New drug treatments for HIV infection and AIDS

A review following the Seventh International Conference on AIDS, Florence 16–21 June 1991

G. R. VENNING¹ & G. M. S. SCOTT²

¹14 Lucas Road, High Wycombe, Bucks HP13 6QG and ²Department of Microbiology, University College Hospital, Gower Street, London WC1E 6AU

- 1 Objective** To evaluate the status of clinical development of zidovudine and new drugs for the treatment of Human Immunodeficiency Virus (HIV) infections.
- 2 Method** A critical review of the clinical trial reports and assessment of the design and methodology of the therapeutic trials. Evaluation of the drugs being tested and of the specific difficulties in testing drugs in AIDS.
- 3 Conclusions** Drugs are being tested in a unique climate of public opinion characterised by (1) fast track criteria for regulatory approval (2) parallel track (compassionate release) of new drugs before adequate determination of safety and efficacy (3) resistance to the use of placebos in controlled trials.

Keywords AIDS HIV infection

Introduction

The attempts to accelerate drug development have in fact resulted in a slowing down of the process. Six years after the start of clinical research with zidovudine the minimum effective dose has still not been determined. The dosage regimen originally licensed is too high and many patients have been exposed to unnecessary toxicity. The data are still inadequate to meet the criteria that would apply for F & DA approval of a new drug in a different therapeutic category. The 'second generation' reverse transcriptase inhibitors are in similar disarray and most of the new drugs in the early stages of development are tested in trials which fail to meet the standards accepted for drugs in other categories. The prospects for development of effective vaccines are better than was previously thought but there is a serious risk that first class preclinical work will be negated by inadequate clinical research unless the climate, described as 'HIV exceptionalism' is changed, with a return to the discipline of properly controlled therapeutic trials with randomized dose response studies against placebo.

Background

About 10,000 people attended this conference, which covered basic sciences, clinical studies, epidemiology and social aspects of AIDS in the approximate propor-

tions of 2:1:1:1. Most of the clinical studies were descriptions of aspects of HIV infection in various categories of patient.

Of the reports relating to clinical pharmacology and therapeutics, many dealt with the treatment of opportunistic infections so the evaluation of new drugs directed against the Human Immunodeficiency Viruses (HIV) which is the topic of this report, represented only a minor part of the proceedings. It should be recognized however that there may be agents whose mechanism of action is unknown and whose effect against HIV disease may depend in whole or in part upon the prevention of opportunistic infections rather than upon a specific anti-retroviral action e.g. isoprinosine; (VII International Conference on AIDS, 1991, abstract WB2162).

The attitudes of sufferers and of society and the resulting policies have resulted in major restrictions and difficulties for clinical trials. A powerful political lobby was successful in modifying the response of regulatory authorities to the approval of zidovudine, the first licensed antiretroviral agent, and to the pattern of release of other agents for compassionate use prior to licensing. A new category of approval (expanded access or parallel track development) has allowed more than 10,000 patients in the USA to be given new dideoxynucleotides outside the structure of a proper clinical evaluation. In recent years the United States Food and Drug Administration (F&DA) has increasingly

required rigorous data in support of the dosage proposed for new drugs, specifically including evidence that a lower dosage than that recommended would not be effective. Without such evidence new drug applications are normally and properly rejected on the grounds that unnecessarily high dosage exposes patients to unnecessary toxicity without added benefit.

Difficulties in evaluating drugs for HIV infection and AIDS

Zidovudine (Getting the dose wrong)

The normal F&DA criteria for new drug approval were relaxed for zidovudine which was licensed in 1987 for the treatment of established AIDS at a dosage of 1500 mg daily, and subsequently in 1990 for asymptomatic HIV seropositive individuals at a dosage of 500 mg daily and also for paediatric use. In advanced AIDS, with CD4 counts below $0.2 \times 10^9 \text{ l}^{-1}$ zidovudine is associated with granulocytopenia ($< 0.75 \times 10^9 \text{ l}^{-1}$) in 47% of patients and anaemia ($< 7.5 \text{ g dl}^{-1}$) in 29% (manufacturer's data sheet). The toxicity associated with zidovudine is not negligible, but in the absence of any better treatment this is considered acceptable for the benefit of a proven reduction in mortality in comparison with placebo.

