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ORIGINAL ARTICLE

The Effectiveness of Sorafenib over Other Targeted Agents in the Second-Line Treatment of Metastatic Renal Cell Carcinoma: a Meta-Analysis

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Abstract
The aim of the study was to perform a meta-analysis to compare the therapeutic effects and adverse events (AEs) of sorafenib in second-line treatments of metastatic renal cell carcinoma (mRCC). We searched online electronic databases: Pubmed, Embase, Cochrane library updated on November 2017.Trials of the effectiveness of sorafenib in second-line treatments of advanced RCC were included, of which the main outcomes were objective response rate (ORR), progression-free survival (PFS), overall survival (OS) and grade 3/4 AE. Other TAs significantly reduced the risk of PFS compared to sorafenib with respect to second-line treatment (HR = 0.74; 95% CI, 0.65–0.83; $p < 0.00001$). No significant differences were, however, found in patients in terms of the ORR (HR = 1.82; 95% CI, 0.98–3.35; $p = 0.06$). Frequencies of the most common toxicities were overall similar and adverse events differed only in sensitivity analysis in rash with exclusion of other TAs (HR = 0.16; 95% CI, 0.05–0.52; $p = 0.002$). Overall survival was not debated between groups. In patients with mRCC, second-line sorafenib is associated with similar ORR as other target agents. While, sorafenib did not demonstrate a PFS advantage compared with other target agents, suggests sorafenib may not benefit patients with mRCC. Tolerability due to toxicities is similar compared sorafenib with other target agents. Further characterization of the RCC oncogenic pathway, and the ongoing clinical trials should help optimize the treatment option for second-line therapy of advanced renal cell carcinoma.

Keywords Sorafenib · Metastatic renal cell carcinoma · Second-line therapy · Meta-analysis

Introduction

Renal cell carcinomas (RCCs) arise from the renal cortex and represent 90% of all kidney tumors [1]. The lack of reliable predictors and initial symptoms results in one third to one half of RCCs presenting with locally advanced or progressing to metastatic stage (mRCC) [2].

The prognosis for mRCC is poor, which can be largely attributed to relative resistant nature of mRCC to conventional chemotherapy [3]. In recent years, targeted therapies have proven beneficial in terms of median survival [4], which have recently replaced cytokine treatments as the gold standard for management of metastatic renal cell carcinoma (mRCC).

The tyrosine kinase inhibitor (TKI), sorafenib, is a synthetic compound targeting growth signaling and angiogenesis. It inhibits the VEGFR-2/PDGFR-beta signaling cascade, thereby blocking tumor angiogenesis. Sorafenib was the first targeted agent (TA) for superior overall survival (OS) and inferior PFS compared with other TAs [5, 6]. However, this is challenged by more TAs (axitinib, sunitinib and tivozanib) compared to sorafenib as an optional treatment in first-line and second-line treatments in that have shown significantly increased PFS of mRCC [7].

In addition, evidence from randomized trials in mRCC does not directly shown impacts on OS, due to crossovers between treatment arms following disease progression. Given the large number of treatment

