·循证神经病学·

干扰素-β治疗复发-缓解型多发性硬化系统评价

贺电 李娅 徐竹 周红雨 楚兰 蔡刚 戴庆箐 张艺凡

【摘要】 **目的** 评价干扰素-β(IFN-β)治疗复发-缓解型多发性硬化的有效性和安全性。**方法** 检索Cochrane临床对照试验中心注册库、美国国立医学图书馆、荷兰医学文摘、CINAHL、LILACS、PEDRO、中国生物医学文献数据库、临床试验注册中心和世界卫生组织国际临床试验注册平台(检索截止时间:2014年6月);并通过阅读相关论文参考文献,联系参与IFN-β治疗多发性硬化临床试验的研究者和企业,进一步获取研究信息或未发表的数据。由两名评价人员独立筛选研究、提取研究信息和数据、评价偏倚风险。应用Review Manager软件(Version 5.3.3)进行Meta分析,GRADEpro软件评价研究设计和实施过程中的局限性(偏倚风险)、结果的不一致性和不精确性、证据的间接性和发表偏倚对主体证据质量的影响。**结果** 共检索相关文献576篇,阅读标题和摘要后初步筛选出26项研究;进一步阅读全文后纳入5项研究(共2129例复发-缓解型多发性硬化患者:高剂量IFN-β组1076例、安慰剂组1053例)。所有纳入的研究均为IFN-β单药治疗且随访时间≥1年的随机双盲安慰剂对照平行临床试验。大多数研究存在方法学局限性,主要缺陷为随访偏倚风险较高,且数据分析未使用意向治疗原则,仅919例受试者(43.17%)的数据可用于分析随访2年时的主要结局。Meta分析显示,IFN-β可轻微减少随访2年时复发病例数(*RR* = 0.810, 95% CI: 0.740 ~ 0.890; *P* = 0.000)和残疾进展病例数(*RR* = 0.700, 95% CI: 0.550 ~ 0.880; *P* = 0.002);敏感性分析(最差情况的演示分析)显示,IFN-β治疗无效(*RR* = 1.110, 95% CI: 0.730 ~ 1.680, *P* = 0.620; *RR* = 1.310, 95% CI: 0.600 ~ 2.890, *P* = 0.500)。共1581例患者(74.26%)的数据可用于分析随访1年时至少复发1次的病例数(*RR* = 0.740, 95% CI: 0.590 ~ 0.930; *P* = 0.010),绝对危险降低率为13.24%,需治疗的病例数为8例,表明需要治疗8例患者才可防止1例在第1年内复发。但在年复发率方面,IFN-β治疗无效。IFN-β常导致注射部位局部反应、寒颤、发热、肌肉疼痛、流感样症状、头痛、血清丙氨酸转氨酶和天冬氨酸转氨酶水平升高等不良事件,但并不增加外周血淋巴细胞和中性粒细胞减少、抑郁、自杀行为或自杀观念的发生。**结论** 高质量证据显示,IFN-β治疗复发-缓解型多发性硬化可轻微降低第1年内的复发病例数,但超过1年的疗效尚不能确定。目前尚无足够证据证明IFN-β在减少残疾进展病例数方面的疗效,尚待高质量的随机对照临床试验评价其长期有效性。

【关键词】 干扰素β; 多发性硬化; Meta分析

Interferon-beta for relapsing-remitting multiple sclerosis: a systematic review

HE Dian[1], LI Ya[1], XU Zhu[1], ZHOU Hong-yu[2], CHU Lan[1], CAI Gang[1], DAI Qing-qing[1], ZHANG Yi-fan[1]
[1]*Department of Neurology, Affiliated Hospital of Guiyang Medical College, Guiyang 550004, Guizhou, China*
[2]*Department of Neurology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China*
Corresponding author: HE Dian (Email: ileks@163.com)

【**Abstract**】 **Objective** To assess the efficacy and safety of interferon-beta (IFN-β) as monotherapy versus placebo for patients with relapsing-remitting multiple sclerosis (RRMS). **Methods** We searched Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, CINAHL, LILACS, PEDRO, China Biology Medicine Disc (CBMDisc), as well as clinical trial registries and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP, retrieval deadline: June 2014). Furthermore, we checked reference lists of published reviews and retrieved articles, and communicated personally with investigators and biotechnology companies participating in trials of IFN-β in an effort to

doi:10.3969/j.issn.1672-6731.2014.09.007
基金项目:贵州省科技计划项目(项目编号:黔科合LG字[2011]044号)
作者单位:550004 贵阳医学院附属医院神经内科(贺电,李娅,徐竹, 楚兰,蔡刚,戴庆箐,张艺凡);610041 成都,四川大学华西医院神经内科(周红雨)
通讯作者:贺电(Email:ileks@163.com)

identify further studies or unpublished data. Two review authors independently screened studies, extracted data and evaluated the risk of bias. Formal Meta-analysis were conducted by using Review Manager software (Version 5.3.3) and the impacts of limitations in study design or execution (risk of bias), inconsistency in results, imprecision of results, indirectness of evidence and publication bias on the quality of the body of evidence were assessed. **Results** A total of 576 articles were retrieved. After screening of titles and abstracts, 26 studies were provisionally selected. The full text of papers were obtained for further assessment of eligibility. Finally, 5 studies were included, involving 2129 patients with RRMS (high-dose IFN-β group: N = 1076; placebo group: N = 1053). All studies were randomized, double-blind, controlled, parallel-group clinical trials with a follow-up for at least one year, evaluating IFN-β versus placebo as monotherapy for patients with RRMS. Most studies had methodological limitations, mainly on a high risk of attrition bias. Moreover, the intention to treat (ITT) principle was not used in data analysis. Data from only 919 patients (43.17%) were available to calculate the primary outcomes at 2 years of follow-up. Meta-analysis indicated IFN-β slightly reduced the number of patients with at least one relapse [risk ratio (*RR*) = 0.810, 95% CI: 0.740–0.890; *P* = 0.000] and the number of patients with disability progression during the first 2 years of follow-up (*RR* = 0.700, 95% CI: 0.550–0.880; *P* = 0.002). However, the sensitivity analysis (worst-case scenario analysis) showed no treatment effect (*RR* = 1.110, 95% CI: 0.730–1.680, *P* = 0.620; *RR* = 1.310, 95% CI: 0.600–2.890, *P* = 0.500, respectively). Data from 1581 patients (74.26%) were available to analyze the number of patients with at least one relapse during the first year of follow-up (*RR* = 0.740, 95% CI: 0.590–0.930; *P* = 0.010). Absolute risk reduction (ARR) was 13.24% and number needed to treat (NNT) was 8, which meant 8 patients were needed to treat to prevent one patient against relapse. However, the pooled results showed no treatment effect on the annualized relapse rate. The adverse events frequently caused by IFN-β included injection-site reactions, chills, pyrexia, myalgia, influenza-like symptoms, headache, increased alanine aminotransferase (ALT) and increased aspartate aminotransferase (AST). However, the incidences of lymphocytopenia, leucopenia, depression and committed or attempted suicide were not significantly increased by IFN-β. **Conclusions** There is high-quality evidence to support that IFN-β slightly reduces the number of patients with RRMS having relapse during the first year of follow-up, but the clinical effect beyond one year is uncertain. There is insufficient evidence to determine the efficacy of IFN-β in reducing the number of patients with disability progression. New randomized controlled trials of high quality are needed to assess the long-term efficacy.

【Key words】 Interferon-beta; Multiple sclerosis; Meta-analysis

This study was supported by Guizhou Provincial Science and Technology Plan Program (No. LG[2011]044).