When the first studies of an important new drug in the treatment of a serious disease indicate efficacy but fail to provide rigorous dose response data it becomes unethical to include placebo controls. It becomes much more difficult to obtain the required information subsequently, even with much larger sample sizes. Neglect of proper dose response investigation in Phase I and II thus leads to unnecessary exposure of many patients to unnecessary drug toxicity in the following years.

It cannot be over-emphasised that it is vital to get the dose right in an early placebo controlled randomised trial involving a range of doses. It has been estimated that the expectation of life of AIDS patients has been prolonged since the advent of zidovudine by a mean of 140 days (Moore *et al.*, 1990). This is achieved despite substantial bone marrow toxicity which, although not recognised as a 'fatal' complication, may well shorten the life of some patients. Fischl *et al.* (1990) comparing 600 mg with 1500 mg zidovudine daily found better 1 year and 2 year survival rates with the lower dose in a study of 524 patients with advanced disease. A lower effective dosage would probably further improve the quality of life and possibly the duration.

The papers presented at this conference have indeed confirmed that 1500 mg daily for the treatment of AIDS as approved by the F&DA was the wrong dose. A Danish comparative study of 474 patients (abstract WB 2124) has shown that 400 mg is apparently not different from 800 or 1200 mg in terms of survival or time to new AIDS events but is less toxic. Leucopenia and anaemia were dose dependent. 400 mg daily may still not be the optimum (i.e. minimum effective) dose. Collier *et al.* (1990) compared 300, 600 and 1500 mg daily in a pilot study and found similar clinical virological and immunological effects at all doses with better quality

of life at the lower doses. They suggested the need for study of even lower doses.

The Danish study compared 400, 800 and 1200 mg daily doses – an arithmetic progression. This is less efficient than a geometric progression as normally studied by animal pharmacologists. The next study should compare 400 mg daily with two lower doses in a geometric series. The choice of interval is problematical. If 400 vs 200 vs 100 were to be chosen and 100 were to prove equally effective then yet another study would be needed. It would be interesting to see a study of 400 vs 40 vs 4 mg daily. This would be more likely to succeed in identifying an ineffective dose but a result showing both the lower doses to be ineffective would be undesirable. A 10-fold progression may no longer be possible. It will probably be necessary to compromise, e.g. with a three-fold series such as 400-150-50.

The efficacy and safety data available for zidovudine treatment of established AIDS would still be rejected by the F&DA if they were to apply the criteria normally used in assessing new drug applications.

The pivotal study against placebo 4 years previously (Fischl *et al.*, 1987), leading to the licensing of the wrong dose should have included three different doses. Such a design need have lost little or no power.

The two highest doses could have been compared with the lowest dose plus placebo. The Danish protocol was not optimal as it was no longer possible to include placebo.

Whether even lower doses would be equally effective and even less toxic has not been tested. The sample size needed to establish efficacy in comparative trials against a known active dose is of course much larger than would be required in a placebo controlled study. This is not the only disadvantage. The Danish study is convincing but, strictly speaking, statistically significant efficacy of the lowest dose has not been demonstrated. For this there would be a requirement to analyse data from the outcome of a placebo group in a sample that could be shown to be comparable in all relevant characteristics.

The problem of resistance

A second major problem is now apparent with increasing evidence of the magnitude and speed of the development of *in vitro* viral resistance to zidovudine. Prophylactic use in asymptomatic seropositive individuals with CD4 counts below $0.5 \times 10^9 \text{ l}^{-1}$ is now available and was encouraged by several experts at a special session on zidovudine sponsored by the manufacturers. There is evidence that such treatment can delay the onset of symptomatic disease. It is widely feared, however, that the outcome for people treated early may not necessarily be favourable. The emergence of *in vitro* resistance is slower in the asymptomatic (30% at 1 year) than in the symptomatic patient (100% at 1 year). Although the relevance of *in vitro* resistance has not yet been shown, when symptomatic disease arises the possibility of effective therapy may no longer exist. Against this background it is important that new drugs be tested effectively and it is of particular interest to review the clinical trials of new agents reported at the conference.

