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TRAb对GD早期药物治疗的预测价值

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摘　要

Graves病目前有ATDs、甲状腺手术及RAI三种治疗方法。ATDs在亚欧地区为首选，存在复发率高、药物不良反应等缺点。若能在疾病初期评估预后，医师可以精准地推荐治疗方案。我们发现存在甲状腺体积大、发病早、甲状腺毒症重、男性、有吸烟史、甲状腺低回声、高血流、碘缺乏状态、并发眼病、妊娠期等因素的GD甲亢患者中，ATDs治疗后复发的风险较高；而初诊及停药时TRAb (Thyrotropin receptor antibody)滴度越高或停药后抗体水平短期内升高的患者也更容易复发。TRAb对Graves病的诊断有明确意义，也可以一定程度上反映Graves病的预后，只是具体的预测价值尚有争议。许多国家和地区的指南也开始推荐TRAb作为指导用药和治疗的预测因素。因此，我们可以在临床工作中通过患者的性别、年龄、甲状腺形态、病史、生化等因素来综合评估GD预后、指导治疗，但仍需要进一步探索TRAb与Graves病复发概率的数量关系。

关键词

Graves病，药物治疗，促甲状腺素受体抗体，预测价值

Predictive Value of TRAb in the Early Drug Treatment of GD

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Abstract

Graves' disease has three therapeutic methods as ATDs, thyroidectomy and radioactive iodine

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(RAI). ATDs, as the first choice in Asia and Europe, have weakness like high recurrence rate and adverse drug reactions. If we can evaluate the prognosis in the early stage, clinicians can accurately recommend treatment. We find that GD hyperthyroidism patients with large thyroid volume, early onset, severe thyrotoxicosis, male, smoking history, hypothyroidism, hyperblood flow, iodine deficiency status, concurrent ophthalmopathy, pregnancy have higher risk of recurrence after ATDs treatment. Patients with higher thyrotropin receptor antibody (TRAb) titer at initial and withdrawal or with elevated antibody level in a short time after withdrawal are also easy to relapse. TRAb has definite significance in the diagnosis of Graves' disease and can also reflect the prognosis of Graves' disease to a certain extent, but the exactly predictive value of TRAb is still controversial. However, many national and regional guidelines have already recommend TRAb as a predictor of drug use and treatment. Therefore, we can comprehensively evaluate the prognosis of GD and guide treatment through the patient's gender, age, thyroid morphology, medical history, biochemistry and other factors in clinical work, but we still need to further explore the corresponding relationship between TRAb and the recurrence probability of Graves' disease.

Keywords

Graves' Disease, Drug Therapy, Thyrotropin Receptor Antibody, Predictive Value

1. Graves 病

甲状腺功能亢进症是指甲状腺激素合成和分泌增加引起的甲状腺毒症，在碘充足地区最常见的病因是 Graves 病(Graves' disease, GD)，其次是毒性结节性甲状腺肿、孤立性高功能腺瘤[1] [2] [3]。Graves 病是一种自身免疫性甲状腺疾病，是一种多因素疾病。它由遗传及环境因素共同作用，如：免疫调节相关基因(*HLA-DR*、*CD40*、*CD25*、*CTLA4*、*PTPN22* 和 *FCRL3*)、甲状腺自身抗原基因(如甲状腺球蛋白和 tsh 受体基因)、性别、人种、发病年龄、碘摄入、吸烟、感染、情绪压力、药物等[1] [2] [3] [4]。老年人临床表现可能不典型，但房颤及心衰等心血管并发症的风险会增加[1] [3] [4] [5]。除此之外，GD 在甲状腺外也可引起一系列的甲外并发症，其中 GO 是最常见也是最严重的并发症[1] [2] [4] [6]。

2. Graves 病的治疗

GD 目前有三种治疗方案：抗甲亢药物治疗(Anti-Thyroid Drugs, ATDs)、碘 131 治疗(131I 治疗，RAI)以及甲状腺切除术。在欧洲和亚洲，ATDs 作为 GD 首选治疗方法具有经济、方便的优点，常见的 ATDs 包括丙基硫氧嘧啶(Propylthiouracil, PTU)、甲巯咪唑(Methimazole, MMI)和卡比马唑(Carbimazole, CMZ)。它通过抑制甲状腺过氧化物酶的作用减少甲状腺素的合成，PTU 困扰同时抑制外环 T4 脱氢酶减少外周 T4 转化为 T3。ATDs 治疗疗程一般为 12~18 个月，多采用滴定法，阻断替代法由于副作用较大临床几乎不选择。ATDs 常见的不良反应包括肝功能损害、骨髓移植(粒细胞减少多见)、药物过敏等，严重时甚至可能需要停药或进一步住院治疗[7] [8] [9]。

