Sundhedsstyrelsen

Center for Evaluering og Medicinsk Teknologivurdering
KOMMENTERET VARSEL OM NY MEDICINSK TEKNOLOGI

Kommentarer til:

Ximelagatran for Prevention and Treatment of Venous Thromboembolism

KOMMENTERET VARSEL – 1. ÅRG. – NR. 2 – OKTOBER 2004

Teknologien

I juni 2004 udsendte Canadian Coordinating Office for Health Technology Assessment, CCOHTA, et varsel med titlen "Ximelagatran for Prevention and Treatment of Venous Thromboembolism" [*]. Ximelagatran er et nyt lægemiddel i tabletform til forebyggelse af blodpropper. Lægemidlet er beregnet til kortvarig ensartet dosering uden tilbagevendende laboratoriekontroller af koagulationsstatus.

Anvendelse i Danmark

AstraZeneca har fra Lægemiddelstyrelsen den 22. juni 2004 fået markedsføringstilladelse af Ximelagatran under navnet Exanta [*]. Exanta er samtidig godkendt i 15 EU-lande efter den gensidige anerkendelsesprocedure, hvor den franske markedsføringstilladelse har været udgangspunktet.

Markedsføringstilladelsen er udelukkende givet til indikationen: Forebyggelse af venøs tromboemboli hos patienter som gennemgår planlagt hofte- eller knæledsalloplastik. Samtidig er der givet markedsføringstilladelse til injektionsvæsken melagatran under handelsnavnet: Melagatran "AstraZeneca" [*]. Ifølge produktresumeet bør den samlede behandlingstid med Melagatran efterfulgt af Exanta ikke overstige 11 dage, idet der endnu ikke foreligger tilstrækkelig viden om virkning og sikkerhed ved længere tids anvendelse.

Produktet vil ifølge AstraZeneca A/S blive markedsført i Danmark fra den 25. oktober 2004. Gældende pris vil da kunne ses på www.medicinpriser.dk [*].

Det danske patientgrundlag

Produktet er godkendt til brug i forbindelse med hofte- eller knæalloplastik. I 2003 udførtes i Danmark 7.321 hofte- og 4.650 knæalloplastikker [*],[*].

Lægemidlets sikkerhed og situationen i USA

I oktober 2004 har AstraZeneca meddelt, at den amerikanske Food and Drug Administration (FDA) ikke har godkendt Exanta (ximelagatran) [*] [*]. Dette er bl.a. sket med baggrund i et møde i FDA's Cardiovascular and Renal Drugs Advisory Committee den 10. september 2004 [*]. Især usikkerheden omkring risikoen for levertoksicitet har givet anledning til bekymring [*]. Der foreligger ikke dokumentation for leverpåvirkning ved korttidsanvendelse af Ximelagatran. Derfor vurderes FDA's afslag på registrering af lægemidlet til denne indikation at være udtryk for et forsigtighedsprincip.

Fremtidsperspektiver

De franske myndigheder behandler for tiden en EU-ansøgning om anvendelse til langtidsbehandling ved atrieflimmer samt til behandling af dyb venetrombose [*]. En sådan godkendelse vil senere kunne danne grundlag for godkendelse i de øvrige EU-lande.

Indtil der foreligger en markedsføringstilladelse til de endnu ikke godkendte indikationer, bør ximelagatran kun anvendes til disse formål i forbindelse med protokollerede forsøg.

[*] *angiver links til referencer på Internettet*

CEMTVs Kommenterede varsler om ny medicinsk teknologi er udvalgte udenlandske varsler, som publiceres og kommenteres i relation til danske forhold. CEMTVs kommentarer går alene på særlige danske forhold såsom størrelsen af den danske patientgruppe, dennes nuværende behandling og resultater heraf.

Formålet med CEMTVs kommenterede varsler om ny medicinsk teknologi er at give beslutningstagere et kvalificeret bidrag til beslutning. Varslet skal ikke ses som en anbefaling af eller en advarsel imod den omhandlende teknologi.

