ELSEVIER

Anti-infectives

Editorial overview

Erik deClercq and Paul Tulkens

Current Opinion in Pharmacology 2004, **4**:429–430

This overview comes from a themed issue on
Anti-infectives
Edited by Erik deClercq and Paul Tulkens

Available online 23rd August 2004

1471-4892/$ – see front matter

DOI 10.1016/j.coph.2004.08.002

Erik deClercq

Katholieke Universiteit Leuven, Rega Institute, Minderbroedersstraat 10, B-3000 Leuven, Belgium

Erik De Clercq received his MD degree and his PhD both from the K.U.Leuven in Belgium. After having spent two years at Stanford University Medical School as a postdoctoral fellow, he returned to the K.U.Leuven Medical School, where he became docent (assistant professor) in 1973, professor in 1975, and full professor in 1977. Prof. E De Clercq served as chairman of the Department of Microbiology from 1986–1991. Since 1999 (until 2004) he is, again, serving as chairman of the Department of Microbiology and Immunology. In 1985, he became President of the Rega Foundation and, in 1986, Chairman of the Directory Board of the Rega Institute for Medical Research. He is a titular member of the Belgian Royal Academy of Medicine and the Academia Europaea, and has also held the Prof. P De Somer Chair of Microbiology at the K.U.Leuven. His scientific interests are in the antiviral chemotherapy field, and, in particular, the development of new antiviral agents for the treatment of various viral infections, including AIDS.

Paul Tulkens

Cellular and Molecular Pharmacology, Université Catholique de Louvain, UCL 73.70, Avenue E. Mounier 73, 1200 Bruxelles, Belgium

Paul Tulkens is Professor of Pharmacology at the Faculty of Medicine (Department of Pharmaceutical Sciences) of the Université Catholique de Louvain. He is also Chair-holder of the GSK-Chair of Infectious Diseases (co-organised by the Université catholique de Louvain and the Katholieke Universiteit Leuven). His current research interests lie in the interactions of drugs and chemicals with subcellular organelles, antibiotic toxicity (molecular, cellular and clinical aspects), chemotherapy of intracellular infection, pharmacodynamics and pharmacokinetics of anti-infective drugs (*in vitro* models and clinical trials), and new antibiotic discovery and development.

Abbreviations

HBV	hepatitis B virus
HCV	hepatitis C virus
MRSA	methicllin-resistant *Staphylococcus aureus*
NNRTI	non-nucleoside reverse transcriptase inhibitor
N(t)RTI	nucleoside (nucleotide) reverse transcriptase inhibitor

In the past couple of years, considerable progress has been made towards the development of new compounds and strategies for the treatment of virus infections, particularly HIV, DNA virus (i.e. herpes virus and hepatitis B virus [HBV]) and hepatitis C virus (HCV) infections. In this themed issue on anti-infectives, some of the most important recent developments in the antiviral research field have been highlighted.

Nucleoside (or nucleotide) reverse transcriptase inhibitors [N(t)RTIs] have remained the cornerstone for all anti-HIV drug regimens. Approved drugs include the NRTIs zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir and the NtRTI tenofovir (disoproxil fumarate) (TDF). Emtricitabine, another NRTI, has also been approved and a fixed dose combination of TDF with emtricitabine has been recently authorized for marketing (Truvada^{TM}). In his article on new NRTIs, Otto addresses, in addition to emtricitabine, several other NRTIs (i.e. alovudine, amdoxovir, racivir, reverset, SPD 754 and elvucitabine) that show potential for the treatment of HIV infections, which may (or not) be realized after further clinical follow-up studies.

In combination drug regimens used for the treatment of HIV infections, one or more N(t)RTIs are often combined with a non-nucleoside reverse transcriptase inhibitor (NNRTI). Three NNRTIs (i.e. nevirapine, delavirdine and efavirenz) have been formally approved, the latter already six years ago and, although many more NNRTIs have been described, they have not been brought forward, primarily because of insufficient *in vivo* potency against NNRTI-resistant viruses. Emphasis has thus been placed on the development of new NNRTIs that would retain sufficient potency against these mutants. Two particularly potent new NNRTIs were identified that might fit the bill, namely capravirine and etravirine (TMC 125) but, as we learn from the treatise by Pauwels, the route to success for an NNRTI can be particularly long and hazardous.

