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Outcomes of clofazimine for the treatment of drug-resistant tuberculosis: a systematic review and meta-analysis

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Background: Current anti-tuberculosis therapeutics are not sufficiently effective against drug-resistant tuberculosis (DR-TB), and there is a need for new drugs and therapeutic approaches. It has been proposed that repurposing clofazimine for DR-TB treatment might be one way to increase therapeutic options.

Methods: We conducted a systematic review of studies reporting on the efficacy and safety of clofazimine as part of combination therapy for DR-TB. Six databases and six conference abstract sites were searched from inception until April 2012. All studies involving the use of clofazimine in the treatment of DR-TB were included.

Results: Twelve studies, comprising 3489 patients across 10 countries, were included in this review. Treatment success ranged from 16.5% (95% CI 2.7%–38.7%) to 87.8% (95% CI 76.8%–95.6%), with an overall pooled proportion of 61.96% achieving treatment success (95% CI 52.79%–71.12%) (τ^2 0.07). Mortality, treatment interruptions, defaulting and adverse events were all in line with DR-TB treatment outcomes overall. The most commonly reported adverse events were gastrointestinal disturbances and skin pigmentation.

Conclusions: The available evidence to date suggests that clofazimine could be considered as an additional therapeutic option in the treatment of DR-TB. The optimal dose of clofazimine and duration of use require further investigation.

Keywords: treatment success, multidrug-resistant tuberculosis, repurposed drugs

Introduction

The global burden of drug-resistant tuberculosis (DR-TB) is growing. In 2010, an estimated 650 000 cases of DR-TB were reported worldwide. Alongside the rising prevalence of DR-TB, there has been an increase in the spread of cases due to direct contact with DR-TB patients, making DR-TB an epidemic in its own right, especially in high-burden settings.[1] Current guidelines recommend at least 20 months of treatment, but current regimens are toxic, poorly tolerated and inadequately effective, with cure rates as low as 36% and default rates as high as 50%.[2–8]

Given these challenges, and the growing number of cases resistant to traditional tuberculosis (TB) drugs, there is a pressing need for new drugs and approaches to treating DR-TB. However, despite recent advances, therapeutic options are still limited. An additional, complementary strategy is to repurpose existing drugs.[9] One such drug that has recently attracted interest for use in the management of DR-TB is clofazimine. Clofazimine, a member of the riminophenazine antibiotic class, was initially studied for use in TB. However, after it was found to have poor *in vivo* efficacy in guinea pig and simian models, its clinical development was abandoned.[2,10] Since then, clofazimine has been found in both pre-clinical and clinical studies to be effective against other mycobacterial diseases including those caused by *Mycobacterium leprae*, *Mycobacterium avium* complex and *Mycobacterium kansasii*.[10–13] The effectiveness of clofazimine against mycobacteria is thought to be due to its long half-life (65–70 days), slow metabolic elimination, high concentration in macrophages and rapid localization within phagocytes.[9,14,15] Recent *in vitro* and *in vivo* trials show good efficacy and low toxicity against DR-TB mycobacterial strains in mice.[16]

Additionally, a number of recent clinical studies have noted successful outcomes of shortened DR-TB treatment regimens containing clofazimine. One recent study in Bangladesh reported cure rates as high as 84.2% using a 9 month regimen containing clofazimine.[17] With these promising early results, clofazimine is being considered for future new regimens, including through a large multi-country, randomized control trial (the STREAM trial).

In order to frame recent studies within the broader evidence base, we systematically reviewed the currently available clinical data regarding the efficacy and safety of clofazimine in the treatment of DR-TB.

Methods

This review was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines for reporting systematic reviews.[18]

Search strategy and selection criteria

An initial protocol was developed (see Supplementary data, available at *JAC* Online). Articles were searched in MEDLINE, EMBASE, Toxnet, Lilacs, Clinicaltrials.gov and The Cochrane Central Register of Controlled Trials (CENTRAL) electronic databases from inception until 18 May 2012. No language, date, or geographical restrictions were applied. A search strategy was developed combining search terms for 'drug-resistance', 'tuberculosis', 'treatment outcomes' and 'clofazimine' as exploded MESH headings and free-text terms. Additionally, abstracts from the following electronic conference sites until April 2012 were searched: Union World Conference on Lung Health, Interscience Conference on Antimicrobial Agents and Chemotherapy, Society of General Microbiology, British Thoracic Society, European Respiratory Society, American Thoracic Society. Bibliographies of all relevant articles were also reviewed.

