Summary


The glycoprotein (GP) IIb/IIIa receptor is a platelet-specific adhesion receptor, which is the final pathway of platelet aggregation. It is blocked by abciximab, a chimeric (murine-human) Fab fragment of a monoclonal antibody. Animal studies have shown that GP IIb/IIIa antagonists improve blood flow in the cerebral microcirculation. Angiographic studies performed in patients with acute myocardial infarction have demonstrated that abciximab on top of aspirin and adjusted-dose heparin reopens about 40–50% of thrombosed coronaries to Thrombolysis in Myocardial Infarction (TIMI) flow grades II or III. Systemic abciximab was studied in a prospective, placebo-controlled, randomised, dose escalation safety and pilot efficacy trial, which was performed in 74 patients with acute ischaemic stroke who were treated within 24 hours after symptoms onset. Patients of the active group suffered no symptomatic intracranial haemorrhage and showed a trend to have more often a minimal disability. In the “Abciximab in Emergent Stroke Treatment Trial”, a randomised, double-blind study, 400 patients with acute ischaemic stroke were treated within the 6-hour time window with systemic abciximab or placebo. The unpublished study data suggest that abciximab may improve the clinical outcome also in patients with acute ischaemic stroke who were treated within the 3–6-hour time window and that it has an acceptable safety. A case report and a small series have reported that systemic abciximab successfully revascularised reocclusion occurring during or immediately after successful thrombolysis of the middle cerebral artery, intracranial vertebral or basilar arteries. Ongoing and planned trials investigate the safety and efficacy of systemic abciximab in acute ischaemic stroke within the 6-hour time window, in wake-up stroke and in carotid artery disease, or its combination with systemic or local intraarterial fibrinolysis. New strategies such as combining systemic GP IIb/IIIa inhibitors with fibrinolysis might improve the insufficient recanalisation rates of systemic fibrinolysis or avoid the need for local intraarterial fibrinolysis.

Keywords: abciximab; cerebrovascular disease; GP IIb/IIIa; platelet inhibitors; stroke; thrombolysis

Introduction

The National Institute of Neurological Disorders and Stroke (NINDS) study has shown that in selected patients with acute ischaemic stroke systemic administration of recombinant tissue plasminogen activator (rt-PA) within 3 hours of symptom onset is beneficial [1]. Subsequently, systemic rt-PA became the first and is still the only approved therapy for acute ischaemic stroke. The most important limitation of systemic fibrinolysis with rt-PA is the short therapeutic time window, which is the main cause that only a few per cent of stroke patients undergo this therapy [2, 3]. A small-scale, placebo-controlled study has demonstrated that local intraarterial fibrinolysis (LIF) with prourokinase administered with the 6-hour time window is beneficial for patients with symptomatic middle cerebral artery (MCA) occlusion [4]. Local intraarterial fibrinolysis requires the presence of a team of interventional neuroradiologists, which is available for 24 hours. Because only a few academic centres have such teams, drugs that can be administered systemically and are effective in the 3–6-hour time window are preferable. The glycoprotein (GP) IIb/IIIa receptor antagonist abciximab might be such an agent because the unpub-
lished data of the Abciximab in Emergent Stroke Treatment Trial (AbESTT) suggest that this drug might be safe and efficient in patients with ischaemic stroke treated within the 6-hour time window [5, 6].

This review reports pharmacological aspects of the platelet GP IIb/IIIa receptor and abciximab, gives a short overview of the role of abciximab in cardiology and summarises studies done with this agent in patients with acute ischaemic stroke.

Pharmacology of the platelet GP IIb/IIIa receptor

The GP IIb/IIIa receptor, the αIIb/β3 integrin, is a platelet-specific adhesion receptor with broad specificity for some ligands, e.g. fibrinogen and the von Willebrand factor (vWF). Platelet agonists (thrombin, collagen, platelet activating factor, epinephrine, vasopressin, etc.) change the conformation of the GP IIb/IIIa receptor by the stimulation of intracellular signalling pathways (inside-out signalling). This conformation change transforms the GP IIb/IIIa receptor from a low- into a high-affinity state. Thus, ligands can be bound and platelet aggregates are formed. In addition, receptor clusters are expressed, and the platelet cytoskeleton is activated and contracts (outside-in signalling) [7].

