Rifampin-Ofloxacin-Minocycline (ROM) for the Treatment of Paucibacillary Leprosy: A Systematic Review

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Introduction

- Standard WHO multi-drug treatment (MDT) for leprosy consists of medications that are potentially harmful and cause a range of adverse systemic effects
- Paucibacillary leprosy, characterized by limited skin lesions and a low bacillary load, may be most amenable to a fluoroquinolone-based treatment protocol
- Monthly- or single dosing of ROM has emerged as a potential treatment option for leprosy, however, a synthesis of the evidence supporting ROM does not exist

Methods

- Abstracts reporting the efficacy & safety of monthly ROM treatment in paucibacillary leprosy in human patients were targeted using combinations of the search terms “ROM” & “Leprosy” from inception to May 11, 2022
- During all phases of screening a tertiary arbitrator arbitrated any inclusion/exclusion discrepancies
- Inclusion Criteria: Systematic reviews, randomized controlled trials, clinical trials, cohort studies, observational studies, case-control studies, case series (N>5), English and non-English publications
- Exclusion Criteria: Case reports, case series (N<4)

Results

Study	Country	Study Design	Sample Size, No.	Mean Age, y	Male, %	Follow-Up, (SD), mo	Diagnosis of Leprosy	# Lesions	Treatment	Comparator
[1]Alam et al., 2007	Bangladesh	Retrospective	270	-	-	96	Not reported	Single	ROM, single dose	No Comparator
[2]Babu et al., 1997	India	Randomized Control Trial	1483	23	42.28	12	Clinical	Single	ROM, single dose	WHO-MDT
[3]Desikan & Gupte, 2001	India	Randomized Control Trial	236	-	46.19	12-18	Clinical + Histological	2-3	ROM, single dose	WHO-MDT
[4]Deshmukj et al., 2003	India	Randomized Control Trial	32	-	75	6	Clinical + Histological	1-3	ROM, single dose	WHO-MDT
[5]Diniz et al., 2010	Brazil	Cohort	54	31	31.48	12	Clinical + Histological	Single	ROM, single dose	No Comparator
[6]Ebenezer et al., 1999	India	Case series	13	26 (11.4)	62	12	Clinical	1-3	ROM, single dose	No Comparator
[7]Emmanuel & Gupte, 2005	India	Randomized Control Trial	51	-	58.82	24	Clinical + Histological	2-3	ROM, single dose	WHO-MDT
[8]Ganapati et al., 1999	India	Case series	634	-	-	-	Clinical	2-5	ROM, single dose	No Comparator
[9]Girdhar et al., 2011	India	Randomized Control Trial	300	30.9 (16.2)	41	36.76 (14.8)	Clinical	Single	ROM, single dose	ROM + clarithromycin
[10]Gomes et al., 2008	Brazil	Cohort	259	32.4 (16)	38.2	36	Clinical + Histological	Single	ROM, single dose	No Comparator
[11]Kumar et al., 2015	India	Randomized Control Trial	268	-	37.7	60	Clinical	1-5	ROM, monthly	WHO-MDT
[12]Kumar et al., 2014	India	Cohort	289	41.6	61.8	12	Clinical	1-5	ROM, monthly	WHO-MDT
[13]Majumder et al., 2000	India	Clinical Trial	90	-	-	12	Clinical + Histological	Single	ROM, single dose	ROM, single dose + Convit vaccine*
[14]Mane et al., 1997	Senegal	Case series	220	-	60	12	Clinical + Histological	2-5	ROM, monthly	No Comparator
[15]Manickam et al., 2012	India	Randomized Control Trial	1526	27	47.5	36	Clinical	2-5	ROM, single dose	WHO-MDT
[16]Martelli et al., 2000	Brazil	No outcomes reported	259	32.4 (16.0)	38.22	-	Clinical + Histological	Single	ROM, single dose	No Comparator
[17]Pai et al., 1999	India	Case series	634	-	-	-	Clinical	1-5	ROM, single dose	No Comparator
[18]Ravenkar et al., 2002	India	Cohort	335	-	-	6-70	Clinical	2-5	ROM, single dose	No Comparator
[19]Shetty et al, 2011	India	Retrospective cohort	62	-	-	-	Clinical + Histological	1-5	ROM, single dose	i) WHO-MDT, ii) dapsone, iii) RO
[20]Shinde et al., 2000	India	Case series	26	-	-	-	Clinical	Single	ROM, single dose	No Comparator
[21]Shukla et al., 2000	India	Clinical Trial	61	-	55.7	12	Clinical + Histological	Single	ROM, single dose	No Comparator
[22]Sousa et al., 2007	Brazil	Case series	135	30.5 (15.4)	44.4	31.4	Clinical	Single	ROM, single dose	No Comparator
[23]Stefani et al., 2003	Brazil	Case series	39	33.4 (15.3)	51.28	32.4 (16.0)	Histological	Single	ROM, single dose	No Comparator
[24]Vivekkumar et al., 2010	India	Randomized Control Trial	72	-	61	6	Clinical	1-5	ROM, single dose	RLM, single dose

