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Consensus Statement

Summary of the II International Consensus Symposium on Combined Antiviral Therapy and implications for future therapies

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1. Introduction

Current antiviral treatment has limited efficacy for several viral infections, including those caused by hepatitis viruses, respiratory viruses, human immunodeficiency virus (HIV) and herpesviruses, necessitating the identification of improved therapeutic options. While the quest for novel potent antiviral agents continues, the strategy of combined antiviral therapy with available antiviral drugs is potentially beneficial, and has, in fact, proven its usefulness for a number of viral diseases. Enhanced antiviral efficacy of combined treatment is mediated by synergistic or additive activity of the combination, antiviral activities in a broad range of viral reservoirs, broad coverage of established resistant viral populations and prevention of antiviral resistance. In addition, combined treatment with two synergistically active drugs may enable dose reduction of the toxic components of the combination.

In 1995, a consensus symposium on combined antiviral therapy was organized and convened by The Macrae Group (New York City, NY, USA) to review the progress in the field of combined therapy for a variety of viral diseases, and to make recommendations for the future use of po-

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tentially effective combinations with available antiviral drugs (De Jong et al., 1996). In view of the rapidly evolving field of antiviral therapy, a second edition of this successful meeting was organized by The Macrae Group in Barcelona, Spain on September 8–10, 1996. Again, leading researchers in the laboratory and clinical fields reviewed the successes and limitations of current antiviral monotherapy and the status of combined therapy. This article provides a review of the information presented at this symposium, and where appropriate, the consensus reached in certain areas based on this information.

Members of the consensus panel were C.A.B. Boucher (co-chair), Utrecht University, Netherlands; D.A. Cooper (co-chair), University of New South Wales, Australia; G.J. Galasso, National Foundation for Biomedical Research, USA; B. Gazzard, Chelsea and Westminster Hospital, UK; J.M.A. Lange (co-chair), University of Amsterdam, Netherlands; J. Montaner, St. Paul's hospital, Canada; D.D. Richman (co-chair), University of California San Diego, USA; and H. Thomas, St. Mary's Hospital, UK. The presenters at the symposium were J. Gatell, Hospital Clinic i Provincial, Spain; M.D. de Jong, University of Amsterdam, Netherlands; P. Lietman, Johns Hopkins University, USA; H. zur Hausen, Institut für Krebsforschungszentrum, Germany; J. Englund, Baylor College, USA; J. Huggins, US Army Medical Research Institute, USA; C. Boshoff, Chester Beatty Labs, UK; S. Sacks, Viridae Clinical Sciences, Canada; S. Spector, University of California San Diego, USA; S. Schalm, Rotterdam University Hospital, Netherlands; S. Locarnini, Fairfield Hospital, Australia; H. Thomas, St. Mary's Hospital, UK; D.D. Richman, University of California San Diego, USA; D. Katzenstein, Stanford University, USA; D.A. Cooper, University of New South Wales, Australia; C.A.B. Boucher, Utrecht University, Netherlands; J. Gathe Jr., Houston Clinical Research Network, USA; D. Kuritzkes, University of Colorado, USA; J. Montaner, St. Paul's Hospital, Canada; J. Vila, Compagnie de Developpement Aguettant, France; M. Markowitz, Aaron Diamond AIDS Research Center, USA; S. Vella, Istituto Superiore di Sanita, Italy; E. Sun, Abbott Laboratories, USA; H.C. Lane, National Institutes of Health, USA; J. van Hattum, University Hospital Utrecht, Netherlands; B. Gazzard, Chelsea and Westminster Hospital, UK; and R. Schuurman, Utrecht University, Netherlands.

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2. Current insights in combined antiviral therapy

2.1. Respiratory viruses

Respiratory viruses, which include respiratory syncytial virus (RSV), influenza and parainfluenza viruses, and the rhinoviruses, are an important cause of morbidity, work-related absenteeism and medical expenditure. While it is well established that the acute respiratory illnesses caused by this class of viruses commonly warrants hospitalization in certain well-defined populations, i.e. young infants and toddlers, elderly people and patients with chronic obstructive pulmonary disease, it has become clear in recent years that these infections are also associated with significant morbidity and mortality in other high risk populations, such as recipients of bone marrow or organ-transplants and patients receiving cytotoxic chemotherapy.

Progress in the development of antiviral therapy for respiratory virus infections has been constrained by a number of obstacles. First of all, the clinical syndromes caused by the respective viruses exhibit considerable overlap, and with a few exceptions, e.g. detection of RSV antigen in infants, rapid specific diagnostic assays are not available. Secondly, the role of the immune system in the disease process is not well understood. The secondary effects of the inflammatory mediators, such as cytokines, which lead to the symptoms of disease may actually be more problematic than the virus infection itself. Thirdly, easily administered, cost-effective and efficacious antiviral agents are not widely available, with the possible

exception of amantadine and rimantadine for influenza A virus infections. Finally, the significant mortality of respiratory virus infections in high-risk populations has only recently been appreciated.

However, while the progress in antiviral therapy for respiratory virus infections lags behind the chemotherapeutic advances for a number of other viruses, e.g. HIV and CMV, there have been considerable advances in the development of immunotherapy and immunoprophylaxis. Prevention of respiratory virus infections is cheaper, easier and more likely to succeed. For this purpose, new improved vaccines and adjuvants are available, as well as a variety of monoclonal and polyclonal antibodies for passive immunoprophylaxis. In addition, active maternal immunization during the last trimester of pregnancy may prove worthwhile by providing passive immunization to the infants.

