·标准与讨论·

2024 中国类风湿关节炎诊疗指南

国家皮肤与免疫疾病临床医学研究中心(北京协和医院)　中国医师协会风湿免疫专科医师分会　中国康复医学会风湿免疫病康复专业委员会　中国研究型医院学会风湿免疫专业委员会　北京整合医学学会风湿免疫分会

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【摘要】 类风湿关节炎(RA)是一种以侵蚀性关节炎为主要临床特征的自身免疫病,是我国人群致残的重要原因。制订和更新符合国际指南制订标准又贴近我国临床实践的RA诊疗指南具有重要意义。由国家皮肤与免疫疾病临床医学研究中心组织发起,联合中国医师协会风湿免疫专科医师分会、中国康复医学会风湿免疫病康复专业委员会、中国研究型医院学会风湿免疫专业委员会和北京整合医学学会风湿免疫分会,采用推荐意见分级评估、制订及评价(GRADE)分级体系和国际实践指南报告标准(RIGHT),对《2018 中国类风湿关节炎诊疗指南》进行更新,就我国风湿免疫科医师关注的10个临床问题,给出了循证推荐,形成了本指南,旨在整体提高我国RA的诊治水平和治疗规范度,提高患者的生活质量,改善患者预后。

【关键词】 关节炎,类风湿;　诊断;　治疗;　指南

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2024 Chinese guidelines for the diagnosis and treatment of rheumatoid arthritis

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【Abstract】 Rheumatoid arthritis(RA) is an autoimmune disease characterized by erosive arthritis, which is an important cause of disability in Chinese population. It is of great significance to

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formulate and update RA diagnosis and treatment guidelines that meet the standards of international guidelines and clinical practice in China. The update of the Chinese guidelines for the diagnosis and treatment of RA was initiated by National Clinical Research Center for Dermatologic and Immunologic Diseases, jointly with the Chinese Association of Rheumatology and Immunology Physicians, the Rheumatology and Immunology Professional Committee of Chinese Rehabilitation Medical Association, the Rheumatology and Immunology Professional Committee of Chinese Research Hospital Association, and the Rheumatology and Immunology Branch of Beijing Association of Holistic Integrative Medicine. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and the Reporting Items for Practice Guidelines in Healthcare (RIGHT) checklist were followed to update the guidelines. The guidelines provide evidence-based recommendations on 10 clinical issues which were concerned by Chinese rheumatologists. The aim is to improve the level of diagnosis and standard treatment of RA in China, and to improve the quality of life and prognosis of patients.

【**Key words**】 Arthritis, rheumatoid; Diagnosis; Treatment; Guideline

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类风湿关节炎(rheumatoid arthritis, RA)是一种以侵蚀性关节炎为主要临床表现的自身免疫病,发病高峰年龄为45~60岁,但可发生于任何年龄[1]。流行病学调查显示,RA的全球发病率为0.5%~1%[1],我国大陆地区发病率为0.42%,据此估测,我国目前有RA患者超过500万人[2],男女患病比率约为1∶4[3-4]。虽然RA的病因与发病机制目前尚未完全阐明,但已明确其基本病理改变为滑膜炎、血管翳形成,并逐渐造成关节软骨和骨破坏,最终导致关节畸形和功能丧失[5]。RA是一种高致残性疾病,是造成我国人群残疾的重要原因,且随着病程延长,RA患者的残疾率不断上升[6-7]。除此之外,RA亦可并发肺部和心脑血管疾病、骨质疏松及恶性肿瘤等[8-10],不仅造成患者身体机能、生活质量和社会参与度下降,亦给其家庭和社会带来巨大的经济负担[11-12]。

近年来,美国风湿病学会(ACR)、欧洲风湿病学会联盟(EULAR)、亚太风湿病学会联盟(APLAR)等多个国际风湿病学术组织分别更新了各自的RA诊疗指南或推荐意见[13-15],中华医学会风湿病学分会亦于2018年更新了RA诊疗指南[16]。然而,随着RA的治疗药物不断更新,越来越多的新药在我国获批上市,而国外风湿科医师关注的临床诊疗问题和用药习惯与我国风湿科医师有所不同,我国医院的风湿免疫科人才培养、专科设置及患者就医情况与国外亦存在明显差异。因此,修订更新我国的RA临床诊疗指南,对提高风湿免疫科、内科、骨科等从事RA相关诊疗的临床医师,特别是基层医疗机构医师正确诊断和治疗RA的能力、加强患者教育、提高我国RA诊疗水平将起到至关重要的作用。鉴于此,国家皮肤与免疫疾病临床医学研究中心(National Clinical Research Center for Dermatologic and Immunologic Diseases, NCRC-DID)(北京协和医院)组织发起,联合中国医师协会风湿免疫专科医师分会、中国康复医学会风湿免疫病康复专业委员会、中国研究型医院学会风湿免疫专业委员会及北京整合医学学会风湿免疫分会,按照循证临床实践指南制订的方法和步骤,基于当前的最佳证据,结合临床医师的经验,结合我国患者的偏好与价值观,平衡干预措施的利与弊,对《2018中国类风湿关节炎诊疗指南》进行更新修订,形成了本指南。

