

# 英夫利西单抗用于克罗恩病患者的治疗药物监测研究进展<sup>△</sup>

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**摘要** 英夫利西单抗(IFX)是目前临床广泛用于治疗克罗恩病(CD)的肿瘤坏死因子 $\alpha$ 抑制剂,但其常规剂量难以获得较佳疗效,建议疗效欠佳的患者进行治疗药物监测(TDM)以指导临床决策。本文综述了IFX的药动学特点、暴露-效应关系、药动学差异的影响因素、TDM方法等内容。IFX不经肝肾代谢,在CD诱导期和维持期均具有明显的暴露-效应关系,疾病活动度、白蛋白和抗IFX抗体(ATI)等因素影响其体内暴露。建议CD维持期患者通过TDM将IFX谷浓度保持在 $3\ \mu\text{g/mL}$ 以上,对于疾病程度重、白蛋白水平低下、形成ATI等患者应考虑增加IFX剂量或缩短给药间隔,以提高IFX的疗效。建议同一患者采用同一种检测方法进行IFX的TDM。

**关键词** 英夫利西单抗; 克罗恩病; 治疗药物监测; 暴露-效应关系; 药动学差异

## Advances in therapeutic drug monitoring of infliximab in patients with Crohn disease

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**ABSTRACT** Infliximab (IFX), tumor necrosis factor- $\alpha$  inhibitor, is widely used in clinical practice for treating Crohn disease (CD), but it is difficult to obtain the optimal therapeutic effect according to the conventional dose. It is recommended to perform therapeutic drug monitoring (TDM) for patients with poor therapeutic efficacy to guide clinical decisions. This paper reviews the pharmacokinetic characteristics of IFX, exposure-response relationship, the influencing factors of pharmacokinetic differences, and analytical methods in TDM. It is found that IFX doesn't undergo liver or kidney metabolism, exhibits obvious exposure-response relationships in both the induction and maintenance phases of CD treatment; disease activity, albumin, antibodies to IFX (ATI) and other factors influence IFX's exposure. It is recommended that trough concentration of IFX in the maintenance period should be kept above  $3\ \mu\text{g/mL}$ ; the dose of IFX should be increased or medication interval should be shortened for patients with severe disease, low albumin levels and ATI formation, to promote therapeutic efficacy of IFX. It is suggested to use the same detection method for TDM of IFX in the same patient.

**KEYWORDS** infliximab; Crohn disease; therapeutic drug monitoring; exposure-response relationship; pharmacokinetic variation

克罗恩病(Crohn disease, CD)是一组病因尚不明确的慢性非特异性肠道炎症性疾病,属于炎症性肠病(inflammatory bowel diseases, IBD)的主要类型之一。肿瘤坏死因子 $\alpha$ (tumor necrosis factor- $\alpha$ , TNF- $\alpha$ )抑制剂可通过阻断TNF- $\alpha$ 与TNF受体的相互作用,诱导表达TNF- $\alpha$ 的免疫细胞凋亡,最终抑制TNF- $\alpha$ 介导的免疫炎症反应,从而达到治疗CD的目的<sup>[1]</sup>。

英夫利西单抗(infliximab, IFX)是目前临床广泛用

于治疗CD的TNF- $\alpha$ 抑制剂,先后被我国药品监管部门批准用于成人CD患者的诱导/持续缓解治疗和瘻管性CD、儿童CD的治疗。虽然IFX极大地改善了患者的治疗结局,但在治疗过程中仍存在常规剂量下血药浓度不足,导致疗效欠佳的问题。治疗药物监测(therapeutic drug monitoring, TDM)可通过测定患者体内IFX的血药浓度和(或)抗IFX抗体(antibodies to infliximab, ATI)水平,评估相关药动学、药效学参数,从而指导临床个体化给药和分析导致治疗失败的原因。本文综述了IFX的药动学特点、暴露-效应关系、药动学差异的影响因素、TDM方法等内容,以期CD患者个体化给药方案的制定提供参考。

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## 1 IFX的药动学特点

IFX为人鼠嵌合的免疫球蛋白G<sub>1</sub>(immunoglobulin G<sub>1</sub>, IgG<sub>1</sub>)单抗,经静脉输注给药,有较高的峰浓度和较低的谷浓度,具有分子量大(149.1 kDa)和亲水性强的特点,因此该药主要在血液循环中分布,分布容积为3~6 L,半衰期为7~12 d<sup>[2]</sup>。

