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Review Article

The Curative Innovation of Novel Triple-Drug Compared to Double-Drug Regimen in Lymphatic Filariasis: A Systematic Review

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ABSTRACT

The World Health Organization has established a global program for the elimination of lymphatic filariasis by 2020; recent data has shown an impracticable result accomplishing it. Therefore, this study aims to identify the efficacy and safety between triple-drugs (DEC, ALB, IVM) and double-drugs (DEC & ALB/IVM & ALB) for lymphatic filariasis treatment. A systematic review was conducted with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement guidelines. The literature search was done using five databases: PubMed, ProQuest, ScienceDirect, EBSCO, and CENTRAL until December 3, 2020 without any publication date range imposed. Data collection was done by three independent reviewers and entered into a predesigned data extraction form. Cochrane risk of bias tool 2.0 was utilized in the quality assessment of the studies. Search strategies identified 209 studies. Three relevant full-text articles met our inclusion criteria. Overall studies had low risk of bias. The main findings are as follows: (a) Administration of single dose of triple-drug regimen resulted in a total elimination of microfilaria 12 months after treatment whilst 91% participants given with double-drug remained microfilaremic (p=0.002); (b) In larger samples (n=182), triple drug cleared microfilaria in 96% of the participants and only 32% of the participants receiving double-drug regimen after 12 months observation; (c) Statistically, the triple-drug safety has a lower degree than the double-drug regimen (p=0.02). The triple-drug treatment has a better efficacy compared to the double-drug regimen in treating lymphatic filariasis. Furthermore, both regimens are proven safe with no serious adverse events elicited.

Keywords: *albendazole; diethylcarbamazin; ivermectin; lymphatic filariasis; systematic review*

ABSTRAK

Organisasi Kesehatan Dunia (WHO) telah menetapkan program global untuk mengeliminasi filariasis limfatik pada tahun 2020; data terbaru menunjukkan ketidakberhasilan pencapaian target tersebut. Oleh karena itu penelitian ini bertujuan untuk mengidentifikasi efikasi dan keamanan antara terapi menggunakan tiga obat (DEC, ALB, IVM) dan terapi dua obat (DEC & ALB/IVM & ALB) untuk pengobatan filariasis limfatik. Telaah sistematis dilakukan dengan pedoman pernyataan Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA). Pencarian literatur dilakukan melalui lima database: PubMed, ProQuest, ScienceDirect, EBSCO, dan CENTRAL hingga 3 Desember 2020 tanpa adanya batas rentang waktu publikasi. Pengumpulan data dilakukan oleh tiga peninjau secara independen dan dimasukkan ke dalam formulir ekstraksi data yang telah dirancang sebelumnya. Cochrane risk of bias 2.0 digunakan dalam penilaian kualitas studi.Strategi pencarian mengidentifikasi 209 studi. Tiga artikel yang relevan memenuhi kriteria inklusi studi. Keseluruhan studi memiliki risiko bias yang rendah berdasarkan penilaian penulis. Temuan utama adalah sebagai berikut: (a) Pemberian dosis tunggal pada terapi tiga obat mengeliminasi seluruh mikrofilaria setelah 12 bulan pengobatan sedangkan 91% peserta yang diberi terapi dua obat masih mengalami mikrofilaremia (p=0,002); (b) Dalam sampel yang lebih besar (n=182), mikrofilaria tereliminasi pada 96% peserta yang menerima

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terapi tiga obat dan 32% peserta yang menerima terapi dua obat setelah 12 bulan observasi; (c) Secara statistik, terapi menggunakan tiga obat lebih aman digunakan dibandingkan dengan terapi dua obat (p=0,02). Terapi tiga obat memiliki efikasi yang lebih baik dibandingkan dengan terapi dua obat dalam menangani filariasis limfatik. Kedua terapi juga terbukti aman tanpa adanya efek samping berat yang ditimbulkan.