多发性硬化(MS)是由免疫介导的侵及中枢神经系统的慢性疾病,好发于中青年人群,以炎症、脱髓鞘、轴突变性和神经元丢失为病理特征,临床表现为反复发作和(或)进展,最终导致严重神经功能缺损。多发性硬化分为4种临床类型:其中80%~85%患者最初呈复发-缓解病程,以神经系统症状与体征急性加重伴完全或不完全缓解为特征,称为复发-缓解型多发性硬化(RRMS)[1];约50%RRMS患者于发病10年后进入继发进展阶段,残疾持续进展,无复发或伴复发和不完全缓解,称继发进展型多发性硬化(SPMS)[2];原发进展型多发性硬化(PPMS)约占10%,发病时残疾持续进展且持续至少1年,无复发[1];约5%患者发病时残疾持续进展,伴复发和不完全缓解,称进展复发型多发性硬化(PRMS)[3]。其中,复发-缓解型、进展复发型和伴复发的继发进展型统称为复发型多发性硬化。随着疾病复发和残疾进展,患者生活质量逐渐下降,其对个人和社会所造成的经济负担不断增加[4-5]。采用有效治疗可以减少复发、防止进展,有助于改善患者生活质量、降低社会负担[6]。干扰素-β(IFN-β)能够抑制T细胞增殖,下调促炎性因子表达、上调抗炎性因子表达,通过干扰细胞间黏附分子(ICAM)阻断血-脑屏障开放,减少炎性细胞透过血-脑屏障,增加神经生长因子(NGF)产生[7]。多种IFN-β已被美国食品与药品管理局(FDA)批准用于治疗复发型多发性硬化20余年,旨在减少病情复发、延缓残疾进展。2001年,Rice等[8]对重组人干扰素-α(IFN-α)和IFN-β的随机对照试验(RCT)进行系统评价,结果显示,重组人干扰素连续治疗1或2年对减少RRMS患者复发和延缓疾病进展疗效轻微。2003年,Filippini等[9]更新的系统评价结果显示,重组人干扰素治疗RRMS 1年仅能使复发病例数略减少。近

年新开展的临床试验进一步对IFN-β治疗RRMS的有效性和安全性进行评价。然而，目前仍缺乏单独针对IFN-β治疗RRMS的系统评价。本研究旨在评价IFN-β单药治疗RRMS的绝对有效性和安全性。

资料与方法

一、纳入标准

1. 研究类型　选择IFN-β单药治疗RRMS的随机、双盲、安慰剂对照且随访时间≥1年的平行临床试验作为本系统评价的原始研究，排除IFN-β联合其他药物治疗或以其他活性药物治疗为对照的临床研究。

2. 研究对象　(1)年龄18～60岁。(2)根据Poser标准[10]或McDonald标准[11-13]明确诊断为多发性硬化的病例，同时根据Lublin和Reingold分类标准[1]符合RRMS类型。(3)扩展残疾状态量表(EDSS)[14]评分≤6分。(4)排除PPMS、SPMS和PRMS患者。

3. 干预措施　(1)试验组：治疗药物为重组人IFN-β或聚乙二醇IFN-β，给药途径、频率和治疗时间无限制。(2)对照组：治疗药物为安慰剂。

4. 结局指标　以治疗期或随访结束时的数据与基线资料比较，评价随访1年、2年或更长时间的结局。(1)主要结局：疗效评价包括①至少复发1次的病例数。“复发”定义为出现新症状或原处于稳定或已改善的症状与体征恶化，与发热或感染无关，发生时间距前次复发≥30 d并持续>24 h，经神经科医师评估，发现新的、客观的神经系统异常。②残疾进展的病例数。“残疾进展”定义为基线EDSS评分≥1分者，EDSS评分至少增加1分；基线EDSS评分为零者，EDSS评分至少增加1.5分并持续6个月。如果在原始研究中，残疾进展的确认时间不足6个月，也纳入本研究，但使用GRADE标准评价证据质量时，基于证据的间接性降低该结局的证据级别。安全性评价包括，①发生常见不良事件的病例数。②因不良事件退出研究的病例数。(2)次要结局。①年复发率(ARR)。②T_1WI增强扫描病灶数目。③新发或扩大的T_2WI高信号病灶数目。④脑体积变化百分比。⑤健康相关生活质量(HRQoL)评分变化。本研究采用以下量表评价多发性硬化患者的生活质量：美国医学结局研究组(MOS)开发的36条简明健康状况调查表(SF-36)[15]、多发性硬化生活质量量表-54(MSQoL-54)[16]、多发性硬化生活质量问卷(MSQLI)[17]或多发性硬化功能评价(FAMS)[18]。

二、文献检索

检索Cochrane临床对照试验中心注册库(CENTRAL)、美国国立医学图书馆(PubMed)、荷兰医学文摘(EMBASE)、CINAHL、LILACS、PEDRO、中国生物医学文献数据库(CBMdisc)、临床试验注册中心(http://clinicaltrials.gov/)和世界卫生组织国际临床试验注册平台(WHO ICTRP，http://apps.who.int/trialsearch/；检索截止时间：2014年6月)；并通过阅读相关论文参考文献获得进一步研究信息，联系研究者获得更多发表或未发表的数据，同时经由德国Bayer Healthcare Pharmaceuticals公司、Merck Serono公司、美国Biogen Idec公司、瑞士Novartis Pharmaceuticals公司的医疗信息部门获得进一步研究信息。

三、数据收集与分析

1. 筛选研究　由两名评价员根据论文标题和摘要独立筛选经检索获得的文献。对可能相关的研究查找全文，并逐一阅读，进一步确定是否符合纳入标准。不符合纳入标准的临床试验注明排除理由。对于存在分歧的临床试验，通过本研究组集体讨论确定。

2. 数据提取　由两名评价员独立提取各项临床试验的信息和数据，包括试验设计、受试者信息、干预措施和结局指标，通过联系主要研究者确认试验方法或获取额外数据。

3. 评价研究偏倚风险　根据Cochrane系统评价员手册5.1.0[19]所提供的方法学标准，由两名评价员采用偏倚风险评价工具对各项临床试验的方法学质量进行独立评价，包括随机序列产生方法、分配隐藏方法、受试者、研究人员，以及结局测量者的设盲情况、结局数据的完整性、选择性结局报告和其他偏倚情况。

4. 效应量的选择　采用危险比(*RR*)或相对危险度(*RR*)作为表达以下结局的效应量：(1)至少复发1次的病例数。(2)残疾进展的病例数。(3)发生常见不良事件的病例数和因不良事件退出的病例数。(4)以率比(*RR*)作为表达年复发率、T_1WI增强扫描病灶数目、新发或扩大的T_2WI高信号病灶数目的效应量。(5)以均数差(MD)作为表达脑体积变化百分比的效应量，若纳入的试验采用同一量表评价健康相关生活质量则以均数差作为表达生活质量变

化的效应量；若采用不同量表，则以标准化均数差（SMD）作为效应量。此外，通过计算绝对危险降低率[*ARR*，也称危险差（*RD*）]，计算防止1例患者复发或进展而需治疗的病例数（NNT）：NNT = 1 / *ARR*。

5. 分析单位　大多数IFN-β治疗多发性硬化的临床试验为多臂研究，具有多个不同剂量的试验组和1个共同的安慰剂组。根据预先设定的随访时间，选择高剂量组和安慰剂组数据进入分析。

6. 缺失数据的处理　通过联系研究者获得文献中未报告的数据和信息，仅分析可利用的数据而抛弃随机缺失的数据。但对于非随机缺失的数据，假定试验中每组失访者和未被纳入分析的受试者均有结果，根据3种假设（最佳情况、可能情况和最差情况）进行敏感性分析，并根据意向治疗（ITT）原则进行数据合成。

7. 异质性评价　通过比较研究特征、受试者、干预措施和结局指标的相似性，评价临床异质性，同时评价试验设计变异性和偏倚风险，即方法学异质性。若各项试验之间的临床异质性和方法学异质性不明显，则进一步计算I^2值，以评价统计学异质性。$I^2 > 30.000\%$，提示各项临床试验之间存在统计学异质性[19]。

8. 发表偏倚评价　若纳入Meta分析的临床试验数量充足（≥ 10个），对连续性变量的结局以均数差作为横坐标、标准误为纵坐标绘制漏斗图以检验发表偏倚；二分类变量结局，则以*RR*为横坐标、*RR*对数值（*lnRR*）的标准误作为纵坐标绘制漏斗图。

9. 数据合成　对临床同质性和方法学同质性较好且异质性检验显示$I^2 \leq 30.000\%$的临床试验，或异质性检验具有统计学差异但个体检测结果提示合并数据仍合理时，采用Review Manager软件（Version 5.3.3）[20]进行数据合成。根据异质性结果，选择固定效应模型或随机效应模型，各项临床试验之间同质性良好时，采用固定效应模型，否则采用随机效应模型。对于二分类变量结局，如至少复发1次的病例数、残疾进展的病例数、发生常见不良事件的病例数和因不良事件退出的病例数，采用Mantel-Haenszel方法进行数据合并；对于连续性变量结局，如脑体积变化百分比或健康相关生活质量评分变化，采用Inverse-variance方法进行数据合并；对于涉及计数和百分比的结局，如年复发率、T_1WI增强扫描病灶数目、新发或扩大的T_2WI高信号病灶数目，均采用Generic inverse-variance方法进行数据合并。

