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Tenecteplase: Single-Bolus Thrombolytic Therapy for Acute Myocardial Infarction

Summary

- Tenecteplase is a new fibrin-specific, third generation thrombolytic agent.
- Health Canada and European authorities are currently reviewing tenecteplase for use in the treatment of acute myocardial infarction (MI). Tenecteplase has received approval for use in the United States.
- Tenecteplase is the first thrombolytic agent formulated for intravenous needle-less administration over 5 seconds.
- In clinical trials, 30-day mortality rates were similar in patients who received tenecteplase and those who received the second generation thrombolytic agent, alteplase. However, patients receiving tenecteplase had a lower incidence of non-cerebral bleeding.

The Technology

Tenecteplase is a new, fibrin-specific, third generation thrombolytic agent produced by recombinant DNA technology.¹ It was developed by Genentech, Incorporated (South San Francisco, California) and marketed under the trade-name TNKase™. Tenecteplase is the first "clot-busting" drug to be formulated for administration as a single, rapid, injectable dose and offers prompt administration for the treatment of acute MI.²

In acute MI, the survival and preservation of left ventricular function are related to the amount of functioning tissue remaining after infarction. There is a window of opportunity of several hours when it is possible to reverse coronary blockage and salvage myocardial tissue. Thrombolytic agents have been

developed to break down clots, allowing reperfusion of the heart muscle. The efficacy of thrombolytic therapy depends on how quickly it can be initiated and administered and the efficiency with which it dissolves the clot.³

Tenecteplase is a modified form of a natural clot-dissolving protein, the human tissue plasminogen activator (t-PA). This compound, t-PA, stimulates the body's own clot-dissolving mechanism by activating plasminogen, a component of intracoronary clots that is released into arteries when they are injured. Upon activation, plasminogen is converted to plasmin. Plasmin breaks down the fibrin mesh that holds the clot together. The clot is dissolved and blood flow is restored to the heart muscle.

Tenecteplase is a bioengineered variant of alteplase, a commonly used second generation thrombolytic agent. The "TNK" of TNKase™ refers to sites of amino acid modification. These modifications result in increased fibrin specificity, reduced plasma clearance and improved resistance to inactivation.^{4,5,6}

Regulatory Status

On June 2, 2000, the United States Food and Drug Administration approved the use of tenecteplase to reduce mortality associated with acute MI.⁷ Tenecteplase is under review by European regulatory authorities.⁸ As of December 2000, tenecteplase had not been approved for use in Canada;⁹ however, Health Canada is currently reviewing the drug for the treatment of acute MI.¹⁰

Patient Group

In Canada, acute MI accounts for 38% of the deaths due to heart disease or 23,000 deaths

annually.^{15,16} More cases of acute MI are likely to be identified as a result of a recent redefinition of MI by consensus groups in the United States and Europe.¹⁴ Only a specific subset of patients diagnosed with acute MI have been shown to benefit from treatment with thrombolytic agents.

Procedures that open blocked arteries have been shown to significantly improve survival provided they are administered within a few hours of onset of chest pain.³ The benefits of thrombolytic therapy diminish with later administration. In addition, risks for such complications as myocardial rupture or stroke increase. Also, thrombolytic agents can prove fatal if administered to patients with MI as a result of aortic dissection where coronary artery openings near the aortic valve are compromised.

In older patients, those with an increased risk of bleeding, and pregnant and nursing women, the benefits of tenecteplase in prevention of death should be weighed carefully against the risk of increased adverse events, including bleeding and risk to the fetus.¹⁷ While clinical trials have not addressed whether adjusted doses are required for patients with significant liver dysfunction, caution is advised, as tenecteplase is almost completely eliminated by liver metabolism.¹ The safety and efficacy of tenecteplase have not been established in pediatric patients.

