Cardiol Young 2003; 13: 420–423

ISSN 1047-9511

Original Article

Recommendations for the use of palivizumab as prophylaxis against respiratory syncytial virus in infants with congenital cardiac disease

Robert Tulloh,[1] Michael Marsh,[2] Michael Blackburn,[3] Frank Casey,[4] Warren Lenney,[5] Peter Weller,[6] Barry R. Keeton[2]

[1]Guy's Hospital, London; [2]Southampton General Hospital, Southampton; [3]Leeds General Infirmary, Leeds; [4]Royal Hospital for Sick Children, Belfast; [5]Stoke City General Hospital, Stoke on Trent; [6]Birmingham Children's Hospital, Birmingham, UK

Abstract New data are emerging on the use of palivizumab as prophylaxis against infection with the respiratory syncytial virus in infants with congenital cardiac disease. Following a 4-year multicentre randomised trial, it was shown that prophylactic injections with palivizumab were effective and safe for such children. Prophylaxis consists of 5, monthly, intramuscular injections of palivizumab, at a dose of 15 mg/kg, given during the season for infection with the respiratory syncytial virus. Timing is at the discretion of the physician, depending on the onset of the season locally. It is suggested that, in the United Kingdom, this should be commenced in mid-September. To help clinicians to identify appropriate candidates for palivizumab, a working group of the British Paediatric Cardiac Association has developed recommendations.

Infants, namely those under 1 year old, with congenital cardiac disease likely to benefit from prophylaxis include those with haemodynamically significant lesions, particularly increased pulmonary blood flow with or without cyanosis; pulmonary venous congestion, pulmonary hypertension or long-term pulmonary complications, residual haemodynamic abnormalities following medical or surgical intervention (patients who have undergone cardiopulmonary bypass should receive an injection as soon as they are medically stable), cardiomyopathy requiring treatment, and congenital cardiac disease likely to need hospital admission for medical or surgical intervention during the season of infection with the virus. Prophylaxis with palivizumab may also be indicated, at the discretion of the physician, in some children with complex cardiac disease over the age of 1 year. Children less likely to benefit from prophylaxis are those with haemodynamically insignificant disease, or those with lesions adequately corrected by medical or surgical intervention.

Keywords: Respiratory infections; congenital heart disease; paediatrics; drug treatment

Most children will have at least one episode of infection by the respiratory syncytial virus by the age of 2 years. The seasonality of such infections is well recognised,[1] generally starting in October in the United Kingdom, with variation regionally and from year to year.[2,3] In otherwise healthy babies, this infection usually results in mild respiratory illness. In contrast, premature babies, and those with chronic lung disease, congenital cardiac disease or immunodeficiency, may suffer more serious illness,[4] often resulting in infections of the lower respiratory tract, and increased rates of hospitalisation[5,6] and death,[2,4] with the possibility of serious long-term respiratory sequelae.[7] Amongst infants with congenital cardiac disease who are hospitalised with respiratory syncytial viral infection, up to one-third will require management in the paediatric intensive care unit,[3] though there is a significant decrease in the frequency

Correspondence to: Dr B. Keeton, Wessex Cardiothoracic Centre, Paediatric Cardiology, E level, East Wing, Mailpoint 46, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK. Tel: 023 8079 6724; Fax: 023 8079 4526; E-mail: keetob@suht.swest.nhs.uk

Accepted for publication 20 June 2003

of infection of the lower respiratory tract, and hospitalisation in children older than 1 year.[5,8] Patients with symptomatic infection undergoing cardiac surgery are at high risk of postoperative complications, especially postoperative pulmonary hypertension.[9]

The IMpact-RSV study, a randomised, double-blind, placebo-controlled study conducted between 1996 and 1997 in 139 centres across North America and the United Kingdom, demonstrated that palivizumab can be administered safely and effectively to children at high risk for serious infections of the lower respiratory tract, and results in reduced hospitalisation.[10] This study informed the development of guidelines, including those of the American Academy of Pediatrics[11,12] and the European Consensus Guidelines.[13]

In November 2002, at the request of the United Kingdom National Institute of Clinical Excellence, the Department of Health Joint Committee on Vaccination and Immunisation considered the use of the monoclonal antibody, palivizumab, in protecting groups at risk of infection with the respiratory syncytial virus. Their recommendations[14] comprise the current guidelines issued by the National Health Service of the United Kingdom. One of the groups considered to be at risk of infection was: "Babies with rare conditions such as severe multiple congenital abnormalities or severe immunodeficiency; this would include severe congenital cardiac disease". The recommendation from the Joint Committee on Vaccination and Immunisation is that treatment with palivizumab should be recommended on a case-by-case basis, depending on the likelihood of a child being admitted to hospital during the respiratory syncytial season.

