see also page 173

Translated from *Rev Prescrire* March 2014; 34 (365): 173-174

canakinumab for gout attacks

NEW INDICATION

Too risky

● **There are no clinical trials of *canakinumab* in patients with gout attacks refractory to several prior treatments. Adverse effects mainly include infections, hypersensitivity reactions and dizziness.**

NOT ACCEPTABLE

Gout attacks are due to accumulation of uric acid crystals in the joints (1). If left untreated, the associated inflammation and pain subside after a few days. When ice, *paracetamol*, non-steroidal anti-inflammatory drugs (NSAIDs) such as *ibuprofen*, and *colchicine* are not sufficiently effective or cannot be used, systemic corticosteroids are another option (1). Adding an opioid analgesic can help to relieve severe pain that is unresponsive to other treatments (2).

Canakinumab (Ilaris°, Novartis Pharma) is a monoclonal antibody targeting interleukin-1 beta, a cytokine involved in immune and inflammatory processes. After having been authorised in the European Union for serious cryopyrin-associated periodic syndrome, *canakinumab* is also approved for the treatment of gout when NSAIDs and *colchicine* are ineffective and corticosteroids are inappropriate (**a**)(3).

canakinumab powder for solution for SC injection

ILARIS°

• **150 mg** *canakinumab* per vial

immunosuppressive drug; interleukin-1 beta antagonist

■ **New indication:** *"(…) symptomatic treatment of adult patients with frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate (…)".* [EU marketing authorisation, centralised procedure]

Little evaluation after multiple treatment failure. Clinical evaluation of *canakinumab* in this setting is based on two randomised, double-blind, double-dummy trials comparing subcutaneous *canakinumab* (150 mg) with intramuscular *triamcinolone* (40 mg), a long-acting corticosteroid, in 454 patients in whom NSAIDs and/or *colchicine* had failed (2-5). Both NSAIDs and *colchicine* were ineffective, not tolerated or contraindicated in only about one-third of patients. Patients had experienced at least three gout attacks in the year prior to enrolment, and 42% were taking a preventive treatment (mainly *allopurinol*).

At baseline, pain intensity in the most painful joint averaged 74 mm on a visual analogue scale ranging from 0 mm to 100 mm. In a pooled analysis of the two trials, 72 hours after the injection, pain intensity was 25 mm with *canakinumab* versus 36 mm with *triamcinolone* ($p < 0.0001$) (2-5). The clinical relevance of this difference is uncertain. Full pain relief was achieved in respectively 46% and 37% of patients in the *canakinumab* and *triamcinolone* groups, a non-significant difference. Recourse to *paracetamol*, *codeine* or corticosteroids was less frequent with *canakinumab* than with *triamcinolone* (37% versus 55%, $p < 0.0001$).

Infections, hypersensitivity reactions, dizziness. The immunosuppressive effect of *canakinumab*, and its long elimination half-life (nearly a month), create a risk of infections and possibly cancer (6).

In the two trials, 19% of patients receiving *canakinumab* developed an infection, versus 13% of patients receiving *triamcinolone*. The infections mainly included nasopharyngitis, upper respiratory tract infections, urinary tract infections, and bronchitis (2,3). Four patients receiving *canakinumab* and none treated with *triamcinolone* developed serious infections, while respectively 3.2% and 2.4% of patients developed opportunistic infections. It is also noteworthy that two patients treated with *canakinumab*, one for juvenile idiopathic arthritis and one for periodic syndrome, died of septic shock and disseminated tuberculosis (3).

Overall, 63% of patients treated with *canakinumab* versus 51% of those receiving *triamcinolone* experienced at least one adverse event (severe in respectively 7% and 3% of patients) (2, 3). The most common adverse effects associated with *canakinumab* were hypersensitivity reactions (including angioedema), dizziness, haematological disorders (especially neutropenia), and hepatic disorders (2,3). Elevation of serum uric acid levels was more frequent with *canakinumab* than with *triamcinolone*.

The *canakinumab* risk management plan calls for special monitoring of infections and malignancies.

In practice. Given its uncertain efficacy on gout-related pain, *canakinumab* is too risky to use for treatment of gout attacks. Its price is also exorbitant. It is better to stick with existing symptomatic treatments, which should be initiated as early as possible.

a- Scientists consulted by the US Food and Drug Administration (FDA) voted unanimously against authorising canakinumab for the treatment of gout (ref 4).

Selected references from Prescrire's literature search

In response to our request for information, Novartis Pharma provided us with no documentation on its product.

1- Prescrire Editorial Staff "Treatment of gout attacks" *Prescrire Int* 2008; **17** (95): 123.
2- US FDA "Ilaris (canakinumab). FDA Briefing Document for the Arthritis Advisory Committee Meeting" 21 June 2011: 67 pages.
3- EMA - CHMP "Assessment Report-Ilaris (canakinumab). EMEA/H/C/1109/II/10" 17 January 2013: 136 pages.
4- US FDA "Ilaris (canakinumab)-Summary Minutes and Transcript of the Arthritis Advisory Committee Meeting" 21 June 2011: 347 pages.
5- Schlesinger N et al. "Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions" *Ann Rheum Dis* 2012; **71**: 1839-1848 + supplementary appendix (29 pages).
6- Prescrire Rédaction "canakinumab-Ilaris°. Pour quelques formes graves de syndrome périodique associé à la cryopyrine" *Rev Prescrire* 2010; **30** (324): 726-729.