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Summary of Study Results Using National Database of Health Insurance Claims and Specific Health Checkup of Japan (NDB)

February 15, 2024

Study title

Evaluation of the risk of artery dissection due to systemic exposure to VEGF/VEGFR inhibitors

Products investigated

Following vascular endothelial growth factor (VEGF) or its receptor (VEGFR) inhibitors (hereinafter referred to as "VEGF/VEGFR inhibitors"):

Axitinib, aflibercept beta (genetical recombination), cabozantinib malate, sunitinib malate, sorafenib tosilate, nintedanib ethanesulfonate, pazopanib hydrochloride, vandetanib, bevacizumab (genetical recombination)[§], ramucirumab (genetical recombination), regorafenib hydrate, and lenvatinib mesilate

[§]Including biosimilars

Background:

- In August 2019, based on evaluation using EudraVigilance and discussions with marketing authorization holders, the European Medicines Agency (EMA) recommended adding aneurysm and artery dissection to the Special warnings and precautions for use section in the Summary of Product Characteristics for VEGF/VEGFR inhibitors administered systemically[1]. The US Food and Drug Administration (FDA) detected signals of aneurysm and artery dissection with VEGF/VEGFR inhibitors from January to March 2020 in the FDA Adverse Event Reporting System (FAERS)[2], and aneurysm and

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artery dissection were added to the Adverse Reactions section in the United States Prescribing Information.

- In Japan, based on the fact that multiple domestic cases of artery dissection for which a causal relationship to the drug cannot be denied have been reported for bevacizumab (genetical recombination) among VEGF/VEGFR inhibitors, artery dissection was added to the Clinically Significant Adverse Reactions section in the package insert in June 2020. As for VEGF/VEGFR inhibitors other than bevacizumab (genetical recombination) at this point, although it was explainable that artery dissection may be caused by the mechanism of action of VEGF/VEGFR inhibitors, there were no sufficient specific data supporting the relationship; therefore, the package insert was not revised. For these drugs, the necessity of issuing a precaution for artery dissection has been continuously investigated. However, due to reasons including the difficulty to differentiate its onset from onsets associated with background factors such as hypertension based on individual case reports, there was a limitation in the evaluation only with information based on individual case reports. Therefore, to investigate the possibility of occurrence of artery dissection as a class effect in VEGF/VEGFR inhibitors other than bevacizumab (genetical recombination), a study using a nationwide medical information database was planned.

Purpose of the study

The following primary and secondary objectives were set to investigate whether there is a class effect between artery dissection and VEGF/VEGFR inhibitors.

Primary objective: To calculate the frequency of artery dissection during the prescription period of each VEGF/VEGFR inhibitor

Secondary objective: To compare the frequency of artery dissection in patients prescribed docetaxel in combination with ramucirumab (genetical recombination) with that in patients prescribed docetaxel alone in patients with non-small cell lung cancer on a second-line therapy

Reason to select NDB for the study and data period

Reason to select: It was selected because it is the nationwide database in Japan, and it is

possible to collect medical information from nationwide multiple different medical institutions.

Data period: August 1, 2010 to March 31, 2020

Outline of method

Primary objective:

Based on the cohort design, the incidence of artery dissection during the follow-up period was evaluated in patients who received a prescription of any VEGF/VEGFR inhibitor during the period between April 1, 2012 and March 31, 2020. If multiple different VEGF/VEGFR inhibitors were prescribed during this period, a follow-up period was set for each VEGF/VEGFR inhibitor. The following patients were excluded: Patients whose start date and end date of the follow-up period were the same; those who received a prescription of the same VEGF/VEGFR inhibitor as that at the start of the follow-up period during the period between August 1, 2010 and March 31, 2012. A similar evaluation was also performed in the population excluding patients with a history of hypertension, which is a risk factor for artery dissection.

- Definition of the follow-up period:

  For each VEGF/VEGFR inhibitor, the first prescription date during the period between April 1, 2012 and March 31, 2020 was defined as the first prescription date, and the period from the following day to [1] the date of outcome onset; [2] the prescription end date of the VEGF/VEGFR inhibitor* plus 30 days; or [3] the date of completion of the data period; whichever came first, was defined as the follow-up period of the VEGF/VEGFR inhibitor.

