IMPROVING THE MANAGEMENT OF HIV DISEASE

IN THIS ISSUE—

Recent Advances In

- Initiating Antiretroviral Therapy
- Protease Inhibitors
- Novel Therapies for HIV Infection

PLUS ...

Reviews of the Most Recent Clinical Research Findings in

- OI Prophylaxis
- OI Treatment
- Kaposi’s Sarcoma
In This Issue

For the fourth year, the International AIDS Society-USA (IAS-USA) is pleased to distribute *Improving the Management of HIV Disease*, a publication derived from the IAS-USA advanced continuing education programs for physicians treating persons with HIV disease. This first issue for 1996 summarizes selected presentations of the spring conference series, *Improving the Management of HIV Disease: HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management*. Here, presentations from the conferences in Los Angeles and Atlanta on initiating antiretroviral therapy, protease inhibitors, and immune-based therapy are highlighted. The second issue, scheduled for May/June distribution, will include highlights from the New York conferences on HIV pathogenesis, viral quantitation, strategies for continuing antiretroviral therapy, and occupational exposure to HIV.

This issue also introduces a new format for the publication. Beyond presenting highlights from the IAS-USA conferences, we are working to broaden the scope of our publication by including other articles of special interest to HIV care providers. The supplementary articles in this issue review the most important new findings released in the last year on the prevention of opportunistic infections (OIs), the treatment of OIs, and Kaposi’s sarcoma. In future issues we plan to include articles on drug interactions and other topics relevant to the management of HIV disease.

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About IAS-USA

The IAS-USA is a 501(c)(3) not-for-profit organization committed to improving the treatment, care, and quality of life of persons with HIV disease by providing balanced and relevant information to physicians that is particularly intended to bridge clinical research and patient care.

The IAS-USA has developed several strategies for reaching this goal. In addition to this publication, the IAS-USA sponsors the ongoing national CME conference series, *Improving the Management of HIV Disease*, in cities around the country.

Most recently, IAS-USA has commissioned expert panels to develop clinical guidelines in two rapidly evolving and controversial areas: the use of viral load markers and strategies for using antiretroviral therapy. Articles detailing these guidelines are in press and will be updated as further clinical trial data and new options become available.

If you are not on our mailing list and would like to receive this publication and announcements concerning upcoming programs, please contact us.

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IAS-USA Conference in Vancouver
Initiation of antiretroviral therapy was discussed at the Los Angeles conference by Paul A. Volberding, MD, from the University of California San Francisco.

Recent studies have contributed to a growing consensus on when to initiate antiretroviral therapy, although many issues persist. Findings from the AIDS Clinical Trials Group (ACTG) protocol 175 and the Delta trials indicate that antiretroviral therapy should be initiated in asymptomatic patients with CD4+ cell counts less than 500/μL. Data from these and other studies also suggest that even earlier treatment may be warranted in patients with high plasma HIV RNA titers or with rapidly declining CD4+ cell counts. With the growing list of antiretroviral drugs available for use, it is unclear what constitutes optimal therapy. However, there is a healthy consensus that initial therapy should consist of combinations of drugs.

ACTG 175

In ACTG 175, 2467 patients with CD4+ cell counts of 200/μL to 500/μL were randomized to zidovudine, didanosine, zidovudine/didanosine, or zidovudine/zalcitabine. Overall, 82% of patients were asymptomatic, 40% had received no prior zidovudine therapy, and the median CD4+ cell count was 352/μL. Dr Volberding largely confined his discussion to outcome in antiretroviral-naive patients, ie, those in whom the study therapy constituted initial therapy. Based on analyses of progression to the combined endpoint of a 50% decline in CD4+ cell counts, an AIDS-defining condition, or death, and of death as a single endpoint, the combination treatments were superior to monotherapy for antiretroviral-naive patients, with zidovudine/zalcitabine appearing to be the most effective combination on both analyses. Although didanosine monotherapy performed surprisingly well with regard to study end points, there appeared to be a consistent advantage to combination treatment in treatment-naive patients that supports recommendation of its use as initial treatment.

There is a consistent advantage to combination therapy in treatment-naive patients.

The Delta trial was similar in design to ACTG 175 except that it did not include a didanosine monotherapy arm and had a study population with somewhat more advanced disease. The study also showed superiority of combination treatment over zidovudine in zidovudine-naive patients, as well as in the overall population. In this trial, zidovudine/didanosine proved to be the most effective combination regimen.

Some data from virology studies in the ACTG 175 population have recently become available. While the findings with regard to treatment outcome provide firm support for treatment of asymptomatic patients with CD4+ cell counts less than 500/μL, the results regarding the predictive value of plasma HIV RNA also provide support for making treatment decisions on the basis of risk of progression. Measurement of plasma HIV RNA showed decreases of 0.4 log with zidovudine monotherapy, 1 log with zidovudine/zalcitabine, and 1.5 log with zidovudine/didanosine. When the population was apportioned into quartiles based on baseline plasma HIV RNA levels, a dramatically increased risk of progression to an AIDS-defining condition or death was associated with higher plasma HIV RNA levels. Patients with plasma HIV RNA levels of less than 5000 copies/mL and those with 5000 copies/mL to 18,000 copies/mL (first and second quartiles) both had a 3% risk of progression; those with plasma HIV RNA levels of 18,000 copies/mL to 54,000 copies/mL had a 10% risk of progression, while those with levels greater than 54,000 copies/mL had a 32% risk of progression. It was found that baseline and 8-week plasma HIV RNA levels were the best overall predictors of risk of progression. Other factors associated with increased risk of progression were a decrease of 100 CD4+ cells/μL from baseline, which was associated with a 1.5-fold increased risk, and a 1-log increase in plasma HIV RNA levels from baseline, which was associated with a 4- to 6-fold increased risk of progression. Changes in CD4+ cell counts lost much of their predictive value over time, whereas plasma HIV RNA levels retained their predictive value.

According to Dr Volberding, the bottom line of the ACTG 175 findings is that antiretroviral treatment is clearly associated with a survival advantage and that treatment is effective in asymptomatic patients with CD4+ cell counts less than 500/μL. The findings in both ACTG 175 and the Delta trial also suggest that zidovudine/zalcitabine and zidovudine/didanosine as well as didanosine monotherapy are rational choices for initiating therapy. Finally, the virology findings, particularly when coupled with data from the Multicenter AIDS Cohort Study (MACS) showing an increased risk of disease progression with increased plasma HIV RNA levels (see below), suggest that high plasma HIV RNA levels should be considered an important determinant of risk of more rapid progression and a relative indication for treatment initiation.
MACS Study of Plasma HIV RNA as a Predictor of Progression

Several recent clinical studies have pointed to the plasma HIV RNA level as an accurate predictor of risk of progression. In a study in which patients from the MACS in Pittsburgh were followed for several years, those patients who progressed to AIDS exhibited steadily increasing plasma HIV RNA levels, whereas those who did not progress over the same time period had relatively stable viral loads. In a further analysis of this population, the risk of death was shown to dramatically increase with increasing plasma HIV RNA levels as measured by a sensitive branched-DNA assay (sensitivity limit, 500 copies/mL). When the patients were apportioned into quartiles based on the average of two baseline measurements of plasma HIV RNA, the risks of death were as follows: (1) less than 5100 copies/mL, 0%; (2) 5100 copies/mL to 12,800 copies/mL, 5%; (3) 12,800 copies/mL to 34,500 copies/mL, 33%; and (4) greater than 34,500 copies/mL, 65%. In addition to showing the importance of virus burden to disease progression and suggesting that treatment outside of the more conservative CD4+ cell count-defined threshold should be considered in cases in high viral load, these findings also point to the potential importance of viral dynamics in determining disease progression and possibly in helping guide treatment decisions. In particular, studies involving longitudinal follow-up of viral load or changes in viral load with therapeutic intervention have suggested that each HIV-infection person manifests a viral replication set point, i.e., a level of viral replication that persists for a relatively prolonged period (Figure 1). This set point, which may be largely a function of the host immune response, appears to be determined in an HIV-infected person sometime within the first 6 months of infection, after resolution of the initial viremia characteristic of primary infection. Determining whether institution of potent antiretroviral therapy before the establishment of the set point may serve to effectively lower that set point in an individual otherwise destined to have more rapidly progressive disease is an issue that warrants investigation.

Other Potential Initial Regimens

Clinical trial data on a number of other potential initial regimens have become available recently.

Lamivudine/zidovudine. The lamivudine/zidovudine combination has been shown to have persistently lower plasma HIV RNA levels and to maintain CD4+ cell count increases. Figure 2 shows the effects of this combination on plasma HIV RNA levels over the first 48 weeks of treatment in NUCA 3001, one of the recent trials investigating zidovudine/lamivudine. A 76-week follow-up of this study population has shown this combination treatment is associated with (1) persistence of CD4+ cell count benefit; (2) maintenance of an approximately 1-log decrease in plasma HIV RNA levels from baseline; (3) plasma HIV RNA levels below the detection limit in 20% of patients and in 50% of those with low levels at baseline; and (4) a trend toward fewer minor opportunistic infections compared with monotherapy, with very few AIDS-defining conditions having occurred in the study population overall. The proportion of patients who experience decreases in viral load to below assay detection limits is important to consider in weighing the effectiveness of a regimen, since the magnitude and quality of the decrease in these patients are not accurately reflected in the numeric value of the decrease in viral load.

When used alone, lamivudine also showed persistent activity that appeared to be equivalent to zidovudine monotherapy, despite the fact that virtually all patients developed high-level resistance to this drug after a relatively short period of time. This persistent activity may actually depend on the development of the resistance mutation. Although Dr Volberding expressed doubt regarding whether this drug or any other single antiretroviral agent should be used alone in initial treatment, he noted that there may be a place for lamivudine monotherapy, given its low toxicity, in patients who are unable to tolerate other antiretroviral drugs.

