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Mini-review

Clinical toxicity of antiretroviral nucleoside analogs[1]

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1. Introduction

Concerns about potential serious toxicity associated with the use of nucleoside analogs for treatment of viral infections have been highlighted recently by experiences with fialuridine (Brahams, 1994; Marwick, 1994). There are now five nucleoside analogs marketed specifically for treatment of human immunodeficiency virus (HIV) infection, and experience with these to date raises several issues which deserve attention both in the ongoing use of these drugs and in plans for surveillance of other related drugs.

The toxicity problems encountered with antiretroviral nucleosides reflect the complex nature of HIV infection and the population at risk for infection. Because these drugs are used in complex clinical situations, the causal relationship between treatment and adverse event is often difficult or impossible to determine definitively. Yet causation of an adverse event cannot be dismissed for lack of definitive evidence in the individual case.

This review will address major clinical toxicities recognized in clinical trials and included in label information of the currently approved nucleosides used primarily to treat HIV infection, additional events reported in recent literature, and events reported to the Food and Drug Administration in the early postmarketing period. In summarizing

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these apparent toxicities, it is important to note that our understanding of this drug class continues to evolve, and that additional effects may become evident with longer use.

2. The antiretroviral nucleosides

The four nucleoside analogs which have accumulated postmarketing experience in the United States for treatment of HIV are zidovudine, didanosine, zalcitabine and stavudine. A fifth, lamivudine, has recently been added. There are major differences in the qualitative and quantitative experience with these drugs which influence the ability to detect adverse events.

Zidovudine (formerly called azidothymidine and often abbreviated as AZT, trade name Retrovir®) was approved for marketing in March 1987. It has usually been the first-line drug for treatment of patients with HIV infection who have progressed to clinical complications of the acquired immunodeficiency syndrome (AIDS) and has also been widely used by patients with low CD4 lymphocyte counts with no or minimal symptoms. This is also the only drug currently approved for use by pregnant women to reduce the risk of transmission of HIV infection to the fetus or neonate.

Didanosine (dideoxyinosine, DDI, trade name Videx®) was approved in 1991, zalcitabine (dideoxycytosine, DDC, trade name Hivid®) in 1992, and stavudine (d4T, trade name Zerit®) in 1994, although there was extensive premarketing experience with some of these drugs through expanded-access programs. Throughout their early postmarketing period, all three of these more recent drugs have been indicated principally for patients who have failed or have been intolerant of zidovudine, have completed prolonged courses of the older drug, or (in the case of DDC) are receiving zidovudine concomitantly.

Lamivudine (3TC, trade name Epivir®) was approved in late 1995. Like DDC, it has received much attention as a component of combination therapy. Thus, experience with monotherapy in any setting is limited, and overall postmarketing experience is only just beginning to accumulate.

The result of the above patterns is that more information is available on adverse events observed with zidovudine than with any of the other drugs under consideration. In addition, for zidovudine there is more information derived from long-term usage in individual patients and more experience in 'nucleoside-naive' patients, while many of the patients experiencing adverse events with other drugs have also been exposed to zidovudine either previously or concomitantly. These distinctions must be borne in mind when evaluating the adverse event reports which will be discussed in the following sections. Much of the discussion will focus on zidovudine because of the larger amount of available information; this should not be construed as meaning that this drug is more toxic than the others, but as providing a context for surveillance of more recent therapeutic options.

3. The patient population

There are several characteristics common to patients treated with antiretroviral nucleosides which must also be considered in interpreting adverse event reports. These common features affect both the likelihood of specific adverse reactions and the difficulty of assigning causal responsibility.

