Nederlandse Ziekenhuisfarmaciedagen 2023

De hier opgenomen abstracts vormen een selectie, namelijk de vijf best beoordeelde abstracts, uit de presentaties tijdens de Nederlandse Ziekenhuisfarmaciedagen op 16 en 17 november 2023 te Arnhem. De digitale versie van deze publicatie op www.npfo.nl bevat alle gepresenteerde abstracts.

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NON-DESTRUCTIVE DRUG CONTENT PREDICTION OF PERSONALIZED 3D-PRINTED TABLETS PRODUCED AT THE POINT-OF-CARE USING NIR AND RAMAN SPECTROSCOPY

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Background

Three-dimensional (3D) printing is a flexible production technique, enabling the production of tablets for individual patients at the point-of-care, such as in a hospital pharmacy. The quality of these tablets needs to be guaranteed, but conventional quality control is destructive and therefore not feasible. Due to the small batch sizes, non-destructive analytical methods are necessary. In this study, near-infrared (NIR) and Raman spectroscopy were assessed as non-destructive analytical methods for their suitability of predicting the drug content in personalized 3D-printed tablets produced at the point-of-care.

Methods

Tablets with diameters of 2.7 mm, 4.5 mm and 6.2 mm containing 10%, 15%, 20% and 25% w/w furosemide were produced at the hospital pharmacy of the Leiden University Medical Center using semi-solid extrusion 3D printing. Batch average concentrations were determined using high-performance liquid chromatography coupled with ultraviolet detection. Spectra of three tablets of each concentration and each size were measured using a tabletop NIR and a confocal Raman spectroscope. With NIR the tablets were analysed in triplicate from four sides. With Raman spectroscopy four, six or eight areas of 1 mm^2 per tablet were analysed, depending on the tablet size, recording 100 spectra per area. The spectra were preprocessed and partial least squares (PLS) regression models were build using SIMCA software.

Results

Batch average concentrations (SD) were 10.89% (0.20%), 15.60% (0.39%), 20.21% (0.38%) and 25.19% (0.83%) w/w. Standard Normal Variate and data trimming was applied to the NIR spectra to acquire the optimal preliminary regression model (R2 = 0.9958; Q2 = 0.9948; RMSEE = 0.35%; RMSECV = 0.38%). For Raman spectral data, the spectra were averaged per area, cosmic rays removed and background removal applied to obtain the optimal preliminary regression model (R2 = 0.9799; Q2 = 0.9708; RMSEE = 0.77%; RMSECV = 0.96%). The current usability of Raman spectroscopy was assessed to be limited for use at the point-of-care, due to the long analysis time and potentially destructive properties of the laser.

Conclusion

Despite the small sample size, both preliminary models are sufficiently accurate and able to predict the furosemide concentration irrespective of the tablet size, indicating suitability of both NIR and Raman spectroscopy for the prediction of drug content in personalized 3D-printed tablets. NIR is favoured for use at the point-of-care, due to the limitations of Raman spectroscopy.

De abstractpresentatie van Iris Lafeber werd bekroond met de prijs voor Best Abstract 2023.

R-ALGORITHM FOR IDENTIFYING ADVERSE DRUG REACTIONS FROM FREE-TEXT IN ELECTRONIC HEALTH RECORDS IN HOSPITALIZED PATIENTS

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Background
Healthcare professionals often register adverse drug reactions (ADRs) as free-text in clinical notes of electronic health records (EHRs). This makes it difficult to identify ADRs and to use this information in clinical decision support systems (CDSS) aiming at improving patient care.

