Tocilizumab use in paediatric and adolescent rheumatology
Information for health professionals

Name of drug:
Tocilizumab

Brief overview of mechanism:
Tocilizumab is a recombinant humanized, anti-human 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 for drug
Licensed or NICE approved:

- **Systemic onset juvenile idiopathic arthritis (soJIA):** treating active systemic JIA in patients in patients two years of age and older, (IV route) or one year of age and older (S/C route), who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids and methotrexate.

- **Polyarticular course juvenile idiopathic arthritis (pcJIA):** by either IV infusion or S/C injection for treating juvenile idiopathic polyarthritis (rheumatoid factor positive or negative, and extended oligoarthritis) in patients two years and older whose disease has responded inadequately to methotrexate (this is defined as 15mg/m2 given subcutaneously once-weekly for at least three months).

N.B. Tocilizumab is recommended only if the companies provide them with the discounts agreed in the patient access schemes for these technologies.

NB 2. At the time of production of this document the manufacturer has not sought a paediatric and adolescent licence for the S/C pen device and so only the prefilled syringe is licenced for use in children.

Use – licenced/not licenced/NHSE pathway:

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).
- Biochemical markers outside the accepted range.
- Children with latent tuberculosis who have not completed adequate treatment.
- Previous hypersensitivity reaction to tocilizumab or any excipients.
- Intestinal ulceration or diverticulitis.
Cautions (SPC):

- History of intestinal ulceration and diverticulitis.
- History of recurring or chronic infection.
- Underlying conditions:
  - Diverticulitis.
  - Diabetes.

Contraception, pregnancy and breast feeding:

There is insufficient data to recommend use of tocilizumab during pregnancy and tocilizumab should be stopped at least three months pre-conception, but unintentional exposure early in the first trimester is unlikely to be harmful. There is no data on tocilizumab use in breastfeeding. There is no data relating to paternal exposure to tocilizumab, but it is unlikely to be harmful.

Screening and recommendations before starting:

<table>
<thead>
<tr>
<th>Clearly documented decision to start tocilizumab treatment with the indication noted.</th>
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<tbody>
<tr>
<td>Documented adherence to concomitant medication plan (e.g. DMARDs, steroids, other immunosuppression, prophylactic antibiotics/antivirals etc).</td>
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<tr>
<td>Paediatric rheumatology nurse specialist has delivered appropriate education regarding the medication with documentation of appropriate discussions and date of patient information sheets given.</td>
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<tr>
<td>Patient should be given a biologics alert card.</td>
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<tr>
<td>Core data set should be recorded in the clinical notes (active joint count, restricted joint count, physician global, parent global, parent/patient pain, CHAQ) within a month of planned first infusion.</td>
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<tr>
<td>Baseline bloods documented including FBC, LFT, ESR, CRP, U/E's, LDH HDL, Triglycerides and Lipid profile (do not initiate if absolute neutrophil count less than 2x10^9/litre).</td>
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<tr>
<td>Complete Blueteq form if part of NHS England.</td>
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<td>Ensure family know attending for regular blood tests is a requirement to receiving biologic treatment.</td>
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<tr>
<td>Confirm who will be prescribing the treatment (this will usually be tertiary care).</td>
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<tr>
<td>Confirm who will be administering the medication. If appropriate, members of the family may be trained to administer subcutaneous medication.</td>
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<td>If commencing subcutaneous therapy, consider using homecare services to supply medication.</td>
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<td>See above and ensure information is given about using contraception, ideally continuing for three months after treatment cessation.</td>
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Infection screening

TB:

- Interferon-gamma release assay investigation test for latent TB (T-spot or Quantiferon (qTB)) is negative.
- Consider chest X-ray dependent on local population risk and prevalence. If taken ensure is reported as negative for evidence of tuberculosis.
Hepatitis B&C/HIV:
- Most children are low risk and do not require testing but each centre should consider their individual population risk. Some centres screen all patients routinely. Local practice should be agreed, documented and followed.

VZV and measles:
- VZV and measles immune status should be checked before starting treatment.
- Consideration of vaccine(s) before starting but not to delay treatment.

Varicella zoster vaccine (Varilrix or Varivax) and the measles, mumps and rubella (MMR) vaccine are live attenuated vaccines and, if needed, ideally should be given at least four weeks before initiation of biologic therapies. Live vaccines must be avoided within two weeks of biologic initiation.

- Chickenpox contact in non-immune patients should be treated as per recommendations of green book/PHE guidelines.
- Consider immunisation of non-immune household contacts.

Dosage and route/methods of administration:

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<th>Systemic JIA</th>
<th>IV Route</th>
<th>Administered once every two weeks by intravenous infusion.</th>
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<td></td>
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<td>Patients under 30kg 12mg/kg (max 800mg)</td>
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<th>S/C route</th>
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<td>Patients from 10kg up to 30kg 162mg every two weeks</td>
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<td>Patients ≥30kg 162mg weekly</td>
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<th>Polyarticular JIA</th>
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Side effects
Infusion reactions:
Serious reactions (anaphylaxis) and infusion-related reactions (such as angioedema) have been reported (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.
Follow anaphylaxis protocol if signs/symptoms develop. Manage according to local guidelines.
Hypersensitivity reactions – can occur up to 24 hours post-infusion:
  o Especially if patient has experienced allergic reactions in the past.
  o Reactions occur most commonly during the infusion.
    ▪ Headache.
    ▪ Nausea.
    ▪ Hypotension.
  o Post infusion patient/parent to seek medical attention if:
    ▪ Rash, itching or hives.
    ▪ Shortness of breath.
    ▪ Swelling of lips, face or tongue.
    ▪ Chest pain.
    ▪ Dizziness.
    ▪ Severe stomach pain or vomiting.
    ▪ Low blood pressure.

