Taurolidine/Citrate Lock Therapy for Primary Prevention of Catheter-Related Infections in Cancer Patients: Results of a Prospective, Randomized, Phase IV Trial (ATAPAC)

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Key Words
Catheter · Totally implantable venous access port · Taurolidine · Infection

Abstract
Background: Totally implantable venous access port (TIVAP)-related infections (RIs) remain a serious health problem in cancer patients receiving an intravenous (i.v.) therapy. The primary endpoint was the TIVAP-RI incidence rate. From December 2014 to September 2015, 163 patients were enrolled in the study (taurolidine: n = 86 vs. control: n = 77). Four patients in the control group (5%) had a Staphylococcus epidermidis TIVAP-RI, and 1 patient (1%) in the taurolidine group had a Staphylococcus aureus infection. The TIVAP-RI incidence rate was 0.4 and 0.1‰ catheter-days, respectively (p = 0.21). The infection-free TIVAP survival was not statistically significant (p = 0.09). TIVAP-RI required a total of 22 hospitalization days in the taurolidine group versus 106 days in the control arm with associated costs of EUR 4,849 and EUR 36,020, respectively. Taurolidine-related toxicity was transitory and classified as grade I. Conclusions: The ATAPAC trial did not show a significant risk-infection reduction by TauroLock™. A larger, prospective, randomized trial is needed to assess TauroLock efficacy for primary TIVAP-RI prevention in low-risk cancer patients.

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Introduction

Totally implantable venous access port (TIVAP)-related infections (RIs) represent a serious and persistent health problem in cancer patients with significantly increased morbidity and hospital costs [1, 2]. In cancer patients, the TIVAP-RI risk is of 0.20‰ catheter-days [1–3], coagulase-negative staphylococci being the most common cause [4]. TIVAP-RIs are usually classified
into 3 subtypes: (1) local site infections; (2) TIVAP-related bloodstream infections (BSI); and (3) catheter-related infections [5]. Bacterial biofilm plays a pivotal role in TIVAP-RI and is usually resistant to high antibiotic concentrations [6]. Thus, systemic antibiotics might not be able to eradicate the catheter-bacterial source, unless the catheter is removed or intraluminal treatment used, and infection relapse is possible [6]. Tauroidine [bis-(1, 1-dioxoperhydro-1, 2, 4-thiadiazinyl-4) methane], a derivative of the amino acid taurine, is an antimicrobial agent which kills and inhibits a wide range of microorganisms in vitro, including multidrug-resistant bacteria [7, 8]. TauroLock™, a catheter taurolidine lock solution containing 1.35% taurolidine and 4% citrate, can avoid bacterial adhesion to the inner TIVAP surface and, consequently, biofilm formation [9]. Some clinical trials have demonstrated the efficacy of TauroLock in reducing the TIVAP-RI incidence in patients on home total parenteral nutrition (TPN), in hemodialysis patients, and in pediatric cancer patients [10–13]. Recent data seem to support the use of TauroLock in the TIVAP-RI prevention, even in cancer patients, particularly in those at higher risk of TIVAP-RIs [14]. However, considering the limits of several published studies, the evidence grade of these recommendations is moderate [11].

The effectiveness of TauroLock as primary prevention in adult patients with solid tumors receiving anti-tumor treatment by a TIVAP and not at high risk is still unknown and remains to be prospectively assessed.

**Patients and Methods**

**Patients**

Eligible patients were those ≥18 years of age, with a performance status ECOG (Eastern Cooperative Oncology Group) score ≤2, with a solid cancer, and receiving an intravenous (i.v.) metastatic and/or (neo)-adjuvant chemotherapy administered by a TIVAP. Both, in- and outpatients were included. Exclusions criteria included: hematological cancer patients, known HIV infection, patients receiving an active immunosuppressive or antibiotic therapy, patients presenting a febrile episode and/or a neutropenia grade ≥2 within 4 days prior to randomization, patients on TPN or receiving in-house TIVAP handling (e.g., 5-FU continuous infusion), patients with a previous TIVAP-RI history, and with a known allergy to citrate or taurolidine. A written, informed consent was obtained from all patients before study inclusion and randomization. The study was carried out in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol was approved by the independent CPP Est III regional ethics committee and the ANSM (French drug regulatory agency).