Stavudine. In a recent placebo-controlled trial of stavudine as initial monotherapy in patients with CD4+ cell counts of 350/μL to 750/μL, full-dose stavudine treatment for 12 weeks was associated with a median 0.5- to 0.8-log decrease in plasma HIV RNA and a median increase in CD4+ cell count of 40 cells/μL. During an open-label half-dose continuation phase, the viral load and CD4+ cell count benefits were lost.

Didanosine/stavudine. In a recent trial, 76 patients with CD4+ cell counts of 200/μL to 500/μL were given various doses of didanosine/stavudine for 52 weeks. Plasma HIV RNA decreases of 1.2 to 1.4 log were observed, with 60% of patients exhibiting a decrease of at least 1 log and 15% to 30% exhibiting a decrease of at least 2 log. In the standard-dose combination group, CD4+ cells increased by 140 cells/μL. Almost no neurotoxicity was reported with this combination regimen.

Protease inhibitors. Dr Volberding did not discuss recent findings with regard to protease inhibitor treatment, since the topic was extensively treated by another speaker at the Los Angeles meeting [see “Protease Inhibitors” (Steven A. Miles, MD, and Kathleen E. Squires, MD) in this issue]. However, he noted that protease inhibitors exhibit remarkable potency, and that a combination regimen of protease inhibitors with one or two nucleoside analogues may prove to be the most potent antiretro-
viral treatment strategy in the near future. Such combinations are currently being investigated.

Summary

A conservative approach to initial antiretroviral therapy, ie, one based primarily on available clinical trial results, can be summarized as follows: With regard to general principles of initiation, treatment should be begun before symptom onset: if the patient has a CD4+ cell count greater than 500 cells/µL, the burden of proof is on the decision to treat; if the patient has a CD4+ cell count less than 500 cells/µL, the burden of proof is on the decision not to treat. Unique indications for treatment include postexposure (occupational, sexual) treatment, treatment during pregnancy of infected women, and treatment during primary infection. There are now data that clearly demonstrate benefit of treatment in the first two indications and data that suggest benefit of treatment in the third. The importance of viral burden as a predictor of progression is increasingly being recognized. Thus, it seems likely that high viral load will eventually be taken as an indication for treatment regardless of CD4+ cell count.

A conservative approach to selecting the initial treatment regimen would be to choose among the combinations of zidovudine/didanosine, zidovudine/azidothymidine, or zidovudine/lamivudine. Dr Volberding noted that although didanosine monotherapy may be considered as a first-line option given its performance in ACTG 175, he would generally not recommend monotherapy for initial treatment with any currently available agent.

For patients who become zidovudine-intolerant or who refuse zidovudine, the combinations of stavudine/didanosine or stavudine/lamivudine should be considered, as well as monotherapy with either didanosine or stavudine. The addition of one of the protease inhibitors (ritonavir, indinavir, or the newer formulation of saquinavir with increased bioavailability if and when it becomes available) to nucleoside analogue treatment may be considered in patients with a high risk of progression as indicated by low or declining CD4+ cell counts or high plasma HIV RNA levels.

With regard to trends in the near future, there may well be a continuing movement toward early aggressive initial therapy, the addition of protease inhibitors to such treatment, and the use of viral quantitation as a standard tool in the management of HIV-infected patients.

It seems likely that high viral load will eventually be taken as an indication for treatment regardless of CD4+ cell count.

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PROTEASE INHIBITORS

Protease inhibitors were discussed at the Los Angeles conference by Steven A. Miles, MD, from the University of California, Los Angeles, and at the Atlanta conference by Kathleen E. Squires, MD, from the University of Alabama at Birmingham. At the time of these conferences, saquinavir was the only protease inhibitor approved for use in the treatment of HIV disease. Shortly thereafter, the protease inhibitors ritonavir and indinavir were granted accelerated approval by the FDA.

Saquinavir

Saquinavir (Ro31-8959) was the first protease inhibitor to be approved for use in the treatment of HIV disease. Initial studies of the current formulation of this drug used alone showed beneficial effects of relatively small magnitude on CD4+ cell counts, p24 antigen levels, and plasma HIV RNA levels in both antiretroviral-naive and -experienced patients in a regimen of 600 mg tid, the highest dose examined. In the AIDS Clinical Trials Group (ACTG) protocol 229, the triple combination of saquinavir, zidovudine, and zalcitabine was associated with beneficial changes in peripheral blood mononuclear cell (PBMC) HIV titers and CD4+ cell counts that were somewhat better than those observed in patients given zidovudine/zalcitabine over 24 weeks of study. Saquinavir is a potent agent in vitro, and it appears that the modest magnitude of benefit observed with this drug is due to the exceedingly poor bioavailability of the current formulation (4%). One group has recently examined use of higher doses of saquinavir; at dosages of 3600 mg/d and 7200 mg/d, reductions of 0.85 to 1.3 log in plasma HIV RNA levels have been observed in association with increases in CD4+ cell counts of 80/µL to 120/µL. A soft gelcap formulation of saquinavir intended to improve bioavailability is under development. This new formulation is expected to provide drug serum levels comparable to those produced by the 7200 mg/d dosage with the current formulation. Such a formulation would likely improve the efficacy of saquinavir.

Ritonavir

In early studies of ritonavir monotherapy (ABT 538), dosages of 500 mg and 600 mg bid for 12 weeks were associated with reductions in plasma HIV RNA levels of greater than 1 log and with increases in CD4+ cell counts of 60/µL to 100/µL. Longer-term monotherapy studies with a range of doses have shown that 600 mg bid of ritonavir is associated with median increases in CD4+ cell counts of 150/µL to 200/µL sustained for at least 30 weeks. At 30 weeks, the increases in CD4+ cell counts observed with lower doses had been lost or dramatically reduced (Figure 1). These data suggest that higher doses are associated with more persistent drug effects, as well as a greater magnitude of effect.

Ritonavir, added to whatever antiretroviral regimen study subjects were already receiving, was recently shown to significantly prolong survival in patients with advanced HIV disease who had received extensive prior antiretroviral treatment. In this trial, patients with advanced disease were randomized to ritonavir 600 mg bid (median CD4+ cell count, 18/µL) or placebo (median CD4+ cell count, 22/µL) and were continued on their other nucleoside analogue medications. During approximately 5.5 months of study, ritonavir treatment was associated with a significant reduction in mortality, with death occurring in 26 (4.8%) of 543 ritonavir-treated patients and in 46 (8.4%) of 547 patients given placebo (P = .02), and with a significant reduction in the rate of AIDS-defining conditions or death (12.7% vs 23.7%; P < .001). Adverse events occurred in 17% of ritonavir-treated patients and in 6% of those given placebo. In ritonavir-treated patients, a mean peak increase of 47 CD4+ cells/µL occurred at 16 weeks, compared with a virtual absence of change in those given placebo. A mean peak decrease of 1.3 log in plasma HIV RNA levels occurred at 2 weeks. In some cases, increased CD4+ cell counts were accompanied by improved immunologic function, skin test reactivity, and clearance of opportunistic infections and neoplasms. The ritonavir-treated group showed a mean peak increase in CD8+ counts of 314 cells/µL at 8 weeks.

Indinavir

In a trial that compared indinavir (L735-524, MK639), zidovudine, and the combination of the two in zidovudine-naive patients with plasma HIV RNA levels greater than or equal to 20,000 copies/mL, indinavir monotherapy and the indinavir/zidovudine combination were both associated with reductions in plasma HIV RNA levels of at least 1.5 log. Indinavir alone was
associated with a reduction of greater than 2 log that was maintained for more than 24 weeks (Figure 2). Assessment of zidovudine-resistant mutations during the course of therapy showed that approximately 60% of patients given zidovudine monotherapy yielded virus with zidovudine-resistant mutations by 24 weeks compared with less than 10% of patients who were given combination treatment; this finding suggests that concomitant use of indinavir may delay development of resistance to zidovudine. In a trial comparing indinavir, zidovudine/lamivudine, and the combination of the three in 97 patients with at least 6 months of prior treatment with zidovudine, CD4+ cell counts of 50/µL to 400/µL, and plasma HIV RNA levels greater than or equal to 20,000 copies/mL, indinavir alone was associated with a 1.5-log reduction in plasma HIV RNA levels. The combination of indinavir, zidovudine, and lamivudine produced a 2-log decrease in plasma HIV RNA levels, while the zidovudine/lamivudine combination resulted in a decrease of approximately 1 log. The triple combination group experienced a median increase in CD4+ cell counts of 146/µL at 24 weeks (Figure 3).

**Resistance**

Resistance has been demonstrated with all protease inhibitors. However, high-level resistance to both indinavir and ritonavir is not conferred by any single mutation or pair of mutations, but is rather the result of stepwise accumulation of multiple mutations. Indinavir-resistant virus is cross-resistant to ritonavir and many other protease inhibitors in development but not to saquinavir; moreover, neither resistance to ritonavir nor to saquinavir is associated with broad-class resistance. Figure 4 shows reported data on resistance mutations to saquinavir, ritonavir, and indinavir in clinical HIV isolates. Since saquinavir was the first protease inhibitor approved for use and since it was feared that resistance to a particular protease inhibitor would confer broad-class resistance, there was concern that using a compound formulation associated with marginal benefit would compromise later use of compounds that appeared to have much greater potency. The data on the distribution of resistance mutations in vivo and those on in vitro sensitivity of virus with saquinavir resistance mutations (codons 48 and 90 mutations) to other protease inhibitors suggest that resistance to saquinavir may not lead to resistance to other compounds. Resistance to saquinavir at higher and more effective doses appears to occur at approximately the same rate as that seen with lower doses. In the small-scale studies to date using higher doses, 25% to 45% of patients have yielded virus with either the codon 48 or the codon 90 mutation by 24 weeks. Longer-term follow-up has indicated that 40% to 45% of patients develop the mutations associated with resistance after 1 year of treatment.

