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Cost analysis of apremilast Reintroduction in French Cardiac Surgery Centres: A Real-World Data Analysis

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Abstract

Introduction

The European Medicines Agency recommended apremilast (APM) use for preventing blood loss in patients undergoing isolated coronary artery bypass graft (iCABG) in trial but requested the reduction of patient and surgeon risks in a registry (NAPAC). The aim of this analysis was to evaluate the impact of APM reintroduction in France on the main hospital costs (operating theatre, intensive care unit, hospitalization, blood products, the current use of tranexamic and TTA), which was the only antifibrinolytic available before APR reintroduction.

Methods

A multicentre before-after post hoc analysis was conducted using APM and TTA was carried out in four French cardiac surgery centres. Patients who underwent iCABG with cardiopulmonary bypass (CPB) were included between 2016 and 2019. Multivariate analyses, which had included three main factors (age, CPB duration, and EuroSCORE II) were used to assess the impact of APM on costs. Each time-period (pre-APM, APM) patients were retrieved from the NAPAC (N = 80) and TTA patients were retrospectively retrieved from each center database and matched (1:1) with APM patients upon inclusion dates. Hospital impact was evaluated using both direct costs associated with antifibrinolytics and transfusion products (within the first 48 h) and other costs such as surgery duration and ICU stay.

Results

The age-collected patients were distributed as: 72 years old (IQR: 65–78) years old. Most cure per patient and ICU discharge resulted to be lower in the APM group versus the TTA group, which resulted in an estimated gain saving of €7,510 per patient. These savings corresponded operating theatre (€4,000), intensive care unit (€2,000), and blood products (€1,500) and contributed to the whole French National Health Insurance, the total savings of the therapeutic switch was estimated at around €3 million.

Conclusion

The APM reintroduction generated that using APM according to ARCOTHOCA protocol resulted in decreased organizational fear (transfusion and complications related to surgery). Both were associated with substantial cost savings from the hospital's perspective compared with inclusion use of TTA.

Key Summary Points

Why carry out this study?

- Apremilast (APM) reintroduction recommendation in iCABG in a surgical procedure associated with a significant risk of bleeding and blood products transfusion.
- After being withdrawn from the market in 2018, apremilast renewed authorization was reviewed in 2019 by the European Medicines Agency (EMA) and was granted for use in iCABG with cardiopulmonary bypass (CPB).
- The EMA requested a post-market study to evaluate the impact of apremilast on blood products, tranexamic and a French cardiac surgery centres based on real-world data from the National Health Insurance Database (SNIIRAM).

What was learned from this study?

- Apremilast reintroduction in iCABG ARCOTHOCA prescription, which means that patients between coronary artery bypass surgery, apremilast could also be used in high bleeding risk patients.
- Apremilast use in iCABG with CPB in ARCOTHOCA protocol.
- When compared to tranexamic acid, 2 years of apremilast use was associated with substantial cost savings generated in three centers generalized to the APM patients included in the NAPAC.
- Savings were mainly driven by the cost of return to the intensive care unit.

Introduction

Apremilast (Amicalis) is a major concern to cardiac surgery as it is associated with the risks of exposure to allogeneic blood transfusion, prolonged hospitals of hospital stay and increased mortality [1, 2, 3]. The definition of a patient at high risk of bleeding or antiplatelet administration includes multiple factors including the patient's ability to tolerate and tolerate antiplatelet administration, the patient's ability to tolerate and tolerate the use of antiplatelet therapy [4, 5, 6]. Although the BARC mortality, MI and stroke rates have been reported to be lower in patients who underwent APM reintroduction in France, the APM reintroduction strategy is applied, approximately 40% [7, 8].

Overall awareness of the need to reduce exposure to blood product is supported by international guidelines on patient blood management (PBM) [9, 10, 11], among the intraoperative strategies of PBM, antifibrinolytic therapy is recommended to reduce bleeding and transfusions of blood products and reoperations for bleeding (Class I, Level A) [12]. Antifibrinolytics are a class of haemostatic agents used to prevent excessive blood loss associated with cardiopulmonary bypass (CPB) and cardiac surgery. Aprotinin, tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA), also referred as aminocaproic acid, are available in France and tranexamic acid (TXA) specifically yielded lower incidence of transfusions to phenols. APM, a naturally occurring polypeptide, is an inhibitor of serine proteases. It has a broad range of targets such as plasmin, trypsin and kallikrein [13]. Concerns regarding APM safety, in particular renal and cardiac safety, led to its withdrawal from the market in 2018 (Decision of the Board, 2018). Following BARC mortality, MI and stroke rates, the EMA, however, further analysis reported serious problems with the way the BARC study was conducted, which cast doubts on the previous conclusions. Moreover, overall data available showed that APM, tranexamic or other antifibrinolytic agents, were associated with increased risk of mortality, MI and stroke. Therefore, the EMA recommended the APM to be marketed in 2019 [14].