  * For intravenous infusions, the prescription end date was defined as the latest prescription date plus 20 days. For capsules or tablets, the date was calculated as the latest prescription date plus the number of prescription days minus one day.

- Outcome definition[3]: The onset of artery dissection was defined as the case where either of the following A or B was met, and the date of outcome onset was defined as the earliest onset date during the follow-up period. The index date was defined as the date of admission for the artery dissection.

  A: All of the following 1) to 3) are met.

  1) A disease name related to artery dissection (excluding suspected conditions) is

listed in the injury/disease name in the medicine, diagnosis, and procedure codes of Diagnosis Procedure Combination (DPC) receipt (Diagnoses were identified using data items that corresponded to any of the following: Main diagnosis, admission-precipitating diagnosis, most resource-consuming diagnosis, second resource-consuming diagnosis, comorbidities at admission or comorbidities after admission).

2) Patients who underwent either thoracic endovascular aortic repair or aortic aneurysmectomy (including anastomosis or grafting; regarding the ascending aorta, aortic arch, and simultaneous surgery of the ascending aorta and aortic arch) or who were prescribed nicardipine injection on the index date or the following day.
3) Patients who did not undergo vascular embolization (hemostasis in the head, thoracic cavity, intraperitoneal vessels, etc. or other procedures) on the day of or within 7 days after the index date.

B: The following is met.

1) A disease name related to artery dissection is listed in the injury/disease name in the medicine, diagnosis, and procedure codes of DPC receipt (Diagnoses were identified using data items that corresponded to any of the following: Main diagnosis, admission-precipitating diagnosis, most resource-consuming diagnosis, second resource-consuming diagnosis, comorbidities at admission and comorbidities after admission), and the day of discharge is the same day as or the day following the index date.

Secondary objective:

Based on the cohort design, in patients with non-small cell lung cancer on second-line therapy who were prescribed docetaxel or ramucirumab (genetical recombination) during the period between April 1, 2014 and March 31, 2020, the incidence of artery dissection in patients prescribed docetaxel in combination with ramucirumab (genetical recombination) and that in patients prescribed docetaxel alone were compared. The following patients were excluded: Patients whose start date and end date of the follow-up period were the same; patients at high risk of artery dissection; patients who may have cancer other than non-small cell lung cancer; and patients who received a prescription of docetaxel alone after the

indication for non-small cell lung cancer was approved for ramucirumab (genetical recombination). In order to include only newly prescribed patients, those prescribed docetaxel between August 1, 2010 and March 31, 2014 were also excluded.

- Follow-up period:

  The first prescription date was defined as the earliest date on which either docetaxel or ramucirumab (genetical recombination) was prescribed during the period between April 1, 2014 and March 31, 2020. The follow-up period was defined as the period from the following day of the first prescription date to [1] the date of outcome onset; [2] the prescription end date of docetaxel or ramucirumab (genetical recombination)**; [3] the start date of prescriptions of ramucirumab (genetical recombination) in the docetaxel group; or [4] the date of completion of the data period; whichever came first.

  ** The prescriptions end date was defined as [1] the prescription end date of docetaxel for the docetaxel group, and as [2] the prescription end date of ramucirumab (genetical recombination) for the group prescribed docetaxel in combination with ramucirumab (genetical recombination). In the secondary objective, the end date of prescriptions was intended to be the time point when a series of treatment was completed. If the start date of the following prescription was within 90 days from the start date of the preceding prescription, the series of treatment was judged to be continuous. The end date of each prescription unit was determined by adding 20 days to the start date of the prescription, in consideration of the dosing intervals.
- Outcome definition: The same definition as the primary objective was used.

Outline of results

■ Patient background

Table 1 (appended to the end of this document) shows the number of patients prescribed each VEGF/VEGFR inhibitor and patient background information. The number of patients aged 50 years or older was high for all drugs in common. As for sex, it is considered that the distribution differed depending on the indication of the drug. No obvious difference was observed in the distribution of the past medical history.

