R E V I E W

Tirofiban: A Review of its Use in Patients with ST and Non ST Elevation Myocardial Infarction

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Abstract: Acute coronary syndrome is one of the major health problems worldwide and accounts for a great number of cardiac hospitalizations in the Western world. Atherosclerotic plaque rupture or erosion followed by platelet activation and total occlusion of a coronary artery is involved in the pathogenesis of acute coronary syndrome and myocardial infarction. The glycoprotein IIb/IIIa receptor, a platelet surface integrin, plays a key role in platelet aggregation once it has been activated. In order to improve myocardial tissue reperfusion, platelet inhibition with glycoprotein IIb/IIIa inhibitors (in combination with aspirin, clopidogrel, and heparin) has been shown as beneficial adjuvant therapy in patients with acute myocardial infarction. Tirofiban is a glycoprotein IIb/IIIa inhibitor. This article reviews the data concerning its use in patients with ST elevation myocardial infarction, the pharmacokinetic profile, contraindications, an adjuvant anticoagulation therapy and the surveillance.

Keywords: ST elevation myocardial infarction, glycoprotein IIb/IIIa receptor antagonists, pharmacotherapy, tirofiban

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Introduction

Acute coronary syndrome (ACS) is one of the major health problems worldwide and accounts for a great number of cardiac hospitalizations in the Western world.[1] It offers different clinical presentations, including silent ischemia, unstable angina, myocardial infarction (MI), and sudden cardiac death.[1] According to the guidelines and clinical criteria, ACS patients can be divided into two broad groups on the basis of admission electrocardiogram (ECG)—those with and without ST-segment elevation.[2] ST-elevation myocardial infarction (STEMI) results from coronary atherosclerotic plaque rupture or erosion[1] followed by total occlusion of an infarct related coronary artery.[3] Acute STEMI is associated with a worse short term prognosis and thus presents a particular challenge to emergency medicine physicians in respect of diagnosis and treatment.

Early and complete restoration of blood flow in infarct related coronary arteries after STEMI is associated with superior survival and clinical outcome.[4,5] Primary percutaneous coronary intervention (PCI) with stenting by providing high rate of early and adequate revascularization of the infarct related artery is the treatment of choice for patients with STEMI[6,7] and leads to improved clinical outcomes (short-term and long-term), if compared to fibrinolytic therapy.[6,8] Despite perfect recanalization of the epicardial artery, microvascular damage may occur[9] and is associated with an adverse prognosis, even if good epicardial flow has been restored. In conjunction with microvascular damage platelet activation and aggregation may lead to thrombotic complications during or after PCI.[10] Furthermore, insufficient inhibition of platelet aggregation at the time of PCI correlates with an increased probability of major adverse cardiovascular events (MACE) after the procedure.[11]

In order to improve myocardial tissue reperfusion and to reduce MACE, platelet inhibition[12] with glycoprotein (GP) IIb/IIIa inhibitors (in combination with aspirin, clopidogrel, a thienopyridine, and heparin) has been shown as beneficial adjuvant therapy in patients with acute myocardial infarction.[13,14] Tirofiban is a small molecule, non-peptide derivate, which belongs to the group of GP IIb/IIIa inhibitors and prevents the binding of fibrinogen and von Willebrand factor to the GP IIb/IIIa receptor on the surface of the platelets.[15,16]

Pharmacokinetic Profile

Tirofiban possesses a high specificity and affinity for the GP IIb/IIIa receptor.[16] It has a long plasma half-value period and short biological half-value period leading to a rapid recovery of platelet function approximately 4 hours after termination of the application (Table 1).[17,18] It binds to the peptide sequence arginine-glycine-aspartic acid on the gamma chain of the GP IIb/IIIa receptor. 35% of tirofiban are unbound in the circulation with predominant renal clearance (65%)—elimination of tirofiban from plasma via haemodialysis is also possible (Table 1).[19] Levothyroxine and omeprazole may lead to an enhancement of tirofiban clearance.[20] Dose adjustments have to be made in renal insufficiency while severe renal failure is a contraindication for its use.[20] No reduction of dosage is necessary in patients with hepatic failure or in elderly patients with ACS who are otherwise healthy.[21] Finally, storage of tirofiban seems to be easy, because vials could be kept at room temperature.[19]

Table 1. Overview and characteristics of tirofiban. (Modified after data in[19,21,52,53]).