指南形成方法

1. 指南发起机构与专家组成员:本指南由国家皮肤与免疫疾病临床医学研究中心(北京协和医院)撰写发起。启动时间为2023年6月9日,定稿时间为2024年3月7日。

2. 指南工作组:本指南成立了多学科专家组,主要由风湿免疫科、循证医学等学科专家组成。工作组包含共识专家组和证据评价组,共识专家组参加德尔菲共识调查,主要负责对推荐意见提出修改建议,以及审阅指南终稿;证据评价组主要负责检索、筛选和评价证据,撰写推荐意见总结,形成指南初稿。所有工作组成员均申明,不存在与本指南直

接或间接相关的利益冲突。

3. 指南注册与计划书撰写：本指南已于2023年7月12日在国际实践指南注册平台[17]（Practice guideline REgistration for transPAREncy，PREPARE）进行注册，注册号为PREPARE-2023CN490。本指南是对《2018中国类风湿关节炎诊疗指南》[16]的更新，更新方法主要参考国际指南更新手册[18]、2014年世界卫生组织发布的《世界卫生组织指南制定手册》[19]、2022年中华医学会发布的《中国制订/修订临床诊疗指南的指导原则（2022版）》[20]，并参考卫生保健实践指南的报告规范（Reporting Items for Practice Guidelines in Healthcare，RIGHT）[21]和指南更新的报告清单[22]进行指南撰写。

4. 指南使用者与应用目标人群：本指南供风湿免疫科医师、骨科医师、全科医师、临床药师、影像诊断医师及与RA诊疗和管理相关的专业人员使用。本指南推荐意见的应用目标人群为RA患者。

5. 临床问题的遴选和确定：基于《2018中国类风湿关节炎诊疗指南》[16]的临床问题，邀请67位专家，重新进行问题收集和扩展，经专家组讨论，最终遴选出本指南拟解决的10个临床问题。

6. 证据检索：证据评价组针对最终纳入的临床问题和结局指标，按照人群、干预、对照和结局（Population，Intervention，Comparison and Outcome，PICO）的原则对其进行解构，并根据解构的问题进行检索。（1）PubMed、Cochrane Library、中国知网数据库、中国生物医学文献数据库，主要纳入系统评价、Meta分析和网状Meta分析、随机对照试验、队列研究、病例对照研究、病例系列、流行病学调查等原始研究，检索时间为2018年1月1日至2023年12月31日；（2）英国国家卫生与临床优化研究所（NICE）、ACR、EULAR和APLAR等官方网站，以及MEDLINE和中国知网数据库，主要检索RA领域相关指南与共识；（3）补充检索Google学术等网站。

7. 证据的评价与分级：证据评价组运用系统评价偏倚风险评价工具[23]（A Measurement Tool to Assess systematic Reviews，AMSTAR）对纳入的系统评价、Meta分析和网状Meta分析进行偏倚风险评价。使用Cochrane偏倚风险评价工具[24]（Risk of Bias，ROB；针对随机对照试验研究）、诊断准确性研究的质量评价工具[25]（Quality Assessment of Diagnostic Accuracy Studies，QUADAS-2；针对诊断准确性试验研究）、纽卡斯尔-渥太华量表[26]（Newcastle-Ottawa Scale，NOS；针对观察性研究）等对相应类型的原始研究进行方法学质量评价。评价过程由两人独立完成，若存在分歧，则共同讨论或咨询第三方解决。使用推荐意见分级的评估、制订及评价（Grading of Recommendations Assessment，Development and Evaluation，GRADE）方法对证据体和推荐意见进行分级[27-30]，见表1。

表1　证据质量与推荐强度分级

项目	内容
证据质量分级	
高（A）	非常有把握：观察值接近真实值
中（B）	对观察值有中等把握：观察值有可能接近真实值，但亦有可能差别很大
低（C）	对观察值的把握有限：观察值可能与真实值有很大差别
极低（D）	对观察值几乎无把握：观察值与真实值可能有极大差别
推荐强度分级	
强（1）	明确显示干预措施利大于弊或弊大于利
弱（2）	利弊不确定或无论质量高低的证据均显示利弊相当

8. 推荐意见的形成：专家组基于证据评价组提供的国内外证据汇总表，同时结合我国患者的偏好与价值观、干预措施的成本和利弊后，提出了符合我国临床诊疗实践的推荐意见，分别于2024年1月19日和29日进行两轮德尔菲推荐意见调查，共收集116条反馈建议，进行共识及进一步修改，于2024年3月7日召开定稿会后确定指南终稿。

9. 指南的更新：计划在5年内对本指南的推荐意见进行更新，按照国际指南更新要求的方法进行[22]。

指南推荐意见

推荐意见1：RA的早期诊断对治疗和预后影响重大，临床医师应结合患者的临床表现、实验室检查、影像学检查做出诊断（1A）；建议参照1987年ACR发布的RA分类标准与2010年ACR/EULAR发布的RA分类标准进行诊断（2B）

RA的诊断需结合患者的临床表现、实验室检查、影像学检查结果。越来越多的证据表明，早期诊断和尽早开始治疗可减少RA患者关节损伤，降低致残发生率，改善患者预后[31-34]。目前国际上主要有两种分类标准可参考用于RA的诊断。1987年ACR发布的RA分类标准对识别早期RA有