而据统计，ATDs 停药复发的风险约为 50%到 67%，而 RAI 是 15%，甲状腺切除术则为 10%。因此 131I 治疗在北美洲仍是治疗 GD 的首选，却因高昂的费用以及放射源管理在其他地区多为 ATDs 的二线替代治疗。它也可同时治疗中毒性腺瘤、中毒性多结节性甲状腺肿[10]。但由于 131I 治疗后 TRAb 滴度

可能进一步升高或长期存在，一般仅在无 GO 或轻度 GO 患者中进行 131I 治疗。

甲状腺切除术包括甲状腺次全切及甲状腺全切术，甲状腺全切术后甲亢完全缓解几乎不会复发，但会导致永久性甲减；部分切除术的复发率较低，但仍有甲亢复发的风险。并且甲状腺切除术为有创性操作，费用高。故甲状腺切除术多于前两种方法无效或禁忌时选用[4] [11]。

3. 促甲状腺激素受体自身抗体(Thyrotropin Receptor Antibody, TRAb)

促甲状腺激素受体自身抗体(TRAb)是由 Adams 和 Purves 在 1956 年发现。它与促甲状腺激素(TSH)竞争性结合促甲状腺素受体(TSHR)的胞外部分。TSHR 胞外部分脱落可产生自身抗原，通过 MHC II 类分子呈递产生 TRAb [4] [6] [12]-[17]。根据 TRAb 与 TSHR 结合后产生的不同效应，可分为三种类型抗体，即阻断型(thyroid-blocking autoantibodies, TBAbs)、刺激型(TSAbs)以及中性抗体。其中，TSAbs 通过激活腺苷酸环化酶(AC)影响甲状腺细胞代谢；TBAbs 则与 TSHR 结合阻断 TSH 作用引起甲减，也与甲亢的腺外表现有关；中性抗体不影响甲状腺细胞代谢，但能通过细胞凋亡引起甲状腺细胞死亡以及腺外炎症，具体机制尚不明确。这三种抗体之间可以相互转化[6] [18] [19] [20] [21]。

由于血清 TRAb 在初次诊断 GD 的患者中阳性率可达 99%，是 GD 的特征性物质，也可以用于其他原因甲状腺疾病的鉴别[3] [4] [6] [22] [23]。ATDs 及手术治疗后 TRAb 水平逐渐下降，但 RAI 治疗后会出现一过性升高，随后下降或维持在一定水平[12] [14] [24] [25] [26]。在妊娠早期和晚期由于免疫耐受可出现 TRAb 水平下降，但会在产后反弹[27] [28]。GO 患者的 TRAb 水平高于无 GO 患者，且 GO 活动程度与抗体效价相关[29] [30] [31]。

4. GD 药物治疗预后的预测指标

4.1. 临床常用预测指标

因此，若能在 GD 初期预测 ATDs 治疗效果，临床医师就可以根据患者的复发风险选择治疗方案。综合现有研究，不难发现影响 GD 预后的因素包括甲状腺体积[32] [33] [34] [35] [36]、发病年龄(≤40 岁)[32] [34] [35] [37] [38]、性别[32] [35] [38]、甲状腺毒症的程度[32] [34] [37]、吸烟[15] [33] [37] [38] [39]、甲状腺血管状况[32] [35]、碘状态[32] [40]、甲状腺眼病病史[41]、妊娠[42]等，但与复发概率都没有具体的数量关系；而 ATDs 治疗疗程、剂量以及方案都不会影响 GD 预后[15]。

4.2. TRAb 与 GD 预后

TRAb 对 Graves 病的诊断有明确价值，而作为 GD 及其腺外并发症的特异性抗体能否用于预测 GD 预后尚存在争议。

Nyo Nyo 等人发现发病年龄(HR 0.95; p = 0.02)、诊断时(HR 1.06; p = 0.38)和停药时 TRAb 水平(HR 1.79; P = 0.002)是 ATDAs 治疗 GD 患者复发的独立预测因素。停药时 TRAb 高值组(>1.5 IU/L)的 1 年复发率明显高于低值组(<0.9 IU/L)。同时停药 TRAb 低值组的缓解时间明显长于高值组的缓解时间。因此研究者建议停药时、停药后 12 个月及 18 个月分别测量 TRAb，若停药时 TRAbs > 1.5 IU/L 的患者应该考虑长期小剂量 ATDs 维持治疗预防复发；TRAb 逐步升高则颖考虑甲状腺消融治疗[43]。Massart 等人发现当终点局限于停药后 6 个月内的复发时，检测 TSAbs 对 GD 预后具有极好的预测价值。其中识别复发患者的最佳临界值高于诊断 GD 的临界值(分别为 5.0 和 3.8 IU/L) [44]。Quadbeck B 等人认为停药 4 周后测量 TRAb 对判断复发风险有很好的价值[45]。

