Rapid Health Technology Evaluation of Off-label Use of Magnesium Isoglycyrrhizinate Injection

Yao Lan, Li Lin, Tian Lijuan*

(School of Business Administration, Shenyang Pharmaceutical University, Shenyang 110016, China)

Abstract

Objective To evaluate the preventive drug use of magnesium isoglycyrrhizinate injection beyond the instructions by rapid health technology, and to provide reference for its rational clinical application. **Methods** The databases such as PubMed, Embase, the Cochrane Library, HowNet, Wanfang, VIP and HTA websites were searched. Two researchers screened the literature to extract data according to the inclusion and exclusion criteria. If necessary, a third researcher was consulted. The included literature was analyzed and concluded through corresponding quality evaluation. **Results and Conclusion** Four meta-analysis articles and five pharmacoeconomics articles were included. In terms of effectiveness, compared with the blank group and the control group (diammonium glycyrrhizinate, glutathione, and polyene phosphatidylcholine), the preventive use of magnesium isoglycyrrhizinate injection had a lower incidence of drug-induced liver injury with a more significant reduction in the levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin. In terms of safety, except for an economic study in which some patients had a transient increase in blood pressure during the use of magnesium isoglycyrrhizinate injection, other studies did not show the increasing risk of adverse reactions due to preventive medication. In terms of economy, the use of magnesium isoglycyrrhizinate injection for prevention of different diseases did not necessarily have economic advantages over the control group (blank group and reduced glutathione, polyene phosphatidylcholine injection, traditional Chinese medicine combined with magnesium isoglycyrrhizinate injection). In the prevention of drug induced liver injury, magnesium isoglycyrrhizinate injection used beyond the instructions has certain efficacy and safety, but it may not be the economic optimal for other different diseases.

Keywords: magnesium isoglycyrrhizinate; preventive medication; rapid health technology assessment

As a kind of cell protective agent, magnesium isoglycyrrhizinate injection can improve liver function by anti-inflammatory and protecting liver cell membrane. Its indications in the instruction manual show that it is used for the treatment of chronic viral hepatitis and acute drug-induced liver injury [1], but not as a preventive drug. However, it is commonly used as a clinical prevention drug beyond the instruction manual to prevent drug-induced liver injury. In 2015, the Therapeutic Drug Monitoring Committee of the Chinese Pharmacological Society issued the "Expert Consensus on the Off-Label Drug Use", which stipulated that the pharmaceutical administration department of medical institutions should adopt an access system for the off-label use of drugs, and organize medical and pharmaceutical staffs to conduct access approval and regular evaluation for these drugs, so as to prevent and

* Corresponding author: Tian Lijuan, associate professor. Major research area: Pharmaceutical laws and regulations, drug policy and rational drug use. Tel: 024-24517422, E-mail: tianlijuan_8@126.com.

control the risk of drug use. Therefore, safer drug use needs to be evaluated in many aspects.

Drug-induced liver injury (DILI) refers to the liver injury caused by some traditional Chinese medicines, western medicines, biological agents, and natural medicines, which can lead to various acute and chronic liver diseases, serious liver failure and even death [1]. At present, there is no guide to clearly indicate whether some preventive medicines should be used for drug-induced liver injury. In 2021, the latest "Drug Induced Liver Injury: The Consensus Guide of the Asia Pacific Society for Research on Hepatology" issued by the Asia Pacific Society for Research on Hepatology only proposed to timely detect liver function for high-risk drug users, which did not mention the preventive medicine [1]. There are many kinds of drugs that can cause liver injury. If we can effectively prevent the occurrence of liver injury and reduce the pain of patients, we will save more social medical system resources [2].

Rapid health technology assessment is mainly to search, collect and evaluate existing evidence systematically, and summarize and analyze it in a short time. Then, it comprehensively evaluate medical decision-making from three aspects of effectiveness, economy and safety. It is widely used in medical institutions at home and abroad [3]. In this paper, the rapid health technology evaluation method was used to evaluate the effect of magnesium isoglycyrrhizinate on off-label drug use from three aspects of safety, effectiveness and economy, so as to provide reference for the safe use of magnesium isoglycyrrhizinate.

1 Data and methods

1.1 Literature retrieval strategy

The keywords such as magnesium isoglycyrrhizinate, systematic review, meta, economic, cost, and assessment are used to search PubMed, Embase, and the Cochrane Library. Magnesium isoglycyrrhizinate, systematic review, meta, meta-analysis, cost, and economy are used to search Chinese databases such as CNKI, Wanfang Medical Network, and VIP. The time limit is from the establishment of each database to May 2022.