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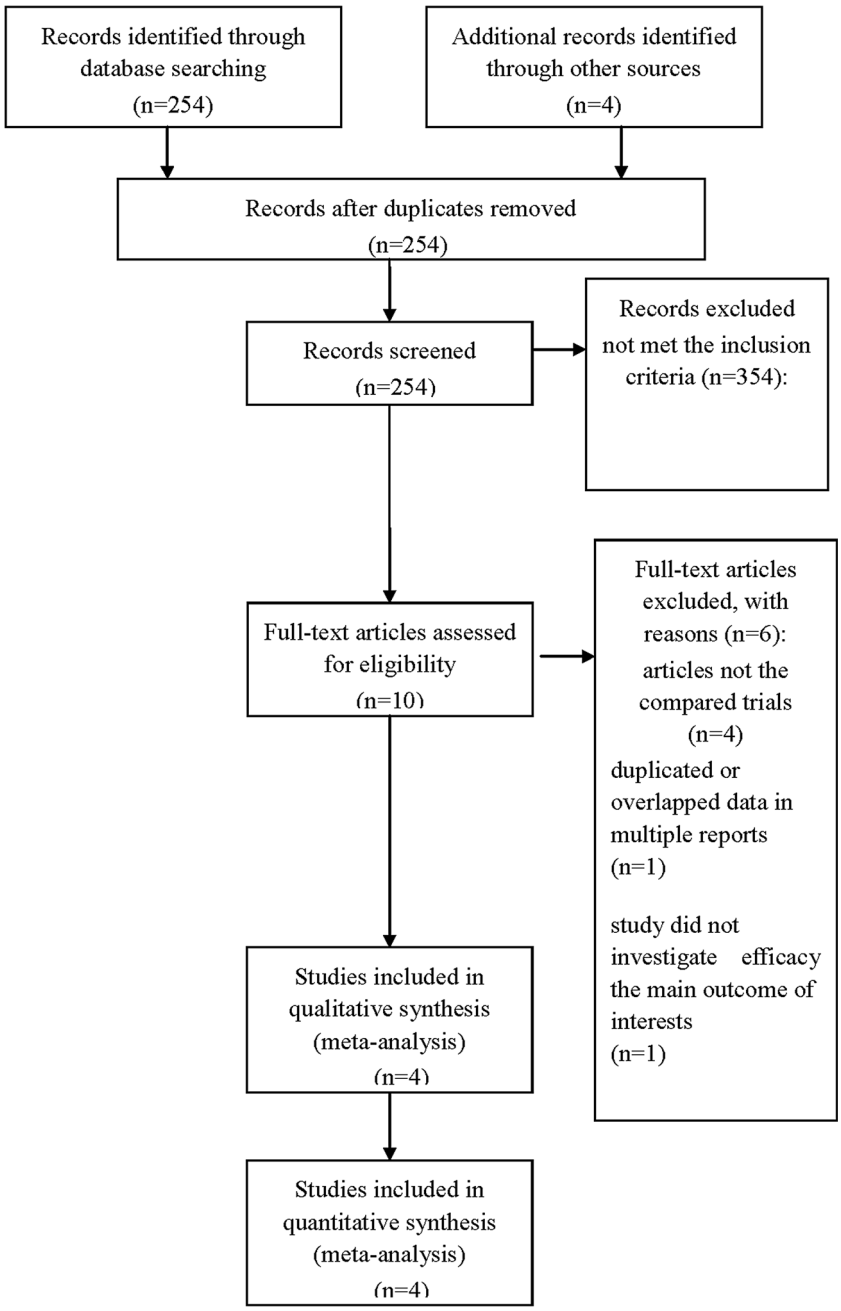

Fig. 1 PRISMA flow chart of selection process to identify studies eligible for pooling

options for RCC following the disease progression or the failure of a first targeted therapy, the comparative effectiveness of different sequential treatment strategies for mRCC, especially in terms of OS, is of high interest to physicians and patients [8]. Guidelines have recommend sorafenib as sequential treatment of care for mRCC. A number of studies have been conducted to compare outcomes with sorafenib. However, there is no consensus on the optimal sequencing of sorafenib after the failure of first- line treatment [7, 9].

In order to make more rational choice of second-line treatment for mRCC patients, we perform a meta-analysis of studies was to evaluate the therapeutic effect and adverse effects of sorafenib compared to other TAs in second-line treatments of mRCC.

Methods and Materials

Search Strategy

Two investigators independently searched electronic databases: Pubmed, Embase, Cochrane library up to November 2017.The process was established to find all

Table 1 the primary characteristics of the eligible studies in more detail

Study,Year	other TAs	Sorafenib	Treatment regimen
T.E. Hutson [5]	259	253	intravenous temsirolimus 25 mg once weekly or oral sorafenib 400 mg twice per day
B.I Rini [6]	361	362	axitinib (5 mg twice daily) or sorafenib (400 mg twice daily)
R.J Motzer [12]	359	355	axitinib (5 mg twice daily) or sorafenib (400 mg twice daily)
shukui Qin, [13]	135	69	axitinib (5 mg twice daily) or sorafenib (400 mg twice daily)

articles with the keywords: "renal cell carcinoma" AND "second line", AND "sorafenib", and relevant Medical Subject Heading (MeSH) terms were utilized. The reference lists of all articles that dealt with the topic of interest were also hand-searched to check for additional relevant publications.