Kata kunci: *albendazol; dietilkarbamazin; filariasis limfatik; ivermektin; telaah sistematis*

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INTRODUCTION

Lymphatic filariasis (LF) is a severe manifestation caused by a parasitic infection of worms belonging to the genus Wuchereria and Brugia, that is transmissible by means of a mosquito vector.[1] This infection does not kill its host but significantly reduces their quality of life.[2] Latest data reported from the World Health Organization (WHO), which is in the year 2000, recorded over 120 million people were infected and about 40 million disfigured.[3] In Indonesia alone, the ministry of health reported over 14,000 people suffered from chronic filariasis (elephantiasis) in the year 2014.[4] There is still an estimate of 893 million people worldwide remain at risk of getting LF.[3] Thus, this spectrum of disease is considered globally as one of the many neglected tropical diseases (NTD) requiring further interventions.[5]

The Global Programme to Eliminate Lymphatic Filariasis (GPELF) was initially established by the World Health Organization (WHO) in 2000 with the aim to achieve global elimination of LF by 2020.[6] The proposed strategy includes the interruption LF transmission using mass drug administration as well as Managing Morbidity and Preventing Disability (MMPD) by providing access to primary recommended care. Latest reported data in 2019 on the progress of this program concluded a total of 37.3% are still at risk worldwide, which discourages the previous statement of it being completed in the year 2020.[7] Nevertheless, it is best to focus on the treatment rather than the prevention in order to minimize the damage being done in the meantime.

Currently, there are several regimens to treat LF.[8] The well-known single-drug therapy is using Diethylcarbamazine (DEC) with a dosage of 6 mg/kg.[9] Other drugs, such as Ivermectin (IVM) or Albendazole (ALB), rose to amplify the efficacy of DEC when combined.[10] However, some research found flaws in this double-drug therapy, a detection of microfilaria at one year posttreatment. A systematic review on the combination of ALBwith DEC also yielded little or even no differences compared[11] to using single-drug. In 2015, a pilot randomized controlled trial (RCT) was done with the hypothesis that a triple-drugcombination of DEC, ALB, and IVM might manifest a better result and coverage compared to only using two drugs.[12] The downside is that in accordance with medical scientific theory, more drug consumption is equivalent to more adverse events (AEs). Through this hypothesis, the objective of our systematic review is to analyze the efficacy and safety between a triple-drug and double-drug regimen in LF curative management qualitatively.

METHODS

A systematic review was conducted with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement guidelines to identify the efficacy and safety between a triple-drug and double-drug lymphatic filariasis treatment.[13] Population, Intervention, Comparison, and Outcomes (PICO) questions were also used to formulate the inclusion criteria of this systematic review. The answer of those questions consecutively: Patients confirmed

suffering from LF with no prior antifilarial treatment; Intervention with a triple-drug regimen consisting of DEC, ALB, and IVM; Comparison with a double-drug regimen consisting of DEC and ALB or IVM and ALB; Outcomes measured are efficacy and safety of both regimens. Differences between regimen doses and duration will be analyzed qualitatively based on the outcomes. The other inclusion criteria for this study is the study design and full-text availability. The study design had to be a RCT with participants confirmed as LF patients, and all included studies must have full text.

The literature search was done using five databases: PubMed, ProQuest, ScienceDirect, EBSCO, and CENTRAL with "*lymphatic filariasis*," "*Ivermectin*," "*Albendazole*," and "*Diethylcarbamazine*" as the main keywords until December 3, 2020 without any publication date range imposed. No language restrictions were imposed. The complete keywords are listed in Table 1 in the appendix. The result of the search was then imported to EndNote X9, and the duplicates were removed. All authors participated through each phase of the review independently by screening the titles and abstracts, assessing the full text for eligibility criteria, then including the relevant studies. Data collection was done by three independent reviewers (RR, EA, and C) and entered into a predesigned data extraction form. Differences arising between the three reviewers regarding study eligibility were resolved by consensus.

