Evaluation of current medical approaches for COVID-19: a systematic review and meta-analysis

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ABSTRACT
Background Because of the lack of vaccination, it is urgent to find effective antiviral agents for COVID-19 treatment.
Method Online databases were searched for articles published before or on 22 June 2020. Studies reporting the effectiveness and safety of antiviral agents for COVID-19 were analysed.
Results A total of 42 studies were included in this analysis. Hydroxychloroquine (HCQ) was not associated with the incidence of death (risk ratio (RR)=1.08; 95% CI 0.81 to 1.44) and severe cases (RR=1.05; 95% CI 0.61 to 1.81). Patients treated with HCQ obtained few benefits with respect to the clearance of viral RNA and were more likely to have adverse reactions. HCO treatment could shorten the body temperature recovery time (weighted mean difference = –1.04; 95% CI –1.64 to –0.45). Lopinavir/ritonavir (LPV/r) (RR=0.90; 95% CI 0.76 to 1.07) and Arbidol (RR=1.09; 95% CI 0.92 to 1.29) were not associated with the negative conversion rate. Integrative Chinese-Western medicine alleviated clinical symptoms and decreased the incidence of severe cases (RR=0.38; 95% CI 0.25 to 0.59). Remdesivir treatment reduced the 14-day mortality rate of patients with severe COVID-19 (RR=0.64; 95% CI 0.44 to 0.94). Convalescent plasma (CP) tended to increase the negative conversion rate (RR=2.47; 95% CI 1.70 to 3.57).
Conclusion HCQ, LPV/r and Arbidol bring little benefit in COVID-19 treatment. Integrative Chinese-Western medicine improved the clinical symptoms of patients with COVID-19. Remdesivir and CP might be the potential treatments for patients with severe COVID-19. However, large-scale clinical randomised trials are needed to validate our conclusions.

INTRODUCTION
In late December 2019 COVID-19, which is caused by SARS-CoV-2, spread rampantly. SARS-CoV-2 belongs to the beta-coronaviruses, which also include SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV). The comparison of full-length genome sequences revealed that SARS-CoV-2 shares 79.5% sequence identity with SARS-CoV-1 and is 50% similar to MERS-CoV.1 Various potential hosts of SARS-CoV-2 have been proposed, but this issue remains a matter of debate. Most studies have indicated that bats might be the original host of the virus, while several animals, including snakes, minks, pangolins and turtles, might be the intermediate hosts, which have ultimately transmitted SARS-CoV-2 to humans.2-3 The initial manifestations of COVID-19 are not specific, which has contributed to many misdiagnoses and the rapid outbreak of the virus, and they are similar to the symptoms of other coronavirus infections, including SARS and MERS.6-8 Compared with SARS and MERS, COVID-19 has a relatively low case fatality rate, but a higher basic reproduction number and higher transmission rates.9

Currently, there is no specific vaccine against SARS-CoV-2, and guidelines recommend the application of antiviral agents, including hydroxychloroquine/chloroquine (HCQ/CQ), lopinavir/ritonavir (LPV/r) and Arbidol, which may help to improve clinical outcomes in patients with COVID-19.10 The ability of HCQ/CQ to inhibit SARS-CoV-2 in vitro has been shown to be promising,11 and in vitro studies, HCQ was able to inhibit SARS-CoV-2 activity more effectively than CQ.12 LPV/r has been applied in the treatment of SARS and MERS.13,14 Arbidol is another antiviral agent that has been proven to treat influenza and other viruses.15 Potential benefits of antiviral...
agents in vitro and promising clinical outcomes in the treatment of other viral infections persuaded clinicians to use these agents for COVID-19 treatment. To date, clinical studies on the role of antiviral agents in treating COVID-19 are very limited, and the effectiveness and safety remain uncertain due to the controversial results. Therefore, we collected the latest available data for a meta-analysis of clinical studies to summarise the efficacy and safety of antiviral agents currently in use for COVID-19 treatment. Specifically, traditional Chinese medicine (CM) is widely recommended in China and has demonstrated encouraging results, thus we also collected the recent data about CM.

METHODS
This study was registered in PROSPERO, with registration No. CRD42020183662.

