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♦ EDITORIAL

Since the introduction of the HMG-CoA reductase inhibitors, or statins, we have been inundated with data on this therapeutic class. Over the years there has been a clear progression of trials, the results of which have changed the focus from treatment of hyperlipidaemia to treatment of the high risk patient.

Earlier trials sought to establish the impact of regular doses of statins on treating hyperlipidaemia in different patient groups, with a variety of primary and secondary endpoints. More recent trials have focussed on the clinical impact of high dose statin therapy. One of the most recently published trials is the ASTEROID trial, the objective of which was to establish whether aggressive statin therapy can regress coronary atherosclerosis. This trial is reviewed in some detail below.

This article gives an overview of the evolution of knowledge gained from various statin trials and the resultant clinical implications.

In addition a brief overview of Oseltamivir in the management of influenza is provided.

STATIN THERAPY: WHERE ARE WE TO DATE?

INTRODUCTION

In an editorial in the NEJM in January 2005, Ehrenstein *et al* stated, "If ever there were a perfect marriage of drug with disease it might be between statins and atherosclerosis….Just as married couples often adapt to each other, so it is with statins and atheroma, or to be more precise, an increased understanding of their relationship has revealed an apparent adaptation."[1]

In the last 20 years, statins (inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A, HMG-CoA, reductase) have been one of the most studied antiatherosclerotic therapies. As the trials have progressed the actions of the statins have turned out to be far more complex and extensive than originally thought. These potent anti-athrogenic therapeutic agents have been shown to lower arthrogenic low-density lipoprotein (LDL), improve endothelial function, have multiple immunologic actions, reduce inflammation and thrombus formation, and stabilize atherosclerotic plaques.[1,2] Recently the ASTEROID trial has suggested that high-dose rosuvastatin may actually *regress atherosclerotic plaques*.[3] Many trials have indicated that *statin* drugs can *reduce the rate of cardiovascular disease (CVD) and death.* However there has been much controversy as to what the optimal levels of LDL should be.

TRIALS USING STANDARD THERAPY

In the past two decades there has been a flood of data and trials on the role of statins in the management of *primary* and *secondary* prevention of coronary artery disease (CAD).[3] The Scandinavian Simvastatin Survival Study (4S) ushered in this era, establishing the importance of treating hypercholesterolemia in patients with established CAD.[4,5] This *secondary preventative* benefit was realized in further trials such as CARE, LIPID and LIPS.[4,6,7]

Other landmark trials, which show the *primary preventative* benefit of statins, include the WOSCOPS and AFCAPS/TEXCAPS trials.[4,8,9] In WOSCOPS patients were at risk of developing heart disease, but without established CAD - they were middle-aged men with markedly elevated lipid levels, elevated BMI and one third were smokers. The number of coronary events was significantly reduced, but, unlike secondary prevention studies, there was no significant reduction in non-cardiovascular mortality or total mortality.[8] AFCAPS/TEXCAPS patients were at average risk, with normal total cholesterol, but low HDL cholesterol.[4,9] After a mean follow-up of 5.2 years, treatment with Lovastatin (20-40mg daily) significantly reduced the risk for first acute major coronary event (defined as myocardial infarction, unstable angina or sudden death), but also showed no difference in total mortality.[4,9] Both trials showed cholesterol lowering therapy does not have as great a benefit in patients with no history of CVD, emphasizing the need to target the *patient at higher risk*.[4]

In the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA), another primary prevention study, 10,305 hypertensive patients with non-fasting total cholesterol values of 6.5mmol/l or less, and at least 3 other cardiovascular risk factors, were randomised to atorvastatin 10mg daily or placebo. Stroke, total cardiovascular and total coronary events were significantly reduced over 3.3 years.[4,10] In the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – Lipid Lowering Trial (ALLHAT-LLT), 10,355 hypertensive and moderately hyperlipidaemic patients with 1 additional CHD risk factor were treated with pravastatin 40mg/day or placebo.[4,11] In contrast to ASCOT-LLA, pravastatin did cause significant reductions in all-cause mortality or CHD, thus highlighting the importance of risk stratification of individual patients.[4]