Table 1. Search Keywords

Database	Keywords	Articles
PubMed	(((((((((Elephantiasis, Filarial[MeSH Terms]) OR (Elephantiasis, Filarial[Title/Abstract])) OR (Lymphatic Filariasis[Title/Abstract]))OR (Lymphatic Filariases[Title/Abstract])) OR (Bancroftian Filariasis[Title/Abstract])) OR (Malayi Filariasis[Title/Abstract])) OR (Elephantiasis[Title/Abstract])) AND ((((Ivermectin[MeSH Terms]) OR (Ivermectin[Title/Abstract])) OR (Ivomec[Title/Abstract])) OR(IVM[Title/Abstract]))) AND ((((albendazole[MeSH Terms])) OR (albendazole[Title/Abstract])) OR (ALB[Title/Abstract]))) AND (((Diethylcarbamazine[MeSH Terms]) OR(Diethylcarbamazine[Title/Abstract])) OR ("Diethylcarbamazine Citrate"[Title/Abstract]))	105
ProQuest	(ab(Elephantiasis, Filarial OR Lymphatic Filariasis OR Lymphatic Filariases OR Bancroftian Filariasis OR Malayi Filariasis OR Elephantiasis) OR ti(Elephantiasis, Filarial OR Lymphatic Filariasis OR Lymphatic Filariases OR Bancroftian Filariasis OR Malayi Filariasis OR Elephantiasis)) AND (ab(Ivermectin OR Ivomec OR IVM) OR ti(Ivermectin OR Ivomec OR IVM)) AND (ab(albendazoleOR ALB) OR ti(albendazole OR ALB)) AND (ab(Diethylcarbamazine OR Diethylcarbamazine Citrate) OR ti(Diethylcarbamazine OR Diethylcarbamazine Citrate))	44
Science Direct	(Elephantiasis, Filarial OR Lymphatic Filariasis OR Lymphatic Filariases OR Bancroftian Filariasis OR Elephantiasis) AND Ivermectin AND albendazole AND (Diethylcarbamazine OR Diethylcarbamazine Citrate)	**27**
EBSCO	(ab(Elephantiasis, Filarial OR Lymphatic Filariasis OR Lymphatic Filariases OR Bancroftian Filariasis OR Malayi Filariasis OR Elephantiasis) OR ti(Elephantiasis, Filarial OR Lymphatic Filariasis OR Lymphatic Filariases OR Bancroftian Filariasis OR Malayi Filariasis OR Elephantiasis)) AND (ab(Ivermectin OR Ivomec OR IVM) OR ti(Ivermectin OR Ivomec OR IVM)) AND (ab(albendazoleOR ALB) OR ti(albendazole OR ALB)) AND (ab(Diethylcarbamazine OR Diethylcarbamazine Citrate) OR ti(Diethylcarbamazine OR Diethylcarbamazine Citrate))	98
CENTRAL	Elephantiasis, Filarial[MeSH Terms] AND Ivermectin[MeSH Terms]AND albendazole[MeSH Terms] AND Diethylcarbamazine[MeSH Terms]	13

Cochrane risk of bias tool 2.0 was utilized in the quality assessment of the studieswhich covers the following seven domains ofrisk. Included study quality will be classified as low, unclear, or high risk of bias.[14] Disagreements arising in the process of the evaluation were all resolved by discussion among the review team.

RESULTS AND DISCUSSION

Search Results

A literature search from electronic databases yielded 287 studies. After removing the duplicates, 209 remaining studies. Screening through the titles and abstracts, the authors excluded studies with eight other studies that met the inclusion criteria. The result showed that three studies matched the criteria for inclusion.[12,15,16] Search flowchart and selection method was summarized in Figure 1.

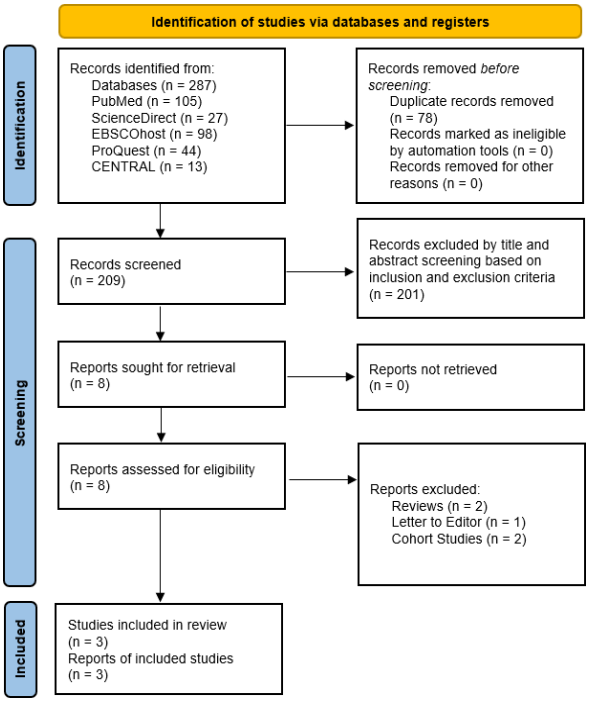

Figure 1. PRISMA Flow Diagram of the Identification and Selection of Studies Included in the Analysis

Study Characteristics

All of the included studies were done using the RCT design. Inclusion and exclusion criteria across studies showed similarities. Most of the study populations included were from Papua New Guinea[12,15] and Côte d'Ivoire in West Africa[16] that showed small sample varieties. The regimen dosage and duration has slight differences amongst studies with efficacy and safety analysis. Detailed characteristics of the included studies were summarized in Table 2.