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Ximelagatran for Prevention and Treatment of Venous Thromboembolism

Summary

- ✓ **Ximelagatran (Exanta™) is the first oral agent in a new class of anticoagulants called direct thrombin inhibitors.**
- ✓ **Most of the available evidence regarding venous thromboembolism is from studies focusing on its prevention after major orthopedic surgery. Ximelagatran's efficacy is comparable to that of warfarin and low-molecular-weight heparin in this setting.**
- ✓ **The rates of bleeding complications for ximelagatran and its comparators were not statistically different.**
- ✓ **The elevation of liver enzymes was observed in longer term trials.**

The Technology

Ximelagatran (Exanta™) is the first oral agent in a new class of anticoagulants called direct thrombin inhibitors.[1] After absorption, it is converted to its active form, melagatran.[2,3] Ximelagatran binds to free and clot-bound thrombin, thereby preventing the conversion of fibrinogen to fibrin, the primary component of blood clots.[3] Ximelagatran has a wide therapeutic window that permits fixed dosing and no routine laboratory monitoring. There is a low potential for drug interactions.[2,3]

Regulatory Status

Ximelagatran was approved in France for the prevention of venous thromboembolism (VTE) after total hip (THR) or total knee replacement (TKR) surgery.[4] In the US, AstraZeneca is seeking approval for its use in VTE prevention after TKR, long-term secondary prevention of VTE and stroke prevention in patients with atrial fibrillation.[4] Approval for its use in stroke prevention and the treatment of VTE is also being sought in Europe.[4]

Patient Group

VTE, which is a common condition, consists of deep vein thrombosis (DVT) and its potentially fatal complication, pulmonary embolism (PE).[1] Proximal DVTs can recur, result in post-phlebitic symptoms and carry a higher risk of fatal PE than distal DVTs.[5] The risk factors for VTE include age, hospitalization, trauma and cancer.[1] After an acute proximal DVT, the risk of recurrence at three months is 50% in the absence of anticoagulation.[6] After major orthopedic surgery, patients are at a high risk of developing VTE.[7] Venography studies indicate that, without anticoagulation, about 50% of THR and TKR patients will develop a DVT.[8] With anticoagulation, early venographic DVT occurs in 10% to 20% of patients with subsequent confirmed clinical VTE in 1% to 2% of patients. Fatal PE occurs in 0.1% to 0.2% of patients.[7] Venography is a valid surrogate for symptomatic DVTs.[9]

Current Practice

Warfarin and low-molecular-weight heparin (LMWH) are standard components of drug therapy for the management of VTE.[7] The use of warfarin is associated with many drug interactions and the need for coagulation monitoring.[3] LMWH must be injected subcutaneously. After an episode of acute VTE, three months of warfarin therapy reduces the risk of recurrence to about 5%.[6] The use of oral (adjusted-dose) warfarin or subcutaneous LMWH for seven to 10 days reduces the prevalence of total DVT by 27% to 70% after major orthopedic surgery.[8]

Long-term secondary prevention with warfarin is usually reserved for patients with multiple episodes of VTE, hypercoagulability or cancer.[6]

The Evidence

The evidence used in the evaluation of ximelagatran consists of six trials for surgical VTE prevention, one trial for acute DVT treatment and one trial for the long-term secondary prevention of VTE.

Prevention of VTE Post-orthopedic Surgery
Comparison with LMWH: METHRO III[10] and EXPRESS[11] are similarly designed European clinical trials that enrolled patients undergoing THR or TKR. Participants were randomized to receive subcutaneous enoxaparin 40 mg daily (started 12 hours before surgery) or one dose of subcutaneous melagatran 3 mg after surgery, then oral ximelagatran 24 mg twice daily started the day after surgery. Participants in the EXPRESS trial also received subcutaneous melagatran 2 mg immediately before surgery.[11] Venography was performed after the treatment period of eight to 11 days. Overall, 81% to 82% of patients had evaluable venograms. In METHRO III, the only statistically significant difference was a lower rate of total VTE (proximal or distal DVT, PE or all-cause death) with enoxaparin in THR subjects (Table 1). In EXPRESS, ximelagatran significantly reduced the rate of total VTE and major VTE (proximal DVT, PE or all-cause death) when compared with enoxaparin in all groups (Table 1).