We sought randomized trials and observational studies involving adults or children testing positive for DR-TB, including multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), in which clofazimine was used as part of the treatment regimen. If studies used clofazimine for some patients and did not disaggregate outcomes overall, authors were contacted for clarification. Given the anticipated paucity of data, case series of five or more patients were also included. In the case of duplicate publications from the same study site, the most complete study was included.

Data extraction and management

Data were extracted from studies in duplicate by two researchers (T. D. and N. F.). The primary outcome was treatment success; secondary outcomes were death, failure, treatment stoppage/interruption, transfer, default, and adverse events.

Treatment outcomes were recorded in line with adapted definitions of those given in WHO guidelines,[2] as follows: treatment success, defined as the number of patients cured or who completed treatment combined; death, defined as death from any cause while on treatment; failure, defined as unsuccessful treatment as determined by positive cultures at the end of the treatment regimen; stoppage/interruption, defined as cessation or interruption of clofazimine-containing treatment regimen because of adverse reactions; transfer, defined as transfer to another facility but known to be still under care; and default, defined as dropout from the programme with unknown outcome. Study quality was assessed using a modified Newcastle–Ottawa scale.[19]

A pre-defined data extraction form (Excel) was used to extract data from each study selected for review. The following information was recorded: study characteristics (authors, setting, study design and hospitalization), patient characteristics [age, populations, drug susceptibility testing (DST) availability, drug resistance pattern, resistance to clofazimine, previous TB regimens, HIV status and other comorbidities], treatment characteristics (number of patients receiving clofazimine, duration of whole treatment, duration of treatment involving clofazimine, dose of clofazimine and partner drugs included in treatment regimen) and treatment outcomes.

Data analysis

Point estimates and 95% CIs for the proportion of patients achieving treatment outcomes were calculated, after stabilizing the variance of the raw data using a Freeman–Tukey-type arcsine square-root transformation. Estimates were then pooled for the primary outcome of treatment success using a DerSimonian–Laird random effects model. We report the τ^2 statistic as a measure of between-study variance. All analyses were conducted using Stata (version 12, Stata Corp., College Station, TX, USA).

Results

The search strategy retrieved 1456 potential articles, of which 72 were screened as full-text articles and six were taken through for analysis.[17,20–24] One additional article was included through bibliography screening,[25] and five studies were included as conference abstracts,[26–30] giving a total of 12 studies comprising 3489 patients across 10 countries taken through for analysis (Figure 1). One study used six different treatment regimens collapsed into two treatment arms: those treated with clofazimine in the intensive phase, and those treated with clofazimine throughout therapy. These two arms are reported separately, giving 13 data sources overall.[17]

Study and treatment characteristics are summarized in Tables 1 and 2. All studies were observational studies. Seven studies included only patients with MDR-TB, two studies included only patients with XDR-TB and three included both MDR-TB and XDR-TB patients. Ten studies reported that DST was carried out for all patients to confirm DR-TB, two studies specified that DST was carried out for first-line anti-TB drugs and two carried out DST for both first- and second-line drugs. No study reported any resistance to clofazimine, although eight studies stated that this was not tested.

Ten studies provided information on HIV status. In one study, 8% of patients (184/2305) were HIV positive.[26] In three studies, one patient was HIV positive.[17,23,29] Another study reported that some patients were HIV positive, but did not report numbers.[25] The remaining studies all reported that all patients tested for HIV were negative.[22,24,27,28,30] Four studies listed patients having additional comorbidities.[17,24,25,29]

Ten studies provided data on duration of therapy, which ranged from 2 to 1729 days, and also provided data on the length of therapy involving clofazimine. Nine of these studies reported the same duration as for therapy overall; however, in one study[17] some patients were given clofazimine solely in the intensive phase (3 months), while the rest received clofazimine throughout treatment. Only five studies detailed the dose of clofazimine: all five studies gave clofazimine as a daily dose, which ranged between 50 and 300 mg. Seven studies reported that patients were hospitalized for a part or all of