进入人体后,IFX不通过肝脏细胞色素P450酶系代谢,也不经肾排泄,其消除途径主要包括以下3种:(1)IFX与靶标TNF- $\alpha$ 结合形成的复合物经免疫系统消除;(2)人体产生的ATI与IFX形成免疫复合物,通过细胞内吞作用在胞内降解,从而参与IFX的消除;(3)内吞后的分解代谢(非特异性),即IFX与新生儿Fc受体(the neonatal Fc receptor, FcRn)结合后,内吞进入胞内再重新释放回血液,而未与FcRn结合的IFX则进入胞内,被溶酶体分解代谢<sup>[3]</sup>。

## 2 IFX的暴露-效应关系

适合使用TDM的药物一般具有明确的暴露-效应关系。IFX用于CD治疗的用法用量为第0、2、6周静脉输注5 mg/kg的IFX作为诱导缓解,然后每隔8周各给予1次相同剂量作为维持缓解,治疗期间可调整使用间隔和剂量。随着研究的不断深入,越来越多的证据表明,IFX在CD的治疗过程中存在明显的暴露-效应关系。本文将从IFX治疗CD的诱导期和维持期两个阶段来揭示IFX的暴露-效应关系。

### 2.1 诱导期

多项研究表明,临床缓解、瘘管应答、内镜缓解等疗效指标与诱导期IFX的血药浓度有关:美国一项纳入72例22岁以下CD患者的前瞻性队列研究结果显示,患者第2、6周IFX的血药浓度分别不低于26.7、15.9  $\mu\text{g/mL}$ ,可用于预测第14周临床应答<sup>[4]</sup>。Gonczi等<sup>[5]</sup>在纳入184例CD患者的前瞻性研究中发现,患者第2、6周IFX的血药浓度分别不低于20.4、16.9  $\mu\text{g/mL}$ ,能分别用于预测第14周临床缓解和临床应答。Davidov等<sup>[6]</sup>研究显示,瘘管性CD患者第2、6周IFX的血药浓度分别不低于9.5、7.25  $\mu\text{g/mL}$ ,可用于预测第14周的瘘管应答。来自随机对照试验的事后分析表明,患者第2、6周IFX的血药浓度分别不低于23.1、10  $\mu\text{g/mL}$ ,可预测第12周的内镜缓解<sup>[7]</sup>。上述结果提示,对处于诱导期的CD患者进行TDM能有助于临床结局的改善。此外有研究指出,对诱导期CD患者进行TDM,在药动学和药物经济学上也有益处<sup>[8]</sup>。但一项多中心开放标签的随机对照研究结果却显示,在CD诱导期对IFX进行TDM并未改善患者的临床缓解<sup>[9]</sup>。该研究共纳入57例CD患者,随机分为TDM组(29例)和标准治疗组(28例),若TDM组患者第2周的IFX血药浓度 $<20 \mu\text{g/mL}$ 或第6周的IFX血药浓度 $<15 \mu\text{g/mL}$ 或第14周的IFX血药浓度 $<3 \mu\text{g/mL}$ ,则可缩短给药间隔2周,但两组患者在第30周时的临床

缓解率比较差异无统计学意义( $P>0.05$ )。进一步分析发现,TDM组和标准治疗组患者第2、6、14周IFX的血药浓度没有差异可能是造成疗效没有差异的原因。

目前还没有指南推荐IFX在CD诱导期的有效浓度范围。2021年,来自美国、加拿大和新西兰等国的10名IBD领域的专家建议,CD患者第2、6周的IFX血药浓度应分别不低于20~25、15~20  $\mu\text{g/mL}$ <sup>[10]</sup>。

