系统性红斑狼疮的诊治方向与研究前沿

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摘要 系统性红斑狼疮(systemic lupus erythematosus, SLE)是一种以多脏器受累及多种自身抗体阳性为主要特点的自身免疫性疾病, 多发于育龄期女性。全基因组关联研究、宏基因组研究、表观遗传学研究、单细胞测序、免疫代谢研究及多组学研究在SLE的发病机制研究中发挥着日益重要的作用。自身抗体在SLE的诊断和病情监测中起重要作用。目前临床研究和临床实践中最常应用的是2012年系统性红斑狼疮国际合作组制定的分类标准和2019年欧洲抗风湿病联盟/美国风湿病学会制定的分类标准。SLE的诊治应贯彻早期诊断、早期治疗的原则, 以实现尽快控制病情、减少器官损伤累积、改善患者的长期生活质量和提高长期存活率的目标。“达标治疗”理念的提出, 将进一步提高SLE的整体治疗水平, 但由于SLE疾病的高度异质性, 应在遵循规范治疗的前提下, 体现个体化。除常用的治疗药物如糖皮质激素、抗疟药、免疫抑制剂外, 以B细胞为靶向的生物制剂为SLE的治疗提供了新的选择, 将成为未来的发展方向。干细胞治疗也有着良好的应用前景。随着SLE患者预后的改善, 围妊娠期管理和早发动脉粥样硬化症的防治越来越受到风湿免疫科医师的重视。本文综述了近年来SLE的诊治方向和研究前沿, 以期风湿科医师和研究者提供参考。

关键词 系统性红斑狼疮, 流行病学, 发病机制, 诊断, 治疗方案, 研究进展

系统性红斑狼疮(systemic lupus erythematosus, SLE)是一种经典的系统性自身免疫性疾病, 以多脏器受累及多种自身抗体阳性为主要临床特点, 如果不及诊治或控制不佳, 将导致脏器的不可逆损害, 甚至导致死亡^[1,2]。SLE患病率地区差异较大, 全球约为0~241/10万, 北京协和医院张乃峥教授最早报道

了我国SLE患病率为40/10万^[3], 之后陆续报道的中国大陆地区的患病率约为30~70/10万^[4,5]。SLE多发于育龄期女性, 我国SLE患者的平均年龄约29岁, 男女比例约为1:10^[6]。随着风湿免疫学科的发展和诊疗水平的提高, SLE患者的生存率显著改善, 5年生存率从20世纪50年代的50%~60%提升到90年代的90%以

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上^[7], 我国SLE患者5年和10年生存率分别为94%和89%^[8].

早在20世纪90年代, 国际上开始相继建立了LUMINA, Hopkins, Toronto, GLADEL队列及系统性红斑狼疮国际合作组(Systemic Lupus International Collaborating Clinics, SLICC)队列, 在SLE的发病风险、临床表型、早期诊断、疾病评估和长期预后方面进行了大量研究. 以LUMINA队列为例, 从1998年至今已有79篇有关SLE的研究报道^[9,10]. 亚洲地区的SLE队列研究起步较晚, 2012年成立了亚太系统性红斑狼疮协作组(Asia Pacific Lupus Collaboration, APLC)^[11]. 值得欣喜的是, 中国系统性红斑狼疮研究协作组(Chinese SLE Treatment And Research Group, CSTAR)于2009年启动, 创建了国家级SLE注册数据库, 该数据库的数据质控、监测与数据评估体系已经相对完善, 已成为具有代表性的中国风湿免疫病研究平台^[6,12]. CSTAR利用此平台建立了覆盖全国的SLE患者队列, 初步摸清了我国SLE的临床特点, 已成为我国SLE研究的“基础设施”.

诚然, SLE作为最具挑战性的致死性风湿免疫病, 多年来得到国际上多领域、多学科的持续关注, 在队列研究的基础上, 临床诊治和转化研究方面突破不断. 本文综述了近年来SLE的诊治方向和研究前沿, 以供借鉴与思考.