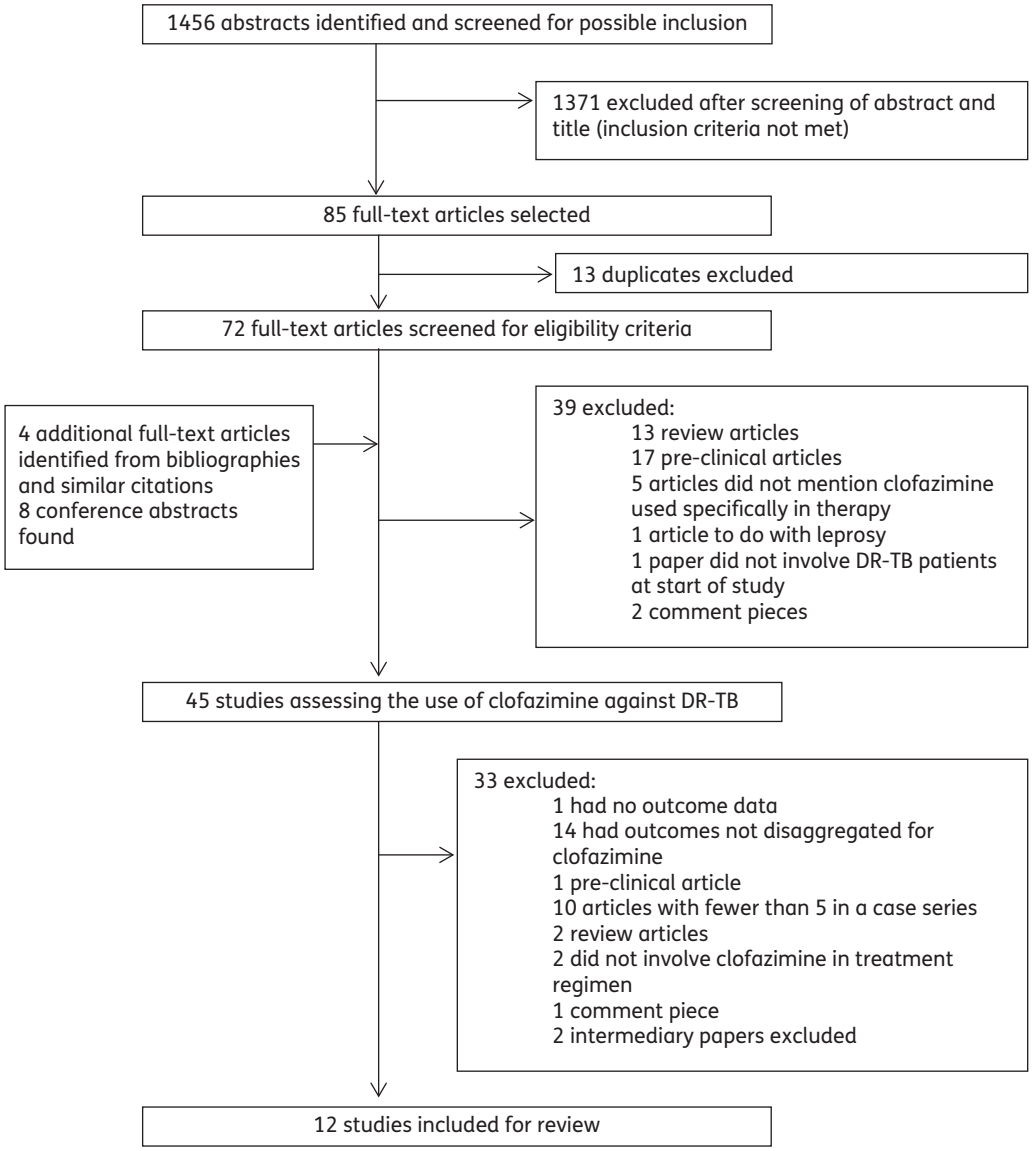

Figure 1. Identification of studies for inclusion.

therapy; of these, two studies stated that patients were hospitalized for the intensive part of therapy.[20,22] Three studies reported that patients were hospitalized throughout therapy.[21,23,24] One study reported that hospitalization was offered to patients, but was not mandatory.[25] In one study, 80% (12/15) of patients were treated under direct observation and hospitalized.[29]

Study quality

When methodological quality was assessed on the modified Newcastle–Ottawa scale, most studies had a medium risk for selection bias, a low risk for measurement bias and a medium to high risk for bias in the assessment of outcomes (Table 3).