New developments in antiviral therapy for respiratory virus infections are summarized below. This summary is restricted to RSV, influenza and rhinoviruses. Other respiratory viruses, such as the adenoviruses, coronaviruses and human herpesvirus-6 (HHV-6) are excluded since research on antiviral therapy against these viruses has not yet approached clinical development.

2.1.1. Influenza

The M2 protein-inhibitors amantadine and rimantadine are licensed for the treatment or prophylaxis of influenza A virus infections. While these agents are effective as prophylactic or therapeutic agents, the potential for development of viral resistance against these drugs is large (Hayden and Hay, 1992). Up to 25% of children excrete resistant virus during treatment with these drugs. Similarly, resistant virus has been isolated from 33% of immunocompromised patients who were treated with amantadine or rimantadine for severe influenza virus infections, a number of whom suffered a fatal rimantadine-resistant influenza pneumonia.

Ribavirin is an antiviral agent which is licensed for the treatment of infections with RSV, but which also shows antiviral effects against influenza viruses in vitro and in animal models, as well as in some clinical studies (Gilbert et al., 1992; Hosoya et al., 1993; Rollins et al., 1993; Rodriguez et al., 1994). The use of ribavirin for infections with rimantadine-resistant influenza virus is currently being studied. Combined treatment with rimantadine and ribavirin shows synergistic antiviral activity in vitro and in animal models (Hayden, 1986), and has been reported to be beneficial in hospitalized patients with severe influenza pneumonia.

A novel promising agent is the neuraminidase-inhibitor GG167, which is still in clinical development. Preclinical testing of this agent showed potent inhibition of viral replication, and an apparent lower potential for development of resistance in vitro than amantadine or rimantadine, which may prove to be a major advantage (Woods et al., 1993; Ryan et al., 1994; 1995). Topically administered GG167 has been shown to be highly effective as a prophylactic agent (Hayden et al., 1996). For therapeutic purposes, a reduction in viral titers and symptomatology was observed only when the drug was given within 24 h after the onset of symptoms (Hayden et al., 1996). No differences between GG167 and placebo in viral titers or symptoms were observed when the drug was administered at a later timepoint. Another drawback, which may limit the use of this agent, is the poor bioavailability of the drug. Antiviral effects are only observed when the drug is administered topically.

2.1.2. Respiratory syncytial virus

RSV can cause severe pulmonary disease in newborns. In children at high risk for complications of RSV disease, e.g. infants with congenital heart or pulmonary disease and premature or immunocompromised infants, prevention of infection with immunoprophylaxis and infection control is probably more effective than treating established infections (Levin, 1994; Hemming et al., 1995).

To date, active immunization has been discouraging for this purpose (Levin, 1994; Hemming et al., 1995). The findings in early studies with a formalin-inactivated vaccine, demonstrating that, rather than preventing infection, this vaccine increased the severity of the illness in children who

became infected, have substantially influenced the progess in the clinical development of RSV vaccines (Fulginiti et al., 1969; Kapikian et al., 1969; Kim et al., 1969).

Passive immunization with intravenously administered polyclonal immunoglobulins is licensed for young children at high risk for serious RSV disease (children < 2 years old with pulmonary disease). However, this prophylaxis is expensive and has practical limitations, since it requires monthly intravenous infusions of 6–8 h duration. Several other monoclonal and polyclonal antibody preparations with different routes of administration, e.g. intramuscular or intranasal, are currently undergoing clinical evaluation (Hemming et al., 1995; Taylor et al., 1995). In addition, passive immunization of the infant by active immunization of the mother may be beneficial (Bruhn and Yeager, 1977; Glezen et al., 1981).

Immunoglobulins are not effective in the treatment of established RSV infections, either in previously healthy children, or in patients at high risk for serious RSV disease (Hemming et al., 1987). The only licensed drug for RSV disease is the guanosine-analogue ribavirin. Viral resistance against ribavirin has not been observed, presumably due to the multiple mechanisms of action of this agent (Patterson and Fernandez-Larsson, 1990). However, the antiviral potency of the drug is limited, and the role of ribavirin treatment remains controversial (Levin, 1994). Current standard treatment of severe RSV disease in high-risk children consists of aerosolized ribavirin at a dosage of 20 mg/ml given over 12–18 h daily. The long duration of administration has a number of disadvantages, including compliance problems, health hazards from exposure of the drug to personnel, and contamination of the environment. For this reason, the safety and efficacy of high dose treatment during 6 h/day has been studied, and was shown to be safe and equally effective when compared to the standard regimen, while environmental contamination was reduced.

In immunocompromised adults, RSV pneumonia carries a mortality rate of approximately 70–100% if untreated (Englund et al., 1988; Martin et al., 1988; Hertz et al., 1989; Harrington et al., 1992), which, as suggested by uncontrolled case series, is only reduced to 60–70% during treatment with ribavirin alone (Hertz et al., 1989; Harrington et al., 1992). Improved treatment strategies are thus clearly needed in this patient population. Combined treatment with ribavirin and immunoglobulins, if instituted early during the course of infection, has shown promising results (Whimbey et al., 1995). In a small uncontrolled study, hospitalized bone marrow transplant-recipients with RSV pneumonia were treated with aerosolized ribavirin and intravenous immunoglobulins. The mortality rate was 100% in untreated patients and patients treated late in the course of infection, i.e. patients who were already ventilation-dependent or were approaching this stage. Strikingly, in patients treated early in the course of disease, the mortality rate was reduced to 22%. Preliminary results show a similar trend in leukemic patients with RSV pneumonia. These encouraging results clearly invite further study of this particular combination in hospitalized patients with severe RSV disease.