The new clinical trials and their problems

Before reviewing the results of clinical trials it is of interest to mention the progress reported at the conference of two important multicentre randomised controlled studies organised jointly by the Medical Research Council (MRC) and the French INSERM organisation. Both have suffered from the problems already discussed. The CONCORDE trial is testing 1000 mg zidovudine daily *vs* placebo in asymptomatic HIV seropositive subjects. (The dose was chosen between two dose levels in a similar study in the USA but is now known to be no different in terms of efficacy but more toxic than 400 mg in the treatment of AIDS). 1671 subjects have been entered and an interim analysis by the data safety advisory board is expected later in 1991. This board will decide when the endpoints of the trial have been achieved.

It may have been difficult for the MRC to avoid testing an inappropriate dose. It is particularly sad in view of the fact that they conducted a controlled trial involving 18000 patients with mild hypertension, in which bendrofluazide was tested at 10 mg daily, whereas much lower doses (1.25–2.5 mg daily) are now known to be equally effective with fewer side effects. (Carlsen *et al.*, 1990; MRC Working Party, 1981).

The problems of the other trial can best be described in the words of the authors' abstract 'The objective of the MRC/INSERM alpha trial was to determine the efficacy and toxicity of didanosine (DDI) in patients with HIV disease intolerant of zidovudine. Patients are randomised to either high dose or low dose didanosine or placebo (in all countries except France) in a double-blind design. If they are certain they wish to receive the drug they are randomised to the same two dose levels (in all countries). Over 1200 patients have been enrolled, 16 of them to the placebo controlled option. It is a sad reflection on today's attitude to placebo controlled clinical trials that 99% of patients decided *on the basis of information and advice provided by their physicians*

that it is a foregone conclusion that the benefits of a new drug will outweigh the hazards – even before the probability and extent of the benefits and the nature of the hazards are known.

The truth may now never come to light. The main adverse reactions probably attributable to DDI have been pancreatitis, peripheral neuropathy and diarrhoea, in contrast to the haematological toxicity of zidovudine.

Results presented at the meeting

There were 44 clinical trials reported at the meeting relating to the safety and/or efficacy of 29 new therapeutic agents or regimens with possible therapeutic benefit for HIV infection or AIDS. Eleven studies involving 11 different agents were primarily concerned with pharmacokinetics, bioavailability and tolerance. These are shown in Table 1. This classification is arbitrary as there is some overlap with the efficacy trials. The approaches adopted in the initial trials in man are of some interest.

It is just as easy to study a range of doses in a tolerance test as to study a single arbitrary dose, and obviously desirable that this should be done. As a number of these studies have produced trends indicative of activity, there is no good reason to conduct open uncontrolled, non-random studies. It would be feasible and preferable for studies even at this stage to be randomised. Randomisation protocols can be devised which ensure that the first patient gets the lowest dose and that the first of each of a series of incremental doses are given in ascending order. Only one of the 11 studies was randomised. One procedure adopted in large trials would be for the clinical investigator to be blinded and a colleague to be responsible for ensuring safe dose escalation. The validity of data indicating efficacy trends would be enhanced.

Thirty-three clinical trial reports involving 20 drugs or other therapeutic agents had a stated objective of evaluating potential or actual therapeutic activity.

