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在线全文

靶向B细胞疗法介导的B细胞精细亚群免疫重建模式特征分析*

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【摘要】 目的 分析CD20单抗奥法妥木与CD19单抗伊奈利珠治疗后患者体内B细胞精细亚群的重建模式，评估个体化B细胞精细亚群动态分型在靶向治疗策略中的临床应用价值。**方法** 前瞻性纳入2023年10月–2025年5月期间在四川大学华西医院接受奥法妥木单抗治疗的30例天疱疮患者，以及26例接受伊奈利珠单抗治疗的视神经脊髓炎谱系疾病（neuromyelitis optica spectrum disorders, NMOSD）患者。同期以30名健康个体作为对照组进行基线比较，动态监测靶向治疗后3个时间点（1个月、3个月和6个月）患者体内B细胞精细亚群、抗桥粒芯糖蛋白（desmoglein, Dsg）及免疫球蛋白的变化。运用自然三次样条法拟合趋势曲线，并结合差异分析来评估群体免疫重建情况。**结果** 基线期（T0）天疱疮组多个B细胞亚群高于健康对照组，其中总B细胞计数〔347.50（250.40～621.8）cells/μL vs. 217.50（143.50～275.30）cells/μL〕、记忆B细胞计数〔127.30（74.63～196.70）cells/μL vs. 57.00（41.75～88.25）cells/μL〕及浆母细胞计数〔5.63（2.02～11.48）cells/μL vs. 1.00（1.00～2.00）cells/μL〕均升高（P<0.05）。而NMOSD患者仅浆母细胞计数高于健康对照组〔2.07（1.60～3.58）cells/μL vs. 1.00（1.00～2.00）cells/μL〕（P=0.04）。接受靶向治疗后，两组患者表现出不同的免疫重建特征。天疱疮组在治疗的前3个月，B细胞的免疫重建以记忆B细胞再生为主，计数由T1的4.46 cells/μL升至T3的10.47 cells/μL（P<0.01）；3个月后，初始B细胞的增生速度加快，计数由T3的0.95 cells/μL升至T6的3.25 cells/μL（P=0.001）。在整个动态监测期内，记忆B细胞的比例始终高于初始B细胞和浆母细胞。对于NMOSD患者，治疗后B细胞再生速度缓慢，总B细胞计数直至T6才较T1显著升高（由0 cells/μL升至2.65 cells/μL，P=0.026），其中以初始B细胞增长为主。天疱疮组T1及T3时点的浆母细胞计数均显著高于NMOSD组（P<0.01），至T6时差异消失。本组患者中，有2例天疱疮患者出现异常的B细胞重建，伴随浆母细胞异常升高或Dsg未降低的情况；1例NMOSD患者B细胞亚群的比例发生了逆转，记忆B细胞的数量超过了初始B细胞，同时浆细胞数量增高伴IgG免疫球蛋白增高。**结论** 针对CD20和CD19的靶向治疗所引发的B细胞重建模式明显不同。经过奥法妥木单抗治疗后，B细胞会经历一个阶段性的再生过程，而伊奈利珠单抗的治疗则导致再生的延迟。浆母细胞的增加、记忆B细胞的异常增殖以及Dsg抗体的反弹可能暗示着潜在的不良事件，这进一步支持了对B细胞精细亚群的监测，以便进行个性化治疗的精准免疫评估。

【关键词】 天疱疮　视神经脊髓炎谱系疾病　B细胞亚群　奥法妥木单抗　伊奈利珠单抗　免疫重建

Characterization of Immune Reconstitution Patterns in B-cell Subsets Mediated by B-cell Targeted Therapies

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[**Abstract**] **Objective** To analyze the reconstitution patterns of fine B-cell subsets in patients following treatment with the CD20 monoclonal antibody ofatumumab and the CD19 monoclonal antibody inebilizumab, and to evaluate the clinical application value of individualized fine B-cell subset dynamic profiling in guiding targeted therapy strategies. **Methods** This prospective study enrolled 30 patients with pemphigus receiving ofatumumab and 26 patients with neuromyelitis optica spectrum disorders (NMOSD) receiving inebilizumab at West China Hospital of Sichuan University between October 2023 and May 2025. Thirty healthy individuals were enrolled as controls for baseline comparison. Dynamic monitoring of fine B-cell subsets, anti-desmoglein (Dsg) antibodies, and immunoglobulins was performed at three post-treatment time points (1 month, 3 months, and 6 months). A natural cubic spline model was used to fit trend curves, combined with differential analysis to assess population-level immune reconstitution. **Results** At baseline (T0), patients in the pemphigus group had higher levels of several B-cell subsets compared to healthy controls. Total B-cell counts were 347.50 (250.40-621.8) cells/μL versus 217.50 (143.50-275.30) cells/μL, memory B-cell counts were 127.30 (74.63-196.70) cells/μL versus 57.00 (41.75-88.25) cells/μL, and plasmablast counts were 5.63 (2.02-11.48) cells/μL versus 1.00 (1.00-2.00) cells/μL. These differences were significant ($P < 0.05$). In contrast, NMOSD patients showed significantly higher plasmablast counts compared to healthy controls (2.07 [1.60-3.58] cells/μL vs. 1.00 [1.00-2.00] cells/μL) ($P = 0.04$). After three months, the proliferation rate of naive B cells increased, with counts rising from 0.95 cells/μL at T3 to 3.25 cells/μL at T6 ($P = 0.001$). Throughout the entire monitoring period, the proportion of memory B cells consistently remained higher than that of naive B cells and plasmablasts. In NMOSD patients, B-cell regeneration was slow after treatment. Total B-cell counts showed a significant increase only by T6 compared to T1 (from 0 cells/μL to 2.65 cells/μL, $P = 0.026$), with the increase primarily due to naive B cells. Plasmablast counts in the pemphigus group were significantly higher than those in the NMOSD group at T1 and T3 ($P < 0.01$), but this difference disappeared by T6. Among the cohort, two pemphigus patients showed abnormal B-cell reconstitution, characterized by persistently elevated plasmablasts or undetectable Dsg antibody decline. One NMOSD patient exhibited a reversal in B-cell subset proportions, with memory B-cell counts exceeding naive B-cell counts, along with increased plasma cell counts and elevated IgG immunoglobulin levels. **Conclusion** Targeted therapies against CD19 and CD20 induce distinctly different patterns of B-cell reconstitution. Ofatumumab treatment leads to a phased regenerative process in B cells, whereas inebilizumab treatment results in delayed regeneration. Increased plasmablasts, aberrant memory B-cell proliferation, and rebounding Dsg antibodies may signal potential adverse events. These findings support monitoring fine B-cell subsets for precise immunological assessment to guide personalized treatment.