Quality Assessment

There were unclear risks for all studies from the domain of selection and reporting bias. Concealment of the randomization done between the control and interventional group was unexplained.[12,15,16] Also, two studies excluded incomplete data from the statistical testing; thus can alter the results.[12,15] Two studies have an unclear risk in detection bias resulting from inadequate data.[12,15] Overall studies had a low risk of bias based on the author's judgement, was summarized in Figure 2.

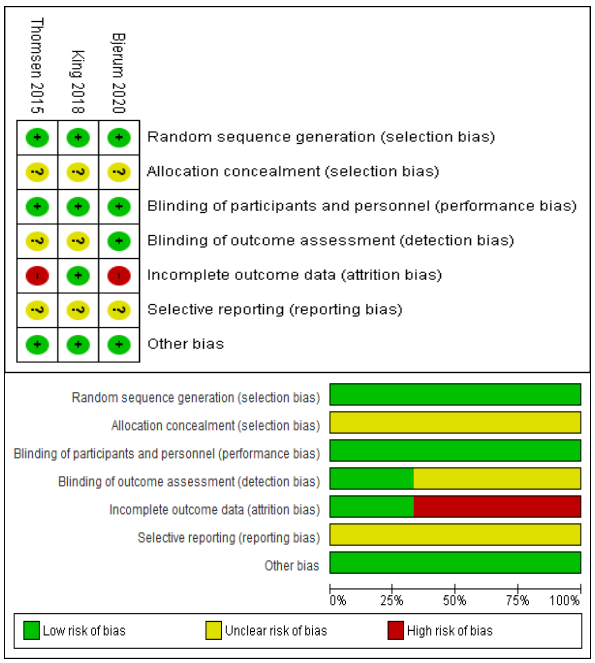

Figure 2. Risk of Bias Summary: Review Authors' Judgements about Each Risk of Bias Item for Each Included Study

Study Characteristics

The pilot study done by Thomsen et al.[12] Included 24 participants with no chronic illnesses or prior LF infection. Participants

also have not got the MDA prophylaxis. Included participants divided into two parallel groups with every 12 participants that received the triple-drug (DEC + ALB + IVM) or the double-drug regimen (DEC + ALB). The study yielded higher efficacy in the triple-drug regimen with total eradication until 12 months follow-up than the double-drug regimen still resulting in 10 of 11 participants having positive microfilaremia (p=0.002). After two years of follow-up, both regimens showed complete eradication of microfilaremia.[12]

In 2018, another comparison of a RCT study done by King et al. is conducted to evaluate the efficacy of a single dose of triple-drug regimen in sustaining clearance being higher than a single dose of double-drug regimen for LF. A total of 182 participants were included, 60 of which were assigned to receive the triple-drug regimen administered once, and 61 for each double-drug regimen administered once and once a year for three years. Among 182 participants, 172 (95%) were evaluated at 12 months, 165 (91%) at 24 months, and 158 (87%) at 36 months after trial initiation–several were excluded for similar reasons, including a withdrawal, moved from the area, died, took a second dose by mistake or merely lost to follow-up. However, despite the decrease of the number of participants, the outcome of triple-drug regimen still result in significantly greater microfilarial clearance at 36 months than a single dose of the double- drug regimen, with a p-value lower than 0.025 (p=0.02), and was non-inferior to that with the double-drug regimen administered once a year for three years, with a one-sided P value for noninferiority lower than 0.025 (P=0.004).[15]

The most recent study was done in 2020 by Bjerum et al. consisting of 97 participants and using a similar triple-drug regimen but a somewhat different double-drug regimen consisting of IVM and ALB. The triple-drug group (45 participants) was given a single dose at the beginning of the research, while the double-drug group (52 participants) was given annually for three years. Results measured were the clearance of microfilaremia at 6, 12, 24, and 36 months posttreatment. The triple-drug regimen was significantly better compared to the double-drug regimen in clearing microfilaremia at 6 and 12 months (both with the value of p<0.001). However, superiority is the exact opposite in the 36 months (p=0.045). At the 24 months posttreatment, the triple-drug regimen was still better but with an insignificant value (p=0.53). This concludes that although the triple-drug group was only given once at the beginning of the study, it can maintain a better clearance up to 24 months posttreatment.[16]