■ Risk assessment

- Table 2 shows the total duration of follow-up for each VEGF/VEGFR inhibitor, the number of onsets and incidence of artery dissection, as well as the incidence ratio and adjusted incidence ratio compared with those for bevacizumab (genetical recombination). Table 3 shows the results in the population excluding patients with a

past medical history of hypertension.

Table 2. Total duration of follow-up for each VEGF/VEGFR inhibitor, the number of onsets and incidence of artery dissection, as well as the incidence ratio and adjusted incidence ratio compared with those for bevacizumab (genetical recombination)

	Number of patients (persons)	Total follow-up duration (PY)	Number of onsets (persons)	Incidence rate (/100 000 PY)	Incidence rate ratio (95% CI)	Adjusted incidence rate ratio* (95% CI)
Bevacizumab (genetical recombination)	278 722	281 401.43	125	44.4	Reference	Reference
Axitinib	13 082	13 010.07	23	176.8	3.98 (2.55−6.21)	3.37 (2.15−5.28)
Aflibercept beta (genetical recombination)	5 657	2 439.76	<10†	–†	–† (1.89−11.28)	4.30 (1.76−10.52)
Sunitinib malate	16 870	13 370.37	29	216.9	4.88 (3.26−7.31)	4.39 (2.91−6.60)
Sorafenib tosilate	33 849	20 539.99	23	112.0	2.52 (1.62−3.93)	1.90 (1.21−3.00)
Nintedanib ethanesulfonate	20 276	21 324.71	21	98.5	2.22 (1.40−3.52)	1.61 (1.00−2.59)
Pazopanib hydrochloride	15 141	9,880.31	15	151.8	3.42 (2.00−5.84)	3.19 (1.87−5.46)
Vandetanib	102	125.52	<10†	–†	–† (2.51−128.32)	21.47 (2.99−154.15)
Ramucirumab (genetical recombination)	73 593	33 322.10	21	63.0	1.42 (0.89−2.25)	1.19 (0.75−1.90)
Regorafenib hydrate	25 691	8 721.58	10	114.7	2.58 (1.36−4.92)	2.22 (1.16−4.24)
Lenvatinib mesilate	20 359	13 687.92	19	138.8	3.12 (1.93−5.06)	2.51 (1.54−4.09)
Cabozantinib malate	0	0	0	0.0	−	−

* Adjusted covariates: Sex and age (< 65 years/≥ 65 years)
† The data are masked so that the number of patients (less than 10) cannot be identified according to the publication criteria of NDB.
As a result of additional analysis for the natural incidence rate of artery dissection using the overall population of the NDB, the crude incidence was 1.66 (95% CI: 1.59−1.73) [/100 000 person-years], and the standardized incidence rate (Sex and age were standardized to the bevacizumab (genetical recombination)-prescribed patient population.) was 2.18 (95% CI: 1.86 - 2.50) [/100 000 person-years].
As a result of another additional analysis, adjusted incidence ratio was calculated using each history of hypertension, artery dissection, cardiovascular events, diabetes mellitus, and dyslipidemia as adjusted covariates, in addition to sex and age (< 65 years/≥ 65 years). The results of this additional analysis showed a similar trend to the results in Table 2. (For each VEGF/VEGFR inhibitor, the risk of artery dissection was consistently comparable or higher than that for bevacizumab (genetical recombination).)
Abbreviations: CI, confidence interval; PY, person-years.