[**Key words**] Pemphigus Neuromyelitis optica spectrum disorders B-cell subsets Ofatumumab Inebilizumab Immune reconstitution

近年来，B细胞靶向治疗已成为自身免疫疾病治疗的关键策略之一[1-3]。目前，以CD20为靶点的奥法妥木单抗和以CD19为靶点的伊奈利珠单抗是两类重要的B细胞耗竭疗法。奥法妥木单抗可有效清除成熟B细胞谱系，而伊奈利珠单抗因其靶点表达谱更早更广，能进一步清除浆母细胞[4-5]。奥法妥木单抗已用于多发性硬化和难治性天疱疮[6]；伊奈利珠单抗则是视神经脊髓炎谱系疾病（neuromyelitis optica spectrum disorders, NMOSD）的一线用药[7]。值得注意的是，深度的B细胞耗竭在发挥治疗作用的同时，也伴随着感染等潜在风险[4, 8-10]。因此，治疗后动态监测B淋巴细胞的重建，对于指导临床决策至关重要。

在重建监测中，浆母细胞升高往往先于或伴随自身抗体的反弹[11-12]，是预测临床复发的早期敏感指标。记忆B细胞的优势增殖，则可能代表了致病性免疫记忆的恢复[13-14]。因此，动态监测这些B细胞精细亚群及特异性自身抗体，如NMOSD中的抗水通道蛋白4（anti-aquaporin-4, AQP4）抗体和天疱疮中的抗桥粒芯糖蛋白（desmoglein, Dsg）1抗体和Dsg3抗体，已成为评估靶向治疗疗效、预警疾病活动及指导治疗决策（如决定是否需加强免疫抑制或提前干预）的关键手段[11-12, 15-16]。然而，目前尚缺乏一个基于不同作用机制药物的、系统性的免疫重建图谱来指导这一精准监测实践。

尽管天疱疮与NMOSD分属不同的自身免疫病范畴，但二者均以B细胞异常活化及自身抗体产生为病理机制核心[11, 17]。这为探究B细胞靶向治疗后免疫重建规律提供了理想模型。本研究采用了一种跨疾病平行对照策略，聚焦于药物靶点本身对免疫重建的根本影响，旨在识别由靶点决定的重建规律，为临床精准免疫监测与治疗管理提供理论依据。

因此，本研究前瞻性地纳入了我院接受奥法妥木单抗治疗的天疱疮患者和接受伊奈利珠单抗治疗的NMOSD

患者，通过动态监测B细胞精细亚群，绘制免疫重建图谱，评估以亚群动态分型为基础的监测策略在B细胞靶向治疗管理中的临床应用价值。

1　资料与方法

1.1　研究对象

本研究收集了四川大学华西医院在2023年10月–2025年6月，使用奥法妥木单抗治疗天疱疮患者及使用伊奈利珠单抗治疗NMOSD患者临床资料和实验室检查结果。同时，纳入健康人群作为对照组开展基线分析。纳入标准为所有研究对象需动态监测B细胞精细亚群至少两次，而排除标准为患者接受过其他治疗或B细胞精细亚群监测次数不足两次。本研究均已获得华西医院伦理委员会的批准(批准号: 202486)，根据国家法律法规及机构要求，参与者无需提供书面知情同意书。

1.2　资料收集及随访

本研究收集的临床资料包括人口学特征、随访时间、B淋巴细胞精细亚群、抗Dsg1/3抗体、免疫球蛋白(IgA、IgG、IgM)和药物治疗持续时间等实验室检测指标。本研究将治疗后关键时间点定义为随访时间窗：T1(1个月)、T3(3个月)、T6(6个月)，对应时间范围分别为(30±7) d、(90±14) d及(180±21) d。选择依据如下：T1为B细胞快速耗竭期，基于抗CD20单抗Ⅲ期临床试验，此时> 95%患者B细胞已低于正常下限[18-19]；T3为早期免疫重建起始点，已有研究在此观察到B细胞早期重建及亚群选择性耗竭[18, 20-21]；T6为免疫重建稳定期及下一治疗周期前基线水平，与抗CD20单抗标准给药周期及B细胞恢复至正常下限的中位时间(约24.6周)吻合[18, 21-22]。本研究为真实世界观察性研究，各时间点样本量存在差异。中位随访时间基于所有患者末次随访时间计算，可能因随访完成度差异存在一定偏倚。若患者在预设时间窗内有多次检测记录，取各次检测值的算术平均值作为该时间点代表值。对于存在多个治疗周期T6数据的NMOSD患者，取各周期T6检测值的平均值作为其T6代表值。