Pharmacology of abciximab

Abciximab is the chimeric (murine-human) Fab fragment of a monoclonal antibody, which blocks the GP IIb/IIIa receptor. Because this receptor is the final pathway of platelet aggregation, abciximab and other GP IIb/IIIa inhibitors (e.g. eptifibatide and tirofiban) are more efficacious than the conventional antiplatelet agents aspirin and the thienopyridines ticlopidine or clopidogrel. The latter drugs inhibit specific amplification loops of platelet activation, the thromboxane A2- or ADP-induced signalling pathways, eventually resulting in a smaller number of activated GP IIb/IIIa receptors. Thus, conventional antiplatelet agents are most efficient if the inhibited pathways become critical in platelet-dependent thrombus formation. However, aspirin and thienopyridines can be bypassed by other platelet agonists.

The binding site of abciximab is located at the β-chain of the GP IIb/IIIa receptor [8]. The antibody fragment causes a steric barrier for the access of ligands to their binding pocket. This also explains its effectiveness for inhibition of the vitronectin receptor at the surface of the vascular endothelium and smooth muscle. Abciximab also interacts with the activated Mac-1 receptor on leukocytes [9]. In opposite to natural protein ligands, abciximab binds at comparable affinity to both resting and activated platelet receptors.

An occupation of at least 80% of the receptors appears to be necessary for a clinically relevant inhibition of platelet-dependent thrombus formation. After bolus injection, 50% of the drug is bound to platelets within the first 10 minutes. The half-life of abciximab dissociation from the GP IIb/IIIa receptor lasts up to 4 hours and does not correlate with the rather short half-life in plasma, due to rapid degradation by proteolysis. Abciximab also redistributes from platelet to platelet or vascular cells carrying the vitronectin receptor [10]. An estimated 29% and 13% of GP IIb/IIIa receptors are still occupied by abciximab at 8 and 15 days after completion of infusion [11].

The estimated number of GP IIb/IIIa receptors per platelet is 50,000–100,000. In the resting platelet about 50–60% of them are located at the surface. The other receptors are in the platelet and can travel to the surface after platelet stimulation [12, 13]. In addition, a part of the secreted GP IIb/IIIa complexes already contain bound fibrinogen from the platelet α-granules, which is only partially blocked by abciximab [14, 15]. This may result in the expression of unblocked GP IIb/IIIa receptors at the platelet surface [16]. Thus, the consistency of inhibition during infusion of abciximab may become less uniform [11, 17]. The effect of abciximab is antagonised by the administration of platelets. If rapid antagonisation is needed, fibrinogen and fresh frozen plasma alone are given [18].

Abciximab in cardiology

Controlled percutaneous coronary intervention (PCI) trials in patients with ischaemic heart disease have shown that the periprocedural administration of systemic abciximab on the top of aspirin and adjusted-dose heparin reduced the rates of thrombotic complications, particularly myocardial infarction, and death within 30 days [19–22]. Symptomatic intracranial haemorrhage (ICH) occurred in 0.0–0.1% of 2535 patients [21, 22]. During percutaneous coronary intervention the vessel wall is disrupted or dissected, which leads to exposure of plaque contents and other wall components to the blood, resulting in platelet activation and thrombosis [19–22]. The presumed mechanisms of action of abciximab are the prevention of platelet accumulation at the site of balloon injury, decreased
platelet aggregation in the microcirculation and perhaps improvement in coronary blood flow by blocking the release of vasoactive amines from activated platelets [23].

Until now only three systemic GP IIb/IIIa antagonists, abciximab, eptifibatide and tirofiban, have been approved by the FDA for cardiologic indications.

**Abciximab in acute ischaemic stroke**

**Rationale for abciximab**

Animal studies have shown that GP IIb/IIIa antagonists may improve blood flow in the cerebral microcirculation [24, 25]. Abciximab might also reduce inflammation, and thus thrombosis and oedema through its reactivity with the Mac-1 integrin [26].

Angiographic studies in patients with acute myocardial infarction have demonstrated that abciximab in addition to aspirin and adjusted-dose heparin reopens about 40–50% of thrombosed coronaries to Thrombolysis in Myocardial Infarction (TIMI) flow grades II or III [27, 28]. The mechanism of revascularisation is unknown.

**The Abciximab Study**

This prospective, placebo-controlled, randomised, dose-escalation safety and pilot efficacy trial [29] was performed in 74 patients with acute ischaemic stroke who were treated within 24 hours after symptoms onset. Patients of the active group suffered no symptomatic intracranial haemorrhage and showed a trend to have more often a minimal disability. The optimal abciximab dose turned out to be a bolus (0.25 mg/kg) followed by a 12-hour infusion of 0.125 μg/kg/min, no heparin or aspirin were administered.

**AbESTT**

In AbESTT [5, 6], a randomised, double-blind study, 400 patients with acute ischaemic stroke were treated within the 6-hours time window with the abciximab dose mentioned above or placebo. The unpublished study data suggest that abciximab may improve the clinical outcome in patients with acute ischaemic stroke who were also treated within the 3–6-hour time window and that this GP IIb/IIIa antagonist has an acceptable safety.

