Improving antiplatelet therapy for atherothrombotic disease

Preclinical and clinical results with SCH 530348, the first oral thrombin receptor antagonist selective for PAR-1

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Keywords
Atherothrombosis, antiplatelet therapy, PAR-1, SCH 530348, thrombin receptor antagonist

Summary
Morbidity and mortality in patients with atherothrombotic disease remain high despite the use of antiplatelet therapy with aspirin and an ADP receptor antagonist. Selective inhibition of the principal protease-activated receptor (PAR)-1 for thrombin, the most potent agonist for platelet activation, represents a promising novel strategy to reduce thrombosis and ischaemic events. SCH 530348, a potent thrombin receptor antagonist (TRA) selective for PAR-1, has been evaluated in preclinical studies, demonstrating complete and sustained inhibition of thrombin/TRAP-induced platelet aggregation without a concomitant increase in the risk of bleeding. Phase 2 studies in patients undergoing non-urgent or urgent PCI showed that treatment with SCH 530348 in addition to the standard of care (aspirin plus an ADP receptor antagonist) is not associated with an increased risk of TIMI bleeding and is well tolerated, with a rate of adverse events comparable to standard therapy alone. These studies also demonstrated that the use of SCH 530348 in combination with aspirin and an ADP receptor antagonist may reduce the incidence of major adverse cardiac events, specifically periprocedural myocardial infarction, vs aspirin plus an ADP receptor antagonist alone. On the basis of these encouraging results, 2 ongoing large phase 3 randomized trials are evaluating the efficacy and safety of SCH 530348 in combination with the standard-of-care therapy in ~35 000 patients with NSTE ACS or established atherosclerosis.

Schlüsselwörter
Arteriosklerose, anti-platelet Therapie, PAR-1, SCH 530348, Thrombinrezeptor-Antagonist

Zusammenfassung

Clinical manifestations of atherothrombotic disease, including ACS, ischaemic stroke, and peripheral artery disease, are the leading cause of morbidity and mortality in Europe (1) and the United States (2). Platelets have a central role in the aetiopathogenesis of atherothrombotic disease and in normal haemostasis, as revealed by the benefits and bleeding risks associated with current antiplatelet agents (3). Multiple agonists, including thrombin, thromboxane A2, and ADP, may lead to platelet activation (3, 4), which is critical for thrombosis as well as for haemostasis.

The current standard of care in antiplatelet therapy for atherothrombotic disease includes aspirin and a P2Y12 ADP receptor antagonist (such as ticlopidine, clopidogrel or
prasugrel), which inhibit the thromboxane A2 and P2Y12 ADP platelet activation pathways, respectively. Despite the proven benefits of aspirin and P2Y12 ADP receptor antagonists, the residual risk of thrombotic/ischaemic events remains high (5–8), and the risk of bleeding is increased (7, 9). For example, in the recently published TRITON-TIMI 38 trial in patients with ACS undergoing PCI, the combination of aspirin and prasugrel significantly reduced the composite ischaemic end point (death, MI, or stroke) vs. aspirin plus clopidogrel by ~20%, but the composite ischaemic end point rate remained high (10%) (7). Furthermore, the rate of TIMI major bleeding in the aspirin plus prasugrel arm was ~30% higher than in the aspirin plus clopidogrel arm (2.4% vs 1.8%, respectively; p = 0.03) (7).

These findings underscore the need for novel antiplatelet agents that can reduce the residual risk for ischaemic/thrombotic events, ideally without increasing the risk for bleeding.

**Development of SCH 530348**

Thrombin is one of the most potent platelet activators, as only sub-nanomolar concentrations of thrombin are needed to activate the human platelets through the PAR-1 receptor (Fig. 1) (10, 11). PAR-4 is a secondary receptor for thrombin that is activated at higher thrombin concentrations (3, 12). Hence, the addition of a thrombin receptor antagonist selective for PAR-1 to aspirin and a P2Y12 ADP receptor antagonist may provide incremental antithrombotic effects and reduction in ischaemic events.

**Candidate PAR-1 antagonists for clinical development**

Unlike species such as mice, rats, guinea pigs and dogs, non-human primates express PAR-1 on platelets and are thus suitable for the identification of candidate PAR-1 antagonists intended for human use (18). Studies in baboons and cynomolgus monkeys with PAR-1 inhibitors SCH 205831 and SCH 602539, analogs of SCH 530348, confirmed the value of these animal models in the development of novel thrombin receptor antagonists (19, 20). One of these studies used the Folts model of thrombosis in cynomolgus monkeys to document a clear antithrombotic effect of PAR-1 inhibition alone, as well as the synergistic antithrombotic effects of combined inhibition of the PAR-1 and P2Y12 ADP platelet activation pathways with SCH 602539 and cangrelor, respectively (20).

