Evaluation of activated protein C resistance in patients on tamoxifen

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Evaluation of activated protein C resistance in patients on tamoxifen : a pilot study

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INTRODUCTION

- Tamoxifen, a selective estrogen receptor modulator (SERM), is known to reduce hormone-dependent breast cancer recurrence but is associated with an increased risk of venous thromboembolism.[1,2]
- Similar to the effect observed with combined oral contraceptives (COCs), compounds interacting with estrogen receptors can impact haemostasis by inducing a resistance towards the activated protein C (APC).[3]
- Nevertheless, the underlying mechanism of tamoxifen-induced procoagulable state remains unclear.

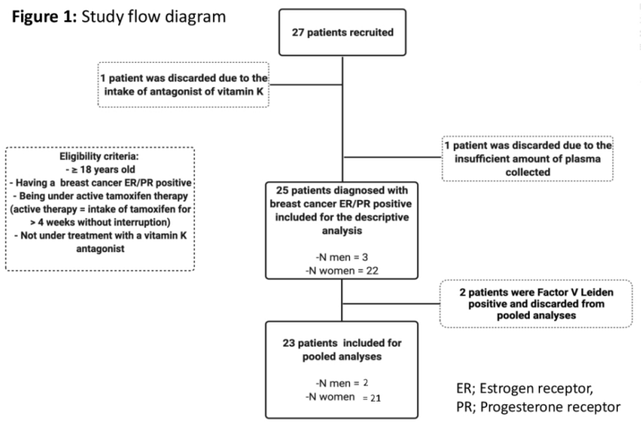
AIM

To assess APC resistance in patients with hormono-dependent breast cancer undergoing tamoxifen therapy, using the validated ETP-based APC resistance assay.[4]

METHOD

- 21 women and 2 men (mean age = 57 yo) under tamoxifen therapy were included.

Figure 1: Study flow diagram



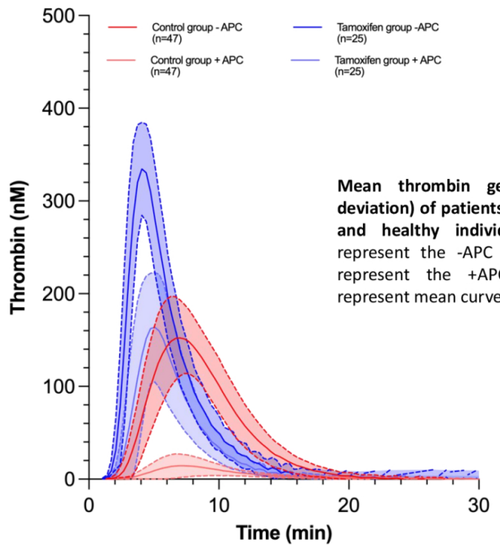
- The ETP based APC resistance assay was assessed on the CAT system, using ThromboScreen-TM® (Diagnostica Stago, France) in absence and in presence of exogenous APC.
- All samples were treated with the DP-Filter® device (5-Diagnostics, Switzerlands) to remove the impact of DOAC therapy on thrombin generation.
- To estimate the influence of tamoxifen on the normalized APC sensitivity ratio (nAPCsr), results were compared to a historical reference cohort of 47 healthy individuals (19 women and 28 men; mean age = 24 yo).

RESULTS

Study population

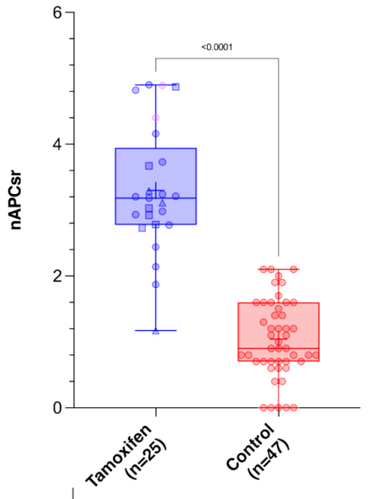
Demographic characteristics	Patients under tamoxifen (n=23)	Control group (n=47)
Sex (n)	Male (2) Female (21)	Male (28) Female (19)
Age (mean ± standard deviation, SD)- years	57 ± 10	24 ± 10
Body mass index (mean ± SD) – kg/m²	26.7 ± 6.1	22.7 ± 2.7
Cancer stage – grade (n)	0 (4), I (11), II (3), III(3), IV (1)	n/a
Use of anticoagulant drugs – n (%)	11 (42.3)	0 (0.0)
nAPCsr (mean ±SD [Min-Max])	3.18 ± 0.91 [1.17-4.90]	1.04 ±0.59 [0.00-2.08]

Thrombin generation

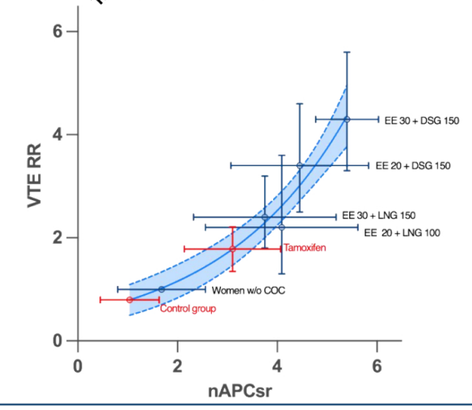


Mean thrombin generation curves (± standard deviation) of patients under tamoxifen therapy (blue) and healthy individuals (red). The dark curves represent the -APC condition and the light curves represent the +APC condition. Continuous lines represent mean curves and dotted lines represent SDs.

ETP-based APC resistance assay



Normalized activated protein C (APC) sensitivity ratio (nAPCsr) of individuals under tamoxifen therapy ("Tamoxifen") and healthy controls ("Controls).
The median and the 25th - 75th percentiles are symbolized by boxes; whiskers represent minimum and maximum values. The mean value is represented by a cross. The pink circles represent the patients who were carriers of a heterozygous FV Leiden mutation. Squares symbolize patients that experienced a thrombotic event under tamoxifen. Triangles represent patients that suffered from thrombosis before induction of tamoxifen. An unpaired t-test was used to perform comparisons between groups.



Correlation between normalized APC sensitivity ratio (nAPCsr) and relative risk (RR) of venous thromboembolism (VTE) (de Bastos, 2014) depending on the type of combined oral contraceptives
The control group used in this study showed a mean nAPCsr of 1.04 and an intrapolated VTE RR (CI 95%) of 0.80 (0.50-1.09). The tamoxifen group showed a mean nAPCsr of 3.18 and an intrapolated VTE risk (CI 95%) of 1.78 (1.35-2.21).

This is in line with the meta-analysis of Cuzick et al. in which the mean RR of VTE at 5 years under tamoxifen equaled 1.90 (range from 1.40 - 2.60).[5]

CONCLUSIONS

- This observational cohort study confirmed the tendency of tamoxifen to induce APC resistance and to influence thrombin generation towards a prothrombotic state.
- The impact of tamoxifen on APC resistance and thrombin generation suggests that the etiology of tamoxifen induced-VTE is likely to be similar to that of COCs.
- Furthermore, the results of this study also supports the concept that the nAPCsr could become an interesting scale to determine an individual's overall risk for developing VTE when being considered for hormonal therapies characterized by estrogenic activity, among which tamoxifen.

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