**Effect of Ritonavir on Blood Drug-Levels**

One potential motivation for using protease inhibitors in combination is the interaction between ritonavir and virtually all other protease inhibitors developed to date; ritonavir increases blood levels of other protease inhibitors by inhibiting the cytochrome P450 3A4 isoenzyme. Studies in rats have indicated that a single dose of ritonavir increases levels of saquinavir in the blood by more than 290-fold. Smaller but significant increases have reportedly been observed with virtually all other protease inhibitors currently in clinical development. Given the absence of cross-resistance between saquinavir and ritonavir, it may make sense to take advantage of this interaction to increase blood levels of saquinavir. Further elucidation of the pharmacokinetic interaction in terms of toxic effects is necessary before this approach can be used clinically.

**Adverse Effects**

The protease inhibitors currently available have both shared and distinctive adverse effects. Although saquinavir has thus far been associated with the fewest side effects at currently recommended doses, use of higher doses has been associated with a significant incidence of stomach distress (ie, bloating and gas). Indinavir has been associated with nephrolithiasis attributable to precipitation of indinavir in the urine. Ritonavir has been associated with significant nausea; the soft gelcap formulation of ritonavir is somewhat better tolerated. Most patients given ritonavir have reported perioral dysesthesia during the first 1 or 2 weeks of treatment, typically described as a numbness or tin-
gling. Ritonavir is also associated with diarrhea. Most of the compounds evaluated to date have been associated with hepatitis, with clinical development of a number of potentially useful compounds having been halted due to a significant incidence of this adverse effect. Lipid abnormalities have also been observed with use of most of these compounds. Pancreatitis is common in patients with HIV disease, and with the burgeoning use of liposomal preparations of a variety of frequently used medications, the lipid interactions of protease inhibitors with liposomal drugs need to be investigated. Less common significant adverse effects include rash and fever, which have been observed in patients given indinavir. Most studies have shown that adverse effects occur in 15% to 20% of patients with advanced HIV disease who are treated with protease inhibitors. The effect of ritonavir on hepatic cytochrome P450 induction also affects the metabolism of other medications, and, therefore, careful observation is required for potential drug-drug interactions.

**Drugs Under Development**

Newer protease inhibitors include second-generation compounds being developed by Agouron, Glaxo-Wellcome, Upjohn, Ciba-Geigy, and other manufacturers. The Agouron compound, currently in phase III testing, is furthest along in development; early studies have indicated that this drug produces substantial decreases in viral load when used alone or in combination with stavudine. According to Drs Miles and Squires, the drugs in development have either superior pharmacologic characteristics or superior manufacturing processes that may translate into increased therapeutic benefit and reduced treatment costs.

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Kathleen E. Squires is Assistant Professor of Medicine and Associate Director of the AIDS Outpatient Clinic at the University of Alabama at Birmingham.

**Suggested Readings**


Collier AC, Coombs RW, Schoenfeld DA, et al. for the AIDS Clinical Trials Group Protocol 229 team. A comparative study of saquinavir (SAQ) and zidovudine (ZDV) vs. ZDV and zalcitabine (ddC) vs. SAQ, ZDV and ddC. Presented at Thirty fourth Interscience Conference on Antimicrobial Agents and Chemotherapy; October 4–7, 1994; Orlando, Fla.

Collier AC, Coombs RW, Schoenfeld DA, Bassett R et al. Extended treatment with saquinavir (SAQ), zidovudine (ZDV) and zalcitabine (ddC) vs SAQ and ZDV vs ddC and ZDV. Presented at Thirty fifth Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 1995; San Francisco, Calif.


Emmi E. HIV-1 protease inhibitors. Presented at Third Conference on Retroviruses and Opportunistic Infections; January 28–February 1, 1996; Washington, DC.


Novel Therapies for HIV-1 Infection

Novel therapies for HIV-1 infection were discussed at the Atlanta conference by Robert T. Schooley, MD, from the University of Colorado School of Medicine in Denver. Dr. Schooley's presentation focused primarily on immune-based therapies and included a brief overview of genetic therapies.

Recent enthusiasm over the development of new antiretroviral drugs and strategies that have been effective in decreasing viral replication must be tempered with the knowledge that there are limitations to the benefits from these currently employed treatments. Dose-limiting toxicities, the emergence of virus with reduced susceptibility to antiretroviral drugs, and incomplete control of viral replication all contribute to the failure of current therapies to completely restore immune responsiveness in patients with HIV disease. It has also been observed that the increases achieved in CD4+ cell counts appear to plateau even with very effective antiretroviral drugs, at least in patients who have already experienced significant quantitative loss of CD4+ cells. In this context, there remains interest in developing such alternative treatment approaches as immune-based and genetic therapies.

General Immune Modulation

There are two general approaches to immune-based intervention: (1) enhancement of HIV-1-specific immune-effector mechanisms; and (2) general augmentation or restoration of immune response. With regard to general immune modulation, there are continuing attempts to identify and use cytokines that are deficient in late-stage HIV infection (eg, interleukin [IL]-2) or that may enhance cellular immune function (eg, interferon [IFN]-α, IFN-γ, IL-2, IL-7, IL-12, and IL-15), as well as to down-regulate cytokines that may enhance HIV replication (eg, tumor necrosis factor [TNF] or IL-6).

Interleukin-2. Early in vitro studies showed that the ability to mount an Epstein-Barr virus (EBV)-specific cytopotoxic T-cell (CTL) declined with advancing HIV infection. The ability to elaborate IL-2 in vitro was lost in association with this progressive decline in the induction of EBV-specific CTL activity. The addition of IL-2 to peripheral blood mononuclear cells (PBMCs) from AIDS patients restored EBV-specific cytolytic activity in most patients, except those with far advanced disease. In these patients, the addition of IL-2 augmented natural killer (NK) cell activity, but not EBV-specific CTL activity. Early clinical investigations at Stanford showed that IL-2 administration was associated with enhanced CTL activity against a variety of HIV gene products. In the most extensive clinical experience to date, investigators at the National Institutes of Health (NIH) administered intermittent courses of high-dose IL-2 (12–18 million units/d for 5 days every 4 weeks) to patients with HIV disease who were on standard single-agent nucleoside analogue therapy. It was found that 60% of those with initial CD4+ counts greater than 200 cells/μL showed substantial increases in their CD4+ counts after the infusions; those patients with lower CD4+ counts frequently exhibited no increase. Assessment of the effect of infusion on plasma HIV RNA using a sensitive branched-chain DNA (bDNA) assay showed that a burst of replication frequently accompanied the infusions. In patients with higher CD4+ counts, plasma HIV RNA levels typically decreased to their original levels after the acute increase, whereas plasma HIV RNA levels could remain elevated compared with pretreatment levels in some patients with lower CD4+ cell counts. Study of V_{β} chain distributions before and after treatment with IL-2 has suggested that the CD4+ lymphocyte expansion is primarily limited to the existing repertoire at the time of treatment, with existing lineages being expanded rather than new lineages being added. Administration of IL-2 is associated with significant systemic side effects in the majority of patients, and with capillary leak syndrome in many. Issues in the clinical development of IL-2 that remain to be answered include the clinical significance of the rise in CD4+ cell counts induced by IL-2; the durability of these CD4+ cell count increases and the functioning of the cells produced under treatment; whether the viral burst accompanying treatment is deleterious in terms of augmenting viral diversity in the host; and whether this viral burst can be contained with more effective antiretroviral therapy.

Interleukin-12. Interleukin-12 induces production of IFN-γ in T- and NK cells and augments the cytotoxic activity of resting and cultured NK cells. Interleukin-12 is synergistic with IL-2 in stimulating CD8+ cell proliferation in animal models. Studies of samples in vitro from patients at various stages of HIV disease have shown the addition of IL-12 significantly enhances proliferative responses to recall antigens in samples from patients with CD4+ cell counts greater than 200/μL, but not in those patients with cell counts less than 200/μL. To date, clinical use of IL-12 has been associated with significant adverse reactions; however, some of the toxicities can be avoided by giving a priming dose.

Cytokine down-regulation. Early studies of the ability of different cytokines to modulate HIV replication included the observation that certain cytokines stimulated HIV replication in some cell lines. Those found to have an up-regulating effect in at least some cell lines include TNF, IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Tumor necrosis factor up-regulates replication in several cell types, thus becoming a target for expression as a means of controlling TNF-induced replication. Drugs known to inhibit TNF production include pentoxifylline and thalidomide. Clinical study of the former thus far has demonstrated dose-related gastrointestinal (GI) toxicity, which has prevented administration of high enough doses of the drug to significantly alter TNF expression in vivo or to decrease HIV replication. In an ongoing placebo-controlled study (ACTG 267),

A number of questions remain in the use of IL-2 in HIV disease: Does the viral burst observed with treatment augment viral diversity? How well do the CD4+ cells produced under treatment function?
patients with CD4+ cell counts of 200/μL to 500/μL are being given thalidomide at 50, 150, or 300 mg/d to assess tolerability to the drug and the drug’s effect on viral load.

**CD8+ HIV replication suppressor factor.** Attempts to identify and isolate the putative soluble factor(s) mediating the anti-HIV effect of CD8+ cells have been ongoing for several years. A number of molecules have recently been suggested as candidates. One (IL-16) has been shown to produce only modest suppressive effects on HIV replication. Another group of investigators has suggested that this in vitro activity is mediated by the three chemokines RANTES, MIP-1α, and MIP-1β. Although these molecules were reported to have a significant effect in curtailing HIV replication, the lack of information on the specific experimental procedures used in the publication of the findings makes the results difficult to interpret. High concentrations of these chemokines were required for in vitro activity.

**Cytokine caveats.** Although many of the findings involving cytokine modulation are intriguing, it is important to remember that cytokines are autocrine or paracrine molecules that normally operate in a complex and tightly regulated network. Thus, attempts to achieve isolated effects on one of the factors may be unsuccessful due to compensatory responses by other cytokines. In addition, there is the possibility of detrimental effects occurring distally in the network. The findings on how the cytokines mediate functions important in HIV disease often are based on highly artificial experimental systems that are incapable of capturing the complex effects of this modulation. It is also true that “bad” cytokines are not necessarily all bad; for example, it is known that blocking TNF effects in murine mycobacterial infection models results in increased mortality.

