Efficacy and Safety of Levoketoconazole in Managing Cushing's Syndrome: A Systematic Review

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Abstract

No systematic review has holistically analysed the efficacy and safety of levoketoconazole, a novel purified 2S,4R enantiomer of ketoconazole, believed to be 15- to 25-fold more potent than ketoconazole for managing Cushing's syndrome (CS). We undertook this meta-analysis to address this knowledge gap. Electronic databases were searched for studies involving patients with CS receiving levoketoconazole in the intervention arm. The primary outcome was to evaluate changes in mean 24-hour urine-free cortisol (mUFC) levels. Secondary outcomes were to evaluate alterations in cortisol and adverse events. SONICS study showed that normalisation of mUFC was seen in 61%, 55%, and 41% of the patients at the end of 6, 9, and 12 months therapy, respectively. The LOGICs study showed that withdrawal of levoketoconazole was associated with a significant increase in mUFC from 81.3 ± 35.7 to 220.8 ± 333.5 nmol/24h. The late-night salivary-cortisol (LNSC) increase during the drug withdrawal phase was 2.6 nmol/L in the placebo group (PG) compared to 2.2 nmol/L in the levoketoconazole group (LG) ($P < 0.05$). Re-initiation of levoketoconazole in original LG was associated with a decrease in mUFC from 224.3 ± 341.3 to 135.6 ± 87.3 nmol/24h. Initiation of levoketoconazole in the original PG was associated with a decrease in mUFC from 537.9 ± 346.0 to 141.3 ± 130.3 nmol/24h. Normalisation of mUFC was observed in 50.0% patients in LG compared to 4.5% in the placebo group. The median time for the response was 25 days. The median time to loss of therapeutic response was significantly shorter for PG (24 days) compared to LG (62 days) ($P < 0.0001$). Levoketoconazole has good efficacy and safety in CS. Bigger and longer studies are warranted to establish its superiority over ketoconazole.

Keywords: Cushing's disease, cushing's syndrome, levoketoconazole, systematic review

Introduction

Cushing's syndrome (CS) is characterised by chronic over-production of cortisol, which is most commonly caused by ACTH (adrenocorticotropic hormone), secreting pituitary adenomas besides inadvertent use of glucocorticoids as exogenous CS.[1] This disease is debilitating and fatal due to its multiple co-morbidities and numerous cardiovascular complications along with increased risk of infections and neuropsychiatric manifestations.[2,3] Surgery is the primary modality of treatment in all types of endogenous CS be it a pituitary, ectopic, or adrenal source.[4–6] However, many a time, it is difficult to localise the culprit lesion causing hypercortisolism, which leads to an unfeasible surgical cure. This is primarily a problem with ectopic CS. Even for eutopic (pituitary) CS, sometimes, the pituitary adenoma is not localised even with the best of imaging modalities, making surgical cure difficult. Also in some patients, due to the small size of the culprit lesion, poor localisation, and relatively difficult surgical techniques, the remission rate after surgery is not quite satisfactory.[7,8] So, almost more than half of the patients need second-line treatment following surgery in such non-localisable, persistent, or recurrent diseases.[5,9] The usual second-line treatment options include re-surgery, radiotherapy, and medical therapy.[10] The medically directed therapies vary in their mechanism and efficacy. Pasireotide and cabergoline are the chief pituitary directed therapies, whereas ketoconazole,

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mitotane, metyrapone, and etomidate are the chief adrenal directed therapies.[11] Mifepristone is a separate class of drug which acts on the glucocorticoid receptor and antagonises it. The basic limitation of such drugs is their relatively limited availability, higher cost, and less real-life evidence.