Search strategies

Eligibility criteria
Eligible studies were included in the meta-analysis according to the following criteria: (1) Type of participants: patients (≥18 years old) in each study were diagnosed with COVID-19 and (2) Type of study; clinical studies that provide information about effectiveness and safety associated with the treatment with antiviral agents. Trials were excluded if any of the following factors were identified: (1) Study design: comments, letters, abstracts or reviews and (2) Type of participants: animals and patients <18 years old.

Trial selection
After eliminating duplicates, two independent investigators reviewed the identified trials to confirm that they fulfilled the inclusion criteria. All disagreements were discussed and solved after rechecking the source data with a third investigator; in all cases one person recognised an error.

Data extraction and quality assessment
Two researchers independently extracted data from included studies using a predefined data extraction form. All disagreements were discussed and solved after rechecking the source data with a third investigator. The data extracted included: last name of the first author, country, details of the treatment strategies, primary outcomes, study design, sample size (n) and basic characteristics of participants. The Newcastle-Ottawa Scale (NOS) was employed for quality assessment of included cohort studies. NOS Scores of 1–3, 4–6 and 7–9 indicated low, intermediate and high quality, respectively. The quality of randomised controlled trials (RCTs) was assessed by the Cochrane risk of bias tool. For included clinical controlled trials (CCTs), we used the methodological index for non-randomised studies. Scores of 0–12, 13–18 and 19–24 indicated low, moderate and high quality, respectively.

Case series studies were evaluated by items created by the Institute of Health Economics. We resolved all disagreements through discussion.

Statistical analysis
The weighted mean difference (WMD) and risk ratio (RR) were used to compare continuous and dichotomous variables, respectively. All results are reported with 95% CIs. Median (range) or median (IQR) were converted to the form mean (SD). We pooled the effect estimates of outcomes using fixed-effect models. A random-effect model was used when significant heterogeneity was detected. Heterogeneity was assessed using the $I^2$ value, where $I^2 > 50\%$ was considered significant. The sensitivity analyses were made by excluding one study at a time to observe the change of effects for outcomes. Funnel plots, Egger’s test and Begger’s test (p<0.10) were used to suggest the possible publication bias of outcomes. We performed all statistical analyses with the STATA V12.0 statistical software package (StataCorporation, College Station, Texas, USA).

RESULTS
Selection of included studies and study characteristics
A total of 2437 relevant articles were identified. The screening and selection process of eligible trials is presented in figure 1. Finally, 42 studies were included in the systematic review. Among these studies, 10 were RCTs, 22 were retrospective studies, 5 were prospective studies, 4 were case series and the last one was CCT.16–57 A total of 34 articles were included in the meta-analysis. The characteristics of the included trials are listed in online supplemental table S1. The results of our quality assessment are presented in online supplemental tables S1,S2.

Hydroxychloroquine treatment
HCQ treatment was not associated with the risk of overall mortality (RR=$1.08$; 95% CI $0.81$ to $1.44$). There was no significant difference in the incidence of severe COVID-19 cases (RR=$1.05$; 95% CI $0.61$ to $1.81$). HCQ treatment could shorten the body temperature recovery time compared with the control group (WMD = −1.04; 95% CI −1.64 to −0.45). However, patients treated with HCQ were more likely
to have adverse reactions (RR=3.62; 95% CI 1.93 to 6.79). Indeed, the results of our pooled analysis show HCQ therapy tended to delay the clearance of viral RNA, but didn’t have significance (WMD=3.22; 95% CI −0.34 to 6.78). The risk of overall mortality was similar in the HCQ plus azithromycin group and the control group (RR=1.13; 95% CI 0.90 to 1.42).

Lopinavir/ritonavir

There was no significant difference in negative PCR results between patients treated with LPV/r and the standard care group. We analysed the negative conversion time (WMD = −1.85; 95% CI −5.56 to 1.86) and the negative conversion rate (RR=0.90; 95% CI 0.76 to 1.07). The results of our pooled analysis were consistent. There was no relationship between LPV/r therapy and the incidence of adverse reactions (RR=2.61; 95% CI 0.18 to 38.17) (table 1 and online supplemental figure S1).