1.3　监测方法

本研究使用流式细胞术测量标记的单个淋巴细胞，$CD3^-CD14^-CD19^+CD27^-$细胞被鉴定为初始B细胞，$CD3^-CD14^-CD19^+CD27^+$细胞亚群代表记忆B细胞，而$CD3^-CD14^-CD27^{high}CD38^{high}$代表浆母细胞。其中$CD19^+$淋巴细胞定义为总B细胞，浆母细胞群体独立于CD19进行鉴定。细胞亚群频率的计算方式如下：初始B细胞和记忆B细胞的百分比以其父群$CD19^+$ B细胞为基准计算；浆母细胞的百分比则以$CD3^-CD14^-$淋巴细胞为基准计算。

1.4　统计学方法

使用Shapiro-Wilk法进行正态性检验，符合正态分布的计量数据采用$\bar{x} \pm s$表示，不符合正态分布的计量数据采用中位数和四分位数表示。两组间比较使用非参数检验Mann-Whitney U，多组间比较使用Kruskal-Wallis H检验，同一组内不同时间点的比较采用配对Wilcoxon符号秩检验，并报告校正后的P值(采用Bonferroni法校正)。配对Wilcoxon符号秩检验仅纳入具有完整配对数据的患者，文中报告的中位数及差异检验结果均基于相应时间点的配对样本，与表格中基于全体患者的描述性统计可能存在差异。校正后$P < 0.05$被认为差异具有统计学意义。使用平滑样条(自然三次样条)拟合群体趋势曲线进行探索性分析，该分析基于原始数据(包含所有重复测量)进行，旨在可视化整体趋势。所有统计分析和绘图在GraphPad Prism 10.4.1中完成。

2　结果

2.1　基线资料

本研究共纳入30名使用奥法妥木单抗治疗的天疱疮患者、26名使用伊奈利珠单抗的NMOSD患者以及30名未患病健康对照。其中天疱疮组男性占比43.3%，年龄均值为(49.7±16.9)岁，NMOSD组女性占比(88.5%)明显高于男性(11.5%)，年龄为(46.6±14.8)岁，对照组男性占比43.3%，年龄为(47.9±16.4)岁。天疱疮组和NMOSD组靶向治疗后中位随访时间分别为159 d和345 d，后者存在半年一次的治疗周期。

天疱疮组与健康对照组相比，基线期(T0)多个B细胞亚群存在差异(图1)。天疱疮组浆母细胞占比的中位数为1.19%(0.75% ~ 3.68%)，高于健康对照组0.50%(0.28% ~ 0.80%)($P < 0.001$)。在绝对计数方面，天疱疮组的总B细胞计数〔347.50(250.40 ~ 621.8) cells/μL vs. 217.50(143.50 ~ 275.30) cells/μL〕、初始B细胞计数〔222.60(134.80 ~ 374.70) cells/μL vs. 137.50(95.75 ~ 204.5) cells/μL〕、记忆B细胞计数〔127.30(74.63 ~ 196.70) cells/μL vs. 57.00 (41.75 ~ 88.25) cells/μL〕及浆母细胞计数〔5.63(2.02 ~ 11.48) cells/μL vs. 1.00(1.00 ~ 2.00) cells/μL〕均高于健康对照组($P < 0.05$)。而在NMOSD患者中仅发现浆母细胞计数高于健康对照组〔2.07(1.60 ~ 3.58) cells/μL vs. 1.00 (1.00 ~ 2.00) cells/μL〕($P = 0.04$)。天疱疮组所有监测共102次，中位检测次数3次/患者，范围为2 ~ 6次。NMOSD组所有监测共84次，中位检测次数3次/患者，范围为2 ~ 6次。

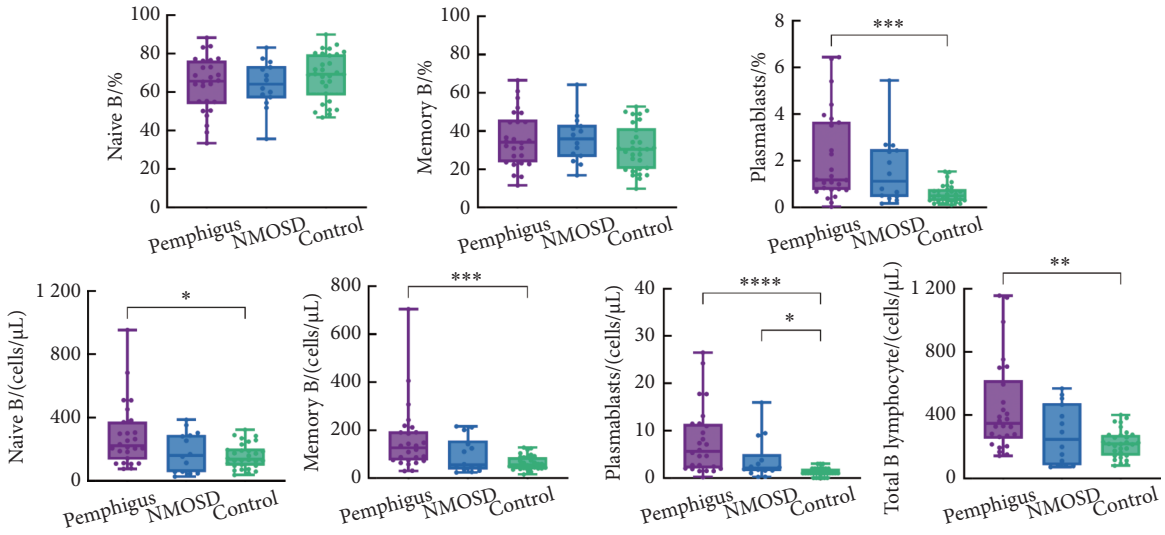

图 1 天疱疮和NMOSD患者与健康对照者的B淋巴细胞及亚群基线差异分析

Fig 1 Analysis of baseline differences in B lymphocytes and their subsets among patients with pemphigus (n = 30), patients with NMOSD (n = 26), and healthy controls (n = 30)

* P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.000 1.

