A review of the immune response to bluetongue virus

M.H. JEGGO*

Summary: This review presents a series of conclusions based on immunological studies carried out on bluetongue (BT) infections in mice, sheep and cattle over the last five years at the Animal Virus Research Institute (AVRI). These studies highlight the role of both the humoral and cellular components of the immune response and conclude that current vaccination protocols could be improved by the use of serial inoculations of monovalent bluetongue virus (BTV) vaccine preparations.

In identifying areas for further research, this review pinpoints the need to investigate the possibility of immunotolerance in cattle following a BTV infection in utero and the importance of this in terms of import/export regulations.


INTRODUCTION

In the past five years, a number of studies have been carried out at AVRI on the immune response to the inoculation of bluetongue virus (BTV) into mice, sheep and cattle. In particular, those components of the immune response involved in recovery and protection have been investigated with the aim of improving current control measures. At all times the BTV strains used to inoculate animals had been plaque purified three times in baby hamster kidney (BHK) cells and thus were relatively avirulent but type-specific. Measurement of the response to virus inoculation was based on viraemic and pyrexic changes correlated to specific immune responses.

Experiments involving the passive transfer of BTV-specific humoral and cellular components were carried out to elucidate in more detail those processes involved in protection and recovery from bluetongue. This review presents the conclusions from these studies, highlights where they may have application in the control of the disease, and details further research objectives.

SUMMARY OF EXPERIMENTAL RESULTS AND CONCLUSIONS

1. Studies on the serial inoculation of BTV (1, 2)

Both sheep and cattle were inoculated serially with three different BTV types. Each virus was inoculated only when no evidence could be found in the blood of

* Department of Immunology, Animal Virus Research Institute, Pirbright, Surrey GU24 0NF, United Kingdom.
the previously inoculated virus. The development of antibodies, not only to the inoculated virus but to all other BTV types, was examined and the following conclusions were reached:

(a) The inoculation of one BTV type does not protect an animal from challenge with other BTV types.

(b) The serial inoculation of two BTV types protects against challenge with a third BTV type.

(c) The serial inoculation of two BTV types gives rise to a broad heterotypic antibody response.

2. Studies on the simultaneous inoculation of BTV (3)

The simultaneous inoculation of three BTV types into sheep resulted in the replication of only two types and a failure in the production of heterotypic antibodies.

3. Studies in mice on the cell-mediated immune response to BTV inoculation (4, 5, 6)

(a) The inoculation of live BTV into mice gives rise to cytotoxic T lymphocytes (CTL) whose activity peaks around day 7 post-inoculation (pi).

(b) The level of the murine CTL response is dependent on the BTV type and does not occur when inactivated virus is used.

(c) Anti-BTV murine CTL are capable of varying degrees of cross-reactive lysis within the BTV group.

4. Studies on the role of humoral immunity (7)

A series of experiments involving the passive transfer of BTV-specific antibody in both immune sera and colostrum was carried out to elucidate the role of humoral immunity in BTV infections. The following conclusions were arrived at:

(a) Immune serum has a role to play in protection from re-infection with BTV.

(b) This protection is type-specific only.

(c) The degree of protection does not correlate with levels of neutralising antibody.

5. Studies on the role of cell-mediated responses in protection and recovery from BTV infections in sheep (8)

These studies involved the identification in sheep of BTV-specific cytotoxic lymphocytes and their passive transfer in monozygotic animals from an immune to a non-immune twin.

(a) Sheep produce BTV cytotoxic lymphocytes whose activity peaks around 12 days pi.

(b) These effector cells alone are capable of reducing, to a large extent, the activity of BTV in sheep.

(c) The activity of these cells is short-lived (14 days) but in certain circumstances they can completely protect sheep from a BTV infection.
6. Studies involving the inoculation of animals with a second BTV type at various times following a first BTV inoculation (9).

(a) Animals are protected from challenge with a second BTV type for up to 14 days after the inoculation of the first virus type.
(b) This occurs through the action of short-lived cross-reactive cytotoxic lymphocytes and antibody is not involved.
(c) Other components of the immune system are induced which limit the activity of these cells to a 10-12 day period post-inoculation (i.e. suppressor cells and/or anti-CTL idiotype antibody).
(d) A prerequisite to the formation of heterotypic antibody is the inoculation of two live BTV types administered at least 14 days apart.