Laurberg 等人在一项前瞻性研究中将 131 例者随机分为 ATDs、131I 以及手术治疗三组，其中 ATDs

治疗组约 1/3 出现停药后复发，这些患者在治疗 18 个月后 TRAb 水平持续阳性，并且在复发时水平进一步升高[26] [46]。

Anupam 等人也认为高 TRAb 滴度者使用 ATDs 治疗容易复发，因此 131I 或甲状腺手术治疗更适合这类人群选择。使用 ATDs 过程中出现 TRAb 滴度升高也预示着 GD 复发风险较大。但 TRAb 阴性或低滴度并不意味着 GD 的长期缓解[6]。Carella 等人则是发现 ATDs 治疗结束时的 TRAb 滴度与复发率呈正比，与复发时间呈反比[46]。Giuseppe 等人则认为，由于反复高滴度 TRAb 对 TSHR 的刺激可能影响机体产生甲亢反应的刺激阈值，TRAb 滴度水平与甲亢严重程度可能不存在线性关系[15]。

C. Carella 等人对 58 名 GD 患者进行回顾性分析发现停药时 TRAb 的界值为 3.85 UI/L，即 TRAb > 3.85 IU/L 对 GD 复发的阳性预测率为 96.7%，并且是否复发与 TRAb 滴度变化无关；但 TRAb < 3.85 IU/L 的患者中也有 20%的复发。并且与 TRAb 高于界值组相比，低于界值组复发发生的更晚(中位复发时间分别为 8 周 vs 56 周)，且复发时 TRAb 滴度较停药时升高[46]。

Eckstein AK 等人认为停药前 TRAb 可将预测复发的效率提高到 90%。治疗后 12 和 18 个月的 TRAb 截断值分别为 7.5 IU/L 和 3.85 IU/L，但低于该值并不完全排除复发。因此停药时 TRAb 滴度对 GD 复发具有良好的特异性和阳性预测价值(>96%) [41] [46]。2016 年美国甲状腺协会(ATA)指南也推荐在停药前进行 TRAb 检测：若 TRAb 持续升高，则建议行消融治疗或继续低剂量 ATDs 治疗，并在 12~18 个月后复测[47]。因此初诊 GD 以及停药前再次评估 TRAb，可以筛选出复发风险较高的患者，尤其是针对使用甲巯咪唑超过 5 mg/天的患者。

对于妊娠期前已接受 ATDs 治疗的 GD 患者，Nedrebo BG 等人发现 TRAb 阴性的患者只有 5%会在停药后 8 个月内复发，而高 TRAb 滴度停药后复发的风险极高[48]。Noboru 等人认为妊娠期 TRAb 持续高值也可能造成新生儿甲亢，影响育龄期女性的预后[25] [49]。并且 Li Y 等人发现 TRAb 也是流产的独立危险因素[50]，因此 TRAb 也可以用于 GO 以及新生儿甲亢的风险预测，其阳性预测价值为 42% [49] [51] [52]。一项针对 47 例 TRAb 阳性孕妇的研究发现妊娠中期 TRAb 滴度超过 3 倍参考范围上限时发生新生儿甲亢的风险较高，需要长期随访孕期甲功[53]。接受过 GD 治疗的孕妇若 TRAb > 5 IU/L，胎儿和新生儿甲亢的风险将会显著增加[14]。美国甲状腺协会也建议如果服用 ATDs 的妇女在怀孕期间无法检测 TRAb，则应该减少或停用 ATD [54]。妊娠期尤其是妊娠早期，使用 ATDs 会增加新生儿先天性异常及出生缺陷的风险，因此对于 GD 复发风险高的育龄期女性应考虑在计划怀孕前早期予以消融治疗(RAI 或甲状腺切除术) [14] [49] [55]。