Table 3. Total duration of follow-up for each VEGF/VEGFR inhibitor, the number of onsets and incidence of artery dissection, as well as the incidence ratio and adjusted incidence ratio compared with those for bevacizumab (genetical recombination) in patients without a past medical history of hypertension

	Number of patients (persons)	Total follow-up duration (PY)	Number of onsets (persons)	Incidence rate (/100 000 PY)	Incidence rate ratio (95% CI)	Adjusted incidence rate ratio* (95% CI)
Bevacizumab (genetical recombination)	197 453	206 388.37	77	37.3	Reference	Reference
Axitinib	5 731	–†	–†	132.0	3.54 (1.71−7.33)	2.96 (1.42−6.15)
Aflibercept beta (genetical recombination)	3 028	–†	<10†	223.5	5.99 (1.89−18.99)	5.61 (1.77−17.79)
Sunitinib malate	9 704	8 167.55	11	134.7	3.61 (1.92−6.79)	3.17 (1.68−6.01)
Sorafenib tosilate	16 275	10 205.77	10	98.0	2.63 (1.36−5.08)	1.91 (0.98−3.73)
Nintedanib ethanesulfonate	11 727	12 815.01	10	78.0	2.09 (1.08−4.04)	1.40 (0.72−2.75)
Pazopanib hydrochloride	7 830	–†	<10†	115.3	3.09 (1.35−7.09)	3.13 (1.36−7.19)
Vandetanib	65	–†	<10†	1183.3	31.72 (4.41−228.03)	38.68 (5.36−279.09)
Ramucirumab (genetical recombination)	44 971	–†	–†	43.1	1.15 (0.58−2.30)	0.94 (0.47−1.89)
Regorafenib hydrate	12 992	–†	<10†	69.0	1.85 (0.58−5.86)	1.59 (0.50−5.06)
Lenvatinib mesilate	8 265	–†	–†	130.1	3.49 (1.68−7.22)	2.80 (1.35−5.83)
Cabozantinib malate	0	0	0	0.0	−	−

* Adjusted covariates: Sex and age (< 65 years/≥ 65 years)
† The data are masked so that the number of patients (less than 10) cannot be identified according to the publication criteria of NDB.
Abbreviations: CI, confidence interval; PY, person-years.

- In the investigation of the secondary objective, the number of patients who developed artery dissection among patients who met the inclusion criteria was 0 in patients prescribed docetaxel in combination with ramucirumab (genetical recombination) and less than 10 in patients prescribed docetaxel alone, making it impossible to conduct a comparative analysis.

■ **Discussion based on the results**

- For each VEGF/VEGFR inhibitor, the risk of artery dissection was consistently comparable or higher than that for bevacizumab (genetical recombination) (Table 2). Results in the patient population without a history of hypertension showed the same trend as those in Table 2 (Table 3).
- The results for vandetanib showed the highest incidence rate ratio in comparison to bevacizumab (genetical recombination). However, the number of patients prescribed vandetanib was markedly smaller than that for other VEGF/VEGFR inhibitors, which may have affected the results.
- Given that a precaution for the risk of artery dissection has already been issued for bevacizumab (genetical recombination), these results above are considered to indicate that there is a class effect between VEGF/VEGFR inhibitors and the onset of artery dissection. Since this study uses the NDB, which has traceability across medical institutions, the onsets of artery dissection during the prescription period of VEGF/VEGFR inhibitors observed in this study are deemed highly comprehensive. On the other hand, it should be noted that there are certain limitations in the evaluation of the results, including the following: Although the outcome definition validated in MID-NET® was referred to, the validation study in the NDB has been unachievable due to the prohibition of identifying patients and linking to the other electronic health records; there is a certain limit to the reliability of information on exposure and patient traceability; the unmeasured confounders may have affected the results; the differences in the indications for each drug may have resulted in a bias due to confounding by indications when estimating the incidence rate ratios using bevacizumab (genetical recombination) as a reference.

[1] European Medicines Agency; PRAC recommendations on signals, Adopted at the 8-11 July 2019 PRAC meeting; (https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-8-11-july-2019-prac-meeting_en.pdf). Accessed on Oct 4, 2023.
[2] Food and Drug Agency ; Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS); January - March 2020.; (https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/january-march-2020-potential-signals-serious-risksnew-safety-information-identified-fda-adverse). Accessed on Oct

4, 2023.

[3] The definition of acute artery dissection (including dissecting aneurysm) requiring hospitalization that was implemented in the "Research on Characterization and Methods of Extraction and Analysis of MID-NET® Data, under the Research on Regulatory Science of Pharmaceuticals and Medical Devices supported by the Japan Agency for Medical Research and Development" was used as the definition in this study after making minimum corrections required to match the data items available in the NDB.