Table 2. Characteristics of the Included Studies

Author	Study Design	Samples	Interventions		Duration of Follow-up	Result	
			Triple Drug	Double Drug		Effectivity	Adverse Event
King et al., 2018	Randomized Controlled Trial	N=182 This includes a total of 60 patients assigned IVM+DEC+ALB administered once, 61 to DEC+ALB administered once, and 61 to DEC+ALB once a year for 3 years	DEC + ALB + IVM IVM 200 µg/kg plus DEC 6mg/kg plus ALB 400mg administered once at trial initiation	DEC + ALB DEC 6 mg/kg plus ALB 400mg administered once at trial initiation	Follow-up was done at 12,24 and 36 months after trial initiation	Triple-drug regimen cleared microfilaremia in 55 (96%), 52 (96%) and 55 participants (96%) at 12, 24 and 36 months respectively. A single dose of double-drug regimen cleared microfilaremia in 18 (32%), 31 (56%), 43 (83%) participants at 12, 24 and 36 months respectively.	Moderate AEs after the initial treatment were more frequent with the triple-drug regimen than with the double-drug regimen.
Thomsen et al. 2015	Randomized Controlled Trial - Single blinded parallel - group	N=24 This includes a total of 12 patients assigned to DEC + ALB group and 12 patients assigned to DEC + ALB + IVM groups	DEC + ALB + IVM Single dose IVM 200 µg/kg; ALB 400 mg; DEC 6 mg/kg	DEC + ALB Single dose DEC 6 mg/kg; ALB	Follow up was done until 2 years posttreatment	Triple-drug regimen resulting total elimination of microfilaria after 36 h and 7 days treatments and remain so at 12 months posttreatment, than the double-drug regimen 10 of 11 participants remained microfilaremic at 12 months follow-up	No serious AE was found in both treatment groups. Most common AEs elicited were fever, myalgia, pruritus, and proteinuria/hematuria. Adverse events were more on the triple-drug groups compared to the double- drug groups (83% and 50%, respectively; p=0.02).
Bjerum et al. 2020	Randomized Controlled Trial	N=97 This includes a total of 52 patients assigned to IVM+ALB group and 45 patients assigned to IVM+DEC+ALB group	DEC + ALB + IVM IVM 200 µg/kg and ALB 400 mg plus DEC 6 mg/kg were given only once at the beginning of the study.	IVM + ALB IVM 200 µg/ kg and ALB 400 mg were given in a 3 annual dose.	Follow-up was done at 6, 12, 24, and 36 months posttreatment	Triple-drug regimen resulted in a Mf complete clearance of 89%, 71%, 61%, and 55% at a follow-up time of 6, 12, 24, and 36 months, respectively. While double-drug regimen resulted in a Mf complete clearance of 34%, 26%, 54%, and 79% at similar follow-up time, respectively.	Both groups resulted in similar AEs, which are none in the severe (grade 3) category and a similar one at the mild (grade 1) category. However, triple-drug therapy elicited more moderate (grade 2) AEs compared to double-drug therapy.

Abbreviation:
AE, Adverse Events; ALB, Albendazole; ALT, Alanine Transferase; AST, Aspartate Transferase; DEC, Diethylcarbamazine; dl, Deciliter; g, Gram; IVM, Ivermectin; kg, Kilogram; mf, Microfilaria; mg, Milligram; ml. Milliliter; µg, Microgram; N, Number of Participants; N/A, Not Available

Safety Regarding the Adverse Events

All three studies reported that triple- drug therapy resulted in a much more AE compared to double-drug therapy. This is supported by the basic medical lessons that more drugs are equal to greater side effects. However, the AEs reported are mild to moderate AEs like fever, myalgias, headache, nausea, and the like. There are no serious or severe (e.g. grade 3) AEs reported.[12,15,16]

This systematic review concludes a similar result found in all three studies.[12,15,16] All things considered, the triple-drug regimen was revealed for being the more effective option compared to the double-drug regimen in treating LF. The clearance of

microfilaremia measures this effectiveness at their given posttreatment, follow-up time. Study by Bjerum et al., however, showed that the double-drug regimen was significantly superior at 36 months posttreatment.[16] Another important aspect is the therapy's safety, which is measured by listing all AEs elicited after drug consumption. Both regimens are considered safe by means of no serious or severe AEs obtained. Mild to moderate AEs like fever, nausea, headache, and the like are more commonly found in patients treated with the triple-drug compared to the double-drug regimen.[12,15,16]