2.2 天疱疮患者靶向治疗后B淋巴细胞亚群重建动态监测

天疱疮组靶向治疗后6个月内获得的68次B淋巴细胞亚群检测结果详见表1，B淋巴细胞、特异性抗体及免疫球蛋白群体趋势见图2。总B淋巴细胞数量在T1至T6的时间窗内整体呈增长趋势，其中总B细胞计数中位数由T1的4.64 cells/μL升至T3的11.46 cells/μL，至T6进一步升至20.06 cells/μL（T1 vs. T3及T1 vs. T6校正后P均< 0.01）。不同亚群呈现差异化的重建动力学特征，记忆B细胞计数在T1至T3呈上升趋势（中位数由4.46 cells/μL升至10.47 cells/μL，校正后P< 0.01），初始B细胞同期亦有所增长（0.32 cells/μL升至0.95 cells/μL，校正后P< 0.01），T3后初始B细胞进入快速增长阶段，至T6时中位数达3.25 cells/μL（T3 vs. T6校正后P= 0.001），浆母细胞计数各时间点间差异均无统计学意义。横向比较显示，T3时记忆B细胞计数高于初始B及浆母细胞（10.47 cells/μL vs. 0.95及1.43 cells/μL，校正后P均< 0.01）；T6时记忆B细胞计数相比初始B细胞计数差异无统计学意义，但仍高于浆母细胞（14.82 vs. 1.90 cells/μL，P< 0.001）。细胞百分比方面，各时间点记忆B细胞比例始终高于初始B及浆母细胞（校正后P均< 0.05）；初始B细胞比例在T3至T6间上升（14.78%升至18.75%，P= 0.048），浆母细胞比例在T1至T6间下降（26.74%降至9.06%，P= 0.016）。Dsg1及Dsg3抗体水平均在T3较T1显著下降（中位数分别由46.85 AU/mL降至20.1 AU/mL、102.4 AU/mL降至72.6 AU/mL，校正后P均< 0.01），至T6略有回升但与T3相比差异无统计学意义。免

表 1 天疱疮患者靶向治疗后T1、T3和T6的B淋巴细胞及亚群分布

Table 1 Distribution of B lymphocytes and their subgroups in pemphigus patients after ofatumumab-targeted therapy at T1, T3, and T6

Item	T1 (n = 27)			T3 (n = 24)			T6 (n = 17)		
	$\bar{x} \pm s$	Median (IQR)	Min-Max	$\bar{x} \pm s$	Median (IQR)	Min-Max	$\bar{x} \pm s$	Median (IQR)	Min-Max
Naive B/%	12.99 ± 12.11	9.09 (3.85-20.5)	0-38.24	20.82 ± 22.19	14.78 (6.47-19.46)	2.83-81.42	27.05 ± 25.31	20.21 (13.68-29.62)	4.05-92.39
Memory B/%	86.47 ± 11.83	90.91 (79.03-94.3)	61.76-100	79.04 ± 22.12	85.22 (80.52-93.53)	18.58-97.14	72.93 ± 25.32	79.79 (70.19-86.32)	7.53-95.95
Plasmablasts/%	39.98 ± 30.45	28.47 (20-61.3)	0-96	28.95 ± 23.15	30.98 (6.47-44.38)	0-70.35	16.19 ± 20.76	10.28 (5.47-13.33)	0.88-82.66
Total B/(cells/μL)	5.61 ± 4.11	4.9 (2.66-7.43)	0.29-18.43	14.48 ± 11.75	11.46 (6.21-18.18)	1.02-41.56	27.47 ± 18.48	20.51 (15.59-41.4)	7.49-67.45
Naive B/(cells/μL)	0.76 ± 1.38	0.39 (0.14-0.76)	0-7.04	3.55 ± 6.13	0.95 (0.49-2.99)	0.1-27.38	10.6 ± 16.41	3.35 (1.93-8.86)	0.3-57.56
Memory B/(cells/μL)	4.85 ± 3.35	4.21 (1.99-7.33)	0.29-12.57	10.92 ± 8.47	10.47 (4.16-14.17)	0.66-31.3	16.87 ± 10.44	14.82 (10.28-19.68)	4.69-42.92
Plasmablasts/(cells/μL)	2.14 ± 2.28	1.39 (0.72-2.92)	0-9.66	3.37 ± 4.77	1.43 (0.7-4.13)	0-22.65	2.68 ± 2.09	1.9 (1.28-3.01)	0.27-7.52

IQR: interquartile range.