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Table 1. Patient background

	Axitinib		Aflibercept beta (genetical recombination)		Sunitinib malate		Sorafenib tosilate		Nintedanib ethanesulfonate		Pazopanib hydrochloride	
Number of patients (persons)	13 082		5 657		16 870		33 849		20 276		15 141	
Age												
0-9 years old	0	0%	0	0%	<10	<0.06%	29	0.09%	0	0%	31	0.20%
10-19 years old	10	0.08%	0	0%	<20	<0.12%	59	0.17%	<10	<0.05%	181	1.20%
20-29 years old	26	0.20%	<20	<0.35%	71	0.42%	45	0.13%	<20	<0.10%	290	1.92%
30-39 years old	108	0.83%	108	1.91%	239	1.42%	154	0.45%	55	0.27%	514	3.39%
40-49 years old	651	4.98%	386	6.82%	1 076	6.38%	763	2.25%	210	1.04%	1 171	7.73%
50-59 years old	1 764	13.48%	932	16.48%	2 416	14.32%	2 689	7.94%	1 055	5.20%	2 117	13.98%
60-69 years old	4 434	33.89%	2 037	36.01%	5 840	34.62%	9 441	27.89%	5 265	25.97%	4 342	28.68%
70-79 years old	4 587	35.06%	1 900	33.59%	5 512	32.67%	13 795	40.75%	10 215	50.38%	4 618	30.50%
80-89 years	1 475	11.28%	278	4.91%	1 657	9.82%	6 695	19.78%	3 368	16.61%	1 807	11.93%
90 years or older	27	0.21%	<10	<0.18%	43	0.25%	179	0.53%	90	0.44%	70	0.46%
Sex												
Female	3 357	25.66%	2 325	41.10%	4 682	27.75%	7 475	22.08%	4 856	23.95%	5 756	38.02%
Male	9 725	74.34%	3 332	58.90%	12 188	72.25%	26 374	77.92%	15 420	76.05%	9 385	61.98%
Past medical history												
Artery dissection	40	0.31%	10	0.18%	24	0.14%	61	0.18%	30	0.15%	39	0.26%
Cardiovascular events	293	2.24%	58	1.03%	237	1.40%	640	1.89%	758	3.74%	338	2.23%
Hypertension	7 351	56.19%	2 629	46.47%	7 166	42.48%	17 574	51.92%	8 549	42.16%	7 311	48.29%
Diabetes mellitus	2 408	18.41%	919	16.25%	2 815	16.69%	9 270	27.39%	5 109	25.20%	2 617	17.28%
Dyslipidemia	3 646	27.87%	1 423	25.15%	3 944	23.38%	6 130	18.11%	7 610	37.53%	4 322	28.55%
Indications												
Unknown	364	2.78%	48	0.85%	1 086	6.44%	607	1.79%	234	1.15%	1 743	11.51%
Lung cancer	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Gastric cancer	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Breast cancer	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Colorectal cancer	0	0%	5 609	99.15%	0	0%	0	0%	0	0%	0	0%
Renal cell carcinoma	12 718	97.22%	0	0%	12 780	75.76%	3 851	11.38%	0	0%	8 988	59.36%
Hepatocellular carcinoma	0	0%	0	0%	0	0%	28 373	83.82%	0	0%	0	0%
Pancreatic neuroendocrine tumor	0	0%	0	0%	1 108	6.57%	0	0%	0	0%	0	0%
Cervical cancer	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Ovarian cancer	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Thyroid cancer	0	0%	0	0%	0	0%	1 194	3.53%	0	0%	0	0%
Gastrointestinal stromal tumor	0	0%	0	0%	2 056	12.19%	0	0%	0	0%	0	0%
Malignant soft tissue tumor	0	0%	0	0%	0	0%	0	0%	0	0%	4 616	30.49%
Malignant glioma	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Interstitial lung disease	0	0%	0	0%	0	0%	0	0%	20 042	98.85%	0	0%