There are, besides the reverse transcriptase, several other virus-specific processes that could be envisaged as targets for chemotherapeutic

intervention with the HIV replicative cycle. One such process is viral entry into the cell, which could be stopped at any of the following levels: virus adsorption to the cell surface, virus interaction with its receptor CD4 or its coreceptor (CXCR4 for the X4 virus strains; CCR5 for the R5 virus strains) and virus-cell fusion. Proof-of-principle that viral entry, and in particular virus-cell fusion, is a validated target has been provided by the fusion inhibitor enfuvirtide (T-20). HIV inhibitors targeted at CXCR4 and CCR5 are under development. This includes AMD070 for CXCR4 and, as reviewed in the article of Maeda *et al*., several compounds for CCR5 (i.e. TAK-220, SCH-D, UK-427 857 and AK602).

As 'spin-off' compounds from anti-HIV drug research, lamivudine and adefovir dipivoxil are now the only two chemicals approved for the treatment of (chronic) HBV infections. Other antivirals such as emtricitabine, entecavir, telbivudine, elvucitabine and valtorcitabine are emerging, and so is a new therapeutic concept for the treatment of chronic HBV, as we learn from Hewlett, Hallenberger and Rübsamen-Waigmann. In their article, they also address current (approved) and future (potential) antiviral drugs for the treatment of infections with herpes virus (herpes simplex virus, varicella-zoster virus, human cytomegalovirus and others). They noted that for the treatment of HBV, as well as herpes simplex virus and human cytomegalovirus infections, there is a trend towards the development of non-nucleosidic compounds.

For HCV, the last of the major viral pathogens to be identified, current therapy consists of (pegylated) interferon combined with ribavirin, a far from optimal treatment regime, as it is only successful in half of patients infected with HCV genotype 1 and, furthermore, is compounded by severe side effects. Tan *et al*. examine the different strategies for the chemotherapy of HCV infections. Among these approaches, the viral NS3/4A protease inhibitors and viral NS5B polymerase inhibitors certainly look the most promising. Antisense-, ribozyme- and small interfering RNA-based approaches, as well as preventive or therapeutic vaccines, may also be considered. As has proven to be the case for HIV, and is most likely going to be shown for HBV also, successful therapy of HCV infections might require the combined use of different compounds (and/or approaches).

Van Bambeke discusses the pharmacological profile and clinical perspectives of new glycopeptides in clinical development. These drugs, discovered in the early 1960s, act as inhibitors of peptidoglycan synthesis. With vancomycin as the flagship, they have, however, long been considered 'old antibiotics' that only attracted the clinician's interest when methicllin-resistant *Staphylococcus aureus* (MRSA) started to emerge as a significant problem in the mid 1980s. Soon, however, resistance to vancomycin, mainly in Enteroccoci, started to spread (a few reports of resistance of MRSA have now appeared). Industry has been fast to react and a series of new glycopeptides (oritavancin, telavancin and dalbavancin) have emerged, giving rise to a real race among companies. These new drugs hold much promise because two of them (orutavancin and telavancin), in contrast to vancomycin, are highly bactericidal and should be more effective than vancomycin even against sensitive strains (new anti-staphylococcal agents such as linezolid are only bacteriostatic). Dalvbavancin offers the unique advantage of being a once-weekly drug (something almost never see in the antibiotic arena). However, there is also a consensus among tenants of good antibiotic practice (having Public Health as their main concern) to restrict the use of such agents to severe infections by multiresistant organisms to limit the risk of further selection of resistance. In some respects, these new drugs illustrate a paradoxical situation that will certainly be the subject of hot debates in the near future; that is, how to let coexist the need to stimulate industry to develop new antibiotics (to face present and future microbial threats) with the need to prevent that same industry from selling them too widely (so as not to kill those wonder drugs prematurely).

In the final review, McKeegan, Borges-Walmsley and Walmsley review the escalating problem of multidrug resistance, and how effective treatment of bacterial, fungal and protozoan infections, along with certain cancer treatments, has been compromised by the presence of multidrug transporters. This topic is of absolutely new and paramount interest for anyone interested in the future of chemotherapy. Unlike 'conventional' mechanisms of resistance that tend to be drug specific (e.g. production of β-lactamases to destroy β-lactams), efflux pumps are not acting against a specific drug. They are part of our constitutive armamentarium to keep the cell protected from inordely invasion by amphiphilic compounds (i.e. compounds of various nature but which have the common ability to easily pass across biological membranes). In this respect, anti-infective drugs are only one of the many compounds efflux pumps may be targeting. However, efflux of chemotherapeutic agents from the bacterial, fungal or protozoan cell confers an advanatge to this cell when the corresponding drug is present. Hence, efflux pumps now appear a major and widespread mechanism of resistance in all cell types. Because of the lack of specific strcuture-activity relationship (beyond amphiphilicity), cross resistance to apparently unrelated drugs is common, and might include anticancer drugs. However, recent advances in the elucidation of several three-dimensional structures of multidrug pumps could lead to the development of novel 'anti-efflux' therapies.