1 抗CD38单克隆抗体 达雷妥尤单抗（daratumumab，DARA）是一种新型抗CD38单克隆抗体，目前已临床应用于多发性骨髓瘤的治疗[70]。与硼替佐米等其他浆细胞消耗剂相比，CD38在浆细胞和T细胞上的共同表达，扩大了达雷妥尤单抗的潜在治疗益处，同时达雷妥尤单抗具有通过血脑屏障的作用。目前仅有1例病例报告达雷妥尤单抗成功治疗1例难治性抗NMDAR脑炎和1例重症难治性抗CASPR2抗体脑炎[71-72]。Scheibe F等[73]对达雷妥尤单抗治疗AE、CIDP、重症肌无力等自身免疫性疾病的回顾性研究结果进一步证明达雷妥尤单抗临床疗效确切。

4.3.2 抗CD19单克隆抗体 伊奈利珠单抗（inebilizumab）是一种靶向CD19阳性B细胞的IgG1单克隆抗体。因CD19广泛表达于B细胞谱系的各种亚型，故与利妥昔单抗相比，伊奈利珠单抗不仅消耗CD20阳性B细胞，还消耗CD20阴性浆母细胞和浆细胞，导致B细胞更广泛和持续地抑制[74]。因该药物在NMOSDII/Ⅲ期临床研究N-MOmentum（NCT02200770）中显示了良好的安全性和有效性，目前已被批准用于治疗AQP4阳性的NMOSD[75]。在AE中的研究，目前缺乏有效的临床证据，仅有一项抗NMDAR脑炎的临床RCT试验正在开展（NCT04372615）。

4.3.3 抗CD20单克隆抗体 除经典的RTX外的代表药物有奥美珠单抗（ocrelizumab，OCR）和奥法妥木单抗（ofatumumab，OFA）。OCR是靶向CD20阳性B细胞的人源化IgG1单克隆抗体，其抗原表位部分与利妥昔单抗重叠[76]。OCR的B细胞再增殖周期明显长于利妥昔单抗，但其在AE中的临床意义暂不明确，开展的单中心随机双盲试验（NCT03835728）

最终因人员招募不足而终止。OFA是靶向CD20阳性B细胞的全人源化IgG1单克隆抗体。与RTX相比，OFA与CD20上2个不同的非连续表位结合，与CD20抗原的解离较慢，提供有效和持续的效应活性。CDC活性明显致其治疗效率更高，起效剂量低[76-77]。同时OFA为全人源化抗体，可皮下注射，故OFA具有安全、高效、使用方便等优势。目前FDA批准用于RRMS的治疗。在AE的研究中，少量OFA治疗难治性抗NMDAR和LGI1脑炎的病例报道提示了OFA的治疗潜力[78-81]。

4.4 针对鞘内免疫细胞

4.4.1 鞘内注射甲氨蝶呤 甲氨蝶呤治疗脑炎的机制暂不明确，鞘内注射可以增加其脑脊液浓度并减少其全身毒性。目前有少量病例报告及一项研究提示甲氨蝶呤鞘内注射能够改善难治性抗NMDAR脑炎的症状[82-86]，为其临床应用提供依据。虽然这些病例未报道该药的严重副作用，但是鞘内注射甲氨蝶呤可能出现神经毒性，表现为癫痫、中风样症状或脑病[87]。

4.4.2 那他珠单抗 那他珠单抗是一种选择性黏附分子抑制剂，阻断中枢免疫细胞，多用于治疗多发性硬化症[88]。那他珠单抗是T细胞介导脑炎的治疗药物[89-90]，目前仅有一项纳他珠单抗治疗抗Hu相关副肿瘤神经系统综合征的Ⅱ期临床试验提示那他珠单抗可改善AE病程[89]。