Firstly, almost all patients who take these drugs are infected with HIV. There is a limited amount of experience with short-term use of zidovudine for prophylaxis after needlestick exposures in uninfected individuals (Puro et al., 1992; Tokars et al., 1993; Schmitz et al., 1994; Forseter et al., 1994), and recent use of this drug in HTLV-I infections (Sheremata et al., 1993; Gill et al., 1995; Hermine et al., 1995) may also provide information about a different population, but use of didanosine, zalcitabine, and stavudine is essentially limited to HIV, and lamivudine has been approved only for treatment of HIV although there is limited investigational experience with its use in chronic hepatitis (Dienstag et al., 1995). Because HIV itself can have insidious effects on many organ systems, it is often a challenge to separate adverse effects of antiretroviral agents

from the manifestations of the underlying disease. In addition, patients infected with HIV appear to be especially predisposed to adverse drug reactions (Lee et al., 1993; Stern, 1994), for reasons which are not well defined but may be related to the effects of the infection on the immune response.

Secondly, as a consequence of HIV infection, patients are at risk for opportunistic infections which may have multisystem effects that are not comparable to those of the same pathogens in the absence of HIV. Thus, when adverse events occur, it may be difficult to separate out drug effects from previously unrecognized manifestations of secondary infection.

Thirdly, as a further consequence of these two factors, patients who received antiretroviral nucleosides are likely to be taking multiple other drugs with the potential to cause similar side effects. Recent recommendations (CDC, 1995) for expanded use of prophylactic antimicrobials may increase the number of patients receiving multiple drugs to reduce the incidence of severe opportunistic infections. This frequent use of multiple therapies increases the potential both for drug interactions and for misattribution of an adverse event caused by one drug to the concomitant use of another drug.

The complex clinical situations in which antiretrovirals are used not only make it hard to define causality of adverse events but also increase the risk that genuine drug reactions with substantial morbidity will occur. Thus, the frustrating exercise of trying to evaluate causality is necessary to the optimal use of these and future drugs in this class.

4. Sources of adverse event information

Initial information on the adverse effect profiles of the antiretroviral nucleosides has come principally from clinical trials, ideally from randomized placebo-controlled studies. While such studies are generally the best indicators of whether a given adverse event is specifically attributable to a given drug, they usually have insufficient numbers of exposed patients to detect rare adverse events. In addition, early trials often exclude patients in certain high-risk groups that are likely to receive the drug in practice, and are usually relatively short-term in comparison with the indefinite duration of antiretroviral treatment that may be desirable for HIV and may lead to different adverse event patterns after longer therapy.

Published trials will be cited here for some of the principal short-term toxicities of antiretrovirals. Much of this information is also summarized in the standard label information and can be reviewed in the Physicians' Desk Reference (1995).

Other sources of adverse event information are more anecdotal and less well suited to drawing conclusions about causality. Literature case reports are obviously highly selected. The Spontaneous Reporting System (SRS) of the Food and Drug Administration is a voluntary reporting system which is subject to several limitations which should be considered in evaluating the information in this review (Baum et al., 1994). These include substantial underreporting, presence of undetected duplicate reports, incomplete information in many reports, and inability to assess causality in most instances. A single case may be reported in association with several drugs and several adverse event terms, further complicating the interpretation of information from this system.

As of March 1995, the cumulative number of SRS reports for which zidovudine was a suspect drug exceeded 2000. There were over 1000 reports for didanosine, 139 for zalcitabine, and 52 for stavudine. These numbers reflect the different duration of marketing and extent of use of each drug, and probably also the differing likelihood that patients receiving one of the nucleoside analogs will also be receiving multiple other drugs to which adverse events may alternatively be attributed. Thus, they provide little information about differences in aggregate toxicity.

Despite these drawbacks, published cases and the SRS can be useful in drawing attention to possible adverse drug effects that were not detected during clinical trials. Sometimes a sequence of reports may show a sufficiently convincing pattern to add to the acknowledged toxicity

profile of a drug. In other instances, individual reports may be inconclusive in themselves but may provide the impetus for additional epidemiologic studies or clinical trials to confirm or refute an association. Even though it may not be possible to determine from SRS reports which drugs within a class are most toxic overall, the different prominence of specific organ-system events in each drug's reporting profile may help to distinguish variations in pattern and mechanism of toxicity, as well as guiding additional study plans.