一定的局限性[35-37]，2010 年 ACR/EULAR 发布的 RA 分类标准能在出现滑膜炎的炎性关节病中筛选出早期 RA，从而使患者能够早期获得诊断，早期开始使用改善病情抗风湿药物（DMARD）治疗，有效延缓疾病进展[34-35, 38]。大量研究显示，与 1987 年 ACR 发布的 RA 分类标准比，2010 年 ACR/EULAR 发布的 RA 分类标准对早期 RA 的诊断敏感性更高（72.3% 比 39.1%），尤其对老年 RA 患者[34, 38-39]，但对血清学阴性，即类风湿因子（RF）和抗瓜氨酸肽抗体（ACPA）均阴性的 RA 患者的诊断敏感性则较 1987 年 ACR 发布的 RA 分类标准低[40-41]，而影像学检查如关节超声、磁共振成像（MRI）可用于辅助诊断此类患者。2010 年 ACR/EULAR 发布的 RA 分类标准的特异性较 1987 年 ACR 发布的 RA 分类标准低（83.2% 比 92.4%），尤其是在老年 RA 患者中，而 1987 年 ACR 发布的 RA 年分类标准对 RA 特征性的骨侵蚀预测能力更佳[39]。如果将 2010 年 ACR/EULAR 发布的 RA 分类标准用于所有关节痛患者，可能会将部分非特异性关节炎患者误诊为 RA[34]。

综上，RA 的诊断应结合患者的临床表现、实验室检查、影像学检查，1987 年和 2010 年的 RA 分类标准对诊断 RA 各有优势，临床医师可同时参考 1987 年和 2010 年的 RA 分类标准对 RA 进行准确诊断。早期诊断 RA 有利于早期干预，延缓疾病进展。

推荐意见 2：建议临床医师根据 RA 患者的症状和体征，恰当选用 X 线、超声、CT 和磁共振成像等影像学检查（2B）

影像学检查是临床医师诊断和评估 RA 的有效手段。各种影像技术对 RA 的诊断和疾病监测价值及优劣见表 2。2013 年 EULAR 发布的针对 RA 选择影像学检查的循证医学建议、2018 年我国发布的 RA 诊疗指南均对临床医师选择 RA 的影像学检查提出了指导建议[16, 42]。考虑不同地区的影像设备和技术条件等差异，建议临床医师根据实际情况，选择合适的影像学检查[42-47]。

推荐意见 3：RA 的治疗原则为早期、规范治疗，定期监测与随访（1A）；RA 的治疗目标是达到疾病缓解或低疾病活动度，最终目标为控制病情，减少致残率，提高患者的生活质量（1B）

RA 的关节病变以炎性细胞浸润及其释放的炎性介质所致的滑膜炎症为发病基础，因此，尽早抑

表 2 影像学检查在类风湿关节炎（RA）诊断和随诊中的价值

影像学检查	适用情况	优势	劣势
X 线	（1）X 线是最常用的影像学工具； （2）病程小于半年的 RA 患者常规 X 线表现可能是正常的[42]	（1）成本低； （2）易获取	（1）三维病变的二维表现； （2）存在电离辐射； （3）对早期骨损害的检测敏感度低
超声	（1）可比临床查体和 X 线更早发现组织炎症，辅助诊断 RA[42-43]； （2）早期 RA，超声下腱鞘炎和滑膜炎的表现能辅助评估和预测影像学进展，但不能预测治疗效果[44]； （3）可用于疾病复发的评估和监测[43]； （4）可用于指导关节穿刺及治疗[42]	（1）成本居中； （2）无电离辐射； （3）检测早期炎症和结构损伤； （4）可用于复发监测	（1）操作者依赖性强； （2）对深部关节的检测能力较差
CT	对大关节病变及合并肺部疾病的检测有一定价值，但无法检测活动性炎症，如滑膜炎、腱鞘炎等[42, 45]	可用于大关节的骨侵蚀病变及合并肺部病变的监测	（1）成本较高； （2）电离辐射量较大； （3）无法检测活动性炎症
磁共振成像	（1）MRI 是检测早期 RA 病变最敏感的影像学检查。可在早期发现骨水肿、滑膜增厚、骨侵蚀等变化[42]； （2）可检测到早期炎症，有助于预测未分化关节炎是否会进展为 RA[42]； （3）虽然骨髓水肿可以预测影像学进展，但不能预测疗效[44, 46]； （4）MRI 可用来评估临床症状改善后的持续性炎症，但不推荐使用 MRI 的影像学改变联合达标治疗策略指导治疗[46]	（1）敏感度高； （2）无电离辐射； （3）对深部或复杂关节的检测敏感度高	（1）成本高； （2）设备可及性有限； （3）检查时间长； （4）每次检查仅限于 1 个部位
特殊影像学检查	（1）正电子发射计算机断层显像（PET/CT）可发现关节和组织的炎症性病变，有利于鉴别关节炎相关疾病[47]； （2）PET/CT 的变化与 RA 疾病活动度相关，但不能作为常规评估监测手段[47]	既能评估全身多处关节组织炎症，亦能对炎症水平进行半定量分析	（1）成本很高； （2）电离辐射量大； （3）设备可及性有限； （4）检查时间长

制炎性因子的产生及其作用，控制滑膜炎症能有效阻止或减缓关节滑膜及软骨病变[48]，故RA一经确诊，应及时给予规范治疗[49]。研究显示，DMARD使用不规范是导致RA患者关节功能受限的独立危险因素之一[6]。

