

· 临床研究 ·

# 超声观察英夫利西单抗治疗强直性脊柱炎患者骨质改变的研究

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**摘要:** **目的** 应用超声观察英夫利西单抗治疗前、后强直性脊柱炎患者骨质改变的情况,并探讨其临床意义。**方法** 48例活动性AS患者均满足1984年改良的纽约分类标准,并签署知情同意书,所有患者均接受6次infiximab 5 mg/kg 静脉输注。用高分辨率B超和能量型多普勒超声观察英夫利西单抗治疗前、后下肢关节及肌腱附着点的骨质形态学及血流供应的变化。并分别在0和30w记录背痛VAS评分,关节肿痛及CRP、ESR和BASDAI、BASFI、BASMI等指标。**结果** 48例AS患者完成试验,其中31例复查了超声检查。治疗前48例患者超声检查发现骨侵蚀有37处,骨赘有2处,肌腱增厚有17处,滑囊炎有15处,肌腱钙化1处,异常血流数有22处,关节积液11处,滑膜增生1处。英夫利西单抗治疗后30w,31例患者复查超声发现骨侵蚀8处,多普勒异常血流1处,与治疗前比较统计学有显著差异( $P < 0.01$ ),滑囊炎3处,与治疗前比较统计学有差异( $P < 0.05$ )。骨侵蚀中以股骨大转子肌腱点最多,有13处,治疗后只有2处;膝关节内侧副韧带7处,治疗后为2处,与治疗前相比有统计学差异( $P < 0.05$ )。骨赘治疗前有2处,治疗后无进展,仍为2处,与治疗前相比无统计学差异( $P > 0.05$ )。治疗前后各临床指标均有明显好转,统计学有显著差异( $P < 0.01$ )。**结论** 超声可清晰显示肌腱附着点及关节的骨侵蚀、骨赘形成,并可发现肌腱增厚、滑囊炎、关节滑膜增生及异常血流等情况,能更实时反映AS患者骨质改变的过程及监测疗效。

**关键词:** 超声; 脊柱炎; 强直性; 骨侵蚀; 骨赘

## Study of therapeutic effects of infliximab on bone in patients with ankylosing spondylitis using ultrasonography

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**Abstract: Objective** To observe the bone change before and after infliximab treatment in patients with ankylosing spondylitis (AS) using ultrasonography, and to explore its clinical significance. **Methods** All the 48 cases of active AS patients met the modified New York criteria (1984), signed informed consent forms, and received 6 times of intravenous infusion of infliximab 5 mg/kg. Bone change on lower limb joints and tendon insertion sites in terms of morphology and blood flow after infliximab treatment was observed using high-resolution B ultrasonography and energy Doppler ultrasonography. Back pain VAS scores, joint swelling and pain, CRP, ESR, BASDAI, DASFI, and BASMI were recorded on week 0 and week 30, respectively. **Results** Forty-eight cases of AS patients completed the trial, and 31 of them had recheck using ultrasonography. Before the treatment, 37 sites of bone erosion, 2 sites of osteophyte, 17 sites of tendon thickening, 15 sites of bursitis, 1 site of tendon calcification, 22 sites of abnormal blood flow, 11 sites of joint effusion, and 1 site of synovial proliferation were found among the 48 cases using ultrasonography. Thirty weeks after infliximab treatment, 8 sites of bone erosion and 1 site of abnormal blood flow were found among the 31 patients who underwent recheck using ultrasonography. The difference was statistically significant ( $P < 0.01$ )

compared to the amount before the treatment. Three sites of bursitis were found after the treatment, which was statistically different ( $P < 0.05$ ) compared to the amount before the treatment. There were 13 sites of bone erosion found in the tendons of greater trochanter of the femur and 7 sites in the medial collateral ligaments of knee joints before the treatment. However, only 2 sites in the tendons of greater trochanter of the femur and 2 sites in the medial collateral ligaments of knee joints remained after the treatment, and the difference was significant ( $P < 0.05$ ). Two sites of osteophyte remained after the treatment ( $P > 0.05$ ). All the clinical indicators improved after the treatment, and the difference was statistically significant ( $P < 0.01$ ) compared to those before the treatment. **Conclusion** Ultrasonography can clearly show the formation of bone erosion and osteophyte on tendon insertion sites and joints, and identify abnormalities such as tendon thickening, bursitis, synovial proliferation, and abnormal blood flow. Particularly, it can reflect bone change in AS patients in a real-time manner and monitor the treatment efficacy.