In this review, attention will focus on adverse events which either have been prominent in the side effect profile of the drug in question or form part of an adverse event pattern that suggests a specific mechanism of action. Literature citations will emphasize publications which focus on adverse effects and were so indexed in the Medline database, but are intended to be illustrative rather than exhaustive.

A wide variety of adverse events in all organ systems has been reported with each of these drugs, with low frequency and uncertain causality in many instances, and these may be difficult to evaluate in view of the many and varied complications to which HIV-infected individuals are predisposed. Most of these uncommon or dubious effects will not be discussed here unless they serve to illustrate a point about diagnostic confusion or causal mechanisms.

5. Adverse events reported with zidovudine

In early controlled clinical trials of zidovudine, the most common adverse events included clinical symptoms such as nausea, fatigue, and headache (Richman et al., 1987; Fischl et al., 1990b; McLeod and Hammer, 1992). These events have continued to be reported as the drug encounters wider use (Gelmon et al., 1989; Gimenez et al., 1990), and have been seen in uninfected health care workers receiving prophylaxis after needlesticks (Puro et al., 1992; Tokars et al., 1993; Forseter et al., 1994; Schmitz et al., 1994) as well as in HIV patients. They are generally not life-threatening or dose-limiting for most patients, but can diminish quality of life and for some individuals limit the dose or duration of treatment that is tolerated.

The most common major toxicity of zidovudine has been hematologic. Both anemia and leukopenia were prominent in early clinical trials (Richman et al., 1987; Gelmon et al., 1989), and have been dose-limiting in many instances. These toxicities are often dose-related (Volberding et al., 1990; Koch et al., 1992; Drusano et al., 1994) and have led to widespread use of transfusions, erythropoietin, and colony-stimulating factors (Miles et al., 1991); more recent use of the drug has emphasized lower dosages which tend to have fewer marrow-suppressive effects (Fischl et al., 1990a). Inhibition of heme synthesis has been proposed as a partial explanation for the erythrocyte-related component of the marrow suppression (Lutton et al., 1990).

Anemia and leukopenia have been reported during short-term prophylactic use by health-care workers after HIV exposure (Puro et al., 1992; Schmitz et al., 1994), although not to the same extent as seen in treatment of late HIV infection. Hematologic toxicities have also been the most prominent problem encountered with use of the drug in pediatric HIV infection (Warrier and Lusher, 1990; McKinney et al., 1990, 1991; Blanche et al., 1991).

Hematologic toxicities are also among the more common adverse events reported to the SRS for zidovudine. It would be reasonable to expect that the tendency to report these events diminishes as practitioners become more familiar with the drug and expect the marrow effects as concomitants of therapy. Indeed, macrocytosis is most commonly caused by zidovudine in some populations (Snower and Weil, 1993) and is sometimes used as an indicator of compliance with zidovudine. Even allowing for this, as of March 1995 anemia was the second and leukopenia was the fourth most common adverse reaction term (COSTART, Coding Symbols for Thesaurus of Adverse Reaction Terms) reported to the SRS. The most common term was fever, which is difficult to evaluate as a drug-related event in patients who often have multiple reasons to be febrile. Fever has not appeared with the same prominence in reports for other antiretrovirals (seventh on the list for di-

danosine, 26th for zalcitabine, seventh for stavudine). Drug fever and febrile hypersensitivity reactions do appear in a few published reports (Jacobson et al., 1989; Wassef and Keiser, 1995) with zidovudine, but it is unclear how often they actually occur.

Common management of HIV infection has evolved to include use of zidovudine for much longer treatment periods than were evaluated in early controlled trials. Thus, there is little or no adverse event information from controlled clinical trials relevant to more prolonged therapy. Much of the available information is strictly anecdotal, although a few systematic observational studies have been done and continue to be conducted.