Ketoconazole is one of the most used off-label drug for CS. It is a mixture of two enantiomers [levoketoconazole (2S,4R-ketoconazole) and dextroketoconazole (2R,4S-ketoconazole)].[12] Even with limited data from observational studies on ketoconazole, it has been approved by European Medicines Agency. No prospective clinical studies like randomised controlled trials (RCTs) are available.[13] Ketoconazole is an effective medical therapy against CS owing to its holistic inhibitions of adrenal steroidogenesis. Multiple steroidogenic pathways are effectively inhibited by ketoconazole.[14] Extensive research has suggested that levoketoconazole is the most important enantiomer and involved in the enzyme inhibition and may have therapeutic advantages (more efficacy with lesser side effects) over conventional ketoconazole.[15]

The real challenge in using levoketoconazole in CS is the paucity of data from RCTs. In this regard, the phase III open label study SONICS and the phase III double-blind, placebo-controlled, randomised withdrawal study LOGICS are the only two studies which have prospectively evaluated levoketoconazole.[16,17] SONICS study had an extensive follow-up phase whose results were published thereafter.[18] Both studies found that a significant percentage of the population achieved the primary end point of 24 hours urinary cortisol normalisation.

However, to date, no systematic review or meta-analysis is available which has holistically analysed and summarized the clinical efficacy and safety of this novel molecule for the medical management of CS. Hence, this systematic review aimed to evaluate the efficacy and safety of levoketoconazole in managing CS.

Methods

The PICOS criteria were used to screen and select the studies for this mini-review with patients (P) being people living with CS, intervention (I) being use of levoketoconazole for managing CS, and control (C) being patients on either placebo or any other approved medication for managing CS; the outcomes (O) being evaluated were impact on 24-hour urine-free cortisol (UFC), late night salivary cortisol (LNSC), and serum cortisol levels after 1 mg dexamethasone suppression tests. Three articles were found after the systematic search. These were SONICS, SONIC's extension study, and LOGICS. SONICS was a phase 3 study on levoketoconazole which had looked upon safety and efficacy without any placebo arm. It had three phases, that is, dose titration (2–21 weeks to achieve an effective and tolerable therapeutic dose), maintenance (6 months of treatment at the therapeutic dose), and extended evaluation (6 months of continued treatment). It was a multi-national study that included 19 countries (15 European countries and Canada, Israel, Turkey, and USA) and 60 medical institutions.[16] The key inclusion criteria included confirmed diagnosis of persistent, recurrent, or de novo Cushing's disease or endogenous CS of other causes. Patients with known surgical failures with surgery taking place 6 months back were also considered for inclusion. Previous radiation therapies which were given 4 years back were also included. The extended evaluation part has been published separately in another paper.[18] LOGICS was a phase 3, placebo-controlled, randomised-withdrawal study which also had three phases: titration-maintenance (14–19 weeks) (TM), double-blind, randomised-withdrawal (~8 weeks) (RW), and restoration (~8 weeks) (RES).[17] LOGICS inclusion criteria were SONIC's completers and other uncontrolled CS patients. After the TM phase, the randomisation occurred, where a group received continuous fixed dose levoketoconazole and the other group received placebo tablets. After the end of the RW phase, both groups received levoketoconazole for around 8 weeks. Some patients, however, needed early levoketoconazole restoration due to Cushing's relapse. Patients with all the different types of CS were considered for this study (pituitary, adrenal, or ectopic). Patients with exogenous CS or CS due to any malignancy were excluded. Suspected pseudo-CS and cyclic CS were also excluded.

Search method for identification of studies

A detailed electronic database of Medline (Via PubMed), Embase (via Ovid SP), Cochrane central register of controlled trials (CENTRAL) (for trials only), ctri.nic.in, clinicaltrials.gov, global health, and Google scholar were searched using a Boolean search strategy: (levoketoconazole) AND ((Cushing) OR (Adrenal) OR (Pituitary))

Data extraction and study selection

Data extraction was carried out independently by three authors using standard data extraction forms. In cases where more than one publication of a single study group was found, results were grouped and relevant data from each report were used in the analyses. Data on the primary and secondary outcomes as stated above were extracted. All disagreements were resolved by the third author.

Assessment of risk of bias in included studies

Three authors independently assessed the risk of bias using the risk of bias assessment tool in Review Manager (Revman) Version 5.4 (The Cochrane Collaboration, Oxford, UK 2014) software. The following points were taken into consideration: adequate sequence generation (selection bias), adequate allocation concealment (selection bias), and adequate blinding (the knowledge of the allocated interventions adequately prevented during the study). Participants and personnel (performance bias) blinding were specifically looked for, and so was the blinding of the outcome assessors (detection bias). We looked for whether the incomplete outcome data issue was adequately addressed or not (attrition bias). Reports of the study free of suggestion of selective outcome reporting (reporting bias) were also evaluated. Last, we also

looked for whether the study was apparently free of other problems that could put it at risk of bias. Any disagreements were resolved by the fourth author.