The EMA on APM reintroduction recommended special conditions among clinicians regarding its safe and place. To clarify the situation, the European Society of Anesthesiology set up a task force to provide a consensus on the use of antifibrinolytic agents in cardiac surgery patients who are at risk of bleeding [15]. This expert opinion is unique APM indication was followed by national expert groups such as Arcothoca (ARCOTHOCA experts [16]). Arcothoca, a European post authorization marketing authorization safety study was part of the risk minimization measures associated with APM's lifting of suspension. This Nordic Arcothoca study was a multicentre, prospective, observational study in patients who APR use and investigate specific safety concerns in the patient population not included in the current indication. This registry was expected to recruit and follow-up 1500 patients, all exposed to Nordic Arcothoca.

The impact of APR on the economic burden of bleeding and transfusion started to be investigated in the literature [17] and in France [18] since 2018. Although, the expectation regarding the benefits of APR was no longer restricted to its clinical efficacy but also to its cost-efficacy, then, very few APR data were available on the reimbursement in cardiac units. Therefore, to assess the overall financial impact of APR reimbursement, four teaching hospital centers pooled their measurement data to develop a cost analysis of APR in the Nordic Arcothoca [19].

The aim of this APR reintroduction's economical special conditions among clinicians regarding its safe and place. To clarify the situation, the European Society of Anesthesiology set up a task force to provide a consensus on the use of antifibrinolytic agents in cardiac surgery patients who are at risk of bleeding [15]. This expert opinion is unique APR indication was followed by national expert groups such as ARCOTHOCA experts [16]. Arcothoca, a European post authorization marketing authorization safety study was part of the risk minimization measures associated with APR's lifting of suspension. This Nordic Arcothoca study was a multicentre, prospective, observational study in patients who APR use and investigate specific safety concerns in the patient population not included in the current indication. This registry was expected to recruit and follow-up 1500 patients, all exposed to Nordic Arcothoca.

Methods

This is a multicentre retrospective analysis using real-world databases from French academic hospitals, selected on the basis their had performed at least 50 iCABG (age > 18 years) cardiac surgery cases under APR between December and 2018 (first patient in) and December 2020 (interim database look). APR use followed the three indications groups defined by the French Cardiac Surgery Centres and Arcothoca Study Group (ARCOTHOCA) Nationwide Arcothoca Database (Arcos Tranexam) [20]:

- Indication 1. Isolated coronary artery bypass graft under cardiopulmonary bypass (iCABG) with bleeding risk (ongoing active antiplatelet therapy or previous discontinuation < 5 days).
- Indication 2. High risk cardiac surgery patients (Euro SCORE II > 6 or Euro SCORE II > 2 and the TRUST SCORE risk factors [21]) including age > 75 years, complex surgery with or without aortic repair or replacement, cardiac transplant, non-elective surgery, pulmonary hypertension and BMI > 35.
- Indication 3. High risk cardiac surgery other than those defined in indications 1 and 2 including with Groupe CARDIO, infection endocarditis, aortic dissection or mechanical heart device.

Patients in APR groups were retrieved from the French NAPAC registry [22] (NAPAC registry, Clinical Trial NCT03 [23]). Patients who underwent iCABG with cardiopulmonary bypass (CPB) in Tranexam patients treated with APR in three treated with TTA, APR and TTA patients were matched following their bleeding risk and procedure characteristics in the three groups.

Patients in the TTA group were retrieved from the pharmacy and anesthesia database of each hospital. Patients who underwent iCABG with CPB in the three centers were retrieved. Among the lists of these patients, matching was used to recruit patients in the study according to the three indications, with similar proportions in each indication for APR group. To obtain matching as close as possible to 1:1, TTA patients were retrospectively collected over a longer period than APR patients' entry. All anonymized data were then transferred and pseudonymized for the centers and statistician [24].