尽管RA无法根治，但通过达标（treat-to-target）治疗可有效缓解症状和控制病情[50]。达标治疗指疾病达到临床缓解或低疾病活动度，目前临床缓解定义为28个关节疾病活动度（DAS28）≤2.6，或临床疾病活动指数（CDAI）≤2.8，或简化疾病活动指数（SDAI）≤3.3；低疾病活动度定义为DAS28≤3.2或CDAI≤10或SDAI≤11。但基于评估工具进行疾病活动度评价亦存在一定局限性，有研究显示，有关节肿胀的RA患者即使DAS28≤2.6，仍会发生进一步的关节损害[51]。2011年，ACR和EULAR推出Boolean缓解标准，即压痛关节数、肿胀关节数、C反应蛋白（CRP）水平及患者对疾病的整体评价≤1[52]，由于其特异度较高，便于评价和记忆，因此已逐渐在临床实践中应用。然而，原Boolean标准达标率较低[53]，且有研究发现该标准会高估疾病的严重程度，高于实际滑膜炎程度[54-55]，因此，2023年ACR和EULAR推出更新版Boolean缓解标准（Boolean2.0标准），与2011年Boolean缓解标准比，主要更新点为将患者对疾病的整体评价值从≤1改为≤2[56]。此外需注意，使用生物DMARD（bDMARD）或靶向合成DMARD（tsDMARD）的RA患者，使用包含急性期炎症指标（ESR或CRP）的复合病情活动指标（如DAS28或SDAI）评价疗效时，疗效可能被高估[57]。因此，临床医师应根据实际情况选择恰当的评估标准。

推荐意见4：对初始治疗或治疗未达标的RA患者，建议每1~3个月进行一次疾病活动度评估（2B）；对已达标的RA患者，建议每3~6个月进行一次疾病活动度评估（2B）

一项系统评价评估了22项RA治疗指南，其中18项指南建议使用各种临床评估方法对RA进行定期评估[58]。一项RA患者达标治疗的真实世界队列研究发现，每3个月评估一次RA疾病活动性，且持续采用达标治疗策略，可提高RA患者的缓解率[59]。一项对比RA患者强化管理与常规管理效果的随机对照试验（RCT）结果显示，每个月评估1次RA患者疾病活动度并调整用药，与每3个月评估1次RA疾病活动度比，可以获得更好的治疗反应[60]。对初始治疗的RA患者，考虑到DMARD起效时间长及不良反应的发生，建议每个月对RA疾病活动度评估1次；对治疗已达标者，可将评估频率调整为每3~6个月1次。

推荐意见5：RA患者治疗方案的选择应综合考虑疾病活动度及预后不良因素，同时兼顾关节外受累情况及合并疾病（1B）

RA患者疾病活动度及预后不良因素评估是临床医师调整治疗方案和选择相应药物的依据，在RA治疗中具有重要意义。如前所述，包含肿胀关节数、压痛关节数、ESR、CRP等指标的复合指数如DAS28、SDAI、CDAI，可较为准确地反映RA疾病活动度，为制定治疗目标及治疗方案的选择与调整提供依据。此外，多项RA患者关节损害的预后研究及预后预测模型显示，除疾病活动度外，RF和ACPA亦是关节损害进展的重要预测因素[61-63]，但需注意其与RA疾病活动度并无直接关系，不应将RF和ACPA滴度降低作为治疗RA的目标。RA疾病活动度及预后不良因素可协助医师确定最佳治疗方案。

此外RA患者，特别是病程长、病情控制不佳者可出现关节外组织器官受累，包括类风湿结节、肺间质病变、胸膜炎、心包炎、血管炎、周围神经病变、角膜炎、巩膜炎、Felty综合征等[8]。合并关节外受累的RA患者并发症更多，预后更差，特别是肺间质病变严重影响RA患者的预后[8, 64-66]。

研究表明，与一般人群比，RA患者发生心脑血管疾病[67-69]、骨质疏松与脆性骨折[70]、肌少症[71-72]、恶性肿瘤[73]和结核感染[74]等的风险增加。合并这些疾病亦会对RA患者的疾病活动度、关节损害进展、治疗方案等产生不良影响[8, 75-76]。

因此，临床医师应全面了解RA患者的病情，对RA疾病活动度、预后不良因素、关节外受累及合并疾病进行充分评估和定期监测，合理制订和调整用药方案。

推荐意见6：RA一经确诊，应尽早开始传统合成DMARD（csDMARD）治疗（1A）；推荐甲氨蝶呤单药作为初始治疗的首选药物，当存在甲氨蝶呤禁忌或不耐受时，应选择其他传统合成DMARD（1B）

RA一经确诊，应尽早开始csDMARD治疗，有利于缓解临床症状、延缓影像学进展、改善患者预后。目前国际各大RA指南均推荐甲氨蝶呤单药作为RA初始治疗的首选药物[13-15]。甲氨蝶呤治疗RA的口服剂量通常为7.5~20 mg/周，并应根据病

情、治疗效果及不良反应及时调整剂量[77-78]。在甲氨蝶呤治疗时建议每周补充叶酸5 mg以减少不良反应[79-80]。当存在甲氨蝶呤禁忌或不耐受时，建议使用柳氮磺吡啶或来氟米特[14, 81-84]。柳氮磺吡啶的推荐剂量为每日3 g。来氟米特的推荐剂量为每日20 mg。常用于治疗RA的csDMARD的作用机制、常用剂量与常见不良反应见表3。

