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生物制剂用于成人慢性原发免疫性血小板减少症的治疗进展

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摘 要: 原发免疫性血小板减少症(ITP)多以糖皮质激素和(或)静脉注射免疫球蛋白等一线治疗为主,但不少慢性ITP患者需二线或更高级药物治疗,如促血小板生成素受体激动剂、利妥昔单抗或联合药物治疗等。现发现新型药物如fostamatinib、新生儿Fc受体(FcRn)抑制剂及新一代促血小板生成素受体激动剂或对成人慢性ITP有较好的疗效。该文就生物制剂如何应用于成人慢性ITP的治疗作一综述。

关键词: 原发免疫性血小板减少症; 生物制剂; 促血小板生成素受体激动剂
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Biological agents in adult chronic primary immune thrombocytopenia

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Abstract: Primary immune thrombocytopenia (ITP) is generally treated with first-line therapy such as glucocorticoids and/or intravenous immunoglobulin. However, second-line or advanced drug therapies including thrombopoietin receptor agonists, rituximab or combination therapy are necessary for some patients with chronic ITP. It has been found that new drugs such as fostamatinib, neonatal Fc receptor (FcRn) inhibitors and new generation thrombopoietin receptor agonists may be effective in adult chronic ITP.This paper reviews the application of biologics in adult chronic ITP.

Key words: Primary immune thrombocytopenia; biologics; thrombopoietin receptor agonists

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原发免疫性血小板减少症（ITP）的治疗以减少血小板破坏及促进血小板生成为主要手段。糖皮质激素、利妥昔单抗（RTX）等可抑制抗血小板抗体的产生；新型药物fostamatinib及新生儿Fc受体（FcRn）抑制剂等通过减少Fc受体激活从而减少血小板破坏；血小板生成素受体激动剂（TPO-RAs）可以刺激巨核细胞分化成熟，增加血小板生成[1]。成人慢性ITP通常对一线药物治疗耐受，fostamatinib、FcRn抑制剂及新一代TPO-RAs等生物制剂或能弥补一线药物的不足，提高疗效及安全性。由于ITP复杂性、不稳定性及复发性等特点，其治疗暂未有统一共识，本文就生物制剂如何用于成人慢性ITP治疗作一综述。

1　减少血小板破坏的药物

1.1　RTX

RTX是一种可耗竭B淋巴细胞的嵌合单克隆抗CD20抗体，能够抑制B淋巴细胞产生自身抗体，减少血小板的破坏[2]。标准剂量（375 mg/m²，每周1次，连续4周）治疗慢性ITP患者，首剂治疗后第24周血小板计数高于50×10⁹/L的患者比例约为30.8%，且发生初步反应的患者中超过一半能获得长期缓解[3-4]。该药物初始总体反应率为54.0%~66.7%[5]。标准剂量RTX治疗的患者中年龄小于40岁的年轻女性获得总体缓解（73%）和完全缓解（56%）的概率更大，能够达到和维持反应接近脾切除术的治疗效果[6]。有研究发现小剂量（100 mg/m²，每周1次，持续4周）RTX治疗效果与标准剂量间无明显差别，且能减少药物副作用及降低成本，其初始总体反应率为52.0%~60.5%[7]。RTX起效时间较长，约5.5周的反应时间，并可能诱发低丙种球蛋白血症，增加出血、感染的风险，但通常可控制[2]。关于RTX长期随访的研究较少，慢性ITP患者使用RTX的介入时间及最佳剂量仍未确定，其长期疗效及安全性仍需进一步研究。

1.2　fostamatinib

fostamatinib是一种脾脏酪氨酸激酶（SYK）抑制剂，被用于对先前治疗反应不足的ITP。SYK途径通过Fc受体激活加速血小板的破坏，fostamatinib在肠道内经肠道碱性磷酸酶代谢为R406特异性抑制SYK依赖的Fc受体介导的信号转导，阻断B细胞受体介导的B淋巴细胞激活。剂量通常从100 mg，每天2次开始；如果持续1个月血小板计数未能升至50×10⁹/L，则将剂量加至150 mg，每天2次；如果治疗12周后血小板数量未上升至可避免出血水平时应停药[8]。在针对成人持续性或慢性ITP患者的两项多中心临床研究中，fostamatinib组稳定反应率为18%，安慰剂组仅为2%。在最初治疗12周内，fostamatinib组的总有效率也高于安慰剂组[9]。Bussel等[10]研究发现18%慢性ITP患者稳定缓解超过28个月，总体缓解率为44%，即使是经促血小板生成药物治疗失败的患者也有34%对fostamatinib总体反应良好。药物中位反应时间为15天，83%的患者在8周内有反应，常见的不良事件是腹泻、高血压、恶心、头晕、肝酶升高、中性粒细胞减少等，但多数可自发或通过药物治疗解决[11]。可见，fostamatinib对成人慢性ITP患者有良好的有效性及安全性。