**Study Design and Treatment**

The ATAPAC trial was an open-label, single-center, controlled, and randomized phase IV study designed to compare the efficacy of TauroLock versus a standard saline solution for primary TIVAP-RI prevention in adult patients treated with i.v. chemotherapy for a solid tumor. TIVAP-RIs were classified into 3 subtypes: (1) TIVAP-related BSI defined as an isolation of the same organism from a percutaneous blood culture and one of the following: (a) an exudate at the catheter site, (b) a semiquantitative catheter segment culture following catheter removal, and (c) qualitative blood culture defined as blood culture with differential time to positivity at least 2 h between bloodstream cultures obtained from a peripheral vein and TIVAP; (2) local infections defined as an evidence of cellulitis around the exit TIVAP site; and (3) catheter-related infection, defined as a temporal succession of chills and fever after TIVAP flushing.

Eligible patients were registered on the trial during a hospital stay for cancer chemotherapy and then randomly assigned (1:1) to either the experimental (TauroLock™; Tauropharm, Waldbüttelbrunn, Germany) or control group (normal saline; BD PosiFlush† XS Syringe, 0.9% sodium chloride; Becton, Dickinson and Company, Franklin Lakes, NJ, USA) using a simple randomization scheme. Randomization was done locally via numbered sealed envelopes. According to French guidelines and in the absence of any validated data supporting the routinely use of heparin for TIVAP flushing, a normal saline solution was used in the control group. Patients were stratified by 2 criteria: chemotherapy indication (metastatic vs. [neo]-adjuvant) and age (≤/≥70 years). Treatment allocation was not masked because it was not possible to obtain an appropriate placebo packaging and because TauroLock is known to sometimes cause a metallic taste in the mouth.

Patients were recruited at the Medical Oncology Division of the Metz-Thionville Regional Hospital Center during their regular visits for i.v. chemotherapy cure. All patients included in the study carried a silicone, single-chamber, standard size TIVAP (Celsite® Implantofix). A signed informed consent was obtained before patient’s inclusion in the study and randomization. Hematological laboratory, physical examination, and clinical assessments were obtained before any treatment cycle. Concomitant medication and adverse events (AEs) were collected at each visit. For patients in the experimental group, at the beginning of each cure (>1), the TauroLock solution was removed before and then re-installed after chemotherapy treatment. Considering the TIVAP volume of 2 ml (1.5 ml of the inner chamber + 0.5 ml of the internal collector) and the volume of 0.8 ml of the external Huber needle system, a vial of 3 ml of TauroLock solution was used. In both groups, TIVAP was flushed using 10 mL of normal saline solution before and after chemotherapy administration, following the standard handling procedures of the hospital. Standard aseptic procedures were used during TIVAP surgical insertion and at each catheter handling. Patients were followed according to the same rhythm of their antitumor treatment program up to the end of the study that included the end of chemotherapy and/or the TIVAP removal for mechanical complications or a TIVAP-RI. A follow-up visit was performed 7–30 days after the study end. Two sets of 2 10-mL blood samples (BacT/ALERT™; Biomérieux), taken within 30 min from a peripheral vein and TIVAP, were drawn from patients hospitalized for fever (>38°C) and/or any clinical TIVAP suspicion (e.g., chills and fever after TIVAP flushing, local cellulitis around the exit TIVAP site, severe hypothermia [<36°C]). Microbial iden-
Identification was performed using Matrix Assisted Laser Desorption/Ionization – Time Of Flight (MALDI-TOF; Bruker BioSpin S.A.S.). Antibiotic susceptibility was determined by the disc diffusion method (SIRSCAN™; I2A). The microbial analysis was blindly performed at the Department of Clinical Microbiology.

Safety Assessment
The primary endpoint was the TIVAP-RI incidence rate, defined as the number of incident TIVAP-RIs which occurred during the study, divided by the number of catheter-days and expressed per thousand (‰). Secondary endpoints included: (1) infection-free TIVAP survival, (2) hospitalization-days associated to TIVAP-RI, (3) chemotherapy delay due to TIVAP-RI, (4) TIVAP removal for TIVAP-RI, (5) costs associated with the TIVAP-RI management in the perspective of the health French insurance, and (6) TauroLock-related toxicity.