Measures of treatment effect

For continuous variables, the outcomes were expressed as mean differences (MDs). Conventional units were used for analysis, and all studies reporting results in SI units were converted to conventional units for analysis. For dichotomous outcomes (treatment success), results were expressed as risk ratios (RRs) with 95% confidence intervals (CIs). For adverse events, results were expressed as post-treatment absolute risk differences. RevMan 5.4 was used for comparing MDs of the different primary and secondary outcomes between levoketoconazole and the control groups of the included studies.

Results

Risk of bias in the included studies

The summaries of risk of bias of the two studies included in the meta-analysis are elaborated in Figure 1a and b. Attrition bias and reporting bias were low in both studies (100%). Random sequence generation (selection bias) was low in one study (50%). Allocation concealment (selection bias), performance bias, and detection bias were high in both the studies (100%). Sources of funding, especially pharmaceutical, authors from the pharmaceutical organisations, and conflict of interests were looked into the "other bias" section. Other bias was judged to be at high risk in both the studies (100%).

Efficacy analysis

SONICS study had enrolled 94 patients, among which 77 patients entered the maintenance phase. The mean 24 hours urinary cortisol (mUFC) least square mean change response rate was 0·30 (0·21–0·40) at the end of 6 months without an increase in drug dose. The other outcome of the study was more than 50% decrease in the mUFC or normalisation of the same. This response rate in least square mean change was 0·46 (0·35–0·56) (mean and range). In the extended evaluation phase of the SONICS study (60 patients among those 94 who entered this phase), the baseline mUFC and LNSC were 528.1 (438.8) nmol/24h and 11.7 (17.1) nmol/L (mean and SD), respectively. The reduction in these parameters was 328.1 (475.6) nmol/24h and 2.9 (24.2) nmol/L, respectively. The random serum cortisol had also reduced to 74.3 (225.3) nmol/L from the baseline value of 525.2 (150.0) nmol/L [Table 1].

With regard to the cortisol response rate, the normalisation of the mUFC was seen in 61%, 55%, and 41% of the