2.1.3. Parainfluenza virus

While there is no licensed treatment for parainfluenzavirus infections, patients at high risk to develop complications of these infections can be identified, including immunocompromised children, patients receiving chemotherapy and recipients of bonemarrow or organ-transplants. Based on uncontrolled and anecdotal data, the only current experimental treatment option for parainfluenzavirus infections appears to be ribavirin, administered by aerosol, bolus or continuous intravenous infusion (Gelfand, 1983; Cobian et al., 1995). Antibody preparations against parainfluenzavirus are not available.

2.1.4. Rhinoviruses

Rhinoviruses are an important cause of morbidity and work- and school-related absenteeism. In addition, asthmatic exacerbations may be associated with rhinovirus infections. For these reasons, an effective therapeutic regimen would be desirable.

Intranasally administered recombinant truncated intracellular adhesion molecule-1 (ICAM-1) appears the most promising agent, and is cur-

rently undergoing clinical testing (Martin et al., 1993; Crump et al., 1994; Ohlin et al., 1994). Since this agent shows enhanced antiviral activity in vitro when combined with interferon, this combination may also warrant clinical evaluation.

2.2. Herpesviruses

The herpesvirus family includes viruses for which the greatest successes in antiviral therapy have been observed. However, the potential role of combined antiviral treatment is limited to certain manifestations of herpesvirus infections, e.g. CMV disease in immunocompromised patients or neonatal and cerebral herpes simplex virus (HSV) infections. Several manifestations of herpesvirus infections are self-limiting or can be treated effectively with monotherapy.

2.2.1. Herpes simplex virus

In addition to aciclovir, several other licensed or investigational antiviral drugs are available for HSV infections. These include valaciclovir, penciclovir, famciclovir, cidofovir, and foscarnet. Valaciclovir is a prodrug of aciclovir, which is readily converted to aciclovir by a cellular hydrolase. The advantage of valaciclovir, compared to aciclovir, is a lower dosing frequency due to an increased oral bioavailability (55 versus 15% respectively) (Weller et al., 1993; Soul-Lawton et al., 1995). However, the clinical efficacy of both drugs in the treatment of mucocutaneous HSV infections is comparable. Penciclovir and its prodrug famciclovir exhibit similar antiviral effects to aciclovir.

In the phosphorylation pathway of aciclovir and penciclovir to their active triphosphate-derivatives, the first rate-limiting phosphorylation-step is mediated by the viral thymidine kinase. The most common cause of viral resistance against these agents is a deficiency of this viral enzyme (Pottage and Kessler, 1995). The cytosine-analogue cidofovir is a potent anti-HSV agent, which does not require viral thymidine kinase since it is already monophosphorylated, and therefore may be useful for the treatment of aciclovir-resistant HSV infections. Similarly, the pyrophosphate analogue foscarnet, which directly inhibits the viral DNA polymerase and does not require phosphorylation, is also active against aciclovir-resistant virus. However, viral resistance to foscarnet, and even dual resistance to foscarnet and aciclovir, has been reported (Safrin et al., 1994).

In immunocompetent adults, primary or recurrent mucocutaneous HSV infections generally respond well to monotherapy, and viral resistance does not appear to pose a major problem. Therapeutic failure in this patient group is mostly due to pharmocokinetic problems, which can be resolved by switching to a prodrug. Combined antiviral treatment therefore does not seem warranted in immunocompetent adults. However, there may be a role for combination therapy in immunocompromised patients with mucocutaneous HSV infection. In this patient group, the virus load is high, spontaneous clearance is slow, and the manifestations of infection can be severe. Combined antiviral treatment may be more effective in reducing the virus load, while the development of viral drug resistance, which does provide a significant clinical problem in these patients, may be prevented. However, clinical studies of combined antiviral treatment in this patient population have not been performed to date.

Other manifestations of HSV infection which are potentially amenable to combined antiviral treatment are neonatal infections and HSV encephalitis. For HSV encephalitis, the efficacy of aciclovir monotherapy may be hampered by limited penetration of the drug in the central nervous system. Famciclovir, which has been shown to have improved CNS penetration in mice compared to aciclovir, may provide a good alternative to aciclovir, either as monotherapy or in combined treatment regimens. Finally, combination therapy may be useful for prevention of neonatal HSV infections. It has been shown that secondary prophylaxis with aciclovir alone reduces the reactivation rate and asymptomatic viral shedding, albeit not completely (Spruance, 1993; Epstein et al., 1996). Combined treatment may result in more complete suppression of asymptomatic viral shedding, which would reduce the risk of HSV transmission.

Beside combining antiviral drugs, other combination strategies, e.g. antivirals with immunomodulators, antibodies or wound-healing enhancers, may also be beneficial. In addition, by modulating endogenous nucleotide pools, the antiviral effects of nucleoside analogues may be enhanced by combining them with ribonucleotide reductase-inhibitors (Prichard and Shipman, 1995). Finally, the development of vaccines is being pursued aggressively, not only for prevention but also for therapeutic purposes.

2.2.2. Varicella zoster virus

Aciclovir and valaciclovir, as well as famciclovir and sorivudine are very effective in the acute stage of herpes zoster. Valaciclovir and famciclovir have never been compared directly, but both appear to have a beneficial effect on postherpetic neuralgia as well (Beutner et al., 1995). Combination strategies of aciclovir with the newer generation analgesics and/or corticosteroids have been studied, and have shown improvement in the quality of life in immunocompetent herpes zoster patients (Whitley et al., 1996).

Combined antiviral treatment may be beneficial in immunocompromised patients, in whom herpes zoster can be an unrelenting disease with severe disseminated manifestations. However, clinical trials of combined antiviral treatment for herpes zoster have not been reported to date.

