Long-term Adverse Effects Associated with Ebola Virus Disease and the Current Recommendations for Treating These Effects - Literature Review

Abstract

Ebola virus disease (EVD) is a rare disease with no effective treatment. Consequently, EVD survivors mostly experience short- and long-term adverse effects collectively designated post-Ebola syndrome (PES). The criteria of PES and long-term consequences in survivors have not been well addressed previously. The focus of this literature review is to assess the long-term adverse effects associated with EVD and current recommendations for treating these effects.

We identified 48 articles by searching PubMed and selected 20 relevant articles for this review. Due to lack of an effective treatment for EVD, the survivors after EVD recovery experience more health problems and diminished ability to work. The most commonly reported PES symptoms that last from 2 weeks to more than 2 years were arthralgia, myalgia, blurred vision, headache, auditory problems, depression, and difficulty in sleeping. From reviewed studies, it is clear that treatment is required to manage long-term PES. The survivors should be advised to have routine check-ups or follow-ups for at least 1 year after EVD recovery. The World Health Organization recommended treatment for PES in EVD survivors. A prospective study (PREVAIL IV) is being conducted to evaluate the antiviral activity of GS-5734 (Remdesivir) for the clearance of persistent Ebola virus in male survivors. A well-designed clinical trial to determine the efficacy and safety of cannabidiol is also being considered for the treatment of PES.

In conclusion, due to lack of an effective treatment for EVD, the prevalence of PES is high. Therefore, long-term follow-up studies for EVD survivors need to be conducted to understand the pathogenesis of sequelae and how to treat these effects.

Introduction

Ebola virus disease (EVD) is a rare, often fatal disease characterized by severe haemorrhagic fever, muscle pain, and vomiting. In 1976, an outbreak of EVD first appeared in two regions: one in Sudan and another in the Democratic Republic of Congo (DRC). Since 2000, EVD outbreaks are being reported almost every year, and in 2014 ten EVD outbreaks were reported.[1, 2] In March 2014, the most severe and largest EVD outbreak thus far was reported in West Africa.[3] The World Health Organization (WHO) announced the latest outbreak in the DRC on May 8, 2018; this outbreak, which ended on July 24, 2018, infected 54 people, 33 (61%) of whom died.[4]

The 2014 Ebola outbreak has significantly accelerated the development of Ebola vaccines. Currently, there is no effective treatment available for EVD. However, a few new agents have completed preclinical stage and are currently in clinical stage testing.[5] Due to limited treatment availability, patients recovered from EVD mostly experience short- and long-term adverse effects, known as post-Ebola syndrome (PES). The most commonly reported adverse effects for more than 2 years after EVD recovery were difficulty swallowing, fatigue, arthralgia, and retro-orbital pain. Neither the pathogenesis of PES nor why these symptoms persist is clearly understood, but PES could result, in part, due to the persistence of Ebola RNA, most notably in the semen of male survivors. The majority of PES studies were not controlled, therefore, the criteria that define PES and long-term consequences in survivors have not been well addressed in the literature.[6, 7, 8]

The focus of this literature review is to assess the long-term adverse effects associated with EVD and current recommendations for treating these effects which have been of significant recent interest.

Methods

This literature review was conducted to describe the evidence-based literature related to the long-term adverse effects associated with EVD and current recommendations for treating these effects. We identified 48 articles by searching PubMed and 20 relevant published articles were selected for this review. To create a search strategy, the following terms were used: “Ebola virus disease”, “EVD outbreaks”, “Post-Ebola Syndrome”, “Long-term PES”, “PES treatment”, and “Ebola survivors”. Important data from selected studies were extracted into a separate bibliographic report.

Discussion/Observations

Long-term Adverse Effects Associated with Ebola Infection

Long-term adverse effects in EVD survivors are presented in

Table 1 and **Table 2**, and discussed in this section.

A retrospective cohort study in 70 EVD survivors from a 2007 outbreak in Uganda evaluated the long-term adverse effects 29 months after recovery from EVD. The most commonly reported (>70%) symptoms for more than 2 years after EVD recovery were difficulty swallowing, fatigue, arthralgia, and retro-orbital pain.[8] Another cross-sectional study was conducted to determine the prevalence of PES, onset, and duration among 242 EVD survivors from the 2014-15 outbreak in Montserrado County, Liberia. The most commonly reported (>30%) symptoms at >10 months after discharge were joint pain, headache, eye problems, and muscle pain. Long-term prevalence of PES in Montserrado County was ascribed to the lack of clinical care as very few survivors have received appropriate treatment for these symptoms.[9]