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Table 1 Patient Background (continued)

	Vandetanib		Bevacizumab (genetical recombination)		Ramucirumab (genetical recombination)		Regorafenib hydrate		Lenvatinib mesilate		Cabozantinib malate	
Number of patients (persons)	102		278 722		73 593		25 691		20 359		0	
Age												
0-9 years old	0	0%	347	0.12%	<10	<0.01%	0	0%	0	0%	0	0%
10-19 years old	<10	<9.80%	386	0.14%	<10	<0.01%	15	0.06%	<10	<0.05%	0	0%
20-29 years old	<10	<9.80%	1 150	0.41%	139	0.19%	51	0.20%	<30	<0.15%	0	0%
30-39 years old	<10	<9.80%	6 579	2.36%	986	1.34%	360	1.40%	82	0.40%	0	0%
40-49 years old	13	12.75%	23 140	8.30%	3 732	5.07%	1 456	5.67%	441	2.17%	0	0%
50-59 years old	17	16.67%	46 357	16.63%	8 861	12.04%	3 771	14.68%	1 400	6.88%	0	0%
60-69 years old	34	33.33%	95 495	34.26%	25 848	35.12%	9 104	35.44%	4 937	24.25%	0	0%
70-79 years old	22	21.57%	85 335	30.62%	28 271	38.42%	8 869	34.52%	8 658	42.53%	0	0%
80-89 years	<10	<9.80%	19 558	7.02%	5 661	7.69%	2 033	7.91%	4 606	22.62%	0	0%
90 years or older	<10	<9.80%	375	0.13%	86	0.12%	32	0.12%	204	1.00%	0	0%
Sex												
Female	39	38.24%	143 338	51.43%	22 818	31.01%	9 455	36.80%	5 805	28.51%	0	0%
Male	63	61.76%	135 384	48.57%	50 775	68.99%	16 236	63.20%	14 554	71.49%	0	0%
Past medical history												
Artery dissection	0	0%	215	0.08%	100	0.14%	55	0.21%	40	0.20%	0	0%
Cardiovascular events	<10	<9.80%	2 064	0.74%	1 131	1.54%	301	1.17%	518	2.54%	0	0%
Hypertension	37	36.27%	81 269	29.16%	28 622	38.89%	12 699	49.43%	12 094	59.40%	0	0%
Diabetes mellitus	18	17.65%	33 487	12.01%	11 902	16.17%	4 814	18.74%	6 580	32.32%	0	0%
Dyslipidemia	16	15.69%	54 662	19.61%	17 390	23.63%	5 683	22.12%	5 159	25.34%	0	0%
Indications												
Unknown	<10	<9.80%	11 020	3.95%	3 613	4.91%	542	2.11%	151	0.74%	0	0%
Lung cancer	0	0%	47 114	16.9%	13 695	18.61%	0	0%	0	0%	0	0%
Gastric cancer	0	0%	0	0%	41 802	56.80%	0	0%	0	0%	0	0%
Breast cancer	0	0%	32 932	11.82%	0	0%	0	0%	0	0%	0	0%
Colorectal cancer	0	0%	158 149	56.74%	15 954	21.68%	21 426	83%	0	0%	0	0%
Renal cell carcinoma	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Hepatocellular carcinoma	0	0%	1 158	0.42%	1 215	1.65%	3 052	11.88%	15 934	78.27%	0	0%
Pancreatic neuroendocrine tumor	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Cervical cancer	0	0%	5 283	1.90%	0	0%	0	0%	0	0%	0	0%
Ovarian cancer	0	0%	17 706	6.35%	0	0%	0	0%	0	0%	0	0%
Thyroid cancer	<102	<100%	0	0%	0	0%	0	0%	4 481	22.01%	0	0%
Gastrointestinal stromal tumor	0	0%	0	0%	0	0%	1 089	4.24%	0	0%	0	0%
Malignant soft tissue tumor	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Malignant glioma	0	0%	12 664	4.54%	0	0%	0	0%	0	0%	0	0%
Interstitial lung disease	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%

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