	Tirofiban
Molecular weight (D)	495
Compound	Peptidomimetic nonpeptide
Receptor selectivity	
GP IIb/IIIa (α_{IIb}/β_3)	+++
GP IIb/IIIa (α_{IIb}/β_3)	+
GP IIb/IIIa (α_{IIM}/β_2)	0
Physiological binding site at GP IIb/IIIa	RGD-sequence
Stochiometry of binding	>250
Plasma half-life	1.8 hours
Platelet bound half-life	Seconds
Dose: loading dose	0.4 µg/kg → 30 min
infusion dose	0.1 µg/kg/min
Clearance	renal (60%–70%) biliar (20%–30%)
Renal failure	dose reduction necessary
Duration of infusion	12–48 hours
Antigenicity	None
Reversibility of effect	<4 hours
Reversibility with platelet transfusion	Yes
FDA approved	May 1998

Dose Administration

Different regimes of administration may be required subject to patient's diagnosis and the timing of PCI. In patients with non-STEMI when administered at least 4 hours prior to PCI, a regime with a bolus of 10 μg/kg over 3 minutes followed by an infusion of 0.15 μg/kg/min has been suggested in different studies.[22,23] Unfortunately, a higher incidence of MI after PCI (compared with abciximab) was seen in patients receiving the mentioned regime.[24] This finding was most likely the result of suboptimal platelet inhibition caused by short gap among tirofiban administration and PCI.[25] Suboptimal platelet inhibition could be overcome by a regime including a higher bolus dose of tirofiban (25 μg/kg) followed by an infusion of 0.15 μg/kg/min immediately prior to PCI.[26] The high dose bolus regime produces significantly higher levels of platelet inhibition and similar results in clinical outcome when compared to abciximab.[27]

Adjuvant Anticoagulation Therapy

Therapy with tirofiban should always be administrated in combination with aspirin, clopidogrel, a thienopyridine, and unfractionated heparin.[28] In patients treated with PCI, administration of clopidogrel leads to a benefit in preventing ischemic complication (compared to aspirin).[29] Additional prehospital initiation of high bolus tirofiban (bolus: 25 μg/kg; infusion: 0.15 μg/kg/min for 18 h) improved ST-segment resolution and clinical outcome in these patients, emphasizing that further platelet aggregation inhibition is useful in patients with STEMI undergoing PCI.[12]

The clinical benefit of GP IIb/IIIa inhibitors in combination with unfractionated heparin has been analysed in the PRISM-PLUS trial. During this study, the study arm testing tirofiban without unfractionated heparin was discontinued within 7 days, because of extended mortality rates. The combination of tirofiban and unfractionated heparin revealed a statistically significant reduction in death or MI when compared to unfractionated heparin alone (4.9% vs. 8.3%; $P = 0.006$).[23]

Adverse Effects

Suppression of platelet function is associated with an increased risk of minor or major bleeding.[30,31] Studies, analyzing the risk of bleeding after tirofiban administration showed, that the incidence of bleeding was more frequent when compared to patients treated with unfractionated heparin—the incidence of major bleeding complications was not significantly different in both groups.[22,23] When compared with abciximab, bleeding is overall numerically lower with high dose bolus tirofiban administration immediately prior to PCI (without statistical significance).[31,32] The risk of bleeding under tirofiban can be reduced by the use of low dose adjunctive heparin (instead of unfractionated heparin), early sheath removal, and meticulous post procedure care of the vascular access site.[33]

Thrombocytopenia is another side effect of tirofiban.[34] Time frame of developing thrombocytopenia is broad, and platelet count may start to decrease from two hours to several days after initiation of therapy.[19] Mild thrombocytopenia (platelet count > 100.000/mm^3) associated with tirofiban occurs in 1.1% to 1.9% of patients, while severe thrombocytopenia (platelet count < 100.000/mm^3) occurs in 0,2% to 0.5% of patients.[22,23,35] Different immune mediated mechanisms have been discussed as reason for severe thrombocytopenia. First, the GP IIb/IIIa inhibitor may act as antigen itself. Second, the GP IIb/IIIa inhibitor may cause a conformational change which may lead to direct binding by an antibody. Third, binding of GP IIb/IIIa inhibitor to the receptor may cause direct platelet activation and consumption.[36–38]

Surveillance

A specific surveillance is not necessary in patients receiving tirofiban therapy. Platelet count may be useful after initiating the therapy to detect thrombocytopenia.[39] Patients should be generally monitored for bleeding, especially patients with renal insufficiency. These patients are more likely to develop GP IIb/IIIa inhibitor overdose leading to elevated risk of bleeding complications.[40] Therefore, in patients with renal insufficiency (creatinin clearance < 30 ml/min) reducing the dose of tirofiban should be debated.[2,28]

Contraindications

The contraindications to use tirofiban are similar to those of thrombolytic agents and include sensitivity to any component of the product; active internal bleeding or bleeding diathesis within 30 days; known intracranial pathology including haemorrhage, vascular

malformation, aneurysm or neoplasm; cerebrovascular accident or hemorrhagic stroke within 30 days; uncontrolled hypertension; acute pericarditis; major surgery or trauma within 30 days; aortic dissection; and presumed or documented history of vasculitis. Caution is suggested in patients with known thrombocytopenia or hemorrhagic retinopathy.[19]

Clinical Studies and Place in Therapy

The routine administration of GP IIb/IIIa inhibitors is a class IIa indication in patients with acute STEMI according to the current guidelines.[41] Interestingly, a registry study showed that during daily routine only 25% to 30% of patients with STEMI receive GP IIb/IIIa inhibitors.[42] However, an optimal timing of reperfusion is essential to prevent extensive infracted areas and to improve left ventricular function.[43] Findings of several large observational studies advise that CP IIb/IIIa inhibitors can improve reperfusion and clinical outcome of patients with STEMI.[44,45] Table 2 gives an overview of randomized clinical trials of patients with STEMI and administration of tirofiban.