A randomised, controlled, open-label trial revealed that LPV/r therapy did not reduce the risk of death of patients with COVID-19 (RR=0.68; 95% CI 0.39 to 1.19). The incidence of severe cases was similar in the LPV/r group and the standard care group (RR=2.00; 95% CI 0.48 to 8.41). Treatment with LPV/r was not associated with a shorter hospital stay (HR=1.12; 95% CI 0.8 to 1.56) (table 1).

Arbidol

Arbidol brought little benefit with respect to the negative conversion time (WMD=0.08; 95% CI −1.65 to 1.81) or the number of patients with negative PCR results (RR=1.09; 95% CI 0.92 to 1.29) (table 1 and online supplemental figure S1).

No significant difference was observed in the proportion of severe cases between the Arbidol group and the standard care group (RR=0.73; 95% CI 0.13 to 3.96). Compared with controls, patients receiving Arbidol therapy had no benefit with respect to the length of hospital stay (HR=0.50; 95% CI 0.75 to 1.28) or the incidence of adverse reactions (RR=5.50; 95% CI 0.32 to 94.06). Compared with LPV/r, Arbidol tended to shorten the duration of positive RNA tests (WMD=0.75; 95% CI −0.97 to 2.48) and increase the negative conversion rate (RR=0.76; 95% CI 0.57 to 1.01). However, these differences were not statistically significant (table 1 and online supplemental figure S1).

Chinese medicine

The pooled results revealed that the proportion of severe cases was lower in patients who received Chinese and Western medicine compared with patients who received Western medicine alone (RR=0.38; 95% CI 0.25 to 0.59). Patients who received combined therapy had a shorter fever duration (WMD = −1.18; 95% CI −1.43 to −0.92), cough duration (WMD = −1.62; 95% CI −1.89 to −1.35) and hospital stay (WMD = −2.79; 95% CI −2.97 to −2.62). CM therapy was more likely to promote the absorption of lesions in CT scans (RR=1.20; 95% CI 1.09 to 1.31). Meanwhile,
Review

Table 1  Meta-analysis of effect of LPV/r and Arbidol on COVID-19

<table>
<thead>
<tr>
<th>HR/RR/WMD, 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall mortality</strong></td>
<td></td>
</tr>
<tr>
<td>LPV/r/control*</td>
<td>RR=0.68; 95% CI 0.39 to 1.19 p=0.179</td>
</tr>
<tr>
<td><strong>Case severity rate</strong></td>
<td></td>
</tr>
<tr>
<td>LPV/r/control*</td>
<td>RR=2.00; 95% CI 0.48 to 8.41 p=0.344</td>
</tr>
<tr>
<td>Arbidol/control*</td>
<td>RR=0.73; 95% CI 0.13 to 3.96 p=0.714</td>
</tr>
<tr>
<td>LPV/r/Arbidol*</td>
<td>RR=2.75; 95% CI 0.79 to 9.49 p=0.110</td>
</tr>
<tr>
<td><strong>The negative conversion time</strong></td>
<td></td>
</tr>
<tr>
<td>LPV/r/control</td>
<td>WMD=−1.85; 95% CI −5.56 to 1.86 p=0.373</td>
</tr>
<tr>
<td>Arbidol/control</td>
<td>WMD=0.08; 95% CI −1.65 to 1.81 p=0.690</td>
</tr>
<tr>
<td>LPV/r/Arbidol</td>
<td>WMD=0.75; 95% CI −0.97 to 2.48 p=0.288</td>
</tr>
<tr>
<td><strong>The negative conversion rate</strong></td>
<td></td>
</tr>
<tr>
<td>LPV/r/control</td>
<td>RR=0.90; 95% CI 0.76 to 1.07 p=0.225</td>
</tr>
<tr>
<td>Arbidol/control</td>
<td>RR=1.09; 95% CI 0.92 to 1.29 p=0.340</td>
</tr>
<tr>
<td>LPV/r/Arbidol</td>
<td>RR=0.76; 95% CI 0.57 to 1.01 p=0.063</td>
</tr>
<tr>
<td><strong>The length of hospital days</strong></td>
<td></td>
</tr>
<tr>
<td>LPV/r/control*</td>
<td>HR=1.12; 95% CI 0.8 to 1.56</td>
</tr>
<tr>
<td>Arbidol/control*</td>
<td>HR=0.50; 95% CI 0.75 to 1.28</td>
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<tr>
<td><strong>Adverse effects</strong></td>
<td></td>
</tr>
<tr>
<td>LPV/r/control</td>
<td>RR=2.61; 95% CI 0.18 to 38.17 p=0.483</td>
</tr>
<tr>
<td>Arbidol/control*</td>
<td>RR=5.50; 95% CI 0.32 to 94.06 p=0.239</td>
</tr>
</tbody>
</table>

*Means data from the published article.