7. Studies on BTV intra-uterine infections and the possible development of immuno-tolerance (10, 11, 12)

(a) The infection of a foetus early in gestation results in abortion or absorption of the foetus.
(b) The infection of a foetus in mid or late gestation may result in an animal viraemic at birth, but will result in an animal having BTV-specific antibodies.
(c) The infection of a foetus during the period of gestation when the immune system is developing (80 to 120 days in the case of the bovine) may possibly result in a normal full-term offspring periodically viraemic and incapable of developing BTV antibodies.

8. Induction of the immune response (13, 14)

(a) Group-specific antibodies are induced by the outer capsid protein 7.
(b) Type-specific (neutralising) antibodies are induced primarily by outer capsid protein 2 but also by protein 5.
(c) It is not known what induces cell-mediated immune responses.

IMPLICATIONS

The conclusions reached in these studies can aid in the control of BTV in two ways: firstly, through the use of better vaccines and, secondly, through improvement in export/import control measures.

Considering first vaccine design, it would appear that multivalent preparations offer no advantage, that neutralising antibody levels are a poor measure of protection and that repeat inoculation within 14 days is disadvantageous through the action of cross-reactive CTL. Therefore, it is suggested that a single inoculation of a live monovalent preparation just prior to the period of virus activity with a
repeat, one month later, of a different serotype, will give rise to heterologous immunity and the desired protection during periods of risk in endemic areas. However, there are risks associated with live vaccines and this protocol may not give long-term protection, giving rise to the need to vaccinate annually. There may also be problems associated with the interfering effect of suppressor cells and/or anti-idiotype antibody.

In terms of import and export control measures, these studies highlight the need for further understanding of immuno-tolerance in a BTV infection. The potential risk from an animal viraemic, but not showing an antibody response, on which current import/export tests are based, must be evaluated.

**AREAS OF FURTHER RESEARCH**

These studies have identified areas in which further research into the immune response to BTV should be conducted. These are:

(a) Further studies on the induction of the ovine cross-reactive cell-mediated immune response.

(b) Studies on the role of other T-cells (helper and suppressor cells) in modulating the immune response.

(c) Studies on the potential for immuno-tolerance to develop following intra-uterine BTV infection in bovines.

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**REVUE SUR LA RÉPONSE IMMUNITAIRE AU VIRUS DE LA FIÈVRE CATA-RHALE OVINE. — M.H. Jeggo.**

*Résumé : Dans cette revue, l’auteur présente une série de conclusions basées sur des recherches immunologiques. Celles-ci ont été réalisées sur des infections par le virus de la fièvre catarrhale ovine (BTV = bluetongue virus) chez la souris, le mouton et le bovin au cours des cinq dernières années à l’Institut de Recherche sur les virus animaux de Pirbright. Ces études soulignent le rôle des composantes humorale et cellulaire de la réponse immunitaire et mènent à la conclusion que les protocoles de vaccination actuels pourraient être améliorés par l’administration d’injections en série de préparations vaccinales à base de BTV monovalent.

En formulant des thèmes de recherches pour l’avenir, l’auteur estime nécessaire d’étudier s’il serait possible d’induire une immunotolérance chez les bovins à la suite d’une infection in utero par le BTV. Il en souligne l’importance du point de vue des réglementations d’importation et d’exportation.

**REVISIÓN DE LA RESPUESTA INMUNITARIA AL VIRUS DE LA LENGUA AZUL.**
—— M. H. Jeggo.

_Resumen_: En esta revisión, presenta el autor una serie de conclusiones que se basan en investigaciones inmunológicas, las cuales fueron realizadas en infecciones por el virus de la lengua azul (BTV = bluetongue virus) en ratones, ovejas y vacunos en el último lustro en el Instituto de Investigaciones de virus animales de Pirbright. Los estudios señalan el papel de las componentes humoral y celular de la respuesta inmunitaria, llevando a concluir que se podrían mejorar los actuales protocolos de vacunación administrando inyecciones en serie de preparaciones vacunales a base de BTV monovalente.

_Al formular temas de investigación para el futuro, estima el autor que hay que estudiar si se podría inducir una inmunotolerancia en los vacunos después de una infección in utero por el BTV_. Destaca su importancia desde la óptica de las reglamentaciones de importación y exportación.

**PALABRAS CLAVE**: Enfermedades de ovinos - Enfermedades de vacunos - Infección experimental - Inmunidad de mediación celular - Inmunidad humoral - Inmunotolerancia - Orbivirus - Ratones - Vacunación - Virus de la lengua azul.

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**REFERENCES**