目前尚无足够证据支持将bDMARD或tsDMARD作为RA的一线治疗药物。现有的绝大多数证据为csDMARD治疗RA的效果不佳或不耐受后方联合使用bDMARD/tsDMARD。虽有研究表明，未经甲氨蝶呤治疗的RA患者，使用甲氨蝶呤联合生物制剂治疗的疗效优于甲氨蝶呤单药治疗，但并无充分证据证明生物制剂单药不联合甲氨蝶呤优于甲氨蝶呤单药[85-86]。综合考虑药物的疗效、不良反应、经济性、应用便利性，并结合我国风湿免疫科医师的经验，目前仍推荐以甲氨蝶呤为首选的csDMARD作为我国初治RA患者的一线治疗药物。

推荐意见7：csDMARD初始治疗RA或改变csDMARD方案时，可根据疾病活动度短期联合小剂量糖皮质激素（2B）；治疗过程中密切监测其相关不良反应，不推荐糖皮质激素单用、长期或大剂量使用（1A）

糖皮质激素具有高效的抗炎作用，可用于抑制RA的急性炎症。大量研究证据表明，在csDMARD治疗的基础上短期联合小剂量糖皮质激素可改善活动性RA患者的疼痛症状，缩短晨僵时间，减少肿胀和压痛关节数，改善身体机能，提高患者生活质量，提高医师和患者对疾病的整体评分[87-89]。但糖皮质激素无法阻止或延缓RA的关节侵蚀，故不应单独应用，且由于糖皮质激素可增加感染、心脑血管疾病、骨质疏松等多种并发症的风险[90-92]，故不推荐长期或大剂量使用。糖皮质激素治疗RA的剂量不应超过泼尼松10 mg或其等效剂量糖皮质激素，并应尽早减停，应用时间最长不应超过6个月。而对使用bMDARD/tsDMARD的RA患者，目前多认为不需要继续应用糖皮质激素。EULAR发布的RA管理推荐建议，一旦启用bDMARD/tsDMARD治疗，应尽快停用糖皮质激素[14]。非甾体抗炎药（NSAIDs）可用于改善RA患者的疼痛症状，但使用时需注意其心血管和消化道不良反应的风险[90, 93]，特别是老年RA患者及有相关基础疾病的RA患者。

推荐意见8：单一csDMARD治疗3个月无临床改善或6个月未达到治疗目标，应调整csDMARD治疗药物，可更换或联合其他csDMARD，或使用一种csDMARD联合一种bDMARD/tsDMARD进行RA的治疗（2B）

经甲氨蝶呤、柳氮磺吡啶或来氟米特等csDMARD单药规范治疗效果不佳的RA患者，应及时对DMARD治疗方案做出调整。一般认为，RA患者治疗3个月未达到疾病缓解或低疾病活动度且复合疾病活动度指数改善不足50%，或治疗6个月仍未达到缓解或低疾病活动度时均定义为疗效不佳，应使用二线治疗药物。RA二线治疗优先选择更换或联合csDMARD，抑或加用bDMARD或tsDMARD，目前尚无足够的临床研究证据明确前述两种治疗策略的优劣。有限的RCT显示，更换/联合csDMARD与加用bDMARD/tsDMARD的差异并不显著[94]。尽管EULAR发布的RA治疗推荐和ACR发布的RA治疗指南中有条件地推荐，RA在某些情况下优先加用bDMARD或tsDMARD，但

表3 治疗类风湿关节炎常用的传统合成改善病情抗风湿药

药物	作用机制	给药途径	常用剂量	常见不良反应
甲氨蝶呤	抑制叶酸代谢	口服、肌肉注射、静脉给药	7.5~20 mg/周	胃肠道反应，肝功能损伤，口炎，脱发，皮疹，偶见骨髓抑制，罕见药物性肺炎
柳氮磺吡啶	5-氨基水杨酸抑制前列腺素、白三烯合成及中性粒细胞功能	口服	2~6 g/d，分2~4次口服	过敏反应（磺胺类抗菌药物过敏者不宜使用），偶见胃肠道反应、骨髓抑制
来氟米特	抑制嘧啶合成	口服	10~20 mg/d，顿服	肝功能损伤，胃肠道反应，偶见脱发、皮疹，罕见药物性肺炎
羟氯喹	稳定溶酶体膜，抑制多种酶活性，抑制前列腺和白细胞介素1合成，抑制中性粒细胞	口服	0.2~0.4 g/d，分1~3次口服	过敏反应，眼底病变
雷公藤多苷	多种免疫抑制及抗炎作用，作用机制尚未完全阐明	口服	30~60 mg/d，分2~3次口服	性腺毒性，肝功能异常，偶见胃肠道反应、皮疹、骨髓抑制
艾拉莫德	抑制核因子-κB活性，抑制免疫球蛋白合成，抑制环氧化酶-2	口服	50 mg/d，分2次口服	肝功能异常，偶见胃肠道反应、皮疹

证据级别较低，推荐主要是出于对起效时间、药物保留性等方面的考虑[13-14]。基于现有证据，并考虑到我国患者的经济条件、病毒性肝炎及结核感染等合并症，本指南并未对更换/联合csDMARD与加用bDMARD/tsDMARD两种治疗策略的优先性做出区别推荐。此外，本指南并未根据有无RA预后不良因素对治疗方案加以特殊区分，虽然这是临床医师在制定治疗方案时需要考虑的重要因素，但现有的证据尚不足以说明仅根据有无预后不良因素决定二线治疗时应选择调整csDMARD抑或加用bDMARD/tsDMARD[13, 95]。