LPV/r, lopinavir/ ritonavir ; RR, risk ratio ; WMD, weighted mean difference.

Figure 3  Meta-analysis of effect of Chinese medicine (CM) on COVID-19. RR, risk ratio, WMD, weighted mean difference.

Figure 4  Meta-analysis of effect of remdesivir and convalescent plasma (CP) on COVID-19. RR, risk ratio.

the percentage of patients who showed clinical improvement was higher in the combined group than in the Western medicine alone group (figure 3).

Remdesivir

The results demonstrated that remdesivir was associated with reduced 14-day mortality rate of patients with severe COVID-19 (RR=0.64; 95% CI 0.44 to 0.94). There was significant difference in the incidence of adverse effects between the remdesivir group and control group (RR=0.77; 95% CI 0.63 to 0.94) (figure 4). An RCT with 237 patients revealed that 28-day mortality was similar between the remdesivir group and the control group (difference, 1.1%; 95% CI −8.1% to 10.3%). There was no significant difference in the time to clinical improvement between the two groups (HR=1.23; 95% CI 0.87 to 1.35). Remdesivir therapy was not associated with higher clinical improvement rates at day 14 (difference, 3.5%; 95% CI −8.1% to 15.1%) or day 28 (difference, 7.5%; 95% CI −5.7% to 20.7%). The cumulative rate of negative viral RNA tests by day 28 was similar between the two groups (difference, 7.5%; 95% CI −19.2% to 4.2%).46 However, a study pointed that patients in the remdesivir group had a shorter time to recovery than patients in the placebo group.47

Intravenous immunoglobulin

Two studies with a total of 383 patients evaluated the clinical outcomes of intravenous immunoglobulin (IVIG) therapy in critical patients with COVID-19. The use of immunoglobulin was closely associated with an increased 60-day overall survival rate (HR=0.252; 95% CI 0.107 to 0.591). Lower 28-day (p=0.044) and 60-day (p=0.049) mortality was observed in the high-dose IVIG group (>15 g/day) compared with the low-dose IVIG group (<15 g/day). Early use of IVIG (within 7 days) decreased the 60-day overall mortality (p=0.008).56 The 28-day mortality rate was significantly lower among patients who received IVIG within
2 days (p = 0.009). The length of hospital stay was shorter in the early use IVIG group (within 7 days) than in the delayed use IVIG group (p = 0.025). This effect was even more pronounced in patients treated with IVIG within 2 days (p = 0.006).

Convalescent plasma

The pooled result shown that there was a higher viral nucleic acid negative rate in patients treated with convalescent plasma (CP) (RR = 2.47; 95% CI 1.70 to 3.57). CP treatment tended to decrease the risk of mortality of patients with severe COVID-19 (RR = 0.65; 95% CI 0.42 to 1.02) (figure 4). In a study with 10 patients, 5 patients showed significantly higher levels of neutralising antibody (1:640). In another study, neutralising antibody levels of all five patients increased following transfusion (range, 40–60 before transfusion and 80–320 on day 7). Patients treated with CP showed significantly higher levels of neutralising antibody, with a range of 1:160 to 1:640. Neutralising antibody titre was undetectable in three patients on day 2, and for all seven patients, negative PCR results were obtained within 6 days after CP therapy. In another study, viral RNA tests became negative within 12 days after transfusion in 24 of 27 patients. No adverse reaction was reported after CP therapy.

PUBLICATIONS BIAS AND SENSITIVITY ANALYSIS

Funnel plots, Egger’s test and Begger’s test were performed to detect the publication bias. Sensitivity analyses revealed no meaningful differences in outcomes. The results indicated possible publication bias existed in the outcome: the cough recovery rate (CM/control) (Begger = 0.462, Egger = 0.028). More articles should be included in further studies to reduce publication bias.