Pharmacological Aspects between the Regimen

Each single drug has variability in their pharmacokinetics profile. Albendazole alone has poor absorption in gastrointestinal tract[17,19] compared with ivermectin or DEC that achieve peak plasma concentration faster than albendazole.[20] Well distribution is confirmed by each drug, but ivermectin has high lipophilicity,[21,22] opposites with DEC.[23,24] Metabolism of each drug occurs mostly in liver. Only DEC shows partial metabolism that slows down the elimination process. Most of the drugs excreted through feces and bile, less in urine. Nevertheless, lipophilicity profile that ivermectin has and partial metabolism in DEC reflects higher half-time for both drugs.[21,25]

Mechanism of action each drug also differs one to the other. Active metabolites of albendazole (albendazole sulfoxide) causes degeneration of cytoplasmic microtubules helminths with the decrease of parasite's glycogen stores.[17,18] Then, DEC yields sensitization of macrophage to microfilaria that ease the clearance process.[23,25] Lastly, ivermectin can causes hyperpolarization, however other study shows that ivermectin has the ability to sterilize the adult filarial.[26,27]

Combining of these drugs creates better pharmacokinetics and efficacy profiles because of uniqueness of each drugs. Using triple regimen shows superiority rather than double regimen. Half-life ($t_{1/2}$) and concentration max (C_{max}) higher if we add ivermectin in standard double regimen (DEC and ALB). Figure 3 illustrates slightly higher serum concentration of DEC in initial times after consumed if combined as triple-drug regimen. Similar profile also obtains from serum concentration of albendazole that increase in triple-drug regimen. Those pharmacological profiles raise the efficacy of triple-drug regimen than double-drug regimen.[12]

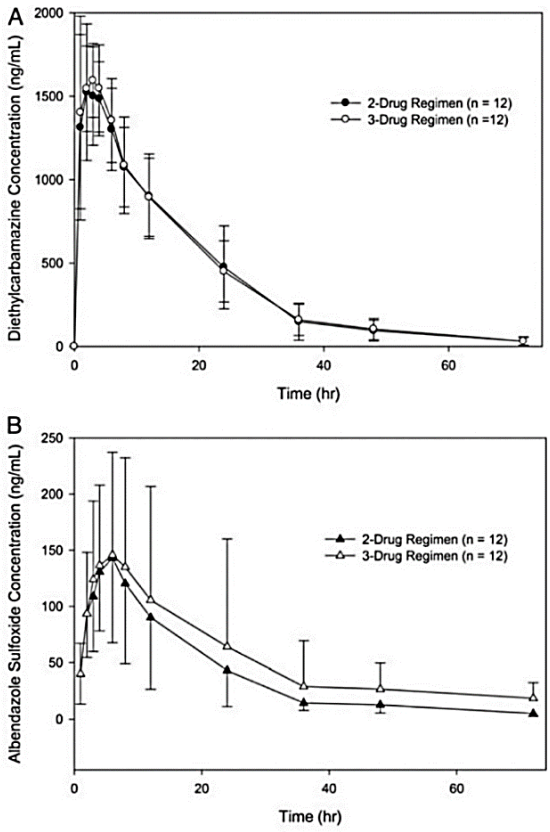

Figure 3. Concentration of lymphatic filariasis regimen in correlation with duration. (A) Mean serum plasma of DEC (B) Active metabolite of ALB[12]

Multimodal mechanism of actions also improves the efficacy of triple-drug regimen. Different sites of parasites killing process increase the chances of microfilaria deaths. Both albendazole and DEC can directly kill microfilaria. Addition to that, ivermectin will improves reduction of microfilaria with sterilization of adult worms that reflects lower microfilaremia level in longer times.