A survey of adverse events in patients receiving zidovudine for a mean duration of 21 months was published in 1989 (Fischl et al., 1989). Because all patients had been offered zidovudine after the initial placebo-controlled phase showed benefit, there was no untreated or blinded control group for the long-term study. Increases in liver function tests were noted in a large proportion of patients receiving more than 10 months of therapy but dose adjustment was required in only 10 out of the total group of 229 patients. Other events noted in this setting included five patients with myopathy, two with cardiac dysfunction, and one with a grand mal seizure. No other new or unexpected adverse events were reported. Another study (Moore et al., 1991) of patients receiving zidovudine for up to 2 years found no previously unreported adverse events.

Individual reports in the literature and the SRS have further expanded the spectrum of uncommon adverse events associated with zidovudine, especially in the areas of liver and muscle abnormalities suggested by the long-term study cited above. There have been numerous reports of myopathy in patients receiving long-term zidovudine (Gertner et al., 1989; Dalakas et al., 1990; Grau et al., 1993). Characteristics of this myopathy have included muscle pain, tenderness and weakness, with 'ragged-red' fibers on histologic examination corresponding to abnormal mitochondria on electron microscopy. There has been controversy over whether and how zidovudine-related myopathy can be distinguished from the myopathy that can be seen in HIV patients not receiving antiretroviral treatment (Till and MacDonell, 1990; Manji et al., 1993; Simpson et al., 1993; Lane et al., 1993). However, some authors have reported ultrastructural, biochemical, or immunochemical differences between the two entities (Pezeshkpour et al., 1991; Chariot et al., 1993; Gherardi et al., 1994), and improvement with cessation of zidovudine has been reported in many instances (Panegyres et al., 1990; Chalmers et al., 1991; Arnaudo et al., 1991; Mhiri et al., 1991; Peters et al., 1993). Elevated creatine kinase values have been reported in children receiving prolonged treatment with zidovudine, but it is unclear how often this might progress to clinically evident myopathy (Walter et al., 1991).

In view of the reports of skeletal myopathy, the question of whether cardiomyopathy can be associated with zidovudine also arises. A few suggestive cases have been reported (Herskowitz et al., 1992), and a recent series notes evidence of cardiomyopathy in children treated with zidovudine (Domanski et al., 1995). Again, however, it may be difficult to distinguish this phenomenon from the cardiac abnormalities that may be caused by HIV itself, especially when trying to evaluate causality in an individual complex case.

Some degree of liver abnormality has been noted with almost all antiviral drugs on the market, as noted in a previous review (Styrt and Freiman, 1995). Occasional reports of serious liver damage in patients on zidovudine (Dubin and Braffman, 1989; Gradon et al., 1992; Shintaku et al., 1993) appeared within several years after the drug was marketed. The causes of hepatic dysfunction in zidovudine-treated patients have often been difficult to delineate precisely because of complicating factors including underlying diseases (Glasgow et al., 1985; Astagneau et al., 1990; Boag et al., 1992), concomitant drugs (Shriner and Goetz, 1992), and zidovudine-related (Pollack and Weaver, 1993) or transfusion-related (Wetton et al., 1993; Goldin et al., 1993) siderosis.

In 1993, a review of several characteristic cases prompted a 'dear doctor' letter and a boxed warning added to the zidovudine label, describing the risk of severe hepatomegaly with steatosis, in some instances fatal. This phenomenon was noted

in patients who had received zidovudine for prolonged periods of time, usually longer than 6 months, and presented with nonspecific abdominal symptoms; most of the original reports were in female patients (Freiman et al., 1993). Some had coexisting metabolic acidosis which was identified in a few as lactic acidosis. The SRS received 35–40 (precise number unclear because of inadequate information in some cases) reports of 'fatty liver' in association with antiretrovirals, mostly zidovudine, between the time period covered by the published series and March 1995. These included 17 deaths and 15–17 reports with concomitant lactic acidosis. The female predominance was less striking in these subsequent reports than in the published series, but most had received at least 6 months of zidovudine, and three patients reported with shorter courses may have been exposed to more than one antiretroviral drug.