Mixed secondary and primary prevention studies include the Heart Protection Study (HPS) and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study. HPS (n=20,536) demonstrated that statin therapy reduced myocardial infarction, stroke and revascularisation in patients at high risk of CVD by about 25%, regardless of initial lipid levels. High risk patients included those with existing CAD (secondary prevention) as well as patients with diabetes and non-coronary occlusive arterial disease (primary prevention).[4,12] PROSPER, a large study (n=5,804) of elderly patients who had with existing vascular disease or were at risk due to smoking, diabetes or hypertension, showed a significantly lowered risk of coronary death and non-fatal myocardial infarction, but no significant change in stroke incidence. [4,13]

TRIALS EVALUATING HIGHER DOSE STATINS

Two earlier studies evaluated the use of aggressive statin therapy:

- In the Atorvastatin versus Revascularization Treatment (AVERT) study, low-risk patients with stable CAD were treated with aggressive statin therapy (atorvastatin 80mg/day) or angioplasty. The study suggested that aggressive statin therapy was as effective as angioplasty in reducing ischaemic events in this population group.[4,14]
- The MIRACL (Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering) study showed that early aggressive statin treatment following an acute coronary syndrome (atorvastatin 80mg/day initiated 24 to 96 hours after ACS) reduced the risk of symptomatic ischaemia at 16 weeks, but did not show a significant reduction in death, non-fatal myocardial ischaemia or cardiac arrest.[4,15]

Following the outcomes of these trials, the next obvious question posed was, "Would intensive lowering of LDL to "biological normal" levels derive more benefit?"[4,16] Consequently, current generation statin studies evaluate the benefit of "aggressive" statin therapy in high-risk patients.

The recent comparative statin trials in which aggressive doses of statins were used - PROVE-IT, ALLIANCE, TNT, Phase Z of the A to Z and REVERSAL - have all suggested that intensive statin therapy resulting in lower LDL values may provide optimal management in the reduction of cardiovascular events in patients with existing CAD.[4,17-21] However, although high-dose statin therapy has been shown to reduce cardiovascular events, there is an associated increase in adverse effects eg liver enzyme elevation.[4]

In the REVERSAL study, which compared intensive therapy (atorvastatin 80mg) with moderate-intensity therapy (pravastatin 40mg) in patients with stable CAD, atorvastatin 80mg was shown to *prevent the progression* of atherosclerosis after 18 months.[17] This was evaluated using intravascular ultrasound imaging (IVUS) of the coronary arteries, a technique in which a tiny ultrasound probe is inserted into the coronary arteries and measures plaque by visualizing the coronary arterial intima. However, statistically significant *regression* of atheroma plaques in the coronary arteries was not observed in

the atorvastatin group.[3,17] A difference in clinical events was however not demonstrated due to the size of the study.[4]

ASTEROID STUDY

Subsequent to the REVERSAL study, the investigators of the recent ASTEROID trial (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) set out to determine whether intensive statin therapy could *regress* coronary atherosclerosis.[3]

Design and Patient Selection

This study was a prospective, open-labelled blinded end-points trial, performed at 53 community and tertiary care centres in the USA, Canada, Europe and Australia, over a period of 24 months.[3]

The patient entry criteria specified in the study protocol included[3]:

- Age at least 18 years
- Statin-naivety (defined as no use of statin therapy for more than 3 months within the previous 12 months)
- A requirement for a coronary angiography for a clinical indication (i.e. typically stable or unstable ischaemic chest pain or abnormal exercise testing)
- The presence of at least one major coronary artery obstruction with more than 20% stenosis. (The target vessel for IVUS should not have undergone angioplasty and contain no more than 50% stenosis through a minimum length of 40mm)
- Any baseline level of LDL-C
- Absence of uncontrolled triglycerides
- Absence of poorly controlled diabetes

507 patients were enrolled and all received 40mg rosuvastatin per day. However, no control group was provided for, as the investigators decided that it would be unethical to administer placebo or low-dose statins to these high-risk patients.[3] Of the patients enrolled, only 349 completed the trial and had evaluable serial IVUS (which were performed at baseline and after 24 months of treatment).[3]