10. 亚组分析　基于IFN-β的不同种类（如重组IFN-β1a、重组IFN-β1b或聚乙二醇IFN-β1a）进行亚组分析。

11. 敏感性分析　假设各项临床试验每组失访者和未被纳入分析的受试者均有结果，根据3种假设情况（最佳情况、可能情况以及最差情况）进行演示分析。最佳情况的演示分析中，假设安慰剂组失访者和未被纳入分析的受试者发生不良结果，而高剂量IFN-β组此类受试者具有良好结果；最差情况的演示分析则相反，假设高剂量IFN-β组失访者和未被纳入分析的受试者发生不良结果，而安慰剂组此类受试者具有良好结果；进行可能情况的演示分析时，假设两组失访者和未被纳入分析的受试者均发生不良结果。

12. 证据质量评价　建立以下结局的结果汇总统计表：（1）随访1和2年时至少复发1次的病例数。（2）随访2年时残疾进展的病例数。（3）发生常见不良事件的病例数。根据Cochrane系统评价员手册5.1.0[19]所提供的方法，采用GRADEpro软件[21]进一步评价各项临床试验设计和实施过程中的局限性和偏倚风险、研究结果的不一致性（研究结果间无法解释的异质性）和不精确性（95%可信区间过宽）、证据的间接性，以及发表偏倚对主体证据质量的影响。

结　果

一、文献检索结果

通过上述检索途径共计检出相关文献576篇，其中英文文献386篇、中文文献190 篇。经阅读标题和摘要，初步筛选出26项临床试验，均为英文文献。再进一步阅读原文，排除21项不符合入选条件的临床试验：1项天然IFN-β试验[22]、2项开放性临床试验[23-24]、4项仅进行重组人IFN-β剂量对比而无安慰剂对照的临床试验[25-28]、1项重组人IFN-β1a生物仿制药而无安慰剂对照的临床试验[29]、2项随访时间 < 1年的临床试验[30-31]、1项剂量调整前随访时间仅24周的皮下注射重组人IFN-β1a临床试验[32]、9项多发性硬化确诊前即开始治疗的临床试验[33-39]和1项未描述临床结局的非双盲临床试验[40]。

本研究纳入5项临床试验2129例受试者[41-45]，1076例接受高剂量IFN-β治疗、1053例接受安慰剂治疗；其中最早的一项试验发表于1993年[41]，最近

的一项试验发表于2014年[45]。最近报道的一项关于聚乙二醇IFN-β1a治疗RRMS的多中心临床试验共纳入1012例受试者，占本研究所有纳入受试者的47.53%[45]。本研究未检索到正在进行的IFN-β单药治疗RRMS的随机双盲安慰剂对照临床试验。

二、研究特征

1. 研究设计类型　所纳入的5项临床试验均为随机双盲安慰剂对照平行临床试验，随访时间分别为1年[44-45]和2年[41-43]（表1）。

2. 研究对象特征　除1项研究[45]受试者符合2005年McDonald标准[12]外，其余4项研究[41-44]所纳入的受试者均符合Poser标准[10]。所有纳入的受试者均为RRMS病例，且大多数研究各组别受试者的基线特征一致，具有可比性。

3. 干预措施　所有研究均以安慰剂作为对照，试验组分别为重组人IFN-β1b（倍泰龙）[41]、重组人IFN-β1a（Avonex）[42]、重组人IFN-β1a（利比）[43-44]和聚乙二醇IFN-β1a[45]（表1）。

4. 结局指标　各项临床试验所包含本研究预设的结局分别为：（1）复发病例数，随访1年时至少复发1次的病例数3项[43-45]、随访2年时至少复发1次的病例数3项[41-43]。（2）残疾进展病例数，随访1年时残疾进展的病例数1项[45]和随访2年时残疾进展的病例数3项[41-43]。（3）年复发率，包括随访1年时年复发率3项[44-46]，以及随访2年时年复发率3项[41-43]。（4）影像学结局，包括随访1年时T_1WI增强扫描病灶数目2项[42,45]、随访2年时T_1WI增强扫描病灶数目1项[45]、随访1年时新发或扩大的T_2WI高信号病灶数目1项[45]、随访2年时新发或扩大的T_2WI高信号病灶数目1项[47]和随访1年时脑体积变化的百分比1项[45]（表1）。（5）上述所有临床试验均报告了IFN-β不良事件和因不良事件退出的病例数，但均未将健康相关生活质量作为研究终点。

各项临床试验对“复发”的定义相类似：新出现或再发的神经系统症状与体征，与发热或感染无关，发现有客观的神经系统异常，症状出现时间距前次复发≥30 d且持续时间>24 h。但是对“进展”的定义不尽一致：1项研究为基线EDSS评分≥1分者、EDSS评分至少增加1分，基线EDSS评分为零者、EDSS评分至少增加1.5分并持续至少3个月[45]；2项研究为EDSS评分至少增加1分并持续至少3个月[41,43]；1项研究为EDSS评分至少增加1分并持续至少6个月[42]。对于影像学结局的评价，各项临床试验头部MRI检查时间之间隔不尽一致：1项研究每4周检查1次，连续检查24周[44]；2项研究1年检查1次[41-42]（其中1所试验中心每6周检查1次[41]）；2项试验每6个月检查1次[43,45]（其中1项试验中的亚组每月检查1次，连续实行9个月[43]）。

三、研究质量和偏倚风险评价

本研究中有2项原始研究选择性偏倚风险不清楚，其中一项研究由于随机序列产生方法和分配隐藏方法不详[41]；另一项研究则因随机序列产生方法属不完全随机方法且随机隐藏不充分[42]。其余3项研究选择性偏倚风险均较低[43-45]。

尽管各项临床试验对研究者和受试者均采用了盲法，但IFN-β常见不良反应，如注射部位局部反应和流感样症状很可能影响患者设盲。其中，1项研究随访结束后让受试者猜测治疗所用药物，高剂量组80%患者猜测正确，安慰剂组仅有30%猜测正确[41]。事实上，许多患者在治疗过程中已经晓知其所接受的治疗药物，故这些试验应被视为单盲。

纳入的临床试验中共计有346例（16.25%）患者于随机分组后退出或失访，其中高剂量组203例（18.87%）、安慰剂组143例（13.58%）。其中1项临床试验高剂量组56例（46.20%）、安慰剂组73例（39.16%）因试验提前结束未完成2年随访时间[42]，1项试验高剂量组24例（19.35%）、安慰剂组23例（18.70%）退出或失访[41]，随访偏倚风险均较高，其余3项临床试验随访偏倚风险均较低[43-45]。

尽管所有入选的临床试验发表时均提及意向治疗，但并非所有随机化的病例均纳入数据分析。所有试验的结局在结果中均有报告，报告偏倚风险较低（表2）。

四、效应量的合并

1. 临床结局　对3项随访1年时至少复发1次的病例数的试验（1581例占74.26%）进行异质性检验，结果提示各研究之间具有明显异质性（I^2 = 74.000%，P = 0.020）[43-45]。其原因可能与IFN-β剂量和给药频率不同有关，其中1项试验治疗时间仅为24周[44]，采用随机效应模型，合并的RR为0.740（95%CI：0.590～0.930，P = 0.010；图1a）；绝对危险降低率为13.24%，需治疗的病例数为8例，表明需要治疗8例患者方可防止1例在第1年内复发。对重组人IFN-β1a（利比）的两项临床试验[43-44]进行亚组分析显示，随访1年时并未减少复发病例数（RR = 0.800，95%CI：0.610～1.070，P = 0.130；图1b）。来自

表1 本系统评价所纳入临床试验之特征

Table 1. The characteristics of relevant studies included in this systematic review