4.5 针对其他靶位药物

4.5.1 针对FC受体的单克隆抗体 以艾加莫德（Efgartigimod）、罗扎诺利昔单抗（Rozanolixizumab）为代表的针对FC受体的单克隆抗体，专门靶向FcRn，通过抑制FcRn与IgG的相互作用来阻止IgG的再循环，导致未结合的IgG被消除。有类似于IVIG和血浆置换的治疗作用，但经济优势明显。多项RCT结果提示该药治疗重症肌无力安全有效[91-94]，目前已被美国食品与药物管理局（Food and Drug Administration，FDA）批准用于治疗重症肌无力的治疗。在AE的研究中，目前仅有1项IGI1脑炎的2期临床试验（NCT04875975）正在开展。

4.5.2 针对补体级联反应的抗体 依库珠单抗（Eculizumab）也可用于治疗AE，但缺乏关于补体介导抗CASPR2和抗LGI1脑炎的神经元毒性的死后研究的证据[95]。在抗NMDAR脑炎发病机制中补体参与证据不足[96-97]。

## 5 总结与展望

AE的免疫治疗目前主要是一种逐步升级的方法。急性期，从一线免疫治疗开始，主要涉及大剂量类固醇和免疫球蛋白或血浆交换。当一线治疗失败时，就会转为以利妥昔单抗为主的二线治疗。而对于一线及二线免疫治疗均无效的难治性AE患者，治疗选择则面临很多挑战。虽然随着对AE的广泛研究，产生了许多新的治疗药物，但大多数临床证据仍停留在病例报告或小样本研究水平，仍处于探索阶段。目前国内外专家共识建议考虑升级至静脉注射托珠单抗治疗或添加免疫治疗，包括甲氨蝶呤鞘内注射、硼替佐米和低剂量白细胞介素2等药物，但是关于治疗药物的选择及应用时间的确定仍然是很大的挑战。

目前抗NMDAR脑炎的研究较多，未来有必要加强对其他亚型AE的研究。近年来，针对AE各种靶点的抗体进展较快，多项RCT的开展的结果值得进一步关注。此外对AE遗传易感性的研究已经展开，靶向AE特定基因的探索将持续进行。

## 参 考 文 献


[1] Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes[J]. J Neurol Neurosurg Psychiatry, 2004, 75(8): 1135-1140.

[2] Dalmau J, Tüzün E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma[J]. Ann Neurol, 2007, 61(1): 25-36.

[3] Probst C, Saschenbrecker S, Stoecker W, et al. Anti-neuronal autoantibodies: current diagnostic challenges[J]. Mult Scler Relat Disord, 2014, 3(3): 303-320.

[4] Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis[J]. Lancet Neurol, 2016, 15(4): 391-404.

[5] 中华医学会神经病学分会神经感染性疾病与脑脊液细胞学学组，王佳伟，关鸿志，等. 中国自身免疫性脑炎诊治专家共识（2022年版）[J]. 中华神经科杂志，2022，8(9)：931-949.
Chinese Society of Neuroinfectious Diseases and Cerebrospinal Fluid Cytology, Wang JW, Guan HZ, et al. Chinese expert consensus on the diagnosis and management of autoimmune encephalitis (2022 edition)[J]. Chin J Neurol, 2022, 8(9): 931-949.

[6] Nosadini M, Eyre M, Molteni E, et al. Use and safety of immunotherapeutic management of N-methyl-d-aspartate receptor antibody encephalitis: a meta-analysis[J]. JAMA Neurol, 2021, 78(11): 1333-1344.

[7] Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study[J]. Lancet Neurol, 2013, 12(2): 157-165.

[8] Abboud H, Probasco JC, Irani S, et al. Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management[J]. J Neurol Neurosurg Psychiatry, 2021, 92(7): 757-768.

[9] Wiseman AC. Immunosuppressive medications[J]. Clin J Am Soc Nephrol, 2016, 11(2): 332-343.

[10] Rodriguez A, Klein CJ, Sechi, et al. LGI1 antibody encephalitis: acute treatment comparisons and outcome[J]. J Neurol Neurosurg Psychiatry, 2022, 93(3): 309-315.