The findings of a 4-year randomised, placebo-controlled trial of prophylaxis with palivizumab against the respiratory syncytial virus in children 2 years of age or younger with serious congenital cardiac disease have recently been reported.[15,16] In all, 1287 children from 76 centres in the United States of America, Canada, Sweden, Germany, Poland, France and the United Kingdom were randomised. The groups were balanced for demographic factors, risk factors for infection with the respiratory syncytial virus, and cardiac parameters such as pulmonary hypertension, congestive cardiac failure, cyanotic heart disease, and use of cardiac medications. This study showed that palivizumab given intramuscularly during the season of infection with the respiratory syncytial virus is well tolerated, and effective in reducing hospitalisation. Compared with placebo, prophylaxis with palivizumab is associated with a reduction of almost half in hospitalisation of babies with haemodynamically significant congenital cardiac disease. It should be noted that, in previously treated patients, levels of palivizumab in the serum fell by 58% following cardiopulmonary bypass.

In the light of these data, and advice from the Joint Committee on Vaccination and Immunisation, the British Paediatric Cardiac Association convened this Working Group to provide recommendations as to which infants with congenital cardiac disease are most likely to benefit from prophylaxis with palivizumab against the respiratory syncytial virus. With the next season for infection with the virus upon us, the Group feels that these recommendations will help clinicians working with infants to consider their practice, and to identify those infants in whom palivizumab will be most cost-effective.[17] The recommendations are as follows.

Recommendations from the Working Group of the British Paediatric Cardiac Association for the use of palivizumab as prophylaxis against the respiratory syncytial virus in children with congenital cardiac disease

Education is important

- The parents, families, and carers of children at high risk should be educated about respiratory syncytial virus, the aim of prophylaxis against it, and the preventative measures that can be taken to avoid infection. They can be taught how to help keep these children free from infection by the virus at home.[11]
- Hospital staff should be educated about the importance of strict observance of practices for control of infection.[11]

Appropriate timing of prophylaxis

- Prophylaxis consists of 5, monthly, intramuscular injections of palivizumab at 15 mg/kg during the season of infection. It is possible that some babies may need more than 5 injections, while others may not need all 5 injections.
- The season in the United Kingdom extends from October to March, but there are regional and annual variations. The season peaks during December to January. Timing of prophylaxis is at the discretion of the physician, depending on the onset of the season locally.

Children most likely to benefit from prophylaxis

- Infants aged 1 year or younger with documented haemodynamically significant congenital cardiac disease.
  - Includes: conditions with increased pulmonary blood flow; those with cyanotic heart disease; pulmonary venous congestion; pulmonary hypertension; long-term pulmonary complications; unoperated or partially corrected complex congenital cardiac disease.

https://doi.org/10.1017/S1047951103000891 Published online by Cambridge University Press

  - Excludes: children with uncomplicated small atrial or ventricular septal defects or patency of the arterial duct, and other mild forms of structural cardiac disease.

- Infants who have residual haemodynamically significant congenital cardiac disease following medical or surgical intervention. Patients in this category who have undergone cardiopulmonary bypass should receive an injection as soon as they are medically stable.
- Infants with pulmonary hypertension.
- Infants receiving treatment for cardiomyopathy.
- Infants with congenital cardiac disease under the age of 1 year who are expected to need admission to hospital for medical or surgical intervention during the season of infection by the virus should be considered for prophylaxis.
- In some children aged over one year, and having complex cardiac disease, prophylaxis with palivizumab may be indicated at the discretion of the physician.

Children who are less likely to benefit from prophylaxis

- Children with haemodynamically insignificant congenital cardiac disease.
- Children with lesions adequately corrected by medical or surgical intervention.

Funding for prophylaxis

- Currently, there are no defined routes to obtaining funding for prophylaxis in babies with congenital cardiac disease in the various regions of the United Kingdom. It is suggested that funding is discussed at a local level with agencies responsible for commissioning healthcare.
- Bodies commissioning healthcare, such as Primary Care Trusts and specialist commissioning groups in the United Kingdom, will need to be persuaded of the benefits to the individual patient, their families, and to hospital resources, of protecting groups at high risk from this potentially serious illness. The evaluation of cost-benefit, by analysis of subgroups from existing studies and prospective studies, with measurement of benefits for health, is still required.

Acknowledgements

The authors would like to thank Dr Frances Bu'Lock (Glenfield Hospital, Leicester), Dr Jonathan Coutts (Royal Hospital for Sick Children, Glasgow), Professor Anne Greenough (King's College Hospital, London), Dr Anne Thomson (John Radcliffe Hospital, Oxford) and Dr Christopher Wren (Freeman Hospital, Newcastle upon Tyne) for their valuable input into the development of these recommendations.