Therapy of reocclusion following successful thrombolysis

A case report and a small series have reported that systemic abciximab successfully revascularised reocclusion occurring during or immediately after successful thrombolysis of the middle cerebral artery, intracranial vertebral or basilar arteries [30, 31].

**Ongoing and planned studies**

The ongoing FAST study evaluates whether the combination of local intraarterial fibrinolysis with rt-PA and systemic abciximab compared to local intraarterial fibrinolysis alone speeds up recanalisation of symptomatic MCA occlusion [32].

Based on the results of AbESTT, a follow-up study (AbESTT II) study will investigate the benefit of abciximab in another 1800 patients with ischaemic stroke. The inclusion and exclusion criteria are similar compared to AbESTT with the exception that also patients with wake-up strokes of three hours’ duration will be included.

The ongoing “ReoPro Retavase Reperfusion of Stroke Safety Study – Imaging Evaluation” (ROSIE) is an open-label, dose escalation, safety and proof-of-principle study of the combination of systemic abciximab and reteplase in the treatment of acute ischaemic stroke with proven perfusion defects [33]. The goal of this clinical investigation is to determine the acceptable dose of reteplase in combination with a fixed dose of abciximab for the therapy of ischaemic stroke within the 3–24-hour window. The study will include one MRI and one CT arm [33].

A small scale, placebo-controlled, double-blind MR study will investigate the benefit of abciximab in about 50 patients who woke up with stroke in the 3–6-hour time window and show a region-at-risk defined by diffusion and perfusion-weighted MR imaging.

Endarterectomy is beneficial for stroke prevention in patients with symptomatic severe or moderate carotid stenosis [34, 35], but the risk of a recurrent stroke while waiting 4 to 6 weeks for carotid surgery was 4.9–9.5% in prospective studies [36, 37]. Abciximab is assumed to reduce the amount of carotid thrombosis and to stabilise the carotid plaque, which may thus reduce (1) the risk of platelet-rich carotid thromboembolism [38] and recurrent stroke, and (2) the progression of carotid stenosis to occlusion. A prospective, randomised, double-blind, double dummy controlled multi-centre pilot study (ASTERICS) will investigate...
whether abciximab compared with aspirin is able to reduce the rate of recurrent ischaemic strokes before and during carotid endarterectomy, the degree of carotid stenosis, the number of MES counts and the amount of intraluminal thrombus at pathological examination in patients with ischaemic stroke due to a >70% carotid stenosis that will be treated by endarterectomy.

**Future**

Systemic fibrinolysis does not revascularise occluded basal cerebral arteries in more than 70% of patients with ischaemic stroke [39]. Thus, new strategies such as adding GP IIb/IIIa inhibitors to the fibrinolytics might prove useful [27, 40]. The GUSTO V trial compared rt-PA with a combination of half-dose rt-PA and abciximab [41, 42]. The combination reduced the rate of myocardial re-infarcts significantly, whereas mortality after 30 days and 1 year was not significantly affected [41, 42]. Preliminary data in patients with ischaemic stroke suggest that systemic fibrinolysis with rt-PA followed by systemic thrombolysis with GP IIb/IIIa inhibitors may also be safe and more effective than systemic rt-PA alone [43, 44]. The treatment strategy of adding GP IIb/IIIa inhibitors to systemic fibrinolysis is based on the assumption that (1) during systemic fibrinolysis platelet activators are set free leading to subsequent de novo thrombus formation, (2) fibrinolytics activate platelet aggregation and (3) atherosclerotic thrombo-emboli are platelet rich [38, 45, 46].

**References**


22 The EPISTENT Investigators. Randomised placebo-con-
trolled and balloon-angioplasty-controlled trial to assess
safety of coronary stenting with use of platelet glycopro-

23 Bogousslavsky J, Leclerc JR. Platelet glycoprotein IIb/IIIa
antagonists for acute ischemic stroke.

24 Choudhri TF, Hoh BL, Zerwes HG, Prestigiacomo CJ,
Kim SC, Connolly ESJ, et al. Reduced microvascular
thrombosis and improved outcome in acute murine stroke
by inhibiting GP IIb/IIIa receptor-mediated platelet

25 Kaku S, Umemura K, Mizuno A, Yano S, Suzuki K,
Kawasaki T, et al. Evaluation of a GP IIb/IIIa antagonist
YM337 in a primate model of middle cerebral artery

26 Altieri D, Edgington TS. A monoclonal antibody reacting
with distinct adhesion molecules defines a transition
in the functional state of the receptor CD11b/CD18

27 Antman EM, Giugliano RP, Gibson CM, McCabe CH,
Coussement P, Kleiman NS, et al. Abciximab facilitates
the rate and extent of thrombolysis: results of the
Thrombolysis in Myocardial Infarction (TIMI) 14 Trial.