A double-dummy randomized controlled North American trial compared oral ximelagatran 24 mg twice daily to subcutaneous enoxaparin 30 mg twice daily in patients undergoing THR.[12] Treatment was started the morning after surgery and continued for seven to 12 days; 85% of the venograms were evaluable. Ximelagatran was associated with a higher rate

Table 1: Efficacy of Ximelagatran – Surgical VTE Prevention Trials

Trial (dose) (n)	Total VTE			Major VTE		
	Ximelagatran %	Control %	RD % (variance*)	Ximelagatran %	Control %	RD % (variance*)
Comparison with enoxaparin						
METHRO III[10] (24 mg bid)						
All (n=2,788)	31	27.3	3.7 (0.0, 7.4)	5.7	6.2	-0.5 (-2.5, 1.4)
THR (n=1,923)	25.4	19.4	6 (2, 10.1)	6.1	6.1	0 (-2.3, 2.4)
TKR (n=865)	44.1	46	-1.8 (-9.4, 5.7)	4.6	6.5	-1.9 (-5.4, 1.7)
EXPRESS[11] (24 mg bid)						
All (n=2,764)	20.3	26.6	-6.4 (-9.8, -2.9)	2.3	6.3	-4.0 (-5.6, -2.4)
THR (n=1,865)	12.9	18.2	-5.3 (-8.9, -1.7)	1.8	5.5	-3.7 (-5.6, -1.8)
TKR (n=908)	35.1	44.1	-9 (-16, -2.1)	3.3	8.2	-4.9 (-8.3, -1.5)
Colwell *et al.*[12] (24 mg bid)						
THR (n=1,838)	7.9	4.6	3.3 (0.9, 5.7)†	3.6	1.2	2.4 (0.9, 3.9)‡
Comparison with warfarin						
Francis *et al.*[13] (24 mg bid)						
TKR (n=680)	19.2	25.7	-6.5 (-13.5, 0.6)†	3.3	5	-1.8 (-5.2, 1.6)‡
EXULT A[14] TKR (n=2,301)						
(24 mg bid)	24.9	27.6	-2.7 (-7.6, 2.2)#	2.5	4.1	-1.7 (-3.7, 0.3)¥
(36 mg bid)	20.3	27.6	-7.3 (-12, -2.5)#	2.7	4.1	-1.4 (-3.5, 0.6)¥
EXULT B[15] (36 mg bid)						
TKR (n=2,303)	22.5	31.9	-9.4 (p<0.001)§	3.9	4.1	-0.2 (p=0.802)ß

Total VTE: proximal or distal DVT, PE or death; major VTE: proximal DVT, PE or death; THR=total hip replacement; TKR=total knee replacement; RD=risk difference; *95% confidence interval (CI) or p value where available; n=number of study participants; †DVT (proximal or distal) or PE; ‡proximal DVT or PE; #total VTE and/or death; §total VTE and/or death; ¥proximal VTE or death; ßproximal VTE and/or death.

of VTE compared with enoxaparin (Table 1). Differences in efficacy between the trials may be explained by differences in European and North American dosing strategies.[16]

Comparison with warfarin: Three North American trials[13-15] compared oral ximelagatran (24 mg or 36 mg twice daily) to warfarin [target international normalized ratio (INR) of 2.5] in patients undergoing TKR. Between 79% and 85% of study subjects had evaluable venograms. Ximelagatran 36 mg significantly reduced the rate of total VTE compared with warfarin[14,15] (Table 1). No significant difference was seen with ximelagatran 24 mg.[13,14] There was no between-group difference in rates of major VTE for either 24 mg or 36 mg regimens (Table 1).

Treatment of VTE

The results of a non-inferiority trial involving 2,489 patients with acute DVT, with or without PE, were presented in an abstract.[17] Oral ximelagatran 36 mg twice daily was compared to subcutaneous enoxaparin 1 mg/kg twice daily for >5 days followed by warfarin (target INR 2 to 3). Treatment continued for six months. There was no statistically significant difference between ximelagatran and enoxaparin-warfarin for the primary end point of VTE recurrence (2.1% versus 2%, RD: 0.2%; 95% CI: -1, 1.3).