Safety assessment included recording of all AEs and serious AEs (SAEs) and their severity and relationship to study treatments. The severity of AEs and SAEs was graded according to the National Cancer Institute Common Terminology Criteria for AEs (version 4.0). Safety data were collected up to 30 days after the last dose of study medication or until resolution of AEs related to TauroLock.

Statistical Analysis
TIVAP-RI incidence rates and their exact 95% confidence intervals were calculated as Poisson event rates, and compared by computing odds ratios (OR) and their 95% confidence intervals and by the Fisher exact test. Infection-free TIVAP survival was estimated using the Kaplan-Meier method and compared by log-rank test. All analyses were calculated as 2-sided tests, and p values <0.05 were considered to be statistically significant. With 81 patients per group and a mean follow-up time of 4 months, this study had 90% power and a 2.5% 2-sided significance to detect changes in the TIVAP-RI incidence rate from 3 to 1‰ TIVAP-utilization days in the control and TauroLock group, respectively. The expected TIVAP-RI incidence rate in the control group was based on the frequency of TIVAP-RIs previously observed in the Medical Oncology Division of the Metz-Thionville Regional Hospital Center according to the surveillance conducted by the infection control team. The expected TIVAP-RI incidence rate in the experimental arm was based on the efficacy of TauroLock to prevent TIVAP-RIs in pediatric oncology reported in the literature [12–15]. Analysis was on an intention-to-treat basis, and all analyses were done with SAS/STAT software version 9.3 (SAS Institute Inc.).

TauroLock™ Activity in Adult Cancer Patients

DOI: 10.1159/000470911

Fig. 1. Trial profile.

Table 1. Clinical characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Taulodeline/citrate lock therapy (n=84)</th>
<th>Standard saline solution (n=76)</th>
</tr>
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<tr>
<td>Age, years</td>
<td>62 (54–70)</td>
<td>61 (53–69)</td>
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<td>Age &gt;70 years</td>
<td>23 (27)</td>
<td>18 (24)</td>
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<tr>
<td>Female sex</td>
<td>60 (71)</td>
<td>53 (70)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>0 or 1 79 (94)</td>
<td>70 (92)</td>
</tr>
<tr>
<td>Chemotherapy setting</td>
<td>(Neo)-adjuvant 36 (43)</td>
<td>33 (43)</td>
</tr>
<tr>
<td>Chemotherapy protocol</td>
<td>Metastatic 48 (57)</td>
<td>43 (57)</td>
</tr>
<tr>
<td>Weekly</td>
<td>23 (27)</td>
<td>22 (29)</td>
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<tr>
<td>Biweekly</td>
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<tr>
<td>Trweekly</td>
<td>53 (63)</td>
<td>47 (62)</td>
</tr>
<tr>
<td>Monthly</td>
<td>5 (6)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Outpatients</td>
<td>73 (87)</td>
<td>66 (87)</td>
</tr>
</tbody>
</table>

Data are n (%) or median (IQR), unless otherwise stated.
From December 2014 to September 2015, 163 patients were recruited at the Medical Oncology Division of the Metz-Thionville Regional Hospital Center and randomly assigned to either TauroLock (n = 86) or standard saline solution (n = 77) (Fig. 1). Two patients in the experimental group and 1 patient in the control group were excluded from the study because of consent withdrawal. Eighty-four patients in the TauroLock group and 76 patients in the control group were analyzed. Baseline patient and tumor characteristics were well-balanced between the 2 groups (Table 1). The median follow-up was of 104 days (range, 56–173) versus 107 days (range, 69–142) in the experimental and control group, respectively. The median number of chemotherapy cycles was comparable in both groups (6.0 vs. 6.5) (Table 2).