2.2.3. Epstein-Barr virus

Epstein-Barr virus causes malignant lymphomas in immunocompromised patients, which may theoretically be prevented by antiviral (combination-)therapy (Davis et al., 1995). Aciclovir treatment does not seem to be effective against EBV infections (Luxton et al., 1993). Compared to aciclovir, penciclovir shows enhanced activity against EBV in vitro, and may thus be a potential candidate for treatment of EBV infections and prevention of lymphoma (Bacon and Boyd, 1995). A study is ongoing to evaluate the efficacy of ganciclovir for this purpose.

2.2.4. Cytomegalovirus

The advances in diagnosis, treatment, and prophylaxis of CMV infection were subject of a separate consensus symposium, a summary of which has been published previously in this journal (Van der Meer et al., 1996). Neonatal infections with CMV and CMV disease in immunocompromised patients, including transplant recipients and HIV-infected persons, are important targets for improved therapeutic modalities. While it has long been known that congenital CMV infections can have severe sequelae, data on antiviral treatment of CMV infections are largely restricted to CMV disease in immunocompromised patients, most notably CMV retinitis in HIV-infected patients and CMV pneumonitis in transplant recipients.

Currently available treatment options for CMV infections are the CMV DNA polymerase-inhibitors ganciclovir, foscarnet, and cidofovir. For CMV retinitis, all three drugs have been shown to be effective as monotherapy in prolonging the time to recurrence (Van der Meer et al., 1996). However, despite chronic maintenance therapy, relapses of retinitis almost invariably occur. In part, this may be due to the acquisition of suboptimal intraocular drug-concentrations during systemic therapy. While the problem of drug delivery can be circumvented by intravitreal administration, this does not protect against the development of retinitis in the contralateral eye or of CMV disease elsewhere. Another important cause of failure of maintenance therapy is the development of viral resistance. The emergence of virus variants with reduced susceptibility to foscarnet and ganciclovir during prolonged monotherapy is well documented, and is associated with increases in plasma CMV load during treatment (Boivin et al., 1996). Ganciclovir resistance is conferred by specific mutations in the UL97 gene, which encodes for the viral phosphotransferase responsible for the first phosphorylation step. Resistance can also result from mutations in the gene encoding for the viral DNA polymerase. Since foscarnet does not require phosphorylation for its activity and cidofovir is already monophosphorylated, resistance to these drugs is conferred by amino acid changes in the viral DNA polymerase only. Dual,

and even triple resistance to the respective drugs is commonly observed (Knox et al., 1991; Sarasini et al., 1995; Baldantini et al., 1996; Van der Meer et al., 1996). It has been shown that high level, but not low level, ganciclovir-resistant virus variants are cross-resistant to cidofovir, indicating that specific mutations in the polymerase-gene are required for both cidofovir-resistance and high levels of ganciclovir resistance. In addition, reductions in foscarnet-susceptibility have been reported in ganciclovir-resistant virus isolates, and resistance to foscarnet seems to develop more rapidly in patients pretreated with ganciclovir, suggesting a degree of cross-resistance between ganciclovir and foscarnet as well. Interestingly, foscarnet-resistant virus appears to remain sensitive to cidofovir, as is the case for low level ganciclovir resistant virus.

Limited efficacy and resistance have made CMV retinitis an important target for combined antiviral treatment. Combinations of ganciclovir with foscarnet or cidofovir show additive to synergistic activities in vitro, as does a combination of foscarnet and cidofovir. However, synergistic nephrotoxicity precludes the latter combination for systemic therapy.

Combined treatment with ganciclovir and foscarnet significantly prolongs the progression-free interval in patients with relapsed retinitis, when compared to monotherapy with either ganciclovir or foscarnet (Jacobson et al., 1994; Studies of Ocular Complications of AIDS Research Group, 1996). However, visual acuity assessments in patients receiving combined treatment were similar to patients treated with monotherapy. Furthermore, longer infusion-times and increased toxicity significantly diminished the quality of life in patients receiving the combination.

A combination of ganciclovir or foscarnet with polyclonal or monoclonal antibodies also displays additive to synergistic activity in vitro (Pollard, 1996). However, a placebo-controlled study comparing the efficacy of ganciclovir alone and in combination with the monoclonal antibody MSL109 in newly diagnosed and recurrent CMV retinitis, showed no additional benefit of combined treatment. This study was terminated prematurely because of increased mortality in previously treated patients receiving combined treatment, the cause of which remains unknown.

CMV pneumonitis and encephalitis are also potential targets for combined antiviral treatment. Treatment with either ganciclovir or foscarnet does not have much impact on the overall survival of CMV pneumonitis (Shepp et al., 1985; Aschan et al., 1992). There are no data on the effects of combined treatment with the two drugs. The efficacy of high dose intravenous immune globulin (IVIG) in combination with ganciclovir for CMV pneumonia remains controversial (Emanuel et al., 1988; Reed et al., 1988; Verdonck et al., 1989). While some benefit of this combination was initially observed, it does not appear to improve survival when compared to ganciclovir alone.

For cerebral CMV infections, monotherapy with ganciclovir or foscarnet at best stabilizes the disease process. Sufficient penetration of the blood-brain barrier is a concern, as is the development of viral resistance since CNS disease often occurs in patients receiving long-term maintenance therapy for CMV retinitis. Uncontrolled case-series suggest a benefit of combined treatment with ganciclovir and foscarnet in the treatment of CMV encephalitis (Enting et al., 1992; Peters et al., 1992).