[11] Slade JD, Hepburn B. Prednisone-induced alterations of circulating human lymphocyte subsets[J]. J Lab Clin Med, 1983, 101(3): 479-

487.

[12] Lahood N, Emerson SS, Kumar P, et al. Antibody levels and response to pneumococcal vaccine in steroid-dependent asthma[J]. Ann Allergy, 1993, 70(4): 289-294.

[13] 中国免疫学会神经免疫分会. 静脉注射人免疫球蛋白治疗神经系统免疫疾病中国指南[J]. 中国神经免疫学和神经病学杂志, 2022, 29(6): 437-448.
Neuroimmunology Branch of Chinese Society for Immunology. Chinese guidelines for intravenous immunoglobulin in the treatment of immune-mediated neuropathies[J]. Chin J Neuroimmunol Neurol, 2022, 29(6): 437-448.

[14] Li TR, Zhang YD, Wang Q, et al. Intravenous methylprednisolone or immunoglobulin for anti-glutamic acid decarboxylase 65 antibody autoimmune encephalitis: which is better? [J]. BMC Neurosci, 2020, 21(1): 13.

[15] Xu X, Lu Q, Huang Y, et al. Anti-NMDAR encephalitis: a single-center, longitudinal study in China[J]. Neurol Neuroimmunol Neuroinflamm, 2020, 7(1): e633.

[16] Zuliani L, Nosadini M, Gastaldi M, et al. Management of antibody-mediated autoimmune encephalitis in adults and children: literature review and consensus-based practical recommendations[J]. Neurol Sci, 2019, 40(10): 2017-2030.

[17] Dalakas MC. IgG4-mediated neurologic autoimmunities: understanding the pathogenicity of IgG4, ineffectiveness of IVIg, and long-lasting benefits of anti-B cell therapies[J]. Neurol Neuroimmunol Neuroinflamm, 2022, 9(1): e1116.

[18] Dubey D, Britton J, McKeon A, et al. Randomized placebo-controlled trial of intravenous immunoglobulin in autoimmune LGI1/CASPR2 epilepsy[J]. Ann Neurol, 2020, 87(2): 313-323.

[19] Reeves HM, Winters JL. The mechanisms of action of plasma exchange[J]. Br J Haematol, 2014, 164(3): 342-351.

[20] Suppiej A, Nosadini M, Zuliani L, et al. Plasma exchange in pediatric anti-NMDAR encephalitis: a systematic review[J]. Brain Dev, 2016, 38(7): 613-622.

[21] DeSena AD, Noland DK, Matevosyan K, et al. Intravenous methylprednisolone versus therapeutic plasma exchange for treatment of anti-N-methyl-D-aspartate receptor antibody encephalitis: a retrospective review[J]. J Clin Apher, 2015, 30(4): 212-216.

[22] Dogan Onugoren M, Golombeck KS, Bien C, et al. Immunoadsorption therapy in autoimmune encephalitides[J]. Neurol Neuroimmunol Neuroinflamm, 2016, 3(2): e207.

[23] Fassbender C, Klingel R, Köhler W. Immunoadsorption for autoimmune encephalitis[J]. Atheroscler Suppl, 2017, 30: 257-263.

[24] Hermetter C, Fazekas F, Hochmeister S. Systematic review: syndromes, early diagnosis, and treatment in autoimmune encephalitis[J]. Front Neurol, 2018, 9: 706.

[25] Boedecker SC, Luessi F, Engel S, et al. Immunoadsorption and plasma exchange-Efficient treatment options for neurological autoimmune diseases[J]. J Clin Apher, 2022, 37(1): 70-81.

[26] Heine J, Ly LT, Lieker I, et al. Immunoadsorption or plasma exchange in the treatment of autoimmune encephalitis: a pilot study[J]. J Neurol, 2016, 263(12): 2395-2402.