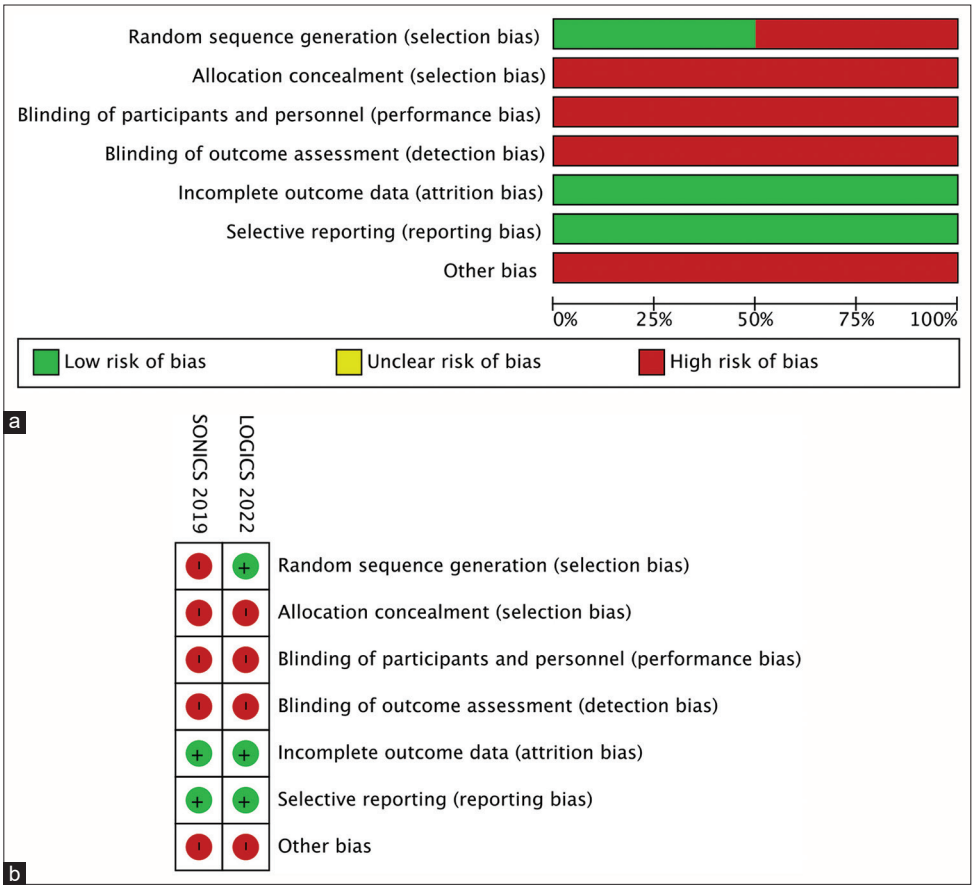

Figure 1: (a) Risk of bias graph presenting the review authors' judgements about each risk of bias item shown as percentages across all included studies. (b) Risk of bias summary presenting the review authors' judgements about each risk of bias item for each included study

patients at the end of 6, 9, and 12 months, respectively. Even if we take the denominator as intention to treat the population, the response rate was 36%, 29%, and 19% of the patient's group, respectively, at the end of 6, 9, and 12 months.

The LOGICs study had a placebo arm where the randomisation took place before the randomisation and withdrawal (RW) phase. It had enrolled 84 patients; among them, 12 were from the SONICS trial. Levoketoconazole arm patients continued to receive levoketoconazole, whereas the placebo arm received suitable placebo tablets. This phase was followed by the restoration phase, where both groups had the levoketoconazole. In the RW phase, the mUFC rose 139.4 nmol/24h from 81.3 (35.7) nmol/24h to 220.8 (333.5) nmol/24h (mean and SD) in the levoketoconazole arm. The placebo arm had a rise of 453.5 nmol/24h in this RW phase. So, the baseline mUFC value rose from 88.4 (48.1) nmol/24h to 541.9 (341.4) nmol/24h. Obviously, the treatment difference was significant 314.0 (P = 0.0027). The LNSC increased 2.6 nmol/L in the placebo group during this RW phase compared to 2.2 nmol/L in the treatment group. This difference was also statistically significant. In the restoration phase, the mean decrease in mUFC was significantly higher in the placebo group compared to the treatment arm (396.6 vs 88.7 nmol/24h). The levoketoconazole group's mUFC decreased from 224.3 (341.3) nmol/24h to 135.6 (87.3) nmol/24h, and the placebo's mUFC decreased significantly higher than the levoketoconazole group [537.9 (346.0) to 141.3 (130.3) nmol/24h (mean and SD)]. The normalisation of the mUFC was observed in 11 (50.0%) (n = 22) patients compared to 1 (4.5%) patient in the placebo group. Similarly, the loss of mUFC response was far more in the placebo group compared to the levoketoconazole group [21 (95.5%) vs 9 (40.9%)] (n = 22). The treatment difference was significant in both the occasions [45.5% (95% CI 19.2, 67.9; P = 0.0015)] and 54.5% [(95% CI − 75.7, −27.4; P = 0.0002)] [Table 2].

Table 1: Cortisol response rate (extended evaluation phase) in SONICS study

	At baseline`	Change after 12 months of follow-up
mUFC, nmol/24h	528.1 (438.8)	–328.1 (475.6)
LNSC, nmol/L	11.7 (17.1)	–2.9 (24.2)
Random serum cortisol, nmol/L	525.2 (150.0)	–74.3 (225.3)

UFC: urine-free cortisol; LNSC: late night salivary cortisol

The median time from the start of the restoration phase to first normalisation for the placebo group was 25 days. The time to loss of therapeutic response or early rescue was significantly shorter for the placebo group, with a Kaplan–Meier estimated median time of 24 days (95% CI 19, 31) compared with 62 days for the levoketoconazole group (log-rank P < 0.0001).