Table 1 Pharmacokinetic bioavailability and tolerance studies

Drug	Reference	n	Study design	Randomised
Janssen R82913	ThB86	22	Oral pharmacokinetics in AIDS patients. Escalating dose tolerance, trends in p24 antigenaemia and CD4 counts (but no controls).	No
Deoxyfluorocytidine FLT	WB2114	16	Single oral administration pharmacokinetics 4 dose escalation in asymptomatic HIV seropositive patients.	Not applicable
Genelabs GLQ223	WB2080	11	Escalating dose tolerance	No
Recombinant CD4 immunoglobulin G	WB2123	25	i.v. and s.c. repeat dose pharmacokinetics; escalating dose tolerance with and without zidovudine in HIV seropositive subjects	No
Hypericin	WB2071	40	4 dose tolerance, parallel group	No
Dideoxycytidine DDC	ThB84	21	Tolerance in serial regimen with zidovudine and DDI	No
Monoclonal antibody – CD4	WB2157	30	Tolerance in patients with rheumatoid arthritis	No
Monoclonal antibody – V3 region	WB2147	7	Multiple dose tolerance in HIV seropositive patients	No
Methionine encephalin	WB2139	25	A dose tolerance in AIDS, ARC and asymptomatic HIV seropositive patients	No
Autologous cells, expanded in vitro with PHA r – IL2	ThB83	5	Tolerance, half life	No
Thymotrinitin TP3	WB2144	23	Randomised tolerance study, 3 doses plus placebo	Yes

Table 2 a) Clinical trials of new drugs or therapeutic agents; reverse transcriptase inhibitors and other antiviral agents

	<i>Drug or therapeutic agent</i>	<i>Abstract number</i>	<i>n</i>	<i>Comparator</i>	<i>Randomized (R)</i>	<i>Symptomatic (S) Asymptomatic (A)</i>
<i>Reverse transcriptase inhibitors</i>						
1	Dideoxyinosine DDI	WB 2051	64	None	R	S
		WB 2069	8	3 doses		S
		WB 2090	105	None		S
		WB 2092	90	None		S
		WB 2111	153	None		S
		WB 2113	65	None		S
2	Zidovudine low dose	WB 2121	289	None		S
		WB 2103	17	None	R	A
		WB 2124	474	3 doses		S
		WB 2125	10	None		A
3	DDI/zidovudine combination	TU B 2	52	5 doses		A
<i>Other antivirals etc.</i>						
4	Isoprinosine	WB 2162	866	Placebo	R	A
5	Trichosanthin	WB 2171	112	None		A
6	Ampligen (synthetic polynucleotide)	WB 2136	40	6 doses		A
7	Ribavirin	WB 2105	39	Placebo	R	A
8	d Aspartic β hydroxamate (DAH)	WB 2101	15	None		S
9	Egg yolk lipid AL721	WB 2167	21	untreated controls		A

b) Clinical trials of new drugs or therapeutic agents with efficacy as an aim. Cytokines, immune modulators and miscellaneous biologicals

Human interferon alpha IFN α s.c.i.	WB 2095	15	None	R	S
	Th B 35	40	zidovudine*		S
	Th B 34	19	4 doses		S
Human interferon alpha IFN α oral	WB 2140	20	Placebo	R	A
IFN α plus thymosin plus zidovudine	WB 2148	33	zidovudine*		A
IFN β	WB 2149	16	None		S
Interleukin-2 (IL-2)	WB 2154	15	None		A.S.
Thymopentin TP5 (plus zidovudine)	WB 2130	33	untreated controls		A
Ditiocarb (Imuthiol)	WB 2163	100	untreated controls		A.S.
	WB 2128		None		A.S.
Methionine encephalin (MEK)	WB 2137	60	Placebo		S
Immune plasma	WB 2132	8	Placebo		S
	WB 2161	1	None		S
	Th B 85	(?)	None		S
recombinant CD4 immunoglobulin G (Genentech) (r - CD4 - IgG)	WB 2156	6	None		S
Autologous enriched vaccine	WB 2172	220	None		S

*Failures of controls in these two studies are discussed in the text.

These are summarised in Tables 2a and 2b. Such studies certainly require the incorporation of randomisation and other controls to achieve their objectives.

The British Medical Journal is rejecting for publication reports of clinical trials deficient in respect of the quality of randomisation (Altman, 1991).

