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WHO Advisory Committee on Variola Virus Research

Report of the Tenth Meeting

Geneva, Switzerland
19–20 November 2008

EPIDEMIC AND PANDEMIC
ALERT AND RESPONSE

World Health Organization

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Executive summary

The major accomplishments in the variola virus research programme were as follows:

- Combinations of chimeric chimpanzee/human monoclonal antibodies fully protected mice challenged with vaccinia virus. The combinations were also active therapeutically, with protection against death even when administered three days after challenge.

- Submission for regulatory approval of the therapeutic agent ST-246 was aimed for 2010. Alternative formulations of ST-246, such as capsules for adults, oral suspensions for children and older people, and intravenous injectable forms for emergency situations are being investigated. WHO would act as a facilitator between potential users and SIGA Technologies for the availability of ST-246 in the case of a requirement for emergency compassionate use.

- The Committee considered that it would be premature to establish a WHO stockpile of any drug that did not yet have approval for use by drug regulatory authorities.

- Two diagnostic assays designed for field use based on real-time polymerase chain reaction (PCR) technology are currently being evaluated. It is anticipated that the assays will become available to Member States through international networks of commercial products.

- Two protein-based "point-of-care" diagnostic assays are in development.

- Discussions pointed out that currently available technology could allow the recreation of a full-length variola virus genome by chemical synthesis.

Content

1. Report from the Secretariat

1.1. The WHO Advisory Committee on Variola virus Research met from 19 - 20 November 2008 with Dr David Evans as Chairman and Mr David FitzSimons as Rapporteur.

1.2 Dr Daniel Lavanchy recalled that the report of the ninth meeting had been noted by the Sixtieth World Health Assembly in May 2008. Over the past year, interest in antiviral drugs had subsequently increased and at the same time the need for transparency and for greater and equitable access to results was recognized. The mandate of the Committee was to consider research of public health importance.

1.3 A list of currently approved proposals was included in the documentation for participants, and the Committee updated the list. The review of research requested by Member States in 2010 expected that research projects that were currently ongoing would be concluded by that date, extension being considered after the review is finalized; that did not preclude submission of research proposals in the mean time or in the future but it did mean that clear goals were vital for assessing further research.

2. Update on variola virus strains held in the United States and Russian Federation repositories

2.1. Dr I. Damon reported on the status of stocks held at the Centers for Disease Control and Prevention (CDC) in the United States of America and the time frames allotted for her research group to perform the WHO-approved research. She noted that the existing BSL-4 laboratory at the CDC is not scheduled to be re-opened until the end of 2008. The planned introduction of a new BSL-4 laboratory in 2009 will increase capacity for research. Since the previous report to the Committee, there have been no additions to or withdrawals from the long-term repository, but material was withdrawn from the laboratory stocks for work on agreed research protocols.

2.2. Dr A. Sergeev informed the Committee that, since November 2007, work at the State Research Centre of Virology and Biotechnology VECTOR in the Russian Federation has continued in four main areas: transfer of stocks from glass to polypropylene vials; study of viability of Asian strains of variola virus; antiviral agents; and neutralizing monoclonal antibodies. In particular, a new repository has been created in the same building where research is done, with high physical security, including automatic temperature controls and visual monitoring. No viable strain was detected among the Asian viruses studied. During the year, 200 working stocks of non-viable or duplicate material were destroyed, bringing the total number of vials in the repository to 691.

3. Update on prophylaxis and therapeutics

3.1. Dr B. Moss outlined progress in research into chimeric chimpanzee/human monoclonal antibodies. Combinations that targeted envelope and mature virion particle proteins fully protect mice infected intratracheally with the WR strain of vaccinia virus, with good dose-response values. The combinations were also active therapeutically, with protection against death even when administered three days after challenge, when mice had already suffered weight loss. The monoclonal antibodies acted synergistically, the combination of monoclonal antibodies Ch7D11 and Ch12F being the most potent.