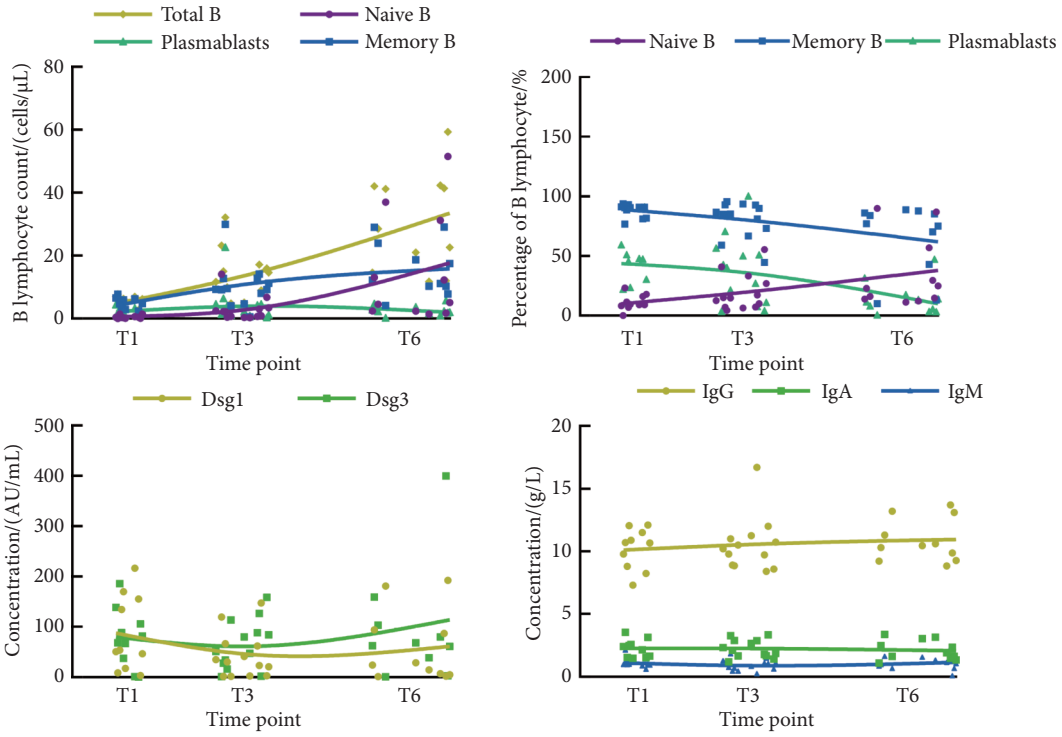

图 2 天疱疮患者靶向治疗后B淋巴细胞、特异性抗体及免疫球蛋白群体趋势

Fig 2 Trends of B lymphocytes, specific antibodies, and immunoglobulin populations in the pemphigus group after ofatumumab-targeted therapy

The curve shows the population average trend fitted using the natural cubic spline method. T1, T3, and T6, correspond to first follow-up (approximately 1 month), second follow-up (approximately 3 months), and third follow-up (approximately 6 months), respectively. The scattered points in the figure are plotted according to the actual visit times of the patients.

疫球蛋白IgG、IgM水平在整个观察期内保持稳定，仅IgA在T1与T3间出现有统计学意义的下降（1.92 g/L降至1.68 g/L, P= 0.033）。

通过绘制天疱疮组患者治疗前后的B细胞个体动态变化轨迹（图3）发现有2例患者变化轨迹与其他患者不同，其中病例1（寻常型天疱疮）在随访81 d时检测到浆母细胞数量（22.65 cells/μL）异常高于T3时中位数（1.34 cells/μL），初始B细胞和记忆B细胞数量和比例升高趋势同T3整体，亦高于T3中位数，Dsg1和Dsg3浓度缓慢下降，该病例在治疗后3个月时的B细胞精细亚群监测提示病情异常，结合

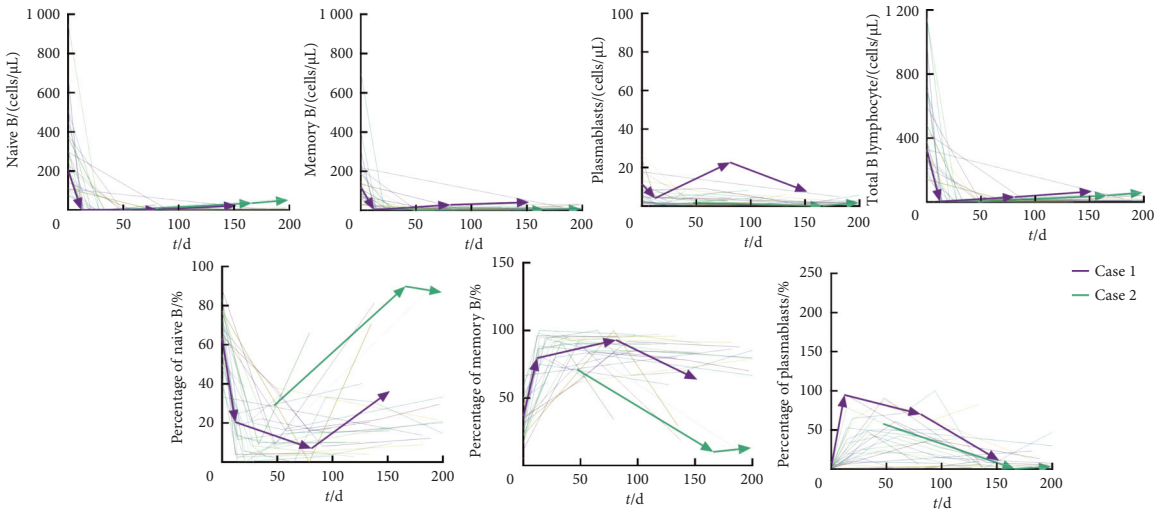

图 3 天疱疮患者靶向治疗前后B淋巴细胞及亚群的个体轨迹

Fig 3 Individual trajectories of B lymphocytes and their subsets in pemphigus patients before and after ofatumumab-targeted therapy

The change trajectories of case 1 and case 2 differ from those of the other patients.

患者临床症状,使用醋酸泼尼松激素增量治疗,于T6复查时发现B淋巴细胞及亚群重建情况与群体变化方向一致,临床症状有明显改善。病例2为落叶型天疱疮,治疗166 d后主诉皮损面积增大,检测到初始B细胞数量和比例增长明显快于群体趋势,Dsg1浓度不见下降。结合B细胞精细亚群检测结果和患者临床症状,该病例处于病情复发阶段,需及时采取临床干预措施。两例患者免疫球蛋白水平均未见明显异常。