1.2 Inclusion and exclusion criteria

Inclusive criteria: (1) Adverse reactions of drugs include liver injury; (2) Preventive drugs and the study group treated with magnesium isoglycyrrhizinate injection alone, while the control group treated with blank or other liver protecting drugs, and the dose should not exceed the maximum amount of the instructions; (3) The efficacy indexes are the effective rate and liver function indexes. Including total bilirubin (TBIL) and direct bilirubin (DBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) after administration. The frequency and severity of adverse reactions are safety indicators, and the WHO grading standard of adverse reactions is used as reference for the grading of severity. Economic indicators are cost effectiveness ratio and incremental cost effectiveness ratio; (4) The types of literature included are previously published HTA reports, meta-analysis and system ratings, and pharmacoeconomic studies.

Exclusion criteria: (1) Patients are younger than 18 years old; (2) Magnesium isoglycyrrhizinate is used as non-preventive drug use; (3) Full text literature is unavailable; (4) Documents must be-published in Chinese or English.

1.3 Document screening, data extraction and quality evaluation

Literature was screened and data and materials were extracted by two researchers in strict accordance with inclusion and exclusion criteria. After discussion, the above researchers decided to incorporate the document into the literature. If the document could not be determined, a third researcher would be consulted to solve the problem. INAHTA checklist would be used for HTA report quality evaluation. The latest version of AMSTAR-2 scales was used to evaluate the quality of meta-analysis during system evaluation, evaluation and measurement. CHEERS scale, as the consensus of health economics evaluation report

standards, would be used to evaluate the quality of pharmacoeconomics literature [4].

1.4 Results and process of literature screening

After preliminary search, 136 papers were obtained. Then, 32 papers were finally obtained by removing repetitive papers and reading titles and abstracts. After reading the full text, they were re-screened, and 4 meta-analysis research papers and 5 economics research papers were included. The results and flow chart of literature screening are shown in Fig. 1.

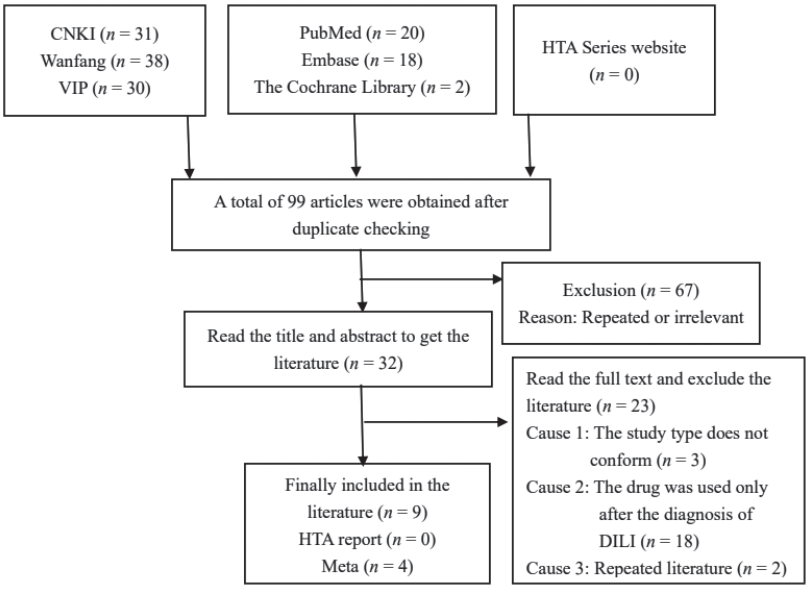

Fig. 1 Results and flow chart of literature screening

1.5 Basic characteristics of the finally included literature

The basic characteristics of the included literature are shown in Table 1 and Table 2.