Current Treatment

While coronary angioplasty (expansion of arteries using a balloon-tipped catheter) has been shown to effectively open obstructed arteries, it is not always practical or available in many institutions.¹⁸

Pharmaceutical treatments for acute MI have been shown to reduce mortality in large-scale randomized clinical trials. Patterns of practice for the management of acute MI in populations from ten countries in Europe and North America

were surveyed. Results showed utilization rates of 63.7% for thrombolysis, 88% for aspirin, and 65.9% for beta-adrenergic blocking agents.¹⁹

Three thrombolytic agents: streptokinase, (Streptase™, Hoechst-Roussel), reteplase (Retavase™, Boehringer Mannheim), and alteplase (Activase™, Genentech) are currently used to treat acute MI. The use of fibrin-specific alteplase has been associated with significantly lower mortality than streptokinase.²¹ While easier to administer, reteplase showed no additional survival benefit in comparison to an accelerated infusion of alteplase.²² However, aggressive treatment with these agents fails to achieve rapid, complete artery opening in 40-50% of patients and these agents require continuous intravenous infusion over at least 90 minutes.

Dosage and Potential Cost

Tenecteplase is the first thrombolytic agent for administration using a needle-less injection system. TNKase™ is marketed as a vial containing 52.5 mg of the active agent tenecteplase. It is supplied with one 10 ml vial of sterile water for a single, intravenous bolus administration over 5 seconds. Unlike the double bolus reteplase, it is compatible with heparin.

Tenecteplase must be weight adjusted. The recommended dosage ranges from 30-50 mg, approximately 0.5 mg/Kg patient weight.¹ Aspirin and heparin are co-administered to lower the chance of the artery becoming blocked again. The reduced plasma clearance and longer half-life of tenecteplase compared to alteplase allow for more convenient dosing in comparison with the front-loaded infusion regimen required for alteplase.

The average wholesale prices per dose for the three thrombolytics are: US\$2,200 per 50 mg of tenecteplase, US\$2,684 per 20 U of reteplase and US \$2,750 per 100 mg of alteplase.¹⁸

Concurrent Developments

Several third-generation thrombolytic agents have been developed. There are conjugates of plasminogen activators with monoclonal antibodies against fibrin, platelets, or thrombomodulin; mutants, variants, and hybrids of alteplase and prourokinase; and new molecules of animal or bacterial origin. Variations to molecule structure may lengthen the drug's half-life, increase resistance to plasma protease inhibitors, or increase selective binding to fibrin. Other third generation thrombolytic agents include monteplase, lanoteplase, pamiteplase, and staphylokinase. Thus far, mortality rates associated with third generation agents have been similar to mortality rates observed using second-generation agents based on data for the few drugs that have been studied in large-scale trials.⁶

Four clinical trials, involving 9,000 patients, are underway to evaluate various treatment regimens for tenecteplase in combination with other agents for the treatment of acute MI.²³ The largest of these studies is ASSENT III, a 6,000-patient, multi-centre trial evaluating the safety and efficacy of tenecteplase at different dosages along with enoxaparin, heparin, or heparin and abciximab. Another study, the ASSENT III Plus, will examine the use of tenecteplase with enoxaparin or heparin in the pre-hospital setting. Further studies will examine the rates of reperfusion when tenecteplase is administered in combination with eptifibatid or tirofiban or various antithrombotic combinations.³

Projected Rate of Diffusion

Tenecteplase may replace alteplase in the emergency room due to its therapeutic equivalence with alteplase and its shorter administration time and reduced adverse effect profile.

Assessing the Evidence

According to a phase III, international, randomized, double-blind trial (ASSENT II),

single-bolus tenecteplase therapy is statistically and therapeutically equivalent to gold-standard recombinant alteplase therapy in patients with acute MI, but is associated with fewer bleeding complications.²⁴ The trial compared 30-day mortality rates in 16,949 patients with acute MI confirmed by electrocardiogram. Patients were treated within 6 hours of onset of symptoms with either a single IV bolus of tenecteplase or an accelerated infusion of alteplase over 90 minutes. All patients received aspirin and heparin. The total mortality rates at 30 days were essentially the same in the tenecteplase group (6.18%) and the alteplase group (6.15%). In patients receiving treatment between 4 and 6 hours, those receiving tenecteplase had a mortality rate of 7.04% while the mortality rate in the alteplase group was 9.19% ($p=0.018$; Relative Risk Reduction=0.77). Major bleeding that required transfusion and/or other intervention was significantly lower in patients receiving tenecteplase compared to those receiving alteplase (4.68% versus 5.94%, $p<0.01$).