DISCUSSION

In the present study, data from 42 studies were analysed and the following conclusions were drawn. Compared with control groups, HCQ treatment wasn’t associated with a lower risk of death. HCQ seems to be promising in terms of clinical symptom alleviation. HCQ brought few benefits with respect to the incidence of severe COVID-19 cases and clearance of viral RNA, but was more likely to have adverse reactions. LPV/r and Arbidol had no effects on the viral clearance. Integrative Chinese-Western medicine could significantly alleviate clinical symptoms and decrease the incidence of severe cases. Remdesivir has the potential to reduce the 14-day mortality rate and adverse reactions. CP therapy was associated with a higher PCR test negativity rate and had a tendency to reduce risk of death. IVIG therapy showed promising results for the treatment of COVID-19, but definite conclusions have not yet been reached due to limited higher-quality clinical studies.

CQ and HCQ have a long-standing history in the prevention and treatment of malaria and the treatment of chronic inflammatory diseases. In an in vitro study, CQ was found to inhibit SARS-CoV-2 activity, with a half-maximal effective concentration of 1.13 µM and a half-cytotoxic concentration greater than 100 µM. HCQ, a derivative of CQ, was found to be more effective than CQ in vitro. Guidelines for COVID-19 treatment have included HCQ/CQ, even though clinical data remain uncertain and scarce. Our results suggested that HCQ brought few benefits with respect to the mortality rate, which might be attributable to adverse reactions during treatment. It is also consistent with the results from our pooled analysis that patients treated with HCQ are more likely to experience adverse reactions. HCQ alone can cause QT prolongation and is known to cause torsades de pointes, especially among patients with a history of cardiac dysfunction. The use of HCQ in patients with COVID-19 has been associated with cardiac toxicity.

It is known that patients with a history of cardiovascular disease are more likely to develop into severe cases, as COVID-19 can promote acute cardiac injury. Therefore, the application of HCQ may pose a particular risk to critically ill patients. In addition, adverse gastrointestinal events were frequent in the HCQ group. Chorin et al reported that 30% of patients treated with HCQ plus azithromycin developed new QT prolongation of >40 ms, and in 11% of patients, QT prolonged to >500 ms, which is a marker of an increased risk of sudden cardiac death. Therefore, we strongly recommend close monitoring of ECGs with QT evaluation and correction of any electrolyte imbalance before administering HCQ. The results of our pooled analysis demonstrated that HCQ wasn’t associated with viral clearance, which was consistent with the conclusions from another meta-analysis. Our meta-analysis indicates that treatment with HCQ may be beneficial in terms of time to body temperature normalisation, suggesting HCQ may alleviate clinical symptoms. However, due to the limited sample size, more data are needed to validate these results.

Lopinavir, a protease inhibitor, is approved to treat HIV by the US Food and Drug Administration (FDA) with ritonavir as a booster. Although RCTs of LPV/r therapy are still ongoing, our results and current data suggest a limited role for LPV/r in COVID-19 treatment. LPV/r therapy did not decrease the time to clinical improvement compared with the standard care group. A subgroup analysis found that earlier treatment initiation with LPV/r was not associated with shorter times to clinical improvement for patients with COVID-19. Similarly, the mortality rate was lower among patients who received LPV/r therapy within 12 days, but this difference was not statistically significant, supporting the notion that LPV/r therapy brings little benefit in the treatment of COVID-19. In terms of adverse reactions, although our pooled results revealed no significant difference between the LPV/r and control groups, liver biopsies have indicated the possibility of drug-induced acute liver injury. It has been reported...
that liver injury observed in patients with COVID-19 after admission might be caused by LPV/r treatment.\textsuperscript{66} In the present meta-analysis, LPV/r and Arbidol monotherapy seemed to have similar effects on SARS-CoV-2 clearance, and they do not significantly reduce the viral clearance time. A retrospective cohort study including 33 patients concluded that a favourable clinical response was observed in patients treated with the combination of LPV/r and Arbidol.\textsuperscript{67} However, based on the available data, it is difficult to assess whether the combined use of LPV/r and other antiviral agents is effective for the treatment of COVID-19.