Additional literature reports have described lactic acidosis (Chattha et al., 1993). In several cases there has been concomitant occurrence of lactic acidosis with liver damage and/or skeletal myopathy (Gopinath et al., 1992; Chen et al., 1992; Le Bras et al., 1994; Olano et al., 1995).

It remains unclear how frequently liver toxicity should be anticipated. Most of the reports of this event are single case reports or case series. One retrospective study (Fortgang et al., 1995) suggested an incidence of about 1 event per 1000 person-years; this should be contrasted with the likelihood of finding some evidence of hematologic dysfunction in a very high proportion of patients, often greater than 40%, even with relatively short-term treatment (Richman et al., 1987; Gelmon et al., 1989; Fischl et al., 1990a).

Many other adverse events have been reported in small proportions of patients receiving zidovudine. Causal assessments are often difficult to determine in the complex clinical settings in which the drug is used, and continued surveillance and study is needed to evaluate the relative importance of those events which may be listed in the label but have not been investigated in detail. One particularly important event which limits the usefulness of the nucleoside analogs is the induction or selection of resistant retrovirus: although not conventionally discussed as part of the adverse reaction profile, emergence of resistance is increasingly recognized as a common (Larder et al., 1989; Richman et al., 1990) and clinically significant (D'Aquila et al., 1995; Nielsen et al., 1995) concomitant of prolonged usage.

6. Adverse events with didanosine

Prominent adverse events reported in early use of didanosine (Yarchoan et al., 1989; Pike and Nicaise, 1993; Kahn et al., 1992) included pancreatitis and neuropathy. Gastrointestinal symptoms including diarrhea were also relatively frequent and were often attributed to the buffer used in preparation of the drug.

Pancreatitis (which can be fatal) and neuropathy have continued to be reported (Allan et al., 1993; Montaner et al., 1994; Moyle et al., 1993; Nguyen et al., 1995; Dolin et al., 1995) from clinical trials (Phase III, Phase IV and the Expanded Access Program) and from clinical usage. Pancreatitis and neuropathy-related events (which may be reported and coded as either neuropathy or neuritis) have been among the most frequent adverse events reported to the SRS as well.

Pancreatitis has been reported in percentages of didanosine recipients as low as 5% or less, up to over 20% in various series (Maxson et al., 1992). Its occurrence may be dose-related (Grasela et al., 1994), and prior history of pancreatitis has also been considered as a risk factor. Disorders of pancreatic function including glucose intolerance and overt diabetes mellitus have been reported occasionally (Albrecht et al., 1993; Vittecoq et al., 1994; Chidiac et al., 1995). Pancreatitis and abnormal liver chemistries have also been noted in children during didanosine treatment (Butler et al., 1991).

Manifestations of neuropathy have been predominantly sensory (pain and dysesthesias) although motor involvement also occurs (Keiburtz et al., 1992). This adverse event may also be dose-related and often improves after cessation of the drug.

A few cases of liver damage resembling hepatitis have been reported with didanosine (Lai et al., 1991; Bissuel et al., 1994). Death from hepatic

failure was noted in clinical trials and is mentioned in the label. Most of the patients reported as having serious hepatic problems on didanosine have had either underlying liver abnormalities or prior exposure to zidovudine or both, not a surprising finding given that a principal indication for use of this drug is in patients who have not done well on zidovudine. However, this makes it difficult to judge causality or relative incidence of this complication with the two drugs.

Cardiomyopathy has been reported in a few patients receiving didanosine. As with zidovudine, it may be difficult to distinguish the effects of treatment from those of the underlying HIV infection; also in the case of didanosine, it has been suggested that the buffer content of early preparations contributed to development of clinically evident heart failure (de Jong and Borleffs, 1992). Also as seen with zidovudine, a wide variety of events in other organ systems are reported sporadically, with little conclusive evidence of which ones are causally related.