[27] Kosmidis ML, Dalakas MC. Practical considerations on the use of rituximab in autoimmune neurological disorders[J]. Ther Adv Neurol Disord, 2010, 3(2): 93-105.

[28] Thaler FS, Zimmermann L, Kammermeier S, et al. Rituximab treatment and long-term outcome of patients with autoimmune encephalitis: real-world evidence from the GENERATE registry[J]. Neurol Neuroimmunol Neuroinflamm, 2021, 8(6): e1088.

[29] Dalakas MC. Autoimmune neurological disorders with IgG4 antibodies: a distinct disease spectrum with unique IgG4 functions responding to anti-B cell therapies[J]. Neurotherapeutics, 2022, 19(3): 741-752.

[30] Strippel C, Heidbreder A, Schulte-Mecklenbeck A, et al. Increased intrathecal B and plasma cells in patients with anti-IgLON5 disease: a case series[J]. Neurol Neuroimmunol Neuroinflamm, 2022, 9(2): e1137.

[31] 中华医学会神经病学分会. 中国自身免疫性脑炎诊治专家共识[J]. 中华神经科杂志, 2017, 50(2): 91-98.
Chinese society of Neurology. Expert consensus on diagnosis and treatment of autoimmune encephalitis in China[J]. Chin J Neurol, 2017, 50(2): 91-98.

[32] Martin ST, Cardwell SM, Nailor MD, et al. Hepatitis B reactivation and rituximab: a new boxed warning and considerations for solid organ transplantation[J]. Am J Transplant, 2014, 14(4): 788-796.

[33] Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports Project[J]. Blood, 2009, 113(20): 4834-4840.

[34] Gourley MF, Austin HA 3rd, Scott D, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial[J]. Ann Intern Med, 1996, 125(7): 549-557.

[35] Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma[J]. N Engl J Med, 2002, 346(4): 235-242.

[36] Shin YW, Lee ST, Park KI, et al. Treatment strategies for autoimmune encephalitis[J]. Ther Adv Neurol Disord, 2018, 11: 1756285617722347.

[37] Abboud H, Probasco J, Irani SR, et al. Autoimmune encephalitis: proposed recommendations for symptomatic and long-term management [J]. J Neurol Neurosurg Psychiatry, 2021, 92(8): 897-907.

[38] 关鸿志, 徐晓璐, 朱以诚, 等. 吗替麦考酚酯治疗抗富亮氨酸胶质瘤失活蛋白1脑炎的临床与免疫参数观察[J]. 中华神经科杂志, 2018, 51(4): 281-286.
Guan HZ, Xu XL, Zhu YC, et al. Clinical and immunological analysis of mycophenolate mofetil treatment in anti-leucine-rich glioma-inactivated protein 1 encephalitis[J]. Chin J Neurol, 2018, 51(4): 281-286.

[39] Hao XS, Wang JT, Chen C, et al. Effectiveness of mycophenolate

mofetil in the treatment of pediatric anti-NMDAR encephalitis: a retrospective analysis of 6 cases[J]. Front Neurol, 2020, 11: 584446.

[40] Nosadini M, Gadian J, Lim M, et al. Mycophenolate mofetil in paediatric autoimmune or immune-mediated diseases of the central nervous system: clinical experience and recommendations[J]. Dev Med Child Neurol, 2019, 61(4): 458-468.

[41] Lee WJ, Lee ST, Byun JI, et al. Rituximab treatment for autoimmune limbic encephalitis in an institutional cohort[J]. Neurology, 2016, 86(18): 1683-1691.

[42] Kang SJ, Tanaka T, Kishimoto T. Therapeutic uses of anti-interleukin-6 receptor antibody[J]. Int Immunol, 2015, 27(1): 21-29.

[43] Erta M, Quintana A, Hidalgo J. Interleukin-6, a major cytokine in the central nervous system[J]. Int J Biol Sci, 2012, 8(9): 1254-1266.