The *primary efficacy* parameters were changes in percent atheroma volume (PAV) and changes in nominal atheroma volume in the 10-mm subsegment with the greatest disease severity at baseline, and the *secondary efficacy* parameter was changes in normalized total atheroma volume (TAV).[3]

Results

There was no significant difference in baseline characteristics between those completing and not completing the trial in terms of gender, race, weight, age, body mass index (BMI), concomitant use of medication, prevalence of hypertension and diabetes and history of an ACS, or myocardial infarction (MI).[3]

A. Laboratory Results

In the group of patients that completed the trial, there was a 53.2% reduction of LDL from baseline ($p<0.001$) and high-density lipoprotein cholesterol (HDL) increased by 14.7% ($p<0.001$) (See Table 1).[3]

B. Results of Baseline and Follow-up IVUS

The pre-specified primary and secondary efficacy parameters showed a statistically significant regression (See Table 2).[2] A schematic adaptation of an IVUS image showing the regression of atherosclerosis is presented in Figure 1.[3,22]

Safety

Adverse events were infrequent and similar to other statin trials, using maximum doses. Cases of rhabdomyolysis were not present. Adverse events experienced by patients included musculoskeletal complaints, gastrointestinal complaints, increased creatinine kinase, neoplasms, increased bilirubin or ALT and cardiovascular disorders. Four deaths, ten myocardial infarctions and three strokes were reported, but the number of these clinical events was too small to provide clinical or statistical significance.[3]

Study Conclusion

The authors of the study concluded that the ASTEROID study suggests that aggressive, high-intensity rosuvastatin therapy, which significantly lowered levels of LDL and markedly increased HDL, can reverse atherosclerosis in coronary disease patients.[3]

Study Limitations

However, the authors do acknowledge that clinical outcome studies would be more appropriate to assess the impact of the benefits observed in the ASTEROID study. The study was unable to determine whether the degree to which regression documented by IVUS can be *directly* translated into a reduction in morbidity and mortality.[3] (Studies indicate that plaque stabilization – conferred by statins, rather than prevention of artery stenosis, prevents adverse coronary events).[23]

Further acknowledgement of study limitations included:

- the lack of a control group receiving either placebo or a less potent statin
- the potential that the withdrawal of 22 patients for ischaemic events may be a source of bias, as they may represent atheroma progressors[3]

Discussions

In an accompanying editorial to the ASTEROID study, Roger S. Blumenthal, and Navin K. Kapur, of The Johns Hopkins Ciccarone Preventive Cardiology Center, Baltimore, pointed out: "While IVUS-documented atherosclerotic regression is an intriguing finding, clinicians must remember that this may not be the best measure of the treatment's effect on hard cardiovascular end points. The results of several ongoing trials will help determine what agent or combination of pharmacological agents is most efficacious in the long-term management of at-risk patients".[24]

Moreover, patients enrolled in the study were statin naïve, or if they were on a statin, were required to undergo a 28-day washout period.[3,16] This raises the question whether the degree of atheroma regression was a "statin" effect or a rosuvastatin-specific effect. Drs. Blumenthal and Kapur suggested a comparative trial of rosuvastatin with simvastatin.[16]

It has also been pointed out that the ASTEROID patients were not at extremely high risk (Median baseline levels of TC = 197 mg/dL

TABLE 1: Lipid Results – Mean Values (n=346)[3]

	Baseline (SD)	During Treatment (SD)	% Change, Least-Square Mean (95% CI)	p-value
Total cholesterol (mmol/L)	5.28 (41.2)	3.47 (25.4)	-33.8% (-35.6 to 31.9)	p<0.001
LDL (mmol/L)	3.38 (34.3)	1.57 (20.0)	-53.2% (-55.6 to -50.9)	p<0.001
HDL (mmol/L)	1.12 (11.1)	1.27(12.6)	+14.7% (12.3 to 17.1)	p<0.001
Triglycerides (mmol/L)	1.72 (81.7)	1.37 (56.8)	-14.5% (-19.4 to -9.6)	p<0.001
LDL / HDL ratio	3.2 (1.1)	1.3 (0.5)	-58.5% (-60.7 to -56.2)	p<0.001
Non-HDL cholesterol (mmol/L)	4.17 (40.2)	2.20 (23.2)	-47.2% (-49.4 to -45.1)	p<0.001