Eligibility Criteria

Studies were included in the meta-analysis should meet the following criteria: [1] the studies are designed as randomized controlled trials; [2] second-line treatment with sorafenib was considered to be the control arm and treatment with other TAs the experimental arm for each trial; [3] the articles that enrolled mRCC patients and/or advanced RCC patients; [4] the outcomes of interest were efficacy (survival, tumor response) and toxicity (incidence of severe adverse effects (SAEs)), and HRs with corresponding 95% CIs were provided; If we found duplicated or overlapped data in multiple reports, we just include the one with most complete information.

Quality Assessment

Two investigators separately rated the quality of the retrieved studies. We choose the risk of bias items (ROBI) recommended by The Cochrane Handbook for Systematic Reviews of Interventions.

Data Extraction

Two authors independently extracted the relevant data from each trial. Disagreement was revolved by consensus. From each of the eligible studies, the main categories were based on the following: first author family name, publication year, treatment regimen, end-point of interests. We extracted the corresponding hazard ratios (HRs) and risk ratios (RRs) to describe the strength of the association for survival (overall (OS) and progression-free survival (PFS)) and dichotomous (overall response rate (ORR) and serve adverse effect (SAE) rate (grade ≥ 3)) data, respectively, with corresponding 95% confidence intervals (CIs).

Statistical Analysis

The endpoints of interest in the pooled analysis were OS、PFS 、ORR and SAE data, and the endpoint outcome were considered as a weighted average of individual estimate of the HR in every included study, using the inverse variance method. If HRs and corresponding 95% CIs were reported, lnHRs and the corresponding lnLLs and lnULs were used as data points in pooling analysis.

A sensitivity analysis was also performed to examine the impact on the overall results, depending on the heterogeneity across the included studies. The heterogeneity across studies was examined the I^2 statistic [10]. Studies with an I^2 of 25–50%, 50–75%, or > 75% were considered to have low, moderate, or high heterogeneity, respectively [11]. When there was low heterogeneity among studies, the fixed-effects model was used. Otherwise, the random effects model was used. A *P* value less than 0.05 was considered statistically significant. The statistical analyses were performed using Review Manager version 5.3 software (Revman; The Cochrane collaboration Oxford, United Kingdom). Findings of our meta-analysis were shown in forest

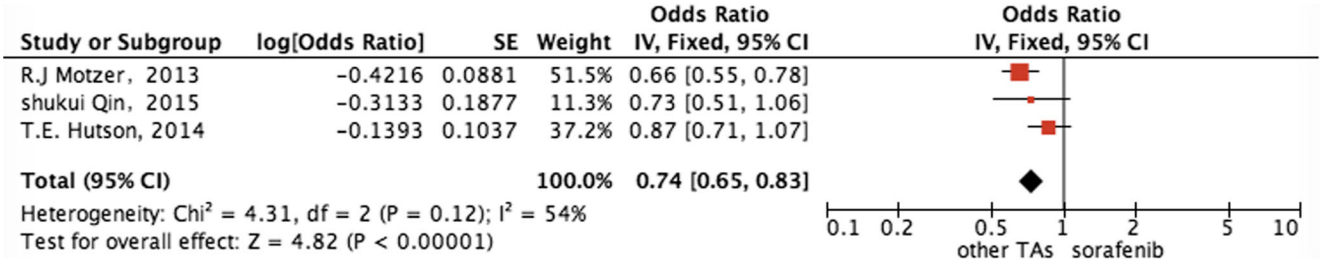

Fig. 2 Pooled analysis of PFS comparing the addition of sorafenib with chemotherapy