Trial	Recruitment period	Follow-up (month)	Intervention	Number of patients	Subjects´ characteristic	Outcome measure
ADVANCE[45]	2009–2011	12	Pegylated IFN-β1a 125 μg injected subcutaneously every 2 weeks for 12 months	512	Age 18–65 years, a diagnosis of RRMS as defined by the McDonald´s criteria; a score of 0–5 on the EDSS; at least two clinically documented relapses in the previous 3 years, with at least one within the past 12 months	Primary outcome: annualized relapse rate Secondary outcome: proportion of patients who relapsed; proportion of patients with disability progression; number of new or newly enlarging T_2WI hyperintense lesions; number of gadolinium-enhancing lesions; volume of brain atrophy
			Pegylated IFN-β1a 125 μg injected subcutaneously every 4 weeks for 12 months	500		
			Placebo	500		
IFNB MS Group[41]	1988–1990	24	IFN-β1b (Betaseron) 1.60×10^6 IU (50 μg) injected subcutaneously every other day for 24 months	125	Age 18–50 years; clinical or laboratory-supported definite RRMS as defined by the Poser´s criteria; EDSS ≤ 5; disease duration > 1 year; at least two relapses in the 2 years before randomization, no recurrence for at least 1 month before randomization	Primary outcome: annualized relapse rate and proportion of exacerbation-free patients Secondary outcome: proportion of patients with disability progression; number of new or newly enlarging T_2WI hyperintense lesions
			IFN-β1b (Betaseron) 8×10^6 IU (250 μg) injected subcutaneously every other day for 24 months	124		
			Placebo	123		
MSCRG[42]	1990–1993	24	IFN-β1a (Avonex) 6×10^6 IU (30 μg) injected intramuscularly once a week for 104 weeks	158	Age 18–55 years; definite RRMS as defined by the Poser´s criteria; EDSS 1–3.5; disease duration > 1 year; at least two relapses in the 3 years before randomization; no recurrence for at least 2 months before randomization	Primary outcome: time to onset of sustained worsening in disability Secondary outcome: number of exacerbation-free patients; annualized relapse rate; number of gadolinium-enhancing T_1WI lesions
			Placebo	143		
OWIMS[44]	1995	12	IFN-β1a (Rebif) 6×10^6 IU (22 μg) injected subcutaneously once a week for 24 months	95	Age 18–50 years; clinical or laboratory-supported definite RRMS as defined by the Poser´s criteria; EDSS 0–5; disease duration ≥ 1 year; at least one relapse in the 2 years before randomization; no recurrence for at least 2 months before randomization	Primary outcome: number of gadolinium-enhancing lesions Secondary outcome: exacerbation count per patient; proportion of patients remaining exacerbation-free
			IFN-β1a (Rebif) 12×10^6 IU (44 μg) injected subcutaneously once a week for 24 months	98		
			Placebo	100		
PRISMS[43]	1994–1995	24	IFN-β1a (Rebif) 6×10^6 IU (22 μg) injected subcutaneously 3 times a week for 24 months	189	Age: not reported; clinical or laboratory-supported definite RRMS as defined by the Poser´s criteria; EDSS 0–5; disease duration ≥ 1 year; at least two relapses in the 2 years before randomization	Primary outcome: mean number of relapses Secondary outcome: proportion of exacerbation-free patients; proportion of patients with disability progression
			IFN-β1a (Rebif) 12×10^6 IU (44 μg) injected subcutaneously 3 times a week for 24 months	184		
			Placebo	187		

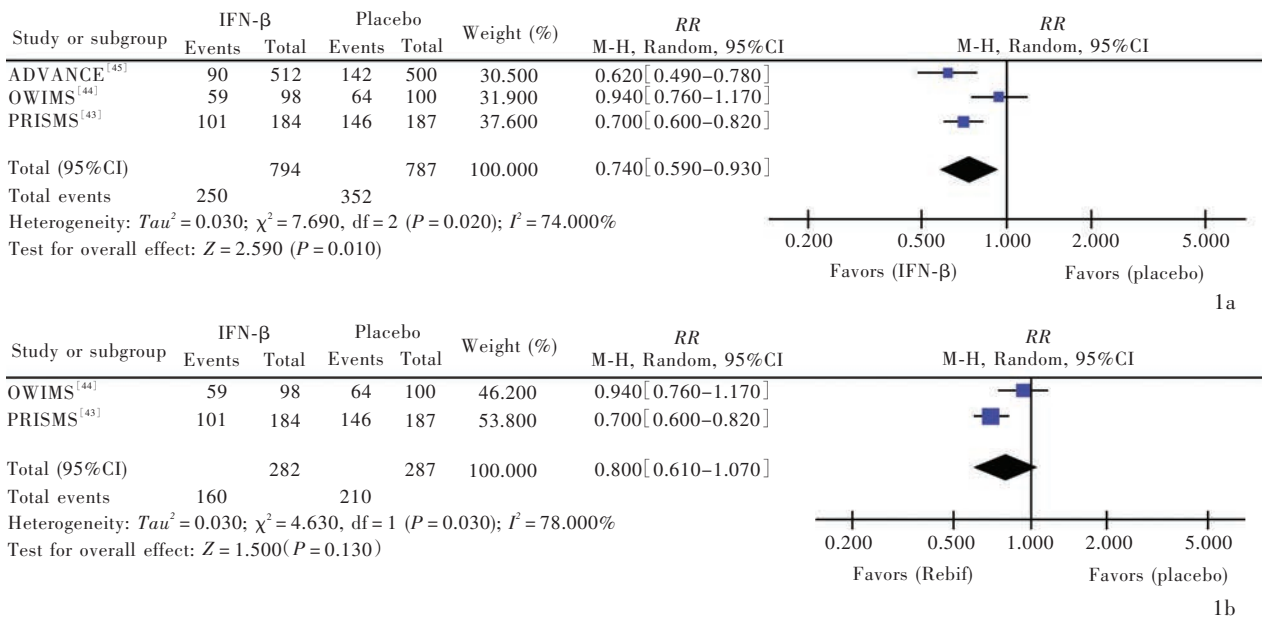
IFN-β，interferon-beta，干扰素-β；RRMS，relapsing-remitting multiple sclerosis，复发-缓解型多发性硬化；EDSS，Expanded Disability Status Scale，扩展残疾状态量表

表2 本系统评价所纳入临床试验的方法学质量评价

Table 2. The methodological quality of relevant studies included in this systematic review

Trial	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)		ITT	Selective reporting (reporting bias)
					IFN-β group	Placebo group		
ADVANCE[45]	Block randomization stratified by site	Randomization was done by a centralized interactive voice response and web system, stratified by site	All participants and personnel were blinded to treatment assignments	Outcomes were assessed by a separate investigator	74 (14.45%)	44 (8.80%)	No	All listed outcomes were reported adequately
IFNB MS Group[41]	Unclear	Unclear	All participants and personnel were blinded to treatment assignments	Outcomes were assessed by a separate investigator	24 (19.35%)	23 (18.70%)	No	All listed outcomes were reported adequately
MSCRG[42]	Randomization was done by the Efron´s biased coin method in Data Management and Statistical Center before accrual of patients	Patients were sequentially assigned the next ID number from the randomization schedule except one of the four participating centers, where the list of ID numbers used by the staff did not contain the actual treatment arm associated with each ID	All participants and personnel were blinded to treatment assignments	Outcomes were assessed by a separate investigator	73 (46.20%)	56 (39.16%)	No	All listed outcomes were reported adequately
OWIMS[44]	Treatment assignment was determined by a computer-generated randomization list produced by the sponsors	The randomization code for each patient was delivered to the investigator in sealed envelopes	All participants and personnel were blinded to treatment assignments	Outcomes were assessed by a separate investigator	13 (13.27%)	3 (3.00%)	No	All listed outcomes were reported adequately
PRISMS[43]	The randomization list was computer-generated by the sponsors and stratified by center	The study drug was packed according to random numbers and delivered to the centers	All participants and personnel were blinded to treatment assignments	Outcomes were assessed by a separate investigator	19 (10.33%)	17 (9.09%)	No	All listed outcomes were reported adequately

IFN-β, interferon-beta, 干扰素-β; ITT, intention to treat, 意向治疗



IFN-β,interferon-beta,干扰素-β;RR,risk ratio,危险比。The same as Figure 2–3

图1 随访1年时至少复发1次病例数之森林图 1a 高剂量IFN-β治疗 1b 高剂量重组人IFN-β1a(利比)治疗

Figure 1 Forest plot of the number of patients with at least one relapse during the first year of follow-up. High-dose IFN-β therapy (Panel 1a). Treatment with high-dose IFN-β1a (Rebif, Panel 1b).