**Modulation of HIV-specific Effector Mechanisms.**

HIV-specific immune effector mechanisms are likely to play a key role in controlling virus replication in the early phases of HIV infection and may be a major determinant of the natural history of HIV disease. It remains unclear as to whether the cellular or humoral immune response to infection is the most critical or whether both are important in controlling virus replication. It is known that during clearance of initial viremia that there is emergence of CTL activity, which occurs before neutralizing antibodies appear; it is also known that long-term nonprogressors have greater CTL activity against HIV and may also have more potent antibody response. However, these phenomena may simply be characteristics of a good host immune response to infection rather than being directly involved in controlling viral replication. Once infection has been established, the viral population within an individual is constrained by a very potent immune response, but can overcome these constraints by generation of extraordinary genetic diversity. This tremendous genetic diversity is one of the major challenges to immunomodulatory approaches to treatment of HIV.

A number of approaches to enhance humoral and cellular HIV-specific immune responses are under investigation. With regard to humoral mechanisms, a number of monoclonal antibodies that neutralize primary HIV isolates have been produced and an AIDS Clinical Trials Group (ACTG) study of a few of these antibodies is scheduled to begin in the near future.

The ability of CTLs to detect and destroy cells expressing HIV antigens has been recognized for many years. As part of the host’s immune response to HIV, an individual develops CTL clones specific for a number of detectable HIV gene products. Figure 1 illustrates one study in which an HIV-infected person was shown to exhibit specific response to 10 different HIV epitopes derived from three different genes. However, a single amino acid change in one of the gene products can render cells bearing the epitope unrecognizable to a CTL clone that was previously effective in detecting and killing such cells. Attempts to use CTLs in therapeutic regimens will have to consider the ever-increasing heterogeneity of target viral strains.

Progressively sophisticated attempts to create and expand CTLs and reintroduce them into the patient have not yet yielded evidence that such a strategy is effective in reducing viral replication. The initial approach of polyclonal expansion and reinfection of CD8+ cells was not associated with detectable changes in viral load, but with the number of cells infused, no substantial increase in HIV-specific CTL activity would be expected. More recently, studies in which HIV-specific CTLs that have been expanded ex vivo have been initiated, but studies of changes in viral load in this setting have been inconclusive. Another approach that appears to hold significant promise involves genetically modifying the T-cell receptor complex. A technique for fusing the extracellular domain of the CD4 molecule with the zeta chain of the T-cell receptor complex has been developed. Cells thus modified bind the gp120 molecule on the surface of cells undergoing infection with HIV and lyse these cells, effectively functioning as a universal killer of HIV-envelope–expressing cells. In an ongoing study at the NIH, retroviral vectors are used to insert the CD4 molecule into harvested CTLs of an uninfected identical twin to convert them into universal killer cells; these cells are then infused into the HIV-infected twin in an attempt to better control HIV.

**Figure 1.** HIV-1 MHC-class I–restricted CTL epitopes recognized by unstimulated PBMCs from an HIV-infected individual. Adapted with permission from Johnson RP, Walker BD. Curr Top Microbiol Immunol. 1994;189:44.
Genetic Therapies

Genetic therapies for HIV infection are based on the premise that genetic alterations in T-lymphocytes or hematopoietic stem-cells may render them resistant to HIV infection and provide an opportunity to reconstitute normal host immunity with cells not depleted by ongoing viral replication. The methods currently being investigated consist of inserting intracellular genes or proteins that interfere with the viral replication cycle. One approach involves the intracellular expression of RNA sequences that bind either with viral messenger RNA (mRNA) or with viral genomic DNA (antisense approach), or that can cleave specific viral sequences (ribozymes). Another RNA-based approach, ie, the “decoy” approach, involves expressing a defective regulatory viral RNA sequence. Similar strategies have been employed using expression of defective viral proteins instead of RNA. In addition to these transdominant mutant approaches, there are strategies that attempt to exploit the fact that viral production or assembly can be hampered by intracellular antibody fragments directed at viral elements. In yet another approach, termed the “suicide-gene” approach, genes that express proteins that are toxic to mammalian cells, such as diphtheria toxin or ricin, are placed under the control of elements that are up-regulated when HIV replication is initiated. Each of these approaches has several significant practical barriers to successful clinical application. For example, one difficulty is devising vectors for genetic material that can enter all of the cell types capable of being infected by HIV; another barrier is that the genetic diversity of the population of virus within an individual may hinder the success of any single approach whose effectiveness depends on recognition of specific viral sequences.

Despite the potential obstacles to genetic therapies, these approaches continue to hold much scientific interest. As noted by Dr Schooley, apart from the potential direct therapeutic benefits, the study of genetic therapies will provide an opportunity to study the molecular pathogenesis of HIV infection and to work out the barriers to gene therapies for a wide variety of other diseases.

Robert T. Schooley is Professor of Medicine at the University of Colorado School of Medicine in Denver.

Suggested Readings


Announcing an Important Satellite Symposium to the XI International Conference on AIDS in Vancouver...

Guidelines for Antiretroviral Therapy: Bringing the State-of-the-Art to Clinical Practice

Sponsored by: The International AIDS Society-USA and The Canadian HIV Trials Network

Overview

The satellite symposium will comprise lectures and extensive audience discussion/question-and-answer sessions. The current standards for the use of antiretroviral therapies and regimens will be addressed based on the increasing understanding of the pathogenesis of HIV disease and clinical research in the field.

In January of this year, the IAS-USA convened an international panel to develop current guidelines for the use of antiretroviral therapy in HIV disease. This panel will reconvene at the XI International Conference on AIDS in Vancouver to discuss how the new research and information presented will further revise those Guidelines. Attendees will be encouraged to participate in the discussions in order to assist the panel in updating the Guidelines.

Who should attend

The symposium is targeted to physicians and other health care providers involved in HIV/AIDS medical care and attendance is open to all registrants of the XI International Conference on AIDS in Vancouver.

Issues to be discussed

The agenda will be designed around four basic questions in antiretroviral management: When to Start Therapy; What to Start With; When to Change Therapy; including clinical status and lab markers; issues of resistance; and definitions of treatment failure; and What to Change to, including prior treatment history, stage of disease, and time on therapy.

Guidelines Panelists/Symposium Faculty

Symposium Co-Chairs:

Julia Montaner, MD
St. Paul’s Hospital
Vancouver, BC

Stefano Vella, MD
Istituto Superiore di Sanità, Rome, Italy

Paul Volberding, MD
University of California
San Francisco, CA, USA

Speakers:

Charles Carpenter, MD
Brown University
Providence, RI, USA

Martin Hirsch, MD
Harvard Medical School
Boston, MA, USA

Douglas Richman, MD
University of California, San Diego, CA, USA

Margaret Fischl, MD
University of Miami
Miami, FL, USA

Melanie Thompson, MD
AIDS Research Consortium
of Atlanta, GA, USA

Michael Saag, MD
University of Alabama
at Birmingham, AL, USA

Scott Hammer, MD
Harvard Medical School
Boston, MA, USA

David Katzenstein, MD
Stanford University
Stanford, CA, USA

Robert Schooley, MD
University of Colorado HSC
Denver, CO, USA

Patrick Yeni, MD
X. Bichat Medical School
Paris, France

Schedule

Wednesday, July 10
6:30-7:30 pm Reception
Atrium Lobby and Terrace,
Pan Pacific Hotel
7:30-10:30 pm Academic Program
Ballroom A/B
Vancouver Trade and Convention Centre

Welcome and Introductions
P. Volberding
Overview of Guidelines, Guideline Development, Process, and Continuation of Process
C. Carpenter

Part I. Primary Infection Guidelines
Section Moderator: J. Montaner
Presentation: D. Richman
Discussion Leader: M. Saag

Part II. Post Exposure Prophylaxis
Section Moderator: J. Montaner
Presentation: M. Fischl
Discussion Leader: M. Hirsch

Part III. Maternal Fetal Transmission
Section Moderator: J. Montaner
Presentation: M. Thompson
Discussion Leader: R. Schooley

Part IV. Established Infection
Section Moderator: S. Vella
Presentation: P. Volberding
Discussion Leader: P. Yeni

Part V. Continuing Therapy
Section Moderator: S. Vella
Presentation: S. Hammer
Discussion Leader: P. Yeni

Summary Remarks
S. Vella/C. Carpenter

Registration

For more information about the satellite symposium AND FOR REGISTRATION INFORMATION, please contact the International AIDS Society - USA:

By Mail: International AIDS Society-USA
Attn: Vancouver Satellite
353 Kearny Street
San Francisco, CA 94108

By Fax: 415-675-7438
By e-mail: IASUSA1@aol.com
PREVENTION OF OPPORTUNISTIC INFECTIONS

CONSTANCE A. BENSON, MD

Dr Benson was invited by the IAS-USA to select the key clinical findings presented or published in the last year on the prevention of opportunistic infections and to provide a commentary on the current status of this treatment area. Dr Benson is Associate Professor of Medicine at Rush Medical College, Chicago, Illinois.

SELECT STUDIES

Mycobacterium avium Complex


This post-hoc analysis of both the original double-blind and open-label follow-up data from two placebo-controlled clinical trials of rifabutin prophylaxis for Mycobacterium avium complex (MAC) disease confirmed a trend identified in the original on-treatment analysis suggesting that the use of rifabutin improved survival for patients with AIDS at risk for MAC disease. Data from 1146 patients with HIV and baseline CD4+ cell counts at or below 200/μL were analyzed. Adjusting for Karnofsky score and the occurrence of opportunistic disease, and for use of rifabutin as a time-dependent variable, the relative hazard (RH) of dying while receiving prophylaxis was .74 for the entire cohort (P < .0004). For patients with CD4+ cell counts at or below 50/μL, the RH was .75, compared with .69 for those with CD4+ cell counts above 50/μL.