### 2.2 维持期

ACCENT I试验的事后分析表明,若患者第14周的IFX血药浓度 $\geq 3.5 \mu\text{g/mL}$ ,可预测其第54周持续应答<sup>[11]</sup>。Papamichael等<sup>[12]</sup>在多中心横断面研究中纳入了110例CD患者,结果显示,其维持期IFX血药浓度分别大于2.2、9.7、9.8  $\mu\text{g/mL}$ ,能分别预测生物学缓解、内镜缓解和组织缓解。Yarur等<sup>[13]</sup>在纳入117例瘘管性CD患者的横断面研究中发现,黏膜愈合率、瘘管愈合率和瘘管应答率随维持期患者IFX血药浓度(四分位数)升高而升高。TAXIT研究表明,对于IFX血药浓度 $<3 \mu\text{g/mL}$ 的CD患者,经强化治疗后其IFX血药浓度维持在3~7  $\mu\text{g/mL}$ ,其临床缓解率由65%提高到88%;而对于IFX血药浓度 $>7 \mu\text{g/mL}$ 的CD患者,经降低剂量后其IFX血药浓度亦维持在3~7  $\mu\text{g/mL}$ ,但其临床缓解率并没有降低<sup>[14]</sup>。2017年美国胃肠病学会和澳大利亚炎症性肠病工作组分别建议,IBD维持期患者的IFX谷浓度应维持在5  $\mu\text{g/mL}$ 以上<sup>[15]</sup>和3~8  $\mu\text{g/mL}$ <sup>[16]</sup>。2018年中华医学会消化病学分会炎症性肠病学组基于TAXIT研究,推荐3~7  $\mu\text{g/mL}$ 作为IBD患者维持期IFX的有效浓度<sup>[17]</sup>。

综上所述,IFX在CD诱导期和维持期均具有明显的暴露-效应关系,目前已有指南对于IFX在CD维持期进行TDM的推荐,但诱导期IFX体内暴露与疗效的关系尚缺乏深入研究。

## 3 IFX药动学差异的影响因素

按照标准用药方案,CD患者体内的IFX血药浓度个体差异明显,临床实践显示,76.1%的成人CD患者IFX稳态谷浓度 $<3 \mu\text{g/mL}$ ,过低的血药浓度可能导致治疗失败<sup>[18]</sup>。可见,探讨IFX药动学差异的影响因素将有助于实现IFX的个体化给药。

### 3.1 疾病活动度

一项纳入116例CD患者的临床研究结果表明,IFX清除率随CD活动指数和粪便钙卫蛋白表达水平升高而增加,与疾病活动度有关的Harvey-Bradshaw指数影响了IFX的中央室分布容积<sup>[19]</sup>。疾病活动度越高,IFX清除越快,其可能有两种原因:(1)炎症程度重则TNF- $\alpha$ 水平高,IFX与大量TNF- $\alpha$ 结合后IFX浓度降低而导致清除率加快;(2)IFX在网状内皮系统中经蛋白水解消除,炎症程度加重导致巨噬细胞蛋白水解活性增强,使得IFX消除加快<sup>[20]</sup>。

### 3.2 人口学特征

研究指出,CD好发于男性,女性患者的IFX清除率却高于男性患者<sup>[21]</sup>,且成人患者的IFX清除率随年龄的增长而逐渐降低<sup>[22]</sup>,但不同年龄段儿童的IFX清除率差异尚无定论。一项纳入141例儿童IBD患者的研究结果表明,处在生长和发育阶段儿童(0~20岁)的IFX体重归一化清除率与年龄无关<sup>[23]</sup>。数个群体药动学模型证实,患者体重越大,其IFX清除率越低<sup>[24-25]</sup>。

### 3.3 病理生理状态

影响IFX清除的病理生理状态主要为白蛋白水平。2009年,有学者在中重度溃疡性结肠炎患者中首次发现,白蛋白水平与IFX清除率呈负相关<sup>[26]</sup>。2011年,Fasanmade等<sup>[24]</sup>在CD患者中也发现了相似结果。目前,白蛋白水平与IFX清除率的相关性已被群体药动学模型证实<sup>[25]</sup>,但尚未明确白蛋白水平影响IFX消除的具体机制。有学者推测,白蛋白影响IFX消除的可能原因是白蛋白和IFX都能结合血管内皮细胞上的FcRn,白蛋白水平低下时,白蛋白与FcRn结合能力增强,从而导致IFX在胞内降解增多<sup>[20]</sup>。