3项临床试验(919例占43.17%)[41-43]的合并数据显示,IFN-β连续治疗2年对减少复发病例数(*RR* = 0.810,95%CI:0.740 ~ 0.890,*P* = 0.000;图2)和残疾进展病例数(*RR* = 0.700,95%CI:0.550 ~ 0.880,*P* = 0.002;图3)疗效轻微。然而,随机分组后因退出或失访而未被纳入分析的病例数对结果影响较大,敏感性分析(最差情况的演示分析)显示,IFN-β无治疗效应(*RR* = 1.110,95%CI:0.730 ~ 1.680,*P* = 0.620;*RR* = 1.310,95%CI:0.600 ~ 2.890,*P* = 0.500;图2d,3d)。ADVANCE研究显示,聚乙二醇IFN-β1a可显著降低随访1年时残疾进展的病例数[风险比(*HR*) = 0.620,95%CI:0.400 ~ 0.970;*P* = 0.038][45]。有3项临床试验(1457例占68.44%)报告了随访1年时的年复发率[44-46],合并的*RR*为0.720(95%CI:0.120 ~ 4.240,*P* = 0.710;图4a);3项临床试验(919例占43.17%)报告随访2年时的年复发率[41-43],合并的*RR*为0.690(95%CI:0.130 ~ 3.680,*P* = 0.670;图4b),均显示IFN-β治疗无效。

2.影像学结局 头部MRI检查的多项结局指标可作为多发性硬化临床试验的替代性终点。然而由于各项试验所应用的MRI参数标准不尽一致,扫描间隔和次数亦不尽相同,故结局数据表达形式多样,因此仅能对MRI结局数据进行定性分析。MSCRG研究报告了随访1年时的MRI结局,IFN-β组(134例)T_1WI增强扫描病灶数目少于安慰剂组(123例,1.04对1.59;*P* = 0.020),但组间差异在随访2年时不再有统计学意义(83例对82例,0.80对1.65;*P* = 0.050)[42]。ADVANCE研究显示,随访1年时高剂量组T_1WI增强扫描病灶数目显著减少(*P* = 0.000),新发或扩大的T_2WI高信号病灶数目显著减少(*P* = 0.000)[45];IFNB MS Group研究组成员中的一所试验中心的数据分析也获得相似结果(*P* = 0.009)[47]。有关脑体积百分比变化的数据,ADVANCE的研究结果显示,随访1年时IFN-β组与安慰剂组之间差异无统计学意义(*P* > 0.05)[45]。

3.常见不良事件 对本研究所纳入的各项临床试验的数据分析表明,高剂量组约有56.51%和47.40%患者分别出现注射部位局部反应和流感样症状,而安慰剂组仅为10.35%和20.89%;此外,高剂量组寒颤、发热、肌肉疼痛和头痛发生率亦显著高于安慰剂组,而疲倦、抑郁和自杀行为或自杀观念发生率,组间差异未达到统计学意义(*P* > 0.05)。高剂量IFN-β组患者治疗期间血清丙氨酸转氨酶和天冬氨酸转氨酶水平升高发生率显著高于安慰剂组,但外周血淋巴细胞和中性粒细胞比例减少发生率,组间差异无统计学意义。高剂量IFN-β组因不良事

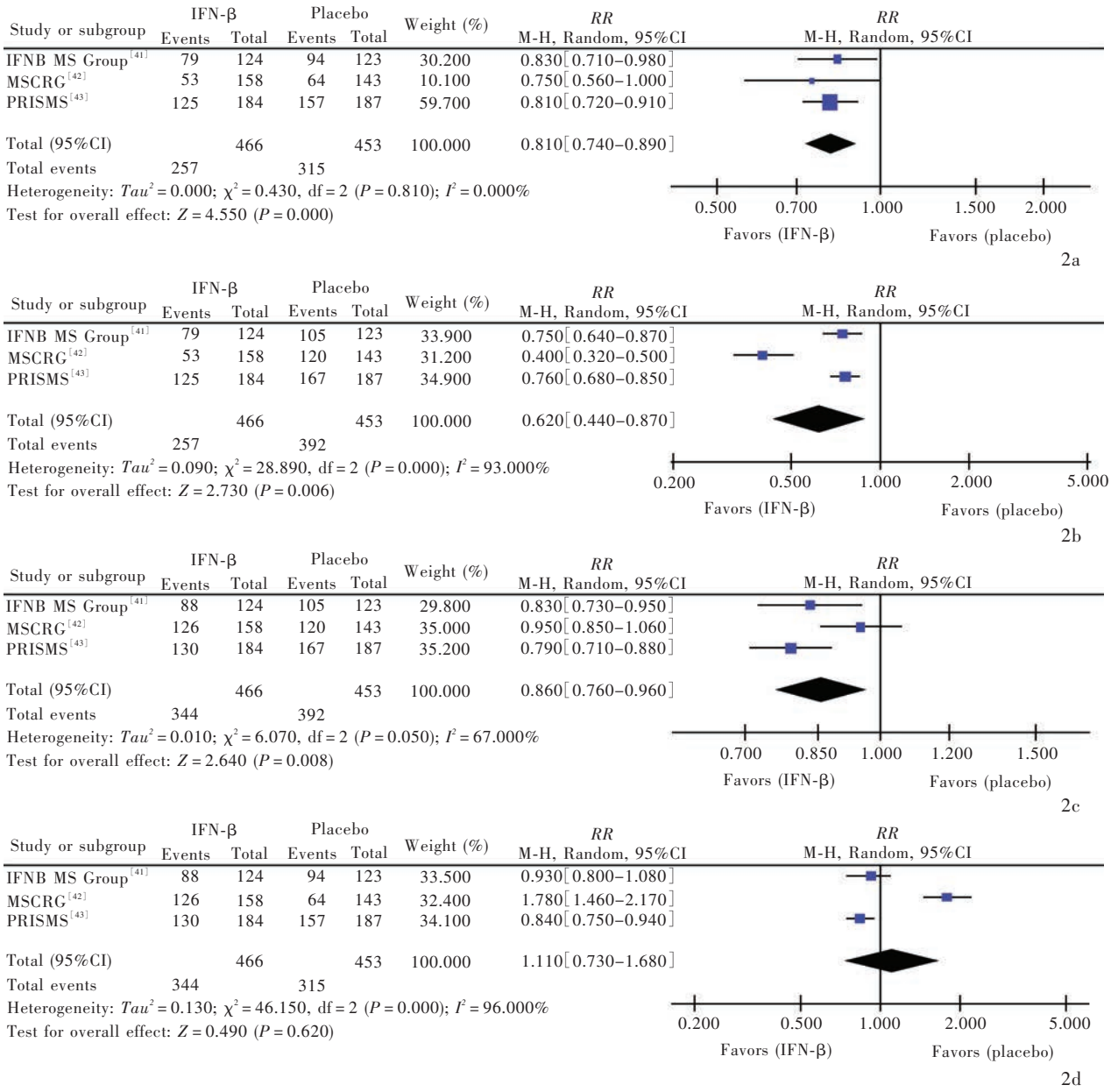


图2 随访2年时至少复发1次病例数之森林图 2a 高剂量IFN-β治疗 2b 最佳情况的演示分析 2c 可能情况的演示分析 2d 最差情况的演示分析

Figure 2 Forest plot of the number of patients with at least one relapse during the first 2 years of follow-up. Treatment with high-dose IFN-β (Panel 2a). Best scenario analysis (Panel 2b). Likely scenario analysis (Panel 2c). Worst scenario analysis (Panel 2d).

件退出试验的病例数显著多于安慰剂组(*RR* = 4.160,95%CI:2.250~7.680,*P* = 0.000;表3)。

五、主要结局的证据质量

应用GRADEpro软件创建结局汇总统计表,并对证据质量进行评价。结果显示,仅有1项结局(随访1年时至少复发1次病例数)的结果被评为高质量证据。以各项临床试验安慰剂组平均风险值作为对照风险,并假设1000例RRMS患者接受高剂量IFN-β,1000例同期接受安慰剂治疗,随访1年时安慰剂组447例复发、高剂量组331例复发。其余主要结局的证据等级因原始研究局限性(主要为随访偏倚的影响)或结果的不精确性而降低。其中1项结局(残疾进展的病例数)由于证据的间接性和结果的不精确性而降级为极低级别证据(表4)。由于本研究纳入的临床试验数目较少,因此未能绘制漏斗图以检验发表性偏倚。