This was the final analysis of a randomized, placebo-controlled clinical trial of clarithromycin for prophylaxis of MAC disease, for which data were initially presented in late 1994. In the study, 642 patients were randomized to receive clarithromycin 500 mg bid or placebo. Development of MAC bacteremia in placebo recipients imparted a relative risk of death 2.6 times greater than the risk of death in patients with AIDS without MAC bacteremia. The use of clarithromycin reduced the risk of developing MAC by 69% (P < .001) and significantly prolonged the median duration of survival (>700 days compared with 573 days) compared with placebo.


This study demonstrated that a weekly dose of azithromycin (1200 mg) may be a more effective alternative to a daily dose of rifabutin (300 mg) as prophylaxis for MAC and that the combination of both drugs is more effective than either single agent. Patients (n = 669) with CD4+ cell counts at or below 100/μL were randomized to receive one of the agents or a combination of the two (same doses). In an intent-to-treat analysis, a significantly lower rate of MAC bacteremia developed in the azithromycin group (13.9%) than in the rifabutin group (23.5%). Fewer events occurred in the combination-treatment group (8.2%) than in the azithromycin (P = 0.06) or rifabutin (P < 0.001) groups. There was no difference in survival. No isolates recovered from those randomized to rifabutin alone or azithromycin plus rifabutin were resistant to azithromycin or clarithromycin; however, 11% of those recovered from those receiving azithromycin alone were resistant.

Tuberculosis


Preliminary results of this study were presented at the 10th International Conference on AIDS in Yokohama in August 1994. More complete data with additional follow-up were presented here. This is the first study to show that a 6-month (short) course of isoniazid was effective in preventing tuberculosis (TB) among HIV-infected individuals at high risk for TB. Seven hundred and eighty-four PPD-positive Haitian adults with HIV were randomized to receive isoniazid (INH) twice weekly for six months or rifampin and pyrazinamide (RIF/PZA) twice weekly for two months. Ten months after randomization, the Kaplan-Meier estimate of risk of TB was 0.8% and 3.5% for the INH group and the RIF/PZA group, respectively (P = .01). While longer-term follow-up and additional comparative data are awaited, these results provide some level of comfort that current recommendations for TB prophylaxis for the non–HIV-infected individual may apply to those with HIV infection as well.

Pneumocystis carinii Pneumonia


In this open-label study, 843 HIV-infected patients with CD4+ cell counts below 200/μL received zidovudine and either trimethoprim-sulfamethoxazole (TMP-SMX), dapsone, or aerosolized pentamidine. The three agents were shown to be equally effective as initial treatment strategies for the primary prevention of Pneumocystis carinii pneumonia (PCP); the estimated 36-month cumulative risk of PCP was 18%, 17%, and 21% in the TMP-SMX, dapsone, and aerosolized pentamidine groups, respectively (P = 0.22). This was the first prospective, randomized clinical trial to show that strategies beginning with TMP-SMX or high-dose dapsone were signifi-
cantly more effective than aerosolized pentamidine (estimated cumulative risks 19%, 22%, and 33%, respectively) for patients who initiated PCP prophylaxis at a time when their CD4+ cell counts were below 200/µL.


This retrospective study demonstrated that the 1991 guidelines used for initiation of PCP prophylaxis in perinatally HIV-exposed children, which are based on age-specific CD4+ cell count thresholds, failed to identify HIV-exposed infants at risk for PCP sufficiently early to reduce the incidence of disease. A review of 300 medical records of children with PCP revealed that 199 (66%) had never received prophylaxis. Of those, 60 (30%) were first evaluated for HIV at the time of PCP diagnosis and 58 (29%) were first evaluated within 30 days of diagnosis. Of the 28 children who were evaluated more than 30 days prior to diagnosis and for whom CD4+ cell counts were performed during this period, 20 (71%) had no counts below the recommended threshold for prophylaxis. These findings served, in part, as the impetus for revision and publication of new guidelines for offering chemoprophylaxis for PCP to infants perinatally exposed to HIV.

**Fungal Infections**


This study unequivocally demonstrated that chronic fluconazole prophylaxis was effective in reducing the incidence of cryptococcosis, esophageal candidiasis, and superficial mucocutaneous candidiasis in HIV-infected individuals with CD4+ cell counts below 200/µL. These findings were based on data (median follow-up of 35 months) from 428 patients receiving either fluconazole 200 mg/d or clotrimazole 10 mg five times/d. At entry, the median CD4+ cell count was 90/µL for the fluconazole group and 114/µL for the clotrimazole group. The study also demonstrated greater efficacy of this prophylaxis strategy in those with more advanced immunosuppression (CD4+ cell counts below 50/µL). However, in neither instance was the reduction in the incidence of these fungal complications accompanied by a survival benefit, calling into question the common practice of providing fungal prophylaxis for HIV-infected patients with advanced immunosuppression and no prior systemic fungal disease.

**Cytomegalovirus Disease**


This study was the first randomized, placebo-controlled study to demonstrate that daily administration of oral ganciclovir (GCV) reduced the incidence of cytomegalovirus (CMV) end-organ disease in HIV-infected patients with advanced immunosuppression who were CMV positive. Subjects were randomized 2:1 to receive oral GCV 1000 mg q 8h (n = 485) or placebo (n = 289). Median CD4+ cell counts for the two groups were 21/µL and 23/µL, respectively. Treatment was associated with a 50% reduction in the incidence of disease, and oral GCV was generally well-tolerated. This was also the first study to demonstrate that any chemoprophylaxis strategy was capable of reducing the incidence of this disease in patients with AIDS.


In contrast to the study reported by Spector et al, this study failed to demonstrate a statistically significant reduction in CMV end-organ disease in patients receiving oral ganciclovir. Subjects received oral GCV (n = 662) or placebo (n = 332); median CD4+ cell count for all patients was 44/µL.

Although the analyses are as yet incomplete, a number of study design differences have been cited as potential explanations for the disparate results, including the fact that baseline ophthalmologic screening exams to exclude asymptomatic CMV retinitis prior to entry were not performed in this study, no routine ophthalmologic or gastrointestinal (GI) evaluations were performed during follow-up unless the patient developed symptoms suggestive of CMV retinitis or GI tract disease. In addition, there was a change midway through the protocol (based on the results of the Syn- tex-sponsored study reported by Spector et al) allowing patients to crossover to receive oral ganciclovir. The magnitude of the impact of these study design differences on the study results remains to be determined.


Valacyclovir (VACV) is an oral prodrug of acyclovir that produces plasma levels of acyclovir comparable to those achieved by intravenous acyclovir dosing. This study was the first and only among several conceptually similar studies to show that prophylaxis with VACV reduced the incidence of CMV retinitis in HIV-infected individuals (n = 1227) with advanced immunosuppression (median CD4+ cell count 32/µL). Although the results cannot be statistically compared with those of the oral ganciclovir studies, the magnitude of reduction in the incidence of CMV retinitis was similar to that seen with oral ganciclovir in the placebo-controlled trial reported by Spector et al. There remains a need, however, to identify an appropriately tolerated dose of VACV for this purpose and to clarify the trend suggesting possibly higher mortality in the VACV arm.
COMMENTARY

A number of studies have come to fruition in the past year, the results of which have led to significant advances in our ability to effectively prevent or delay a number of opportunistic infections associated with HIV disease. The studies by Moore et al and Pierce et al showed that chemoprophylaxis with either clarithromycin or rifabutin for disseminated MAC disease results in improved survival for HIV-infected patients with advanced immunosuppression. Disseminated MAC disease and PCP are the only opportunistic infections for which chemoprophylaxis has been associated with a survival benefit. While there remain difficulties in maintaining long-term prophylaxis with rifabutin, clarithromycin, and azithromycin, each has been shown to be effective in reducing the incidence of MAC bacteremia and symptomatic MAC disease. The availability of three active agents offers patients and clinicians options for individualizing prophylaxis strategies. Results of studies directly comparing the macrolides with rifabutin and comparing single-agent prophylaxis with combinations of drugs for prevention of MAC disease are likely to be published in the coming year. While combinations may be more effective than single drugs, this comes at an increased cost both in dollars and potentially in toxicity or drug interactions. The outcome of these studies should be examined in detail in the context of what is known about single-agent prophylaxis. The task for the future will be to optimize prophylaxis based on these data and to target those individuals at highest risk with the most effective regimen(s). The latter will require further investigation of diagnostic technologies that will detect and/or predict those at highest risk.

Tuberculosis remains a significant individual and public health hazard for HIV-infected individuals in urban and other high-risk settings. The difficulties many individuals have maintaining adherence to isoniazid prophylaxis over prolonged periods and the uncertainties surrounding appropriate chemoprophylaxis for those exposed to multidrug-resistant strains of Mycobacterium tuberculosis highlight the need for more effective prophylaxis. It would appear from the Halsey et al article that a 6-month course of twice weekly isoniazid, one of the recommended regimens for non-HIV-infected persons exposed to or latently infected with drug-susceptible strains of M tuberculosis, may be effective for HIV-infected persons as well. However, shorter-course prophylaxis with multiple drugs may provide a more cost-effective method for reaching the same goal and may expand the spectrum of activity to cover some drug-resistant strains. Additional clinical trials further exploring several such regimens are in progress.

Although numerous studies have demonstrated that chemoprophylaxis is effective in significantly reducing the risk of developing PCP, this remains one of the most common HIV-associated opportunistic infections. Trimethoprim-sulfamethoxazole has emerged as the most effective agent, but a substantial portion of HIV-infected individuals remain intolerant to long-term prophylaxis with this drug. Single-agent chemoprophylaxis may fail in a substantial proportion of patients with very advanced immunosuppression. Continued progress in reducing the incidence and risk of this opportunistic complication requires innovative work in developing effective alternatives for those intolerant of or failing currently available regimens, particularly in the setting of profound immunosuppression. No drug can be effective if it is not prescribed by the clinician or used by the patient, and the exploration of factors related to poor adherence, of novel strategies to encourage adherence to therapy, and of strategic education of practitioners and patients alike is necessary.