When compared to further GP IIb/IIIa inhibitors, a comparative clinical trial showed similar effects for tirofiban and abciximab with respect to improvement of left ventricular function and MACE after 30 days.[44] Furthermore, both agents could reduce mortality during 30 and 180 day follow-up without major bleeding complications.[45]

Some controversies regarding the perfect timing and dose for tirofiban therapy exists.[46,47] Ongoing Tirofiban In Myocardial infarction Evaluation trial 1 and 2 approved that early administration of tirofiban therapy leads to an improved rates of MACE or death.[12] Two further prospective, randomized studies showed that adjuvant tirofiban therapy in patients with STEMI undergoing PCI leads to an improvement in reperfusion and clinical outcome during follow-up.[48,49]

Meta-analysis of randomized trials comparing tirofiban vs. placebo or any anticoagulant revealed a reduction of mortality, the composite of death or MI and an increase in minor bleedings (in the case of tirofiban administration).[31] An early ischemic hazard disfavouring tirofiban was noted when tirofiban administration was compared to abciximab in studies based on 10 but not 25 µg/kg bolus regimen.[31]

Table 2. Overview of randomized clinical trials of patients with STEMI and administration of tirofiban.

Study	Study period	Number of patients	Tirofiban dose	Concomitant anti-thrombotics	Endpoint	Follow-up
RESTORE[35]	1995	2212	bolus: 10 µg/kg; infusion: 15 µg/kg/min	aspirin, unfractionated heparin	death, MI, target vessel revascularization	6 months
TETAMI[54]	1999–2002	1224	bolus: 10 µg/kg; infusion: 15 µg/kg/min	aspirin, enoxaparin or unfractionated heparin	death, MI, recurrent angina	30 days
SASTRE[55]	2000–2002	144	bolus: 0.4 µg/kg/min × 30 min; infusion: 15 µg/kg/min	aspirin, unfractionated heparin, alteplase	TIMI flow grade 3	30 days
Ernst et al[27]	2002–2003	60	bolus: 10 µg/kg; infusion: 15 µg/kg/min	aspirin, unfractionated heparin, clopidogrel	platelet aggregation inhibition	hospital stay
On-Time 2 (open-label study)[12]	2004–2006	414	bolus: 25 µg/kg; infusion: 15 µg/kg/min	aspirin, unfractionated heparin, clopidogrel	None	30 days
Shen et al[48]	2005–2006	115	bolus: 10 µg/kg; infusion: 15 µg/kg/min	aspirin, unfractionated heparin, clopidogrel	MACE at 30 days	6 months
Fu et al[49]	2005–2007	150	bolus: 10 µg/kg; infusion: 15 µg/kg/min	aspirin, unfractionated heparin, clopidogrel	not reported	30 days
On-Time 2[12]	2006–2007	984	bolus: 25 µg/kg; infusion: 15 µg/kg/min	aspirin, unfractionated heparin, clopidogrel	ST-segment deviation at ECG	30 days

Candidates for Tirofiban Therapy

According to the updated guidelines of the American College of Cardiology and the American Heart Association 2004, the use of GP IIb/IIIa inhibitors is a class IIa recommendation.[41] Therefore, the vast majority of patients with STEMI and primary PCI should receive a therapy with GP IIb/IIIa inhibitors.[28] Especially, patients who receive early administration of tirofiban revealed a significantly greater benefit in accordance with post procedural myocardial perfusion.[12]

A small group of patients may not benefit from tirofiban therapy including patients with high risk of bleeding or those who are presented later than six hours after onset of symptoms.[50,51] This is consistent with cognition that across 4 to 5 hours from the onset of symptoms, little myocardium is left to be saved.[28]

Conclusion

Tirofiban administration in combination with aspirin, clopidogrel and unfractionated heparin reduces the mortality, the composition of MI along with MACE and death. The reduction of MACE rate is significant in all available studies testing a combination therapy with tirofiban vs. placebo. An early ischemic hazard was found when compared to abciximab in trials with a 10 µg/kg bolus regime but not in trials with a 25 µg/kg bolus regime. Safety profile of tirofiban revealed a lower incidence of minor bleeding and thrombocytopenia, most likely due to a different chemical structure than to different anti platelet potency.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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