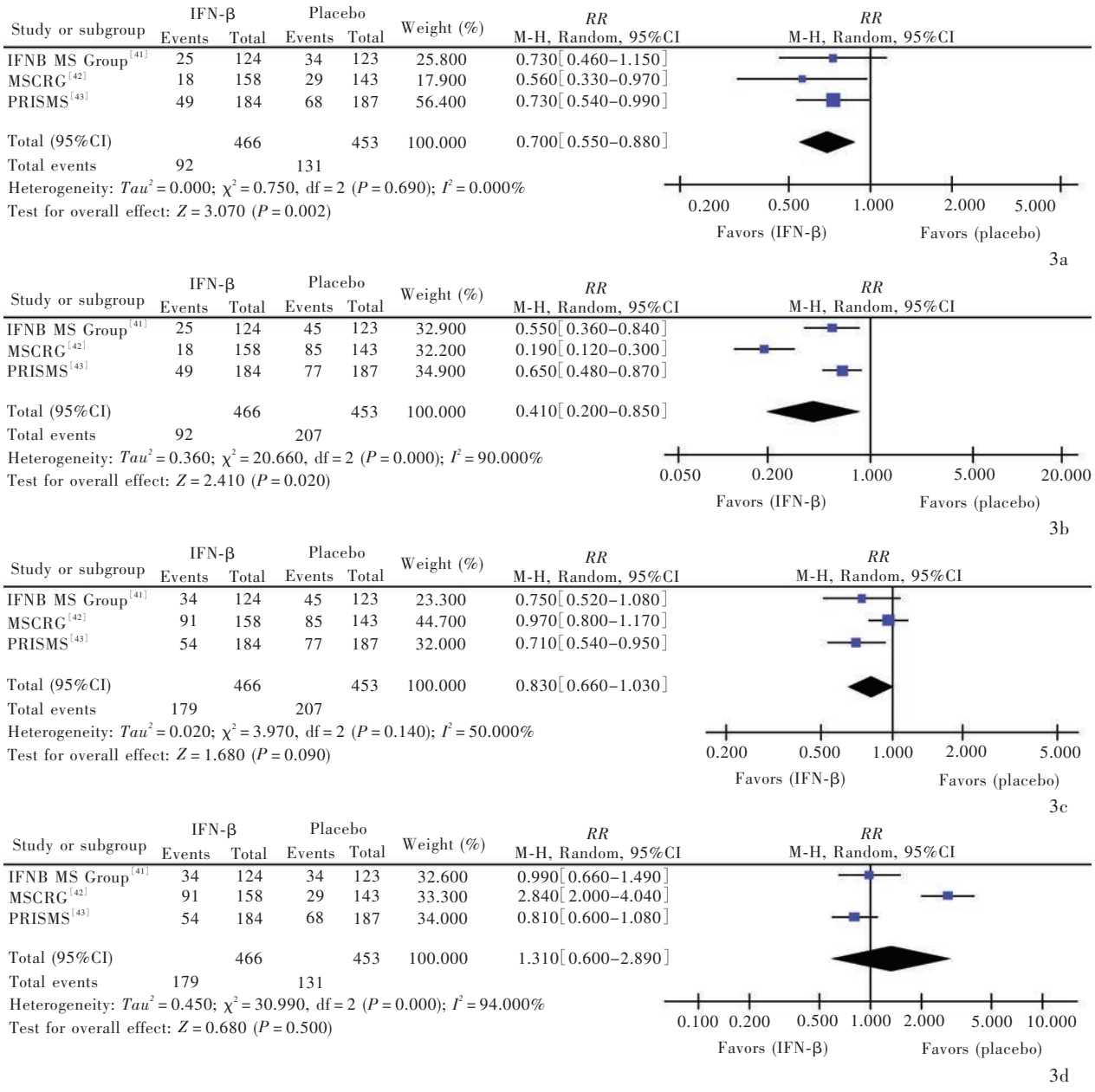


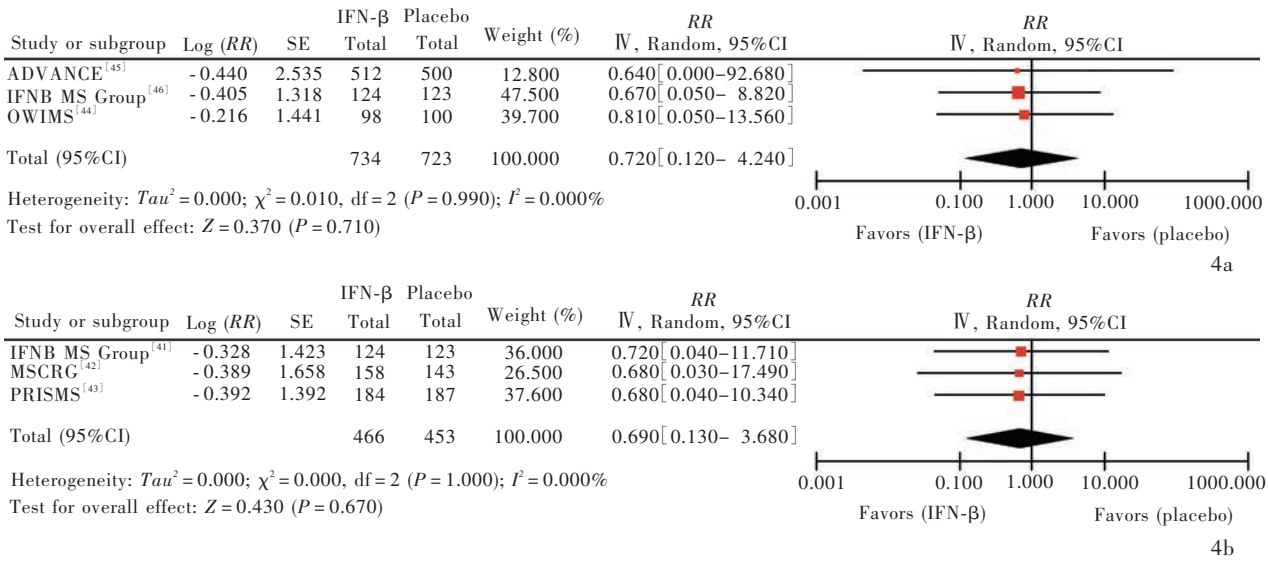
图3 随访2年时残疾进展病例数之森林图 3a 高剂量IFN-β治疗 3b 最佳情况的演示分析 3c 可能情况的演示分析 3d 最差情况的演示分析

Figure 3 Forest plot of the number of patients with disability progression during the first 2 years of follow-up. Treatment with high-dose IFN-β (Panel 3a). Best scenario analysis (Panel 3b). Likely scenario analysis (Panel 3c). Worst scenario analysis (Panel 3d).

讨 论

本研究纳入了迄今为止所有IFN-β单药治疗RRMS的随机安慰剂对照且随访时间≥1年的平行临床试验。多发性硬化的疾病修正治疗(DMT)通常需要足够长的治疗期和随访时间才能够准确评价其药物疗效和安全性。纳入随访时间为1年或以上的临床试验可以在一定程度上避免误导性证据的产生。纳入本研究的大多数临床试验在方法学上存在局限性,主要缺陷为随访偏倚风险较高且结局数据分析未使用意向治疗原则。本研究纳入的2129例受试者中仅919例(43.17%)病例的数据可用于分析随访2年时的主要结局。

本研究结果显示,高剂量IFN-β治疗RRMS可轻微减少第1年内的复发病例数。该结局的数据受各项原始研究偏倚风险的影响较小,试验结果之间



IFN-β, interferon-beta, 干扰素-β; RR, rate ratio, 率比

图4 高剂量IFN-β治疗后年复发率之森林图 4a 随访1年时 4b 随访2年时

Figure 4 Forest plot of the annualized relapse rate after treatment with high-dose IFN-β. The annualized relapse rate during the first year of follow-up (Panel 4a). The annualized relapse rate during the first 2 years of follow-up (Panel 4b).

表3 本系统评价所纳入临床试验报告的常见不良事件

Table 3. The common adverse events reported in relevant studies included in this systematic review

Adverse event	Number of trials	IFN-β group		Placebo group		*RR* value	95%CI	*P* value
		Events	Patients	Events	Patients			
Injection-site reactions[41-45]	5	608	1076	109	1053	4.730	2.300– 9.710	0.000
Chills[42,45-46]	3	133	768	36	743	3.540	2.480– 5.040	0.000
Pyrexia[41-45]	5	383	1076	155	1053	2.230	1.630– 2.790	0.000
Myalgia[41-45]	5	246	1076	107	1053	2.140	1.640– 2.790	0.000
Influenza-like symptoms[42-46]	5	510	1076	220	1053	2.030	1.300– 3.180	0.002
Headache[42-45]	4	463	952	363	930	1.220	1.070– 1.400	0.003
Increased ALT[43,46]	2	37	308	11	310	3.210	1.680– 6.130	0.000
Increased AST[43,46]	2	17	308	6	310	2.830	1.140– 7.060	0.030
Leucopenia[41,43]	2	37	308	14	310	3.220	0.780–13.250	0.110
Lymphocytopenia[41,43]	2	123	308	87	310	1.940	0.620– 6.080	0.250
Fatigue[42-45]	4	127	952	101	930	1.220	0.960– 1.560	0.100
Depression[42-44,46]	4	97	564	93	553	1.010	0.780– 1.310	0.910
Committed or attempted suicide[42-43,46]	3	5	466	5	453	0.900	0.260– 3.090	0.870
The number of patients who withdrew or dropped out from the study because of adverse events[41-45]	5	56	1076	12	1053	4.160	2.250– 7.680	0.000