Table 1 Basic characteristics of four literature in meta-analysis

Literature	Patient population	Number of studies	Total cases	Intervention	Control measure	Observational index
Wang, et al. (2021) [5]	Patients receiving conventional anti-tumor chemotherapy	12	2 230	Magnesium isoglycyrrhizinate injection	Placebo (normal saline, vitamin C, etc.)	DILI incidence rate, ALT, ALP, AST, DBIL, TBIL
Niu, et al. (2021) [6]	Patients receiving tumor chemotherapy	1	216	Magnesium isoglycyrrhizinate injection	Glutathione	DILI incidence rate
Wu, et al. (2021) [7]	Patients receiving systemic anti-tumor chemotherapy drugs	13	1 418	Magnesium isoglycyrrhizinate injection	Tiopronin, diammonium glycyrrhizinate, glutathione, creatinine, polyene phosphatidylcholine, potassium magnesium aspartate and compound diisopropylamine dichloroacetat	DILI incidence rate, ALT, ALP, TBIL
Jiang, et al. (2018) [8]	Patients receiving tumor chemotherapy	9	2 033	Magnesium isoglycyrrhizinate injection	General hydration or no special treatment	DILI incidence rate, ALT, ALP, AST, TBIL

Table 2 Basic features of four economic research documents

Literature	Country	Perspective	Research method	Patient population	Intervention measure	Control measure
Ling, et al. (2021) [9]	China	Medical institution perspective	Cost-effectiveness analysis	Patients receiving chemotherapy drugs for non-small cell lung cancer	Magnesium isoglycyrrhizate injection	Compound glycyrrhizin glycoside group, compound monoammonium glycyrrhizin S, blank
Chen, et al. (2021) [10]	China	Medicare payers	Cost-effectiveness analysis	Patients on antituberculosis drugs	Magnesium isoglycyrrhizate injection	Diammonium glycyrrhizinate, compound glycyrrhizin, blank
Ren, et al. (2020) [11]	China	Society	Cost-effectiveness analysis	Patients receiving chemotherapy drugs for gastric cancer	Magnesium isoglycyrrhizate injection	Magnesium isoglycyrrhizinate injection + Chinese medicine, polyene phosphatidyl bile alkali injection, blank
Zheng, et al. (2019) [12]	China	Medical institution perspective	Minimum cost analysis	Patients receiving chemotherapy for non-Hodgkin's lymphoma	Magnesium isoglycyrrhizate injection	Polyene phosphatidylcholine injection
Li, et al. (2017) [13]	China	Medical institution perspective	Cost-effectiveness analysis	Patients receiving chemotherapy for gastrointestinal tumors	Magnesium isoglycyrrhizate injection	Reduced glutathione and polyene phosphatidylcholine for injection

1.6 Quality evaluation of finally included documents

The document quality is graded by using the ASMER2 scale and CHEERS scale, as shown in Table 3 and Table 4.

Table 3 Quality evaluation of meta-analysis literature

Literature	Evaluation items																Quality
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Jiang, et al. (2018) [8]	√	√	×	√	√	√	√	√	√	×	√	√	×	×	√	×	Low
Wang, et al. (2021) [5]	√	√	×	√	√	√	√	√	√	×	√	√	√	√	√	×	Medium
Wu, et al. (2021) [7]	√	√	×	√	√	√	√	√	√	×	√	√	√	√	√	×	Medium
Niu, et al. (2021) [6]	√	√	√	√	√	√	√	√	√	×	√	√	√	√	×	√	Low

Table 4 Quality evaluation of economic research documents

Evaluation item	Literature				
	Li, et al. (2017) [13]	Chen, et al. (2021) [10]	Ling, et al. (2021) [9]	Zheng, et al. (2019) [12]	Ren, et al. (2020) [11]
1	√	√	√	√	√
2	√	√	√	√	√
3	√	√	√	√	√
4	√	√	√	√	√
5	√	√	√	√	√

(to be continued)

Continued Table 4

Evaluation item	Literature				
	Li, et al. (2017) [13]	Chen, et al. (2021) [10]	Ling, et al. (2021) [9]	Zheng, et al. (2019) [12]	Ren, et al. (2020) [11]
6	√	√	√	√	√
7	√	√	√	√	√
8	×	×	×	×	×
9	√	×	×	×	×
10	√	√	√	√	√
11	√	×	√	√	√
12	√	√	√	√	√
13	√	√	√	√	√
14	√	×	×	×	×
15	×	×	×	×	×
16	×	×	×	×	×
17	×	×	×	×	×
18	√	√	√	√	√
19	√	×	√	√	√
20	√	×	×	×	×
21	√	√	√	√	√
22	√	√	√	√	√
23	×	×	×	×	×
24	×	×	×	×	×
Percentage (%)	75.00	54.17	66.67	66.67	66.67
Quality	Good	Moderate	Moderate	Moderate	Moderate

2 Results

2.1 Effectiveness evaluation

(1) Total efficiency. Four articles [5-8] were used to evaluate the incidence of DILI caused by preventive drugs with magnesium isoglycyrrhizinate. The results showed that the incidence of the observation group was lower than that of the control group ($P < 0.01$).