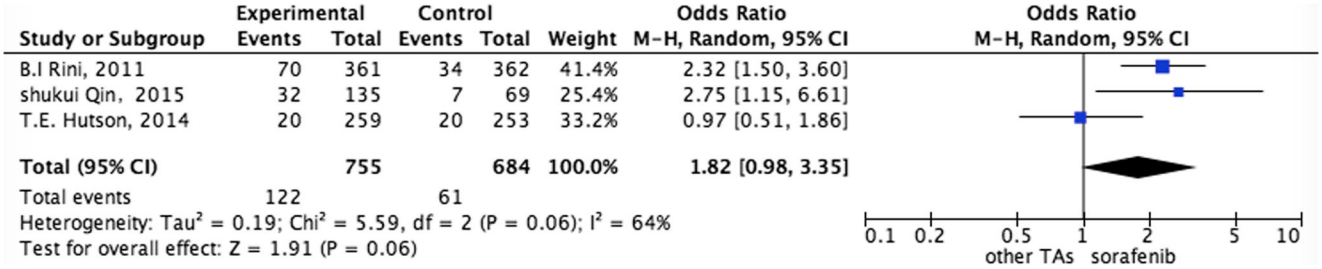

Fig. 3 Pooled analysis of ORR comparing the addition of sorafenib with chemotherapy

plots. The Begg test and the Egger test were conducted to evaluate publication bias.

Results

Overview of Literature Search and Study Characteristics

A total of 254 studies were retrieved initially for evaluation. Based on the criteria described in the methods, 10 publications were evaluated in more detail, but some did not provide enough detail of outcomes of two approaches. Therefore, a final total of four RCTs [5, 6, 12, 13] met the criterion. The search process is described in Fig. 1.

All included studies in this study were based on moderate to high quality evidence. Table 1 describes the primary characteristics of the eligible studies in more detail.

Clinical and Methodological Heterogeneity

Pooled Analysis of PFS Comparing Sorafenib with Other TAs

Pooling the PFS data from three studies [5, 12, 13] showed that significant differences were found in terms of the PFS in the patients favoring other TAs compared with the sorafenib group(HR = 0.74; 95% CI, 0.65–0.83; $p < 0.00001$) (Fig. 2).

Pooled Analysis of OS Comparing Sorafenib with Other TAs

Only two studies reported available data on OS, so it was therefore not possible to perform meta-analysis. Motzer [12] showed that overall survival did not differ between axitinib and sorafenib. While, in Hutson's study [5], there was a significant OS difference in favor of sorafenib.

Pooled Analysis of ORR Comparing Sorafenib with Other TAs

A random- effects model was used to pool the ORR data [5, 6, 13], since the heterogeneity across the four studies was high. The pooling data showed that there is no difference between other TAs agents and sorafenib (HR = 1.82; 95% CI, 0.98–3.35; $p = 0.06$) (Fig. 3).

Pooled Analysis of AEs Comparing Sorafenib with Other TAs

Systematic evaluations of AEs data analysis were shown in the (Figs. 4, 5, 6 and 7). The most common treatment-related adverse events are decreased appetite (OR = 0.73,95%CI = 0.17–3.11, $P = 0.67$) (Fig. 4), fatigue (OR = 1.66,95%CI = 0.67–4.10, $P = 0.28$) (Fig. 5), and weight decrease (OR = 1.22,95%CI = 0.62–2.43, $P = 0.56$) (Fig. 6), the difference between the two groups had no statistical significance. The adverse events differed only in sensitivity analysis in rash with exclusion of other TAs (HR = 0.16; 95% CI, 0.05–0.52; $p = 0.002$) (Fig. 7).

Discussion

Targeted therapy is in a period of rapid development and many new drugs are drastically used in metastatic renal cell carcinoma, with the purpose of achieving benefit of PFS and OS, while maintaining an acceptable safety profile [14]

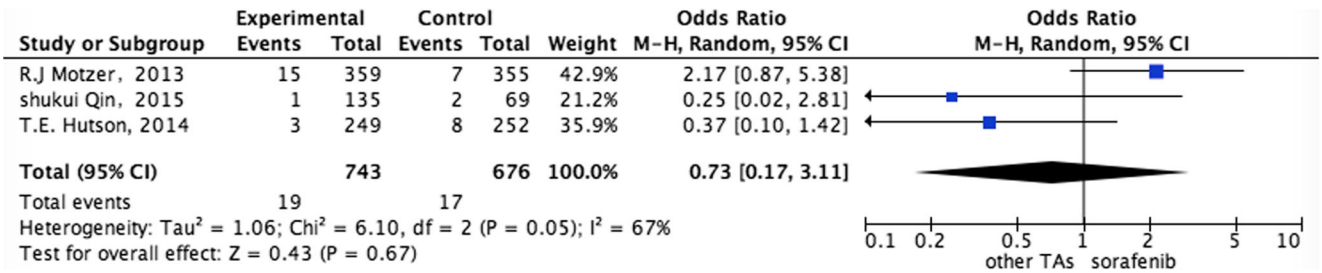

Fig. 4 Pooled analysis of appetite decreased comparing the addition of sorafenib with chemotherapy