Safety analysis

In our safety analysis, we have included two of our studies SONICS and LOGICS, but forest plots were drawn in respect to LOGICS study only as it had a placebo group. All the relevant side effects were significantly higher in the levoketoconazole group compared to the placebo group in the LOGICS study. The occurrence of total adverse events [OR 1.20 (95% CI: 0.37–3.92); P = 0.76] [Figure 2a], serious adverse events (SAEs) [OR 2.10 (95% CI: 0.18–25.01); P = 0.56;] [Figure 2b], adrenal insufficiency [OR 3.14 (95% CI: 0.12–81.35); P = 0.49] [Figure 2c], adverse events of special interest [OR 3.14 (95% CI: 0.12–81.35); P = 0.49] [Figure 2d] (terminology used in pharmacovigilance where a new drug is evaluated for any adverse events which have not been defined before. This refers to one scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate), total bilirubin above normal limit (ULN) [OR 3.14 (95% CI: 0.12–81.35); P = 0.49] [Figure 2e], and AST [OR 2.10 (95% CI: 0.18–25.01); P = 0.56] [Figure 2f] were all significantly higher in the levoketoconazole group than in the placebo.

The SONICS study and its extension did not have any placebo arm. Among 94 patients of that study, 92 patients (98%) suffered from any type of adverse events. The drug-related adverse events were seen in 43% of patients. Only 12 patients (13%) had to discontinue the drug due to adverse events. Most of the adverse events were moderate in intensity. The most common adverse events were nausea (32%) and headache (28%), followed by peripheral oedema (19%). Transaminitis was a significant adverse event which was seen in about 15% of trial patients. Hypokalaemia was seen in 11% of patients.

Discussion

This is the first systematic review to evaluate the safety and efficacy of levoketoconazole in patients with CS. Ketoconazole was one of the first medical therapies for CS, and it is still the most prescribed medical therapy in our clinical practice. Two cis enantiomers (2S,4R and 2R,4S) are the main constituents of

Table 2: Treatment response in LOGICS study

	Levoketoconazole group (n=22)	Placebo group (n=22)	Treatment difference
RW phase loss of mUFC response	9 (40.9%)	21 (95.5%)	54.5% ((95% CI−75.7, − 27.4; P=0.0002)
Normalization of mUFC at the end of RW phase	11 (50.0%)	1 (4.5%)	45.5% (95% CI 19.2, 67.9; P=0.0015)
Normalization of mUFC at the end of restoration phase	11 (52%) of 21	14 (64%)	