Design problems in testing drug combinations

In considering the protocol design problems facing trials of new drugs in combination with zidovudine, there are two good examples of how not to proceed. Human interferon alpha (IFN α) was tested in a randomised study in combination with low dose zidovudine (500 mg daily), using high dose zidovudine (1000 mg) as a comparator (abstract Th B 35). Zidovudine

500 mg is however not different from 1000 mg without adding interferon (see abstract WB 2124). Data showing the two regimens selected for testing not to be different in terms of efficacy have thus provided no evidence concerning the activity of interferon. Adding interferon decreased the tolerance to zidovudine.

The consequences could in fact be even worse. It is still theoretically possible that a low dose of interferon might be a useful adjunct to an even lower dose of zidovudine that would be ineffective on its own but well tolerated, but the result of this study may discourage others from testing this hypothesis. The positive lesson to be learned is that the proper protocol for testing a combination with zidovudine should always include the same dose of zidovudine. It is possible to increase the power of such a study without increasing the sample size requirement by using a Latin Square design (e.g.

IFN α + low dose zidovudine/IFN α + high dose zidovudine/low dose zidovudine alone/high dose zidovudine alone). A further difficulty is that the optimum dose of interferon is also not known for this indication.

Another example of how not to test a new drug comes from the trial of thymosin (abstract WB 2148). This new drug was tested in combination with IFN α and zidovudine in a randomised trial using zidovudine alone as the comparator. This has predictably failed to provide evidence for the usefulness of either thymosin or interferon!

Review of the protocols

Ideally these should all have incorporated randomisation, either against placebo or against different doses of the same drug and/or a known active agent. Design features of the studies are summarised in Table 2a (for reverse transcriptase inhibitors and other antivirals) and Table 2b (for cytokines, immune modulators and other biologicals). From these data the extent to which feasible standards of protocol design have been achieved is shown in Table 3.

It can be seen that only 5 of 33 studies employed randomisation against any form of appropriate comparator – placebo in four trials and other doses in 1 trial. Ten included control groups without randomisation. The remaining studies were completely un-

controlled. Samuel Broder, the Director of the National Cancer Institute in his introduction to a symposium on DDC (Broder, 1990), pointed out that 'uncontrolled therapeutic trials can retard progress in this interesting area'. This could indeed be argued by Ethical Committees insofar as it is difficult to justify the risk of giving new drugs to patients under conditions which militate against identifying potential benefits.

Dose-ranging studies

Table 4 shows the extent to which new drugs are being tested over a wide range of dosage. The fact that zidovudine has been tested over rather a narrow range may be relevant to the situation already discussed, namely that the lowest dose tested is as effective as the highest so that there is a need to explore even lower doses to identify the right dose to achieve efficacy with a minimum of toxicity. This suggests the need for new drugs to be tested over a wide range of doses in the earliest clinical trials. Animal pharmacologists normally test drugs over a wide range using geometric progression of doses. Investigators need to consider this for early efficacy trials. For most of the reports of dose finding studies the range tested was 10 or less – almost certainly inadequate for identification of the correct dose. The widest range test (100–1) was for the initial trial of thymotrinin, an immune modulator. The selection of this wide range was based upon the characteristics of the dose response curves observed in animals with this class of drug. Even if it is not feasible to cover such a wide range with other classes of drug it may still be important to design clinical trials with a geometric rather than an arithmetic progression of doses. With the special difficulties involved in arranging placebo controlled randomised studies in HIV infection any feature of protocol design needs to be considered that can reduce the risk of missing the correct dose.