IFN-β, interferon-beta, 干扰素-β; ALT, alanine aminotransferase, 丙氨酸转氨酶; AST, aspartate aminotransferase, 天冬氨酸转氨酶

不存在无法解释的异质性，一致性较好。此外，用于分析该项结局的数据样本量充分，各项临床试验结果的95%可信区间相对较窄、精确度较高，且各项试验对“复发”的定义符合标准、证据直接。因此被评为高级别证据。对随访2年时主要结局的数据分析显示，高剂量IFN-β在减少复发病例数和残疾进展病例数方面疗效轻微。然而，由于随访偏倚对结局数据的显著影响，使最差情况下的敏感性分析结果未显示出IFN-β的疗效，证据质量下降，尚不能确定高剂量IFN-β是否能够降低随访2年时的复发病例数和残疾进展病例数。大多数试验在“残疾进展”的定义中增加的EDSS评分持续时间均＜6个

表4 本系统评价的主要结局汇总

Table 4. Summary of primary outcomes in this systematic review

Outcome	Follow-up (month)	Illustrative comparative risk*			Relative effect		Number of participants (studies)	Quality of the evidence (GRADE)#
		Assumed risk (placebo)	Corresponding risk (IFN-β)	95%CI	*RR* value	95%CI		
The number of patients with at least one relapse	12	447/1000	331/1000	264– 416	0.740	0.590–0.930	1581 (3 studies)	++++ high
The number of patients with at least one relapse	24	695/1000	563/1000	515– 619	0.810	0.740–0.890	919 (3 studies)	+++– moderate[1]
The number of patients with disability progression	24	289/1000	202/1000	159– 254	0.700	0.550–0.880	919 (3 studies)	+––– very low [1-3]
Adverse events: injection-site reactions	12–24	104/1000	490/1000	238–1000	4.730	2.300–9.710	2129 (5 studies)	+++– moderate[1]
Adverse events: influenza-like symptoms	12–24	209/1000	424/1000	272– 664	2.030	1.300–3.180	2129 (5 studies)	+++– moderate[1]
Adverse events: increased ALT	24	35/1000	114/1000	60– 218	3.210	1.680–6.130	618 (2 studies)	+++– moderate[3]
Adverse events: increased AST	24	19/1000	55/1000	22– 137	2.830	1.140–7.060	618 (2 studies)	+++– moderate[3]

*The mean placebo group risk from the studies was assumed to be the control risk. The corresponding risk (and its 95%CI) is based on the assumed risk in control group and the relative effect of the intervention (and its 95% CI). #GRADE Working Group grades of evidence: high quality, further research is very unlikely to change the confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate; very low quality, the estimate is very uncertain. [1]Limitations in study design or execution (risk of bias) existed due to a high dropout rate in one study. [2]Indirectness of evidence existed because disability progression was confirmed in less than six months in two of the studies. [3]Imprecision of results existed due to a wide 95%CI around the estimate of the effect in some of the studies. –, there was any factor of the five GRADE considerations [limitations in study design or execution (risk of bias), inconsistency in results, imprecision of results, indirectness of evidence, publication bias], which could affect the quality of evidence for the outcome. The more the factors there were or the greater impact the factor had, the lower the quality of evidence was. +, the opposite implications. ALT, alanine aminotransferase, 丙氨酸转氨酶; AST, aspartate aminotransferase, 天冬氨酸转氨酶

月,故判定为残疾进展的病例其病情可能并未真正进展,因此,残疾进展的证据具有一定间接性。此外,其中一项临床试验对残疾进展病例数效果估计的95%可信区间过宽,结果精确性差,其残疾进展结局的证据质量进一步下调为极低级别。

IFN-β常导致注射部位局部反应、寒颤、发热、肌肉疼痛、流感样症状、头痛、血清丙氨酸转氨酶和天冬氨酸转氨酶水平升高等不良事件的发生,但并不增加外周血淋巴细胞和中性粒细胞减少、抑郁、自杀行为或自杀观念的发生。但这些证据受原始研究随访偏倚或结果不精确性的影响,其证据质量仅属于中级。

本研究仅评价了IFN-β单药治疗成年RRMS患者的绝对有效性和安全性,证据仅适用于3年内至少有2次复发且EDSS评分 ≤ 5分的成年RRMS患者,并不适用于PRMS和伴复发的SPMS患者。

结 论

高质量证据表明,IFN-β治疗RRMS可轻微降低第1年内的复发病例数。但是目前尚无足够证据证明IFN-β在减少残疾进展病例数方面的疗效。尽管多种IFN-β推荐作为治疗RRMS的一线药物,并在临床广泛应用20余年,个体治疗时间亦超过1年,但IFN-β治疗RRMS超过1年的疗效尚不十分清楚,尚待高质量的随机对照临床试验进一步评价。

志谢 诚挚地感谢Cochrane多发性硬化及中枢神经系统罕见疾病协作组的试验检索协调员Andrea Fittipaldo在文献检索中给予的热心帮助;同时感谢中国循证医学中心刘鸣教授对本研究给予的悉心指导

参 考 文 献

[1] Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology, 1996, 46:907-911.

[2] Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. Brain, 2006, 129(Pt 3):606-616.

[3] Tullman MJ, Oshinsky RJ, Lublin FD, Cutter GR. Clinical characteristics of progressive relapsing multiple sclerosis. Mult Scler, 2004, 10:451-454.

[4] Karampampa K, Gustavsson A, Miltenburger C, Eckert B. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from five European countries. Mult Scler, 2012, 18 Suppl 2:7-15.

