Exploiting real-world data to assist drug repurposing. Safety profiling of valproic acid and simvastatin combination treatment.

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ABSTRACT

REMEDI4ALL is studying the repurposing of valproic acid (VPA) and simvastatin (SIM), administered on top of standard-of-care chemotherapy for metastatic pancreatic cancer.[1] The two drugs are widely used and generally safe. However, we decided to evaluate the safety aspects of their combination using real-world data (RWD).

We analysed Lombardy Region's administrative database (10 M inhabitants). Healthcare in Italy is public, so the data are acquired for administrative and reimbursement purposes. Subjects that acquired at least one package of VAL or SIM in 2015-21 without any package in the previous 5 years entered the cohort. More than 7,000 patients were treated with both drugs. Hospital admissions and outpatient visits showed no significant increase in these patients as compared to those in patients taking either drug individually. We also analysed drug discontinuation rate, assuming that any side effects would lead to interruption of the treatment. The discontinuation rate of SIM was only slightly higher in patients with prior use of VAL than in those taking SIM only (HR 1.05, 95% CI 1.01-1.09). Conversely, there was a considerable decrease in the discontinuation rate of VAL in patients who were already taking SIM (HR 0.77, 95% CI 0.74-0.79).

In parallel, we explored the post-marketing reports of adverse events (AEs) from four databases, which have been standardized, de-duplicated and corrected for masking effects in the CLARITY PV platform. Reassuringly, AE levels were generally lower in patients taking both VAL and SIM, when compared to monotherapy, in agreement with the lower discontinuation rate observed in Lombardy.

We conclude that there are no increased safety concerns in the patients taking both drugs. These results underline the impact of the use of real world data in drug repurposing.

METHODS

Data sources

Data were obtained from the administrative database of Lombardy Region. Lombardy, located in Northern Italy, has approximately 10 million inhabitants: we had access to data on subjects 40 years and older (more than 6 millions). Healthcare in Italy is public, so the data are acquired for administrative and reimbursement purposes. Records contain information on sex, age, drug dispensation, hospital admissions together with primary and secondary diagnoses, ambulatory specialist visits and exemption registries. Drugs were classified according to Anatomical Therapeutic Chemical (ATC) Classification while hospital diagnoses were classified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) classification. All data were managed according to the current Italian law on privacy.

Study cohort

Subjects that acquired at least one package of valproic acid (ATC N03AG01) or simvastatin (ATC C10AA01) from 2015 to 2021 without any package of the same active principle in the previous five years entered the cohort. Beginning time was date of first dispensation of valproic acid or simvastatin and exit time was date of last dispensation, plus 60 days to allow for drug consumption of enclosed drug in last package(s). We considered that subjects had a co-prescription (valproic acid and simvastatin) when both drugs were dispensed in the same solar year. For this subjects beginning time date of dispensation of the second active principle and exit time last dispensation of the same active principle plus 60 days. For these three cohorts we analysed hospitalization, access to emergency room, and ambulatory specialty visits, We calculated a proxy for a comorbidity index using drug prescriptions, the Drug Derived Complexity Index (DDCI) (except for the C10 class, since it was directly included in the analysis).

Statistical analysis

The characteristics of patients included in the analyses were described with mean and standard deviation for continuous variables and numbers with percentages for categorical ones. Kaplan Meier curves were plotted and a log-rank test was performed to assess differences among groups. Cox proportional hazard model were fitted to analyze the interruption of drug assumption and survival, reporting the hazard ratio and 95% confidence intervals as risk estimation. We fitted also a competing-risk regression model based on Fine and Gray method for interruption of drug assumption and competing risk of death. Statistical analysis was performed using SAS software, SAS Institute Inc., Cary, NC, USA.[2]

Adverse drug reaction post-marketing reports

Post-marketing reports of adverse events (AEs) were estracted from four databases (VigiBase[3], FAERS[4], VAERS[5] and JADER[6]), which have been standardized, de-duplicated and corrected for masking effects in the CLARITY PV technology platform.[7]

To identify statistically significant AEs, we used the proportional reporting ratio (PRR), which quantifies the extent to which an AE is more frequently reported with a given drug than with other drugs. More specifically, we focused on those AEs that were detected by CLARITY PV as signals of disproportionate reporting at some point during the lifetime of the drug (PRR > 2), either for valproic acid or simvastatin