Nevertheless, further research is needed to carry out in determining definitive reasons whether it is due to additive or synergistic effect between the triple-drug interactions.[26]

Until now, each drugs using standard dose, even it already combined as triple-drug regimen. The fact that limitation arises from single drug with standard doses can be covered by other drugs. Adverse effects with all standard doses also depict low or minimal events. Nonetheless, specific research about dose adjustment still be needed. The high efficacy of triple-drug regimen can accelerate eradication of LF. This data is supported with a mathematical model that predicts for faster approaches to eliminate LF.[28]

Difference in Various Aspects of the Regimen

Although there are many similarities in the three included RCTs, their differences are a requirement to be discussed. Differences arise across studies yielded hazy analyzes in the overall results. The main distinguishable factor is the inconsistency in the drug combinations used. Bjerum et al. use a different double-drug combination, which includes ALB and IVM, compared with two other studies that used DEC and ALB.[16] A clinical trial in Ghana using a combination of ALB and IVM showed the same efficacy and safety with a controlled group (DEC and ALB) but statistically incomparable.[29] Moreover, a model-analysis results in the same efficacy between both kinds of double-drug regimen (IVM and ALB/DEC and ALB).30 Our analysis also considers IVM mechanisms of action that can be the main reason for DEC substitution in LF. As mentioned previously, ivermectin causes paralysis and death of parasites by interacting with its chloride channel in the cell membrane leading to hyperpolarization.[31,32] Although there are differences among the double-drug regimens, it can be concluded that both showed the same efficacy and safety that can be compared with triple-drug based on the data analyses and each authors' judgments.

Another difference comes from the regimen frequency in which the double-drug regimen is not only given once. This difference can be ignored since a higher frequency of the double-drug regimen still shows inferior outcomes compared to the triple-drug regimen.[23] Moreover, a study showed that the double-drug regimen has minor to none efficacious effect even with more frequency.[33] However, in some studies, it can affect the effectivity outcome on the last day of the treatment follow-up.16

In the safety objectives, a longer duration of follow up showed an extension of the safety observation. Although there are no serious AEs, the triple-drug regimen contains more chemical agents compound which can cause more AEs when compared to the double-drug regimen.[34,35] Risk vs benefit will be the primary consideration when it comes to LF treatment.[11] The highest benefits, besides the side effects, can be found by using the triple-drug regimen. However, in public situations, the doctor's explanations about the triple-drug regimen's potent benefits must be performed to prevent the misunderstanding of its AEs.

Strength and Limitation of Each Study

Included studies also shared some strengths and limitations. By referring to the risk of bias assessment, strengths such as the inclusion of using a random component had been performed, concluding a low risk of bias for random sequence generation, followed by the blinding of participants and the personnel or trial staff, specifically those who assessed the adverse events in the studies done by King et al. and Bjerum et al.[15,16] However, the blinding of outcome assessment was only low risk in the study done by Bjerum et al. since it was specified that although it was an open-label trial, the investigators and staff who evaluated the examinations were masked with respect to treatment arm assignments.[16] Meanwhile, the study done by King et al. gained the upper hand in incomplete outcome data, by conducting a sensitivity analysis (chi-squared analysis) to evaluate the potential effect of the missing data on the

primary outcome at 36 months.[15] There were also no other biases present.

Several inherent limitations are the questionable allocation concealment, as these three studies did not indicate the method to conceal the possibility of foreseeing the assignments. As mentioned before, blinding of outcome assessment is also unclear in the studies done by Thomsen et al. and King et al.[12,15] Another important caveat is the removal of participants which are lost to follow-up without performing a further analysis for the potential effects in the Thomsen et al. and Bjerum et al.'s study.[12,16]

King et al.'s study has also emphasized its limitations when assessing adverse events in the first 10 hours of follow-up since participants may have been aware of the treatment group assignments.[12] Although, the subsequent follow-up of the participants in their communities was performed in a blinded manner by different trial staff. Also, the detection of microfilaremia at follow-up could have been due to reinfection. On the other hand, the limitations from Bjerum et al.'s study include the unreliable outcome of higher infection rate in males due to its higher number of participants.[16] This study is also involved in the retreatment of Mf-positive individuals after 24 months following a single dose of triple-drug therapy; however, this number was later considered as a failure.

SUMMARY

The objective of this systematic review leads to the conclusion that the triple-drug regimen is superior in terms of efficacy, but resulted in the sacrifice of its safety. One of the downsides in these three studies is the small geographic variety in the included respondents. It is crucial that future studies consider and involve a wide variety of people in order for this research to be generalized. To conclude, based on this review, the presence of a triple-drug regimen can really aid in improving the course of lymphatic filariasis; thus, leading to much better outcomes.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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