[44] Cantarín-Extremera V, Jiménez-Legido M, Duat-Rodríguez A, et al. Tocilizumab in pediatric refractory status epilepticus and acute epilepsy: experience in two patients[J]. J Neuroimmunol, 2020, 340: 577142.

[45] Lee WJ, Lee ST, Shin YW, et al. Teratoma removal, steroid, IVIG, rituximab and tocilizumab (T-SIRT) in anti-NMDAR encephalitis[J]. Neurotherapeutics, 2021, 18(1): 474-487.

[46] Yamaguchi Y, Furukawa K, Yamamoto T, et al. Multifocal encephalopathy and autoimmune-mediated limbic encephalitis following tocilizumab therapy[J]. Intern Med, 2014, 53(8): 879-882.

[47] Krogias C, Hoepner R, Müller A, et al. Successful treatment of anti-Caspr2 syndrome by interleukin 6 receptor blockade through tocilizumab[J]. JAMA Neurol, 2013, 70(8): 1056-1059.

[48] Benucci M, Tramacere L, Infantino M, et al. Efficacy of tocilizumab in limbic encephalitis with anti-CASPR2 antibodies[J]. Case Rep Neurol Med, 2020, 2020: 5697670.

[49] Jaafar F, Haddad L, Koleilat N, et al. Super refractory status epilepticus secondary to anti-GAD antibody encephalitis successfully treated with aggressive immunotherapy[J]. Epilepsy Behav Rep, 2020, 14: 100396.

[50] Randell RL, Adams AV, Van Mater H. Tocilizumab in refractory autoimmune encephalitis: a series of pediatric cases[J]. Pediatr Neurol, 2018, 86: 66-68.

[51] van Steenhoven RW, Titulaer MJ. Seronegative autoimmune encephalitis: exploring the unknown[J]. Brain, 2022, 145(10): 3339-3340.

[52] Lee WJ, Lee HS, Kim DY, et al. Seronegative autoimmune encephalitis: clinical characteristics and factors associated with outcomes [J]. Brain, 2022, 145(10): 3509-3521.

[53] Nosadini M, Thomas T, Eyre M, et al. International consensus recommendations for the treatment of pediatric NMDAR antibody encephalitis[J]. Neurol Neuroimmunol Neuroinflamm, 2021, 8(5): e1052.

[54] Malek TR, Castro I. Interleukin-2 receptor signaling: at the interface between tolerance and immunity[J]. Immunity, 2010, 33(2): 153-165.

[55] Liao W, Lin JX, Leonard WJ. Interleukin-2 at the crossroads of effector responses, tolerance, and immunotherapy[J]. Immunity, 2013, 38(1): 13-25.

[56] Yu AX, Zhu LJ, Altman NH, et al. A low interleukin-2 receptor signaling threshold supports the development and homeostasis of T regulatory cells[J]. Immunity, 2009, 30(2): 204-217.

[57] Yu AX, Snowhite I, Vendrame F, et al. Selective IL-2 responsiveness of regulatory T cells through multiple intrinsic mechanisms supports the use of low-dose IL-2 therapy in type 1 diabetes[J]. Diabetes, 2015, 64(6): 2172-2183.

[58] Saadoun D, Rosenzwajg M, Joly F, et al. Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis[J]. N Engl J Med, 2011, 365(22): 2067-2077.

[59] He J, Zhang X, Wei YB, et al. Low-dose interleukin-2 treatment selectively modulates $CD4^+$ T cell subsets in patients with systemic lupus erythematosus[J]. Nat Med, 2016, 22(9): 991-993.

[60] Lim JA, Lee ST, Moon J, et al. New feasible treatment for refractory autoimmune encephalitis: low-dose interleukin-2[J]. J Neuroimmunol, 2016, 299: 107-111.

[61] Ito S. Proteasome inhibitors for the treatment of multiple myeloma [J]. Cancers, 2020, 12(2): 265.