In conclusion, monotherapy with currently available antiviral agents for the treatment of CMV disease in immunocompromised patients is generally inadequate. While combined treatment with these agents may result in increased efficacy, increased toxicity and long infusion times also reduce the quality of life. Better therapeutic options are clearly needed. A number of new anti-CMV agents, including lobucavir, bispom-PMEA, benzimidazole, as well as a number of antisense oligonucleotides, are currently in clinical development and may prove promising in the treatment of CMV disease, either as monotherapy or in combination with existing drugs (Pari et al., 1995; Van der Meer et al., 1996).

2.2.5. Human herpes virus-8

In 1994, the identification of EBV-like DNA sequences in Kaposi's sarcoma (KS)-lesions from AIDS patients has led to the discovery of a new virus, initially termed KS-associated herpes virus

(KSHV), but now also called, but not officially designated as human herpesvirus type 8 (HHV-8) (Chang et al., 1994). HHV-8 sequences have been detected in KS lesions of all forms, including classic-, African endemic- and HIV-associated KS, as well as in the blood, lymphoid tissue, and unaffected skin of KS patients (Ambroziak et al., 1995; Boshoff et al., 1995a,b; De Lellis et al., 1995; Huang et al., 1995; Schalling et al., 1995; Bigoni et al., 1996; Humphrey et al., 1996; Li et al., 1996; Noel et al., 1996; O'Neill et al., 1996). Longitudinal studies suggested that the presence of HHV-8 in the blood is predictive of subsequent development of KS, which is supported by recent serologic studies (Lefrere et al., 1996; Lennette et al., 1996). Beside KS, the presence of HHV-8 is also associated with lymphoproliferative malignancies, especially primary body cavity-based lymphomas, angioimmunoblastic lymphadenopathy, and Castleman's disease (Cesarman et al., 1995; Soulier et al., 1995; Luppi et al., 1996a,b; Nador et al., 1996; Otsuki et al., 1996; Robert et al., 1996; Said et al., 1996; Sander et al., 1996). Epidemiological studies using serology suggest that sexual transmission of HHV-8 is likely, consistent with the reported detection of HHV-8 sequences in semen and prostate (Gao et al., 1996; Kedes et al., 1996; Lennette et al., 1996; Monini et al., 1996).

With respect to treatment, the role of HHV-8 in the pathogenesis of KS clearly needs to be elucidated. Since expression of HHV-8 genes appears to be limited in the majority of KS lesions, suggesting predominantly latent infection, it remains to be studied whether antiviral therapy is beneficial in established KS (Decker et al., 1996; Zhong et al., 1996). Epidemiological studies and a small number of uncontrolled case histories suggest that foscarnet may reduce the risk of developing KS and result in remission of established KS (Morfeldt and Torssander, 1994; Glesby et al., 1996). Based on these reports, several studies are currently ongoing to evaluate the efficacy of foscarnet in the treatment of HIV-associated KS. A recently described culture system may enable in vitro screening of novel antiviral agents for prophylaxis or treatment of KS (Renne et al., 1996).

2.3. Hepatitis B virus

Infection with hepatitis B virus (HBV) results in development of chronic hepatitis in 5–10% of immunocompetent adults, 20–40% of immunocompromised patients, and in 90% of patients infected at birth, and is a major cause of death worldwide due to the development of cirrhosis and hepatocellular carcinoma. As progression of liver disease is driven by viral replication and immune-destruction of hepatocytes, treatment may be targeted at both the immune system and inhibition of viral replication. The only approved treatment for chronic hepatitis B is interferon alpha, which predominantly appears to act by amplifying the existing immune response, resulting in immune lysis of infected hepatocytes, but also has antiviral activity. Only approximately 40% of patients with chronic HBV hepatitis and 35% of cirrhotic patients respond to interferon therapy, as measured by clearance of HBV DNA. Patients with active hepatitis, as reflected by increased serum transaminase levels, detectable hepatitis Be antigen, low HBV DNA levels, and active liver histology generally show the best responses to interferon therapy, while very few responses are observed in the immunotolerant phase of infection with minimal hepatitis (Brook et al., 1989).

In an attempt to increase the therapeutic efficacy, combinations of interferon alpha with several other immunomodulatory agents have been studied. Combined treatment with interferon alpha and levamisole or interferon gamma have not proven to be beneficial (Fattovich et al., 1992; Bosch et al., 1993; Ruiz-Moreno et al., 1993). There is no consensus on the role of pretreatment with prednisone before interferon therapy (Cohard et al., 1994). Due to its immunosuppressive activity, treatment with prednisone allows for increased viral replication, resulting in increased expression of antigens and, on stopping, rebound immunity, which can lead to enhanced elimination of infected hepatocytes during subsequent interferon therapy. While several studies have indeed shown enhanced viral clearance during interferon therapy after withdrawal of prednisone, a metanalysis suggested that these benefits are re-

stricted to patients with low ALT levels (Cohard et al., 1994). Furthermore, the risk of side effects is higher and cases of hepatic decompensation during this regimen have been described. Since HBV-infected individuals who eliminate the virus after infection clearly differ from those who do not with respect to the CD8 lymphocyte response to HBV, immunostimulants which specifically enhance the TH1 cytotoxic immune response, e.g. interleukin-12, are potentially beneficial in the treatment of HBV infection (Milich et al., 1995). Phase I/II studies with this cytokine are currently ongoing.