An adverse event of particular concern in children treated with high dose didanosine is the development of retinal lesions (Whitcup et al., 1994). These have also been noted occasionally in adult patients, and further study may be needed to define their frequency and risk factors.

7. Adverse events with zalcitabine

Based on data from clinical trials, the major toxicities associated with zalcitabine are neuropathy and pancreatitis. Postmarketing reports on this drug have been more difficult to assess because of its primary use in combination with zidovudine, so that it may be unclear which agent is responsible for a given event or whether a drug interaction is involved.

Painful peripheral neuropathy, with predominantly sensory manifestations, has emerged as the most characteristic severe adverse event associated

may be seen in HIV infection without nucleoside therapy.

In a comparative trial of zalcitabine or didanosine following zidovudine therapy (Abrams et al., 1994), neuropathy was noted at a rate of 45.1 events per 100 patient-years (69 of 237 patients) in zalcitabine patients, compared with 22.1 events per 100 patient-years (33 of 230 patients) for didanosine. Conversely, pancreatitis and diarrhea were more frequent in the didanosine than in the zalcitabine group.

Another event that was characteristic of zalcitabine in this comparative trial was stomatitis, occurring in 8 zalcitabine and no didanosine patients. Oral ulcers were quite common in one pediatric trial of zalcitabine (Pizzo et al., 1990), noted in 9 of 15 patients during an 8-week course but requiring treatment cessation only in one.

Elevations of liver function tests were reported in clinical trials of zalcitabine. A few instances of severe hepatic damage have been reported to the SRS, typically in patients who also had histories of zidovudine exposure. Rare cases of cardiac failure have also been reported.

8. Adverse events with stavudine

Stavudine has been in use for a much shorter period of time and experience encompasses a far smaller number of patients than for zidovudine, didanosine, or zalcitabine. Peripheral neuropathy has been the severe and dose-limiting toxicity (Browne et al., 1993; Skowron, 1995). This has been dose-related, occurring in a majority of patients at the maximum tolerated doses (over 2 mg/kg per day) in preliminary dose-ranging studies, and in 15–21% in the clinical trials used to support the approval of the currently recommended doses (which may range up to 40 mg twice daily with adjustment for factors including weight and renal function).

Liver enzyme abnormalities were noted in clinical trials, and were usually asymptomatic. The

Phase I and II studies noted frequent macrocytosis and occasional anemia during stavudine therapy. Hematologic effects have not usually been dose-limiting, although neutropenia recurred and required dose reduction in a few patients with prior intolerance to zidovudine (Skowron, 1995).

Pancreatitis was noted in 1% of stavudine recipients in clinical trials used to derive the label information. In the SRS, occasional reports of cardiomyopathy and of diabetes mellitus have also been received, as with other antiretrovirals; causality is uncertain and surveillance of these reactions continues.

9. Adverse events with lamivudine

Experience with lamivudine to date is limited. Gastrointestinal events including nausea, and neurologic events including headache and peripheral neuropathy, have been reported in clinical trials (Eron et al., 1995; van Leeuwen et al., 1995). Transient changes in hematologic and hepatic laboratory values have been reported, but did not require dose adjustment in one selected study group (van Leeuwen et al., 1995).

Lamivudine has been approved for use in combination with zidovudine. Most adverse events listed in the label information (Epivir® prescribing information (label summary), Glaxo Wellcome, 1995) from controlled trials occurred in similar percentages of patients receiving lamivudine plus zidovudine compared with those receiving zidovudine alone. Although higher percentages were reported with the combination for events such as dizziness (10% vs. 4%), depressive disorders (9% vs. 4%), nasal signs and symptoms (20% vs. 11%), and cough (18% vs. 13%), it is difficult to interpret a group of relatively nonspecific events which may be common at baseline in the relevant population. No information is available on distribution of adverse events during more prolonged use.

