Multiple Sclerosis Vaccines

Vacunas de la esclerosis múltiple.

Profile

Vaccines based on T cells have been investigated for the management of multiple sclerosis.

The use of vaccine-derived polyclonal antibodies from the serum of goats is also under investigation.

◊ References.

1. Hellings N, *et al.* T-cell vaccination in multiple sclerosis: update on clinical application and mode of action. *Autoimmun Rev* 2004; **3:** 267–75.
2. Sospedra M, Martin R. Antigen-specific therapies in multiple sclerosis. *Int Rev Immunol* 2005; **24:** 393–413.
3. Fontoura P, *et al.* Antigen-specific therapies in multiple sclerosis: going beyond proteins and peptides. *Int Rev Immunol* 2005; **24:** 415–46.
4. Correale J, *et al.* Vaccines for multiple sclerosis: progress to date. *CNS Drugs* 2008; **22:** 175–98.

Mumps Immunoglobulins

Inmunoglobulinas contra la parotiditis.

ATC — J06BB15.

Profile

Preparations containing antibodies against mumps virus have been used in some countries for passive immunisation against mumps.

Mumps Vaccines

Vacunas de la parotiditis.

ATC — J07BE01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Mumps Vaccine (Live); Vaccinum Parotitidis Vivum). A freeze-dried preparation containing a suitable live attenuated strain of mumps virus (*Paramyxovirus parotitidis*) grown in cultures of human diploid cells or chick-embryo cells or the amniotic cavity of chick embryos. It is prepared immediately before use by reconstitution from the dried vaccine. The cell-culture medium may contain the lowest effective concentration of a suitable antibacterial. The virus concentration is not less than 3.7 log $CCID_{50}$ per dose. The dried vaccine should be stored at 2° to 8° and be protected from light.

The BP 2008 states that Mumps may be used on the label.

USP 31 (Mumps Virus Vaccine Live). A bacterially sterile preparation of a suitable strain of mumps virus grown in cultures of chick-embryo cells. It contains not less than the equivalent of 5×10^3 $TCID_{50}$ in each immunising dose. It may contain suitable antimicrobial agents. It should be stored at 2° to 8° and be protected from light.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Parotid swelling may occur. Unilateral nerve deafness, aseptic meningitis, and encephalitis have occurred rarely (see below for further discussion).

Mumps vaccines are not generally recommended for children below the age of 1 year in whom maternal antibodies might prevent a response.

Effects on hearing. For a report of sensorineural hearing loss following measles, mumps, and rubella vaccination, see p.2223.

Effects on the nervous system. There have been a few reports of neurological reactions including meningitis and encephalitis after vaccination with measles, mumps, and rubella vaccines. These reactions have been attributed to the mumps component. However, it has not been possible to isolate the virus from the CSF in every case and identify it as either the vaccine strain or a wild-type strain. Meningitis develops up to 35 days after immunisation, is mild, and sequelae are rare.[1,2] One study[3] found the incidence of virus-positive post-immunisation meningitis from the Urabe strain of mumps vaccine to be about 1 in 11 000 immunised children, with the incidence following Jeryl Lynn mumps vaccine being much lower. This result was supported by the incidence of about 1 in 4000 in another study,[4] making it less likely that this was a chance result, and much higher than the estimates of up to 1 in 1 million reported previously.[5] Subsequent research[6] identified the Urabe vaccine strain in CSF samples from all of 20 children with post-vaccination meningitis in the UK, and no isolates of the Jeryl Lynn strain in patients with meningitis among 80 samples tested. Thus, vaccines containing the Urabe strain, including combined measles, mumps, and rubella vaccines are no longer used in the UK and some other countries.[7] A relatively high incidence of meningitis of about 1 in 1000 has also occurred after use of a measles and mumps vaccine prepared from the Leningrad-3 strain of mumps virus.[8,9]

Encephalitis has been associated with mumps vaccination less frequently than meningitis, but may be more serious.[1] The Advisory Committee on Immunization Practices in the USA has reported that the incidence of encephalitis within 30 days of receiving a mumps-containing vaccine is 0.4 per one million doses.[10] This is no higher than the observed background incidence for CNS dysfunction in the general population.

In considering the above data it should be remembered that mumps is the most common cause of meningoencephalitis in children under 15 years of age in the UK and an important cause of permanent sensorineural deafness in childhood.[1] Meningitis after natural mumps infection is estimated to occur in 1 in 400 cases, an incidence that is very considerably above any reported with vaccination.