当采用csDMARD联合治疗RA时，可选择甲氨蝶呤、柳氮磺吡啶、来氟米特中的两种或三种进行组合，但若甲氨蝶呤与来氟米特联用，需注意其肝功能损伤[96-97]及血液系统不良反应[98]。羟氯喹作为csDMARD抑制关节破坏的作用较弱，常用于联合方案，亦可单独用于早期的轻症RA患者[13-14, 99]。此外，羟氯喹可改善患者的血糖和脂肪代谢，适用于合并心脑血管疾病的RA患者[100]。

植物药雷公藤制剂治疗RA的疗效已得到初步认可。有研究显示，雷公藤多苷单药治疗RA的效果不劣于甲氨蝶呤单药，雷公藤联合甲氨蝶呤或肿瘤坏死因子α（TNFα）抑制剂治疗RA亦显示出较好的疗效和安全性[101-102]。雷公藤制剂可作为甲氨蝶呤、柳氮磺吡啶、来氟米特等csDMARD之外的选择之一，但因其具有明确的生殖毒性，禁用于备孕、妊娠、哺乳患者，慎用于有生育需求的RA患者。虽然有少量报道植物药白芍总苷联合csDMARD治疗RA显示出更好的疗效[103-104]，但其对RA的治疗作用尚需更多的证据证实。

艾拉莫德是我国自主研发的抗风湿病药物，具有csDMARD的特征，已广泛用于RA的治疗。有证据显示，艾拉莫德与甲氨蝶呤联用治疗RA优于甲氨蝶呤单药，且安全性良好[105-107]，可作为RA的二线治疗药物。

TNFα抑制剂是目前证据较为充分、应用较为广泛的治疗RA的bDMARD，我国上市的TNFα抑制剂包括单克隆抗体类药物阿达木单抗、英夫利西单抗、戈利木单抗、培塞利珠单抗，以及受体融合蛋白类药物依那西普，均有较充分的证据证明其治疗RA的疗效和安全性[108-119]。TNFα抑制剂用于治疗RA时均建议联合一种csDMARD[120-123]。对接受TNFα抑制剂治疗的RA患者，需特别注意发生肝炎病毒和结核分枝杆菌感染，或原有感染复燃的风险，在使用TNFα抑制剂治疗前应进行筛查，在用药期间应定期监测[124-126]。用药前的筛查内容包括乙型肝炎病毒和丙型肝炎病毒的血清学检查（包括乙型肝炎病毒抗原和抗体、丙型肝炎病毒抗体，必要时进行病毒载量检测）；根据医疗条件选择结核菌素试验（PPD）和/或干扰素γ释放试验（T-SPOT.TB或QuantiFERON-TB GOLD等）；胸部影像学检查（根据医疗条件及患者情况选择X线或CT）[126]。对存在肝炎病毒感染和潜伏性结核分枝杆菌感染的患者，应进行相应的预防治疗，具体治疗方案应参考感染科专家意见，根据患者具体情况制定[15, 126]。

已有较为充分的证据证实，抗白细胞介素6（IL-6）受体的单克隆抗体托珠单抗治疗RA的疗效和安全性。近来有研究证据表明，托珠单抗单药不联合csDMARD治疗RA亦能取得较好的临床疗效[127-131]，故对无法耐受csDMARD的RA患者，可考虑单用托珠单抗治疗。

阿巴西普是一种T细胞共刺激信号抑制剂，通过特异性阻断CD80/86对CD28的激活以抑制T细胞活性[132]。阿巴西普对RA的疗效和安全性已有较多证据[133-135]，可作为bDMARD的选择之一。

Janus激酶（Janus kinase，JAK）抑制剂是一类靶向JAK-STAT信号通路的合成DMARD，属tsDMARD。目前我国已上市的药物包括托法替布、巴瑞替尼、乌帕替尼。目前有研究证据表明，JAK抑制剂对RA具有较好的疗效和安全性[136-144]，但需注意此类药物可能增加心血管不良事件、肿瘤及发生静脉血栓的风险[145-148]。在应用JAK抑制剂前，必须考虑以下心血管事件和恶性肿瘤的危险因素：年龄超过65岁，目前或既往吸烟史，心血管危险因素（如糖尿病，肥胖，高血压），恶性肿瘤危险因素（当前或既往恶性肿瘤病史），血栓栓塞事件危险因素（心肌梗死或心力衰竭史，恶性肿瘤，遗传性凝血疾病或血栓病史，服用避孕药或雌激素替代疗法，接受大手术或制动）[14, 149]，在使用前应对这些相应危险因素进行充分评估，并在用药期间定期监测。

已有较多证据证实，抗CD20单克隆抗体利妥昔单抗治疗RA的疗效[150-152]，可作为对生物制剂和JAK抑制剂疗效不佳或不耐受的RA患者的治疗药物选择。

基于现有证据，各种TNFα抑制剂、托珠单抗和各种JAK抑制剂在治疗RA的使用选择上并无明

确优先顺序[153]。如果一种bDMARD或tsDMARD治疗RA失败，应选择另一种bDMARD或tsDMARD。有证据表明，一种TNFα抑制剂治疗RA失败后换用另一种TNFα抑制剂、托珠单抗、利妥昔单抗、阿巴西普或JAK抑制剂均有效[154-158]，但一种JAK抑制剂治疗RA失败后换用另一种JAK抑制剂的疗效尚不确定。如果托珠单抗或一种JAK抑制剂治疗RA失败，可考虑换用另一种作用机制不同的药物。研究显示，使用bDMARD和tsDMARD相较于csDMRAD具有更高的感染风险[159-161]。对所有接受bDMARD或tsDMARD治疗的RA患者，除前述对TNFα抑制剂和JAK抑制剂需特别关注的不良反应外，亦应注意其他各种感染风险，特别是呼吸道感染（包括流感病毒感染、肺炎链球菌感染等）和带状疱疹病毒感染，对无禁忌的RA患者应考虑接种相应疫苗[126, 162-163]。