2.3 NMOSD患者靶向治疗后B淋巴细胞亚群重建的动态监测

NMOSD组26名靶向治疗后6个月内获得的50次B细胞亚群检测结果(表2),使用所有数据绘制三次样条曲线进行探索性研究(图4),发现NMOSD患者使用伊奈利珠靶向治疗后B淋巴细胞再生极缓,配对Wilcoxon符号秩检验结果显示总B细胞计数在T6时间点较T1显著升高(中位数由0 cells/μL升至2.65 cells/μL,校正后P= 0.026),T3与T6间差异无统计学意义(校正后P= 0.073)。初始B细胞计数在T6较T1亦显著升高(0 cells/μL升至1.59 cells/μL,校正后P= 0.043),而记忆B细胞计数及浆母细胞计数在各时间点间差异均无统计学意义。免疫球蛋白IgG、IgA和IgM的变化在免疫重建过程均无统计学差异。

通过绘制NMOSD患者治疗前后的B淋巴细胞个体轨迹图(图5)发现,大多数NMOSD患者每半年规律接受一次伊奈利珠输注,在T1到T6之间B淋巴细胞稳定增生,以初始B细胞增长为主。只有1例在6个月时B细胞精细亚群检测到浆母细胞数量增高到9.85 cells/μL,记忆B细胞的数量超过了初始B细胞,IgA始终高于群体均值,结合临床症状需及时进行再次输注预防复发。

2.4 天疱疮和视神经脊髓炎靶向治疗前后浆母细胞差异分析

如图6所示,天疱疮组浆母细胞计数在T1(1.39 cells/μL vs. 0.10 cells/μL,校正后P= 0.002)及T3(1.43 cells/μL vs. 0.08 cells/μL,校正后P< 0.001)均显著高于NMOSD组,至T6时两组差异消失;浆母细胞百分比在各时间点两组间均无显著差异。天疱疮组靶向治疗后仅T1浆母细胞计数相比T0明显下降(5.35 cells/μL vs. 1.37 cells/μL,校正后

表 2 NMOSD患者靶向治疗后T1、T3和T6的B淋巴细胞及亚群分布

Table 2 Distribution of B lymphocytes and their subpopulations in NMOSD patients after inebilizumab-targeted therapy at T1, T3, and T6

Item	T1 (n = 14)			T3 (n = 11)			T6 (n = 25)		
	$\bar{x} \pm s$	Median (IQR)	Min-Max	$\bar{x} \pm s$	Median (IQR)	Min-Max	$\bar{x} \pm s$	Median (IQR)	Min-Max
Naive B/%	21.05 ± 35.49	0 (0-38.24)	0-100	35.65 ± 44.88	0 (0-79.38)	0-100	50.26 ± 38.73	60 (2.98-82.49)	0-100
Memory B/%	12.71 ± 28.92	0 (0-2.23)	0-100	5.57 ± 11.45	0 (0-3.22)	0-34.78	21.06 ± 26.44	3.98 (2.98-33.33)	0-100
Plasmablasts/%	59.14 ± 114.07	0.02 (0-68.75)	0-400	44.09 ± 118.74	0 (0-21.5)	0-400	44.61 ± 105.67	3.98 (1.82-33.34)	0-500
Total B/(cells/μL)	0.26 ± 0.79	0 (0-0.11)	0-2.98	0.46 ± 0.85	0.08 (0.01-0.25)	0-2.57	4.45 ± 10.09	1.68 (0.17-2.98)	0-47.5
Naive B/(cells/μL)	0.24 ± 0.79	0 (0-0.1)	0-2.98	0.37 ± 0.75	0.07 (0-0.21)	0-2.4	3.46 ± 8.67	0.59 (0.15-2.98)	0-43.6
Memory B/(cells/μL)	0.23 ± 0.79	0 (0-0.03)	0-2.98	0.09 ± 0.18	0 (0-0.08)	0-0.58	2.04 ± 3.58	0.31 (0.03-2.98)	0-15.64
Plasmablasts/(cells/μL)	0.37 ± 0.77	0.1 (0.07-0.34)	0-2.98	0.11 ± 0.15	0.08 (0-0.15)	0-0.48	1.85 ± 2.98	0.2 (0.06-2.98)	0-9.85

IQR: interquartile range.

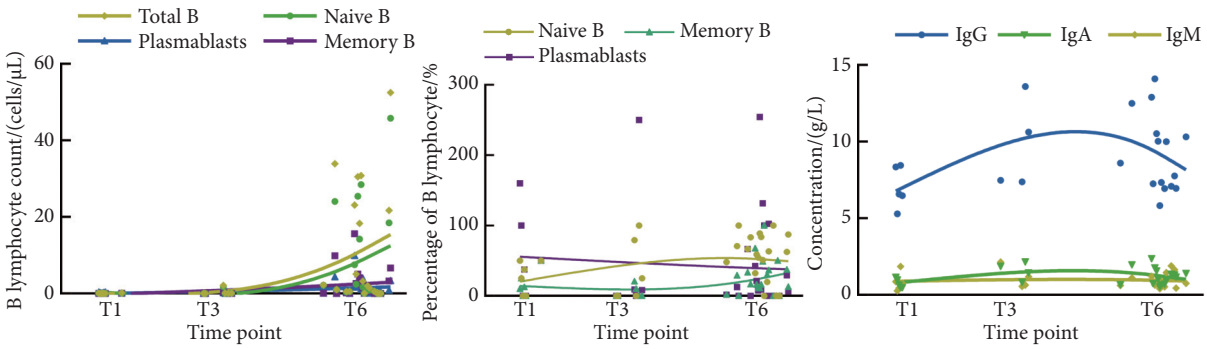

图 4 NMOSD患者靶向治疗后B淋巴细胞和免疫球蛋白群体趋势

Fig 4 Trends of B lymphocytes and immunoglobulin populations in the NMOSD group after inebilizumab-targeted therapy

The curve shows the population average trend fitted using the natural cubic spline method. T1, T3, and T6, correspond to first follow-up (approximately 1 month), second follow-up (approximately 3 months), and third follow-up (approximately 6 months), respectively. The scattered points in the figure are plotted according to the actual visit times of the patients.