1 系统性红斑狼疮的临床表现

1.1 狼疮肾炎

狼疮肾炎(lupus nephritis, LN)是SLE常见的重要脏器受累表现, SLE患者出现肾脏受累的比例约为50%^[6,13], 国内外报道相似. LN的主要临床表现包括蛋白尿、镜下血尿、管型尿和肾功能受损等. 如无禁忌, 推荐有LN表现的患者均应行肾穿刺活检^[14,15]. 根据肾脏病理表现, LN可分为I~VI型, 分别为轻微系膜病变性、系膜增殖性、局灶增殖性、弥漫增殖性、膜性及晚期硬化性, 特殊类型包括足细胞病和血栓性微血管病^[15~17], 同时根据肾脏病理还可进行病变活动性/慢性程度评分^[17].

抗dsDNA抗体、抗C1q抗体和补体水平对LN的诊断和病情活动度评估具有重要意义^[14], 已证实抗磷脂抗体阳性与LN的不良预后相关^[18]. 北京协和医院发表

的研究证实, 抗C1q抗体与LN的发病及病情活动相关, 其主要机制为促进补体C1q介导的免疫复合物及凋亡细胞与凋亡小体在肾脏组织中的沉积^[19,20].

SLICC队列1999~2012年的数据显示, LN患者进展为终末期肾病及死亡的风险明显升高^[21]. 北京协和医院的单中心回顾性分析显示, 2005年以前LN一直是中国SLE患者3个最常见的死因之一, 直到2006年才被肺动脉高压所取代^[22]. 尽管一项研究表明, 2005~2010年间LN缓解情况有所改善, 进展为终末期肾病的患者比例有所下降^[23], 但LN仍是SLE最不可忽视的脏器受累.

1.2 神经精神狼疮

神经精神狼疮(neuropsychiatric SLE, NPSLE)虽发病率远低于LN, 却是SLE的严重并发症. NPSLE的发病机制尚不明确, 可能是由脑血管、血脑屏障和脑实质损伤引起的. 自身抗体、细胞因子和补体激活等可能介导损伤, 导致中枢神经系统的局灶性或弥漫性病变^[24], 其中抗核糖体P蛋白抗体和抗磷脂抗体与NPSLE相关已成为共识^[25]. 在一些NPSLE患者中可以检测到抗N-甲基-D-天冬氨酸受体抗体^[26,27], 抗水通道蛋白4抗体与视神经脊髓炎的脱髓鞘病变相关^[28], 脑脊液中检测到抗微管相关蛋白2抗体则100%与中枢神经系统疾病相关^[29]. NPSLE的新型影像学检查包括核磁弥散张量成像、功能核磁和正电子发射断层显像等^[30].

1999年, 美国风湿病学会(American College of Rheumatology, ACR)定义了NPSLE的19种表现, 包括12种中枢神经系统表现和7种周围神经系统表现^[31], 亦有报道将NPSLE症状分为炎症诱发表现和血栓栓塞相关表现^[24]. 在NPSLE中, 脑血管事件和癫痫较为常见, 其次为严重认知功能障碍、精神症状和周围神经病变^[32]. CSTAR队列数据显示, 我国SLE患者神经系统受累的比例约为4.8%^[6]. 北京协和医院NPSLE队列数据显示, 抗核糖体P蛋白抗体阳性和高疾病活动度是NPSLE的危险因素, NPSLE降低SLE患者的生存率, 肾功能不全和高疾病活动度是此类患者预后不良的预测因素^[33]. 对SLE横贯性脊髓炎患者的分析发现, 疗效不佳者具有年龄较轻、更易出现发热、C反应蛋白更高、初期脊髓炎严重、长节段脊髓受累等特点^[34].

1.3 肺部及心血管受累

SLE患者肺部及心脏血管受累复杂多样, 其中肺部受累包括: (1) 肺实质病变; (2) 胸膜病变; (3) 肺血管病变, 包括肺动脉高压(pulmonary arterial hypertension, PAH)、肺血栓栓塞、肺血管炎、弥漫性肺泡出血等; (4) 皱缩肺综合征(shrinking lung syndrome)^[35]. 心脏血管受累包括: (1) 心包炎; (2) 心内膜炎, 可伴有瓣膜关闭不全和无菌性赘生物形成(libman-sacks心内膜炎); (3) 心肌炎, 可出现心脏收缩或舒张功能障碍及各种心律失常; (4) 血管病变, 可累及各级血管, 出现血管狭窄、闭塞、扩张和血管瘤.