Adverse Effects

Thrombolytic agents can have serious side effects, notably haemorrhage, including intracranial haemorrhage. They may also prove fatal if an inappropriate dose is administered in an emergency situation.²⁰

The most common complication during tenecteplase therapy is bleeding, the risk of which is dependent on the dosage administered, concurrent use of other agents, coagulation status and patient predisposition.¹⁷ The incidence of mortality, stroke and bleeding is increased in patients over 65 years of age. Thirty-day mortality in the ASSENT-II trial was 2.5% for patients less than 65 years, 8.5% for those aged 65-74 years, and 16.2% for patients over age 75. The intracranial haemorrhage rate was 0.4% for patients less than 65 years, 1.6% for those aged 65-74 years, and 1.7% for patients over 75 years of age. In the ASSENT II trial, overall rates of intracranial haemorrhage were similar for tenecteplase (0.93%) and for alteplase (0.94%), but fewer non-cerebral bleeding complications

(26.43% versus 28.95 %, $p=0.0003$) and less need for blood transfusion (4.25% versus 5.49%, $p=0.0002$) were observed with tenecteplase.²⁴ The rate of death or non-fatal stroke at 30 days was 7.11% with tenecteplase and 7.04% with alteplase.²⁴ The elderly, particularly elderly females, have as much as an eight-fold increased risk of intracerebral haemorrhage after thrombolytic treatment for acute MI²⁵. The risk of intracerebral haemorrhage was significantly reduced from 3.02% to 1.14% (multivariate $p<0.05$) with tenecteplase compared with alteplase in women over the age of 75 weighing less than 67 Kg.²⁶

In clinical trials, the following adverse events have been noted in patients receiving tenecteplase: cardiogenic shock, arrhythmias, atrioventricular block, pulmonary edema, heart failure, cardiac arrest, recurrent myocardial ischemia, myocardial reinfarction, myocardial rupture, mitral regurgitation, and embolism, nausea and/or vomiting, hypotension and fever. All these adverse effects may not be directly due to tenecteplase therapy. It is advised that anti-arrhythmic therapy be available when tenecteplase is administered since arrhythmias can result after reperfusion.¹

Implementation Issues

It has been shown that fewer deaths due to acute MI occur when thrombolysis is initiated within two hours of the onset of symptoms.²⁷ The introduction of tenecteplase has the potential to impact how acute MI patients are treated due to the speed and ease with which it can be administered and the reduction in complications. Strategies to minimize delivery time have been proposed, including the ability to recognize acute MI as a medical emergency by the patient, the coordination of prompt response to patients with chest pain, practice guidelines for thrombolytic therapy, the availability of thrombolytic therapy on-site and the authority to initiate treatment by non-physician health care professionals in the emergency department.²⁸

As with all thrombolytic agents, before using tenecteplase the expected benefits must be weighed against potential risks and costs. Expected disability and the risk of early death as a result of not treating acute MI with thrombolytics must be weighed against the risk of bleeding when thrombolytics are administered. This risk is compounded by the fact that during thrombolytic therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless precautions are taken in laboratory analysis to prevent in vitro artifacts.¹ Whenever a relative contraindication exists, in some institutions, patients are required to sign a consent form to receive thrombolytic therapy.²⁹

The risk of antibody formation against thrombolytic agents such as tenecteplase when they must be readministered in a subsequent acute situation has not been systematically studied.¹ In addition, the long-term effectiveness of tenecteplase therapy and its potential use and interaction with other antithrombotic agents has not yet been determined.

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This brief was prepared by Ms. Lynda McGahan; CCOHTA and has been peer reviewed. The contents of this early assessment are current as of publication date, however new information is anticipated.

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