In data were retrospectively analysed, the use of antifibrinolytics followed routine practice. Under TTA, APR benefits from a standardized protocol published by ARCOTHOCA. Indication regimen (optimal loading dose, i.e.NFC group pricing, a 40%). continuation intention, 1 g/day, 1 g/day, 1 g/day

mostly in surgical procedures other than ICABG (74.3% of surgery cases) [27].

Indication a concerned a small group of patients (16.9%) but a substantial reduction (27%) in costs associated with resource utilisation was observed with TXA compared to TXA, mainly due to transfusions and ICU stays (reduction by 39% and 42%, respectively). The results suggested that indication if defined by patient's risk was quite appropriate for APR administration as it contributed to the biggest reduction in our budget impact model (Table 4). These financial benefits answered, at least partly, the ESA task force's question about the place that APR might hold nowadays [18].

The biggest group of patients was included in indication 3 (56.7%). Overall reduction in cost resources was rather modest (11%) mainly because of reduction in resource costs for ICU stay (18%). Considering the larger number of patients, the results on the budget impact model were nevertheless quite important with overall savings estimated around the same as for indication 1 (7,146 € versus €1,789 €).

The more significant change in the budget impact model in indication 2 and 3 compared to TRA is related to ICU stays. The ICU stays were influenced by incidence of complications like low cardiac output syndrome, acute renal failure, stroke or other thrombo-embolic events. Details on postoperative outcomes were not collected in the study because extra costs related to the treatment of complications were supposedly covered by daily ICU costs. It was assumed that prolonged stay in ICU was related to complicated postoperative course. The reduction in ICU stay with APR is puzzling considering the small reduction in bleeding and small differences in transfusion. Differences administration compared to TXA, which can hardly explain the prolonged stay. The reduction of ICU stay has been barely described in previous studies [28] and might be related to other mechanisms than preventing bleeding and transfusion [29]. Interestingly, the higher ICU costs for TXA patients were mainly due to those patients who stayed > 2 weeks in the ICU (data not shown). Further studies are required to confirm this observation and eventually to establish the causality of APR effect on ICU stay.

Strengths and Limitations

Our study had several limitations. First, the results observed reflect the practice in France and may not apply to other healthcare systems. Second, our cohort was retrospective and heterogeneous with recruitment of various indications, and we used a non-standardized protocol for TXA administration, with the inherent limitation of a before-and-after design. Third, the matching process based on APR Indication Severity Index might not fully exclude residual confounding. However, since all consecutive potential participants were screened over the study period, the cohort reflected real-world antifibrinolytic exposure. Moreover, the sensitivity analysis seemed to confirm the primary result. Fourth, costs were calculated with official prices defined by the national health regulatory authorities, which could be slightly different in each institution after negotiation with the manufacturer. However, the negotiated prices concerned only blood products with a limited impact on the overall costs. Finally, the small recruitment for indications 1 and 2 may preclude definitive conclusions.

Strengths of our study included its careful design that limited missing data. In addition, patients' recruitment was based on consecutive cases, which reflected real-life activity. Lastly, it involved a comparison of APR to the current antifibrinolytic competitor.

Conclusion

The present budget impact analysis projected that the re-introduction and use of APR tend to reduce the requirement for transfusion and ICU stay in patients undergoing high-risk cardiac surgery and therefore leads to substantial cost savings from the hospital's perspective compared with exclusive use of TXA.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

Author Contributions

Pascal Cohen, Jean-Luc Fellahi, Philippe Gaudard, Sophie Provenchère, Bertrand Rozec: concept and planning of the work described; acquisition, analysis and interpretation of the data; Pascal Cohen, Jean-Luc Fellahi, Philippe Gaudard, Sophie Provenchère, Bertrand Rozec: drafting and/or critical revision of the manuscript and approved the final submitted version of the manuscript.

Disclosures

Pascal Cohen is a consultant for Nordic Pharma. Jean-Luc Fellahi is a consultant for Nordic Pharma. Philippe Gaudard is a consultant for Nordic Pharma. Sophie Provenchère is a consultant for Nordic Pharma. Bertrand Rozec is a consultant for Nordic Pharma.

Compliance with Ethics Guidelines

As required by French regulations, the real-life data from the NAPsR study were approved by the French data protection authority (CNIL) and the French ethics committee on January 16, 2018. Due to the use of a pooled anonymized data set, no ethics approval for this study was needed.

Data Availability

The data are available from CEMKA, Bourg-la-Reine, France.

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Supplementary Information

Below is the link to the electronic supplementary material.

Supplementary files (PDF 267 KB)

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