Potential risks
  • Infections:
    o Upper respiratory tract infection is common (>1 in 10 patients), with typical symptoms such as cough, blocked nose, runny nose, sore throat and headache, is one of the most common side effects of tocilizumab (5% for sJIA and in pcJIA 21% under 30kg and 8% over 30kg).
    o 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.
    o Ensure parents/young person aware they must seek medical attention if:
      ▪ Fever >37.7°C on more than two occasions more than four hours apart.
      ▪ Persistent cough for more than a week.
      ▪ Weight loss on two consecutive occasions when admitted for infusion.
        ▪ Note: patients who have had recent reduction in steroid use may have weight loss that is not otherwise concerning.
      ▪ Throat pain or soreness persisting for three days or more.
      ▪ Wheezing.
      ▪ Signs of skin infection (red, hot, painful, swollen or blistered skin, boils/spreading pus spots).
      ▪ TB contact or suspicion of TB symptoms.
  • Gastrointestinal side effects:
    o Severe abdominal pain
    o Haemorrhage
    o 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).

Blood monitoring and follow-up schedule:
The paediatric and adolescent rheumatology clinical affairs committee acknowledges that the monitoring schedule listed in this document differs from that recommended in our guideline for adults. Consensus has agreed these values to reflect the differences in this specific age group of patients but are consistent with safe real-life paediatric and adolescent practice.

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

Patients on IV tocilizumab should have monitoring bloods before each infusion.

Fasting lipids (total, LDL, HDL cholesterol and triglycerides) should be checked at three months and treated appropriately if abnormal. They may be checked again thereafter at physician’s discretion.

- **FBC (neutrophils and platelets)**
  - Absolute neutrophils count (ANC).
    - Caution commencing if neutrophils <2.
    - If >1 on treatment continue same dose.
    - 0.5-1.0 interrupt dosing and restart when levels above 1.0 resume at same dose.
    - Omit if neutrophils <0.5 and consider discontinuing. Discontinuing for a laboratory abnormality should be based on medical assessment of the individual patient.
  - Platelets
    - Caution commencing if platelets <100.
    - 50-100 modify dosing of concomitant MTX if appropriate, interrupt tocilizumab dosing. Resume when platelets are >100.
    - Discontinue if platelets <50.

- **Liver function (ALT/AST)**
  - >1-3 times normal limit – modify MTX if concomitant, if persists interrupt tocilizumab dosing until levels of ALT/AST normalised.
  - >3-5 times normal level – Interrupt until less than three times ULN then as above.
  - If persistently above three times ULN then discontinue.
  - If > 5 times ULN discontinue tocilizumab.

- **Inflammatory markers to check response**
  - ESR.
  - CRP.
*NOTE CRP (and ESR) 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.

Practical tips for administration can be found in the RCN document ‘Assessing managing and monitoring biological therapies for inflammatory arthritis’ available on the RCN website www.rcn.org.uk.

Note that doses for children under 30kg should be prepared in 50ml 0.9% sodium chloride, while doses for children of 30kg or greater should be prepared in 100ml 0.9% sodium chloride. Tocilizumab is infused over one hour.

NB. The solution should be used immediately. Tocilizumab is supplied as a sterile concentrate and does not contain preservatives.

Monitoring during infusion: 15 minute observations score (temperature, pulse, respiration rate, blood pressure, oxygen saturations). This may be extended up to every 30 minutes.

Drug interactions and additional considerations:
Please see current British National Formulary for Children (BNFC) and Summary of Product Characteristics (SPC) for further information.

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. See our biological DMARD safety guidelines in inflammatory arthritis for further information.

Vaccinations:
The Department of Health publication ‘Immunisation against Infectious disease’ (the Green Book) is regularly updated and should be considered as the definitive source of information regarding vaccination.

- Live vaccines: Live vaccines should not be administered to patients receiving biologic therapy.
- Inactivated vaccines: these should be given according to the normal immunization schedule (including HPV), however immunosuppressive treatment may lower the level of immunity achieved.
- 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. They may also benefit from special vaccinations formulated in response to particular threats (e.g. H1N1). See Department of Health ‘Immunisation against infectious disease’ for current advice.
- Pneumococcal vaccine booster may be required depending on the age of the child and their routine vaccination status.
Patients receiving immunosuppressive medication who are exposed to varicella and do not have immunity require prophylactic aciclovir and selected patients may require passive immunisation using VZIG. See Public Health England Guidelines for details. Patients developing chickenpox or shingles should be treated with aciclovir and have their immunosuppressive medication withheld until they have recovered.

**Authors:**
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Clare Nash, BSPAR pharmacy lead (Sheffield Children's Hospital)
Example from: CHEERS network (Cambridge)
Literature sources:

- Sebba A. Tocilizumab: The first interleukin-6-receptor inhibitor American Journal of Health-System Pharmacy August 1, 2008 vol. 65 no. 15 1413-1418 https://www.nice.org.uk/guidance/TA373/chapter/3-The-technologies
- Royal College of Nursing Publications. Assessing, managing and monitoring biologic therapies for inflammatory arthritis RCN guidance for rheumatology practitioners (fourth edition) August 2017
This guidance document was ratified by the council of the paediatric and adolescent rheumatology section within the British Society for Rheumatology and is designed to support the delivery of paediatric and adolescent care in rheumatology.

Ratified by BSPAR Section Council: February 2020

To be reviewed in 2023