1.3　FcRn抑制剂

1.3.1　Rozanolixizumab　Rozanolixizumab是一种皮下注射的人源化单克隆抗体，通过阻断IgG与FcRn的结合减少IgG循环，加速溶酶体的降解，最后降低IgG水平[12-13]。Rozanolixizumab在成人慢性ITP患者中表现出良好的安全性，血小板快速大幅升高与IgG显著降低相一致。一项临床研究按不同给药方式将入组患者分为多剂量及单剂量队列。多剂量队列为每周多次给药，分别为4 mg/kg×5 d，7 mg/kg×3 d或10 mg/kg×2 d，累积剂量为20 mg/kg或21 mg/kg；单剂量队列采用每周单次给药，每次输注15 mg/kg或20 mg/kg。实验结果显示，8周观察期内血小板计数≥50×10⁹/L多见于单剂量队列。单剂量队列患者的最低平均IgG水平和最高平均血小板计数均出现在第8天，而多剂量队列患者的最高血小板计数出现在第11天[14]。66例患者中有19例报告了与治疗相关的不良反应，包括头痛、呕吐和腹泻，反应强度都是轻中度[14]。由于该药临床数据较少，高剂量单次输注是否比低剂量多次输注更有优势仍需进一步研究。

1.3.2　Efgartigimod　Efgartigimod是一种人IgG1抗体Fc片段，在酸性和中性pH下与FcRn的亲和力胜过IgG，导致内源性IgG加速降解[15]。一项2期临床研究中，38名患者分别接受每周4次的安慰剂或Efgartigimod 5 mg/kg或10 mg/kg的静脉滴注，给药后3 d，Efgartigimod组患者IgG水平明显下降，安慰剂组患者的血清IgG水平无变化。血清IgG水平的降低与临床相关的血小板计数增加有关，治疗组的血小板计数平均值均高于对照组。Efgartigimod组出血患者的比例下降，但也出现部分与药物相关的轻中度的出血[16]。Efgartigimod靶向降低IgG是治疗成人慢性ITP的一种潜在的新疗法，长期疗效及安全性有待进一步评估。

2 促血小板生成的药物

2.1 Eltrombopag

Eltrombopag是一种口服非肽类TPO-RAs，通过刺激骨髓中巨核细胞的增殖和分化，使正常功能的血小板呈剂量依赖性增加。Eltrombopag可有效治疗成人慢性ITP，对既往治疗无反应的患者升血小板效果显著，需抢救患者比例较安慰剂组明显降低[17]。Eltrombopag的标准起始剂量为50 mg/d，如果2周内尚未见反应，则加至最大剂量75 mg/d[18]。亚洲患者对本药的药代有所不同，推荐剂量在慢性ITP患者为25 mg/d，急性期一线治疗也建议减低至标准剂量的50%。研究发现长期服用Eltrombopag可有效维持血小板计数>50×10^9/L或更高，可减少大多数持续时间超过6个月的ITP患者出血[19]，用药后可减轻疲劳，改善患者的身体机能[20]。值得注意的是，Eltrombopag治疗后血小板计数越高，发生副作用的可能性就越大[21]。常见副作用是转氨酶升高、血栓栓塞性事件，严重可导致白内障，但通过减少剂量、停药及常规眼科检查可减少事件发生[18]。在整个生命周期范围内使用马尔可夫模型估计每次治疗的收益和成本，发现Eltrombopag或比Romiplostim更具经济优势[22-23]。

2.2 Avatrombopag

多中心研究提示口服剂型Avatrombopag能提升慢性ITP的血小板计数，具有良好的耐受性，最常见不良事件是头痛和挫伤[24]。最近的研究发现，接受20 mg/d剂量Avatrombopag治疗的成人慢性ITP患者在第28天有效（血小板计数≥50×10^9/L）或完全有效（血小板计数≥100×10^9/L）的人数多于安慰剂组，且超过一半患者可减少或停用皮质类固醇[25]。该药具有副作用少、无肝毒性等优点，但缺乏长期安全性数据[26]。在进一步了解该药在成人慢性ITP患者中长期疗效及安全性的情况下，作为不受饮食限制的口服药物或许更能提高患者依从性从而维持患者的持续缓解状态。