PAH既属于肺部病变又属于血管病变, 起病隐匿, 临床表现缺乏特异性, 早期诊断困难, 是SLE的重要死亡原因之一^[8]. 2018年第6届世界肺高压大会将PAH的诊断界值从平均肺动脉压25 mmHg降至20 mmHg^[36], 这将有利于实现SLE相关PAH的早期诊断和治疗. PAH的危险分层研究是近几年重要的进展, 从2015年欧洲心脏病学会/欧洲呼吸学会颁布的肺高压诊治指南到2018年世界肺高压大会提出的简化版PAH危险分层, 以及美国REVEAL队列研究的危险分层公式, 均强调了应根据心功能分级、6分钟步行距离、血生化标志物和血流动力学等指标共同决定PAH预后的危险分层^[37-39]. 北京协和医院最近的研究证实了REVEAL预后模型在中国SLE-PAH队列中的有效性^[40]. 此外, 中国研究者还揭示了SLE相关PAH的临床异质性, 可能存在“血管炎”和“血管病”两种亚型, 需要不同的治疗策略并有不同转归^[41,42]. CSTAR开展了多项SLE-PAH相关研究, 发现SLE患者PAH患病率为3.89%; 相关危险因素为浆膜炎、抗U1核糖核蛋白抗体阳性及肺功能一氧化碳弥散率占预计值<70%; SLE-PAH患者的5年生存率为72.9%, 5年治疗达标率为62.7%, 确诊时存在浆膜炎、6分钟步行距离>380 m及心指数 $\geq 2.5 \text{ L min}^{-1} \text{ m}^{-2}$ 是患者达标的独立预测因素^[6,43-46]. 根据以上证据, CSTAR在国际上首次提出SLE-PAH的双重达标治疗策略, 并于2015年发布了《中国成人系统性红斑狼疮相关肺动脉高压诊治专家共识》^[47], 在国际PAH领域发出了中国声音.

1.4 血液系统受累

SLE血液系统受累十分常见. 来自CSTAR的数据

显示, 我国56%的SLE患者存在血液系统受累^[6], GLADEL队列报道拉丁美洲SLE患者中这一比例为66%^[48]. SLE累及血液系统可表现为白细胞降低、自身免疫性溶血性贫血、免疫性血小板减少、血栓性血小板减少性紫癜(thrombotic thrombocytopenic purpura, TTP)和巨噬细胞活化综合征(macrophage activation syndrome, MAS)等. LUMINA队列报道SLE患者早期出现血小板减少提示更高的疾病活动度和严重程度, 血小板减少是患者死亡的独立危险因素^[49]. CSTAR的数据显示, 血小板减少和白细胞减少与狼疮肾炎和高疾病活动度相关, 血小板减少症患者长期生存率明显降低, 长病程是此类患者死亡的独立危险因素^[50]. 以TTP为代表的血栓性微血管病也是SLE的严重并发症, 北京协和医院的一项研究比较了SLE-TTP与原发TTP的临床特征, 发现SLE-TTP相比原发TTP患者的肾脏受累较轻, 治疗反应和预后较好^[51]. MAS是一种危及生命的炎症风暴表现, 常继发于SLE, 由北京协和医院和北京大学人民医院牵头的一项多中心研究显示, SLE-MAS的发生与SLE原发病活动或感染相关, 死亡率为12.5%^[51]. SLE患者常出现抗磷脂抗体, 其中部分患者可继发抗磷脂综合征(anti-phospholipid syndrome, APS). CSTAR队列数据显示, 我国44%的SLE患者抗磷脂抗体阳性^[6]; 北京协和医院在国内率先报道了多种新型抗磷脂抗体在APS诊断中的价值^[52-54].

1.5 其他系统受累

除上述脏器外, SLE可累及全身所有系统, 其中皮肤黏膜、肌肉关节受累十分常见. CSTAR报道中国SLE患者颊部红斑、光过敏、口腔溃疡、关节炎的比例分别为47.9%, 25.0%, 22.1%和54.5%^[6]. 此外, 眼部、浆膜、消化系统受累也不少见. 基于CSTAR数据库的研究显示, 瘢痕性脱发在中国SLE患者中的患病率为7.8%, 积极的免疫抑制剂治疗有助于阻止其发生^[55]; 浆膜炎患者发生肾脏、肺部、血液系统受累和血清学活动的比例明显升高, SLEDAI评分更高, 应积极治疗^[56]. 北京协和医院对SLE消化系统受累的两种重要亚型——蛋白丢失性肠病(protein-losing enteropathy, PLE)和假性肠梗阻(intestinal pseudo-obstruction, IPO)进行了分析. 结果显示, PLE的发生率为0.9%, 抗SSA抗体阳性、低蛋白血症和高胆固醇血症是发生PLE的预测因素^[57]. 我国SLE患者IPO的发生率为1.96%, 其中