UFC: urine-free cortisol

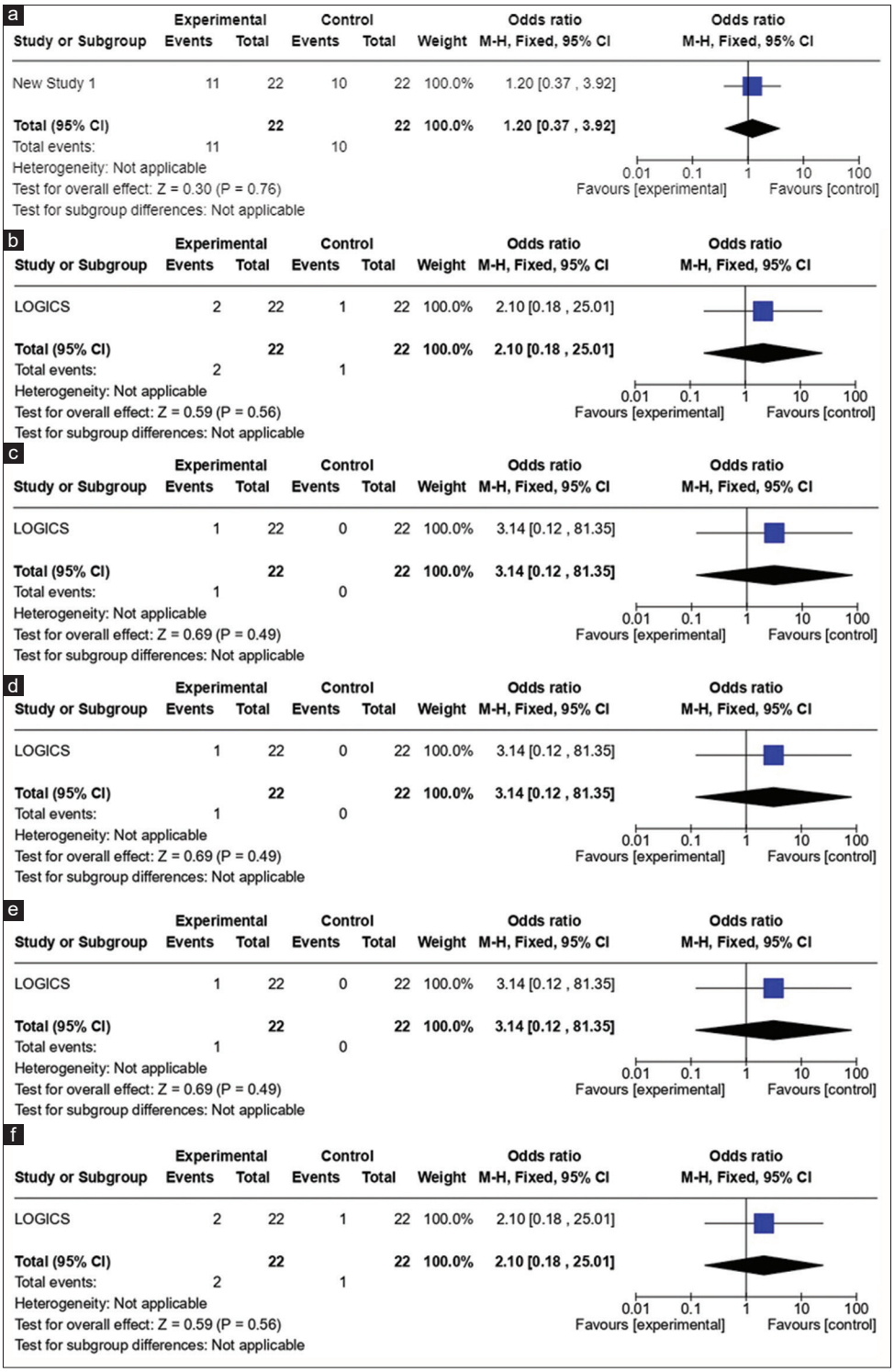

Figure 2: Forest plot highlighting the side effect profile of the use of levoketoconazole focussing on (a) total adverse events, (b) serious adverse events, (c) incidences of adrenal insufficiencies, (d) adverse events of special interests, (e) total bilirubin of more than upper limit of normal (ULN), and (f) AST of more than ULN

the ketoconazole molecule.[15] 2S,4R plasma levels appeared to be 3-fold higher compared to those of the 2R,4S enantiomer.[19] The biggest drawback of using ketoconazole is the severe hepatotoxic side effects along with its frequent dosing schedule due to its short half-life (3.3 hours).[20] Ketoconazole has to be given at least thrice a day.[21] Levoketoconazole (COR-003) is the purified 2S,4R enantiomer of the ketoconazole. It is seen to inhibit CYP11B1, CYP17A1, and CYP21A2 enzymes 15- to 25-fold more potently compared to the 2R,4S enantiomer in early *in vitro* studies.[22] The primary advantage thought to be

of levoketoconazole was less hepatic metabolism, leading to fewer incidences of hepatotoxicity along with more potent actions.

The typical dose of levoketoconazole is 300–1200 mg/day. Its half-life is significantly longer than that of ketoconazole (4–6 hours vs 3.3 hours), which permits twice-daily dosing.[23] The SONICS phase III study has demonstrated that 30.8% of the patients had shown complete response during the maintenance phase. It did not require any drug up-titration. If we consider the drug up-titration, then the response stands at 36.2%.[16] Among the 55 patients who completed the maintenance phase, the overall response rate was 78.2% with complete responders being 61.8% and partial responders being 16.4%. The HbA1c decreased from 6.9% at baseline to 6.2% and from 5.5% to 5.3% in patients with and without DM, respectively, at the end of the maintenance phase. Mean fasting blood glucose decreased from 6.85 mmol/L (123.4 mg/dL) to 5.82 mmol/L (104.9 mg/dL) in patients with DM and from 5.11 mmol/L (92.1 mg/dL) to 4.66 mmol/L (84 mg/dL) in non-diabetic patients.