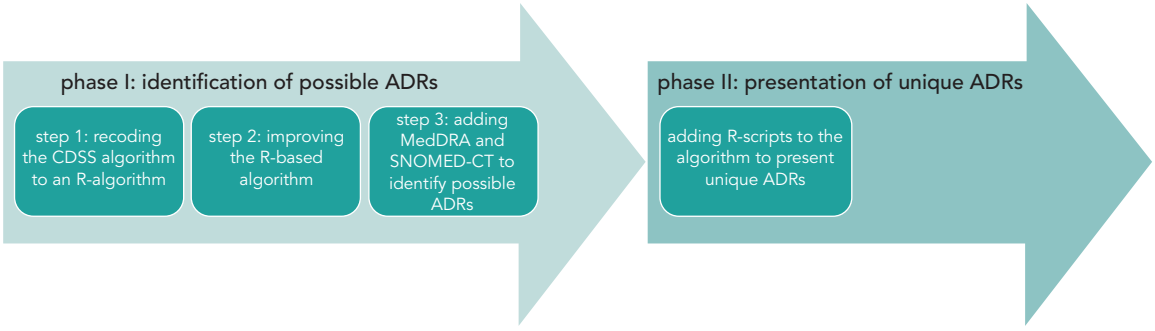
Objective
This study aims to develop a text mining tool using open-source R-algorithms to identify possible ADRs in free-text of Dutch hospital EHRs.

Methods
In our previous study, the complete EHR history of 45 patients were reviewed for ADRs and compared to two key strategies programmed into a CDSS (Gaston Pharma). ADRs were included in the study if the Naranjo causality score was ≥ 1. The defined gold standard found 318 unique EHR notes with possible ADRs, of which 63 potentially serious. In that study we demonstrated that a CDSS achieved a sensitivity of 57% and a positive predictive value (PPV) of 37%. In the present study, in phase I the CDSS algorithm was recoded (step 1) and improved (step 2) using R to identify possible ADRs with MedDRA/SNOMED-CT (step 3). In phase II six existing text mining R-scripts (e.g. deduplication, negation and Levensthein distance) were studied to present unique ADRs and to improve the PPV and sensitivity (figure 1).

Results
In phase I step 1, the R-algorithm performed similarly to the GP algorithm. In step 2, the improved algorithm resulted in a 93% sensitivity and 13% PPV, with a sensitivity of 95% for potentially serious ADRs. The R-algorithm also identified an additional 58 possible ADRs. In step 3, the algorithm achieved a PPV of 10%, a sensitivity of 86% and an F-measure of 0.18. In phase II, four R-scripts enhanced the sensitivity and PPV, resulting in a 71% PPV, 62% sensitivity and 0.69 F-measure (table 1).

Conclusion
The R-algorithm effectively identifies ADRs from free-text Dutch EHRs using R-scripts and MedDRA/SNOMED-CT. Although the R-scripts perform significant better than the CDSS, there is still room for improvement before it can be integrated with a clinical decision support tool.

FIGURE 1 A FLOWCHART OF A PIPELINE FOR IDENTIFYING POSSIBLE ADRS, AND THE STUDY PHASES OF THIS STUDY



The algorithm of the CDSS was developed in our previous work, in step 1 the CDSS algorithm was reprogrammed to an R-algorithm. Step 2, 3 and phase II were developed in this study.

ADRs: adverse drug reactions, CDSS: clinical decision support systems.

TABLE 1 THE PPV (IN %), SENSITIVITY (IN %) AND F-SCORE OF EVERY STEP OF THE PIPELINE

phase	step	identified text blocks			identified ADR			unique identified ADR		
		PPV	sens	F	PPV	sens	F	PPV	sens	F
I	**1 and 2**	13	93	0.22						
	3				10	86	0.18			
II								71	62	0.69

ADR: adverse drug reaction, PPV: positive predictive value, sens: sensitivity.

REAL-WORLD EFFECTIVENESS VERSUS CLINICAL TRIAL RESULTS OF DURVALUMAB IN STAGE III UNRESECTABLE NON-SMALL CELL LUNG CANCER

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Background

We compared the baseline characteristics and effectiveness outcomes of patients with stage III unresectable non-small cell lung cancer (NSCLC) who received durvalumab in a real-world (RW) setting with those from the PACIFIC trial.

Methods

In this retrospective study, we identified all patients diagnosed with stage III unresectable NSCLC who received durvalumab between April 2018 and February 2023 at two Dutch hospitals. We collected baseline and treatment-related characteristics, as well as effectiveness outcomes (overall survival [OS] and progression-free survival [PFS]) from the Electronic Health Record. These findings were then compared to the results of the PACIFIC trial. Patient selection and data collection were performed using a novel text-mining software tool (IQVIA Patient Finder Solution-CTcue B.V., Amsterdam, The Netherlands).