Treatment outcomes

Treatment success, reported by 11 studies (3472 patients), ranged from 16.5% (95% CI 2.7%–38.7%) to 87.8% (95% CI 76.8%–95.6%); the overall pooled proportion of treatment success was 61.96% (95% CI 52.79%–71.12%) (τ^2 0.07) (Figure 2). One large study contributed outcomes for 2305 patients. We investigated the potential influence of this single study in a sensitivity analysis that excluded these data from the meta-analysis; dropping this study did not importantly change the overall estimate of treatment success (59.9%; 95% CI 47.3%–72.5%). There was no apparent difference in the proportion of patients achieving treatment success according to whether the study was an article or an abstract and whether or not patients had comorbidities. Data on dosage, duration of therapy and hospitalization were too poorly reported to be meaningfully assessed.

Table 1. Study characteristics

Study	Number receiving clofazimine	Age (years)	Setting	Study design	Drug resistance pattern	Availability of DST	Previous TB regimens	HIV status	Other comorbidities
Goble *et al.*, 1993[21]	17	>18	USA	retrospective cohort study	MDR+XDR	DST	not stated	not stated	not stated
Senaratne, 2004[22]	10	>18	Sri Lanka	cohort study	MDR	DST for first-line drugs	all had received previous TB treatment; none had previously received second-line treatment	all HIV negative	not stated
von der Lippe, 2006[23]	10	>18	Norway	prospective cohort study	MDR	DST for first- and second-line drugs	8 patients had previous TB treatment (details of the previous TB regimen were not known for 1 patient) and 2 patients did not report previous TB treatment	1 HIV positive	not stated
Oliveira, 2007[29]	15/170[a]	>18	Brazil	retrospective cohort study	MDR	DST	not stated	1 HIV positive	2 diabetic
Dalcolmo, 2006[26]	2305	>18	Brazil	retrospective cohort study	MDR	not stated	not stated	184 HIV positive	not stated
Prasad *et al.*, 2008[27]	6	not stated[b]	India	retrospective cohort study	XDR	DST	not stated	all HIV negative	not stated
Mitnick *et al.*, 2008[25]	447	not stated	Peru	retrospective cohort study	MDR+XDR	DST	median number of previous regimens=3	some (not specified)	mean comorbidities=61, including low body mass index/malnutrition, HIV, diabetes, psychiatric disorder, hepatitis or cirrhosis, seizures/epilepsy, cardiovascular disease, renal insufficiency
Prasad *et al.*, 2009[28]	14	not stated[a]	India	retrospective cohort study	XDR	DST	not stated	all HIV negative	not stated

Continued

Table 1. *Continued*

Study	Number receiving clofazimine	Age (years)	Setting	Study design	Drug resistance pattern	Availability of DST	Previous TB regimens	HIV status	Other comorbidities
Van Deun *et al.*, 2010[17]	427	>18	Bangladesh	prospective cohort study	MDR	DST	nearly all patients enrolled on OFX-based regimens and >90% among the GAT-treated patients had been treated repeatedly with first-line drugs for TB	1 HIV positive	impaired liver function (1), mild renal impairment (2), diabetes mellitus (1)
Piubello *et al.*, 2011[30]	44	not stated	Niger	cohort study (design unclear)	MDR	not stated	43 had been treated for TB; none had received second-line treatment	0/39	not stated
Bonnet *et al.*, 2011[20]	9	>18	Georgia	prospective cohort study	MDR+XDR	DST for first- and second-line drugs	INH+OFX+CPM/KAN+EMB+CYS (2); INH+OFX+CPM/KAN+EMB+CYS+PAS (3); INH+OFX+CPM/KAN+EMB+PAS (3)	not stated	not stated
Xu *et al.*, 2012[24]	30	not stated	China	retrospective cohort study	MDR	DST for first-line drugs	all had previous history of TB treatment	all HIV negative	9/30 had comorbidities: hypertension (1), anaemia (1), hyperprolactinaemia (1), viral hepatitis B (1), chronic obstructive pulmonary disease (4), bronchial asthma (1), gallstones (1), superficial gastritis (1), depressive disorder (1), pneumosilicosis (1), pneumocardial disease (1), diabetes mellitus (1)

CPM, capreomycin; CYS, cycloserine; EMB, ethambutol; GAT, gatifloxacin; INH, isoniazid; KAN, kanamycin; OFX, ofloxacin; PAS, *para*-aminosalicylic acid.
[a]Although 170 patients were given clofazimine, the paper detailed the outcomes of only 15 patients.
[b]Assumed adults as setting was a military hospital.