57.6%的患者以IPO为SLE的首发表现, 容易误诊; 肾病综合征、其他内脏平滑肌受累(肾盂输尿管扩张、胆管扩张)以及IPO作为首发症状时提示预后不良^[58], 而器官受累多、免疫抑制剂依从性差的患者更易复发^[59]。上海仁济医院建立并验证了以CT影像评分来评估SLE胃肠道受累的预后, 可能有助于今后的个体化治疗^[60]。此外, 研究发现, SLE合并原发性胆汁性胆管炎者罕见(0.27%), 此类SLE患者起病年龄高, 诊断更困难, 生存率更低, 3年生存率仅88.4%^[61]。

1.6 并发症及妊娠

如前所述, 近50年来SLE患者的预后得到了显著改善, 因此对影响长期生存和生活质量的合并症, 如早发动脉粥样硬化症、恶性肿瘤等的防治也纳入了SLE的治疗远期目标。2003年, 美国两项研究探讨了SLE患者早发动脉粥样硬化现象, 证实SLE患者出现动脉硬化的概率是健康对照人群的4.8倍和9.8倍^[62,63]。CSTAR数据显示, 发现SLE患者与同龄健康人群之间在作为动脉硬化早期预警指标之一的臂踝脉搏波传导速度上存在显著差异, 也进一步证实了上述现象^[64]。

育龄期女性作为SLE高发群体, 不可避免地会面临生育问题。新近研究发现, SLE患者的妊娠丢失率已随着诊治水平的提升较之前显著降低, 逐渐接近普通人群^[65]。一项荟萃分析共纳入1980~2009年间的37项研究, 共计1842例患者2751次妊娠, 活产率已上升至76.6%, 但早产率仍高达39.4%。其中母亲常见并发症包括狼疮复发(25.6%)、高血压(16.3%)、狼疮肾炎(16.1%)、子痫前期(7.6%)、子痫(0.8%)等, 胎儿常见并发症包括自然流产(16.0%)、死胎(3.6%)、新生儿死亡(2.5%)、宫内发育迟缓(12.7%)等, 显著高于普通人群^[66]。因此妊娠仍然是SLE患者和风湿免疫科医生面临的重要挑战。对CSTAR队列中992例SLE患者2026次妊娠的回顾性分析发现, SLE患者妊娠丢失的危险因素包括抗磷脂抗体阳性、抗SSA抗体阳性和血小板减少^[67]。为了能够实现SLE妊娠期最优管理, 中华医学会风湿病学分会联合国家风湿病数据中心, 于2015年发布了《中国系统性红斑狼疮患者围产期管理建议》^[68], 并于2021年3月在国家皮肤与免疫疾病临床医学研究中心的领导下, 成立了中国风湿免疫病相关生殖及妊娠研究委员会(Chinese Research Committee of Pregnancy and Reproduction in Autoimmune Rheu-

matic Diseases, CHOPARD), 重点关注风湿免疫病患者的生殖功能保护、妊娠期规范管理、子代健康等, 以推进规范诊治, 改善SLE妊娠患者的预后。

