Review

Anti-AIDS Drug Development: Challenges and Strategies

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A myriad of chemical derivatives has been shown to inhibit in vitro replication of the AIDS virus at concentrations that are nontoxic to the host cells. The majority of these agents acts by either (i) inhibiting enzymes such as reverse transcriptase (RT), protease, or glucosidase, (ii) arresting expression of genes or gene products, or (iii) inhibiting viral processes such as giant cell (syncyitia) formation or viral binding to the target cell. The nucleoside RT inhibitors are the most widely studied agents at both the preclinical and the clinical levels. Their inability to cure AIDS has stimulated the discovery of several novel nonnucleoside RT inhibitors, possessing varied structures and demonstrating activity at nanomolar concentrations. These agents demonstrate a unique mode of binding to RT and show a high specificity for HIV-1. Protease inhibitors, soluble CD4 derivatives, oligonucleotides, and many anionic derivatives also demonstrate potent anti-HIV-1 activities. These derivatives possess mechanisms of action different to the nucleosides and exhibit selectivity as exemplified by their high in vitro therapeutic indices. This article discusses the structural parameters that govern activity in these agents, the pros and cons regarding the development of these compounds as putative anti-AIDS agents, and the future promise of searching for newer agents directed at novel targets to inhibit the AIDS virus.

KEY WORDS: Anti-AIDS agents; human immunodeficiency virus 1 (HIV-1); development; inhibitors; mechanism; selectivity.

INTRODUCTION

Since the discovery of a retroviral cause for acquired immunodeficiency syndrome (AIDS) (1–3), many laboratories have actively pursued the search, design, and development of new anti-human immunodeficiency virus (HIV-1) agents. These studies have produced a wide array of agents possessing diverse structures that are capable of inhibiting different sites of the virus life cycle. The discovery of these agents has been the result of one or many approaches. These have included the random anti-HIV-1 screening of a wide inventory of chemical substances, the evaluation of substances with known antiviral activity against other viruses or inhibitory activity against specific targets, such as reverse transcriptase (RT), present in other species (e.g., animal, avian), and rational drug design. In general, the presently known inhibitors of HIV-1 inhibit either specific viral enzymes or viral processes and thereby inhibit viral multiplication.

The fact that the AIDS virus is endowed with unique viral enzymes and genes that are required for replication provides the medicinal chemist with attractive targets for drug design. In this respect, among the enzymes, RT, protease, and the glucosidases have been popular targets, for which there are known inhibitors. In considering viral processes, agents exist that have the ability to prevent viral binding to the target cell, arrest giant cell (syncyitia) formation, or prevent gene expression. Broadly, these ongoing approaches continue both to produce new specific inhibitors and to contribute to the development of known inhibitors. The design of new specific enzyme inhibitors can be rationally strengthened if the relevant enzyme has been functionally characterized and its structural coordinates confirmed by X-ray analysis. However, it must be emphasized that until these data become available, it is still possible to design inhibitors. This is possible only after the discovery of a lead compound and has a greater chance for success if the mechanism of action of the lead compound has been determined. A pertinent example is the discovery of many potent nucleoside inhibitors of HIV-1 RT which were designed without X-ray crystallographic data on the enzyme. Indeed, the retroviral RT still remains a popular target for drug design and synthesis.

REVERSE TRANSCRIPTASE INHIBITORS

Nucleosides and Derivatives

Once it was established that an RNA virus was responsible for AIDS, research groups rushed to test randomly many nucleoside derivatives, among other compounds, for activity against HIV-1. The selection of compounds for antiviral evaluation was narrowed down in certain cases by considering nucleoside derivatives that have been known to possess antiviral activity against several animal and human viruses. In the United States, the first drug to be licensed by
the FDA and used on a wide scale in AIDS patients was 3'-azido-2',3'-dideoxythymidine (AZT) (1) (Scheme I). It is worthy to note that AZT was first synthesized as an antitumor agent in 1964 (4) and was later shown to have inhibitory activity against the Friend leukemia virus (5). In 1985, it was reported that AZT demonstrated in vitro inhibition of the cytopathogenic effect of the AIDS virus (6) and was subsequently administered to AIDS patients (7). The anti-HIV-1 activity of AZT stimulated the evaluation of a wide variety of nucleoside derivatives. For many research groups this was not a formidable task because they possessed a large inventory of already synthesized nucleoside derivatives. These and other investigations led to the discovery of activity in other nucleoside derivatives such as 2',3'-dideoxyctydine (DDC) (2), 2',3'-dideoxyadenosine (DDA) (3), 2',3'-dideoxyinosine (DDI) (4), and 2',3'-dideoxy-2',3'-didehydrothymidine (D4T) (5) and their consequent introduction into clinical trials. Recently, DDI has also gained FDA approval.