Results

Upon starting durvalumab treatment, RW patients exhibited less favorable prognostic indicators compared to the population in the PACIFIC study. Among those who received durvalumab in the RW setting, approximately 30% did not meet the eligibility criteria of the PACIFIC study. The median treatment duration with durvalumab was similar in both populations. However, the rate of treatment discontinuation due to immune-related adverse events was higher in the RW setting compared to the trial population (21% versus 15.4%). OS was similar between both populations (24-month OS: 69.3%; 95% confidence interval [CI] 59.3-80.9 versus 66.3%; 95% CI 61.7-70.4), while PFS was longer in the RW cohort (18-month PFS: 59.1%; 95% CI 49.4-70.7 versus 44.2%; 95% CI 37.7-50.5).

Conclusion

Despite the poor prognostic features of RW patients with stage III unresectable NSCLC, consolidation therapy with durvalumab resulted in a longer PFS than in the pivotal trial. OS was similar in both populations. The role of PD-L1 expression and prior chemoradiation therapy (sequential versus concurrent) as potential predictors for the effectiveness of durvalumab is currently being investigated in a follow-up study with a larger cohort.

STEP-WISE INTRODUCTION OF ELEXACAFTOR-TEZACAFTOR-IVACAFTOR IN PATIENTS WITH CYSTIC FIBROSIS AND LIVER CIRRHOSIS CHILD-PUGH A OR B USING CLINICAL- AND THERAPEUTIC DRUG MONITORING: A CASE SERIES

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Background
Serum liver test abnormalities are described as a common adverse effect of elexacaftor-tezacaftor-ivacator (ETI) in patients with Cystic Fibrosis (pwCF). In the phase I registration studies the PK of ETI have been compared between non-CF people with hepatic impairment and healthy individuals. In the former group exposure of ETI was increased and therefore a reduced dose in pwCF and cirrhosis Child-Pugh B is recommended. To our knowledge there are no data on the exposure of ETI in pwCF and cirrhosis Child-Pugh A or B. In this case series we describe seven pwCF and cirrhosis Child-Pugh A or B where ETI was gradually introduced using clinical and therapeutic drug monitoring (TDM).

Methods
Four dosing steps were defined at which patients underwent clinical examination, routine blood tests and TDM. Exposure of ETI was assessed by determination of the area under the plasma concentration versus time curve (AUC). The decision to proceed with the next dosing step was at the discretion of the treating pulmonologist, taking into account the presence or absence of liver test abnormalities, other side effects, the TDM advice by the pharmacist and the clinical effectiveness of ETI.

Results
In all patients ETI was successfully introduced and maintained. All patients improved in respiratory symptoms, ppFEV1, and BMI. Four patients reported side effects, which resolved in most cases. In pwCF with Child-Pugh B cirrhosis (n = 2) diminishment of the dose as recommended by the label resulted in AUCs that were lower than previously reported mean AUC values in pwCF without hepatic impairment. Therefore, the dose was further increased under careful monitoring.

Conclusion
Stepwise elevation of ETI dose did not induce clinical side effects or increase in serum liver tests under strict clinical and biochemical follow-up and TDM, and may allow safe introduction of this therapy in pwCF and hepatic impairment.

MODIFYING TACROLIMUS-RELATED TOXICITY AFTER LIVER TRANSPLANTATION BY USING LCP-TACROLIMUS: A MULTICENTRE RANDOMIZED, CONTROLLED TRIAL (MOTTO)