Following failure to progress with two earlier TRA candidates, the PAR-1 antagonist selected for further clinical development was SCH 530348. Oral administration of this compound at doses ≥0.1 mg/kg body weight was shown to provide 100% inhibition of TRAP-induced platelet aggregation in cynomolgus monkeys for 24 hours (21). Of note, treatment of cynomolgus monkeys with SCH 530348, either alone or in combination with aspirin plus clopidogrel, did not increase surgical blood loss or bleeding times vs placebo and aspirin plus clopidogrel, respectively (22). In this study, SCH 530348 did not affect platelet aggregation induced by ADP, thromboxane A2 mimetic U46619 and collagen, nor did it affect the coagulation parameters (i.e. activated clotting time), demonstrating selective inhibition of PAR-1 (22). The selectivity of SCH 530348 was also validated in ex vivo studies that used human platelet-rich plasma, which showed that SCH 530348 inhibits thrombin-induced and TRAP-induced platelet aggregation but does not interfere with the aggregation induced by ADP, thromboxane A2 mimetic U46619, and collagen, or the coagulation parameters (i.e. prothrombin time and activated partial thromboplastin time) (21). In addition, SCH 530348 demonstrated excellent oral bioavailability (86%) in monkeys (21).

**Clinical experience with SCH 530348**

**Phase 1 studies**

Phase 1 studies sought to evaluate the safety, pharmacokinetics and pharmacodynamics of SCH 530348. These studies demonstrated that SCH 530348 was safe and well tolerated in healthy Caucasian and Japanese volunteers (23, 24). Following the administration of either single or multiple doses, the pharmacokinetic profile of SCH 530348 was characterized by rapid absorption and distribution, and peak plasma levels were usually reached within 60–90 minutes at all doses (25). After administration of both the single
and multiple doses, the exposure to SCH 530348 was dose-related with low variability of exposure, whereas the elimination was gradual (24, 25). Following the administration of multiple doses, steady-state plasma concentrations of SCH 530348 were attained by day 21 (24, 25). Single and multiple doses of SCH 530348 provided rapid, dose-related and durable inhibition of TRAP-induced platelet aggregation, with gradual recovery of platelet function following treatment discontinuation (26). Importantly, even at the highest dose (40 mg), SCH 530348 exhibited no significant inhibitory effect on platelet aggregation induced by ADP, confirming the selectivity for PAR-1 (26).

In both Caucasian and Japanese subjects, complete inhibition (≥80%) of TRAP-induced platelet aggregation was achieved most rapidly and most consistently with the 40-mg single dose of SCH 530348 (24). Among the three once-daily regimens tested without a prior loading dose (0.5, 1 and 2.5 mg), only the 2.5-mg once-daily regimen consistently showed high levels of complete inhibition of TRAP-induced platelet aggregation at seven days and later time points in both Caucasian and Japanese subjects (24).

**Phase 2 studies, TRA-PCI trial**

**Safety and efficacy in patients undergoing non-urgent PCI**

The multicentre, randomized, double-blind, placebo-controlled TRA-PCI study was designed to assess the safety and tolerability of treatment with SCH 530348 when used in combination with the standard-of-care therapy in patients scheduled to undergo non-urgent PCI (27). Patients ≥45 years of age scheduled to undergo non-urgent PCI and receiving antithrombotic therapy per local standards (e. g. aspirin, a loading dose of clopidogrel and an anticoagulant) were randomized 3:1 to receive either a loading dose of SCH 530348 (10, 20 or 40 mg) or placebo; in patients who underwent PCI (the primary cohort), those who received a loading dose of SCH 530348 were randomly assigned to receive a maintenance dose of SCH 530348 in a 1:1:1:1 fashion (0.5, 1.0 or 2.5 mg once daily for 60 days), whereas those who received the placebo loading dose continued to receive placebo during the maintenance phase (27). These patients were encouraged to continue taking daily aspirin and clopidogrel. Patients who did not undergo PCI constituted the secondary (non-PCI) cohort and were managed either medically or with CABG surgery and did not receive any additional study drug therapy (27).