[5] Oleen - Burkey M, Castelli - Haley J, Lage MJ, Johnson KP. Burden of a multiple sclerosis relapse: the patient's perspective. Patient, 2012, 5:57-69.
[6] Karampampa K, Gustavsson A, Miltenburger C, Kindundu CM, Selchen DH. Treatment experience, burden, and unmet needs (TRIBUNE) in multiple sclerosis: the costs and utilities of MS patients in Canada. J Popul Ther Clin Pharmacol, 2012, 19:E11-25.
[7] Kieseier BC. The mechanism of action of interferon - β in relapsing multiple sclerosis. CNS Drugs, 2011, 25:491-502.
[8] Rice GP, Incorvaia B, Munari L, Ebers G, Polman C, D'Amico R, Filippini G. Interferon in relapsing - remitting multiple sclerosis. Cochrane Database Syst Rev, 2001, (4):CD002002.
[9] Filippini G, Munari L, Incorvaia B, Ebers GC, Polman C, D'Amico R, Rice GP. Interferons in relapsing remitting multiple sclerosis: a systematic review. Lancet, 2003, 361:545-552.
[10] Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, Tourtellotte WW. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol, 1983, 13:227-231.
[11] McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg - Wollheim M, Sibley W, Thompson A, van den Noort S, Weinshenker BY, Wolinsky JS. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol, 2001, 50:121-127.
[12] Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg - Wollheim M, Thompson AJ, Weinshenker BG, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol, 2005, 58:840-846.
[13] Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg - Wollheim M, Thompson AJ, Waubant E, Weinshenker B, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol, 2011, 69:292-302.
[14] Kurtzke JF. Rating neurological impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). Neurology, 1983, 33:1444-1452.
[15] Ware JE Jr, Sherbourne CD. The MOS 36 - item short - form health survey (SF - 36). Ⅰ: conceptual framework and item selection. Med Care, 1992, 30:473-483.
[16] Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW. A health - related quality of life measure for multiple sclerosis. Qual Life Res, 1995, 4:187-206.
[17] Fischer JS, La Rocca NG, Miller DM, Ritvo PG, Andrews H, Paty D. Recent developments in the assessment of quality of life in multiple sclerosis (MS). Mult Scler, 1999, 5:251-259.
[18] Cella DF, Dineen K, Arnason B, Reder A, Webster KA, Karabatsos G, Chang C, Lloyd S, Steward J, Stefoski D. Validation of the functional assessment of multiple sclerosis quality of life instrument. Neurology, 1996, 47:129-139.
[19] Higgins J, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011 [2014 - 08 - 01].http://handbook.cochrane.org/
[20] The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
[21] Schünemann H, Brozek J, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendation. Version 3.2. The GRADE Working Group, 2009[2014-08-01]. http://www.cc-ims.net/gradepro.
[22] Milanese C, Salmaggi A, La Mantia L, Campi A, Eoli M, Savoiardo M, Bianchi G, Nespolo A. Double blind study of intrathecal beta - interferon in multiple sclerosis: clinical and laboratory results. J Neurol Neurosurg Psychiatry, 1990, 53:554-557.
[23] Herndon RM, Jacobs LD, Coats ME, Goodkin DE, Mass MK, Richert JR. Results of an ongoing, open - label, safety extension study of interferon beta - 1a (Avonex) treatment in multiple sclerosis. Int J MS Care, 1999, 2:1-6.
[24] Singer B, Bandari D, Cascione M, LaGanke C, Huddlestone J, Bennett R, Dangond F; REFORMS Study Group. Comparative injection - site pain and tolerability of subcutaneous serum - free formulation of interferon β - 1a versus subcutaneous interferon β - 1b: results of the randomized, multicenter, Phase Ⅲb REFORMS study. BMC Neurol, 2012, 12:154.
[25] Clanet M, Radue EW, Kappos L, Hartung HP, Hohlfeld R, Sandberg - Wollheim M, Kooijmans - Coutinho MF, Tsao EC, Sandrock AW; European IFNbeta-1a (Avonex) Dose-Comparison Study Investigators. A randomized, double - blind, dose - comparison study of weekly interferon beta-1a in relapsing MS. Neurology, 2002, 59:1507-1517.
[26] Panitch H, Goodin DS, Francis G, Chang P, Coyle PK, O'Connor P, Monaghan E, Li D, Weinshenker B; EVIDENCE Study Group. EVidence of Interferon Dose - response: Europian North American Compartative Efficacy; University of British Columbia MS/MRI Research Group. Randomized, comparative study of interferon beta - 1a treatment regimens in MS: the EVIDENCE Trial. Neurology, 2002, 59:1496-1506.
[27] Saida T, Tashiro K, Itoyama Y, Sato T, Ohashi Y, Zhao Z; Interferon Beta - 1b Multiple Sclerosis Study Group of Japan. Interferon beta - 1b is effective in Japanese RRMS patients: a randomized, multicenter study. Neurology, 2005, 64:621-630.
[28] Hurwitz BJ, Jeffery D, Arnason B, Bigley K, Coyle P, Goodin D, Kaba S, Kirzinger S, Lynch S, Mandler R, Mikol D, Rammohan K, Sater R, Sriram S, Thrower B, Boateng F, Jakobs P, Wash MB, Bogumil T. Tolerability and safety profile of 12 - to 28 - week treatment with interferon beta - 1b 250 and 500 microg QOD in patients with relapsing - remitting multiple sclerosis: a multicenter, randomized, double - blind, parallel - group pilot study. Clin Ther, 2008, 30:1102-1112.
[29] Nafissi S, Azimi A, Amini - Harandi A, Salami S, Shahkarami MA, Heshmat R. Comparing efficacy and side effects of a weekly intramuscular biogeneric/biosimilar interferon beta - 1a with Avonex in relapsing remitting multiple sclerosis: a double blind randomized clinical trial. Clin Neurol Neurosurg, 2012, 114:986-989.
[30] Polman C, Barkhof F, Kappos L, Pozzilli C, Sandbrink R, Dahlke F, Jakobs P, Lorenz A; European Oral Interferon Beta - 1a in Relapsing-Remitting MS Study Group. Oral interferon beta-1a in relapsing-remitting multiple sclerosis: a double-blind randomized study. Mult Scler, 2003, 9:342-348.
[31] De Stefano N, Curtin F, Stubinski B, Blevins G, Drulovic J, Issard D, Shotekov P, Gasperini C; IMPROVE Study Investigators. Rapid benefits of a new formulation of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis. Mult Scler, 2010, 16:888-892.
[32] Knobler RL, Greenstein JI, Johnson KP, Lublin FD, Panitch HS, Conway K, Grant - Gorsen SV, Muldoon J, Marcus SG, Wallenberg JC. Systemic recombinant human interferon - beta treatment of relapsing - remitting multiple sclerosis: pilot study

analysis and six-year follow-up. J Interferon Res, 1993, 13:333-340.
[33] Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, Murray TJ, Simonian NA, Slasor PJ, Sandrock AW. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. N Engl J Med, 2000, 343:898-904.
[34] Comi G, Filippi M, Barkhof F, Durelli L, Edan G, Fernández O, Hartung H, Seeldrayers P, Sørensen PS, Rovaris M, Martinelli V, Hommes OR; Early Treatment of Multiple Sclerosis Study Group. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet, 2001, 357:1576-1582.
[35] Filippi M, Rovaris M, Inglese M, Barkhof F, De Stefano N, Smith S, Comi G. Interferon beta-1a for brain tissue loss in patients at presentation with syndromes suggestive of multiple sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet, 2004, 364:1489-1496.
[36] Kappos L, Polman CH, Freedman MS, Edan G, Hartung HP, Miller DH, Montalban X, Barkhof F, Bauer L, Jakobs P, Pohl C, Sandbrink R. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology, 2006, 67:1242-1249.
[37] Barkhof F, Polman CH, Radue EW, Kappos L, Freedman MS, Edan G, Hartung HP, Miller DH, Montalbán X, Poppe P, de Vos M, Lasri F, Bauer L, Dahms S, Wagner K, Pohl C, Sandbrink R. Magnetic resonance imaging effects of interferon beta-1b in the BENEFIT study: integrated 2-year results. Arch Neurol, 2007, 64:1292-1298.
[38] Comi G, De Stefano N, Freedman MS, Barkhof F, Polman CH, Uitdehaag BM, Casset-Semanaz F, Hennessy B, Moraga MS, Rocak S, Stubinski B, Kappos L. Comparison of two dosing frequencies of subcutaneous interferon beta-1a in patients with a first clinical demyelinating event suggestive of multiple sclerosis (REFLEX): a phase 3 randomised controlled trial. Lancet Neurol, 2012, 11:33-41.
[39] De Stefano N, Comi G, Kappos L, Freedman MS, Polman CH, Uitdehaag BM, Hennessy B, Casset-Semanaz F, Lehr L, Stubinski B, Jack DL, Barkhof F. Efficacy of subcutaneous interferon β-1a on MRI outcomes in a randomised controlled trial of patients with clinically isolated syndromes. J Neurol Neurosurg Psychiatry, 2014, 85:647-653.
[40] Schwartz CE, Coulthard-Morris L, Cole B, Vollmer T. The quality-of-life effects of interferon beta-1b in multiple sclerosis: an extended Q-TWiST analysis. Arch Neurol, 1997, 54:1475-1480.
[41] The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. Ⅰ: clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology, 1993, 43:655-661.
[42] Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, Fischer JS, Goodkin DE, Granger CV, Simon JH, Alam JJ, Bartoszak DM, Bourdette DN, Braiman J, Brownscheidle CM, Coats ME, Cohan SL, Dougherty DS, Kinkel RP, Mass MK, Munschauer FE 3rd, Priore RL, Pullicino PM, Scherokman BJ, Whitham RH. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis: the Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol, 1996, 39:285-294.
[43] PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. Lancet, 1998, 352:1498-1504.
[44] The Once Weekly Interferon for MS Study Group. Evidence of interferon beta-1a dose response in relapsing-remitting MS: the OWIMS Study. Neurology, 1999, 53:679-686.
[45] Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J, Liu S, Zhu Y, Seddighzadeh A, Hung S, Deykin A; ADVANCE Study. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol, 2014, 13:657-665.
[46] The IFNB Multiple Sclerosis Study Group, the University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. Neurology, 1995, 45:1277-1285.
[47] Paty DW, Li DK; UBC MS/MRI Study Group, the IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. Ⅱ MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology, 1993, 43:662-667.

（收稿日期：2014-08-11）

·小词典·

中英文对照名词词汇（五）

特发性炎性肌病 idiopathic inflammatory myopathies（IIM）
体感诱发电位 somatosensory-evoked potential（SEP）
36条简明健康状况调查表
Medical Outcomes Study 36-Item Short-Form Health Survey（SF-36）
调节活化正常T细胞表达和分泌因子
regulated on activation normal T cell expressed and secreted（RANTES）
同心圆硬化 Balo's concentric sclerosis（BCS）
同型半胱氨酸 homocysteine（Hcy）
突触素 synaptophysin（Syn）
顽固性呃逆和呕吐 intractable hiccup and nausea（IHN）
微栓子信号 microembolic signal（MES）
无先兆性偏头痛 migraine without aura（MO）
系统性红斑狼疮 systemic lupus erythematosus（SLE）
系统性红斑狼疮疾病活动指数
Systemic Lupus Erythematosus Disease Activity Index（SLEDAI）
细胞间黏附分子 intercellular adhesion molecule（ICAM）
细胞外信号调节激酶
extracellular signal-regulated kinase（ERK）
先兆性偏头痛 migraine with aura（MA）