### Efficacy

Four patients in the control group (5%) presented a TIVAP-BSI versus 1 patient (1%) in the TauroLock group. The TIVAP-RI incidence rate was 0.4 and 0.1‰ catheter-days, respectively (p = 0.21) (Table 2). The incidence rate ratio was 0.23 (95% CI 0.03–2.06). Neither local infection nor catheter-related infection occurred in both groups. Subgroup analysis did not find any statistically significant difference between the 2 groups concerning age, sex, ECOG performance status, chemotherapy setting (metastatic vs. [neo]-adjuvant chemotherapy), and chemotherapy protocol (Table 3). In all 4 patients of the standard saline solution, a *Staphylococcus epidermidis* infection was

### Results

#### Demographics

From December 2014 to September 2015, 163 patients were recruited at the Medical Oncology Division of the Metz-Thionville Regional Hospital Center and randomly assigned to either TauroLock (n = 86) or standard saline solution (n = 77) (Fig. 1). Two patients in the experimental group and 1 patient in the control group were excluded from the study because of consent withdrawal. Eighty-four patients in the TauroLock group and 76 patients in the control group were analyzed. Baseline patient and tumor characteristics were well-balanced between the 2 groups (Table 1). The median follow-up was of 104 days (range, 56–173) versus 107 days (range, 69–142) in the experimental and control group, respectively. The median number of chemotherapy cycles was comparable in both groups (6.0 vs. 6.5) (Table 2).

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observed. The patient in the TauroLock group presented a *Staphylococcus aureus* infection. *S. epidermidis* was methicillin sensible in 1 patient and methicillin resistant/vancomycin sensible in the other 3 patients. All these patients were hospitalized and treated by i.v. antibiotics without any TIVAP removal. *S. aureus* was methicillin sensible and required a TIVAP removal. The median time before TIVAP-RI was 240 days in the TauroLock group versus 110 days in the control group. The infection-free TIVAP survival was not statistically significant in both groups (*p* = 0.09) (Fig. 2). The only TIVAP-RI observed in the experimental arm occurred in the follow-up, post-chemotherapy period, in a patient hospitalized for best supportive care. All TIVAP-RI patients presented an ECOG performance status of 0 or 1 and received a weekly chemotherapy. Only 2 patients in the control arm were treated in an outpatient setting and received a (neo)-adjuvant chemotherapy. For 3 of the 4 patients in the control arm, chemotherapy was definitely discontinued after TIVAP-RI because of tumor progression; the fourth patient did not receive any post-TIVAP-RI treatment because of chemotherapy toxicity and a scheduled surgery. The only patient in the experimental group showed a rapid tumor progression before TIVAP-RI diagnostic and treatment and he was hospitalized for best supportive care.

**Safety**

TauroLock-related toxicity is shown in Table 4. Nine cases (11%) of local paraesthesia were observed. Four patients presented a transitory body warm sensation a few minutes after TauroLock administration. Only 1 case (1%) of dysgeusia and local pain during TauroLock infusion was reported. Two patients (2%) showed both, local paraesthesia and body warm sensation. In all patients, toxicity was classified as grade I (CTCAE v4.0) and quickly resolved in a few minutes. Only 1 patient (1%) in the experimental group presented a TIVAP-associated thrombosis requiring an anticoagulant treatment by a low molecular weight heparin (*p* = 0.99).

**Cost Analysis**

A cost analysis was also performed evaluating the costs associated with TIVAP-RI management according to the health French insurance. The only patient in the experimental arm with a TIVAP-RI was hospitalized for 22 days with a cost of EUR 4,849. The median hospitalization of the 4 patients in the control group was of 25 days (14–38) with a total of 106 hospitalization days. The median cost for each hospitalization in this subgroup was of EUR 6,987 (6,708–9,285). Total costs for these 4 patients were of EUR 36,020.