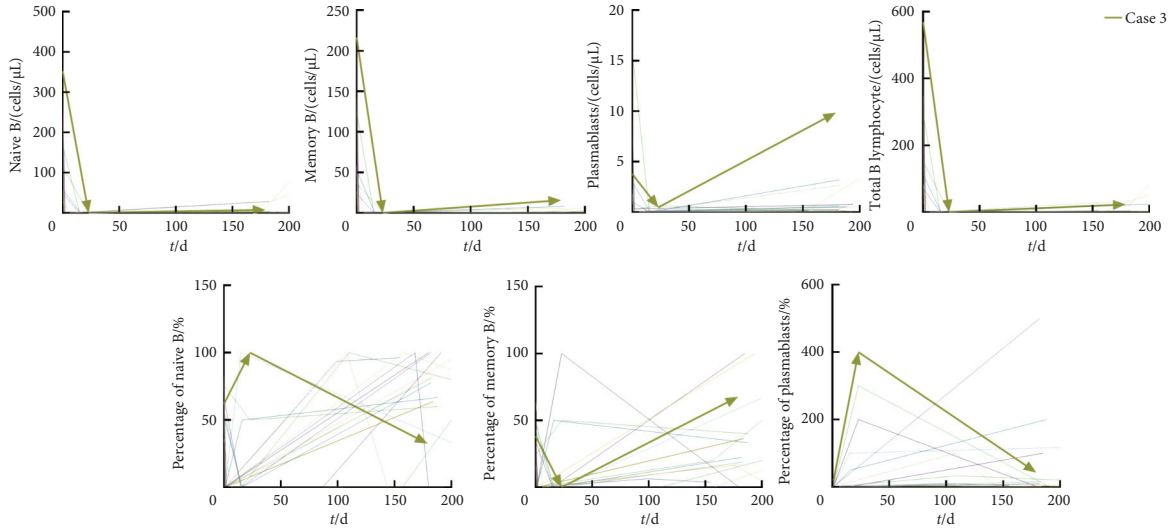

图 5 NMOSD组靶向治疗前后B淋巴细胞及亚群的个体轨迹

Fig 5 Individual trajectories of B lymphocytes and their subsets in NMOSD patients before and after inebilizumab-targeted therapy

The change trajectory of case 3 is different from those of the other patients.

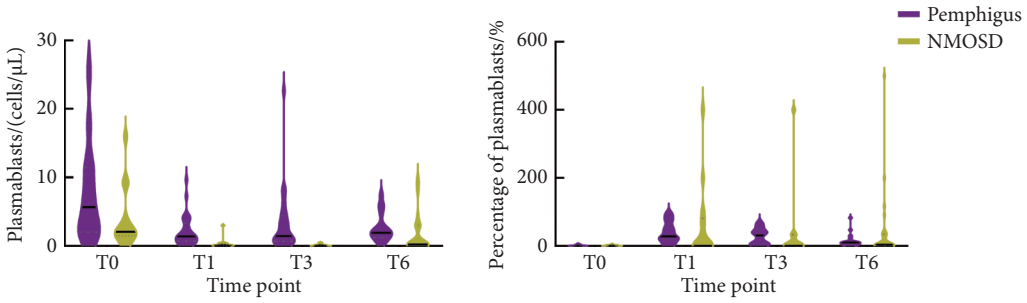

图 6 两种自身免疫性疾病在靶向治疗前后的浆母细胞差异分析

Fig 6 Analysis of differences in plasmablasts in two autoimmune diseases before and after targeted therapy

T0, T1, T3, and T6, correspond to baseline, first follow-up (approximately 1 month), second follow-up (approximately 3 months), and third follow-up (approximately 6 months), respectively.

$P=0.003$)，而浆母细胞百分比显示T0分别至T1、T3、T6均显著升高(中位数分别由1.18%至28.47%、34.68%、10.71%，校正后P均<0.05)；NMOSD组浆母细胞比例及计数在各时间点的变化均无统计学意义。

3　讨论

奥法妥木单抗和伊奈利珠单抗作为靶向CD20和CD19的单克隆抗体，通过不同的作用机制来调节B细胞免疫应答，在B细胞介导的自身免疫性疾病治疗方面有着关键的临床应用价值。本研究首次结合临床前瞻性的治疗队列比较CD20单抗与CD19单抗靶向治疗对自身免疫病B细胞重建的影响。

在靶向治疗前比较两组自身免疫疾病的B细胞基线差异，发现天疱疮患者初始B细胞、记忆B细胞、浆母细胞计数及其占比显著高于健康对照组，这一现象可能与疾病的发生、发展及免疫调控的失衡密切相关[23]。研究报道在天疱疮患者的皮损中，CD19$^+$ B细胞、CD20$^+$ B细胞以及CD138$^+$浆细胞的浸润显著增加，这些细胞可能通过局部产生Dsg抗体，直接参与皮肤屏障的破坏[24]，这与本研究发现一致。相比之下，NMOSD患者仅浆母细胞比例显著增高，其初始及记忆B细胞则相对稳定。研究已证实浆母细胞的高频出现与其核心致病因子AQP4抗体的产生密切相关[25-26]，表明使用伊奈利珠通过选择性耗竭浆母细胞进行靶向治疗的策略意义。这种基线差异可能与两类自身免疫病靶器官的固有特性有关。皮肤作为免疫活跃器官，其炎症反应可能更直接地驱动了系统性B细胞的广泛激活与扩增。相反，中枢神经系统的免疫特性和血脑屏障可能将NMOSD患者的体液免疫应答更多限制在颅内，导致主要在外周血中观察到终末分化的浆母细胞变化。