Evaluation of the new drugs

Major benefits may be identifiable from poorly controlled trials but appropriate designs are essential for detection

Table 3 Use of randomisation and control groups in 33 efficacy studies of 20 drugs

	<i>Randomised</i>	<i>Non random</i>	<i>Total</i>
Placebo	3	2	5
Other doses	1	4	5
Untreated group		3	3
Inappropriate comparator	1	1	2
No comparator (open studies)		18	18
Total	5	28	33

Table 4 Dose ranging patterns in dose finding studies. Range of doses (ratio of highest to lowest dose). Arithmetic and geometric progressions. Numbers of doses tested

<i>Arithmetic progressions</i>				<i>Geometric progressions</i>			
<i>Abstract number</i>	<i>Drug</i>	<i>Ratio of highest/lowest dose</i>	<i>Number of doses</i>	<i>Abstract number</i>	<i>Drug</i>	<i>Ratio of highest/lowest dose</i>	<i>Number of different dose levels</i>
WB 2124	Zidovudine	3	(3)	Th B 34	IFN α	6	(4)
WB 2064	DDI	3.75	(3)	WB 2080	GLQ 223	6.25	(4)
Tu B2	DDI/zidovudine Combined	4.6	(5)	WB 2114	FLT	10	(4)
WB 2139	Methionine encephalin	5	(4)	WB 2123	r CD4 IgG	10	(3)
				WB 2071	Hypericin	16	(4)
				Th B 86	R82913	30	(3)
				WB 2136	Ampligen	57	(6)
				WB 2144	Thymotrinin	100	(3)

Table 5

a) Drugs with preliminary tolerance or pharmacokinetic data reported but no activity data ($n = 14$)

Hypericin	V3 mabs
SLQ 223	CD4 mabs
(+)-aspartic hydroxamate (DAH)	IFN α
Deoxyfluorocytidine (FLT)	Autologous cells
r-CD4-IgG	Thymopentin
Interleukin - 2	Thymosin
Dideoxycytidine (DDC)	Didanosine (DDI)/ zidovudine combination

b) Drugs with negative or discouraging trials ($n = 3$)

Ribavirin	IFN α - low dose oral, IFN β
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c) Drugs with encouraging but preliminary results ($n = 7$)

AL721	Trichosanthin
R82913	Immune plasma
Thymotrinin	Methionine encephalin
	Didanosine (DDI)

d) Drugs with positive activity against surrogate markers ($n = 5$)

Ampligen
Isoprinosine
Ditiocarb
Autovaccination
Low dose zidovudine

of minor benefits. For many new treatment regimens, minor benefits are being sought and if achieved would be clinically significant and valuable. The successes of high technology science in the first decade of AIDS, well reviewed at the conference, have made it possible to identify various surrogate markers of activity but none of the new drugs has yet been shown to be effective. No evidence of proper testing of second generation reverse transcriptase inhibitors was presented at the meeting. Classification of the results reported are based entirely on surrogate marker effects. Tables 5 a-d show the reported outcomes of the clinical research efforts.

14 new drugs have had preliminary human tolerance studies with no contraindication to further trials, three have given negative or discouraging results, seven have given preliminary results that are encouraging and five have shown positive activities.

Of the 14 drugs in Table 5a, two were submitted to badly planned studies designed to test activity but incapable of providing valid evidence, as discussed previously (thymosin, interferon). The manufacturers literature on DDC indicate that the clinical trials were inadequately controlled and incapable of providing valid evidence. This may also apply to the ongoing MRC/INSERM study of didanosine (DDI).

Of the three drugs with negative or discouraging results reported one, ribavirin, has had significant positive results reported previously in small randomised placebo controlled studies in AIDS and ARC patients but it has not been submitted to adequate therapeutic trials. It is still possible that it may have useful activity and it could even have a better risk-benefit ratio than zidovudine.

It would still be both feasible and ethically justifiable to carry out a large placebo controlled study in HIV

seropositive individuals for whom there is doubt concerning the indication for zidovudine. The entry criterion could be a CD4 count greater than 200 but less than 500. In this range there is no good evidence that zidovudine is preferable to placebo. A study design could be a Latin square trial - ribavirin alone, zidovudine alone, the combination of the two agents, and placebo. Another study could compare three doses of ribavirin with placebo.

Of the seven regimens listed in Table 5c, showing preliminary encouraging results, it may be noted that the three studies of immune plasma showed apparently conflicting results. The biological materials tested were not identical and the criteria for assessment were different. The encouraging results were based on reductions of circulating antigens whereas the discouraging trial used a more stringent criterion. There was no effect upon intracellular levels of viral antigen.