Sponsorship: The British Paediatric Cardiac Association acknowledges the receipt of an unrestricted educational grant from Abbott Laboratories Ltd. Abbott Laboratories Ltd has supplied information and details of the congenital heart disease trial to the British Paediatric Cardiac Association as requested. These recommendations have been developed by the Working Group without input from Abbott Laboratories Ltd.

Declaration of interest: The following members of the Working Group and advisors to the Working Group were investigators in the United Kingdom for the MedImmune congenital heart disease palivizumab trial: Dr Robert Tulloh, Dr Michael Marsh, Dr Frank Casey, Dr Mike Blackburn, Dr Anne Thomson.

Note for prescribers: Currently, palivizumab is not licensed for the management of infants with congenital cardiac disease. Supportive data now exist,[15,16] nonetheless, and the manufacturer expects a licence to be granted during 2003.

References

1. Weigl JA, Puppe W, Schmitt HJ. Seasonality of respiratory syncytial virus-positive hospitalizations in children in Kiel, Germany, over a 7-year period. Infection 2002; 30: 186–192.
2. Gilchrist S, Török TJ, Gary HE Jr, Alexander JP, Anderson LJ. National surveillance for respiratory syncytial virus, United States; 1985–1990. J Infect Dis 1994; 170: 986–990.
3. Navas L, Wang E, de Carvalho V, Robinson J and the Pediatric Investigators Collaborative Network on Infections in Canada. Improved outcome of respiratory syncytial virus infection in high-risk hospitalized population of Canadian children. J Pediatr 1992; 121: 348–354.
4. MacDonald NE, Hall CB, Suffin SC, Alexson C, Harris PJ, Manning JA. Respiratory syncytial viral infection in infants with congenital heart disease. N Engl J Med 1982; 307: 397–400.
5. Simoes EA. Immunoprophylaxis of respiratory syncytial virus: global experience. Respir Res 2002; 3 (Suppl 1): S26–S33.
6. Boyce TG, Mellen BG, Mitchel EF Jr, Wright PF, Griffin MR. Rates of hospitalization for respiratory syncytial virus infection among children in Medicaid. J Pediatr 2000; 137: 865–870.
7. Sigurs N. Clinical perspectives on the association between respiratory syncytial virus and reactive airway disease. Respir Res 2002; 3 (Suppl 1): S8–S14.
8. Wang EL, Law BJ, Robinson JL, et al. PICNIC (Pediatric Investigators Collaborative Network on Infections in Canada) Study of the role of age and respiratory syncytial virus neutralizing antibody on respiratory syncytial virus illness in patients with underlying heart or lung disease. Pediatrics 1997; 99: E9.
9. Khongphatthanayothin A, Wong PC, Samara Y, et al. Impact of respiratory syncytial virus infection on surgery for congenital heart disease: postoperative course and outcome. Crit Care Med 1999; 27: 1974–1981.
10. IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 1998; 102: 531–537.
11. American Academy of Pediatrics, Committee on Infectious Diseases and Committee on Fetus and Newborn. Prevention of

respiratory syncytial virus infections: Indications for the use of palivizumab and update on the use of RSV-IGIV. Pediatrics 1998; 102: 1211–1216.
12. Meissner HC. Study: palivizumab safe for children with CHD. AAP News 2002; 21: 271. www.aapnews.org/cgi/content/short/21/6/271-b.
13. Carbonell-Estrany X, Guiffré L, Kimpen JLL, et al. Guidelines for the use of Synagis® (palivizumab), a humanized monoclonal antibody, for the prevention of respiratory syncytial virus (RSV) disease in high-risk infants: a consensus opinion. Infect Med 1999; 16 (Suppl G): 29–33.
14. Joint Committee on Vaccination and Immunisation. Minutes of the meeting held on Friday 1 November 2002. www.doh.gov.uk/jcvi/mins01nov02.htm.
15. Sondheimer HM, Cabalka AK, Feltes TF, Piazza FM, Connor EM and the Cardiac Synagis Study Group. Palivizumab (PV) reduces hospitalization due to respiratory syncytial virus (RSV) in young children with serious congenital heart disease (CHD). Pediatr Cardiol 2002; 23: 664 (Abstr).
16. Feltes TF, Cabalka AK, Meissner HC, et al, for the Cardiac Synagis Study Group. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatrics 2003; 143: 532–540.
17. Greenough A, Cox S, Alexander J, et al. Health care utilisation of infants with chronic lung disease, related to hospitalisation for RSV infection. Arch Dis Child 2001; 85: 463–468.