(2) ALT level. In terms of magnesium isoglycyrrhizinate preventing the change of ALT level caused by drugs, 3 articles were used to [5, 7, 8] evaluate it. The results showed that compared with the control group, the ALT level in the observation group decreased significantly ($P < 0.01$).

(3) ALP level. In terms of magnesium isoglycyrrhizinate preventing the change of ALP level caused by drugs, 3 articles [5, 7, 8] were used to evaluate it. Among them, article 1 [5] showed that compared with placebo, the ALP level in the observation group did not decrease significantly (95% CI: −54.86 to −15.06, MD = −19.90, $P = 0.26 > 0.01$). The other 2 articles [7, 8] showed that the ALP level in the observation group was significantly lower than that in the control group ($P < 0.01$).

(4) AST level. In terms of magnesium

isoglycyrrhizinate preventing changes in AST level caused by drugs, 2 articles were used to [5, 8] evaluate it. The results showed that the AST level in the observation group was significantly lower than that in the control group ($P < 0.01$).

(5) TBIL level. In terms of magnesium isoglycyrrhizinate preventing drug induced changes in TBIL levels, 3 articles were used to [5, 7, 8] evaluate it. The results showed that the TBIL level in the observation group was significantly lower than that in the control group ($P < 0.01$).

(6) DBIL level. In the aspect of magnesium isoglycyrrhizinate preventing the change of DBIL level caused by drugs, 1 article was used [5] evaluate it. The results showed that there was no significant change in the level of DBIL in the observation group compared with placebo (95% CI: −5.12 to −0.95, MD = −2.09, $P = 0.18 > 0.01$).

2.2 Safety evaluation

Two meta-analysis literatures [6, 7] evaluated this aspect. One article [6] clarified that compared with the control group, the preventive medication in the observation group did not increase the risk of adverse events (95% CI: 0.47−1.63, $RR = 1.17$). The other article [7] explained that there was no statistical difference between the observation group and the control group in the incidence of adverse drug reactions (95% CI: 0.37−1.38, $RR = 0.72$, $P = 0.32 > 0.01$). In addition, in an economic literature [13], some patients experienced a transient increase in blood pressure during the use of magnesium isoglycyrrhizinate and recovered to normal after 2−3 days of drug withdrawal.

2.3 Economic evaluation

(1) Li, et al. [13] analyzed the cost-effectiveness of reduced glutathione for injection, magnesium isoglycyrrhizinate injection and polyene phosphatidylcholine injection in preventing liver injury caused by chemotherapy drugs for gastrointestinal cancer. Then, they concluded that the cost effect ratio of magnesium isoglycyrrhizinate in the observation group was better than that of the control group, and the incremental cost effect value of magnesium isoglycyrrhizinate and reduced glutathione was 722.18 yuan. But the blood pressure of some patients increased during the use of magnesium isoglycyrrhizinate. Although the cost effectiveness ratio of reduced glutathione was slightly higher, it had less impact on blood pressure. Therefore, the latter was more appropriate for hypertensive patients.

(2) Chen, et al. [10] conducted a cost-effectiveness analysis on diammonium glycyrrhizinate injection, compound glycyrrhizin injection, magnesium isoglycyrrhizinate injection and non-preventive drugs to prevent liver injury caused by anti-tuberculosis drugs. They concluded that diammonium glycyrrhizinate in the control group was more cost-effective, so it was more economical.

(3) Ling, et al. [9] conducted a cost-effectiveness analysis on the prevention of liver injury caused by chemotherapy drugs in patients with non-small cell lung cancer by compound ammonium glycyrrhizinate S injection, compound glycyrrhizin for injection and magnesium isoglycyrrhizinate injection. They found that when the threshold of maximum willingness to pay for the increase of significant effectiveness per unit patient and the total effectiveness was greater than 466.67 and 91.96 yuan respectively, magnesium isoglycyrrhizinate would have economic advantages, otherwise, compound glycyrrhizin would have economic advantages.

(4) Zheng, et al. [12] analyzed the minimum cost effectiveness of magnesium isoglycyrrhizinate group injection and polyene phosphatidylcholine injection in preventing liver injury caused by chemotherapy in patients with non-Hodgkin's lymphoma. To sum up, the control group of polyene phosphatidylcholine injection has better economic advantages.