Table 1. Preliminary Baseline Characteristics of Included Studies

Abbreviations: Rifampin + Ofloxacin (RO); Standard World Health Organization Multi-drug therapy (WHO-MDT); Rifampin + Levofloxacin + Minocycline (RLM)

*Low-dose Convit vaccine contained $1.6x10^7$ heat-killed *M. leprae* in 0.1ml saline and $1.5x10^7$BCG in 0.1ml saline

Outcome	Study	ROM		Comparator		Difference (%)
		% of patients	Proportion	% of patients	Proportion	
Lesion Clearance	[1]Alam et al., 2007	75.93	205/270	-	-	-
	[2]Babu et al., 1997	44.25	327/739	50.27	374/744	-6.02
	[3]Desikan & Gupte, 2001	96.22	102/106	96.15	100/104	0.07
	[5]Diniz et al., 2010	85.20	45/54	-	-	-
	[6]Ebenezer et al., 1999	84.62	11/13	-	-	-
	[7]Emmanuel & Gupte, 2005	-	-	-	-	-
	6mo	3.85	1/26	16.00	4/25	-
	12mo	38.46	10/26	44.00	11/25	-
	18mo	42.31	11/26	60.00	15/25	-
	24mo	46.15	12/26	64.00	16/25	-
	Mean of first 4 f/u	32.69	-	46.00	-	-13.31
	[10]Gomes et al., 2008	80.69	209/259	-	-	-
	[9]Girdhar et al., 2011	-	-	-	-	-
	6mo	72.85	110/151	78.52	117/149	-
	12mo	89.40	135/151	89.26	133/149	-
	18mo	94.59	140/148	91.72	133/145	-
	Mean of first 3 f/u	86.61	-	86.50	-	0.11
	[11]Kumar et al., 2015	97.22	105/108	93.27	97/104	3.95
	[13]Majumder et al., 2000	46.67	14/30	33.30	20/60	13.37
	[14]Mane et al., 1997	25.00	14/56	-	-	-
	[15]Manickam et al., 2012	72.11	486/674	72.12	494/685	-0.01
	[18]Ravenkar et al., 2002	98.74	626/634	-	-	-
	[23]Stefani et al., 2003	44.00	11/25	-	-	-
	[24]Vivekkumar et al., 2010	36.11	13/36	75.00	27/36	-38.89
	Mean	**52.73**	-	**57.42**	-	**-4.69**
	Median	**75.93**	-	**73.56**	-	**2.37**
	Range	**25.00-98.74**	-	**33.33-96.15**	-	**Negative in favour for ROM**
Treatment Failure	[3]Desikan & Gupte, 2001	3.77	4/106	3.85	4/104	-0.08
	[11]Kumar et al., 2015	0.93	1/108	3.87	4/104	-2.94
	[13]Majumder et al., 2000	23.33	7/30	18.33	11/60	5.00
	[14]Mane et al., 1997	0.98	1/102	-	-	-