生物类似药与原研生物制剂具有相同的作用机制，且价格低，可增加RA患者对生物制剂的可及性[164]，我国已有多种生物类似药上市。一项荟萃分析纳入了27项治疗RA的生物类似药与原研药对比的RCT，其结果显示，已获批的生物类似药在治疗RA的有效性和安全性与原研药无显著差别[165]。2021年ACR更新的RA治疗指南[13]和2022年EULAR更新的RA管理推荐[14]中，均肯定了生物类似药在治疗RA中的疗效与安全性。

关节腔内注射糖皮质激素或依那西普可用于改善RA患者单个受累关节的症状[166]，但应避免过度应用，并需注意关节腔穿刺相关继发感染的风险。有限的研究显示，$^{99}Tc^{m}$亚甲基二膦酸盐可能对RA的治疗有益[167-168]，但尚需更多研究证据证实。

多数RA患者通过规范的疾病管理可以达到疾病缓解或低疾病活动度，然而仍有一定比例的患者即使接受规范治疗后仍存在RA疾病活动，称之为“难治性（refractory或difficult-to-treat，D2T）RA”患者，占RA患者的5%~20%[169-170]。EULAR将难治性RA定义为同时满足下述三条标准者：（1）根据EULAR发布的RA治疗建议，csDMARD治疗失败后（除非存在禁忌），使用超过两种作用机制不同的bDMARD/tsDMARD治疗失败；（2）存在以下至少一种提示RA疾病活动或进展的临床表现：①中度及以上疾病活动度（如基于ESR计算的DAS28>3.2或CDAI>10）；②提示疾病活动的临床表现和/或症状，前者包括急性期炎症指标（ESR、CRP）和影像学表现，后者包括关节相关或其他症状；③无法将糖皮质激素减至小剂量（泼尼松<7.5 mg/d或其等效剂量糖皮质激素）或停用糖皮质激素；④快速影像学进展（伴或不伴活动性疾病的表现）；⑤依上述标准评估RA控制良好，但仍有导致生活质量下降的RA症状；（3）风湿科医生和/或患者认为对疾病症状和/或体征的管理存在困难[169, 171]。形成难治性的原因包括药物失效或存在药物疗效不佳的相关因素（如吸烟、肥胖、患者的基因和免疫功能背景），以及合并症和其他影响疾病预后的因素（如间质性肺炎和纤维肌痛症等）[172]。多因素分析发现，RF滴度高、基于ESR的DAS28评分高及合并肺部疾病是难治性RA的危险因素[170]。针对这类患者需要充分评估造成难治性的原因，制定个体化治疗方案[173-174]。

推荐意见9：RA患者病情持续缓解至少6个月以上，可考虑DMARD（bDMARD/tsDMARD或csDMARD）减量，减量过程中需严密监测，谨防复发（2C）；DMARD联合治疗的RA患者，如一种药物减量后病情仍能持续缓解，可考虑逐渐减停该药物（2C）

基于目前证据，国际上多认为RA患者病情持续缓解一定时间后，可考虑DMARD减量，但仅作为可考虑的选择而非推荐，且对减量的RA患者应进行密切监测[13-14, 175-176]。目前“持续缓解”的具体时间尚无定论，系统综述显示，6个月的缓解期可能较为适合[175]。2021年ACR发布的RA指南中亦认为，6个月是确保疾病稳定控制的最小合理时间[13]。对联用csDMARD和b/tsDMARD的RA患者，优先进行csDMARD抑或bDMARD/tsDMARD减量目前尚无定论[177-179]。由于大多数RA患者停用所有DMARD均存在中至高度复发风险及潜在的发生不可逆损伤风险，故建议患者需维持至少一种DMARD，而不是完全停药[180-181]。对仅达到低疾病活动度而未达到缓解的RA患者，能否进行DMARD减量目前仍存争议。

推荐意见10：对RA患者应进行健康教育（包括疾病性质、病程、治疗、自我管理）和心理支持（1A）；应进行生活方式调整（包括戒烟、控制体重、合理饮食和适当运动等）（1A）

对RA患者健康教育和生活方式调整非常重要。健康教育可以帮助患者充分了解和认识RA的疾病性质、病程、治疗、转归和自我管理等方面的知识，有助于患者更好地理解疾病，增强患者接受规律、规范治疗及随访的信心和依从性，并采取适当

的自我管理措施[182-185]。健康教育亦可提供关于戒烟、控制体重、合理饮食和适当运动等方面的指导，帮助患者优化生活方式。与普通人群比，RA 患者的焦虑和抑郁发生率增加，且伴有焦虑和/或抑郁的 RA 患者的临床治疗效果往往更差[186-188]。研究表明，为 RA 患者提供积极有效的认知干预和心理支持，对缓解疼痛、改善躯体功能、心理健康和疾病活动度均有很大帮助[189-190]。吸烟与 RA 的发生、发展、药物治疗效果及肺间质病变、心血管疾病、骨质疏松、肿瘤的发生都有密切关系[191-193]，因此所有 RA 患者均应戒烟。肥胖者发生 RA 的风险增高[194-195]，且肥胖对 RA 的疾病活动度、药物治疗反应均有不利影响[196-197]，控制体重可帮助 RA 患者改善疾病活动度和预后[198-200]。合理饮食对 RA 患者减轻炎症和改善症状均有帮助[201-205]。适当的运动和物理治疗（如有氧运动、抗阻力运动和功能锻炼）可增强关节的灵活性和稳定性，并改善患者的症状、身体功能及生活质量[206-212]。

