

# Smoking Lessens Response to TNF Blockers

BY NANCY WALSH  
New York Bureau

LIVERPOOL, ENGLAND — Patients with rheumatoid arthritis who have a history of cigarette smoking are more likely to have a poor response to anti-tumor necrosis factor therapy than are those who have never smoked.

Recent studies have provided strong evidence that cigarette smoking is a risk factor in susceptibility to rheumatoid arthri-

tis (RA) and more severe disease. Smokers with RA appear to have increased production of cytokines like tumor necrosis factor, and autoantibodies such as rheumatoid factor. A recent study from the British Society for Rheumatology's biologics register found current smokers had a low response rate to infliximab (Rheumatology [Oxford] 2006;45:1558-65).

"To see if smoking affects the response to therapy in our patients and to determine if there is a relationship between re-

sponse and pack-year history, we collected demographic data and smoking histories for all patients at our hospital who were started on anti-TNF drugs since 2002," said Dr. Derek L. Matthey of Staffordshire Rheumatology Centre, University Hospital of North Staffordshire, Stoke-on-Trent (England). A total of 154 patients whose mean age was 65 years were included. Infliximab was the agent used by 83 patients, etanercept by 55, and adalimumab by 16.

Two-thirds of the patients reported ever having smoked, but only 25% were still current smokers at the time they initiated treatment.

The extent of previous smoking was quantified, with one pack-year being equivalent to 20 cigarettes per day for 1 year, and intensity of smoking stratified as never (0 pack-years), light (1-15 pack-years), moderate (16-30 pack-years), and heavy (more than 30 pack-years).

At baseline, smokers were more likely to be rheumatoid factor positive and have nodular disease, but smokers and non-smokers did not differ in baseline Disease Activity Score (DAS) 28, Health Assessment Questionnaire (HAQ) scores, pain scores, or C-reactive protein level, Dr. Matthey said.

Response was defined according to the EULAR (European League Against Rheumatism) improvement criteria, based on 3-month DAS28 and absolute change in DAS28 from baseline.

At 3 months, there were significant differences between the groups, with patients

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whose smoking history exceeded 30 pack-years having an odds ratio of 7.4 for nonresponse versus patients who never smoked. The odds ratios for those in the light and moderate groups were 1.9 and 1.8, respectively.

Multivariate logistic regression analysis showed that the association of pack-year history with nonresponse was independent of age, sex, disease duration, baseline DAS28, and HAQ scores.

Moreover, the association was independent of smoking status at initiation of anti-TNF treatment.

Analysis also determined that the association of smoking and nonresponse was significant at 3 months only for infliximab, but there also was a trend for nonresponse by 12 months for etanercept.

On the DAS28, the subjective areas of patient global assessment and tender joint count were associated with increased pack-year history, unlike the objective areas of erythrocyte sedimentation rate and swollen joint count. "There also was an inverse relationship between pack-years smoked and change in pain scores," he said at the annual meeting of the British Society for Rheumatology.

Dr. Matthey also undertook an analysis of the cytokine and metalloproteinase profiles in a group of 80 patients with early RA, to identify the possible impact of smoking at this level. In a poster, they reported that on ELISA and multiplex analyses, elevated levels of interleukin-8, vascular endothelial growth factor, and metalloproteinases 1, 8, and 9 were associated with smoking, and vascular endothelial growth factor and metalloproteinases 8 and 9 showed significant associations with number of pack-years. ■



## BRIEF SUMMARY

Please consult package insert for full Prescribing Information.

## INDICATION

EUFLEXXA™ (1% sodium hyaluronate) is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics (e.g., acetaminophen).

## CONTRAINDICATIONS

- Do not use EUFLEXXA™ to treat patients who have a known hypersensitivity to hyaluronan preparations
- Do not use EUFLEXXA™ to treat patients with knee joint infections, infections or skin disease in the area of the injection site

## WARNINGS

- Mixing of quaternary ammonium salts such as benzalkonium chloride with hyaluronan solutions results in formation of a precipitate. EUFLEXXA™ should not be administered through a needle previously used with medical solutions containing benzalkonium chloride. Do not use disinfectants for skin preparation that contain quaternary ammonium salts
- Do not inject intravascularly because intravascular injection may cause systemic adverse events

## PRECAUTIONS

### General

- Patients having repeated exposure to EUFLEXXA™ have the potential for an immune response; however, this has not been assessed in humans
- Safety and effectiveness of injection in conjunction with other intra-articular injectables, or into joints other than the knee has not been studied
- Remove any joint effusion before injecting
- Transient pain or swelling of the injected joint may occur after intra-articular injection with EUFLEXXA™
- Do not use after expiration date
- Protect from light
- Do not re-use—dispose of the syringe after use
- Do not use if the blister package is opened or damaged