2 系统性红斑狼疮的诊断

自身抗体是SLE的重要血清标志, 可在SLE患者出现典型临床症状数年甚至10余年前检测到^[69], 对SLE的诊断和病情监测至关重要。SLE患者体内可检测到180余种自身抗体^[70], 其中多种抗体与SLE诊断和病情相关。自身抗体检测的标准化对于提高SLE诊断的准确性非常重要。自1957年首次采用间接免疫荧光法以冰冻组织为基质检测抗核抗体(anti-nuclear antibody, ANA)^[71]及1975年使用短膜虫为实验基质检测抗双链DNA(double strand DNA, ds-DNA)抗体^[72]以来, 已经历大量技术改进和检测流程标准化。ANA的检测抗原基质已由冰冻组织被敏感性和特异性更高的Hep-2细胞所取代。2014年, 欧洲自身免疫标准化促进会和自身抗体标准化委员会共同发表了抗核抗体检测流程及结果报告的国际建议^[73]。同年在第12届自身抗体和自身免疫国际研讨会期间, 提出了关于ANA荧光模型标准化分类命名的第一个国际共识^[74]。2016年, 北京协和医院联合国内该领域专家在国内首次详细解读了ANA荧光模型国际共识和检测结果报告方式的国际共识^[75], 并在此基础上结合我国国情和临床检测经验制定了《抗核抗体检测的临床应用专家共识》和《抗磷脂抗体检测的临床应用专家共识》^[76,77]。这些共识的制定大大促进了我国SLE相关自身抗体检测方法、结果判断及报告的规范化与标准化, 为临床提供规范可靠的检测结果。近年来, 已有诸多关于SLE新型诊断标志物的研究, 如血清Galectine-9、外泌体miRNA miR-21和miR-155、非编码RNA lnc-FOSB-1:1和TCONS_00483150等, 均显示出对SLE诊断的价值, 但还有待于进一步研究证实^[78-81]。

SLE是一个表现复杂、异质性很强的疾病, 至今还没有国际公认的SLE诊断标准(diagnostic criteria), 但已有多套成熟的分类标准(classification criteria)。这些分类标准不仅能够为临床研究中的患者分类, 为将一组具有共同特质的患者纳入研究起到重要的作用, 使临床研究结果更可靠, 增加研究结果的指导性, 而且能够为临床实践中的患者诊断提供重要的参照标准。

1971年, ACR的前身美国风湿病协会就发布了第一个SLE分类标准草案^[82], 1982年这一分类标准正式发布^[83], 1997年ACR对此标准进行了更新^[84]. 此标准共包括11条临床和免疫学标准, 满足4条者即可被分类为SLE. SLICC于2012年发布的SLE分类标准则包括11条临床标准和6条免疫学标准, 满足4条并至少有1条临床标准和1条免疫学标准者可被分类为SLE; 此外强调了肾脏病理的重要性, 如肾脏病理符合狼疮肾炎并有ANA或抗dsDNA抗体阳性, 也可被分类为SLE^[85]. 相比于1997年的标准, SLICC标准引入了病理作为重要的分类指标, 更加全面且具有更高的敏感性(94.6% vs. 89.6%)和相近的特异性(95.5% vs. 98.1%)^[86]. 2019年, 欧洲抗风湿病联盟(European League Against Rheumatism, EULAR)和ACR共同发布了新的SLE分类标准, 以ANA滴度 $\geq 1:80$ 作为准入标准, 准入后通过对共10类21条临床或免疫学标准进行评分, 每条项目评分为2~10分不等, 每类取最高一条得分计入总分, 如 ≥ 10 分则可被分类为SLE. 验证队列数据显示, 2019年、2012年、1997年SLE分类标准的敏感性分别为96.1%, 96.7%, 82.8%, 特异性分别为93.4%, 83.7%, 93.4%, 新标准的表现最优^[87,88]. SLE分类标准的发展体现了风湿科医师对这一疾病认识的进步、自身抗体检测技术的发展和早期诊断的理念, 基于此, 《2020中国系统性红斑狼疮诊疗指南》推荐使用2012年SLICC标准或2019年EULAR/ACR标准来协助诊断SLE^[89].

3 系统性红斑狼疮的治疗

3.1 治疗原则

SLE治疗方案应根据患者的临床表现、实验室检查、疾病活动度、脏器损伤、合并症、社会经济情况等进行个体化的制定, 并由患者与医生共同决策. 其中, 对疾病病情的正确评估是制定正确治疗方案的关键所在. 目前国际上有数十种SLE病情活动度评分系统, 其中系统性红斑狼疮疾病活动指数(Systemic Lupus Erythematosus Disease Activity Index, SLEDAI)^[90]和不列颠群岛狼疮评估组(British Isles Lupus Assessment Group, BILAG)疾病活动指数^[91]是最为常用的评分系统. SLICC损伤指数(SLICC Damage Index, SDI)是公认的SLE脏器损伤评分系统^[92].