Beside immunomodulatory treatment, suppression of viral replication is clearly important in controlling HBV infection. Lamivudine (3TC), penciclovir and PMEA are nucleoside analogue inhibitors of the viral polymerase with potent antiviral activities in vitro (Heijtink et al., 1993; Shaw et al., 1994). In clinical studies, 100% suppression of HBV DNA levels is observed in virtually all patients treated with lamivudine at dosages in excess of 100 mg/day, accompanied by clearance of HBe antigen in some patients (Benhamou et al., 1995; Dienstag et al., 1995). However, as observed in 6-month studies of lamivudine treatment, relapses of viral replication usually occur following cessation of therapy. The high relapse rate can be explained by the stability and persistence of the covalently closed circular intermediate of HBV DNA (cccDNA), which, if unaffected, acts as a transcriptional template following withdrawal of therapy. In animal model studies, it has been shown that the level of cccDNA is only minimally affected when total viral replication is suppressed less than 90%. In pekin ducks, greater than 90% suppression of total HBV DNA levels, accompanied by declines in the amount of cccDNA, was only observed during treatment with penciclovir or high doses of PMEA, and not with lamivudine. However, even after 6 months of penciclovir therapy, minimal amounts of cccDNA could still be detected in the duck-hepatocytes, which rapidly returned to pretreatment values following therapy withdrawal.

By achieving more effective suppression of viral replication, combined antiviral therapy may result in a reduction of the rate of replenishment of cccDNA below the rate of decay. Combinations of penciclovir and lamivudine or PMEA, and to a lesser extent lamivudine and PMEA, show additive to synergistic antiviral activities in vitro, and may thus prove effective for this purpose (Korba, 1996). Combined penciclovir and lamivudine indeed resulted in a more substantial reduction of total intracellular cccDNA levels in vitro than either agent alone.

Another concern in the treatment of HBV infections that may warrant combined antiviral therapy is the existence of extrahepatic or extrahepatocyte sites of viral replication in which HBV is cleared differently. For example, it has been shown in the duck model that penciclovir does not have any effect in extrahepatic sites of viral replication, such as the pancreas.

Finally, combined antiviral therapy may be effective in preventing drug resistance, which has been reported to develop during monotherapy with lamivudine or penciclovir (Ling et al., 1996; Tipples et al., 1996; Bartholomew et al., 1997). Reductions in susceptibility to the respective agents seem to be conferred by specific mutations in the HBV polymerase gene, and are associated with viral breakthrough during treatment.

Beside combining two antiviral agents, a potentially beneficial approach to therapy is to combine antiviral and immunomodulatory therapy. In vitro, the antiviral activity of interferon alpha is enhanced by lamivudine (Korba, 1996). However, in clinical studies of this combination, interferon alpha does not appear to confer a marked additional benefit when compared to lamivudine alone, which may be explained by the lamivudine-induced reduction in antigen-expressing cells. Theoretically, immune amplification may nevertheless be important for curative therapy, especially in chronic persistent hepatitis. Studies of the viral dynamics of HBV infection indicate that the half-life of infected cells during active disease is only approximately 10 days due to immune lysis (Nowak et al., 1996). Based on this short half-life, it can be estimated that, in case of complete suppression of viral replication by antiviral agents, eradication of HBV would require approximately 1 year of treatment, which could theoretically be shortened to less than 1 year if

immunomodulatory agents were to be added. However, during chronic persistent hepatitis in which immune lysis does not occur, the half-life of infected cells has been calculated to be markedly longer, ranging from 10 to 100 days. With this long half-life, curative therapy would require many years of treatment, and modulation of the immune system to enhance immune lysis theoretically seems important.

2.4. Hepatitis C virus

Hepatitis C virus (HCV) is a major cause of chronic hepatitis, developing in approximately 50% of infected individuals, and progressive liver disease. Interferon alpha comprises the mainstay of treatment. While the initial response rate to interferon therapy in HCV infection is similar to that in HBV infection (40–50%), the relapse rate following cessation of therapy is much higher, and sustained responses are only observed in approximately 25% of patients (Sherlock, 1995). Furthermore, in contrast with HBV infection, the response rate in cirrhotic patients is very low ($\approx 5\%$).

Since the clinical outcome of chronic HCV hepatitis is variable, a problem in the management of HCV hepatitis is the identification of patients who will progress to severe liver disease, and are thus in need of treatment with interferon. Several factors have been correlated with increased severity of disease, including the age, sex, and MHC class II phenotype of the host, and the genotype and quantity of the virus (Sherlock, 1995). However, these factors have not proven to be particularly useful in the management of individual patients. Although there is no consensus on the issue of when and whom to treat, it may be recommended to monitor patients regularly, including histologic examination at 2–3 yearly intervals, and to focus treatment on patients who progress to moderate hepatitis. At later stages of the disease, when cirrhosis has developed, the rate of response to treatment is severely reduced. While the response rate to interferon in HCV infection is relatively low, it would also be helpful to predict which patients would benefit from treatment. Again, several host and viral factors are associated with poor responses to interferon treatment, but none of these are helpful in the individual patient. However, it has been shown that the early changes in plasma HCV RNA load during the first week of treatment are predictive of the response to treatment. While HCV RNA levels generally decline to below detectable levels within a few days in responders, non-responders show sustained levels during the first weeks of treatment. In the latter group, treatment could be stopped after 1–2 weeks of treatment. The occurrence of a relapse after withdrawal of therapy in initial responders cannot be predicted. However, since relapses generally occur within 6–9 months after completion of treatment, the response in patients who are still in remission at this stage will most likely be sustained.

In view of the relatively low response rate and high relapse rate associated with interferon therapy, improved therapeutic options are clearly needed. A number of small, uncontrolled studies have strongly suggested an enhanced efficacy of combined treatment with interferon alpha and ribavirin (Brillanti et al., 1994; Braconier et al., 1995; Brillanti et al., 1995; Chemello et al., 1995; Schvarcz et al., 1995). In these studies, the rate of sustained responses more than doubled when compared to treatment with interferon alone. These promising results need confirmation in larger randomized, placebo-controlled trials, which are currently in progress.