The primary end point of the study was the incidence of TIMI major or minor bleeding during treatment in the primary PCI cohort (27). The secondary end points included the individual components and the composites of CV death, non-fatal MI, and stroke (27).

TRA-PCI randomized a total of 1030 patients, of which 573 subsequently underwent PCI as planned (primary PCI cohort), whereas the remaining 457 patients (secondary cohort) either underwent CABG surgery (n = 76) or were managed medically (n = 381) (27). In the primary PCI cohort, virtually all patients (≥97%) received aspirin and clopidogrel, and a vast majority (≥90%) received either heparin or bivalirudin (27). Oral administration of SCH 530348 in combination with standard therapy was not associated with increased rates of TIMI major or minor bleeding compared with standard therapy alone in the primary PCI cohort (27).

Importantly, none of the patients treated with the combination of the highest loading and maintenance doses of SCH 530348 (40-mg loading dose plus 2.5-mg maintenance dose) experienced TIMI major bleeding (27). The rate of discontinuations due to non-TIMI bleeding in the primary cohort were similar in the combined SCH 530348 and placebo arms (1.4% and 1.3%, respectively) (27). A favourable safety profile of SCH 530348 was also supported by the safety outcomes in patients who underwent CABG surgery, which were generally comparable between the SCH 530348 and the placebo groups (27). Additionally, no clear dose-response relationship for postoperative bleeding was evident in surgical patients (27).

Although the TRA-PCI trial was primarily designed to evaluate safety and was not specifically powered to demonstrate efficacy, treatment with SCH 530348 in combination with standard therapy was associated with a dose-related trend toward a lower rate of MACE, specifically MI, when compared with standard therapy plus placebo (27). The dose-related reduction in ischaemic events paralleled the antithrombotic activity, with the highest 40-mg loading dose of SCH 530348 most consistently providing the com-
(≥80%) inhibition of TRAP-induced platelet aggregation (Fig. 2). A complete inhibition of TRAP-induced platelet aggregation with a 40-mg loading dose of SCH 530348 was evident after 90 minutes in over 80% of patients (Fig. 2) and it was subsequently sustained through day 60 with the 1.0- and 2.5-mg maintenance doses (27). As described previously, a separate pharmacodynamic study demonstrated that the 2.5 mg once-daily dose consistently provided complete inhibition of TRAP-induced platelet aggregation during maintenance therapy, whereas the 1.0 mg once-daily maintenance regimen (when administered without the loading dose) achieved only partial inhibition in most patients (24). Notably, whereas SCH 530348 potently inhibited TRAP-induced platelet aggregation, it did not interfere with platelet aggregation induced by ADP, collagen or arachidonic acid (28), confirming the selectivity of SCH 530348 for PAR-1.

Collectively, the results of the TRA-PCI trial indicate that SCH 530348, administered in combination with standard therapy does not increase the risk of haemorrhage and may reduce the rate of ischaemic events.

The safety and efficacy of SCH 530348 are currently being investigated further in two large ongoing phase 3 trials.

**Safety and efficacy in Japanese patients with ACS undergoing PCI**

In addition to the TRA-PCI trial, a separate phase 2 study evaluated the safety and efficacy of SCH 530348 in combination with the standard of care in Japanese patients with NSTE ACS scheduled for PCI (29). In this study, a total of 117 Japanese patients with NSTE ACS scheduled to undergo PCI and receiving standard therapy (e.g. aspirin, the P2Y12 ADP receptor antagonist ticlopidine and heparin) were randomized 4:1 to receive either SCH 530348 (either 20- or 40-mg loading dose, followed by a 1.0- or a 2.5-mg once-daily maintenance dose for 60 days) or placebo (29). The predefined key safety end point was the combined incidence of TIMI major and minor bleeding (29). The predefined secondary efficacy end points included the individual components and the composites of death, MI, stroke, recurrent ischaemia with hospitalization and urgent coronary revascularization during the 60-day treatment period (29).

