RoACTEMRA®
tocilizumab

Macrophage activation syndrome (MAS) in systemic juvenile idiopathic arthritis (sJIA)

What is MAS?

MAS is a well recognised and potentially life-threatening complication of sJIA with an estimated incidence of between 7% and 13%[1,2] and a reported mortality rate of 8% to 22%.[1,3] MAS is thought to be triggered by infections or changes in medications, but MAS can occur without clear reasons or aetiology.[1]

Due to the severity and life-threatening nature of this complication, coupled with the frequent difficulties in achieving a rapid diagnosis, appropriate vigilance and careful management of patients with active sJIA is necessary.

Diagnosing MAS

There are currently no universally accepted definitive diagnostic criteria although preliminary criteria have been published.[4]

The differential diagnosis of MAS is broad because of the variable and multisystem abnormalities of the disorder and the nonspecific nature of the most prominent clinical features, which include fever, hepatosplenomegaly, and cytopenia. As a result, achieving a rapid clinical diagnosis is often difficult. Other features of MAS include neurologic abnormalities, and laboratory abnormalities including hypofibrinogenaemia.[2,4] Successful treatment of MAS has been reported with ciclosporin and glucocorticoids.[3]

The severity and life-threatening nature of this complication, coupled with the frequent difficulties in achieving a rapid diagnosis, necessitates appropriate vigilance and careful management of patients with active sJIA.

RoActemra and IL-6

RoActemra has recently been approved for use in sJIA patients.[5] It works by binding to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) to inhibit IL-6 mediated signalling.[5]

IL-6 inhibition and MAS

Some of the laboratory features associated with RoActemra administration, related to IL-6 inhibition, are similar to some of the laboratory features associated with the diagnosis of MAS (such as a decline in leukocyte count, neutrophil count, platelet count, serum fibrinogen and erythrocyte sedimentation rate, all of which occur most notably within the week following RoActemra administration).[1,5]

However, the following characteristics: central nervous system dysfunction, haemorrhage, and hepatosplenomegaly, if present, are useful in establishing the diagnosis of MAS in the context of IL-6 inhibition. In addition, ferritin levels frequently decrease with RoActemra administration,[6,7] but often increase with MAS[1,4] and, therefore, may be a useful differential laboratory parameter.

Clinical experience and the clinical status of the patient, coupled with the timing of the laboratory specimens in relation to RoActemra administration, must guide interpretation of these laboratory data and their potential significance in making a diagnosis of MAS.

Incidence of MAS in RoActemra-treated patients

In clinical trials, RoActemra has not been studied in patients during an episode of active MAS.[5]

In a 12 week controlled study, no patient in any treatment group experienced MAS while on assigned treatment. However, during open-label treatment with RoActemra, 3% (3 out of 112) of patients developed MAS. All 3 patients had RoActemra interrupted (2 patients) or discontinued (1 patient) and the MAS resolved with treatment without sequelae. Based on a limited number of cases, the incidence of MAS does not appear to be elevated in the RoActemra sJIA clinical development experience; however no definitive conclusions can be made.[8]

Course of action if MAS is suspected

As stated above, MAS is a serious life-threatening disorder that may develop in sJIA patients. In clinical trials, tocilizumab has not been studied in patients during an episode of active MAS.[5]

In a 12 week controlled study, no patient in any treatment group experienced MAS while on assigned treatment. However, during open-label treatment with RoActemra, 3% (3 out of 112) of patients developed MAS. All 3 patients had RoActemra interrupted (2 patients) or discontinued (1 patient) and the MAS resolved with treatment without sequelae.[8]

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References

1. Sawhney S, *et al. Arch Dis Child* 2001; **85**:421–6.
2. Behrens EM, *et al*. *J Rheumatol* 2007; **34**:1133–8.
3. Stephan JL, *et al*. *Rheumatology (Oxford)* 2001; **40**:1285–92.
4. Ravelli A, *et al*. *J Pediatr* 2005; **146**:598–604.
5. RoACTEMRA Summary of Product Characteristics, August 2011, available from www.medicines.org.uk
6. Choy, E. *Curr Rheumatol Rep.* 2008; **10**(5): 413-417.
7. Yildirim K, *et al. Ann Clin Lab Sci.* 2004; **34**(4) 423-426.
8. Roche data on file RXUKDONF00052, July 2011.