**Key words:** Ultrasound; Spondylitis; Ankylosing; Bone erosion; Osteophyte

强直性脊柱炎(ankylosing spondylitis, AS)是一种慢性、进行性炎症性疾病,主要累及骶髋关节及脊柱,最终可以造成关节功能障碍和畸形,致残率高。AS骨代谢有其自身独有的特点:在发生广泛性骨质疏松的同时还伴有脊柱或关节周围软组织骨化及新骨生成<sup>[1]</sup>,故对其发病机制和演变过程的研究对加深认识该病非常重要。近年研究<sup>[2]</sup>表明,AS患者在早期即可有明显的骨密度降低,骨密度下降与疾病的持续活动性有关,是疾病本身炎症所引起<sup>[3]</sup>,炎症因子(肿瘤坏死因子、白细胞介素-6及白细胞介素-1等)在其中起了非常重要作用,英夫利西是一种单克隆抗TNF- $\alpha$ 拮抗剂,最近较多研究报道在AS患者中使用英夫利西有着良好的临床反应,可以抑制炎症,改善骨质疏松、骨侵蚀。超声对于强直性脊柱炎患者的关节、肌腱附着点等多部位检测极为灵敏和方便,其可以发现骨侵蚀、骨赘形成和软组织骨化等,所以目前被越来越广泛的应用。本研究拟通过高分辨率B超和能量型多普勒超声测定活动期的强直性脊柱炎患者在英夫利西治疗前、后强直性脊柱炎患者骨质改变的情况,并探讨其临床意义。

## 1 材料和方法

### 1.1 研究对象与给药方法

48例AS患者为2010年3月至2013年1月我院肾脏风湿科的住院患者,均满足1984年改良的纽约分类标准<sup>[4]</sup>且病情处于活动期,且Bath AS活动指数(BASDAI)  $\geq 4$ <sup>[5]</sup>。排除标准包括:临床和影像学提示脊柱已完全强直;其他炎症性的风湿性疾病;现患或有活动性结核病史;胸片检查阴性但T-spot试验阳性者;严重感染;活动性乙型肝炎、丙型肝炎;有其他严重心、肝、肾、血液系统等重要脏器疾病和肿瘤。所有患者以前均未接受过TNF生物制剂的治疗。

### 1.2 方法

**1.2.1 使用仪器:** Mylab 90 超声仪超声诊断仪,应用频率为4~6 MHz的灰阶B超和彩色能量图超声,选择骨骼肌肉条件,总增益50 dB,彩色多普勒增益80~90 dB,动态范围50~60 dB,壁滤波30~40 Hz。每例患者均由同一超声医师在治疗前后行超声检查。治疗前后的能量多普勒超声是标准化的。

**1.2.2 检查部位:** 每例患者均由同一名长期从事肌肉骨骼系统疾病的超声医师在基线及30w行超声检查。部位包括双侧髋关节、双侧膝关节、双侧股骨大转子肌腱、双侧股四头肌腱、双侧跟腱、双侧髌韧带起点、双侧髌韧带止点、双侧膝关节内侧副韧带、双侧膝关节外侧副韧带、双侧趾底筋膜等部位。检查膝关节、股四头肌腱、髌韧带时,患者取仰卧位膝关节屈曲30°;检查跟腱及趾底筋膜时,患者取俯卧位,双足屈曲90°放在检查床边缘。

**1.2.3 判读标准:** 检测附着点病变包括附着点肌腱厚度、滑膜炎、骨侵蚀、骨赘。肌腱厚度主要测量肌腱最厚处;滑膜炎为局限于生理性滑囊部位出现可压缩的低或无回声区;骨侵蚀为骨皮质连续性的中断;骨赘是出现在附着点骨皮质末端高回声的隆起。

**1.2.4 临床疗效指标:** 全部患者分别在基线和30w记录评估Bath AS疾病活动性指数(BASDAI)<sup>[6]</sup>、Bath AS疾病功能指数(BASFI)、Bath AS疾病测量指数(BASMI)、AS患者总体评分(PGA)、夜间痛、背痛VAS评分和晨僵时间,关节肿痛等指标。并测定血沉(erythrocyte sedimentation rate, ESR)、C反应蛋白(C reactive protein, CRP),其中ESR的检测采用魏氏法,CRP的检测采用免疫比浊法。

### 1.3 统计学处理

所有数据用 $\bar{x} \pm s$ 表示,用SPSS 11.0统计软件包进行统计学分析,不同组别之间的差异用非参数分析。组间资料比较采用Fisher检验, $P < 0.05$ 即认为差异有统计学意义。

## 2 结果

### 2.1 患者的一般情况

共有 48 例活动性 AS 患者完成研究,其中男性 41 例(占 85.4%),女性 7 例(占 14.6%),平均年龄是  $28.4 \pm 9.9$  岁,平均病程为  $4.6 \pm 4.2$  年,HLA-B27 阳性为 90%。其中 AS 中轴型患者 36 例,中轴合并外周关节的患者共 12 例。其中 31 例患者重复了治疗后的超声检查,见表 1。

### 2.2 治疗前后超声检查 AS 患者骨质改变的比较

治疗前 48 例患者完成 960 处附着点部位和关节的超声检查,而治疗后 31 例患者完成 620 处附着点部位及关节的超声检查。由表 2 可见,治疗前 48 例患者超声检查发现骨侵蚀有 37 处,骨赘有 2 处,肌腱增厚有 17 处,滑囊炎有 15 处,肌腱钙化 1 处,异常血流数有 22 处,关节积液 11 处,滑膜增生 1 处。英夫利西单抗治疗后 30 w,31 例患者复查超声