A similar efficacy analysis was found in the later-conducted LOGICS study. After the end of the randomised withdrawal phase (RW), the response rate was 50%, which is significantly more than the placebo (4.5%). Moreover, at the end of randomised withdrawal, significantly more patients on placebo (95.5%) achieved the primary endpoint of loss of mean urinary free cortisol (mUFC) response, defined as mUFC > 1.5 upper limit of normal range, or, for SONICS completers with mUFC above the upper limit of normal range at baseline, an increase in mUFC > 40% above the baseline value, compared to those who continued on levoketoconazole (40.9%). All metabolic parameters such as body weight, fasting plasma glucose, and lipid profile had a favourable effect with levoketoconazole.[17] Both discussed studies have shown equivocally the efficacy of levoketoconazole in reducing the symptoms of acne, hirsutism in women, peripheral oedema, and body weight. Both had favourable effects on quality of life and depressive status. We have added a comparison table of the various efficacy percentages of medical therapies used in CS [Table 3].[12]

Nausea, headache, hypertension, and hypokalaemia were predominant side effects of levoketoconazole. The incidences vary from 10% to 30% in both studies. Liver enzyme elevations were also found in about 1/3rd of patients. Hypocortisolism and QT prolongation were seen in about 10% of the patients.[23] Levoketoconazole has got approval from Food and Drug Administration (FDA) for the treatment of CS whose surgery is not an option or has not provided remission.[5] Though the side effects profile is like ketoconazole, the efficacy is found to be comparatively in the higher percentages. However, it would be premature to extrapolate this conclusion from the available data. Head-to-head trials between ketoconazole and levoketoconazole can provide further insights into the possible comparative efficacy and safety.

The percentage of QT prolongation in levoketoconazole is a matter of concern. The incidence of around every one person in every 10 people is alarming. Long-term studies are warranted to establish this association. Levoketoconazole is a potent inhibitor of cytochrome P450 enzyme, and that is why drug interactions need to be kept in mind during prescribing it.

Table 3: Remission rates of the various medical therapies used in Cushing's syndrome

Drug	Route of administration	Usual doses	Remission rates
Pituitary directed agents			
Pasireotide	Subcutaneous	300/600/900 µg	17.2–81.8%
Pasireotide LAR	Intramuscular	10/20/40 mg	30–72.2%
Adrenal directed agents			
Metyrapone	Oral	250 mg	45.5–100%
Osilodrostat	Oral	1/2/5/10 mg	66.4–91.7%
Glucocorticoid receptor antagonist			
Mifepristone	Oral	300 mg	38.1–60%
Relacorilant	Oral	50/100mg	41.7–63.6%

Levoketoconazole: Good clinical practices

Levoketoconazole is the purified 2S,4R enantiomer of the ketoconazole and is currently used in 300–1200 mg daily doses. The FDA has granted its usage in CS in patients without surgical remission or patients who could not undergo surgery. The main monitoring indices are liver function tests, serum sodium and potassium, and stimulated cortisol to detect any adrenal insufficiency (once the patient has achieved biochemical remission). Transaminitis is the most important side effect that needs to be monitored. Very importantly, regular monitoring of the patient's ECG is pivotal to detect any QT prolongation, which can be seen in 10% of the cases.

Conclusions

The current systematic review suggests that levoketoconazole is very promising in terms of efficacy point of view for managing CS. Further long-term, prospective, and randomised controlled trials are needed to establish this new medicine in the management of CS.

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None.

Author contributions

The meta-analysis was conceptualized by Deep Dutta. The literature search was done by Shinjan Patra and Deep Dutta. Detailed reviews of articles were done by Shinjan Patra and Deep Dutta. Data entry and statistical analsyis was done by Shinjan Patra, Lakshmi Nagendra and Nishant Raizada. The manuscript has been read and approved by all the authors before final submission.

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Conflicts of interest

There are no conflicts of interest.

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