Secondary Prevention of VTE

The THRIVE III trial evaluated ximelagatran for the secondary prevention of VTE in DVT-PE patients treated with anticoagulants for six months.[18] In this multicentre, double-blind trial, patients were randomized to oral ximelagatran 24 mg twice daily (n=612) or placebo (n=611) for 18 months. Ximelagatran significantly lowered the rate of symptomatic recurrent VTE compared with placebo (2.8% versus 12.6%; hazard ratio (HR): 0.16; 95% CI: 0.09, 0.3).

Adverse Effects

The overall rates of bleeding complications for ximelagatran and comparators were similar, except in the EXPRESS trial (Table 2). Ximelagatran was associated with >3 times the normal limit elevation of the liver enzyme alanine aminotransferase (ALT) in longer term (six to 18 months) VTE trials[17,18] (Table 2). Enzyme levels normalized in all but four of 612 patients in the ximelagatran group (two had known hepatitis).[18] The long-term use (six to 26 months) of ximelagatran was also associated with elevated ALT levels in stroke prevention[19,20] and post-myocardial infarction trials.[21]

Table 2: Safety of Ximelagatran

Trial	Major Bleeding		Any Bleeding (major or minor)		ALT Elevation >3 Times ULN	
	Ximelagatran %	Control %	Ximelagatran %	Control %	Ximelagatran %	Control %
METHRO III[10]	1.4*	1.7*	NR	NR	NR	NR
EXPRESS[11]	3.3*	1.2*	9.2**	7.0**	NR	NR
Colwell *et al.*[12]	0.8†	0.9†	6.1†	5.2†	0.7	5
Francis *et al.*[13]	1.7†	0.9†	9†	7†	NR	NR
EXULT A[14]	0.8 (24 mg) 0.8 (36 mg)	0.7	4.8 (24 mg) 5.3 (36 mg)	4.5	0.6 (24 mg) 0.8 (36 mg)	1.7
EXULT B[15]	1.0†	0.4†	5†	3.8†	NR	NR
THRIVE[17]	1.3†	2.2†	NR	NR	9.6	2
THRIVE III[18]	1.1‡	1.3‡	23.9∫	21∫	6.4¶	1.2¶

ALT=alanine aminotransferase; ULN=upper limit of normal; NR=not reported; *excessive bleeding as judged by the investigator[10] or adjudicate severe bleeding,[10,11] no p value; **other bleeding, no p value; †no statistically significant difference for ximelagatran-control comparison; ‡HR 1. (0.35, 3.8); ∫major, minor bleeding or both HR 1.19 (0.93, 1.53); ¶odds ratio 6.5 (2.7, 15.5).

Administration and Cost

Available studies show that the dosage of ximelagatran will likely be 24 mg or 36 mg twice daily, taken orally, depending on the indication. No cost information is available in Canada.

Concurrent Developments

Another oral direct thrombin inhibitor (BIBR-1048)[1] and an oral active factor Xa inhibitor are being evaluated in VTE prevention trials.[3]

Rate of Technology Diffusion

Given its simplicity of use, ximelagatran may replace, at least partly, the anticoagulants used in the management of VTE. Its use beyond VTE prevention and treatment may be anticipated, given that it has been evaluated in stroke prevention[19,20] and cardiac trials.[21]

Implementation Issues

The evidence indicates that the efficacy of ximelagatran in preventing VTEs after major orthopedic surgery is comparable to that of existing anticoagulants. Further testing of ximelagatran in the treatment of acute VTE and determination of its effect on fatal PE are needed. The bleeding risk associated with the use of ximelagatran is generally comparable to that of existing anticoagulants. Post-marketing surveillance with an emphasis on hepatic toxicity should occur in the early stages of clinical use, particularly for patients on long-term regimens. The cost of the drug is unknown, so no budget-impact or cost-effectiveness analysis can be done.

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