Vaccine programme

The most exciting part of the Florence meeting was the report on progress in the vaccine programme, representing the culmination of a successful scientific effort to unravel the molecular biology of the AIDS viruses. It is also exciting because vaccines have now entered very preliminary human trials. It may be cynical to say that it is exciting because the stage has not yet been reached when the good scientific work is thwarted by sloppy clinical research. This may well happen in the difficult environment of less rigorous regulatory approval criteria and the prevalence of perverse attitudes to the relative merits of controlled trials and compassionate release policies for untested and potentially hazardous drugs.

Background to the development of a vaccine

The conference was opened by a masterly review of the science by Dr Fauci of NIH. Some of his points were as follows:

1. The regulatory genes are not understood.
2. The crystal structures of several proteins are now available. This means that novel specific inhibitory molecules can be computer designed.
3. Virus burden does not correlate directly with disease progression.
4. The process of blood transmission is understood but not the process of transmission by sexual intercourse.
5. The significance of the phase of disappearance of viraemia is not clear. Is viral replication actually halted or does it continue at relatively low level, for example in lymphoid tissue?
6. The relationship of clinical latency to viral latency is obscure.
7. Does the immune response actually propagate the infection?
8. The prospects for Tat gene and protease inhibitors are interesting.
9. Vaccine studies in macaques and chimpanzees are encouraging.
10. The development of vaccine adjuvants is critical.

Primate research with vaccines

This was reviewed by several speakers. Macaques get AIDS but not from HIV1, only from SIV and HIV2. The disease is different from that experienced by man and may not be a suitable test bed for drugs and vaccine. Chimpanzees on the other hand can be infected with HIV1, but don't develop AIDS for up to 7 years. 'Efficacy' in chimpanzees can be assessed only on the basis of surrogate markers. Dr Eichberg of San Antonio, Texas, reported seventeen different HIV vaccine efficacy trials in chimpanzees and emphasized the efficacy of two approaches, recombinant gp120 vaccine and antibodies against the well conserved V3 loop.

The options for vaccine development

Here the problem becomes enormously complex. Whole killed virus may be used, modified by elimination of particular components or alternatively selected viral genes from well conserved parts of the genome may be incorporated into a variety of viral or bacterial vectors. Apart from a multiplicity of potential antigens there are at least 8 different vectors being studied. To cope with testing a vast number of potential vaccine candidates an international infrastructure has already been created. WHO are coordinating the efforts of 6 governments, 12 companies and many more academic institutions. There are already 11 candidate vaccines entering human trials.

Vaccine studies reported

HIVAC, based on gp160 incorporated in a vaccinia vector has been tested in vaccinia naive healthy volunteers who are HIV seronegative and in low risk categories. Vaccination with two doses 8 weeks apart yielded weak titre antibody responses in 80% of subjects fading after 1 year, together with positive long lasting cell mediated immune responses assessed by T cell proliferation assays. Booster doses at 11–27 months using recombinant gp120 induced consistent strong responses in some tests of immune function but less consistent responses in others.

Clinical trials in HIV seropositive individuals were reviewed but not reported in detail. Results claimed have included stabilisation of CD4 counts and weight loss and possible reduction of opportunistic infections. Other trials have shown increases in cytotoxic lymphocyte functions and inhibition of cell cell fusion reactions. There were no proper placebo controlled trials reported involving sufficiently large numbers of patients to know whether these claims are justified.