本课题组前期的研究结果提示总B细胞的定量监测

在临床评估中存在一定的局限性,难以全面反映B细胞的功能状态变化[27]。已有研究进一步表明,靶向治疗后B细胞重建滞后可能与B细胞发育受限密切相关,具体表现为骨髓来源的B细胞向外周释放减少,以及外周循环中B细胞存活率降低[28]。因此,借助流式细胞术对B细胞进行更精细的亚群划分与动态监测,对于准确评估免疫重建状态及治疗相关免疫调控机制具有关键意义。本研究发现奥法妥木单抗治疗后B细胞呈阶段性再生,前3个月记忆B细胞主导增长,3个月后初始B细胞快速再生。此模式可能与CD20靶向治疗保留前浆细胞和长寿命浆细胞有关[29],导致免疫系统通过记忆B细胞的扩增来维持免疫稳态。研究报道在奥法妥木单抗治疗后,尽管B细胞整体被耗竭,但记忆B细胞由于其独特的生存能力和快速增殖特性,能够在较短时间内恢复并扩增[30-31],这与本研究观察结果一致。相比之下,初始B细胞的再生相对延迟,在奥法妥木单抗治疗3个月后才开始出现。这一延迟现象可能与药物作用机制密切相关,高效的B细胞清除能力是其治疗优势,但也可能导致B细胞前体细胞的耗竭,从而延缓初始B细胞再生[32]。该发现提示CD20单抗虽能有效清除外周B细胞,但并未完全抑制骨髓的B细胞新生能力[33],对记忆B细胞恢复程度的评估可能有助于预测疾病复发,这与COLUCCI等[34]的报道相符。而靶向CD19的伊奈利珠单抗深度耗竭的效果在治疗后的3个月内尤为显著,几乎完全抑制了B细胞的再生,这表明伊奈利珠单抗在B细胞清除方面具有极高的效率,能有效地清除多种B细胞亚群,从而阻断B细胞介导的免疫反应[7]。同时,伊奈利珠单抗对B细胞再生的抑制作用并非永久性,治疗6个月后初始B细胞的数量开始显著增长,表明B细胞的再生能力逐渐恢复,这与国内外报道一致[35-37]。这一现象可能与B细胞前体细胞的代偿性增殖有关,同时也提示伊奈利珠单抗的长期疗效可能需要通过重复给药或联合其他治疗手段来维持。研究发现,尽管奥法妥木单抗治疗天疱疮初期显著降低了浆母细胞数量,但在治疗后的6个月内,其数量和比例出现了一定的波动,可能与浆母细胞的再生能力或药物作用的持续时间有关[38-39]。相反,伊奈利珠单抗治疗NMOSD后,浆母细胞数量和比例始终维持在较低水平,这一现象可能与伊奈利珠单抗对B细胞耗竭的彻底性及其对浆母细胞生成的长期抑制作用有关。值得一提的是,本研究将NMOSD患者在不同治疗周期的T6数据取平均值进行分析,重点关注药物靶点对免疫重建的整体影响,未来研究可进一步探讨周期间的重建差异。

奥法妥木单抗治疗期间的天疱疮患者在进行B细胞精细亚群监测时出现偏离群体趋势的B细胞重建模式,病例1在早期分别出现浆母细胞异常升高和初始B细胞异常增生,且伴随自身抗体(Dsg1或Dsg3)下降延迟,提示病情复发可能打破重建平衡。CD20靶向治疗手段通过清除自身反应性免疫细胞来控制疾病活动,但同时也会削弱机体的整体免疫防御能力,增加复发风险[40]。浆母细胞的增加可能与疾病进展呈正相关,其分泌的细胞因子在改变免疫稳态中发挥重要作用[41],而疾病进展引起的免疫应答进一步促进了B细胞的异常分化。病例2的临床表现揭示了免疫重建模式的复杂性。该病例虽呈现出快速的初始B细胞数量重建,但伴随持续高水平的Dsg1抗体及早期异常升高的记忆B细胞与浆母细胞,最终导致临床复发。已有研究表明B细胞亚群的比例与多种疾病活动性和治疗反应相关[42-43],本研究中的案例则表明初始B细胞的增殖速度并非良性重建的可靠指标,其功能属性更具决定性。该案例凸显了将B细胞亚群动态分型与自身抗体水平结合分析的价值,能够早期识别此类“高风险重建模式”,为临床干预提供关键窗口。而对于伊奈利珠治疗的NMOSD患者,本研究发现其在长期随访过程中几乎都保持了B细胞的清除效果,仅存在有限的B细胞再生。这一发现提示伊奈利珠单抗不仅通过清除B细胞直接抑制疾病活动,还可能通过调控B细胞再生的动态平衡,间接影响疾病的长期控制[37, 44]。其中病例3使用伊奈利珠单抗治疗后进行B细胞精细亚群监测,在第6个月复查时发现浆母细胞数量显著增高,可能提示浆母细胞的分化和功能并未完全被抑制,同时IgA水平的升高可能与浆母细胞向IgA分泌型浆细胞的分化有关,这提示伊奈利珠单抗对B细胞亚群的作用可能存在选择性,未能完全抑制所有抗体亚类的产生[8]。而病例3的B细胞亚群的比例发生了逆转,这一现象可能与B细胞再增殖和免疫重建过程中的异常调控有关。研究报道记忆B细胞高比例与NMOSD患者疾病复发密切相关,因其能够通过产生AQP4和激活T细胞,进一步加剧神经炎性反应[45]。

本研究存在一定局限性。由于随访数据的不平衡性,本研究未能采用更复杂的重复测量模型(如混合效应模型或广义估计方程)进行整体分析,而是采用了两两时间点的配对比较并进行了Bonferroni校正。这种策略虽然在一定程度上利用了配对信息并控制了多重比较误差,但无法同时分析所有时间点,且可能因样本量损失而降低检验效能。本研究结果为探索性分析,后续研究需在更大样本中采用完整随访设计以验证结论。

* * *

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