1. Anonymous. Mumps meningitis and MMR vaccination. *Lancet* 1989; **ii:** 1015–16.
2. Maguire HC, *et al.* Meningoencephalitis associated with MMR vaccine. *Commun Dis Rep* 1991; **1** (review 6): R60–R61.
3. Miller E, *et al.* Risk of aseptic meningitis after measles, mumps, and rubella vaccine in UK children. *Lancet* 1993; **341:** 979–82.
4. Colville A, Pugh S. Mumps meningitis and measles, mumps, and rubella vaccine. *Lancet* 1992; **340:** 786. Correction. *ibid.*: 986.
5. McDonald JC, *et al.* Clinical and epidemiologic features of mumps meningoencephalitis and possible vaccine-related disease. *Pediatr Infect Dis J* 1989; **8:** 751–5.
6. Forsey T, *et al.* Mumps vaccine and meningitis. *Lancet* 1992; **340:** 980.
7. Anonymous. Two MMR vaccines withdrawn. *Lancet* 1992; **340:** 722.
8. Čižman M, *et al.* Aseptic meningitis after vaccination against measles and mumps. *Pediatr Infect Dis J* 1989; **8:** 302–8.
9. Tešović G, *et al.* Aseptic meningitis after measles, mumps, and rubella vaccine. *Lancet* 1993; **341:** 1541.
10. Immunization Practices Advisory Committee. Mumps prevention. *MMWR* 1989; **38:** 388–400.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Mumps vaccines are used for active immunisation against mumps.

For primary immunisation a combined measles, mumps, and rubella vaccine (p.2223) is usually used. For discussion of immunisation schedules, see under Vaccines, p.2202.

Many different attenuated strains of mumps virus have been used in vaccines and those commonly used have included Jeryl Lynn, Urabe, Leningrad-3 (and adapted L-Zagreb), and Rubini strains. Efficacy seems to be broadly similar for these strains with the exception of Rubini which is reported to be less effective than Jeryl Lynn or Urabe.

A vaccine prepared from the Jeryl Lynn (B level) strain of mumps virus is available in the USA, and may be given in a dose of 0.5 mL by subcutaneous injection although combined vaccines are usually preferred.

Preparations

Ph. Eur.: Mumps Vaccine (Live);
USP 31: Mumps Virus Vaccine Live.

Proprietary Preparations (details are given in Part 3)
Arg.: Imovax Parotiditis†; ***Braz.:*** Imovax Mumps†; ***Canad.:*** Mumpsvax†; ***Cz.:*** Pavivac; ***Denm.:*** Mumpsvax†; ***Ger.:*** Mumpsvax†; ***Gr.:*** Mumpsvax†; ***Ital.:*** Vaxipar†; ***Spain:*** Vac Antiparotiditis†; ***Switz.:*** Mumpsvax; ***USA:*** Mumpsvax; ***Venez.:*** Imovax Parotiditis†.

Mycobacterium Vaccae Vaccines

SRL-172; Vacunas de Mycobacterium vaccae.

Profile

Vaccines containing *Mycobacterium vaccae* are under investigation for the prevention and immunotherapy of tuberculosis and other mycobacterial infections. They are also being studied for therapeutic use in asthma, eczema, psoriasis, and some malignant neoplasms.

Asthma. Heat-killed *Mycobacterium vaccae* is a potent down-regulator of T-helper 2 cytokines which play a central role in asthma. In a double-blind, randomised, placebo-controlled study[1] in 24 asthmatic men, a bronchial allergen challenge was given 2 weeks before and 3 weeks after a single intradermal injection of *Mycobacterium vaccae* vaccine. The maximum fall in FEV, during the allergic response to the latter challenge was reduced by a mean of 34%, but this was not statistically significant compared with placebo.

1. Camporota L, *et al.* The effects of Mycobacterium vaccae on allergen-induced airway responses in atopic asthma. *Eur Respir J* 2003; **21:** 287–93.

Eczema. In a double-blind, randomised, placebo-controlled study[1] in 41 children aged 5 to 18 years with moderate to severe atopic dermatitis, an intradermal injection of *Mycobacterium vaccae* vaccine resulted in a 48% reduction in the surface area of the skin affected after 3 months compared with 4% in those given placebo. In a later study[2] in 56 children aged 2 to 6 years, these results could not be replicated because the reduction in affected area was not found to be significantly different from placebo.

1. Arkwright PD, David TJ. Intradermal administration of a killed Mycobacterium vaccae suspension (SRL 172) is associated with improvement in atopic dermatitis in children with moderate-to-severe disease. *J Allergy Clin Immunol* 2001; **107:** 531–4.
2. Arkwright PD, David TJ. Effect of Mycobacterium vaccae on atopic dermatitis in children of different ages. *Br J Dermatol* 2003; **149:** 1029–34.

