LRI Children's Hospital

Tocilizumab in Paediatric Rheumatology

Staff relevant to:	Medical, nursing and pharmacy staff providing Tocilizumab therapy within UHL Children's Hospital
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Contents

1. Introduction and Who Guideline applies to

These guidelines provide prescribing and monitoring guidance for all staff providing Childrens Rheumatology Tocilizumab therapy within UHL Children's Hospital. It should be read in conjunction with the relevant Summary of Product Characteristics (SPC) available on https://www.medicines.org.uk/emc/ and the BNFC.

Tocilizumab should only be initiated by and under the direction of a consultant paediatric rheumatologist, or a consultant with an interest in paediatric rheumatology.

2. Tocilizumab use in paediatric rheumatology

Overview of Mechanism (British Society of Rheumatology)
Tocilizumab is a recombinant humanized, monoclonal antibody of the immunoglobulin G1 (IgG1) sub-class directed against soluble and membrane-bound interleukin 6 receptors. Inhibiting the IL-6 receptor complex prevents IL-6 signal transduction to inflammatory mediators that summon B and T cells.

Originator/brands/biosimilar:
Brand name: RoActemra, Roche Products (originator). There are currently no available biosimilars.

Indications:
Systemic onset juvenile idiopathic arthritis (soJIA)
Polyarticular juvenile idiopathic arthritis (polyarticular JIA)
Occasional cases of uveitis (unlicensed use)
PIMS-TS

At the time this guideline is published, only the prefilled syringe is licenced for use in children of all ages. There is no licence for use of prefilled pen for children under 12 years old.

Contraindications:
Severe active infection.
Less than two years old (less than one year or weighing less than 10kg for S/C use for systemic JIA)
Children with latent tuberculosis who have not completed adequate treatment.
Previous hypersensitivity reaction to tocilizumab or any excipients. A list of the excipients can be found in the SPC.
Current intestinal ulceration or diverticulitis.

Cautions (SPC):
History of intestinal ulceration and diverticulitis.
History of recurring or chronic infection.
History of diabetes.
Hepatic impairment
Low absolute neutrophil count
Thrombocytopenia
Multiple Sclerosis or Guillain-Barre Syndrome

Screening before starting:
Baseline bloods including FBC, LFT, plasma viscosity, CRP, U/E's, LDH, HDL, Triglycerides and lipid profile, measles, hepatitis and varicella serology, TB Quantiferon, Chest X-Ray.
Discuss with the rheumatology consultant if the absolute neutrophil count is less than $1.5x10^9$ /litre. Do not initiate if neutrophil count is less than $1.0x10^9$ /litre. Discuss with the rheumatology consultant if ALT >120IU/L.
Please ensure staff go through the biologics screening checklist (Appendix 2) prior to commencing infusion.

A blueteq form must be completed by the consultant or rheumatology pharmacist /nurse specialist prior to commencing treatment. Blueteq link - Hi-Cost Drugs Database Trust Edition - National – but please note, only registered users can access this.

Dosage and routes/method of administration for patients aged 2 and above only:

Systemic JIA:

IV Route Administered once **every two weeks** by intravenous infusion
Patients under 30kg 12mg/kg (max 800mg)
Patients ≥ 30kg 8mg/kg (max 800mg)

S/C route
Patients from 10kg up to 30kg - 162mg **every two weeks**
Patients ≥30kg 162mg **weekly**

Polyarticular JIA

IV Route Administered **once every four weeks** by intravenous infusion.
Patients under 30kg 10mg/kg (max 800mg)
Patients ≥ 30kg 8mg/kg (max 800mg)

S/C route
Patients from 10kg up to 30kg 162mg **every three weeks**
Patients ≥30kg 162mg **every two weeks**

PIMS-TS(Ref no 4):

Tocilizumab can also be used for PIMS-TS for children over 1 year of age under paediatric rheumatologist recommendation only. This will require blue-teq to be completed prior to administration. Dose for the use of Tocilizumab in PIMS-TS is summarized below:

Tocilizumab	Intravenous	Infants < 1 year excluded	
		< 30 kg	For children with PIMS-TS: 12 mg/kg A second dose may be given ≥12 and ≤24 hours later if, in the opinion of the attending clinicians, the patient's condition has not improved.
		≥ 30 kg	For children with PIMS-TS: 8 mg/kg (max 800 mg) A second dose may be given ≥12 and ≤24 hours later if, in the opinion of the attending clinicians, the patient's condition has not improved.