Table 2. Treatment characteristics

Study	Number receiving clofazimine	Dose of clofazimine (patients)	Duration of treatment overall (patients)	Duration of treatment with clofazimine (patients)	Other drugs included in regimen	Hospitalization
Goble *et al.*, 1993[21]	17	300 mg daily	not stated	not stated	range of first- and second-line treatments used	all hospitalized
Senaratne, 2004[22]	10	not stated	3–4 month intensive phase + variable continuation phase	3–4 month intensive phase at least	AMC, CIP, EMB, INH, STR	not stated
von der Lippe, 2006[23]	10	not stated	3–24 months	3–24 months	EMB, INH, STR, CIP, CYS, LZD, PAS, AMK, AMX, ETA, RIF, PZA, CPM	all hospitalized
Oliveira, 2007[29]	15/170	not stated	not stated	not stated	AMK, OFX, TRD, EMB	12 (80%) underwent DOTS
Dalcolmo, 2006[26]	2305	not stated	18 months	18 months	OFX, EMB, TRD, AMK, INH	not stated
Prasad *et al.*, 2008[27]	6	daily dose	20 months	20 months	CYS, ETA, INH, CLR, LZD, PAS	not stated
Mitnick *et al.*, 2008[25]	447	25–600 mg daily	2–1729 days	2–1729 days	INH, RIF, PZA, PAS, CIP, EMB, STR, ETA, KAN, CYS, CLR, OFX, AMC, RFB, CPM, LVX, SPX, AMK, MXF	hospitalization available but not mandatory for all patients
Prasad *et al.*, 2009[28]	14	daily dose	12–24 months	12–24 months	CYS, ETA, INH, CLR, LZD, PAS	not stated
Van Deun *et al.*, 2010[17,a]	183	<33 kg (50 mg), 33–50 kg (100 mg), >50 kg (100 mg)	9–15 months	~3 months	KAN, OFX, EMB, INH, PZA, PTH, GAT,	intensive phase
Van Deun *et al.*, 2010[17,b]	244	<33 kg (50 mg), 33–50 kg (100 mg), >50 kg (100 mg)	9–15 months	9–15 months	KAN, OFX, EMB, INH, PZA, PTH, GAT,	intensive phase
Piubello *et al.*, 2011[30]	44	not stated	12 months	12 months	GAT, KAN, PTH, INH, PZA, EMB	not stated
Bonnet *et al.*, 2011[20]	9	200–300 mg (majority 300 mg) daily (8), 1000 mg (1)	<3 months (3), 3–6 months (3), 12–15 months (3)	<3 months (3), 3–6 months (3), 12–15 months (3)	INH, OFX, CPM, AMC, CLR, EMB, CYS, PAS	intensive phase
Xu *et al.*, 2012[24]	30/44	100 mg daily	mean ± SD = 9.4 ± 7.4 weeks	mean ± SD = 9.4 ± 7.4 weeks	AMK, AMC, CPM, CLR, INH, EMB, LZD, PAS, PZA, PTH, RFB, RFP	all hospitalized

AMC, co-amoxiclav; AMK, amikacin; AMX, amoxicillin; CIP, ciprofloxacin; CLR, clarithromycin; CPM, capreomycin; CYS, cycloserine; DOTS, directly observed therapy, short course; EMB, ethambutol; ETA, ethionamide; GAT, gatifloxacin; INH, isoniazid; KAN, kanamycin; LVX, levofloxacin; LZD, linezolid; MXF, moxifloxacin; OFX, ofloxacin; PAS, *para*-aminosalicylic acid; PTH, prothionamide; PZA, pyrazinamide; RFB, rifabutin; RFP, rifapentine; RIF, rifampicin; SPX, sparfloxacin; STR, streptomycin; TRD, terizidone.
[a]Clofazimine used solely in the intensive phase.
[b]Clofazimine used in intensive phase and continuation phase.

