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). One patient who withdrew from TCZ treatment died of probable MAS 14 months after the last TCZ dose while receiving another biologic for persistent active disease. 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, June 2012, 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
Please refer to RoActemra SPC for full prescribing information.
Indications: Rheumatoid Arthritis (RA): RoActemra, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. 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.
Systemic juvenile idiopathic arthritis (sJIA): Indicated for the treatment of active 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) or in combination with MTX.
Dosage and Administration: Patients should be given the Patient Alert Card. **RA:** 8 mg/kg iv infusion given once every 4 weeks. Doses exceeding 800 mg per infusion are not recommended. **sJIA:** 8 mg/kg for patients weighing ≥ 30 kg or 12 mg/kg for patients weighing < 30 kg, given as iv infusion every 2 weeks.
Dose adjustments: RA: Dose reduction to 4 mg/kg, or interruptions, are recommended in the event of raised liver enzymes, low absolute neutrophil count (ANC) or low platelet count. RoActemra should not be initiated in patients with ANC count below 2 x 10^9/l. **sJIA:** Interrupt treatment in the event of raised liver enzymes, low ANC or low platelet count; dose reductions have not been studied in these patients.
Contraindications: Hypersensitivity to any component of the product; active, severe infections.
Precautions: Both indications: *Infections:* Cases of serious and sometimes fatal infections have been reported; interrupt therapy until controlled. Caution in patients with recurring/chronic infections, or other conditions which may predispose to infection. *Tuberculosis:* Screen for and treat latent TB prior to starting therapy. *Hypersensitivity reactions:* Serious hypersensitivity reactions have been reported and may be more severe and potentially fatal in patients who have experienced hypersensitivity reactions with previous infusions even if they have received premedication with steroids and antihistamines. Appropriate treatment should be available for immediate use if anaphylaxis occurs. If an anaphylactic reaction or other serious hypersensitivity/serious infusion related reaction occurs, permanently discontinue RoActemra. *Hepatic disease/impairment:* Use with caution in patients with active hepatic disease/impairment. *Transaminase elevations:* Not recommended in patients with ALT or AST > 5 x ULN; caution in patients with ALT or AST > 1.5 x ULN. *Haematological abnormalities:* Caution in patients with platelet count < 100 x 10^3/µl. Continued treatment not recommended in patients with ANC < 0.5 x 10^9/l or platelet count < 50 x 10^3/µl. *Lipid parameters:* If elevated, follow local guidelines for managing hyperlipidaemia. *Vaccinations:* Live and live attenuated vaccines should not be given concurrently. *Combined with other biologic treatments:* Not recommended.
RA only: *Viral reactivation:* Has been reported with biologics. *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 other medicines which are metabolised via CYP450 3A4, 1A2, or 2C9 should be monitored as doses may need to be adjusted.
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: *Very common ADRs (≥ 1/10):* URTI, hypercholesterolaemia. *Common ADRs (≥ 1/100 to < 1/10):* cellulitis, pneumonia, oral herpes simplex, herpes zoster, abdominal pain, mouth ulceration, gastritis, rash, pruritus, urticaria, headache, dizziness, increased hepatic transaminases, increased weight and increased total bilirubin, hypertension, leukopenia, neutropenia, peripheral oedema, hypersensitivity reactions, conjunctivitis, cough, dyspnoea. *Medically significant events: Infections:* Opportunistic and serious infections have been reported, some serious infections had a fatal outcome. Impaired lung function may increase the risk of developing infections. There have been post-marketing reports of interstitial lung disease, some of which had a fatal outcome. *GI perforations:* Primarily reported as complications of diverticulitis. *Infusion reactions:* Clinically significant hypersensitivity reactions requiring treatment discontinuation were reported and 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:* A hypersensitivity reaction that resulted in treatment discontinuation occurred in one out of 112 patients (< 1%). *Other:* decreased neutrophil count, decreased platelet count, decreased IgG, hepatic transaminase elevations, lipid parameter increases. Consult SPC for other ADRs.
Legal category: POM.
Presentations and Basic NHS Costs: 80 mg of tocilizumab in 4 ml (20 mg/ml) 1 vial: £102.40, 20 mg of tocilizumab in 10 ml (20 mg/ml) 1 vial: £256.00, 400 mg of tocilizumab in 20 ml (20 mg/ml) 1 vial: £512.00.
Marketing Authorisation Numbers: EU/1/08/492/01 (80 mg), EU/1/08/492/03 (200 mg), EU/1/08/492/05 (400 mg).
Marketing Authorisation Holder: Roche Registration Limited, 6 Falcon Way, Welwyn Garden City, Herts AL7 1TW. RoActemra is a registered trade mark.
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Adverse events should be reported to Roche Products Limited.
Please contact the Drug Safety Centre,
Roche Products Limted, 6 Falcon Way, Shire Park,
Welwyn Garden City, Hertfordshire, England.
Telephone number +44 1707 367554.
Adverse events may otherwise be reported via the national Adverse Drug Reactions (ADRs) reporting system.
Reporting forms and information can be found at:
http://medicinesauthority.gov.mt/phvigilance.htm

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