(5) Ren, et al. [11] conducted a cost-effectiveness analysis on magnesium isoglycyrrhizinate injection, magnesium isoglycyrrhizinate injection combined with traditional Chinese medicine, polyene phosphatidylcholine injection, and non- preventive drugs to prevent liver injury caused by chemotherapy

drugs for gastric cancer. They concluded that preventive magnesium isoglycyrrhizinate had more cost effectiveness advantages and its incremental cost effectiveness ratio with polyene phosphatidylcholine injection in the control group was 1 131.58 yuan, which meant that the observation group had better economic performance when the threshold of maximum willingness to pay for the increase of single health output was greater than 1 131.58 yuan.

3 Discussion

Magnesium isoglycyrrhizinate injection can stabilize cell membrane, protect mitochondria, inhibit inflammation and necrosis in liver cells, reduce liver damage, and help restore liver function [14]. The comprehensive analysis in this paper shows that magnesium isoglycyrrhizinate in preventing DILI beyond the instructions is better than that of placebo, tiopronin, diammonium glycyrrhizinate, glutathione, creatinine, polyene phosphatidylcholine, potassium magnesium aspartate and compound diisopropylamine dichloroacetate in terms of the effectiveness. Besides, compared with the blank group, it can reduce the level of ASP and the level of ALP. One article believed that magnesium isoglycyrrhizinate had no difference compared with placebo, and two articles believed that magnesium isoglycyrrhizinate was superior to placebo and control group. There was no difference in reducing DBIL levels between the placebo group and the placebo group. In terms of safety, only one economic study mentioned that the drug could cause some patients' blood pressure to rise, there was no difference in the incidence of adverse reactions between magnesium isoglycyrrhizinate and the blank group and the control group in other studies. In terms of economy, compared with reduced glutathione, polyene phosphatidylcholine injection, magnesium isoglycyrrhizinate injection combined with traditional Chinese medicine and non-preventive drugs, magnesium isoglycyrrhizinate injection has better cost effectiveness in preventing liver injury caused by chemotherapy of gastrointestinal tumors. Compared with diammonium glycyrrhizinate injection, compound glycyrrhizin injection and diammonium glycyrrhizinate injection, magnesium glycyrrhizinate injection is more cost-effective than magnesium glycyrrhizinate injection to prevent liver injury caused by anti-tuberculosis drugs. Compared with compound monoammonium glycyrrhizinate S injection and compound glycyrrhizin for injection, magnesium isoglycyrrhizinate is more cost-effective in preventing liver injury caused by chemotherapy drugs for non-small cell lung cancer. To prevent liver injury caused by chemotherapy for non-Hodgkin's lymphoma, magnesium isoglycyrrhizinate has better cost effectiveness than polyene phosphatidylcholine injection.

Although the results of the rapid health technology assessment show that magnesium isoglycyrrhizinate injection plays a certain role in the prevention of liver injury, there is no guide or expert consensus clearly indicating that drug induced liver injury can be prevented. Therefore, it is recommended that magnesium isoglycyrrhizinate should not be used blindly in the prevention of liver damage, only for patients with abnormal liver function or with high risk of abnormal liver function. For example, preventive use of magnesium isoglycyrrhizinate is only considered in elderly patients with decreased liver function.

In addition, in terms of the selection of preventive drug varieties, different diseases use different chemotherapy drugs, and the severity of liver injury caused by different chemotherapy drugs is not the same. Therefore, in terms of the types of preventive drugs, the same drug should not be selected for all, but the most economically advantageous drug should be used in combination with specific conditions. The precautions in the instruction manual of magnesium isoglycyrrhizinate include regular monitoring of blood pressure during the treatment process. In combination with a study in this safety evaluation, some patients have elevated blood pressure. Therefore, in addition to monitoring liver function, more attention should be paid to blood pressure fluctuations during the use of magnesium isoglycyrrhizinate injection. Since the literature on the preventive use of magnesium

isoglycyrrhizinate injection mainly concentrates on patients in China and the number is small, the quality of the included literature is low, so the results may be biased. There is less information about the safety of preventive drugs, and the optimal economic plan is different due to the different dosage of drugs used for diseases, so detailed safety and economic research on more diseases still needs to be carried out. In addition, the rapid health technology assessment is not systematic at present, and its development is affected by the lack of guidance of the guidelines and quality control standards [15, 16].

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