Pre-medication:
Medication should be always prescribed in-case required for infusion reactions (see below). This should be in the "when required" page of the drug chart and these drugs should be: PO paracetamol, IV chlorphenamine and IV hydrocortisone. Please consult the BNFc for dosing.

Pre-medication is not routine practice however can be prescribed if the patient has not had a dose of Tocilizumab for 16 weeks or more, or if they have previously had a mild or moderate infusion reaction.

Side effects:

Infusion reactions - serious reactions (anaphylaxis) and infusion-related reactions (such as angioedema) have been reported (4-6% during and 16- 20.2% within 24 hours post-infusion but anaphylaxis in less than 1%). **The infusion should be stopped and not slowed if mild reaction**. Please refer to Appendix 1 – infusion reactions table for further information.

Follow anaphylaxis protocol if signs/symptoms develop. Please contact rheumatology consultant for advice. If the rheumatology team is unavailable, contact the emergency paediatric team.

Hypersensitivity reactions – can occur up to 24 hours post-infusion (especially if the patient had reactions in the past).
Reactions occur most commonly during the infusion:

- Headache
- Nausea
- Hypotension Post infusion
- Patient/parent should be advised to seek medical attention if patient develops rash, itching or hives, shortness of breath, swelling of lips, face or tongue, chest pain, dizziness, severe stomach pain or vomiting.

Potential risks:
Infections - Please note that patients can still present with an active infection despite a normal CRP level. Upper respiratory tract infection is common (>1 in 10 patients). Serious infections and fatal infections have been reported: (4-12.2 per 100 patient years). The most commonly reported serious infections included pneumonia, gastroenteritis, varicella, and otitis media. Ensure parents/young person aware they must seek medical attention if they develop symptoms suggestive of infection.
Gastrointestinal side effects: Severe abdominal pain, haemorrhage, unexplained change in bowel habits
Other reported side effects include rash, urticaria, diarrhoea, epigastric discomfort and arthralgia**.**

Safety:
Several years ago, the Food and Drug Administration issued a warning about the possible increase of tumours (especially lymphomas) associated with longer use of these drugs. There is no scientific evidence that this risk is real, although it has also been suggested that the autoimmune disease itself is associated with a small increase in the rate of malignancy (as occurs in adults). It is important that doctors discuss with the families the risk and benefit profile associated with the use of these drugs (PRINTO 2016). Drug Interactions and additional considerations: Please see current British National Formulary for Children BNFC) and Summary of Product Characteristics (SPC) for further information on this.

Blood monitoring and follow-up schedule:

Patients on IV tocilizumab should have monitoring bloods (FBC, U&E, LFT, Plasma Viscosity & CRP) before each infusion and results should be received prior to commencing infusion.

Patients on S/C tocilizumab should have monitoring bloods every month for the first three months and then every three months

Fasting lipids (total, LDL, HDL cholesterol and triglycerides) should be checked at three months after commencing on Tocilizumab and treated appropriately if abnormal. They may be checked again thereafter at the consultant's discretion.

Consideration on monitoring bloods:
FBC (neutrophils and platelets)
Caution commencing if neutrophils <1.5x10^9/L – discuss with the rheumatology consultant
Liver function (ALT/AST) • >3 times normal limit – discuss with the rheumatology registrar/Consultant as the dosing of concomitant MTX or dosing interval of tocilizumab might need alterations. If > 5 times ULN discontinue tocilizumab
*NOTE CRP (and plasma viscosity) cannot be used as marker/s for infection in presence of tocilizumab treatment since tocilizumab INHIBITS their production. Thus low threshold for suspicion of infection is needed.