Mortality during therapy, reported by 11 studies (3472 patients), ranged from 3.2% (95% CI 1.1%–6.4%) to 29.9% (95% CI 10.3%–54.7%). Treatment failure, reported by eight studies (3409 patients), ranged from 1.0% (95% CI 0.1%–2.6%) to 63.4% (95% CI 38.3%–85.0%). Treatment stoppages/interruptions, reported by four studies (446 patients), ranged from 6.3% (95% CI 3.6%–9.7%) to 14.6% (95% CI 0.7%–41.8%). Defaulting from treatment, reported by four studies (2966 patients), ranged from 3.2% (95% CI 0.1%–10.3%) to 10.4% (95% CI 7.7%–13.4%). Finally, adverse events, reported by six studies (3503 patients), ranged from 13.8% (95% CI 2.2%–32.9%) to 87.8% (95% CI 76.8%–95.6%). The most common adverse events reported were gastrointestinal disturbances, e.g. nausea, vomiting and abdominal pain, and skin pigmentation (Table 4).

Discussion

This review has found that DR-TB patients treated with clofazimine achieved a level of treatment success in line with treatment outcomes for MDR-TB in general (62%).[5,31] There was, however,

Table 3. Quality assessment of included studies using a modified Newcastle–Ottawa scale

	Selection				Measurement		Outcome		
Study	representativeness of the cohort to the average patient on MDR treatment	ascertainment of clofazimine use	baseline clofazimine resistance testing done	risk of bias (high, moderate, low)	MDR confirmed through DST	risk of bias	average follow-up of 1 year post-treatment initiation	long-term follow-up <30% among patients on clofazimine	risk of bias
Goble *et al.*, 1993[21]	*	—	—	medium	*	low	*	—	medium (high)
Senaratne, 2004[22]	*	*	—	medium	*	low	*	—	medium
von der Lippe, 2006[23]	—	*	*	medium	*	low	*	*	low (medium)
Oliveira, 2007[29]	*	*	—	medium	*	low	—	—	high
Dalcolmo, 2006[26]	*	*	—	medium	—	high	*	*	low (medium)
Prasad *et al.*, 2008[27]	*	*	—	medium	—	high	*	*	low (medium)
Mitnick *et al.*, 2008[25]	*	*	—	medium	*	low	*	—	medium
Prasad *et al.*, 2009[28]	*	*	—	medium	—	high	*	*	low (medium)
Van Deun *et al.*, 2010[17]	*	*	—	medium	*	low	*	*	low
Piubello *et al.*, 2011[30]	*	*	—	medium	*	low	—	*	medium (high)
Bonnet *et al.*, 2011[20]	*	*	—	medium	*	low	*	—	medium
Xu *et al.*, 2012[24]	*	*	—	medium	*	low	—	*	medium

substantial variation between studies in the proportion of patients achieving treatment success. Four studies reported a success rate of <40%, but these were smaller studies (≤15 patients), resulting in wide CIs, and so this finding should be interpreted with caution. Of note, two of these studies used clofazimine exclusively for the treatment of patients with XDR-TB, which may explain the lower treatment success rate of these studies. At the other extreme, three studies reported a success rate of greater than 80%. These studies included a relatively larger numbers of patients, and the lower confidence limits for these point estimates were all above 60%. In one study, clofazimine replaced the more poorly accepted and toxic prothionamide and was used in both the intensive and continuation phases.[17] Clofazimine's use may have resulted in fewer defaults from treatment, conferring a more successful outcome.

One study used clofazimine for two different durations of therapy.[17] When clofazimine was used only in the intensive phase, the proportion of patients achieving success was lower (66%) than when clofazimine was used in both the intensive phase and the continuation phase (87%), potentially suggesting that longer duration of therapy with clofazimine may be associated with a better outcome.