2.3 Hetrombopag

国内多中心研究发现，7.5 mg/d持续2周可能是治疗成人慢性ITP较好的剂量。该剂量下66.7%患者在第28天血小板计数超过50×10^9/L，高于2.5 mg/d及5 mg/d的方案[27]。然而，另有研究发现8周治疗期内2.5 mg/d与5 mg/d组患者的疗效相当，在达到血小板计数应答(血小板计数≥50×10^9/L)的患者比例相似的情况下，2.5 mg/d组患者的血小板计数波动更小，可能2.5 mg/d起始剂量更适合中国患者[28]。该药最常见的不良反应是上呼吸道感染、尿路感染、免疫性血小板减少性紫癜和血尿，程度多是轻中度[28]。由于目前相关研究较少，最佳剂量、停药时机和长期疗效等仍需进一步研究。

2.4 Romiplostim

该药通过内源性TPO相同的方式结合到TPO受体的胞外区域促进血小板生成。慢性ITP患者稳定剂量（每周平均5~8 μg/kg），连续5年都可以保持疗效，有良好的耐受性，但亦存在副作用，如骨髓网织蛋白积聚和血栓形成，部分患者停药后可逆转[29]。Romiplostim治疗患者血小板反应率高，并可改善基线健康相关的生活质量，减少患者使用糖皮质激素的时间和剂量，但某些患者对每周皮下注射方式较抵触[30-31]。一项针对成人慢性ITP患者的荟萃分析发现Romiplostim在短期疗效和严重不良事件之间具有优于Eltrombopag的平衡[32]，且使用Romiplostim的慢性ITP患者费用更低，但在意向性治疗中Eltrombopag成本则更低[33-34]。

3 联合用药

3.1 RTX联合糖皮质激素

对于单一治疗难以诱导ITP获得缓解的患者，有学者提出利用不同作用机制或不同时间窗等药物联合治疗可能是一种潜在的有效治疗方案。如4次注射RTX联合3次4 d周期的地塞米松（4R+3Dex）治疗似比单独注射RTX或R+1Dex[2]有更高的长期应答率，且在女性患者中缓解率更高[35]。治疗持续时间小于2年的女性患者，4R+3Dex治疗缓解率与脾切除治疗相似[36]。小剂量RTX（100 mg，每周1次，连续4周）联合泼尼松，并且泼尼松减量维持治疗方法（60 mg/d逐渐减量至10 mg/d）可提高患者早期完全缓解率[37]。但此联合方案增加了临床试验毒性，随着浆细胞的持续抵抗和较低的IgG水平，10%的患者会出现低丙种球蛋白血症和感染，甚至可引起血清病[36]。还有学者发现早期慢性ITP患者中，Dex联合RTX、环孢素三重疗法能维持大部分患者血小板计数≥30×10^9/L，明显提高无治疗生存率，特别是存在治疗相关并发症的情况下[38]。

3.2 RTX联合促血小板生成药物

RTX起效时间较长，而TPO-RAs起效时间快但不能达到长期缓解。因此有研究者尝试将RTX联合TPO-RAs治疗慢性ITP。在慢性难治性ITP患者对激素及Eltrombopag单独治疗无效情况下，RTX与Eltrombopag联合治疗能够降低出患者的出血风险[39]。同样，小剂量RTX与重组人血小板生成素的联合应

用比单一RTX治疗的起效时间短，但两组的长期应答率差异没有统计学意义[40-41]。这种联合方案可提高完全缓解率、降低平均反应时间，为慢性ITP患者的治疗提供新思路。

3.3　RTX联合其他药物

成人持续性或慢性ITP患者在B细胞耗竭的初始阶段加入固定剂量RTX（1 000 mg，间隔2周静脉滴注，共12周）联合贝利木单抗10 mg/kg（12周内间断静脉滴注5次）治疗，80%患者获得了总体缓解，67%患者获得完全缓解，且没有观察到严重的不良事件、感染或严重的低丙种球蛋白血症；联合贝利木单抗治疗后循环T滤泡辅助细胞的数量较单用RTX显著减少[42]。

4　结语

由于ITP致病原因不明、发病机制复杂，对于原发性成人慢性ITP目前仍没有统一可行的治疗方案，在多数情况下需要RTX、TPO-RAs等药物治疗。近年SYK抑制剂、Fc受体抑制剂、新一代TPO-RAs等被证明对慢性ITP有良好效果，但其长期安全性及有效性仍缺乏数据支持，与现有常见的药物缺乏直接的对比。另外联合药物的治疗及各联合方案间的比较目前研究仍较少，且联合药物强调个性化治疗，因此成人慢性ITP的有效、具体及安全的生物制剂治疗方案仍需要进一步研究。

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