Systemic and mucosal fungal infections can be effectively prevented with the chronic use of fluconazole. However, this remains an expensive drug, and in the multicenter study evaluating its daily use in a dose of 200 mg, Powderly et al found it was not associated with a survival benefit. A number of case reports and observational studies have suggested that long-term use of fluconazole may lead to development of azole-resistant candidiasis, which, although not usually life-threatening, can be costly and debilitating. Further investigations of more cost-effective chemoprophylaxis regimens that focus on those at highest risk for systemic or invasive fungal disease and of the factors associated with development of azole-resistant candidiasis in those receiving fungal prophylaxis are in progress, as are studies to identify more effective therapies for azole-resistant disease.

Although oral ganciclovir has been approved by the FDA for use in preventing CMV retinitis in HIV-infected patients with advanced immunosuppression, its widespread use for this purpose remains controversial. From one randomized, placebo-controlled trial, Specter et al showed a 50% reduction in the incidence of CMV retinitis. A second similar clinical trial reported by Brosgart et al did not demonstrate a difference between oral ganciclovir and placebo.

There were a number of differences between the designs of the two studies that may account for the disparate results. Neither study, however, demonstrated a survival benefit, and there was an insufficient number of end points other than CMV retinitis to draw conclusions regarding the effectiveness of oral ganciclovir for prevention of other CMV end-organ disease. The cost and the number of pills required may pose obstacles to a number of individuals at high risk for CMV disease. Of several studies evaluating high dose oral acyclovir for CMV prophylaxis, only the phase III trial of the produg valacyclovir reported by Feinberg has demonstrated a benefit of the agent. Additional studies evaluating quantitative measures of CMV viral load as predictors of development of CMV disease may ultimately point to a manner in which prophylaxis can be earmarked for a patient population likely to derive the most benefit.

The past year has seen significant progress in our ability to delay or prevent opportunistic complications of HIV disease. However, a number of disturbing issues remain. Multiple opportunistic pathogen prophylaxis requires the use of multiple drugs, many of which are associated with significant drug interactions, not only with each other, but also with newly developed classes of antiretroviral agents. The emergence of resistant strains of MAC, M tuberculosis, fungi, and CMV in HIV-infected individuals receiving prophylaxis has posed a challenge to designing effective therapy regimens. These two issues alone underscore the need for continued exploration of the pharmacokinetic and pharmacodynamic interactions between antiretroviral drugs and those used for opportunistic infections and the need for further development of new drugs for opportunistic complications.
TREATMENT OF OPPORTUNISTIC INFECTIONS

WILLIAM G. POWDERLY, MD

Dr. Powderly was invited by the IAS-USA to select the key clinical findings presented or published in the last year on the treatment of opportunistic infections and to provide a commentary on the current status of this treatment area. Dr. Powderly is Associate Professor of Medicine at the Washington University School of Medicine in St. Louis, Missouri.

SELECT STUDIES


These two articles support the use of oral ganciclovir as maintenance therapy after intravenous (IV) ganciclovir induction in select patients with non-sight-threatening cytomegalovirus (CMV) retinitis. In the European/Australian study, 159 patients with AIDS and stable CMV retinitis following an induction course with IV ganciclovir were randomized to receive maintenance therapy with oral ganciclovir (500 mg six times/d) or IV ganciclovir (5 mg/kg once daily infused over 1h). By masked assessment of fundus photographs, investigators found a mean time to progression of 51 days with oral ganciclovir and 62 days with IV ganciclovir (P = .13). As determined by fundoscopy, mean time to progression was 86 days and 109 days, respectively (P = .02).

Similarly, Drew et al found that mean times to progression among 115 patients on the basis of masked assessment of retinal photographs were 62 days in the IV group and 57 days in the oral group (P = .63), compared with 96 days and 68 days, respectively (P = .03), on the basis of fundoscopy by ophthalmologists who knew treatment assignments. In both studies there was no significant difference between the two groups in terms of adverse events. Neutropenia, anemia, sepsis, and other catheter-related adverse events were more common in the IV group, and diarrhea was more common in the oral groups. In addition, Drew et al found no significant difference between groups in the incidence of viral shedding or survival.


Intraocular ganciclovir is an extremely effective way of achieving local control of retinitis; however, it needs to be used in conjunction with systemic therapy because of the high risk of subsequent disease in the other eye or elsewhere. In this study, patients with newly diagnosed CMV retinitis received ganciclovir either IV or as an implant of 1 μg/h or 2 μg/h. Overall, median times to progression were 216 days in the combined implant groups and 104 days in the IV group (P < .0001). No significant differences in survival or fellow-eye involvement were observed. However, 15.3% of the implant group developed extraocular CMV disease and complications in the group included retinal detachment in 5.2% and endophthalmitis in 1.2%.


Results from this preliminary analysis demonstrate that cidofovir is clearly effective; however, nephrotoxicity may limit its usefulness. Patients with CMV-R progression despite systemic ganciclovir and/or foscarnet, and/or intolerance to either agent were randomized to receive an induction course of CDV 5mg/kg once weekly for 2 weeks (induction) and then 5 mg/kg once every other week (Group A), or 3 mg/kg once every other week (Group B). IV normal saline and oral probenecid were given to minimize potential nephrotoxicity. This interim intent-to-treat analysis of the first 60 patients found a median time to CMV-R of 115 days (Group A) compared with 49 days (Group B) (log-rank test P = .12). Seven percent of patients in both groups developed a serum creatinine greater than or equal to 2 mg/dL. Mild-to-moderate probenecid reactions occurred in 48% of patients.


In this open-label trial, 229 HIV-infected adults with MAC bacteremia were randomized to receive four drugs (ciprofloxacin 750 mg bid, ethambutol 15 mg/kg qd, rifampin 600 mg qd, and clofazimine 100 mg qd) or three drugs (clarithromycin 1000 mg bid, rifabutin 600 mg qd, and ethambutol 15 mg/kg qd). The rifabutin dose was halved to 300 mg qd following the development of uveitis in a sizable number of patients. In analysis done on 187 patients, MAC bacteremia was cleared in 67/97 (89%) of patients in the three-drug arm compared with 26/90 (29%) of patients on the four-drug arm (log-rank test, P < .001). Clearance was higher for the three-drug arm at both doses of rifabutin. Median survival times were 8.7 and 5.2 months for patients in the three- and four-drug arms, respectively (log-rank test, P < .001). Clarithromycin-based therapeutic regimens are more effective in clearing Mycobacterium avium complex (MAC) bacteremia and pro-
long survival. These results should end debate about whether MAC is a disease that should be treated.


Dube MP, Sattler F, Torrani F, et al. A randomized study of clarithromycin plus clofazimine, with or without ethambutol, for treatment and prevention of relapse of disseminated MAC in AIDS. Presented at Third Conference on Retroviruses and Opportunistic Infections; January 28–February 1, 1996; Washington, DC.

These two studies suggest that giving clofazimine alone as adjunctive therapy to clarithromycin may not delay the emergence of clarithromycin resistance. In the French open-label trial, HIV-infected adults with MAC bacteremia and no prior treatment with clarithromycin were randomized to Group A (clarithromycin 2000 mg bid 2 months then 1000 mg bid and clofazimine 200 mg qd 2 months then 100 mg qd) or Group B (clarithromycin same dose), rifabutin 450 mg qd and ethambutol 1000 mg qd). One-hundred and twenty-three patients were evaluated during interim analysis. Mean CD4+ cell count was 14/μL; median Karnofsky index was 70. Success was defined as the patient being alive, with a decrease of fever and negative blood culture. At 2 months and 6 months, there was no difference between groups on these criteria or in survival distribution. Fourteen patients in Group A and two patients in Group B acquired resistance to clarithromycin (P < .01).

In the study reported by Dube and colleagues for the California Collaborative Treatment Group, patients with AIDS and disseminated MAC were randomized to receive clarithromycin 2 g/d and clofazimine 100 mg/d, with or without ethambutol 80 mg/d. Sixty-nine percent of patients in both the 2-drug and 3-drug arms responded to therapy. Based on a blinded, post-hoc analysis, defining relapse as any positive culture following response, investigators determined risk estimates for relapse at 36 weeks to be 91% for the 2-drug arm and 50% for the 3-drug arm (P = .014). Twenty-one of 27 relapse isolates were clarithromycin-resistant; median time to development of resistance was 16 weeks with two drugs and 40 weeks with three drugs (P = .004).


The optimal therapy for acute cryptococcal meningitis seems to be an initial period of amphotericin B plus flucytosine (FC) followed by fluconazole (FLU). In this two-part study, 408 patients with a first episode of cryptococcal meningitis and <1 mg/kg prior AMB were randomized to receive AMB .7 mg/kg/d for 14 days or AMB (same dose) plus FC 100 mg/kg/d for 14 days. The median CD4+ cell count was 18/μL. Analyses at 14 days determined that survival was similar in both groups; CSF sterilization was increased in the combination group (P = .06); and there was no difference between groups in terms of toxicity.

The objective of Step 2 was to demonstrate that the efficacy of ITRA was close to that of FLU. Patients who had received a minimum total dose of AMB 7.5 mg/kg in Part 1, had improved or stable mental status, were able to take oral drugs, and were not receiving antiseizure medication or rifampicins, were randomized to receive FLU 400 mg qd, or itraconazole (ITRA) 200 mg bid for 8 weeks. Investigators determined that the CSF sterilization was 72% and 60% for the FLU and ITRA groups, respectively, and that clinical response was 68% and 70% respectively. The overall mortality for the trial was 6%.