	[15]Manickam et al., 2012	0.30	2/674	0.58	4/685	-0.28
	[18]Ravenkar et al., 2002	3.79	24/634	-	-	-
	[22]Sousa et al., 2007	1.48	2/135	-	-	-
	[23]Stefani et al., 2003	2.70	1/37	-	-	-
	Mean	**4.66**	-	**6.66**	-	**-2.00**
	Median	**2.09**	-	**3.86**	-	**-1.77**
	Range	**0.30-23.33**	-	**0.58-18.33**	-	**Positive in favour for ROM**
Relapse	[1]Alam et al., 2007	3.70	10/270	-	-	-
	[2]Babu et al., 1997	0.81	6/739	0.81	6/744	0.00
	[5]Diniz et al., 2010	9.3	5/54	-	-	-
	[18]Ravenkar et al., 2002	1.49	5/335	-	-	-
	[9]Girdhar et al., 2011	2.22	3/135	1.43	2/140	0.79
	[11]Kumar et al., 2015	2.78	3/108	6.73	7/104	-3.95
	[15]Manickam et al., 2012 *	-	29/100py	-	9/100py	20/100py
	Mean	**3.38**	-	**2.99**	-	**0.39**
	Median	**2.50**	-	**1.43**	-	**1.07**
	Range	**0.81-9.3**	-	**0.81-6.73**	-	**Negative in favour for ROM**
Side Effects	[2]Babu et al., 1997	0.68	5/739	0.94	7/744	-0.26
	[3]Desikan & Gupte, 2001	0.00	0/118	1.69	2/118	-1.69
	[13]Majumder et al., 2000	0.00	0/30	0.00	0/60	0
	[14]Mane et al., 1997	0.00	0/220	-	-	-
	[16]Martelli et al., 2000	5.79	15/259	-	-	-
	[24]Vivekkumar et al., 2010	0.00	0/36	0.00	0/36	0
	Mean	**1.08**	-	**0.66**	-	**0.42**
	Median	**3.24**	-	**1.32**	-	**1.93**
	Range	**0.68-5.79**	-	**0.94-1.69**	-	**Negative in favour for ROM**
Reversal Reactions (Type 1&2)	[2]Babu et al., 1997	0.95	7/739	0.40	3/744	0.55
	[5]Diniz et al., 2010	1.85	1/54	-	-	-
	[7]Emmanuel & Gupte, 2005	7.69	2/26	0.00	0/25	7.69
	[10]Gomes et al., 2008	16.20	42/259	-	-	-
	[14]Mane et al., 1997	3.33	1/30	-	-	-
	[21]Shukla et al., 2000	6.50	4/61	-	-	-
	[22]Sousa et al., 2007	14.81	20/135	-	-	-
	[23]Stefani et al., 2003	33.33	13/39	-	-	-
	Mean	**8.35**	-	**0.2**	-	**8.15**
	Median	**7.69**	-	**0.2**	-	**7.49**
	Range	**0.95-33.33**	-	**0.00-0.40**	-	**Negative in favour for ROM**

Table 2. Preliminary Summary of Primary Outcomes; *Not included in mean/median/range