### Information for Patients

- Transient pain and/or swelling of the injected joint may occur after intra-articular injection of EUFLEXXA™
- As with any invasive joint procedure, it is recommended that the patient avoid any strenuous activities or prolonged (i.e., more than 1 hour) weight-bearing activities such as jogging or tennis within 48 hours following intra-articular injection
- The safety and effectiveness of repeated treatment cycles of EUFLEXXA™ have not been established

## ADVERSE EVENTS

Adverse event information regarding the use of EUFLEXXA™ as a treatment for pain in OA of the knee was available from two sources; a multicenter clinical trial conducted in Germany and a single center clinical trial that was conducted in Israel.

### Multicenter Clinical Investigation

This clinical investigation was a prospective randomized, double blinded, active control (commercially available hyaluronan product) study conducted at 10 centers. Three hundred twenty-one patients were randomized into groups of equal size to receive either EUFLEXXA™ (n=160) or the active control (n=161). A total of 119 patients reported 196 adverse events; this number represents 54 (33.8%) of the EUFLEXXA™ group and 65 (44.4%) of the active control group. There were no deaths reported during the study.

Incidences of each event were similar for both groups, except for knee joint effusion, which was reported by 9 patients in the active control group and one patient in the EUFLEXXA™ treatment group. A total of 160 patients received 478 injections of EUFLEXXA™. There were 27 reported adverse

events considered to be related to EUFLEXXA™ injections: arthralgia – 11 (6.9%); back pain – 1 (0.63%); blood pressure increase – 3 (1.88%); joint effusion – 1 (0.63%); joint swelling – 3 (1.88%); nausea – 1 (0.63%); paresthesia – 2 (1.25%); feeling of sickness of injection – 3 (1.88%); skin irritation – 1 (0.63%); tenderness in study knee – 1 (0.63%). Four adverse events were reported for the EUFLEXXA™ group that the relationship to treatment was considered to be unknown: fatigue – 3 (1.88%); nausea – 1 (0.63%).

### Single Center Study

In a single-center, single-blinded, placebo controlled, prospective, two parallel treatment arm clinical trial a total of 49 (25 EUFLEXXA™, 24 placebo) patients were randomized into two treatment groups in a ratio of 1:1 EUFLEXXA™ or placebo. A total of 65 adverse events were reported by 17 (68%) of the patients in the EUFLEXXA™ group and 15 (63%) in the placebo group. Of the 65 total events reported, 20 were regarded as treatment related. Knee pain, hypokinesia of the knee, knee swelling, and rash were considered to be treatment related adverse events.

### DETAILED DEVICE DESCRIPTION

Each syringe of EUFLEXXA™ contains:

|   |         |
|---|---------|
| Sodium hyaluronate                        | 20 mg   |
| Sodium chloride                           | 17 mg   |
| Disodium hydrogen phosphate dodecahydrate | 1.12 mg |
| Sodium dihydrogen phosphate dihydrate     | 0.1 mg  |
| Water for injection                       | q.s.    |

### HOW SUPPLIED

EUFLEXXA™ is supplied in 2.25 ml nominal volume, disposable, pre-filled glass syringes containing 2 ml of EUFLEXXA™. Only the contents of the syringe are sterile. EUFLEXXA™ is nonpyrogenic. 3 disposable syringes per carton.

### This product is latex-free.

### DIRECTIONS FOR USE

- Do not use EUFLEXXA™ if the package is open or damaged. Store in the original package below 77°F (25°C). Do not freeze. Protect from light.
- EUFLEXXA™ is administered by intra-articular injection into the knee synovial capsule using strict aseptic injection procedures. The full content of the syringe is injected into the affected knee at weekly intervals for 3 weeks, for a total of 3 injections.

Toll free number for providers and patients to call with questions: 1-(888)-FERRING (1-(888)-337-7464).

### MANUFACTURED FOR:

**FERRING**  
PHARMACEUTICALS

FERRING PHARMACEUTICALS INC.  
PARSIPPANY, NJ 07054

### MANUFACTURED BY:

Bio-Technology General (Israel) Ltd.  
Be'er Tuvia Industrial Zone, Kiryat Malachi 83104, Israel  
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**References:** 1. Moreland L. Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. *Arthritis Res Ther.* 2003;5:54-67. 2. Balzas EA, Denlinger JL. Viscosupplementation: A new concept in the treatment of osteoarthritis. *J Rheumatol.* 1993;suppl 39(20):3-9.