In a dose-escalation study of lamivudine monotherapy (Pluda et al., 1995), the most commonly reported adverse events were headache, insomnia, nausea and diarrhea; a trend toward decreased neutrophil counts was noted at high doses. Six of 97 patients stopped therapy because of possibly related adverse events, all different (neutropenia, diarrhea, elevated amylase, neuropathy, 'possible seizure', and Henoch-Schoenlein purpura).

Emergence of HIV resistance to lamivudine during therapy has been common (Wainberg et al., 1995; Schuurman et al., 1995). The clinical significance of this observation is not known. In studies summarized in the label information, most patients had lamivudine-resistant isolates within 12 weeks of therapy, but the combination of lamivudine and zidovudine appeared to delay appearance of zidovudine-resistant mutations.

The events of greatest concern so far with lamivudine have been reported in children: pancreatitis and paresthesia or neuropathy occurred in 14–15% and 13%, respectively, of patients in trials summarized in the label information. These events have been reported rarely in adults in early trials. There is no information available on the spectrum of adverse events in children when lamivudine is used in combination with zidovudine.

The most characteristic major toxicities of the five nucleoside analogs are listed in Table 1. It should be re-emphasized that the adverse event profile of the newer drugs is less fully known than that of the older agents.

10. The mitochondrial hypothesis as a mechanism for adverse events

The primary target of the antiretroviral nucleoside analogs is the viral reverse transcriptase. However, various nucleosides or their phosphorylated derivatives can inhibit mammalian DNA polymerases, including gamma polymerase which is important to mitochondrial DNA replication; may damage or deplete mitochondrial DNA in vitro; and may inhibit mitochondrial metabolism (Simpson et al., 1989; Izuta et al., 1991; Hayakawa et al., 1991; Chen and Cheng, 1992; Youssef and Badr, 1992; Modica-Napolitano, 1993). Cultured cells incubated with these agents have been reported to show abnormal mitochondrial morphology (Lewis et al., 1992; Medina et al., 1994).

Mitochondrial toxicity has been proposed as a mechanism for several of the adverse events observed with these drugs including marrow suppression, liver failure, neuropathy, myopathy and lactic acidosis. There is some support for this hypothesis from the muscle biopsy and hematopoietic enzyme findings already described. Zidovudine-treated patients have also been reported to have abnormal calf muscle mitochondrial function as measured by 31P magnetic resonance spectroscopy (Weissman et al., 1992), but non-drug-exposed controls in this study were not HIV-infected, so that it is unclear whether effects of zidovudine on muscle mitochondrial function could be distinguished from effects of HIV itself. Lactic acid production by cultured cells was increased in the presence of antiretroviral nucleosides (Chen et al., 1991), supporting a link between mitochondrial toxicity and the hepatomegaly/acidosis syndrome reported after prolonged nucleoside treatment.

However, these studies do not explain the different organ system spectra of adverse events when antiretrovirals are compared with one another. In addition, results obtained in some systems have produced discordant reports. One study using cultured human muscle cells found little effect of zidovudine on mitochondrial enzyme activity despite a marked inhibition of cellular proliferation (Herzberg et al., 1992). Another recent study (Martin et al., 1994) reported no clear relationship between the capacity of different nucleoside analogs to inhibit DNA polymerase gamma and their inhibition of mitochondrial DNA synthesis in cell culture or their pattern of clinical toxicity. It has been proposed (Chang et al., 1992b) that some of the toxicities of nucleoside analogs may be related to the ability of mammalian cell enzymes to convert them to specific metabolites, that some organ-specific drug activities may be due to local differences in enzyme activities (Chang et al., 1992a), and that some organ-specific differences in toxicities of antivirals may thus be explained by local differences in drug metabolism (Parker and Cheng, 1994); potential implications for antiretroviral drugs in clinical use remain to be delineated fully.

Overall, the mitochondrial hypothesis is intriguing but its precise role in explaining specific toxicities of antiretroviral nucleoside analogs remains unproven. Further study of this issue may help to determine whether in vitro mitochondrial assays can be useful in predicting the toxicity profiles of drugs in early stages of development.