Adapted from Nissen SE, *et al.* Effect of Very High-Intensity Statin Therapy on Regression of Coronary Atherosclerosis (The ASTEROID trial). JAMA 2006;295(13):1556-1565
(All data converted from mg/dl to mmol/L. Conversion factor of 0.0259 used for total cholesterol, HDL and LDL; factor of 0.0113 used for triglycerides conversion.)
*3 of 349 patients completing the trial had missing baseline data
SD - Standard Deviation
CI - Confidence interval

TABLE 2: Median values of primary and secondary efficacy endpoints.[3]

	Base line	Follow-Up	Change	% Change	% with regression	p-value
PAV %	39.9	38.5	-0.79	NA	63.6	p<0.001
Atheroma volume in most diseased 10-mm subsegment, (mm^3)	65.1	58.4	-5.6	-9.1	78.1	p<0.001
Normalized TAV (mm^3)	204.7	186.8	-12.5	-6.8	77.9	p<0.01

Adapted from Nissen SE, *et al*. Effect of Very High-Intensity Statin Therapy on Regression of Coronary Atherosclerosis (The ASTEROID trial). JAMA 2006;295(13):1556-1565
NA - not applicable
PAV% - Percent atheroma volume
TAV - Total atheroma volume

(5.1mmol/L), LDL= 127mg/dL (3.29mmol/L), TG= 135mg/dL (3.5mmol/L) and LDL:HDL = 3.1).[3,16] The role of the severity of stenosis was also not answered, as patients with occlusion of > 50% was excluded.[3,16]

Co-administered medication may also be another confounding factor and it was noted that only 17% of the patients were not taking aspirin.[3,16] (Aspirin is a platelet-modifying agent and regulates the inflammatory aspect of atherosclerosis).[22,24]

Nevertheless, according to Blumenthal and Kapur, "the pioneering work of Nissen *et al*", in the ASTEROID study, "has revolutionized the current approach to understanding the anatomy and patho-physiology of coronary atherosclerosis as well as its responsiveness to medical therapy".[25]

Implications

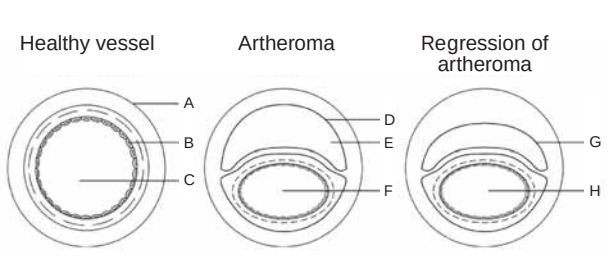
The ASTEROID study has raised important research questions such as what is the role of HDL in atherosclerosis? Was it the decrease in LDL, the increase in HDL or the LDL/HDL ratio (with a value closer to 1) that caused plaque regression? Was plaque regression a class effect or specific to rosuvastatin?

Answers to these questions, amongst others will definitely impact the management of atherosclerotic cardiovascular management in the future.[3,16]

Interestingly, several clinical trials with rosuvastatin are underway. These include the following primary prevention trials:

- JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin). This primary prevention trial is a large, multinational, long-term, double-blind, placebo-controlled, randomized clinical trial. It is evaluating the effect of rosuvastatin 20mg/day in individuals with low LDL levels, but elevated levels of high sensitivity C-reactive protein.[16]
- METEOR (Measuring the Effects on intima media Thickness: an Evaluation Of Rosuvastatin). This is a phase 3, 24-month, placebo-controlled, randomised, double-blind trial of rosuvastatin 40mg on progression of carotid artery atherosclerosis. It mea-sures the intima thickness of the carotid arteries in >800 low-risk, asymptomatic, hypercholesterolaemic, statin-naïve subjects.[16]