**Discussion**

Several studies have confirmed an important activity of TauroLock in TIVAP-RI prevention in high-risk patients [10–13]. In the ATAPAC trial, the TIVAP-RI inci-
ence rate of both groups is consistent with the literature data reporting a rate from 0.11 to 1.45‰ catheter-days [4, 13–17]. Despite a relative risk reduction of 4 times by TauroLock, this difference was not statistically significant because the TIVAP-RI incidence rate observed in the control group was significantly lower than the one chosen as reference of 3‰ catheter-days for sample size calculation. Several hypotheses can explain this difference. Firstly, the incidence rate used as comparator derived from a prospective analysis performed in patients hospitalized in the Oncology Division of our hospital from May 2013 to December 2014 (“in-patient setting” only). This analysis documented a TIVAP-RI incidence rate of 3.2‰ catheter-days in all hospitalized cancer patients, including patients receiving a TPN and/or in best supportive care, and of 2.8‰ catheter-days in patients exclusively receiving a chemotherapy. After this analysis, several handling TIVAP procedures have been taken leading to a better prevention and a consequently lower TIVAP-RI incidence rate of 2.05‰ catheter-days. Secondly, in order to reduce the probability of any important bias, we strictly selected the population included in our study. Effectively, 87% of patients received chemotherapy in an outpatient setting and presented a better performance status and much less comorbidities as compared to inpatients who are usually weaker and at higher risk of nosocomial infections. Likewise, patients on TPN and/or receiving a 5-FU continuous infusion were also excluded from the study in order to avoid any home care TIVAP handling, which highly increases the TIVAP-RI risk [1, 10, 17].

Recently, a statistically significant lower TIVAP-RI rate by TauroLock has been observed in 2 small studies in pediatric patients with hematological malignancies [13, 15]. Results of these studies are very difficult to compare to ours because of many important discrepancies in patient’s characteristics and study procedures, which can well explain the lower TIVAP-RI incidence found in the control arm in the ATAPAC trial (0.4‰ catheter-days) compared to the one observed in both these studies (1.3 and 1.4‰ catheter-days, respectively). However, the magnitude of the relative TIVAP-RI risk reduction found in the ATAPAC trial (4:1) and in Handrup et al.’s [13] study (4.5:1) was similar. Results were not statistically significant in the ATAPAC study because of the expected very high incidence rate used as comparator in sample size calculation leading to an insufficient number of included patients.

Any reliable comparison cannot be made between hemodialysis patients and patients on TPN, who are at high TIVAP-RI risk and cancer patients included in our study who represent a selected population at low TIVAP-RI risk.

Several published studies describe increased hospital costs associated to central-line associated bloodstream infection (CLABSI). Zimlichman et al. [18] showed that CLABSI is the most expensive healthcare-associated infection with a valued cost of USD 45,814 per episode (95% CI, USD 30,919–65,245). In a prospective, nonrandomized study in hemodialysis patients, Taylor et al. [19] documented a cost reduction of EUR 28,700 associated with catheter sepsis treatment by a 6-month use of TauroLock. There is no published data evaluating the cost overrun associated to TIVAP-RIs in cancer patients. In the ATAPAC study, although any statistically significant difference cannot be identified because of the too low incidence rates, the TIVAP-related hospitalization cost reduction in the experimental versus the control group (EUR 4,849 and 36,020, respectively) is far greater than TauroLock-related costs (595 TauroLock vials were used for a total cost of EUR 5,712), suggesting that even if TIVAP-RIs are infrequent in low-risk patients, their prevention by TauroLock might be cost-effective. New, larger, prospective trials are needed to confirm this hypothesis.

Finally, AEs observed in the TauroLock group were transitory, classified as grade 1, and in accordance with the literature data.

In conclusion, the ATAPAC study is the first published trial evaluating the effectiveness of TauroLock as primary prevention in adult cancer patients at no high risk of TIVAP-RIs. Despite a relative risk reduction of 4 times by TauroLock, the ATAPAC trial did not show a significant risk-infection reduction by TauroLock. A larger, prospective, randomized trial is needed to assess the efficacy of TauroLock for primary TIVAP-RI prevention in low-risk cancer patients.

Acknowledgments

We would like to thank all patients and nurses participating to the ATAPAC study. A special thanks to the PARC (platform support for clinical research) team of the Metz-Thionville Regional Center for data collection and elaboration.

This study was sponsored by Theradial, the French retailer of the TauroLock™. No grant number is applicable.

Disclosure Statement

The authors have no competing interests to disclose.
**Author Contributions**

R.L., M.L., C.G., and N.O. made substantial contributions to the conception, acquisition, analysis, and interpretation of data, and to the drafting, writing, and revising of the manuscript. C.G. did the statistical analysis. C.P. and N.E. participated to the clinical analysis acquisition. C.P. contributed to the manuscript writing and revision. J.S. and P.Q. contributed to clinical data analysis and interpretation, and to the manuscript revision.

**References**