在过去的十年中, 类风湿关节炎达标治疗取得的

成功, 促使SLE“达标治疗”理念的提出与发展. 达标治疗(treat-to-target, T2T)已经成为国际公认的SLE治疗理念, 其总体目标为通过控制疾病活动度及尽量减少并发症和药物毒性, 来实现长期生存, 防止器官损伤, 优化健康相关生活质量^[93]. EULAR在2019年更新的SLE管理推荐及《2020中国系统性红斑狼疮诊疗指南》均提出了“达标治疗”的理念. EULAR推荐明确提出SLE病情活动度目标为缓解或低疾病活动度^[94]. 中国指南则进一步细化了阶段目标, 即短期控制疾病活动、改善临床症状, 达到临床缓解或可达到的最低疾病活动度; 长期预防及减少复发, 减少药物不良反应, 预防并控制器官损害, 实现长期持续缓解, 降低病死率, 提高生活质量^[89]. 由于SLE的复杂性和异质性以及治疗的差异性, 导致达标治疗目前仍处于探索阶段, 其中的难点为确定达标治疗的“标准”. 虽然有国际组织提出了SLE的缓解定义(definitions of remission in SLE, DORIS)^[95]和低疾病活动度(lupus low disease activity state, LLDAS)的定义^[96], 但其实际可操作性还需进一步论证.

3.2 传统治疗

SLE的传统治疗药物包括糖皮质激素、抗疟药和免疫抑制剂等. 糖皮质激素是SLE治疗的基础用药. 《2020中国系统性红斑狼疮诊疗指南》指出, 应根据疾病活动度及受累器官的类型和严重程度制定个体化的糖皮质激素方案, 采用所需的最低剂量, 并在我国首次提出, 对于病情长期稳定者可考虑逐渐减停激素^[89].

抗疟药羟氯喹和氯喹是SLE的背景治疗药物, 能够提高SLE患者的生存率, 并有治疗轻症、预防复发、减少血栓栓塞事件、调节血脂代谢和减少母婴并发症的作用^[97]. 2019年EULAR治疗推荐和2020年中国SLE诊疗指南均建议对无禁忌患者应使用羟氯喹作为基础治疗^[89,94].

治疗SLE常用的免疫抑制剂包括环磷酰胺、霉酚酸酯、钙调蛋白酶抑制剂(环孢素、他克莫司)、硫唑嘌呤、甲氨蝶呤、来氟米特等, 需根据患者病情个体化地选择使用. 《2020中国系统性红斑狼疮诊疗指南》建议糖皮质激素联合羟氯喹治疗效果不佳或无法将激素剂量调整至相对安全剂量以下的患者应联合使用免疫抑制剂; 伴有脏器受累者建议初始治疗时即加用免疫抑制剂^[89]. 2019年EULAR和欧洲肾脏病学会-

欧洲透析与移植协会共同制定的狼疮肾炎管理推荐中建议III/IV型狼疮肾炎使用霉酚酸酯或低剂量静脉环磷酰胺进行诱导缓解, 霉酚酸酯联合钙调蛋白酶抑制剂可作为备选方案; 单纯V型狼疮肾炎则首选霉酚酸酯诱导缓解治疗; 狼疮肾炎的维持治疗建议使用霉酚酸酯或硫唑嘌呤^[14]。

基于一项为期52周的III期多中心RCT结果^[98], Voclosporin作为新型钙调蛋白酶抑制剂近期获得了美国食品和药品管理局批准, 成为美国首个获批用于治疗活动性狼疮肾炎的口服药物^[99]。在一项针对常规治疗效果不佳的SLE患者的II期临床研究中, 雷帕霉素作用靶点(或称哺乳动物雷帕霉素靶点)(mechanistic/mammalian target of rapamycin, mTOR)抑制剂西罗莫司治疗12个月的临床缓解率可达66%^[100]。西罗莫司治疗LN的长期预后研究也显示了其疗效和安全性良好^[101]。北京协和医院一项单臂开放标签研究显示, 西罗莫司在难治性SLE相关血小板减少症患者中的有效率为71.4%, 完全缓解率为64.3%^[102]。真实世界研究和荟萃分析也显示了西罗莫司在SLE治疗中的良好疗效和安全性^[103]。