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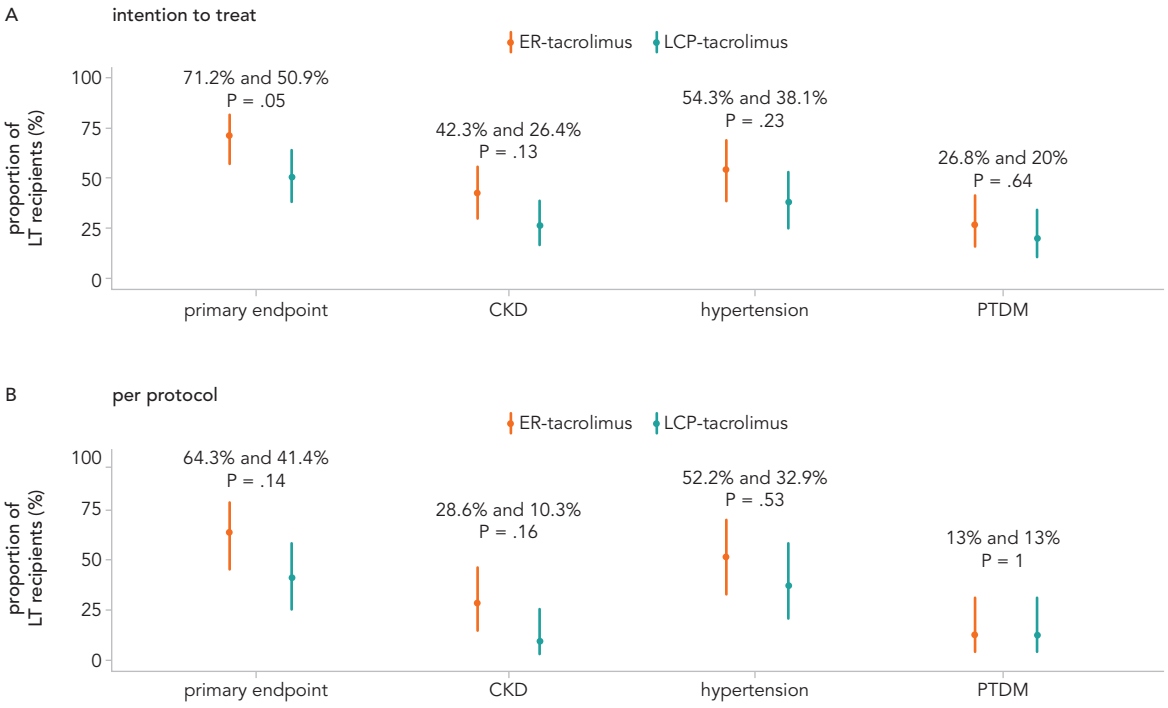
Objective
The aim of this study was to investigate whether LCP-tacrolimus (Envarsus) compared to extended-release (ER)-tacrolimus (Advagraf) formulation results in a difference in the prevalence



ER-tacrolimus: extended-release-tacrolimus, LT: liver transplantation, CKD: chronic kidney disease, PTDM: post-transplant diabetes mellitus.

of post-transplant diabetes mellitus (PTDM), hypertension and chronic kidney disease (CKD) at 12 months after liver transplantation.

Methods

In this multicentre randomized, controlled trial, patients were randomized at discharge after liver transplantation (LT) in a 1:1 ratio to (1) ER-tacrolimus or (2) LCP-tacrolimus. The primary endpoint was a composite endpoint of any of three events at 12 months: CKD defined as eGFR < 60 mL/minute/1.73 m^2 for > 3 months, sustained (> 3 months post LT) PTDM or new-onset hypertension. Secondary endpoints included: safety, quality of life, neurotoxicity (tremors), graft and patient survival, rejection, liver steatosis and fibrosis, pharmacokinetics and -dynamics.

Results

A total of 106 patients were included and baseline characteristics were comparable for both groups. In the intention-to-treat analysis, significantly less LT recipients reached the primary endpoint at 12 months in the interventional group compared to the control group (50.9% versus 71.2%, P = 0.05). The risk difference for the primary endpoint: 0.2021 and 95% confidence interval 0.002415-0.3816. In the intention-to-treat population, fewer LT recipients in the LCP-tacrolimus group developed CKD and new-onset hypertension compared to the ER-tacrolimus group: CKD 26.4% and 42.3%, P = 0.13 and new-onset hypertension 54.3% and 38.1%, P = 0.23. No difference was shown between ER-tacrolimus and LCP-tacrolimus in the percentage of LT recipients developing PTDM. No significant differences were observed in the per protocol analysis (see figure). In total, 95.3% (101/106) of the LT recipients developed serious adverse events (SAEs, n = 160). SAEs most frequently reported: fever (23.1%), infections (10%) and cholangitis and bile duct obstruction (10%).

Conclusion

LCP-tacrolimus results in a significant reduction in the prevalence of clinical relevant outcomes as compared to ER-tacrolimus in the first year after liver transplantation with comparable efficacy. ■