Of the 117 patients 92 underwent PCI and constituted the primary PCI cohort, whereas the remaining 25 patients who underwent CAGB surgery and 22 patients who were managed medically (29). In the primary PCI cohort, the addition of

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**Table 2**

Safety outcomes in patients who underwent coronary artery bypass surgery in the phase 2 TRA-PCI trial (27)

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 24)</th>
<th>SCH 530348 all doses (n = 52)</th>
<th>SCH 530348 loading dose (n = 10)</th>
<th>SCH 530348 loading dose (n = 18)</th>
<th>SCH 530348 loading dose (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI bleeding n (%)</td>
<td>Major/minor</td>
<td>Major</td>
<td>Minor</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19 (79)</td>
<td>47 (90)</td>
<td>9 (90)</td>
<td>17 (94)</td>
<td>21 (88%)</td>
</tr>
<tr>
<td></td>
<td>(n = 24)</td>
<td>(n = 52)</td>
<td>(n = 10)</td>
<td>(n = 18)</td>
<td>(n = 24)</td>
</tr>
<tr>
<td>non-TIMI bleeding n (%)</td>
<td>8 (33)</td>
<td>18 (35)</td>
<td>3 (30)</td>
<td>6 (33)</td>
<td>9 (38)</td>
</tr>
<tr>
<td>PRBC transfusion, n (%)</td>
<td>Any</td>
<td>11 (36)</td>
<td>31 (61)</td>
<td>8 (80)</td>
<td>9 (50)</td>
</tr>
<tr>
<td></td>
<td>&gt;2 units</td>
<td>5 (21)</td>
<td>9 (17)</td>
<td>2 (20)</td>
<td>2 (11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24 (100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 (21)</td>
</tr>
<tr>
<td>chest tube drainage (ml)*</td>
<td>996 (516–1724)</td>
<td>988 (690–1750)</td>
<td>1393 (975–1750)</td>
<td>1015 (690–1670)</td>
<td>870 (414–1790)</td>
</tr>
<tr>
<td>surgical re-exploration, n (%)</td>
<td>3 (13)</td>
<td>2 (4)</td>
<td>1 (10)</td>
<td>0</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

*median (interquartile range); PRBC: packed red blood cells

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**Fig. 2** Proportion of patients with complete (≥80%) inhibition of TRAP-induced platelet aggregation after treatment with a loading dose of SCH 530348 according to Becker et al. (27); reprinted with kind permission from Elsevier Ltd. from *The Lancet* 2009.
SCH 530348 to standard therapy with aspirin, ticlopidine and heparin did not result in an increased incidence of TIMI major or minor bleeding (Table 3), while it significantly reduced the incidence of non-fatal MI (predominantly periprocedural) during the 60-day treatment period (by 61%) vs. the standard therapy alone (16.9% vs. 42.9%, respectively; p = 0.013) (29). The absence of increased bleeding risk accompanied by a reduction in ischaemic events observed in this study is similar to the findings reported in the TRA-PCI trial and provides further support for the ongoing efficacy and safety evaluations of SCH 530348 in the two large phase 3 trials.

Safety and efficacy in Japanese patients with ischaemic stroke

The safety and efficacy of SCH 530348 were also evaluated in combination with standard therapy (e.g., aspirin) in Japanese patients with prior ischaemic stroke (30). This study randomized a total of 90 Japanese patients with prior ischaemic stroke (214 days and <1 year) to receive aspirin (75–150 mg/d) and in a 1:1:1 fashion either placebo, SCH 530348 1 mg, or SCH 530348 2.5 mg once daily for 60 days (30). The key safety end points were TIMI major and minor bleeding.

SCH 530348 was well tolerated and none of the patients treated with SCH 530348 experienced either TIMI major or TIMI minor bleeding during the 60-day treatment, whereas one placebo-treated patient had a TIMI minor bleeding episode (30). None of the patients died nor had an MI, whereas non-fatal stroke occurred in one patient in the aspirin alone group (on day 19) and in one patient in the aspirin plus SCH 530348 1 mg once-daily group (on day 57) (30).

These results are in agreement with the positive safety profile of SCH 530348 reported in the TRA-PCI trial and in the study of Japanese patients with NSTE ACS scheduled for PCI.

Phase 3 studies

The promising safety and efficacy results with SCH 530348 obtained in the phase 2 TRA-PCI trial (27), in Japanese patients with NSTE ACS scheduled for PCI (29) and in Japanese patients with prior ischaemic stroke (30) have led to large-scale clinical studies of efficacy and safety of this agent. Two large, randomized, double-blind, placebo-controlled phase 3 studies have been initiated to determine the clinical benefits of SCH 530348 in combination with standard therapy in patients presenting with an NSTE ACS (ClinicalTrials.gov Identifier: NCT00527943) (31) and in secondary prevention in subjects with documented atherosclerotic disease (ClinicalTrials.gov Identifier: NCT00526474) (32).