The number of deaths and failures are similarly in line with reported outcomes for MDR-TB treatment overall.[5,31] Failure of treatment may be due to increasing resistance to drugs. Although the majority of studies (10/12) stated that DST was carried out, no studies tested for clofazimine, and only two specified that DST was carried out for both first- and second-line drugs.[20,23]

HIV/DR-TB-co-infected patients are often considered to be harder to treat and more likely to die.[23,32] However, the study reporting the highest number of HIV/DR-TB-co-infected patients achieved a 65% success rate, in line with the overall findings.[26]

The proportion of adverse events was high, but again not importantly different from adverse events reported by other DR-TB treatment reviews.[10,15] The majority of side effects reported by the studies in this review were not considered to be serious and could be managed through simple psychological support and symptomatic palliation, an advantage over other second-line therapeutics.[21] This might explain the relatively low number of treatment stoppages. Notably, none of the studies reported cardiac toxicity.[33]

Adverse events are thought to be dose related.[10,34] In one study, lowering the dose of clofazimine to 100 mg every other day was beneficial in managing the side effects of skin discoloration in 20 patients and gastrointestinal side effects in 11 patients.[24] A recent review noted that the reddish-brown skin discoloration is gradually reversible upon cessation of therapy.[10] Nevertheless, another study noted that a patient suffered from depression due to skin discoloration.[24] Depending on the extent of the skin discoloration, it might be prudent to provide additional psychosocial support to patients undergoing clofazimine treatment. Unfortunately, the information reported