Fluconazole is clearly the maintenance therapy of choice for cryptococcal disease. In this phase III double-blind comparison, patients who had been successfully treated for cryptococcal meningitis within the last 4 months (negative CSF fungal culture and no clinical symptoms) were randomized to receive FLU 200 mg/d or ITRA 200 mg/d. Among 107 patients observed for 52 weeks, 2/52 (3.8%) assigned to FLU and 13/55 (23.6%) patients assigned to ITRA had documented CSF culture-positive relapses (P = .003). None of the 19 deaths during the study was due to cryptococcal disease; both drugs were well tolerated.
**COMMENTARY**

**Cytomegalovirus Infections**

Although there were no dramatic breakthroughs in terms of new agents for the treatment of CMV infections, two developments in the delivery of ganciclovir have potential for a major therapeutic impact. Data from two large randomized comparative trials—reported by the Oral Ganciclovir European and Australian Cooperative Study Group and by Drew et al—seemed to confirm that the oral formulation of ganciclovir in a dose of 3000 mg qd is as effective as IV ganciclovir in delaying progression of CMV retinitis after initial induction therapy with the IV drug. There remains some doubt, however, regarding exactly what the trials show, since the results are open to several interpretations. In both trials, when the two treatment strategies were compared using retinal photographs, the mean time to progression of retinitis was similar. However, the oral drug appeared less successful in delaying progression when the assessment of progression was based on direct examination by ophthalmologists. The latter finding may reflect bias, since the ophthalmologists in both trials knew which treatment the patient was receiving, or it may reflect true subtle progression picked up by experienced clinicians. Oral ganciclovir is poorly absorbed, having a bioavailability of less than 10%, so it is not unreasonable to expect it to be somewhat less effective. The observation of reduced efficacy is supported by the fact that for patients entering the studies with unilateral retinitis, retinitis was more likely to develop in the uninvolved eye in patients receiving oral ganciclovir. However, patients on oral drug do not need long-term in-dwelling catheters and have a better quality of life. Consequently, although probably not best suited for patients with sight-threatening retinitis, oral ganciclovir is a useful alternative for select patients.

In contrast, ganciclovir intraocular implants represent a clearly more effective way of delaying the progression of retinitis. The Chiron Ganciclovir Implant Study Group and others reported that the implants were associated with a median time to progression that is superior to that associated with IV ganciclovir. However, it is clearly local therapy, because almost half of all patients treated just with implants developed either retinitis in the other eye or systemic CMV infection. In addition, early surgical complications, such as endophthalmitis and retinal detachment, occurred in 10% to 20% of patients. Although the role of such local therapy needs to be further defined, a combination of local and systemic therapy may lead to more effective control of disease and warrants further study.

This past year Lalezari et al and others reported early promising data on the use of cidofovir given both IV and intraocularly in CMV retinitis. Although parenteral use of the agent may be limited by nephrotoxicity, the results of ongoing trials should allow for a better assessment of the role of this agent.

**Disseminated Mycobacterium avium Complex Infection**

It has become increasingly apparent that MAC infection is associated with reduced survival and that therapy for MAC improves survival. The availability of the macrolides in MAC treatment has also been shown to correlate with an improved outcome for patients with MAC. The AIDS Clinical Trials Group (ACTG) study of clarithromycin monotherapy published in late 1994 demonstrated both considerable efficacy and some limitations of this drug. All three dosage regimens studied (1 g, 2 g, or 4 g per day) effectivly cleared bacteremia and decreased symptoms. A dose-response relationship was observed. The highest dose produced the most rapid response, but also was associated with the greatest amount of gastrointestinal toxicity. Relapses, associated with microbiologic resistance, were common and an unexpectedly higher (and unexplained) risk of death was noted in patients receiving higher doses.

Clarithromycin-based regimens have become the standard of care. Initial results of several trials suggest that this is appropriate. In the Canadian study reported by Shafrazi et al, comparison of a three-drug macrolide-based regimen (clarithromycin, ethambutol, and rifabutin) with a four-drug regimen (clofazimine, ciprofloxacin, ethambutol, and rifampin) previously evaluated by the Canadian Clinical Trials Group (CCTG) demonstrated not only a significantly better rate of clearance of MAC bacteremia (69% vs 30%) but also a significantly longer survival (8.7 months vs 5.2 months) in patients receiving the three-drug clarithromycin-containing regimen.

The issue of which drugs are best used with clarithromycin is still being evaluated, but initial data from two trials suggest that clofazimine is not optimal. The French study reported by May et al, which compared clarithromycin plus clofazimine with clarithromycin plus ethambutol and rifabutin, indicated that clarithromycin resistance was more likely in patients who received clofazimine. In the trial of clarithromycin and clofazimine with or without ethambutol reported by Dube et al, the rate of development of resistance was also higher in patients who received just clofazimine and clarithromycin. This year should bring the results of several additional large trials that may clarify the best available therapy for disseminated MAC.

**Cryptococcal Meningitis**

In fungal disease management, the most significant event was the presentation of the results of two large trials by the National Institute for Allergy and Infectious Diseases (NIAID) ACTG and the Mycoses Study Group that evaluated the initial and maintenance treatment of cryptococcal meningitis. Previous studies had suggested that patients treated with amphotericin B tended to have more rapid cerebrospinal fluid (CSF) clearance than patients treated with azoles. Since the major limitations of amphotericin B are toxicity and the need for parenteral administration, these observations led the Mycoses Study Group and ACTG investigators to perform a trial of initial amphotericin B therapy (with or without concomitant flucytosine) followed by a "consolidation" period of triazole therapy with high doses of either fluconazole or itraconazole. The results of this trial suggest that this approach is very successful, at least compared with previous experience, in the majority of patients. The acute mortality (first 2 weeks) in this trial was 6% and the overall mortality 8%. There was a trend that approached significance for a better microbiologic outcome (clearance of organisms from CSF) at 2 weeks for patients assigned to receive flucytosine and at 10 weeks for patients assigned to fluconazole. The high-dose amphotericin B regimen was well tolerated, and flucytosine appeared to add little additional toxicity. Further support for this approach to disease management comes from data from an Italian center where all patients were treated for 14 days with high-dose (1 mg/kg/d) amphotericin B, followed by maintenance fluconazole or itraconazole. Of 31 patients treated in this fashion, 29 (94%) responded to therapy and there were no deaths due to cryptococcosis. When the Mycoses Study
Group compared fluconazole and iracona-
zole as maintenance therapy, results clearly
demonstrated that fluconazole was supe-
rior. It is of interest that a multivariate
analysis of predictors of relapse showed
that receiving fluconazole as part of the ini-
tial induction therapy was associated with a
lower risk of recurrence. One interpretation
of these results might be that the better ini-
tial microbiologic control of infection seen
with amphotericin B and fluconazole in
combination might be reflective of better
overall response and possibly even cure.

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KAPOSI’S SARCOMA

DAVID J. LOONEY, MD

Dr. Looney was invited by the IAS-USA to select the key clinical and scientific findings presented or published in the last year on Kaposi’s sarcoma and to provide a commentary on the current status of this treatment area. Dr. Looney is Assistant Professor of Medicine at the University of California San Diego and the Department of Veterans Affairs Medical Center, San Diego, California.

SELECT STUDIES


This paper expands upon the elegant Science paper published in late 1994 that described the use of representational difference analysis to detect gammaherpesvirus sequences in Kaposi’s sarcoma (KS) lesions. Using a polymerase chain reaction (PCR) technique, investigators analyzed DNA in tissue samples from patients with AIDS-KS, those with classic KS, and HIV-1-seronegative homosexual males with KS. The analysis demonstrated a very close association between the detection of human herpesvirus type 8 (HHV-8) and the histologic presence of KS, and confirmed the paucity of HHV-8 sequences in (unmatched) control specimens.


This article presents a further characterization of the molecular structure of HHV-8 and analysis of serological reactivity. The introduction of a serological (indirect immunofluorescence) assay for detection and quantitation of antibodies to HHV-8 should pave the way to more meaningful epidemiologic studies. Interesting homologies noted in 18 sequenced open reading frames of this agent with cellular and other viral genes suggest intriguing directions for further research. Finally, data presented on induction of viral replication in cell lines with phorbol esters (TPA) may have served to guide other researchers attempting to culture this virus in vitro (see below).


These investigators conclusively demonstrate that the gammaherpesvirus-like sequences found in Kaposi’s sarcoma belong to a replicating virus, and provide the first electron micrographs of the virus. The availability of systems for studying HHV-8 replication will allow the characterization of activity of a number of anti-herpesvirus agents against HHV-8, potentially providing important information for the development of trials of antivirals in treatment of Kaposi’s sarcoma.


This paper, together with a paper describing the isolation and characterization of this tumorigenic KS cell line published by the same authors a few months later, represent a second new alternative hypothesis of the origin of KS. The authors describe an aneuploid cell line (KS Y-1) derived from KS that is capable of tumorigenesis and metastasis in a murine model; they use this model to demonstrate the inhibitory activity of the beta subunit of human chorionic gonadotropin, which has led to ongoing clinical trials (and a number of letters to journal editors describing anecdotal responses to human chorionic gonadotropin in humans).


Investigators describe chromosomal lesions typical of two aneuploid tumor cell lines derived from KS. The identification of specific deletions and translocations in cell lines allows examination of tissue from lesions using PCR and other more sensitive modalities to be performed. Determination of the prevalence of cells containing such genetic lesions in different stages of the disease may lead to a better definition of the role of such cells in KS oncogenesis.


Appearing the same month as an article by this National Cancer Institute group in the Journal of Immunology, this paper extends upon previously published work that supports yet other distinct mechanisms possibly responsible for the proliferation of spindle cells and development of KS lesions, including the proliferative effects of HIV-1 Tat protein and basic fibroblast growth factor. These data are consistent with the theory that both immunosuppression and immunostimulation are required for the development of KS, illustrating that the phenotype and biologic behavior of activated endothelial cells and cell lines derived from KS lesions are virtually indistinguishable. In this respect, the data may be too convincing, suggesting to the reader that “Kaposi’s” cells studied in vitro represent only activated endothelial cells, while leaving unexplained their distribution and genesis.