CM, a unique and well-established system of medicine, has been widely employed for thousands of years to prevent and treat numerous diseases in China. According to the results of our pooled analysis, integrative Chinese-Western medicine alleviated clinical symptoms without apparent adverse reactions for mild or moderate cases. On 17 February, 2020, it was reported that 60\textsuperscript{107} confirmed patients with COVID-19 in China had been treated with CM with promising outcomes.\textsuperscript{68} An in vitro study confirmed that Shuang Huang Lian oral liquid exerts inhibitory effects on SARS-CoV-2, but Zhang \textit{et al} found no significant difference in the negative conversion rate of PCR tests between the CM therapy and standard care groups.\textsuperscript{69} Therefore, the role of CM in viral clearance needs to be evaluated in future clinical studies.

In vitro experiments indicated that remdesivir is likely to be effective against SARS-CoV-2.\textsuperscript{59} Treatment with remdesivir improved the clinical conditions of the first case in USA.\textsuperscript{58} A cohort study of 53 patients with severe COVID-19 also reported promising effects of remdesivir on clinical improvement.\textsuperscript{71} Our result indicated that remdesivir significantly reduced the risk of death of patients with severe COVID-19. However, there were still some controversial results. The first RCT with remdesivir did not reveal significant clinical improvements or antiviral effects in patients with severe COVID-19.\textsuperscript{61} Preliminary results of another clinical trial indicated that remdesivir significantly shortened the median time to recovery for patients with advanced COVID-19.\textsuperscript{47} Currently, we have no definite answer regarding the clinical benefits of remdesivir for the treatment of COVID-19. Clinical studies examining the effects of earlier administration and different doses of remdesivir to explore its effects on COVID-19 are urgently required.

CP and IVIG therapy may serve as adjunctive therapies for severely ill patients with COVID-19. Recently, the FDA has issued guidelines for administering or studying CP in patients with COVID-19.\textsuperscript{72} Current case series reported promising effects of CP therapy (decreased inflammatory responses and alleviated symptoms) without death or severe adverse events. The pooled result showed that CP therapy had promising result for viral clearance and lower mortality rate. However, due to the limited RCTs, large clinical trials must be undertaken to validate these findings. Two studies evaluated the role of IVIG in COVID-19 treatment and reported encouraging findings.\textsuperscript{56, 57} After correcting for bias, IVIG therapy was associated with decreased 60-day mortality. Moreover, IVIG had a significantly stronger curative effect on critical patients with COVID-19. IVIG could significantly reduce the 28-day mortality rate, decrease the inflammatory response and improve the organ functions in critical patients. Indeed, early admission (\leq 7 days) and high IVIG doses (>15 g/day) significantly improved the outcomes in critical patients.\textsuperscript{56} In another study, severely ill patients with COVID-19 treated with IVIG within 2 days showed a favourable prognosis.\textsuperscript{57} These observations remind clinicians to pay more attention to the timing and dosage of IVIG administration. The most effective strategy to treat this virus will be specific vaccination. However, considering the length of time necessary for vaccine development, it is urgent to investigate the clinical benefits of CP and IVIG for the treatment of COVID-19.

\textbf{LIMITATIONS}

Our meta-analysis has several limitations. First, due to the limited number of clinical studies for each drug, it is difficult to elucidate the source of heterogeneity, and we could not analyse the sensitivity and publication bias of all outcomes to confirm the reliability of our results. Second, most of the included studies are retrospective cohort studies with a low level of evidence, and high-quality RCTs are lacking. However, all studies in the present meta-analysis included a control/conventional/standard group. Third, the treatment regimens of each agent and the duration of follow-up are not consistent between studies. Finally, we cannot exclude the effects of other antiviral agents that have been administered in different studies.

\textbf{CONCLUSION}

HCQ seems to be promising in terms of symptom alleviation, but is associated with more adverse reactions. No significant clinical benefits of LPV/r and Arbidol are observed for the treatment of patients with COVID-19. Integrative Chinese-Western medicine improves the clinical symptoms for mild or moderate patients with COVID-19. However, its role in viral clearance is uncertain. Remdesivir and CP therapy are possible to bring benefits to patients with severe COVID-19. IVIG therapy shows promising results for the treatment of COVID-19. Further large clinical trials should be conducted to obtain more reliable findings.

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Review


51

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