The search for novel antiviral agents has been hindered by the lack of a tissue culture system or animal models for HCV. However, the characterization of the structures and activities of viral enzymes may aid in the identification of novel inhibitors of viral replication. The viral serine protease may prove to be an attractive target for structure-based drug design.

2.5. Hepatitis D virus

Hepatitis D virus (HDV, delta agent) is an RNA virus which is dependent on HBV for its replication. While co-infection of HDV with HBV does generally not progress to chronic HDV hepatitis, super-infection of HDV in HBV-infected patients results in persistent HDV infection in

more than 90% of cases, and is associated with rapidly progressive liver disease and a poor prognosis. In small studies, interferon treatment has been shown to be effective in decreasing HDV RNA levels and improving liver histology in approximately 50% of cases (Farci et al., 1994; Rosina and Cozzolongo, 1994). After completion of treatment, relapses occur almost invariably. Ribavirin inhibits HDV replication in vitro, but has not proven to be of benefit in vivo as monotherapy (Rosina and Cozzolongo, 1994). Ongoing trials are evaluating whether, similar to HCV infection, the addition of ribavirin to interferon treatment increases the rate of response and results in longer lasting benefits.

2.6. Human immunodeficiency virus

The efficacy of treatment of HIV infections with monotherapy is very limited due to incomplete suppression of viral replication and the development of drug resistance. In recent years, these limitations have encouraged efforts to pursue the aggressive development of combined antiviral treatment strategies. Evidence of improved efficacy of several combined antiviral strategies has now dispensed with the use of monotherapy in the management of HIV-1 infection.

In retrospect, with the current knowledge on the viral dynamics of HIV-1 infection, the limited efficacy of monotherapy is not surprising and could have been predicted. High rates of viral replication, with a daily production of 10^9–10^{10} virions, occur throughout the course of infection (Ho et al., 1995; Wei et al., 1995; Perelson et al., 1996). Coupled with the high mutability of HIV-1 RT, these persistent high levels of viral replication allow for the continuous generation of mutations in the viral genome, including those conferring drug-resistance (Coffin, 1995). Since drug-resistant virus populations will thus be present before treatment is started, an important rationale of combined antiviral therapy is the activity against a broad range of these pre-existing mutants. An equally important reason for combined antiviral treatment is to improve suppression of viral replication, thereby diminishing the likelihood of the emergence of resistance-conferring mutations during treatment. Drug resistance will not develop when viral replication is completely suppressed, which is the ultimate goal of antiviral treatment.

Recent studies have demonstrated that the level of circulating HIV-1 RNA, which represents a dynamic equilibrium between virus production and clearance, is determined early after seroconversion and is highly predictive of the subsequent course of disease (Mellors et al., 1995; 1996). In the light of these findings, it is not surprising that several studies have shown a correlation between the magnitude and duration of treatment-associated decreases in HIV-1 RNA load and improved clinical outcome (Yerly et al., 1995; Katzenstein et al., 1996; O'Brien et al., 1996; Schooley et al., 1996). Treatment should thus be aimed at achieving HIV-1 RNA levels as low as possible for as long as possible. Since several antiretroviral combination regimens, especially those involving three drugs, have recently been shown to result in sustained reductions of the plasma virus load to below detectable levels, cautious optimism in the management of HIV-1 infection is now justified.

During potent antiviral treatment, the decline in plasma virus load has been shown to follow a biphasic pattern (Perelson et al., 1996). During the first phase, which is reflective of the high viral turnover, the virus load decreases to low levels within 1–2 days. This is followed by a second slower phase, during which the virus load declines to below detectable levels. The duration of this phase appears to range from 1 to 4 weeks, and is thought to reflect the decay rate of latently infected cells. Based on the duration of this second phase of decay, it has been calculated that, depending on the total number of latently infected cells (10^8 or 10^{12} cells) and the duration of the second phase (1 or 4 weeks), complete eradication of the virus would require approximately 0.5–3 years of fully suppressive treatment. These calculations were made assuming the absence of long-lived populations of infected cells, which are potentially present and could account for a third slow phase of decay and reignition of viral replication after withdrawal of suppressive therapy.

While the concept of eradication of HIV-1 is challenging, several questions need to be addressed, in addition to the possible presence of

long-lived viral reservoirs. Clearly, the long-term follow-up of potent antiretroviral regimens is needed. Furthermore, although promising treatment responses have been observed in lymphoid tissue, it remains to be studied whether sustained complete suppression of viral replication also occurs in these and other solid tissues. The potential existence of sanctuary sites of viral replication which may be cleared differently, e.g. in the central nervous system, also requires investigation. Finally, it remains to be seen whether complete suppression of viral replication is associated with complete immunereconstitution.

At any rate, the progress in the field of antiretroviral treatment during the last 2 years has been considerable. The design of promising combination treatment regimens has been enabled by the discovery of a large number of potent antiretroviral agents. Currently, six reverse transcriptase inhibitors are licensed in the US, including the nucleoside analogues zidovudine, zalcitabine, didanosine, lamivudine, and stavudine, and the non-nucleoside inhibitor nevirapine, as well as the potent HIV protease inhibitors indinavir, ritonavir and saquinavir. In addition, several other protease inhibitors and nucleoside analogue- and nonnucleoside inhibitors of HIV-1 RT are undergoing clinical evaluation, including nelfinavir, 141W92, 1592U89, delavirdine, and loviride.