Discussion

Patients deserve vaccines that have been rigorously tested and which meet the normal criteria of safety and efficacy, including evidence that the dose proposed is correct. Anyone thinking of reducing the requirement for placebo controls in large scale vaccine trials should

be reminded of the story of Japanese B encephalitis, a lethal disease of epidemic proportions feared as much as AIDS. Dr T.C. Hsu, Director General of Health Services for Taiwan carried out a double-blind placebo controlled trial of a vaccine against Japanese B encephalitis (Hsu *et al.*, 1971). He was taken to court for improperly exposing people to an experimental drug. By the time the case was due to be heard the results were coming through. The plaintiffs tried to switch the basis of their case to the improper use of placebo which was denying people a valuable remedy. Eventually, reason prevailed and the highest authority in Taiwan overruled the lawyers and the courts and had the case quashed. When the time comes for large scale vaccine trials, continued adherence to the present compassionate release policies and fast track (more-haste-less-speed) regulatory approval could be disastrous (vaccine disasters are not unknown). In the controversy about the use of placebos it is important that the views of responsible medical scientists should prevail. For this to happen a change of public attitude may be needed.

Discussion

Progress in the development of new drugs for AIDS has been reviewed in the context of papers and exhibits at the 7th International Conference on AIDS in Florence 16–21 June. Clinical research has been conducted against a background described as 'HIV exceptionalism'. This is characterised by the three features of firstly, fast track criteria for regulatory approval of new drugs; secondly, compassionate release of new drugs sometimes sanctioned by the regulatory authorities as 'parallel track' development before the determination of efficacy or safety (making it difficult to recruit patients to controlled trials); thirdly, resistance to the use of placebos in randomised controlled trials. The outcome has been predictable. 'Fast track' release has slowed down the progress of clinical research and the development of safe and effective drugs. Six years after the entry of zidovudine into clinical trials the minimum effective dose is not known, as shown by papers presented.

The available data would still be inadequate to satisfy the criteria used by the U.S. F&DA for other classes of new drug. Evidence is still needed that lower doses would not be equally effective but safer. This applies particularly to second generation drugs including two additional reverse transcriptase inhibitors and one immune modulator which have been widely tested but are in similar disarray. There are two dozen or more third generation drugs that have now entered Phase I and II trials. Several of these have already given indications of useful pharmacological activity in man. Unless the ground rules are changed similar difficulties are likely to be encountered. With many more reverse transcriptase inhibitors now expected to enter clinical trials and compassionate release the situation is likely to drift from disarray into chaos. Temple (1990) has described compassionate release as 'an admission of failing to have enough good trials for people to enter. We should try for the alternative'. Chalmers (1990)

argues for a return to the discipline of randomized trials for the first administration of a new drug as the only way to know the optimal route and dose. He likens retreat from the gold standard of new drug development to the mistakes made 40 years ago in the testing of cancer chemotherapy for solid tumours. His experience in 1954 led him to say 'Neither the patients nor the physicians seem to realise that because of the potential toxicity of newly discovered drugs patients may very well benefit from random assignment to the standard therapy'. This is still true today. Where the benefit-risk ratio of existing therapy is uncertain, as is the case for zidovudine treatment of asymptomatic HIV seropositive patients with CD4 counts above a threshold level the best ethical alternative is a placebo controlled randomised trial. In this situation a randomised trial of a new agent against zidovudine would be an inferior design. It would not be possible to tell from a significant difference whether one drug was beneficial or whether the other was harmful! For this reason ethical committees should reject proposals for trials with inferior designs. The choice of threshold level of CD4 count will be subject to discussion and to change with new information.

The programme of vaccine development in primates

is exciting and the results of early human studies are more promising than predicted in the past. For satisfactory testing of candidate vaccines it will be important that the proponents of controlled clinical trials prevail over the clamour for premature compassionate release.

During the first decade of AIDS the response of society has resulted in a climate in which clinicians have been working with their hands tied behind their backs. This has been most obvious in the restrictions which have hindered the normal public health initiatives necessary for the effective control of a major world epidemic. At its worst, there was a time when even anonymous testing to monitor the progress of the epidemic was perversely considered unethical in the U.K.

This constraint no longer applies but routine testing as part of clinical management of patients is still not considered proper. Whatever may be thought of the validity of the ethical arguments there can be little doubt that the consequences of the exceptional situation have been on balance adverse for present and future patients. A backlash is now reported which may herald the end to 'HIV exceptionalism' (Bayer, 1991; Minerva, 1991).

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