RESULTS AND CONCLUSIONS

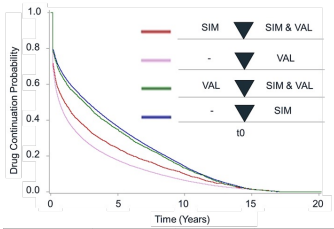
Drug, age, sex and tumor exemption distribution in the Lombardy Region study cohort

2005-2021	VAL	SIM	VAL + SIM
N	67407	656847	7397
45-49	12265 (18.2%)	32045 (4.88%)	491 (6.64%)
50-59	18647 (27.66%)	129696 (19.75%)	15 (20.48%)
60-69	13678 (20.29%)	205623 (31.3%)	2020 (27.31%)
70-79	12281 (18.22%)	201435 (30.67%)	2125 (28.73%)
80-89	8664 (12.85%)	81958 (12.48%)	1135 (15.34%)
90-99	1840 (2.73%)	6032 (0.92%)	111 (1.5%)
100+	32 (0.05%)	58 (0.01%)	-
M	31475 (46.69%)	304712 (46.39%)	3521 (47.6%)

Exemption for Tumor (ese_id=048 e 0043) Dates intervals	VAL	SIM	VAL+ SM
end ex < study entry	1315 (1.95%)	11389 (1.73%)	176 (2.38%)
start ex <=study entry<=end ex	4806 (7.13%)	42716 (6.50%)	544 (7.35%)
study entry<=start ex <=study exit	1812 (2.69%)	36725 (5.59%)	430 (5.81%)
start ex>study exit	3020 (4.48%)	40115 (6.11%)	145 (1.95%)

- A total of 7397 subjects have been taking both VAL and SIM between 2005 and 2021.
- 1295 subjects among them had a tumor (tumor exemption from medical care expenses) before (first row), after (last row), or during the study interval (central rows).
- No patients had chemotherapy treatment in concomitance with VAL+SIM assumption.

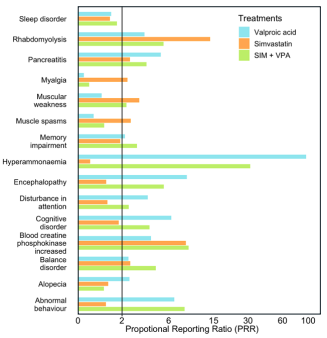
Discontinuation rate as a proxy of adverse effects



HR(95% C.I.)	Unadjusted	Sex and age adjusted	Sex, age and *DDCI adjusted
SIM/VAL vs VAL only	0.85 (0.82; 0.88)	0.78 (0.76; 0.81)	0.77 (0.74; 0.79)
VAL/SIM vs SIM only	1.04 (1.00; 1.08)	1.07 (1.03; 1.11)	1.05 (1.01;1.09)

- There is no increase in the discontinuation rate of either drug, whether treatment was started with or without prior treatment with the other.
- The very slight increase, although significant after adjustment for sex, age and DDCI (HR1.05 CI 1.01-1.09). Rather, there is a decrease in the discontinuation rate of valproate in patients who were already taking simvastatin.

Adverse Drug Reaction post-marketing data (CLARITY PV)



- Reassuringly, except for balance disorder, the proportional reporting ratio (PRR) levels are not higher in patients taking both valproic acid and simvastatin, when compared to monotherapy use of the two drugs. Rather, in most cases, they are lower

Despite the possible metabolic interactions, **no signs of increased safety concerns are evident in the population of patients taking both these drugs**.

We are currently exploring the possibility of accessing similar data in **Campania**, another Italian region, and in **SERMAS**.

This indication of a lower drug toxicity, deriving from two independent sources and data types may be due to a **lower drug bioavailability**, consequent to a metabolic interaction with simvastatin, and warrants further investigations

REFERENCES

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2) https://www.sas.com/

3) https://who-umc.org/vigibase/

4) https://open.fda.gov/data/faers/

5) https://vaers.hhs.gov/

6) Pharmaceuticals and Medical Devices Agency. Japanese adverse drugevent report database. https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0005.html (in Japanese).

7) https://claritypv.com/

AFFILIATIONS AND ACKNOWLEDGMENTS

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