Storage for RoActemra (Tocilizumab):

Store vials in a refrigerator (2°C–8°C). Do not freeze. Keep the vial(s) in the outer carton in order to protect from light. Vials contain concentrate of 20mg/ml for solution for infusion. Available as 80mg, 200mg, 400mg. Solution must be clear to opalescent, colourless to pale yellow and free of visible particles.

Directions for administration:
Intravenous use:
Administer over 1 hour in 0.9% sodium chloride.
Dilution instructions – refer to BNFc or Medusa

After preparation solution must be administered immediately, or within 4 hours if stored in fridge. Allow to reach room temperature prior to infusion. Upon completion flush with 20ml 0.9% sodium chloride at last infusion rate. Complete observations for 1 hour post infusion. Nurse may then discharge patient if no concerns

Subcutaneous use: Rotate injection site and avoid skin that is tender, damaged or scarred**.**

Monitoring during infusion:

Monitor observations every 15 minutes (temperature, pulse, respiration rate, blood pressure, oxygen saturations).

Stopping prior to surgery:

Based on adult data, IV tocilizumab should be stopped at least four weeks prior to surgery and S/C tocilizumab should be stopped at least two weeks prior to surgery; for higher risk procedures consider stopping 3-5 half-lives i.e. 55-65 days before surgery.

Biologics may be recommenced after surgery when there is good wound healing (typically around 14 days), all sutures and staples are out, and there is no evidence of infection.

Vaccinations:

Live vaccines should not be administered to patients receiving biologic therapy. Wait at least 4 weeks from last live vaccination before commencing Tocilizumab.

Children receiving biologics are immunosuppressed and should receive annual influenza immunization. They should not receive the nasal flu vaccine as this is a live vaccine but should be offered the inactivated influenza vaccine injection. Pneumococcal vaccine booster may be required depending on the age of the child and their routine vaccination status and appropriate blood results – this varies with each individual and would be a consultant decision.

Pregnancy and contraception:

Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

There are no adequate data from the use of RoActemra in pregnant women. A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose. The potential risk for humans is unknown.
RoActemra should not be used during pregnancy unless clearly necessary.
For patients of post-menarchal age, a pregnancy test must be done on the day/day prior to infusion, and documented in medical notes. (See Appendix 2 – Biologics checklist)

3. Education and Training

Clinical staff should receive training in safe handling of biologics and also be trained how to use injection devices before administrating Tocilizumab.

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Monitoring of blood results are performed at the recommended intervals	Audit of ICE records	Cons/Specialist Nurse	Annually	Local audit group panel
Blood results are acted on appropriately	Audit of clinical records	Cons/Specialist Nurse	Annually	Local audit group panel

5. Supporting References

1. NHS England pathway: Biologic Therapies for the use in Juvenile Idiopathic Arthritis (2024).
2. BSPAR Guidance -Tocilizumab use in paediatric and adolescent rheumatology Information for health professionals.
3. Medicine complete and BNFc accessed 13/04/2020 https://www.medicinescomplete.com/#/content/bnfc/_774072712?hspl=tocilizumab#content%2Fbnfc%2F_774072712%23potdirectionsForAdministration
4. Recovery trial in paediatrics (5th Feb 2021) - https://www.recoverytrial.net/files/professional-downloads/recovery_paeds_guidance_v11_clean_20210825.pdf

6. Key Words

Tocilizumab, monitoring, infusion, vaccines

The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

CONTACT AND REVIEW DETAILS	
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Details of Changes made during review: New guideline	

Appendix 1: Tocilizumab infusion reactions chart

Details of any reactions should be clearly documented in the patient's notes.