The mechanism of action of these anti-HIV-1 nucleoside agents involves the sequential in vivo phosphorylation of the 5'-hydroxyl group to the active triphosphate species. The triphosphate inhibits the retroviral RT and also acts as a chain terminator (8). Therefore, for the nucleosides, the 5'-hydroxy group is a requirement for activity. One study has analyzed the preferred sugar conformations of certain anti-HIV-1 nucleosides and demonstrated that the location of the 5'-hydroxy group is important in relationship to the base (9). Structurally, AZT is unique in that it has a functionality rare in therapeutic drugs, an azido group in the 3'-position of the sugar ring. It has been postulated that the azido group functions to bind to both the polynucleotide binding site and the mononucleotide 5'-phosphate binding site of RT to contribute to DNA chain termination (10).

Structure–activity studies have revealed that modifications at the 3'-position of the sugar do allow the presence of a hydroxyl (as in DDC, DDA, or DDI), or a fluorine in the α-orientation (erythro compound), or the presence of a 2',3'-double bond (as in D4T). However, these sugar modifications must be matched with the appropriate nucleic acid base to ensure optimum activity. One problem with purine nucleosides (such as DDA and DDI) was their short half-life due to acid lability. This undesirable property was circumvented by preparing 2'-fluoro analogues, which were as active as the parent analogues but these derivatives also exhibited increased toxicity (11). The introduction of a 6-halo substituent into certain 2',3'-dideoxypurine nucleoside derivatives has been shown to confer lipophilicity without decreasing the anti-HIV-1 activity of these compounds (12).

The administration of these nucleoside agents in the clinic has revealed various forms of toxicity. These include bone marrow suppression and anemia (AZT), peripheral neuropathy (DDC, DDI, and D4T), and pancreatitis (DDI) (13). Although these side effects have been shown to be dose-limiting, they may preclude the long-term use of these nucleosides as singular agents against AIDS. Resistance has become a matter of concern after the discovery of AZT-resistant HIV-1 mutants (14). Three amino acid mutations where Asp 67 → Asn, Lys 70 → Arg, Thr 215 → Phe or Tyr, have been shown to be common to several AZT-resistant isolates (15). Recently, it has been shown that it is possible to induce resistance to DDI and sensitivity to AZT by a mutation in HIV-1 reverse transcriptase (16). Nucleoside anti-RT analogues may still prove promising in anti-AIDS therapy if they are prescribed early in asymptomatic patients and/or are used in combination with other nucleosides or with derivatives possessing a different mechanism(s) of action. This type of regimen would have the advantage of reducing or eliminating the toxic effects seen with singular nucleoside agents, as well as delay or abrogate the emergence of nucleoside resistant mutants.

The shortcomings of toxicity and resistance associated with the clinically used nucleosides have provided the impetus for detailed structure–activity relationship studies in the anti-HIV nucleoside area (17). A pertinent structural modification in the development of nucleoside analogues has been the opening of the furanose sugar ring to prepare acyclic derivatives. This strategy is strongly substantiated by the success of the acyclic nucleoside derivative, Acyclovir, for the management of genital herpes. Phosphomethoxyalkyl derivatives of adenine, namely, 9-(2-phosphonomethoxyethyl)adenine (PMEA) (6) and 9-(2-phosphonomethoxyethyl)-2,6-diaminopurine (PMEADAP) (7), demonstrate anti-HIV-1 activity and are more potent than AZT in certain animal models (18,19) (Scheme II). The side chain of Acyclovir has a terminal hydroxy group, a required necessity to form the active triphosphate species. In PMEADAP the terminal side-chain moiety is a phosphonyl group. Since the active species is also the triphosphate derivative, PMEA and PMEDAP need only two more phosphorylations to form the active compound. Other favorable properties of PMEA and PMEDAP are their known inhibi-