FIGURE 1: Schematic Presentation of Intravascular Ultrasound (IVUS) Images.[3,22]



A: Smooth muscle wall
B: Endothelial cells
C: Lumen area
D: Atheroma area = 10.16 mm^2
E: Lipid Core
F: Lumen area = 6.19 mm^2
G: Atheroma area = 5.81 mm^2
H: Lumen area = 5.96 mm^2

(Adapted from Davidsons Principle and Practice of Medicine[22] and the ASTEROID study[3])

GUIDELINES

As a consequence of new data published on statins, international guidelines (such as the American NCEP III and the European Guidelines) have reviewed their recommendations. The European Society of Cardiology (ESC) published their reviewed "European guidelines on cardiovascular disease prevention in clinical practice" in 2003. These guidelines differed from their 1998 version in that:[24]

- The focus is on CVD prevention rather than only CAD prevention.
- The SCORE model and risk charts are used to assess risk for the development of CVD
- As with previous versions of the guidelines, priority patients include those with established CVD and those at high risk of developing CVD. However new imaging techniques may be used to identify those at high risk.
- New clinical trial data was considered, with resultant emphasis on dietary and risk factor management and use of certain drug prophylaxis, including use of certain drugs in patients at high risk with relatively low total cholesterol level. Diabetes (all type 2 diabetes; type 1 with microalbuminuria) is considered a secondary prevention indication.

ESC's recommended target total cholesterol and LDL levels have been lowered to <4.5mmol/l (175mg/dl) and <2.5 mmol/L (<100mg/dL) respectively for patients with established CVD and/or diabetes. A therapeutic option of an even lower LDL level in certain very high-risk patients (i.e. an *optional* LDL level of <1.8mmol/L [70mg/dL]), is recommended in the NCEP III.[3,24,26]

The new South African Guidelines, published in July 2006, support the European guidelines, but, as these guidelines' SCORE assessment is derived from European data which may not be applicable to South Africa, they recommend the continued use of Framingham risk charts to estimate cardiovascular risk. However, once risk has been determined, the management of patients and targets of therapy are the same as those of the European guidelines.[27]

CONCLUSION

Extensive clinical trials leave no doubt that statins reduce adverse cardiovascular events as well as reduce coronary mortality and total mortality in high risk patients. Statins should therefore not be viewed as merely treating hyperlipidaemia, but rather as treatment for the prevention of cardiovascular events.

Evidence gives the clear indication that the "normal lipid profile" approach to therapy must be changed to an emphasis on risk stratification of the individual patient. No decision on the use of statin therapy should ever be made based solely on lipid levels – patient cardiovascular risk factors must be taken into consideration. The higher the patient's risk of cardiovascular disease, the more aggressive the approach to treatment should be. International guidelines now support the practice of treating all high risk patients with a statin, regardless of the initial cholesterol level. Patients with established atherosclerosis, familial hyperlipidaemia, Type 2 diabetes and Type 1 diabetes with micro-albuminuria are considered high risk.

Caution should however be used in management of patients with an abnormal lipid profile but no high risk of cardiovascular events. Before initiating statin therapy, the *risk-benefit ratio* as well as the cost of statin therapy must be carefully considered, as no medicine

is free of adverse effects. Patients not categorized as high-risk, should not be treated intensively with statins, merely because of an abnormal lipid profile.[4]

Therapeutic lifestyle modification remains an integral modality in clinical management.[24,26,27]

Although the ASTEROID study indicates that rosuvastatin can cause plaque regression, it is not clear whether this regression actually plays a role in reducing morbidity and mortality.[3] As mentioned by the American Heart Association (AHA), the ASTEROID study was not an event-driven trial, but provides continued support that "*lower is better*" for LDL levels in *secondary prevention* of coronary events.[28]

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OSELTAMIVIR IN THE MANAGEMENT OF INFLUENZA IN ADULT PATIENTS

Introduction

Influenza is a common and underrated seasonal illness and every year adults and children worldwide are affected. Typically annual outbreaks of influenza epidemics occur in winter months. A substantial demand is inflicted on the healthcare resources and industry each year resulting from increased primary care consultation, drug treatment, clinical complications, referrals, hospitalisations and work absenteeism.[1]