### 3.4 ATI

一项纳入14 651例使用TNF- $\alpha$ 抑制剂的自身免疫性疾病患者的荟萃分析结果显示,使用IFX形成抗药抗体的比例明显高于人源化TNF- $\alpha$ 抑制剂<sup>[27]</sup>。ATI与IFX结合可形成2种不同的免疫复合物,其中较大的免疫复合物在脾脏中被单核吞噬系统消除<sup>[28]</sup>。ATI对IFX清除率的影响首次被学者Ternant等<sup>[29]</sup>报道:研究者在一项纳入33例IBD患者的临床研究中发现,ATI阳性患者的IFX清除率是ATI阴性患者的2.7倍。ATI浓度与IFX血药浓度呈现负相关<sup>[30]</sup>,其能较ATI阳性和ATI阴性这一分类协变量更好地预测患者的IFX清除率<sup>[31]</sup>。Bauman等<sup>[32]</sup>将ATI浓度分为0级(<22 ng/mL)、1级(22~200 ng/mL)、2级(200~1000 ng/mL)和3级(>1 000 ng/mL)共4个等级,并发现IFX清除率随着ATI等级的升高而增加。

### 3.5 遗传因素

在巨噬细胞、自然杀伤(natural killer, NK)细胞、B细胞、T细胞和血小板上表达的Fc $\gamma$ 受体(receptor of Fc portion of IgG, Fc $\gamma$ R)分为Fc $\gamma$ R I (CD64)、Fc $\gamma$ R II和Fc $\gamma$ R III。IFX与Fc $\gamma$ R结合后能够激活免疫细胞的内吞和水解作用,从而介导IFX消除<sup>[33]</sup>。研究发现,中性粒细胞CD64活性比值增加超过12.2,可导致IFX清除率增加约18%<sup>[34]</sup>;血小板Fc $\gamma$ R II a基因多态性可影响IFX的半衰期<sup>[35]</sup>;编码Fc $\gamma$ R III a的FCGR3A基因多态性可影响IFX的清除率,与FF型或VF型携带者相比,VV型携带者的IFX清除率升高16%<sup>[36]</sup>。IFX和另一种与Fc $\gamma$ 起相反作用的FcRn结合后能够避免被细胞内的溶酶体降解<sup>[3]</sup>。编码FcRn的FCGR2基因的启动子存在串联重复

序列(variable number of tandem repeats region, VNTR),其中VNTR3/VNTR3的FcRn mRNA表达量是VNTR3/VNTR2的1.6倍<sup>[37]</sup>,与VNTR3/VNTR3相比,VNTR3/VNTR2患者的IFX药-时曲线下面积下降16%<sup>[38]</sup>。

## 4 IFX的TDM方法

酶联免疫吸附测定(enzyme linked immunosorbent assay, ELISA)已经成为抗体类药物免疫分析领域最常用的分析方法。除ELISA方法外,液相色谱-串联质谱法也可用于检测生物基质中IFX的浓度<sup>[39]</sup>。由于检测方法的不同所测IFX浓度可能存在差异,如ELISA法所测IFX浓度高于荧光免疫层析法所测结果<sup>[40]</sup>。因此,建议同一患者测定IFX浓度时使用同一种检测方法。特别需要注意的是ELISA涉及的关键特异性结合试剂存在交叉反应的可能,如在Lisa-Tracker试剂盒中可能因交叉反应而导致结果出现假阳性<sup>[41]</sup>。

ATI的检测方法主要采用ELISA和放射免疫分析,少部分采用均相迁移率变动分析和电化学发光法<sup>[42]</sup>。目前没有统一的方法检测ATI。在体内,ATI以游离和(或)结合IFX的免疫复合物两种形式存在。药物敏感的ATI检测方法仅能在IFX低浓度时才能检出ATI,而药物耐受的ATI检测方法在IFX高浓度时仍能检出ATI。目前用于ATI检测的商用ELISA试剂盒均采用药物敏感方法<sup>[43]</sup>,容易低估ATI的阳性率。

## 5 结语

IFX体内药物浓度与疗效存在明显的相关性,建议CD维持期患者通过TDM将IFX谷浓度保持在3  $\mu$ g/mL以上,而CD诱导期的有效浓度范围尚缺乏指南/共识推荐。疾病活动度、白蛋白和ATI等因素能影响IFX体内暴露。对于疾病程度重、白蛋白水平低下、形成ATI等患者应考虑增加IFX剂量或缩短给药间隔,以提高IFX的疗效。建议同一患者采用同一种检测方法进行IFX的TDM,以避免方法差异所造成的误差。虽然,目前有多种ATI检测方法,但药物敏感的ATI检测方法容易低估ATI阳性率。因此,需要综合考虑CD患者的IFX血药浓度、ATI水平和病情,然后制定合理的治疗方案。

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