

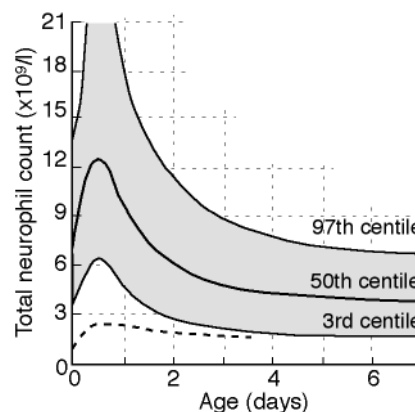
SARGRAMOSTIM

Use

Sargramostim, a granulocyte-macrophage colony-stimulating factor (GM-CSF), and filgrastim (q.v.), a granulocyte colony-stimulating factor (G-CSF) both stimulate the production and release of white blood cells from bone marrow. Trials have failed to show that prophylactic use is helpful, but no trial has yet been done to see whether use with or without immunoglobulin (q.v.) is helpful in babies with signs of overt sepsis.

Pathophysiology

Neutrophil white cells (so called because they form a thin white line above the red cells when blood is spun, and turn neither red nor blue when stained) engulf and kill bacteria. They usually only remain in circulation for ~ 6 hours after leaving the bone marrow pool before entering other body tissues. Birth causes a transient increase in the number in circulation (see fig), especially when this is stressful. Neonatal sepsis can rapidly decrease the number in circulation, because production is already close to its peak at birth. This, and functional immaturity, make babies more vulnerable to infection. Babies of <1.5 kg often have very low counts when 2–4 weeks old when the marrow mounts a first response to the growing post-delivery anaemia, as well as earlier (dotted line). Whether they are at more risk of infection is not known.



Pharmacology

Marrow colony-stimulating factors are naturally occurring glycoprotein growth promoters (cytokines) that stimulate the proliferation and differentiation of red and white blood cell precursors in the bone marrow. A number of these factors – including erythropoietin (q.v.) – have been produced by recombinant DNA technology and brought into clinical use in the last ten years. G-CSF is now widely used to prevent chemotherapy induced neutropenia, and to accelerate neutrophil recovery after bone marrow transplantation. Subcutaneous rather than IV use doubles the elimination half life to about 3 hours, increases therapeutic efficacy, and minimises the risk of toxicity associated with high peak blood levels. Adverse effects, including fever, dyspnoea, nausea and vomiting, seem to have been uncommon with neonatal use. Use during pregnancy is associated with increased fetal death in primates. Use during lactation has not been studied but seems unlikely, on theoretical grounds, to pose any serious risk.

Both G-CSF and GM-CSF have been shown to abolish the postnatal neutropenia, and the sepsis-induced neutropenia seen in preterm neonates, and also to augment neutrophil function. GM-CSF enhances both neutrophil and monocyte production and function, but may have pro-inflammatory side effects. Although the manufacturers have not yet endorsed use in children, no long term toxicity has yet been identified during fifteen years of neonatal use. However prophylactic use failed to reduce the incidence of later infection in any of the neonatal trials completed to date even though it did raise the neutrophil count. Use of G-CSF provokes a more rapid rise in the neutrophil count, and a trial of this product in babies who have developed possible sepsis and are neutropenic might serve to test an alternative, focused, treatment strategy (as outlined in the monograph on filgrastim). Combined use with immunoglobulin might be more effective, but a quicker way to offer effective support might be to try and give a transfusion if white cells (leucopheresis).

Treatment

Trials have usually given 10 micrograms/kg subcutaneously once a day for 5 (or 7) days. Inject the cytokine subcutaneously into alternate thighs using a 1 ml syringe and a 26 or 27 French gauge needle.

Supply and administration

Reconstitute a 250 microgram vial with 2.5 ml of water for subcutaneous use, to obtain a preparation containing 100 micrograms/ml. Store vials at 4°C, and use within 6 hours of reconstitution. Sargramostim is marketed in the United States, but it is not generally available in the UK, and the only other product of a similar nature, molgramostim, was withdrawn from the market in 2004.

References

- See also the relevant Cochrane reviews ©
- Schibler KR, Osborne KA, Leung LY, *et al.* A randomised placebo-controlled trial of granulocyte colony-stimulating factor administration to newborn infants with neutropenia and clinical signs of early-onset sepsis. *Pediatrics* 1998;**102**:6–13. [RCT]
- Cairo MS, Agosti J, Ellis R, *et al.* A randomised double-blind placebo-controlled trial of prophylactic recombinant human granulocyte-macrophage colony-stimulating factor to reduce nosocomial infection in very low birth weight neonates. *J Pediatr* 1999;**134**:64–70. [RCT]
- Bilgin K, Yaramis A, Haspolat K, *et al.* A randomised trial of granulocyte-macrophage colony-stimulating factor in neonates with sepsis and neutropenia. *Pediatrics* 2001;**107**:36–41. [RCT]
- Robinson SP, Marks DI. Granulocyte transfusions in the G-CSF era: where do we stand? *Bone Marrow Transplant* 2004;**34**:316–8.
- Carr R, Brocklehurst P, Doré C *et al.* Granulocyte-macrophage colony stimulating factor administered as prophylaxis for reduction of sepsis in extremely preterm, small for gestational age neonates (the PROGRAMS trial): a single-blind, multicentre, randomised trial. *Lancet* 2009;**373**:226–33. [RCT] (See also 188–91.)