Influenza is debilitating, and a typical case can restrict activity for 5 to 6 days, can cause 3 to 4 days of bed disability and 3 days lost from school or work.[2]

Although rare, global outbreaks called *pandemics* can occur, with significant epidemiological impact. Three pandemics were recorded during the 20th century: the Spanish influenza pandemic in 1918, the so-called 'Asian virus' in 1957 and the most recent pandemic that originated in Hong Kong in 1968-1969. These pandemics caused widespread deaths.[1,3]

Recently a new influenza A strain (H5N1) has been detected in birds from Southeast Asia. The virus has spread to humans and has already caused more than 60 deaths. Based on the fact that 2 of 3 criteria for a pandemic have been met, the WHO (World Health Organization) has warned that an avian influenza (H5N1) pandemic is looming.[1]

The influenza virus

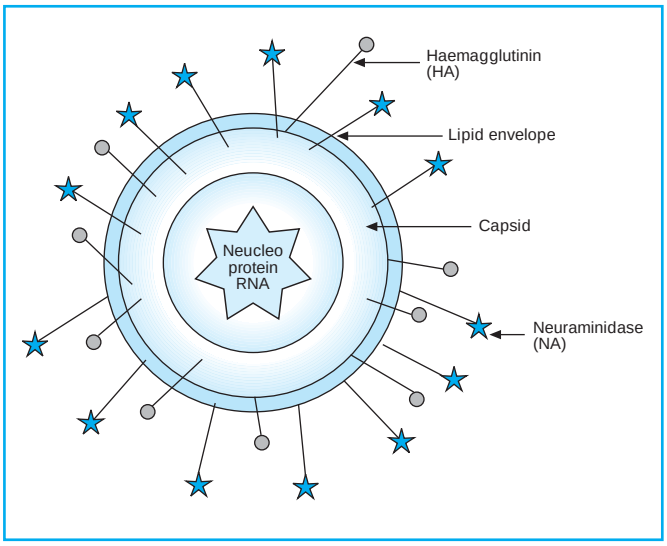
Viral Structure

The influenza virus is a helically shaped, RNA virus of the orthomyxovirus family.[1,4] The capsid mainly consists of two antigenic proteins, haemagglutinin (HA) and neuraminidase (NA), protruding through the lipid layer.[1] (Refer to Figure 1) There are 16 HA subtypes (H1-6) and 9 different NA subtypes (N1-9).[1]

Influenza Antigen Types

The influenza virus is categorised into 3 basic antigen types, A, B and C, based on differences in their nuclear material.[1,4] Influenza A and B each have 8 segments of RNA and influenza C has 7 segments.[1] Influenza A is categorised into further subtypes based on differences

Figure 1: Schematic illustration of the structure of the *Influenza* virus[5]



in surface antigens HA and NA.[4] In humans H1, H2 and H3 are involved in the attachment of virus to cells; N1 and N2 are involved in the process of viral penetration into cells.[4] Clinical features vary between the different subtypes. General characteristics of the influenza viruses are:[4]

Influenza A
- Affects all ages
- Infects animals and humans
- Causes moderate to severe illness
- Natural reservoir of virus is aquatic birds
- Most influenza A viruses are not pathogenic to their natural hosts and do not mutate

Influenza B
- Mainly affects children
- Only in humans
- Causes milder disease

Influenza C
- Not prone to cause epidemics
- Rarely reported in humans as most cases are subclinical

Kaji *et al* did a study to determine the difference in clinical features between certain strains. Patients were divided into 3 groups to compare symptoms and laboratory data for Influenza A H1N1, A H3N2 and Influenza B infections. The study results showed that in Influenza A H3N2-infected patients the fever, leukopenia and increase in C-reactive protein were more severe than in subjects with Influenza A H1N1 or Influenza B infections. Fever, general malaise and sore throat were equally frequent in influenza A H3N2, A H1N1, and B infections. Gastrointestinal symptoms were more common in influenza B.[6]