[62] Sun B, Ramberger M, O'Connor KC, et al. The B cell immunobiology that underlies CNS autoantibody-mediated diseases[J]. Nat Rev Neurol, 2020, 16(9): 481-492.

[63] Scheibe F, Prüss H, Mengel AM, et al. Bortezomib for treatment of therapy-refractory anti-NMDA receptor encephalitis[J]. Neurology, 2017, 88(4): 366-370.

[64] Behrendt V, Krogias C, Reinacher-Schick A, et al. Bortezomib treatment for patients with anti-N-methyl-d-aspartate receptor encephalitis[J]. JAMA Neurol, 2016, 73(10): 1251-1253.

[65] Sveinsson O, Granqvist M, Forslin Y, et al. Successful combined targeting of B- and plasma cells in treatment refractory anti-NMDAR encephalitis[J]. J Neuroimmunol, 2017, 312: 15-18.

[66] Shin YW, Lee ST, Kim TJ, et al. Bortezomib treatment for severe refractory anti-NMDA receptor encephalitis[J]. Ann Clin Transl Neurol, 2018, 5(5): 598-605.

[67] Foran E, Kwon DY, Nofziger JH, et al. CNS uptake of bortezomib is enhanced by P-glycoprotein inhibition: implications for spinal muscular atrophy[J]. Neurobiol Dis, 2016, 88: 118-124.

[68] O'Riordan D, Houghton J, Chisholm R, et al. Breathless on bortezomib[J]. BMJ Case Rep, 2011, 2011: bcr0320114028.

[69] Hou M, Eriksson E, Svechnikov K, et al. Bortezomib treatment causes long-term testicular dysfunction in young male mice[J]. Mol Cancer, 2014, 13: 155.

[70] Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma[J]. N Engl J Med, 2015, 373(13): 1207-1219.

[71] Ratuszny D, Skripuletz T, Wegner F, et al. Case report: daratumumab in a patient with severe refractory anti-NMDA receptor encephalitis[J]. Front Neurol, 2020, 11: 602102.

[72] Scheibe F, Ostendorf L, Reincke SM, et al. Daratumumab treatment for therapy-refractory anti-CASPR2 encephalitis[J]. J Neurol,

2020,267(2):317-323.

[73] Scheibe F, Ostendorf L, Prüss H, et al. Daratumumab for treatment-refractory antibody-mediated diseases in neurology[J]. Eur J Neurol,2022,29(6):1847-1854.

[74] Levy M,Fujihara K,Palace J. New therapies for neuromyelitis optica spectrum disorder[J]. Lancet Neurol,2021,20(1):60-67.

[75] Cree BAC,Bennett JL,Kim HJ,et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind,randomised placebo-controlled phase 2/3 trial[J]. Lancet, 2019,394(10206):1352-1363.

[76] Klein C,Lammens A,Schäfer W,et al. Epitope interactions of monoclonal antibodies targeting CD20 and their relationship to functional properties[J]. MAbs,2013,5(1):22-33.

[77] Semple KM,Gonzaléz CM,Zarr M,et al. Evaluation of the ability of immune humanized mice to demonstrate CD20-specific cytotoxicity induced byOfatumumab[J]. Clin Transl Sci,2019,12(3):283-290.

[78] Zhang R,Wang L,Tao YL,et al. The case report of MOG and NMDAR IgG double positive encephalitis treated with subcutaneous ofatumumab[J]. Front Immunol,2023,14:1183488.

[79] Xue HF,Jiang YS,Qin LZ,et al. Ofatumumab,a fully human anti-CD20 monoclonal antibody,in the treatment of severe refractory anti-N-methyl-D-aspartate receptor encephalitis:two case reports[J]. Ann Indian Acad Neurol,2023,26(5):774-777.

[80] Chen KL,Yang L,Xu L,et al. Ofatumumab for the treatment of refractory anti-LGI1 encephalitis with long-term poor blood glucose control in type 1 diabetes[J]. CNS Neurosci Ther,2023,29(12):4172-4174.