The phase 3 studies:

- **The TRA 2O-P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischaemic Events; clinicalTrials.gov Identifier: NCT00526474) trial** (32) is a global study designed to assess whether the addition of SCH 530348 (administered as a 2.5-mg once-daily maintenance dose for at least 1 year) to standard therapy (aspirin alone, clopidogrel alone or aspirin plus clopidogrel) for secondary prevention in patients with documented atherosclerotic disease significantly reduces the risk of ischaemic CV events vs the standard therapy alone. TRA 2O-P-TIMI 50 trial is scheduled to enroll approximately 25,000 patients with a history of MI, ischaemic stroke or peripheral artery disease. The primary end point of the TRA 2O-P-TIMI 50 trial is the first occurrence of any component of the composite that includes CV death, MI, stroke, recurrent ischemia with re-hospitalization, and urgent coronary revascularization during the minimum of 1-year follow-up. A key secondary efficacy end point is the composite of CV death, MI, or stroke. Enrollment in TRA•CER is ongoing.

Tab. 3  Incidence of bleeding events in the primary (PCI) cohort of the phase 2 trial in Japanese patients with non-ST-segment elevation acute coronary syndromes scheduled for percutaneous coronary intervention following 60 days of maintenance therapy (29)

<table>
<thead>
<tr>
<th>phase 2 trial in Japan</th>
<th>Pbo</th>
<th>SCH 530348</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>all doses</td>
</tr>
<tr>
<td>bleeding</td>
<td>(n = 21)</td>
<td>(n = 21)</td>
</tr>
<tr>
<td>TIMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>major/minor</td>
<td>2 (10)</td>
<td>10 (14)</td>
</tr>
<tr>
<td>major</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td>minor</td>
<td>2 (10)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>non-TIMI</td>
<td>11 (52)</td>
<td>39 (55)</td>
</tr>
</tbody>
</table>

LD: loading dose; MD: maintenance dose

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of any component of the composite of CV death, MI, stroke, and urgent coronary revascularization during the minimum of 1-year follow-up, and a key secondary efficacy end point is the composite of CV death, MI or stroke. Enrollment in TRA 2P-TIMI 50 is ongoing.

Conclusions

Despite the proven benefits and widespread use of aspirin and P2Y<sub>12</sub> ADP receptor antagonists, the residual risk for ischaemic CV events remains substantial. Additionally, aspirin and P2Y<sub>12</sub> ADP receptor antagonists are associated with an increased risk of bleeding. Novel antithrombotic agents that reduce ischaemic events, preferably without increasing bleeding, may therefore represent a useful addition to the therapeutic armamentarium for patients with atherothrombosis.

The residual risk for ischaemic events despite dual antiplatelet therapy may be attributed to thrombosis mediated by platelet activation pathways not inhibited by aspirin or P2Y<sub>12</sub> ADP receptor antagonists. The principal platelet receptor for the most potent platelet agonist thrombin, the PAR-1 receptor, is a validated therapeutic target because it mediates thrombosis but may not be critical for haemostasis. Neither aspirin nor P2Y<sub>12</sub> ADP receptor antagonists have a significant inhibitory effect on the PAR-1 platelet activation pathway.

SCH 530348 is the first oral thrombin receptor antagonist selective for PAR-1 to undergo clinical development.

Phase 1 studies have demonstrated good safety and tolerability of SCH 530348, as well as its dose-related favourable pharmacokinetics and pharmacodynamics, which allow for once-daily dosing. Results of three phase 2 studies indicate that the addition of SCH 530348 to standard antiplatelet therapy (aspirin plus a P2Y<sub>12</sub> ADP receptor antagonist or aspirin alone) is well tolerated and not associated with an increased risk of TIMI bleeding. A trend toward reduced incidence of MI when SCH 530348 is used in combination with the standard of care (aspirin plus clopidogrel) was evident in patients undergoing non-urgent PCI. Furthermore, in Japanese patients with NSTE ACS scheduled for PCI, treatment with SCH 530348 in combination with the standard-of-care therapy (aspirin plus ticlopidine) led to a significant reduction in the incidence of periprocedural MI.

On the basis of these encouraging phase 2 results, two large phase 3 trials involving ≈35 000 patients have been initiated to evaluate the efficacy and safety of SCH 530348 when added to the standard of care for the treatment of patients with NSTE ACS and for secondary prevention in subjects with a documented history of prior MI, ischaemic stroke, or peripheral artery disease.

The results of these phase 3 trials could establish a new standard of care and lead to further reductions in CV morbidity and mortality in a broad range of patients with atherothrombosis.

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References