Viral Life Cycle

The influenza virus is spread from person to person via droplets from coughs or sneezes or other contaminated surfaces or material. The influenza virus then attaches to the host's cell-surface receptors in the upper and lower airway. The virus then enters the cells and the viral RNA uncoating occurs within minutes. The viral genes are then replicated inside the cell nucleus within approximately 6 hours.[1]

Distinctive features of RNA virus replication include high mutation rates, high yields and short replication time.[7] Antigenic *drift* refers to the virus's ability to overcome the body's immune system by means of mutation within the viral antibody-binding sites. This is caused by a *minor* change in surface antigen and may occur in all 3 influenza types. This may result in an epidemic.[4] On the other hand, antigenic *shift* occurs if there is a *major* change at the NA or HA surface antigens, resulting in the emergence of a new strain of Influenza A. This is a sudden change in antigenicity that happens when a cell is simultaneously infected by two different strains of type A influenza, and could potentially cause a pandemic.[4,5]

The enzyme *neuraminidase*, projecting from the surface of the influenza virus, allows the recently-formed viral particles to leave infected cells and spread throughout the body.[8,9]

Drug Prophylaxis and Treatment

One of the biggest challenges in the prophylaxis and treatment of influenza is the genetic variability of the RNA viruses which enable them to overcome vaccine or drug protection.[1] As vaccines inhibit or reduce the likelihood of interspecies transfer, an influenza vaccine remains the ideal way to reduce the spread of the influenza viruses. However vaccination is not always a management option as the preparation of a new vaccine takes 6 months or more.[3]

There are two classes of antiviral drugs available for prophylaxis and treatment of influenza virus:[3,4]

- M2 ion channel blockers (amantadine and rimantadine)
- NA inhibitors (zanamivir and oseltamivir)

In South Africa only amantadine (Symadin®; Symmetrel®) and oseltamivir (Tamiflu®) are available. Symmetrel® is also registered for the treatment of Parkinson's syndrome.

Amantadine

Amantadine blocks the ion channel activity of the M2 protein of most influenza A viruses. By blocking the hydrogen ion flow the viral replication is inhibited when the virus enters the host.[3] Amantadine however has no activity against influenza B viruses. In addition drug resistant variants develop rapidly in treated patients.[2,3]

Oseltamivir

Oseltamivir is a prodrug, the metabolite of which is a potent and specific influenza neuraminidase (NA) inhibitor that inhibits replication of a wide variety of influenza A and B viruses,[1,2,9,10] including the avian influenza virus H5N1.[1] This NA inhibitor blocks an established infection in the late stages by blocking the release of virions from infected cells. This decreases the spread to other cells by inhibiting the viral penetration of mucous secretions.[3]

Indications and Dosing Schedule

Oseltamivir (Tamiflu®) was registered by the MCC (Medicines Control Council) in February 2006 for the following indications:

- The treatment of influenza in adults and children ≥ 1 year of age
- Prophylaxis of influenza in adults and adolescents ≥ 13 years of age[9]

Tamiflu® is currently available at a single exit price (SEP) of R199.50 for 10 capsules. Although Tamiflu® can be taken with or without food, enhanced tolerability in some patients may occur when taken with food.[9]

It is recommended that treatment should commence within the first or second day of the onset of influenza symptoms. In adults and children >40kg or ≥8 years, 75mg twice daily for 5 days is required.[9]

Prophylaxis should be commenced within 2 days following contact with an infected person. The dose required is 75mg once daily for at least 7 days. The duration of protection lasts for as long as dosing is continued.[9]

Efficacy of oseltamivir in treating acute influenza

In a double-blind, stratified, randomised, placebo-controlled, multi-centre trial of 374 patients conducted during the influenza epidemic season from January to March 1998 in the United States, oseltamivir treatment reduced the severity of acute influenza in otherwise healthy adults. A decrease in the incidence of secondary complications was also suggested.[2]

The inclusion criteria for this study were:

- Adult patients between the ages of 18-65 who presented within 36 hours from onset of influenza symptoms
- Oral temperature had to be 38°C or higher
- One or more respiratory symptom e.g. cough, sore throat or nasal symptoms
- One or more constitutional symptom e.g. headache, malaise, myalgia, sweats and/or chills or fatigue

These patients were then randomly assigned to one of three treatment groups:

- Oseltamivir, 75mg orally twice daily for 5 days
- Oseltamivir, 150mg orally twice daily for 5 days
- Placebo twice daily for 5 days

The participants recorded symptoms, their oral temperature and their ability to perform usual activities. In addition, participants were

asked to complete a visual analogue scale of their overall health status. Anterior nose and posterior pharyngeal throat swabs for isolation of influenza virus were taken at pre-defined intervals.

The primary efficacy end points were time to resolution of illness and severity of illness. Duration of illness, defined as the time from start of taking the study drug to the time that the symptoms were relieved, decreased by more than 30% ($p<0.001$) in both oseltamivir groups. In the placebo group this was 4.3 days, in the 75mg-group 3 days and in the 150mg-group 2.9 days. Overall, median severity of illness reduced by approximately 40% ($p<0.001$).The patients who received oseltamivir reported relief from the illness within 24 hours after initiation of therapy more frequently in comparison with those patients who received placebo.[2]

In a meta-analysis by Kaiser *et al*, oseltamivir treatment in adults and adolescents with a proven influenza illness reduced overall antibiotic use for any reason by 26.7% and the incidence of influenza-related lower respiratory tract complications resulting in antibiotic therapy by 55%, relatively to placebo.[10]

Efficacy of oseltamivir for prevention of influenza A and B

A meta-analysis by Cooper *et al* showed a 74% (16%-92%) relative risk reduction in laboratory-confirmed influenza in 2 studies on seasonal prophylaxis of a healthy population group. Post-exposure prophylaxis in households showed a 90% (71%-92%) relative risk reduction in laboratory-confirmed influenza, and seasonal prophylaxis in an elderly population in residential care demonstrated a 92% (39%-99%) relative reduction in laboratory confirmed symptomatic flu.[11]

Resistance to NA Inhibitors

Given the fact that RNA viruses have high mutation rates,[7] the question of drug resistance to antiviral chemotherapy remains relevant.[1] Treatment with amantadine can cause resistant viruses in at least 30% of individuals.[11] Resistance to neuraminidase inhibitors has been observed infrequently in human studies. Resistance rates of <1% of treated adults and 4-8% of children have been reported.[1,3,12] However, rigorous detection techniques did identify resistant mutants in 9 out of 50 (18%) Japanese children during treatment with oseltamivir.[12]

Resistance of the influenza virus to NA inhibitors is associated with mutations of the viral NA. However, in animal models these mutations have been shown to decrease the stability of the NA, thereby compromising viral fitness, including compromised growth and transmissibility.[1,2,12] However, in a recent animal study Yen *et al* indicated that there is a substantial difference in the viral fitness and transmissibility depending on the different levels of NA functional loss during mutations.[12]

Conclusion

The only options available to control influenza infections are vaccines and antiviral chemotherapy.[12] The influenza vaccine remains the mainstay for prophylaxis of influenza A and B viruses, however the time required to develop a new vaccine makes antiviral drugs a very important treatment option.[3]

Oseltamivir has been shown to be effective for the treatment of influenza A and influenza B infections. Intervention should however occur in the early stages of disease progression (i.e. 48 hours into viral replication) as this enhances the efficacy of the drug.[10] Although resistance is less frequent in patients treated with NA inhibitors[11], resistance to antiviral treatment regimens remains a concern.

The unanswered question is whether the NA inhibitors will continue to provide sufficient levels of therapeutic and prophylactic effectiveness against the influenza virus and whether resistant versions will emerge.

In light of the cost of Tamiflu® and previous supply issues, another major concern raised on the role of antiviral drugs in the management of a looming avian 'flu pandemic was the availability and accessibility of these drugs to the target population.[3] In response to these concerns it was announced in May 2006 that Roche has entered into an agreement with Aspen Pharmacare to produce a generic version of oseltamivir for governments and not-for-profit organisations in the African sub-continent.

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