Malignant neoplasms. *Mycobacterium vaccae* vaccines have been used with limited success as adjunctive therapy in the management of a variety of cancers, notably prostate cancer, malignant melanoma, and non-small-cell lung cancer. In a preliminary study[1] 28 patients with inoperable non-small-cell lung cancer and mesothelioma were randomised to receive chemotherapy either with or without adjunctive intradermal injection of a heat-killed *Mycobacterium vaccae* vaccine (SRL-172). A trend towards improved response rate was found in those patients receiving combined therapy, together with improved median survival and 1-year survival rates; some patients given combined therapy were subsequently able to receive curative surgery or radical radiotherapy. A similar subsequent phase III study[2] in 419 patients found a significant improvement in patient quality of life after combined therapy, but the improvements in survival-time could not be replicated. Secondary analyses of these results[3] suggested an improvement in survival time for patients with adenocarcinoma, but not for those with squamous cell carcinoma. There is also some evidence of beneficial effect in patients with metastatic renal cell carcinoma.[4]

1. O'Brien ME, *et al.* A randomized phase II study of SRL172 (Mycobacterium vaccae) combined with chemotherapy in patients with advanced inoperable non-small-cell lung cancer and mesothelioma. *Br J Cancer* 2000; **83:** 853–7.
2. O'Brien ME, *et al.* SRL172 (killed Mycobacterium vaccae) in addition to standard chemotherapy improves quality of life without affecting survival, in patients with advanced non-small-cell lung cancer: phase III results. *Ann Oncol* 2004; **15:** 906–14.
3. Stanford JL, *et al.* Successful immunotherapy with Mycobacterium vaccae in the treatment of adenocarcinoma of the lung. *Eur J Cancer* 2008; **44:** 224–7.
4. Patel PM, *et al.* An evaluation of a preparation of Mycobacterium vaccae (SRL172) as an immunotherapeutic agent in renal cancer. *Eur J Cancer* 2008; **44:** 216–23.

Psoriasis. Preliminary studies have shown that heat-killed *Mycobacterium vaccae* vaccines may induce periods of remission when given intradermally. An open-label study[1] in 24 patients given 2 intradermal injections into lesion-free deltoid skin at a 3-week interval found, 12 weeks after starting treatment: marked improvement (14 patients), moderate improvement (2), no change (6), and worsening of symptoms (2). By 24 weeks, 11 of 22 patients continued to show a greater than 50% improvement and of these 5 had complete clearance of skin lesions lasting for 6 months or more. In another study,[2] a more potent heat-killed, delipidated, deglycolipidated vaccine was given similarly to 20 patients with moderate to severe psoriasis; after 12 weeks, 13 of the 20 patients showed a marked improvement, 3 were unchanged, 3 had worsened, and 1 withdrawn due to an exfoliative flare. At 24 weeks, 13 of 19 patients continued to show a greater than 50% improvement, and in some this lasted for 6 months or more. A double-blind, randomised, placebo-controlled study[3] with the latter vaccine in 36 patients with psoriatic arthritis found no improvement in psoriatic lesions compared with placebo, although there did appear to be some improvement in pain experienced.

1. Balagon MV, *et al.* Improvement in psoriasis after intradermal administration of heat-killed Mycobacterium vaccae. *Int J Dermatol* 2000; **39:** 51–8.
2. Balagon MV, *et al.* Improvement in psoriasis after intradermal administration of delipidated, deglycolipidated Mycobacterium vaccae (PVAC): results of an open-label trial. *Clin Exp Dermatol* 2001; **26:** 233–41.
3. Dalbeth N, *et al.* A randomised placebo controlled trial of delipidated, deglycolipidated Mycobacterium vaccae as immunotherapy for psoriatic arthritis. *Ann Rheum Dis* 2004; **63:** 718–22.

Tuberculosis. ***IMMUNISATION.*** References.

1. von Reyn CF, *et al.* Cellular immune responses to mycobacteria in healthy and human immunodeficiency virus-positive subjects in the United States after a five-dose schedule of Mycobacterium vaccae vaccine. *Clin Infect Dis* 1998; **27:** 1517–20.
2. Waddell RD, *et al.* Safety and immunogenicity of a five-dose series of inactivated Mycobacterium vaccae vaccination for the prevention of HIV-associated tuberculosis. *Clin Infect Dis* 2000; **30** (suppl 3): S309–S315.
3. Vuola JM, *et al.* Immunogenicity of an inactivated mycobacterial vaccine for the prevention of HIV-associated tuberculosis: a randomized, controlled trial. *AIDS* 2003; **17:** 2351–5.

IMMUNOTHERAPY. A systematic review[1] found that immunotherapy with *Mycobacterium vaccae* produced no beneficial effects in patients with tuberculosis.

1. de Bruyn G, Garner P. Mycobacterium vaccae immunotherapy for treating tuberculosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/12/04).

Normal Immunoglobulins

Inmunoglobulinas inespecíficas.

ATC — J06BA01; J06BA02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Human Normal Immunoglobulin; Immunoglobulinum Humanum Normale). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG) antibodies, of normal subjects. Other proteins may be present; it contains not less than 10% and not more than 18% of total protein. It is intended for intramuscular or subcutaneous injection. It is obtained from the pooled plasma collected from at least 1000 donors who must be healthy, must not have been treated with substances of human pituitary origin, and as far as can be ascertained be free from detectable agents of infection transmissible by transfusion of blood or blood components. No antibacterial is