3.2. Professor S. Shchelkunov, on behalf of Dr Tikunova who was unable to attend, described research on neutralizing antibodies against orthopoxviruses. Fully human recombinant antibodies were produced on the basis of mini-antibodies selected by a process of "biopanning" and shown to be specific for the H3L target protein. For the next year animal experiments are planned to analyse these antibodies in an animal model.

3.3. Professor S. Shchelkunov, on behalf of Dr Belanov who was also unable to attend, described recent advances in the development of antiviral agents against orthopoxviruses. A series of adamantane derivatives, nucleoside analogues and heterocyclic compounds have been synthesized and tested for antiviral activity in cell culture against various orthopoxviruses. The most active were then tested against different strains of variola virus in cell culture. Of 84 compounds tested, 74 from all three groups proved to be active. In 2009 it is planned to extend this research to cowpox virus and ectromelia virus in mice.

3.4. Dr J. Huggins reviewed developments in research of small-molecule antiviral agents. Safety concerns, in particular nephrotoxicity in the 300–600 subjects that would be required to establish safety of the four fold higher dose in man that corresponds to the efficacious dose in primates required to treat this acute infection, now preclude further work on cidofovir, even though the risk/benefit to a smallpox patient may be acceptable. The cidofovir lipid conjugated prodrug CMX001 that is designed to be administered orally has much greater activity but appears to be metabolized differently in primate models than in humans, making it impossible to evaluate CMX001 directly in non-human primate models even though it should be active in man, thus precluding evaluation under the Animal Efficacy Rule. A series of pyrimidine-5'-thionucleosides and in particular the 5-iodo compound show good oral activity against cowpox in mouse models and represent a new avenue for antiviral drug research and development.

3.5. ST-246 Advanced Development. Pharmacokinetic studies after oral administration of ST-246 to monkeys and man have established the appropriate equivalent primate dose to the proposed human dose of 400 mg/day. That dose is set at six-fold higher than the minimum effective equivalent primate dose. ST-246, at the primate dose equivalent to the proposed human dose, is efficacious in the monkeypox primate model, even when

treatment is initiated after onset of lesions in all animals, the time most patients would be expected to seek medical care. Recent FDA guidance on the studies required for ST-246 approval indicates that multiple additional variola primate and in vitro studies, requiring several years to complete, may be needed to provide the necessary information to allow drug approval, and also to provide critical information about how to implement a national intervention plan during a smallpox outbreak.

3.6. Dr D. Hruby outlined the timeline for the process of regulatory approval of ST-246, indicating that the aim was for making submissions in 2010 but this date is not fixed because of regulatory issues. Toxicity studies have been completed and all show no toxicity of note. The compound is easy to synthesize and stable, with a predicted shelf-life of at least three years. In clinical trials (whose data were unblinded earlier in 2008) no serious adverse event has been recorded with single or multiple doses. Experiments in numerous animal models all show protective efficacy against disease and death. Studies are in progress to see how vaccine and the antiviral agents can be used together. So far, results show no serious side effects and that the combination induces protective immunity in immunodeficient mice. Initial results in non-human primates indicate also good protection as well as decreased reactogenicity of vaccine and less viral shedding. Alternative formulations of ST-246 are being investigated, such as capsules for adults, oral suspensions for children and older people, and intravenous injectable forms for emergency situations. It was made available for emergency (compassionate) use for the treatment of a clinical case of eczema vaccinatum in 2007. Potential requests for its use should be directed to SIGA Technologies directly.

4. Update on diagnostic assays

4.1. Two presentations described developments in diagnostic assays. In a final report on work authorized until the end of 2008, Dr J. Huggins reported the evaluation of two assays designed for field use that were based on real-time polymerase chain reaction (PCR) technology with freeze-dried reagents and standardized protocols. One assay detected as few as 20 genome copies and differentiated variola virus from other orthopoxviruses, detecting virus in non-human primates infected with variola virus. The other assay, for differentiation between variola major and minor, was based on fluorescence and targeted noncoding sequences common to all variola strains that have been sequenced. Publications have described the probes and other information in