Woo YJ 则认为 TSAbs 可在 GO 静止期预测 GO 预后[56]。Eckstein AK 等人认为 TRAb 可以预测 GO 预后来决定 GO 是否需要治疗[57]。一项前瞻性研究也认为重度 GO 患者在诊断和随访时 TRAb 水平显著升高。若 GO 发病后 5~8 个月 TRAb > 8.8 IU/L 可使发生重度 GO 的风险增加 8.7~31.1 倍[57]。TRAb 水平与 GO 病程同步，因此 TRAb 升高也是使用糖皮质激素预防 RAI 治疗中 GO 进展的指征[14]。

然而 Kazuko Y 等人实验发现停药时 TRAb 持续阴性可能表明缓解持续时间延长，但不会增加儿童 GD 患者的最终缓解率[58]。一项荟萃分析评估了 TRAb 对 ATDs 治疗后远期复发(至少停药 1 年)的预测价值。25%停药时 TRAb 阳性的患者停药 1 年后仍处于缓解状态，而 TRAb 阴性患者中也有 25%复发，表明 TRAb 的预测价值有局限[59]。Zimmermann-Belsing T 等人也在研究中提出当使用 1.5 IU/l 的界值时，TRAb 的阳性和阴性预测值分别仅为 55%和 62%，下限(1 IU/l)以下的阳性预测值和阴性预测值更是分别降至 49%、60%。他们认为 TRAb 用于预测停药后复发的方面几乎没有价值[60]。

虽然有部分研究者认为 TRAb 对 GD 预后没有预测作用，但这些研究大部分进行的比较早，当时可能由于检测手段的限制对结果有一定的影响。目前大部分研究者都认同 TRAb 的预测作用，许多国家和

地区的诊治指南也开始推荐使用 TRAb 预测 GD 甲亢的结局来指导用药治疗。

4.3. TRAb 能否早期预测 GD 预后

既然 TRAb 对 GD 药物治疗的预后有一定的预测作用，那么如果能在疾病早期通过 TRAb 来预测 GD 结局就能更好的指导临床。

Carlo Cappelli 等人认为初诊时 TRAb 滴度、治疗 6 个月后 TRAb 滴度的下降率以及 ATD 停药时的 TRAb 滴度均有助于预测 GD 预后。初诊 TRAb ≥ 46.5 UI/L 的患者难以达到长期缓解，而停药后 6 个月内 TRAb 的下降比例低于 52.3%甚至反而升高的患者不可能完全缓解。因此 ATDs 治疗 6 个月时的 TRAb 滴度和/或下降比例可以用来预测 GD 患者可获得长期缓解的概率(敏感性为 63%，特异性为 88%) [37]。Okamoto Y 等人也认为 TRAb 水平高的患者容易发生复发[61]。另一项观察性研究认为诊断时 TRAb 水平高(>12 IU/L)的患者 2 年复发率为 59%，较 TRAb 低值组(TRAb < 5 IU/L)的 4 年复发率也是明显升高[43]。

XG Vos 等人通过 263 例患者数据建立了预测模型。他们提出 GD 治疗后复发事件(GREAT)评分，包括年龄、甲状腺肿大程度、FT4)和 TRAb 滴度。根据总分可以将患者分为三类评估复发风险。而后又纳入 PTPN22 多态性和 HLA 亚型成为 GREAT+评分，分为四个风险等级。GREAT 和 GREAT 评分最高级别的患者复发风险分别增加了 68%和 84%，但由于基因检测的成本和可用性的限制，其在临床应用仍然受到限制[34]。

Karmisholt J 等人通过研究发现治疗前 TRAb 滴度分别处于 10 IU/L 上下的患者缓解率分别为 39%和 63%，进一步提出基线 TRAb 可以预测患者能否缓解。在初始 TRAb < 10 IU/L 的患者中，ATDs 治疗 6~8 个月后再次评估也可缩短治疗时间。同时他们发现长期 ATDs 联合 L-T4 治疗的患者持续缓解率更高[62]。

5. 总结

部分研究认为 TRAb 的预测价值有局限，但这可能与当时检测手段以及抗体相关研究的缺失有关。目前大多数研究仍支持高 TRAb 水平或持续升高趋势对 GD 复发有预测作用，但并没有确切的线性关系。在今后的研究中也需要更多的数据来分析 TRAb 与 GD 预后的定量关系。而甲状腺体积、发病年龄、甲状腺毒症情况、性别、吸烟史、甲状腺超声形态、碘状态、有无眼病及是否是妊娠期等因素也可以同时作为参考靶点对停药后复发的风险进行预测。

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