[81] Zhou QM,Yin D,Ma JF,et al. The therapeutic effect of ofatumumab in autoimmune encephalitis:a case series[J]. J Neuroimmunol, 2023,377:578062.

[82] Eaton JE,Kleinholz-Owens P,Sriram S,et al. Intrathecal methotrexate-another tool for the treatment of refractory autoimmune encephalitis-single institution cohort and literature review[J]. J Neurol Sci,2021,431:120042.

[83] Liba Z,Sebronova V,Komarek V,et al. Prevalence and treatment of anti-NMDA receptor encephalitis[J]. Lancet Neurol,2013,12(5): 424-425.

[84] Yang XZ,Zhu HD,Ren HT,et al. Utility and safety of intrathecal methotrexate treatment in severe anti-N-methyl-D-aspartate receptor encephalitis:a pilot study[J]. Chin Med J,2018,131(2):156-160.

[85] Tatencloux S,Chretien P,Rogemond V,et al. Intrathecal treatment of anti-N-Methyl-D-aspartate receptor encephalitis in children [J]. Dev Med Child Neurol,2015,57(1):95-99.

[86] Wang DM,Wu YM,Ji Z,et al. A refractory anti-NMDA receptor encephalitis successfully treated by bilateral salpingo-oophorectomy and intrathecal injection of methotrexate and dexamethasone:a case report[J]. J Int Med Res,2020,48(10):300060520925666.

[87] Bhojwani D,Sabin ND,Pei D,et al. Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia[J]. J Clin Oncol,2014,32(9):949-959.

[88] Polman CH,O'Connor PW,Havrdova E,et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis [J]. N Engl J Med,2006,354(9):899-910.

[89] Bastiaansen AEM,de Jongste AHC,de Bruijn MAAM,et al. Phase Ⅱ trial of natalizumab for the treatment of anti-Hu associated paraneoplastic neurological syndromes[J]. Neurooncol Adv,2021,3(1): 145.

[90] Hottinger AF,de Micheli R,Guido V,et al. Natalizumab may control immune checkpoint inhibitor-induced limbic encephalitis[J]. Neurol Neuroimmunol Neuroinflamm,2018,5(2):e439.

[91] Howard JF Jr,Bril V,Burns TM,et al. Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis[J]. Neurology,2019,92(23):2661-2673.

[92] Howard JF Jr,Bril V,Vu T,et al. Safety,efficacy,and tolerability of efgartigimod in patients with generalised myasthenia gravis(ADAPT): a multicentre,randomised,placebo-controlled,phase 3 trial[J]. Lancet Neurol,2021,20(7):526-536.

[93] Heo YA. Efgartigimod Alfa in generalised myasthenia gravis:a profile of its use[J]. CNS Drugs,2023,37(5):467-473.

[94] Bril V,Drużdż A,Grosskreutz J,et al. Safety and efficacy of rozanolixizumab in patients with generalised myasthenia gravis(MycarinG): a randomised,double-blind,placebo-controlled,adaptive phase 3 study [J]. Lancet Neurol,2023,22(5):383-394.

[95] Bien CG,Vincent A,Barnett MH,et al. Immunopathology of autoantibody-associated encephalitides:clues for pathogenesis[J]. Brain, 2012,135(Pt 5):1622-1638.

[96] Zrzavy T,Endmayr V,Bauer J,et al. Neuropathological variability within a spectrum of NMDAR-encephalitis[J]. Ann Neurol,2021,90 (5):725-737.

[97] Martinez-Hernandez E,Horvath J,Shiloh-Malawsky Y,et al. Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis[J]. Neurology,2011,77(6):589-593.

（责任编辑：周一青）

本文引用格式：

陈 静,田仰华. 自身免疫脑炎的免疫治疗研究进展[J]. 重庆医科大学学报,2025,50(2):158-164.