3.3 靶向治疗

SLE治疗的重大进展为针对B细胞的靶向治疗。贝利尤单抗(Belimumab)作为B淋巴细胞刺激因子(B-lymphocyte stimulator, BLyS)抑制剂, 其有效性和安全性在两项III期RCT中得到了验证^[104,105]。北京协和医院作为牵头单位的贝利尤单抗东亚研究, 验证了该药物在中国SLE患者中的有效性和安全性^[106]。该药物在狼疮肾炎的III期RCT中也得到了明确的阳性结果^[107]。泰它西普(Telitacicept)是一种通过双重抑制BLyS和增殖诱导配体(A proliferation inducing ligand, APRIL)来抑制B细胞增殖的融合蛋白。北京协和医院作为牵头单位的IIb期RCT验证了其在高疾病活动度和血清学活动SLE患者中的有效性和安全性, 该药物已于2021年获批于中国上市, 在美国的II期研究也经FDA快速通道获批开展。同为BLyS/APRIL抑制剂的Atacicept也在临床试验中显示出了对SLE的疗效^[108,109]。利妥昔单抗(Rituximab)是一种抗CD20单克隆抗体, 在观察性研究中证实其对SLE和狼疮肾炎的治疗有益^[110,111], 但在RCT中未能达到研究主要终点^[112,113]。在Rituxilup研究中, 不使用口服糖皮质激素, 使用霉酚酸酯和利妥昔单

抗治疗狼疮肾炎, 90%的患者(45/50)在中位时间37周内获得部分或完全缓解^[114]。北京协和医院风湿免疫科应用小剂量利妥昔单抗治疗难治性SLE相关免疫性血小板减少症, 也观察到了明确的疗效^[115]。此外, 近期有应用抗CD38单克隆抗体达雷妥尤单抗(Daratumumab)成功治疗重症SLE的病例报道, 提示了这一药物在SLE中的应用前景^[116]。

Janus激酶(Janus kinase, JAK)通过JAK-STAT通路介导多种细胞因子的细胞内信号传导, 包括1型干扰素和多种白介素(IL-6, IL-12, IL-23等)^[117]。JAK抑制剂巴瑞替尼(Baricitinib)在一项II期RCT中被证实对SLE患者的关节炎治疗有效^[118]。北京协和医院应用JAK抑制剂托法替布(Tofacitinib)治疗SLE的真实世界研究证实该药物对SLE患者的皮疹和关节炎都有良好治疗效果^[119]。

此外, IL-12/IL-23抑制剂乌司奴单抗(Ustekinumab)、I型干扰素抑制剂Anifrolumab也都在临床试验中显示出了对于SLE的疗效, 有望成为治疗SLE的新药^[120,121]。

3.4 干细胞治疗

SLE发病机制中存在B细胞、T细胞功能与调节异常, 这些异常的T、B细胞来源于共同的淋巴祖细胞, 因此SLE也被认为是一种异常祖细胞增殖分化的多克隆疾病。对于传统治疗无效的难治性SLE, 通过干细胞移植(stem cell transplantation, SCT)清除自身反应性免疫记忆并重建免疫系统, 为SLE的治疗提供了新思路。自1997年首次应用自体造血干细胞移植以来, SCT已成为多种自身免疫性疾病的一种替代治疗并用于临床^[122]。北京协和医院早期一项针对18例SLE患者采用外周血造血干细胞移植(peripheral blood SCT, PBSCT)的研究显示在大剂量免疫抑制基础上联合PBSCT治疗重症难治性SLE相对安全且可行, 长达10年的随访显示可提高患者的存活率^[123,124]。有研究发现具有多能分化能力的间充质干细胞(mesenchymal stem cells, MSCs)也存在免疫调节功能^[125,126]。在一项动物模型研究中, 向狼疮模型小鼠输注不同剂量的同种异体MSCs后, 小鼠脾脏中CD3⁺CD4⁺CD8⁺T细胞和CD19⁺B细胞明显低于未治疗组, 且治疗组小鼠的脱毛、皮肤溃疡、蛋白尿、抗dsDNA水平均显著低于未治疗组^[127]。在针对81例难治性活动性狼疮肾炎患者的研究中, 应用同种异体骨髓MSCs后, 随访12个月, 有60%的患者

达到缓解^[128]。尽管SCT治疗SLE有一定的获益,但目前还缺乏强有力的证据支持SCT能作为SLE的常规治疗,需要更多研究、更长随访时间来验证。

4 系统性红斑狼疮的基础研究进展

SLE的经典病理生理机制包括凋亡细胞清除缺陷、中性粒细胞胞外捕获异常、I型干扰素通路异常激活、自身反应性T/B细胞过度活化以及免疫复合物形成激活补体等。随着测序、组学和生物信息技术的发展和微生物菌群、糖脂代谢、转录组学、单细胞研究技术的引入,深化了对SLE免疫病理机制的多层次认知和全景解析。