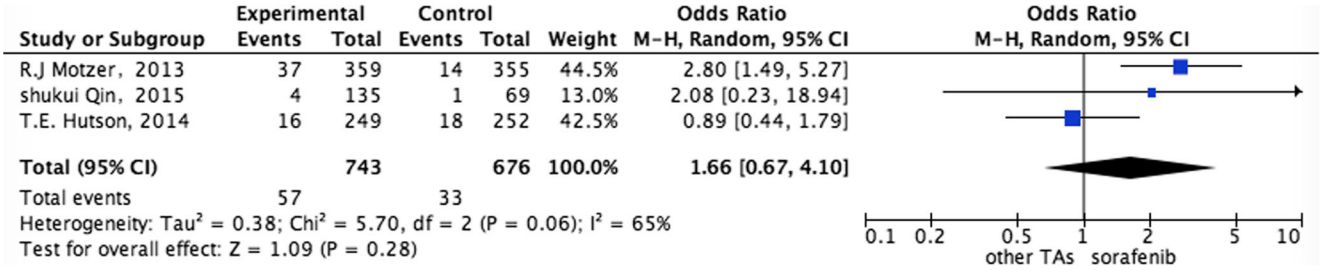

Fig. 5 Pooled analysis of fatigue comparing the addition of sorafenib with chemotherapy

.Controversy exists regarding the optimum sequencing of targeted agents in treatment for metastatic renal cell carcinoma, and, in particular, the use of mTOR inhibitors as second-line treatment after failure of first-line therapy [12].

Sorafenib has been widely used since the TARGET trial proved its efficacy in MRCC patients. It has been the most commonly used TA in second-line therapy for a long time. A recent randomized controlled trial showing comparable PFS but significantly better OS for second-line use of sorafenib versus temsirolimus [5]. According to Lacovelli et al. [7], sorafenib is being challenged by new TAs such as tivozanib, axitinib, and sunitinib, which provide a significant increase in PFS compared to sorafenib in second-line treatments. This raises questions about the role of sorafenib in treatment for MRCC.

Our analysis compared other TAs to sorafenib as second-line therapy after progression on first-line therapy in patients with mRCC. We found that other TAs did show superiority to sorafenib in the PFS, and the ORR was similar between treatments. While,it was not possible to reach a consensus conclusion about comparative effects on OS by pooling these studies.

Potential reasons for heterogeneity in survival data were unclear. MRCC patients switched to variable therapies after the first-line treatment, or a true lack of difference due to an underlying biological mechanism such as an initial response but eventual drug resistance or incomplete cytotoxicity [15, 16]. The potential impact of a rebound effect on patients' overall survival may also be explained by different patient selection factors or unrealized subsequent therapy [5]. The lack of demonstrable survival benefit for MRCC after first-line therapy may thus be due to one or a combination of these causes and remains a barrier to uniform recommendations for a specific sequence of treatments among the multitude of options [17].

Moreover, the aim in the development of selective TAs has been improvement in off-target toxicities. In this meta-analysis, tolerability due to toxicities is similar compared sorafenib with other target agents. No significant differences were found in certain types of AEs. The clinical impact of differences in side-effect profiles between the other TAs and sorafenib may be considered in context of patient-specific factors, to help determine how different safety profiles may affect tolerability for a given patient during counselling for treatment selection.

Efficacy and safety data from all trials may aid oncologists with their choice of second-line treatment. Patients with an intermediate prognosis have a different outcome based on the line of therapy. The characteristics of response first-line therapy or other clinical variables might be important for selecting the best second-line treatment. However, at present, such factors are not well defined and require further study. Additional translational clinical trials are required to understand the different mechanisms of action and identified the patient-specific predictive biomarkers [6]. These factors are indicative of a more aggressive underlying renal cell carcinoma phenotype. The risk factors identified here could be used to counsel patients about prognosis, to design future clinical trials, and to interpret clinical trial data [12].

