

Corticosteroids Confer Highest Infection Risk

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Assistant Editor

Patients with rheumatoid arthritis are at an increased risk of contracting infections that are severe enough to require hospitalization, compared with people without rheumatoid arthritis, and the use of oral corticosteroids exacerbates that risk, according to results from a recent study.

The results further emphasize the no-

tion that patients should be adequately informed about the heightened risk of infection with glucocorticoids.

"Patients should be routinely vaccinated against influenza, [and also] receive a pneumococcal vaccine," Dr. Mark Hochberg, coinvestigator and head of the division of rheumatology and clinical immunology at the University of Maryland, Baltimore, said in an interview.

The researchers conducted a retrospective cohort study based on records from 61

health plans across the United States from Jan. 1, 1999, through July 31, 2006.

A total of 24,530 patients were included in the RA cohort (inclusion criteria for this group were age over 18 years with at least two physician visits more than 2 months apart for RA with an ICD-9-CM diagnosis code of 714), and a random sample of 500,000 people were included in the non-RA cohort (age over 18 years and no RA diagnosis code at follow-up).

Patients in the RA cohort were more

likely to be female than in the non-RA cohort, and a greater portion of RA patients were aged 45-64 years than in the non-RA cohort (66% vs. 39%, respectively).

During the study period, "there were 1,993 cases of a first hospitalized infection in the RA cohort, while 11,977 cases were observed in the non-RA cohort," wrote the authors.

This translated to 3,864 cases per 100,000 person-years in the RA cohort and 1,250 cases per 100,000 years in the non-RA cohort and—adjusted for age, sex, and calendar year—gave a hazard ratio of 2.31 for hospitalized infection (95% confidence interval, 2.20-2.43).

Adjusted again for comorbid conditions and for prescription medication use, the hazard ratio was still 2.03 (95% CI, 1.93-2.13).

The most common infection in both groups was pneumonia, followed by urinary tract infections and after that, skin in-

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fections (J. Rheumatol. 2008;35:387-93).

The study investigators then performed a nested case-control analysis using all 1,993 hospitalized infection cases in the RA cohort and 9,965 RA controls, to ascertain whether the use of RA

drugs further increased the patients' risk of infection.

Adjusted for age, sex, other current RA medication use, and a number of other chronic conditions, as well as the number of hospitalizations between the cohort entry and the index date, the researchers found a slightly increased risk when patients were taking biological disease modifying antirheumatic drugs (DMARDs).

These drugs included infliximab, etanercept, adalimumab, and anakinra (rate ratio 1.21, 95% CI 1.02-1.43).

However, the greatest risk for infection was conferred by current use of oral corticosteroids, and that risk was dose related.

Use of the drugs at less than or equal to 5 mg/day (in prednisone equivalents) was associated with a 1.32 relative risk of infection; use of between 6 mg/day and 10 mg/day, with a 1.94 relative risk.

And use of greater than 10 mg/day had a relative risk for infection of 2.98 (95% CI, 2.41-3.69).

In conclusion, the researchers wrote that methotrexate and hydroxychloroquine were actually associated with decreased risk of hospitalized infection, "whereas for sulfasalazine, leflunomide, and other traditional DMARDs, there was no association."

The authors wrote that their study was limited by the possibility of misclassification of patients into the RA cohort and also by their inability to assess disease severity and patients' history of prior events.

The study received support from Bristol Myers Squibb Co.



NEW

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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

- Store at 2°-25°C (36°-77°F). Protect from light. Do not freeze. If refrigerated, remove from refrigeration at least 20-30 minutes before use.
- 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.
- If refrigerated, twenty to thirty minutes before use, remove the product box from the refrigerator, remove the blister pack from the box and allow the syringe to come to room temperature. Be sure to return any syringes not intended for use to the refrigerator.

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

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