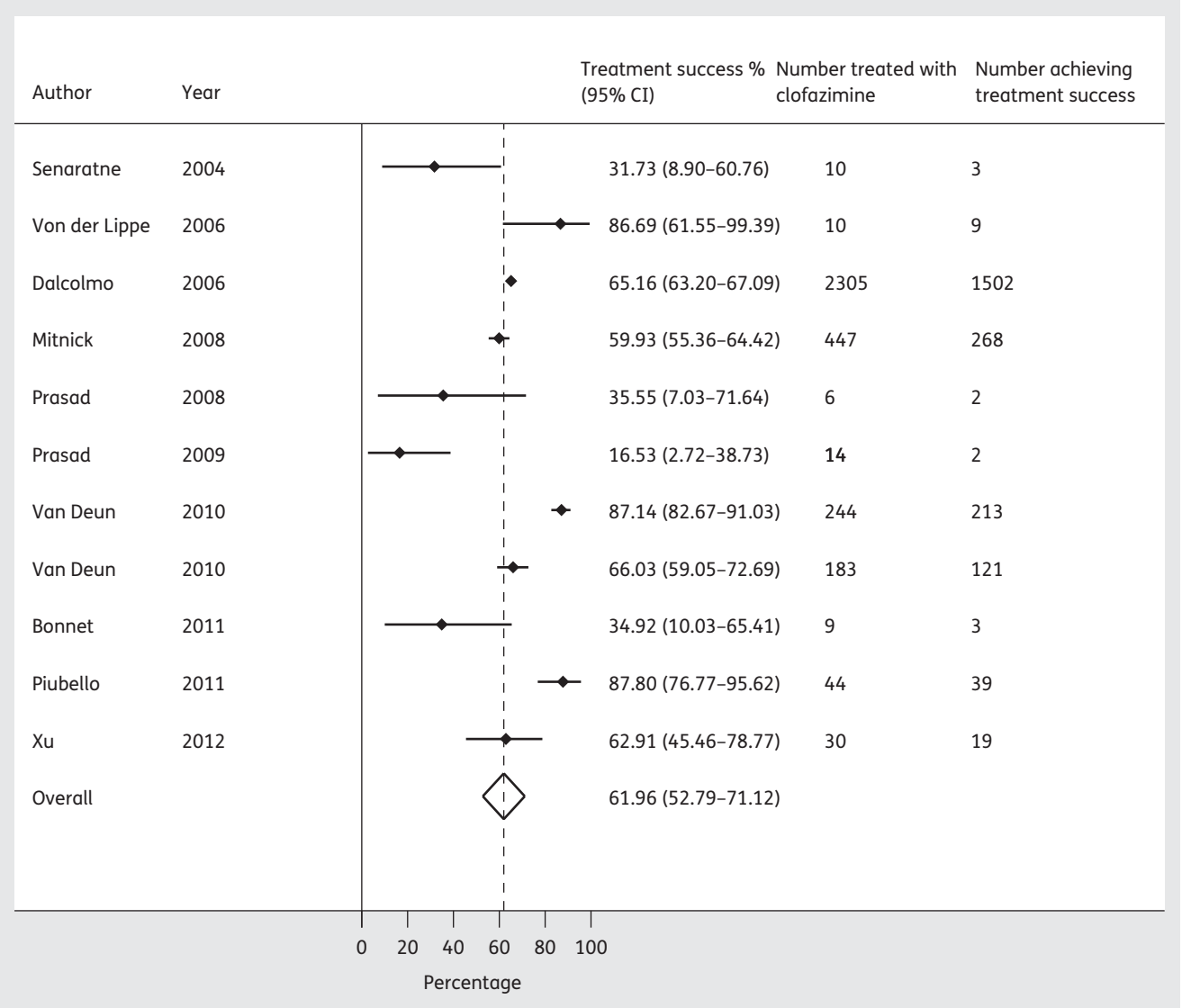

Figure 2. Proportion of patients achieving treatment success.

by studies in this systematic review was insufficient to draw any conclusions about dose-related outcomes.

There are several strengths and limitations to note. We employed a broad search strategy, allowing analysis of 3489 patients from both articles and abstracts. However, outcomes and key study and treatment characteristics were not consistently reported, limiting the number of analyses that could be done. We limited our meta-analysis to the primary outcome of treatment success; nevertheless, the substantial heterogeneity between studies means that this estimate needs to be interpreted with caution.[27,28] Publication bias is an ever-present concern, but is unlikely to be important for this review given the range of reported outcomes. The use of observational data means that all results are potentially subject to unmeasured confounding. Clofazimine was not the only drug used against DR-TB in these studies, so outcomes cannot be definitely ascribed to clofazimine. Finally, the inconsistent use of DST in general, and the lack of reliable DST for clofazimine in particular, means that it was not possible to determine whether observed outcomes were influenced by pre-treatment resistance patterns.

Conclusions

Outcomes of clofazimine-containing regimens are in line with drug-resistant (DR) treatment in general, and clofazimine appears to be associated with a lower incidence of serious adverse effects compared with other second-line therapeutics, suggesting that clofazimine could potentially be considered as an additional therapeutic agent for the treatment of DR-TB. However, there are several important barriers to the use of clofazimine. Currently, most of global supply of clofazimine is used for and restricted to first-line management of leprosy.[10,35,36] Despite recent studies showing the clinical success of repurposing the drug for DR-TB, there are issues accessing clofazimine for

Table 4. Adverse events

Study[a]	Number of patients receiving clofazimine	Number experiencing adverse events	Frequency and type of adverse event (number of patients)
Goble *et al.*, 1993[21]	17	2	liver dysfunction (1), abdominal pain (1)
von der Lippe, 2006[23]	10	7	neuropathy (6), anaemia (4), myelosuppression (1)
Prasad *et al.*, 2008[27]	6	1	haemoptysis (1)
Van Deun *et al.*, 2010[17]	427	203	vomiting (170), dysglycaemia (10), neurological (10), mental (12), ataxia (9), hearing (19), arthralgia (30), jaundice (3)
Bonnet *et al.*, 2011[20]	9	1	gastrointestinal disturbance (1)
Xu *et al.*, 2012[24]	44	39	reddish-brown skin discolouration (36), depression (1), ichthyosis (12), gastrointestinal disturbance (21), dizziness (1)

[a]Six studies did not provide information on adverse events.[22,25,26,28–30]

DR-TB.[37,38] At an annual cost of $114 (300 mg daily) per patient, clofazimine could be potentially more affordable than other DR-TB drugs.[39] A meeting at the WHO in Geneva in March 2012 highlighted that clofazimine is one of the two most important second-line drugs and needs to be made more accessible for use in low-resource settings.[37]

This review points to several directions for future research. Firstly, the optimum duration and dose of clofazimine therapy needs to be established. Although clofazimine is planned to be included in a number of upcoming clinical trials for DR-TB, none will specifically assess clofazimine's action in a treatment regimen for DR-TB. Secondly, more pre-clinical studies assessing the potential synergistic action that clofazimine can have with other TB drugs would be beneficial. Finally, more data on clofazimine use in DR-TB-infected subpopulations such as HIV-positive patients and children are needed.

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Transparency declarations

None to declare.

Supplementary data

The protocol is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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