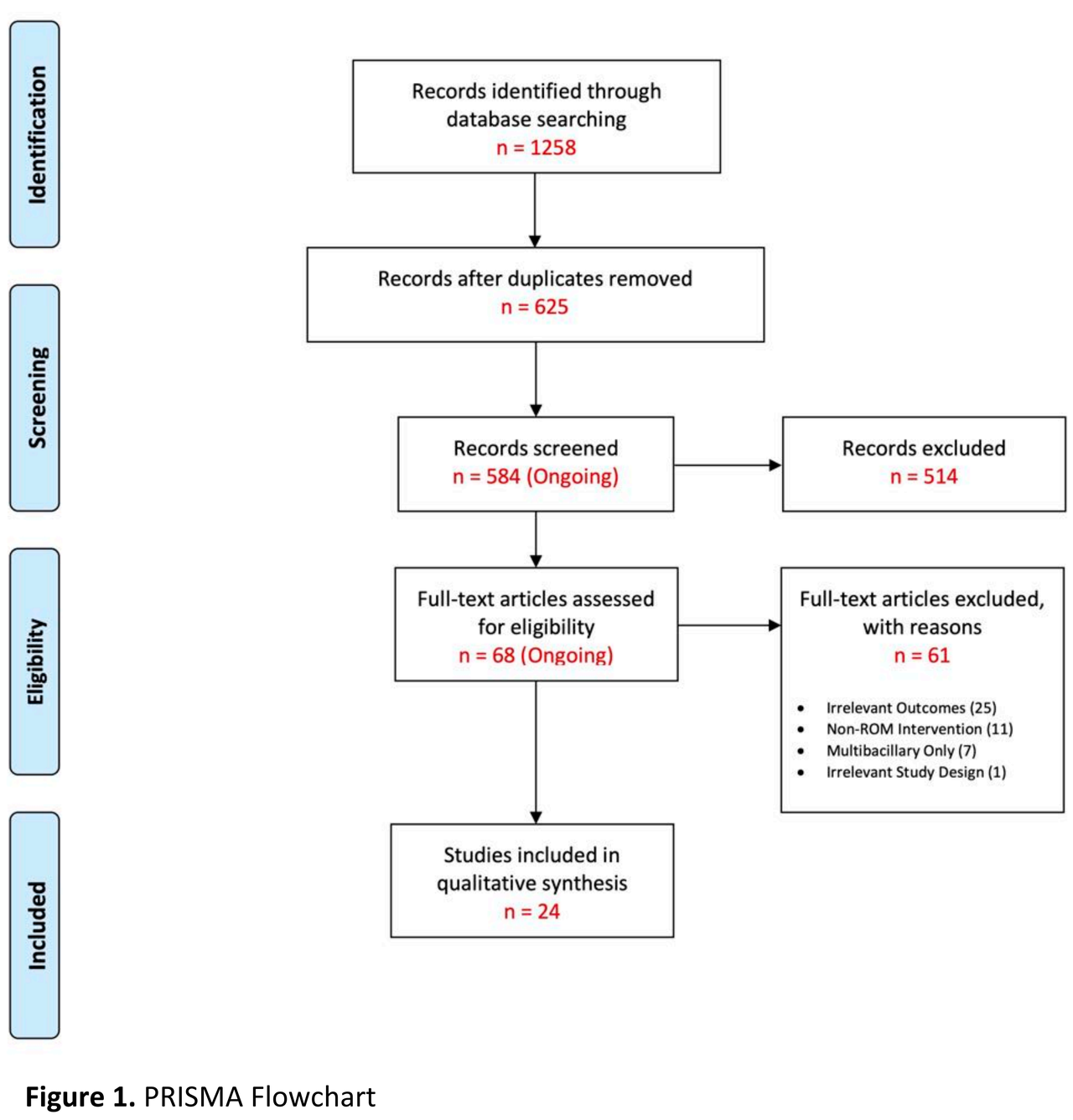

Figure 1. PRISMA Flowchart

Discussion

- Interim findings suggest that patient lesion clearance and treatment failure is greater in the comparator group (+4.69% and +2% respectively), and that relapse, side effects, and reversal reactions are greater in the ROM group (+0.39%, +0.42%, and +8.15% respectively). This suggests that ROM is slightly less efficacious than its comparator, however a more robust analysis is necessary Qualitatively, several determinants of health were identified throughout this analysis including:
  - Social environments – 50% of non-adherent patients denied having leprosy due to potential loss of jobs and/or marriage prospects[25]
  - Patient education – 86% of respondents did not understand the concept of their disease[12]
  - Gender – Women completed treatment at a rate of 65.6% and men at 79.2% ($p<0.05$)[26]
    - Further investigation to better understand gender- and sex-based influences on treatment and prognosis warranted
- Synthesizing the current evidence discussing the efficacy of monthly ROM, will strengthen the current body of knowledge surrounding the treatment of paucibacillary leprosy, and may allow for the development of standardized fluoroquinolone-based treatment protocols.

References