4.1 全基因组关联研究和表观遗传学

基因组测序和疾病关联分析发现了150多个SLE易感基因,与免疫识别、DNA损伤修复、细胞凋亡和耐受、免疫应答和I型干扰素通路等相关^[129,130],揭示了SLE复杂且异质性强的特点。表观遗传修饰,如DNA甲基化/去甲基化等通过影响T/B细胞的功能,参与SLE的发生和发展^[131~133]。

4.2 宏基因组研究

环境触发因素尤其是肠道菌群与易感基因及表观遗传之间的交互作用近年来成为SLE研究的热点。微生物菌群通过细菌组分或代谢物影响免疫系统的发育和调节,通过分子模拟激活自身反应性等^[134]。北京协和医院的研究发现SLE患者与健康人群的肠道菌群存在显著差异,某些富集菌与疾病活动度相关,功能分析提示细菌肽可能通过分子模拟促进SLE患者的免疫细胞释放促炎因子^[135]。

4.3 免疫代谢研究

T细胞线粒体代谢异常参与SLE中T细胞受体过度

活化和T细胞功能异常。SLE患者的T细胞糖酵解、谷氨酰胺代谢和糖源性氧化磷酸化增加,氧化应激,糖苷神经鞘脂增加等均可导致效应T细胞功能异常增强。通过调节代谢相关蛋白酶来改变T细胞代谢可改变Th17/Treg比例,在未来SLE治疗中可能有一定前景^[136]。

4.4 单细胞测序

单细胞测序技术的应用深化了我们对SLE脏器受累机制的理解。通过对狼疮肾炎患者肾脏组织的单细胞测序可发现在肾脏浸润的功能多样的免疫细胞亚群^[137]。研究发现,肾小管细胞呈现干扰素应答特征,并与组织学慢性病变指数相关^[138]。此外,有研究发现肾脏浸润的免疫细胞有21个活化亚群,分别参与促炎或抑炎过程^[139]。

4.5 多组学研究

多组学技术通过综合基因组、转录组、蛋白组、代谢组及宏基因组学等数据,整合分析机体内相互动态关联的生物学反应。该技术未来也有助于构建SLE免疫应答全景模式,成为揭示SLE奥秘的有力工具^[140]。

5 总结与展望

尽管近年来系统性红斑狼疮的诊断与治疗水平取得了长足的进步,但SLE仍然是一种预后不良、严重危害患者健康的疾病。在SLE的发病机制、临床表现异质性、精确诊断、个体化治疗、减少药物毒性、预防长期损伤等方面仍有许多亟待临床医生和研究者解决的问题。多组学研究、转化医学、大数据队列和精准医学将是今后发病机制及诊治方面研究的重要手段。跨学科、跨地区、跨国合作将为促进基础及临床研究、推进疾病规范化诊治提供广阔的合作和交流平台。

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Diagnosis and treatment directions and research frontiers of systemic lupus erythematosus

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Abstract: Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by multi-system involvement and multiple autoantibodies. It mainly occurs in women of childbearing age. Genome-wide association study, metagenomics, epigenetics, single-cell sequencing, immunometabolic study, and multi-omics study are playing an increasingly important role in the pathogenesis research of SLE. Autoantibodies are critical in the diagnosis and disease monitoring of SLE. The 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria and the 2019 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria are most commonly used criteria in clinical research and practice. Early diagnosis and early treatment of SLE are the principles that should be followed to promptly control the disease, prevent organ damage accrual, improve long-term quality of life, and prolong survival. The “treat-to-target (T2T)” concept will help improve the treatment of SLE. However, due to the great heterogeneity of the disease, treatment should be individualized under the premise of following the T2T concept. In addition to commonly used medications for SLE such as glucocorticoids, antimalarials, and immunosuppressants, biologic agents targeting B cells provide new therapeutic choices, and will become a future direction of SLE treatment. Stem cell therapy also has a good application prospect. With the improvement of SLE prognosis, rheumatologists are paying more attention to perinatal management and prevention of early atherosclerosis. This paper reviews the diagnosis and treatment directions and research frontiers of SLE in recent years to provide reference for rheumatologists and researchers.

systemic lupus erythematosus, epidemiology, pathogenesis, diagnosis, therapeutic regimen, research advance

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