The inherent flaws of our study should not be ignored, which might have led to potential bias. First, as this study was a study-level meta-analysis, due to the

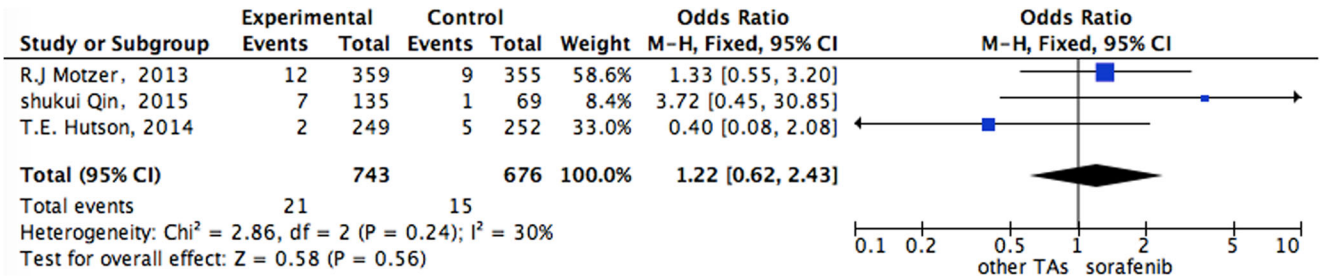

Fig. 6 Pooled analysis of weight decreased comparing the addition of sorafenib with chemotherapy

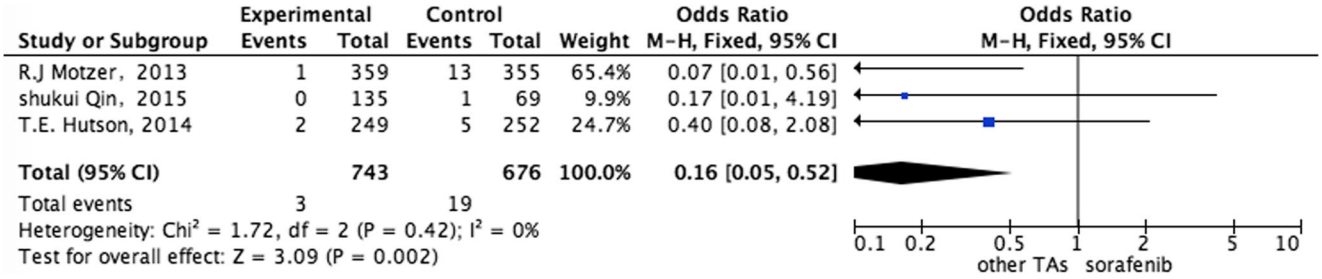

Fig. 7 Pooled analysis of rash comparing the addition of sorafenib with chemotherapy

lack of patient-level data, clinical heterogeneity among trials should be taken into consideration in the interpretation of our findings. Second, there are only two studies reported available data on OS, so we did not have access to predict efficacy in OS.

Conclusion

In conclusion, results from this meta-analysis showed a statistically significant and clinically meaningful improvement in median PFS compared other TAs with sorafenib in MRCC as second-line treatment. The safety profile of other TAs was generally similar to sorafenib and manageable. These results establish the role of sorafenib in second-line therapies of mRCC seems likely to change in favor of newer drugs, since new drugs, such as axitinib and tivozanib, have shown promising response rates and acceptable safety profiles.

Drug selection for individual MRCC patients is an important step, and many factors contribute to treatment selection, including safety profile of the drug and a patient's tolerability to previous therapy, comorbidities, and patient- specific circumstances. The development of validated biomarkers could aid in this regard.

Additional randomized trials assessing comparative effectiveness of treatments are needed to optimize further the use of targeted therapy in renal cell carcinoma and establish appropriate sequencing of drugs. Hence, if ongoing larger studies can confirm this trend, it may be appropriate to update international guidelines regarding sorafenib.

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Analysis and interpretation of data: Hou-Feng Huang and Xin-Rong Fan
Drafting the article: Hou-Feng Huang
Revising the article: Zhi-Gang Ji
GUARANTOR: Zhi-Gang Ji

Compliance with Ethical Standards

Disclosure of Interest The authors declare they have no conflict of interest.

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