Table 1
Serious toxicities characteristic of different antiretroviral nucleoside analogs

Drug	Principal treatment-limiting toxicities
Zidovudine	Anemia, leukopenia
Didanosine	Pancreatitis, peripheral neuropathy
Zalcitabine	Peripheral neuropathy, pancreatitis
Stavudine	Peripheral neuropathy
Lamivudine	
combined with zidovudine	Similar to zidovudine alone
In children	Pancreatitis, paresthesia neuropathy

Adverse events listed are those which have characteristically led to cessation of therapy and or addition of specific treatment for the adverse event, based on published studies and label information. Many other adverse events have been reported but have been less severe, less common, or less clearly associated with the drug in question from information available so far (see text).

11. Conclusions

Understanding of the clinical toxicity of antiretroviral nucleoside analogs continues to evolve as clinical experience with these drugs increases. Minor symptoms such as nausea and fatigue are common; they are usually not dose-limiting but can affect quality of life and aggregate benefit derived by patients from each drug. Serious adverse events differ somewhat between drugs despite their similar mechanism of therapeutic action.

Zidovudine is the oldest and most widely used of these agents, and adverse effects observed after longer experience with this drug may be detected with newer agents after they reach comparable

levels of clinical use. In short-term use, hematologic toxicity is extremely common, but many patients are able to continue treatment with dose adjustments and the use of treatments such as transfusion and hemopoietic growth factors. With prolonged treatment, myopathy has been noted with increasing frequency although differentiation from direct effects of HIV may be difficult. Liver damage and lactic acidosis have also emerged as significant adverse events associated with long-term zidovudine use, but there is insufficient information for estimating incidence of these relatively rare events.

Didanosine, zalcitabine and stavudine share the major toxicities of pancreatitis and neuropathy; pancreatitis has been most prominent with didanosine and neuropathy with the other two drugs. The ability to cause diabetes mellitus may be associated with risk of pancreatitis but is less well described. Hematologic toxicity is less common with these agents. Liver and muscle damage have been reported, but have not been prominent. Because patients receiving one of these drugs usually either have received prolonged pretreatment with other agents or receive them in combination with zidovudine, it is not possible to determine at this time whether these long-term toxicities would occur with comparable frequencies if the drugs were to be used in comparable ways. It seems likely that any of the marketed antiretrovirals can rarely be associated with cardiomyopathy, but definitive information is not available.

Lamivudine has been approved very recently and much of its use has been in combination with zidovudine. A variety of systemic symptoms and laboratory abnormalities have been reported, most of them not requiring major changes in therapeutic approach, but further experience with this drug may lead to better definition of its potential for toxicity. Pancreatitis and peripheral neuropathy have aroused concern, principally in pediatric trials.

Emergence of resistant HIV has been best studied in the setting of zidovudine therapy. However, it also occurs with newer agents (Kozal et al., 1994; Schuurman et al., 1995), and cross-resistance among different antiretrovirals has been reported (Mayers et al., 1994). Although not conventionally included in the toxicity profile, viral resistance may be one of the more important treatment-limiting events associated with any of the antiretroviral agents as their use increases.

While mitochondrial toxicity may be a plausible explanation for many of the specific organ-system toxicities of nucleoside analogs, in vitro studies have not been documented to predict specific patterns of toxicity or their relative incidence with different drugs. Because of the lack of valid predictors and the emergence of new toxicities with prolonged therapy, continued surveillance will be needed to better define the adverse effect profiles of these agents.

Health care providers can help in the delineation of toxicity risks by reporting adverse events to the FDA's MedWatch program at 1-800-FDA-1088. As newer antiviral agents are introduced into clinical use to meet emergent needs, and used in ever more complex combinations in high-risk patients, it will be increasingly important to be vigilant for late adverse effects that may not be detected early in the drug development process.

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