Severity	Symptoms	Immediate Action	Future Infusion
Mild	Headache Nausea Chills Slight fever Pruritis	Stop infusion and inform the senior nurse Administer oral Paracetamol if patient experiences headache, fever or chills. Administer oral Chlorphenamine if needed for pruritis Observe response and restart infusion at 10ml/h. for 20mins then increase Tocilizumab rate as tolerated to: 25ml/h. for 15mins 50ml/h. for 15mins Original rate (50 or 100ml/h.) for duration of infusion. Observe patient every 10mins until symptoms have resolved and patient is stable.	Discuss with the UHL paediatric rheumatology team before administering future infusions.
Moderate	Elevated temperature (>1°C above baseline) Urticaria Mild hypo/hypertension (change ≥ 20mmHg) Mild shortness of breath Palpitation Chest pain	Stop infusion for 20mins until symptoms have resolved and patient is stable and inform senior nurse and Rheum CNS team . Administer Chlorphenamine IV and oral paracetamol. Restart infusion at 10ml/h. for 20mins and increase rate (if tolerated) as described for mild reaction. Observe patient every 10 mins until symptoms have resolved and patient is stable.	Discuss with the UHL paediatric rheumatology team (details below) before administering future infusions.
Severe	Elevated temperature with rigors Significant ↑↓ BP (change ≥ 40mmHg) and symptomatic Significant shortness of breath Difficulty in breathing/stridor Anaphylactic reaction	Stop infusion immediately. Put out paediatric crash call 2222 Contact Named Consultant Give high flow oxygen Airway management Use anaphylaxis kit Contact Named Consultant	Patient not to receive further tocilizumab infusions. Document as allergic reaction in medical and nursing notes and on drug chart.

Appendix 2 - Childrens Rheumatology Biologics Screening Checklist

Patient Name: ……..…… Diagnosis: **……..…..**

DOB: ……. S Number: S…….

Previous systemic therapy:……
……

Other medications:……
……

If required – MDT discussion
Date: ……. Present:
Notes:
Decision:

Biologic Therapy Chosen : Adalimumab Etanercept Infliximab Tocilizumab Rituximab

Biologic Approval: NHS England commissioning criteria to be submitted?: Y/N

Y/N	**If No, IFR**

Dose and Frequency: ……
Date submitted:……

Outcome and treatment plan: ……

Screening

Medical History			**Comments**
H/O Previous serious systemic infection/s	**Y**	**N**	
Signs and symptoms of active TB Past H/O TB or close family member contact with active TB	**Y** **Y**	**N** **N**	
H/O Hep B, Hep C, HIV	**Y**	**N**	
H/O allergies (e.g. latex, egg)	**Y**	**N**	
Past history of malignancy (except NMSC)	**Y**	**N**	
H/O cardiac failure	**Y**	**N**	

H/O heavy smoking (>20/day)	**Y**	**N**	
Contraception/Pregnancy test (follow guidelines)	**Y**	**N**	
Immunodeficiency	**Y**	**N**	

Vaccination and Screening			**Comments**
H/O BCG vaccination	**Y**	**N**	
Childhood vaccinations: up to date • Influenza- Annual FLU vaccine • Pneumococcal • Varicella	**Y** **Y** **Y** **Y**	**N** **N** **N** **N**	

Clinical Examination			**Comments**
Height	**Y**	**N**	
Weight	**Y**	**N**	
Baseline BP	**Y**	**N**	
Full examination joints	**Y**	**N**	
Lymphadenopathy	**Y**	**N**	
Hepatosplenomegaly	**Y**	**N**	
CNS			
Respiratory System			
GIT			
Cardiovascular			
Renal			
Skin			
Negative pregnancy test			
Other findings			

Screening investigations (Month 0)		**Date**	**Results**
TB Screening • CXR • CXR and IGRA (TB ELISpot/QuantiFERON®-TB gold test) if immunosuppressed	☐ ☐		
Bloods • FBC • Plasma viscosity and CRP • U&E/Renal function • LFT and bone group • ANA/Autoimmune screen • VZV serology	☐ ☐ ☐ ☐ ☐ ☐ ☐		

• Measles serology • Hepatitis serology – B and C • EBV IgG & IgM • Lipid profile (Tocilizumab only) • Other tests: ……			
• Urinalysis • Pregnancy test (all females post menarche)	☐ ☐		

Consent

Doctor/CNS discussed side effects/patient leaflet given to parent/Carer:	**Sign:**	**Date:**
Risk of infection, malignancy, Advise on avoiding live vaccines 4 weeks before, during and 6 months after treatments complete		
Consent from from the patient/parents completed	**Sign:**	**Date:**

Meets screening requirements: Y/N Signed: ……..Date: ……..