28 van den Merkhof LF, Zijlstra F, Olsson H, Grip L, Veen G,
Antman EM, Giugliano RP, Gibson CM, McCabe CH,
Altieri D, Edgington TS. A monoclonal antibody reacting
with distinct adhesion molecules defines a transition
in the functional state of the receptor CD11b/CD18

29 The Abciximab in Ischemic Stroke Investigators.
Abciximab in acute ischemic stroke. A randomised,
double-blind, placebo-controlled, dose-escalation study.

30 Heo JH, Lee KY, Kim SH, Kim DI. Immediate reocclusion
following a successful thrombolysis in acute stroke:

31 Wallace RC, Furlan AJ, Molterno DJ, Stevens GHU,
Masaryk TJ, Perl JI. Basilar artery rethrombosis: suc-
cessful treatment with platelet glycoprotein IIb/IIIa

32 Eckert B, Kucinski T, Wittkugel O, Roether J, Solymosi L,
Gödicke J, et al. Kombination einer intraarteriellen rt-PA
plus intravenösen Abciximab-Therapie bei akuten throm-
boembolischen Verschlusßen der Arteria cerebi media.

33 Warach S, Davis L, for the ROSIE Study Group. ReoPro
Retavase Reperfusion of Stroke Safety Study – Imaging
Evaluation (ROSIIE) [oral presentation]. Phoenix, Arizona:

34 Barnett HJM, Taylor DW, Eliaszw M, Fox AJ, Ferguson
GG, Haynes BR, et al., for the North American Sympto-
matic Carotid Endarterectomy Trial Collaborators. Benefit
of carotid endarterectomy in patients with symptomatic
moderate or severe stenosis.

35 European Carotid Surgery Trialists' Collaborative Group.
Randomised trial of endarterectomy for recently sympto-
matic carotid stenosis: final results of the MRC European

36 Dosick SM, Whalen RC, Gale SS, Brown OW. Carotid
endarterectomy in the stroke patient: computerised axial
tomography to determine timing.

37 North American Symptomatic Carotid Endarterectomy
Trial Collaborators. Beneficial effect of carotid end-
arterectomy in symptomatic patients with high-grade

38 Libby P. Molecular bases of the acute coronary syn-

39 Del Zoppo GJ, Poeck K, Pessin MS, Wolpert SM, Furlan
activator in acute thrombotic and embolic stroke.

40 The SPEED Investigators. Trial of abciximab with and
without low-dose reteplase for acute myocardial infarc-

41 The GUSTO V Investigators. Reperfusion therapy for
acute myocardial infarction with fibrinolytic therapy or
combination reduced fibrinolytic therapy and platelet
glycoprotein IIb/IIIa inhibition: the GUSTO V randomised

42 Lincoff AM, Califf RM, Van De Werf F, Willerson JT, White
HD, Armstrong PW, et al.; Global Use of Strategies To
Open Coronary Arteries Investigators (GUSTO). Mortality
at 1 year with combination platelet glycoprotein IIb/IIIa
inhibition and reduced-dose fibrinolytic therapy vs
conventional fibrinolytic therapy for acute myocardial
infarction: GUSTO V randomised trial.

43 Junghans U, Seitz RJ, Wittsack HJ, Aulich A, Siebler M.
Treatment of acute basilar artery thrombosis with a
combination of systemic alteplase and tirofiban, a non-
peptide platelet glycoprotein IIb/IIIa inhibitor: report

44 Seitz RJ, Hamzavi M, Junghans U, Ringleba PA, Schranz C,
Siebler M. Thrombolysis with recombinant tissue plas-
inogen activator in acute thrombotic and embolic stroke.

45 Moser M, Nordt T, Peter K, Ruffe J, Kohler B, Schmittner
M, et al. Platelet function during and after thrombolytic
therapy for acute myocardial infarction or primary percu-
taneous transluminal coronary angioplasty. Results of the
Glycoprotein Receptor Antagonist Patency Evaluation (GRAPE)

46 Callahan KP, Malinin AI, Gurbel PA, Alexander JH,
Haynes BR, et al., for the North American Symptom-
atic Carotid Endarterectomy Trial Collaborators. Benefit
of carotid endarterectomy in patients with symptomatic
moderate or severe stenosis.