本指南依据国际国内现有的循证医学证据，结合我国 RA 疾病特征、医疗条件及风湿免疫科医师经验，对 RA 的诊断、评估、治疗和随访中的重要临床问题给出了推荐意见。风湿科医师及从事 RA 诊疗的其他临床科室的医师，应参照本指南对患者进行规范诊治，以保证医疗质量，提高我国 RA 的诊治水平，改善患者的预后。但由于 RA 存在个体化差异，故在临床实践中需要充分考虑患者的具体情况，通过医患共同决策制定个体化的诊治方案。此外，现有证据尚无法对 RA 诊疗过程中所有的重要临床问题做出明确回答，如，如何识别对 csDMARD 疗效不佳的 RA 患者、如何早期识别难治性 RA 患者并给予相应的有效治疗，亦需进行更多的临床研究，以进一步改善 RA 患者的疗效及预后。

RA 诊疗流程图：见图 1。

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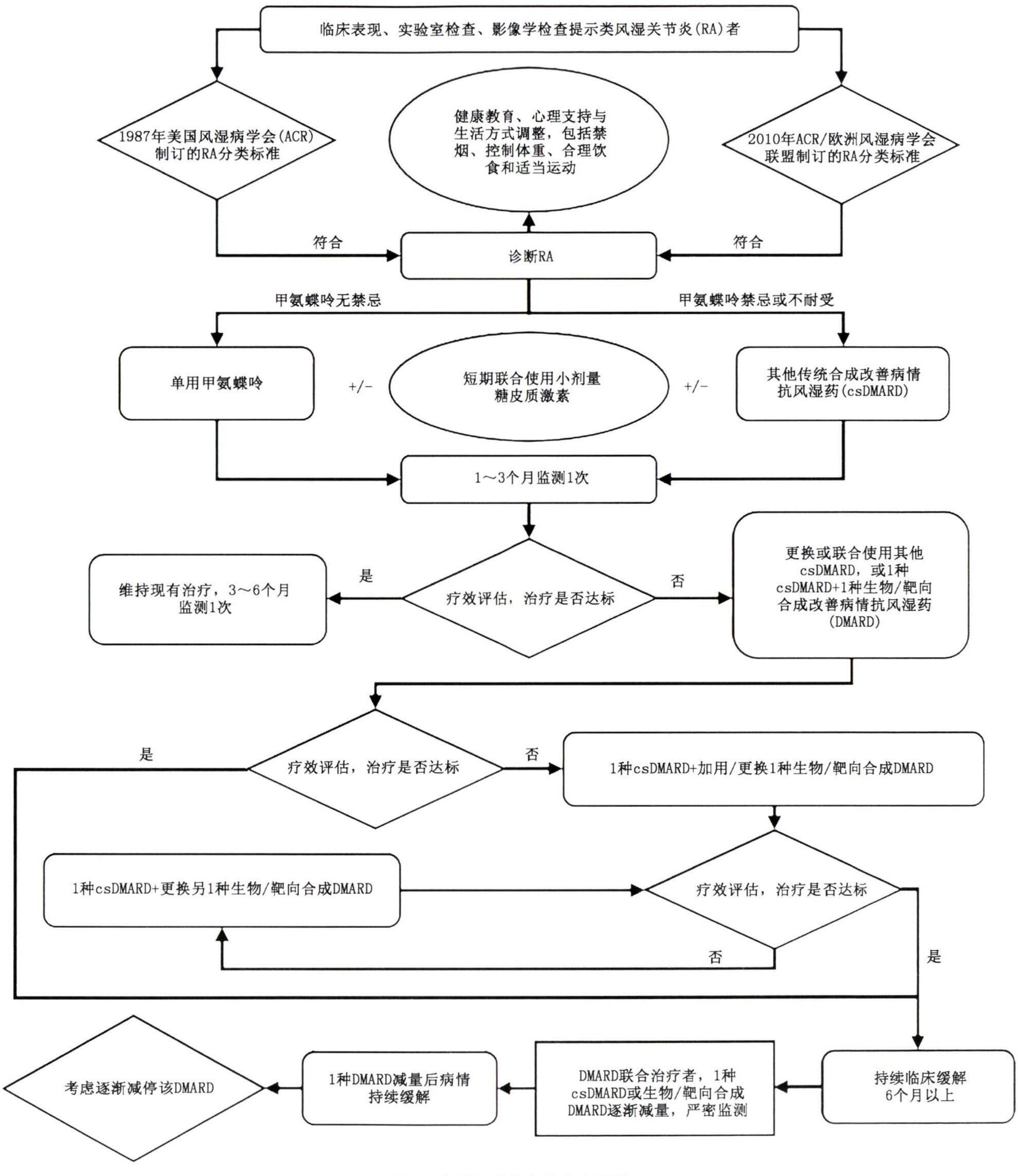

图 1　类风湿关节炎诊疗流程图

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