PRESCRIBING INFORMATION ROACTEMRA® (tocilizumab):Please refer to RoActemra SPC for full prescribing information. Indication: RoActemra, in combination with methotrexate (MTX), is indicated for the treatment of adult patients with moderate to severe active rheumatoid arthritis who have had an inadequate response or intolerance to previous DMARDs or TNF antagonists. RoActemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with MTX. Also, in combination with MTX, for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients ≥2 years of age, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate). **Dosage and Administration: RA:** Recommended posology is 8mg/kg iv infusion given every 4 weeks. For patients with body weight over 100kg, doses exceeding 800mg per infusion are not recommended. Doses above 1.2g have not been evaluated. **sJIA:** Recommended posology is 8mg/kg for patients weighing ≥30kg or 12mg/kg for patients weighing <30kg, given every 2 weeks. Infusions should be given over 1 hour, with 8mg/kg diluted to a volume of 100ml and 12mg/kg diluted to a volume of 50ml. Treatment should be initiated by an appropriately experienced healthcare professional and patients should be given the Patient Alert Card. **Dose adjustments: RA:** No dose adjustments are required in elderly patients, or in patients with mild renal impairment. Dose reduction to 4mg/kg, or interruptions, are recommended in the event of raised liver enzymes, low absolute neutrophil count or low platelet count (see SPC for details). RoActemra should not be initiated in patients with absolute neutrophil count below 2x109/l. **sJIA:** Dose interruptions are recommended in the event of raised liver enzymes, low absolute neutrophil count or low platelet count but dose reductions have not been studied in these patients (see SPC for details). **Contraindications:** Hypersensitivity to any component of the product; active, severe infections. **Precautions: both indications:** *Infections:* Serious and sometimes fatal infections have been reported with RoActemra. In cases of serious infection interrupt therapy until controlled. Caution in patients with recurring/chronic infections, or other conditions which may predispose to infection. Severe neutropenia may be associated with an increased risk of serious infections. *Tuberculosis:* Screen for and treat latent TB prior to starting therapy. *Hypersensitivity reactions:* Fatal anaphylaxis may occur in patients who have experienced hypersensitivity reactions during previous infusions even if they have received premedication with steroids and antihistamines. Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction. If serious hypersensitivity/serious infusion related reactions occur stop RoActemra treatment and permanently discontinue. *Active hepatic disease/impairment:* Use with caution in patients with active hepatic disease/impairment. *Hepatic transaminase elevations:* Not recommended in patients with baseline ALT or AST >5xULN; caution in patients with ALT or AST >1.5xULN. Monitor ALT/AST levels according to SPC. Consider other liver function tests including bilirubin if clinically indicated. *Haematological abnormalities:* Caution in patients with platelet count <100x103/µl; monitor levels according to SPC. If reduced, follow recommendations for dose modification. Continued treatment not recommended in patients with ANC <0.5 x 109/ l or platelet count <50 x 103/µl. *Lipid parameters:* Lipid parameters should be assessed according to SPC, if elevated, patients should be managed according to local guidelines for hyperlipidaemia. *Neurological disorders:* The potential for central demyelination with RoActemra is currently unknown; physicians should be vigilant for symptoms of new onset disease. *Malignancy:* Immunomodulatory medicines may increase the risk of malignancy. *Vaccinations:* Live and live attenuated vaccines should not be given concurrently as safety has not been established. *Cardiovascular risk:* RA patients should have CV risk factors managed as part of usual standard of care. *Combined with other biologic treatments:* Not recommended due to lack of experience. *Sodium:* Product contains 26.55mg sodium per 1200mg. **RA only:** *Viral reactivation:* Viral reactivation (e.g. hepatitis B virus) has been reported with biologic therapies for RA. *Diverticulitis:* Caution in patients with a history of intestinal ulceration or diverticulitis. Patients with symptoms of complicated diverticulitis should be evaluated promptly. **sJIA only:** Macrophage activation syndrome (MAS) is a serious life-threatening disorder which may develop in sJIA patients. Tocilizumab treatment has not been studied during active MAS. **Interactions:** Patients taking medicines which are individually adjusted and metabolised via CYP450 3A4, 1A2, or 2C9 should be monitored when starting or stopping RoActemra, as doses may need adjusting. **Pregnancy and Lactation:** Women should use contraception during and for 3 months after treatment. A decision on whether to continue/discontinue breastfeeding on RoActemra therapy should take into account relative benefits to mother and child. **Undesirable effects: RA:** Most commonly reported ADRs were URTI, nasopharyngitis, headache, hypertension and increased ALT. *Very common ADR:* hypercholesterolaemia. *Common ADRs:* cellulitis, pneumonia, oral herpes simplex, herpes zoster, abdominal pain, mouth ulceration, gastritis, rash, pruritis, urticaria, dizziness, weight increased, total bilirubin increased, leukopenia, neutropenia, peripheral oedema, hypersensitivity reactions, conjunctivitis, cough, dyspnoea. *Medically significant events: Infections:* Serious infections have been reported, some with fatal outcome. Opportunistic infections have been reported. *GI perforations:* primarily reported as complications of diverticulitis. *Infusion reactions:* Hypersensitivity reactions requiring treatment discontinuation occurred in 0.3% of patients treated with tocilizumab. Reactions were generally observed during the 2nd-5th infusions. Fatal anaphylaxis has been reported. *Other:* Decreased neutrophil count, decreased platelet count, hepatic transaminase elevations, lipid parameter increases, very rare cases of pancytopenia. **sJIA:** in general ADRs similar in type to those in RA. *Medically significant events: Infections:* Serious infections were similar to those seen in RA, with additions of varicella and otitis media. *Infusion reactions:* Hypersensitivity reactions requiring treatment discontinuation occurred in <1% of patients treated with tocilizumab. *IgG:* IgG levels decreased during therapy. *Other:* decreased neutrophil count, decreased platelet count, hepatic transaminase elevations, lipid parameter increases. For all indications, prescriber should consult the SPC in relation to other side-effects. **Legal category:** POM **Presentations and Basic NHS Costs:** 80mg of tocilizumab in 4ml (20mg/ml) 1 vial: £102.40, 200mg of tocilizumab in 10ml (20mg/ml) 1 vial: £256.00, 400mg of tocilizumab in 20ml (20mg/ml) 1 vial: £512.00 **Marketing Authorisation Numbers:** EU/1/08/492/01 (80mg), EU/1/08/492/03 (200mg), EU/1/08/492/05 (400mg) **Marketing Authorisation Holder:** Roche Registration Limited, 6 Falcon Way, Welwyn Garden City, Herts AL7 1TW. RoActemra is a registered trade mark. **Date of Prep:** August 2011 RCUKMEDI00006a

Adverse events should be reported to Roche Products Limited.
Please contact UK Drug Safety Centre, Roche Products Ltd,
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Telephone number +44 1707 367554.
Adverse events may otherwise be reported via the yellow card scheme.
Reporting forms and information can be found at:
http://www.medicinesauthority.gov.mt/pub/adr.doc.

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