As mentioned before, several combination regimens have been shown to be capable of reducing virus load in plasma to undetectable levels for extended periods of time. In this respect, triple combinations of two RT inhibitors and one HIV protease inhibitor appear the most promising, although potent efficacy has also been observed with a combination of three RT inhibitors, viz. zidovudine, didanosine and nevirapine. Clinical studies evaluating the efficacy of several dual and triple combinations are currently in progress. These include studies on combined therapy with the protease inhibitors ritonavir and saquinavir, which in addition to an additive antiviral activity without evidence of cross resistance, may have beneficial effects by increasing plasma saquinavir levels due to induction of the cytochrome p450 system by ritonavir.

Furthermore, a study evaluating the efficacy of triple combination treatment initiated early after primary infection is ongoing and shows promising results. Finally, studies are in progress to evaluate whether, following a course of triple combination therapy, complete suppression of HIV-1 RNA levels can be sustained by a less toxic and expensive maintenance regimen. In one of the these studies (ACTG protocol 343), the effect of completely withdrawing therapy will also be assessed.

Beside combinations of two or more antiretroviral agents, alternative combinations also show encouraging results. These include the addition of hydroxyurea to didanosine to enhance the activity of the latter (Biron et al., 1995), and the addition of interleukin-2 to antiviral agents, which has been shown to result in enhanced increases of CD4+ cell counts (Kovacs et al., 1995; 1996). Other immunomodulatory agents, e.g. interferon, have not proven beneficial to date.

2.7. Human papilloma viruses

In addition to causing cutaneous and anogenital warts, human papilloma viruses (HPV) are strongly implicated in the cause of cervical cancer (most notably types 16 and 18), while increasing evidence also indicates an association between HPV and other anogenital squamous cell cancers, non-melanoma skincancers, and malignancies of the oral cavity and esophagus. In view of their carcinogenic potential, the identification of antiviral agents against HPV is desirable. However, progress in this field is hampered by the lack of a tissue culture system for screening of compounds. While inhibitors of viral replication have not been identified to date, treatment strategies may emerge with the increasing knowledge on the pathogenesis of HPV infections. These include the potential use of interferones, anti-oxidants, retinoids and a number of cytokines which may interfere with viral replication by affecting transcriptional pathways (Kelloff et al., 1995).

2.8. Hemorrhagic fever viruses

Hemorrhagic fever viruses are the cause of a wide spectrum of severe clinical syndromes with

high mortality rates, and pose a challenging target for therapeutic intervention. In two classes of this group of viruses, i.e. the hantaviruses and the filoviruses, some progress in the field of antiviral therapy has been made.

2.8.1. Hantaviruses

Hantaviruses are the cause of serious clinical syndromes associated with high mortality. These include hemorrhagic fever with renal syndrome (HFRS), caused by Hantaan-, Seoul-, and Puumulaviruses, and the hantavirus pulmonary syndrome (HPS), caused by the recently discovered Sin Nombre virus. In the treatment of HFRS, intravenous ribavirin has been proven effective in reducing the risk of reaching the oliguric phase, as well as the risk of hemorrhage and the mortality (Huggins et al., 1991). In a small uncontrolled study comparing supportive care with ribavirin in the management of HPS, no beneficial effect of ribavirin treatment was observed (Anon., 1993). However, possibly due to a diagnostic delay, virtually all clinical events had occurred before sufficient ribavirin levels were attained. The rarity of this syndrome since the outbreak in 1993 has precluded further evaluation of ribavirin treatment for HPS. Beside ribavirin, other antiviral agents against hantaviruses have not been identified.

2.8.2. Filoviruses

Since their discovery in 1968, Marburg and Ebolaviruses have been the cause of several documented deadly outbreaks in Africa. In addition, small outbreaks of Ebola virus infections have been documented in the US and Italy, which were all caused by imported primates, the source of which could be traced to a single primate exporter in the Philippines. Research on the development of antiviral agents against Ebola virus is currently ongoing in the US Army Medical Research Institute. Random screening of compounds against Ebola virus is hardly feasible because of the high laboratory biosafety level (level 4) required for filovirus research. For this reason, other viruses were sought which could be predictive of the antiviral activity of compounds against filoviruses. In view of their similar molecular organization, paramyxoviruses, including parainfluenza virus and RSV, were proven to be good candidates for this purpose. Using this method, several classes of compounds with potential anti-filovirus activity were identified, including RNA polymerase inhibitors and inhibitors of the enzyme *s*-adenosylcysteine hydrolase. The latter class of agents has especially been subject to extensive research. In a newly designed mouse model for Ebola virus, high dose prophylaxis with this class of compounds was shown to be protective of infection with Ebola virus. The prophylactic efficacy of high anti-Ebola IgG titres was also evaluated in this model, and showed a 25% increase in the survival. While the efficacy of both treatment strategies was markedly less in primates, which obviously are more similar to humans with respect to pharmacokinetics and the pathogenesis of disease, the results of this challenging research are interesting, and may point the way to effective intervention or prophylaxis against this deadly virus.

3. Conclusion

In recent years, limited efficacy of current antiviral treatment has strongly encouraged continuing efforts to identify improved therapeutic options for several viral infections. Improved efficacy of combined antiviral therapy has now been established in the treatment of HIV-1 infection, while increasing evidence indicates an enhanced benefit of combination therapy for several other viral infections as well. The considerable progress in the field of antiretroviral therapy has even ignited cautious optimism about curative therapy of HIV-1 infection. However, the long-tern follow-up of treatment with current potent antiretroviral regimens needs to be awaited, and several questions regarding the pathogenesis of HIV-1 infection still need to be addressed.

For several viruses, the quest for novel potent antiviral agents continues, the discovery of which enables the design of potentially effective combination strategies. In addition, challenging research is progressing to discover antiviral agents against viruses for which treatment is not yet available, such as HPV and the filoviruses.

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