发现骨侵蚀 8 处,与治疗前比较统计学有差异( $P < 0.01$ ),滑囊炎 3 处,与治疗前比较统计学有差异( $P < 0.05$ ),治疗后仅有 1 处出现多普勒异常血流,与治疗前比较统计学有显著差异( $P < 0.01$ ),而治疗后骨赘 2 例,肌腱附着点钙化 1 例,与治疗前统计学无差异( $P > 0.05$ ),见表 2。

表 1 患者的一般情况( $n=48$ )

Table 1 General information of the patients ( $n=48$ )

参数	结果
性别:男/女( $n$ )	85.4% (39)
平均年龄(岁)	$28.4 \pm 9.9$
病程(年)	$4.6 \pm 4.3$
中轴型;混合型	36:12
夜间背痛 VAS(cm)	$5.40 \pm 2.85$
BASDAI	$5.23 \pm 1.64$
BASFI	$3.99 \pm 2.73$
BASMI	$1.91 \pm 2.47$

表 2 治疗前后超声检查 AS 患者骨质改变的比较(例数)

Table 2 Comparison of the bone change of AS patients before and after the treatment using ultrasonography (cases)

时间	总病例数	骨侵蚀	骨赘	肌腱增厚	滑囊炎	肌腱钙化	异常血流数	关节积液	滑膜增生
0 w	48	37	2	17	15	1	22	11	1
30 w	31	8	2	8	3	1	1	3	0
$P$ 值		$<0.01$	$>0.05$	$>0.05$	$<0.05$	$>0.05$	$<0.01$	$>0.05$	$>0.05$

### 2.3 治疗前后各部位病变超声检查的比较

由表 3 可见治疗前骨侵蚀以股骨大转子肌腱点最多,有 13 处,其次为膝关节内侧副韧带 7 处,治疗后均有明显好转,分别为 2 处,0 处,与治疗前相比有统计学差异( $P < 0.05$ )。肌腱增厚以跟腱最多有 5 处,其次股四头肌腱点 4 处、股骨大转子 2 处、膝关节内侧副韧带 2 处、膝关节外侧副韧带 2 处、跖底筋膜 2 处,治疗后与治疗前相比无统计学差异( $P > 0.05$ )。治疗前股四头肌腱点滑囊炎有 13 处,治疗后有 2 处,与治疗前相比有统计学差异( $P < 0.05$ )。关节积液以膝关节为多,有 9 处,治疗后有 3 处,与治疗前比较,虽有好转,但无统计学差异( $P > 0.05$ )。骨赘治疗前有 2 处,治疗后有 2 处,与治疗前相比无统计学差异( $P > 0.05$ )。见表 3。

### 2.4 治疗前后临床观察指标比较

由表 4 可以看出,治疗 30 w 后 48 例患者的 BASDAI、BASFI、BASMI、AS 患者夜间背痛、总体背痛评分,较基线时有明显改善( $P < 0.01$ ),治疗 30 w 时 ESR、CRP 水平较基线时有明显下降,差异有显

著性( $P < 0.01$ )。见表 4。

## 3 讨论

强直性脊柱炎是一种慢性炎症性疾病,可影响骶髂关节、外周附着点及外周关节等,目前多项临床随机对照研究<sup>[7,8]</sup>已证实抗 TNF- $\alpha$  抑制剂作为靶向治疗可以缓解 AS 的各种症状、有效地控制 AS 的病情活动<sup>[9,10]</sup>,且放射学无进展<sup>[10]</sup>。英夫利西是一种抗肿瘤坏死因子单克隆抗体,我国近年来开始应用其治疗风湿性疾病,由于放射学检查对于 AS 患者早期的骨侵蚀及附着点受累不敏感<sup>[11,12]</sup>,而骨密度只能检测髋关节及腰椎总骨量的情况,不能及时反映关节及肌腱附着点等多部位受累的情况。近年来超声用于检测炎性关节炎是风湿界一大革新,技术的进步使得超声的分辨率和彩色多普勒的敏感性有了显著提高,因其无放射性、灵活、多部位检测、重复性好,促使国内外将超声作为检测四肢关节、肌腱和滑囊等首选的方法之一。国外研究显示高分辨超声可以清晰地 AS 患者的骨侵蚀、骨赘形成、肌腱附着



节炎的肌腱病变的发病机制不仅与机械因素而且与炎症均有关,脊柱关节炎的肌腱端损伤及修复可能触发炎症反应和调节免疫激活<sup>[21]</sup>。

总之,超声相对操作简便易行,可以实时、动态、重复观察关节、肌腱、骨面、关节腔、滑囊既关节周围软组织,能更实时反映 AS 患者骨质改变的过程,有助于对疾病进行正确的判断、监测疗效、评价病变的转归,而且在不同操作者之间也容易达成一致,有利于开展多中心的研究,当然这需要进一步多中心、前瞻性、随机对照研究来证实。

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