Providing yet another piece of the KS puzzle is this first and long-awaited report of the clonality of KS lesions. Using PCR to amplify a fragment of the human androgen receptor gene (X chromosome) containing a methylation restriction
site on tissues from KS lesions from female patients, the investigators detected monoclonal cell populations in two lesions and clonal proliferations in a third. It may be difficult to reconcile such evidence of clonality (reflecting the bulk of cells in the lesion examined) with the existence of only a small population of "true" malignant cells in lesions.


Although this article may be properly viewed as just one of more than 20 articles on the use of liposome-entrapped doxorubicin and daunorubicin appearing over the past 3 years, it is noteworthy for representing Doxil™, recently approved by the FDA, as an emerging standard for the treatment of AIDS-related KS. In addition, this article illustrates the general emphasis on identifying reasonably effective, well-tolerated treatments. In this phase II study, thirty-four patients with AIDS-related KS (median Karnofsky score 70) were treated with 20 mg/m² of liposome-entrapped doxorubicin every three weeks. The overall response rate was 73.5% (25/34 patients); in patients who had received prior chemotherapy, the response rate was 68.4% (13/19 patients). In terms of side effects, neutropenia, alopecia, nausea, and vomiting occurred in 34%, 9%, and 18% of patients, respectively.


Etoposide has been used successfully for treatment of KS. In this dose-ranging study (150 to 400 mg/week), oral etoposide resulted in a partial response rate of 36% (9/25). The agent was well tolerated at lower doses, suggesting another useful, minimally toxic, therapeutic alternative in patients with AIDS and KS.


This paper is the first of several that can be expected on the use of taxol in KS. Use of paclitaxel as a single agent (135 mg/m² IV over 3 hours every 21 days) produced a partial response rate of 65% (13/20 patients), a result comparable to the best overall response rates obtained with liposomal anthracyclines. In addition, paclitaxel was associated with acceptable toxicity (most frequently neutropenia, and some unexpected rash and eosinophilia).

**COMMENTARY**

Kaposi’s sarcoma (KS) is a multicentric, highly vascular, proliferative disorder involving endothelial cells, fibroblasts, and characteristic spindle-shaped mesenchymal cells. HIV-1 infection represents an overwhelming risk factor (20,000:1) for the development of KS, which was a rare tumor in the United States (incidence less than 1/100,000/year) before the HIV-1 epidemic. Today, KS remains the most frequent neoplasm affecting HIV-infected individuals in many parts of the world. Approximately 25% to 30% of homosexual males with HIV infection develop clinically significant KS, and autopsy studies indicate even an higher prevalence of the disease (up to approximately 40%). Aggressive disease, with involvement of the gut, lung, pleura, and lymph nodes, is seen frequently in AIDS-related KS, as is a predilection for lesions of the hard and soft palates.

The etiology of KS, the reasons for the increased incidence of KS in AIDS patients, and the explanation for the marked predilection of KS for the male sex (greater than 15:1 male:female overall, approximately 4:1 male:female in AIDS patients when homosexual males are excluded) have been topics of considerable controversy over the last 2 years. Although KS is associated with immunosuppression due to other conditions, such as renal transplant, chronic lymphocytic leukemia, mycosis fungoides, multiple myeloma, and thymoma, this does not entirely explain the excess of KS seen in HIV disease. Similarly, a rational explanation for the marked predilection of KS for the male sex is still lacking, although a role for the direct or indirect effect of gonadotropine hormones is an intriguing hypothesis (see below).

Epidemiologic evidence has suggested that a transmissible infectious agent might be involved in KS, but only recently have molecular techniques permitted Moore and Chang, and others, to identify a novel gammaherpesvirus ("Kaposi's sarcoma herpesvirus" [KSHV], now referred to as human herpesvirus type 8 [HHV-8]) as a likely candidate. The association of HHV-8 with KS, now well established by a number of papers, does not suffice to establish a causal role for this virus. Note that Moore and Chang, and Chang and colleagues detected HHV-8 sequences in 21% of "matched" control samples (uninvolved skin from KS patients), raising doubts concerning the specificity of the association between virus and lesions in patients known to be positive for the virus. Others have noted that HHV-8 sequences are present in non-KS lesions. Other preliminary results suggest a close relationship of HHV-8 with Epstein-Barr virus (EBV), with EBV frequently being detected in KS tissue but not other tissues from individuals with KS. Other possible explanations for the close association of HHV-8 with KS include a tropism for virus replication in activated endothelial cells or other cell types in KS tumors, or localization in KS lesions due to attachment ("filtration") of circulating B-cells harboring latent virus to activated endothelial cell adhesion molecules. The development of methods to allow culture, replication, and passage of HHV-8 virus by Ganem’s group (Renne R, et al), and similar work being presented by G. Nabel, J.A. Levy and others, together with serological methods for epidemiology should allow rapid determination of prevalence of HHV-8 infection, and shed additional light on causality, and the usefulness of antiviral treatment (see below).

A number of letters have followed a 1994 article describing anecdotal responses of KS to treatment with antiviral agents, such as foscamet sodium. Even if a transforming role for HHV-8 is established in KS, it is not clear that inhibition of virus replication would affect tumor growth. It is also possible that foscamet, having activity against HIV, may have produced a response through action on underlying HIV disease. This appears not unlikely in view of the known activity of zidovudine in

It becomes more difficult to visualize a role for treatment of herpesvirus in KS when considering the recent isolation of aneuploid transformed cells from KS lesions by Lunardi-Iskander and colleagues. Although spindle-shaped diploid cells (KS-cells) morphologically similar to those seen in KS lesions have been cultured\textsuperscript{21–23} from lesions, effusions, and peripheral blood in vitro, these cells have not been found to harbor identifiable chromosomal abnormalities and are neither immortalized nor transformed. Rather, Fiorelli and colleagues and others\textsuperscript{3,5,24,25} found that the cells require growth factors supplied by activated lymphoid cells, and they may be virtually indistinguishable from activated microvascular endothelial cells.

The use of these new tumorigenic KS cell lines in murine models has led to identification of new candidate therapeutic agents. A number of letters have appeared concerning anecdotal treatment with human chorionic gonadotropin,\textsuperscript{26} and trials are in progress. In any case, the use of models with tumorigenic KS cell lines is leading to testable hypotheses, wherein activity or lack of activity in murine models can be compared with findings in human trials.

Although it offers a potential explanation for the paucity of KS in female patients, the predominance of normal diploid cells in KS lesions presents a significant problem to proponents of genetically abnormal, malignant, transformed cell type as a principal cause of KS. The recent data cited by Rabkin and colleagues suggesting clonality of cells within KS lesions makes this all the more difficult to explain, since the techniques used are qualitative, rather than quantitative, indicating a clonal expansion of the bulk of the cells comprising the lesion tissue. The mechanism whereby the “true” tumor cell would induce clonal proliferation in normal surrounding cells is not clear, and if the aneuploid cells themselves are not responsible for the clinical manifestations of the disease, they may not represent the only or the ideal target for treatment.

Fiorelli and colleagues, and others,\textsuperscript{4,5,23–25} have shown a variety of cytokines to be active in the maintenance proliferation of normal diploid KS cells in vitro. It is not surprising that cytokine inhibitors\textsuperscript{27} and other inhibitors of angiogenesis—including thalidomide, metalloproteinase inhibitors, thrombospordin analogues, apolipoprotein E, integrin antagonists, fumagillin (TNP-470), heparin-serotonin conjugates, CM101, SP-PG, and pentosan sulfate\textsuperscript{28–36}—are being pursued as potential therapeutic agents for KS. To date, however, the results from the use of such polycationic angiogenesis inhibitors as pentosan sulfate and suramin have not been promising.\textsuperscript{37} Similarly, results\textsuperscript{38} from initial trials with differentiating agents such as all-trans retinoic acid have fallen short of expectations; however, accumulating evidence from multicenter trials and a number of abstracts submitted to upcoming meetings indicate that topical treatment with retinoids is moderately effective, and the availability of a plethora of retinoid analogues suggests that additional exploration may be indicated.

Conventional treatments for KS are generally considered to be palliative, including localized radiation therapy, immunotherapy and antiviral therapy with zidovudine and alpha interferon, intralésional therapy with a variety of agents, and the use of a number of different conventional cytotoxic chemotherapy agents alone or in combination (including vinblastine, topoisomerase II inhibitors, and anthracyclines). Over the past few years, intense combination chemotherapy has been largely abandoned, with an emphasis being placed on finding therapeutic compromises between efficacy and toxicity in treating KS.

As noted in the paper by Harrison and colleagues, and by others,\textsuperscript{5,6} the use of liposomal preparations of anthracycline drugs as single agents has represented one such emerging compromise. These agents can be administered with relative safety and create little degradation in quality of life for the patient. The availability of granulocyte colony-stimulating factor, to prevent or reduce the principal complication of neutropenia, has also made administration of marrow-suppressive agents to already immunocompromised individuals a less frightening proposition. In addition, the use of oral etoposide and the introduction of taxol represent other attractive treatment alternatives that are likely to see increasing use over the next few years.

In summary, previous efforts to explain the origin of KS have centered on the study of the interaction of host immunity, host immune stimulation, and viral factors, such as the HIV-1 Tat protein. A complex web of growth factors and cytokines has been found to play a role in proliferation of cell lines derived from KS cells in vitro. Two alternative, but not necessarily mutually exclusive, schemas for KS oncogenesis—direct or indirect viral oncogenesis and involvement of “true” malignant cells—were identified in 1995. Novel treatment strategies suggested by all three hypotheses are being explored, including angiogenesis inhibition, antiviral treatment, and hormonal manipulation. In addition, conventional treatment regimens have continued to evolve, with an emphasis on identifying reasonably effective, minimally toxic therapies. The identification of an increasing number of molecules involved in angiogenesis (and inhibitors of these angiogenic moieties), the ability to cure the associated herpesvirus and identify active viral compounds, together with availability of new cell lines and new animal models for testing, indicate promising prospects for the year to come.

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