A prospective study was conducted to evaluate the long-term EVD consequences for up to 21 months in 29 survivors and their 152 household contacts from a 1995 outbreak in Kikwit, Democratic Republic of the Congo (DRC). Overall, in comparison with their household contacts, survivors reported many more health problems (70% vs 17.9%) and a diminished ability to work (70% vs 7.1%) at the 21-month follow-up period. Among the survivors, the most frequently reported health problems were arthralgia (62%) and myalgia (47%).[10] In a case study from this outbreak in the DRC, a 31-year old EVD survivor reported blindness (right eye), atrophic lesion of the fundus, ophthalmoplegia, and a light facial paralysis after 2 years.[11]

An ongoing PostEboGui study is a prospective, multicenter cohort, 2-year follow-up study in EVD survivors from the 2014-15 outbreak in Guinea.[12] The survivors from the PostEboGui study suffering from depressive or musculoskeletal symptoms were assessed separately.[13, 14] Thirty-three survivors were reported with psychological symptoms and 27 of them suffered from depression (mild: 3, moderate: 13, and severe: 11 survivors). Severe

depression was diagnosed between 1 and 19 months after discharge from the Ebola treatment center (ETC). Three patients with severe depression attempted suicide 5, 11, and 12 months after they had been discharged from the ETC.[13] Forty-four survivors were reported with musculoskeletal symptoms; the most commonly reported were joint pain (98%), low back pain (75%), and myalgia (61%). The median time since ETC discharge was 8.8 months. Survivors with chronic musculoskeletal symptoms were more likely to show signs of depression (42%), as chronic pain precipitates psychological symptoms which can lead to depression.[14]

A retrospective cohort study evaluated the disabilities after 1 year of recovery in 27 EVD survivors and 54 of their close contacts in Freetown, Sierra Leone. When compared to their controls, the EVD survivors had increased mean pain scores (adjusted mean difference, 2.51 [95% CI, 1.33–3.69]), fatigue scores (2.23 [1.36–3.09]), depression scores (3.32 [1.95–2.59]), and anxiety scores (1.89 [0.52–3.27]). Overall, the disabilities in vision, mobility, and cognition after 1 year of recovery were more frequent in the EVD survivors than their close contacts.[15] From other Sierra Leone outbreaks, the long-term adverse effects were assessed in two case studies. In one case study, a 34-year old EVD survivor reported chronic fatigue and decreased executive function 7 months after discharge.[16] In another case study, a 43-year old EVD survivor in Kenema reported anterior uveitis after 18 months and received topical prednisolone acetate for over four weeks.[17] From all these studies, it is clear that survivors require treatment for the long-term effects of PES syndrome. A summary table of long-term adverse effects by range of frequencies is presented in **Table 3**.

Current Recommendations for Treating Long-term Post-Ebola Syndrome

Treatment for PES is currently supportive and there is no definitive cure. Therefore, after EVD recovery, survivors may experience sequelae of short- and long- term adverse effects

including musculoskeletal, ocular, social, and mental-health issues. The survivors are advised to have routine medical check-ups or follow-ups for at least 1 year after EVD recovery. Moreover, after discharge from the ETC, survivors should receive education and counselling regarding the possible adverse effects and instructions about who to contact if they experience any health problem. The WHO recommendations for the treatment of long-term adverse effects in EVD survivors are explained below and presented in

Table 4.[18]

WHO Recommendations for the Treatment of PES:

Musculoskeletal problems: The commonly reported musculoskeletal problems are arthralgia and myalgia. Initially, warm or cold compresses and exercise should be recommended to survivors for these adverse effects. If symptoms persist, then for the treatment of arthralgia and myalgia, paracetamol (first-line) and nonsteroidal anti-inflammatory drugs (NSAIDs) as second-line therapy should be given to the survivors. For the treatment of arthritis, NSAIDs as first-line and corticosteroids (adults) and methotrexate (children) as second-line therapy are the treatment options.

Abdominal problems: Paracetamol, H_2 blockers (eg, ranitidine), or omeprazole can be prescribed for the treatment of abdominal pain.

Neurological problems: The most commonly reported long-term neurological problem is headache, which can be treated according to the severity:

- Less severe or infrequent: paracetamol (first-line) and ibuprofen or other NSAIDs (second-line)

- Moderate to severe headache or associated with nausea: promethazine or metoclopramide in combination with NSAIDs
- Very severe or frequent: propranolol or amitriptyline

Amitriptyline for peripheral neuropathy and propranolol for tremor can be the treatment options. For the treatment of seizures, phenytoin (first-line) and carbamazepine (second-line) can be used.

Psychological problems: After discharge from the ETC, many EVD survivors experience stigma and isolation from their community and sometimes from family members, which leads to psychological problems. Depression is a notable long-term adverse effect in EVD survivors and the prescribed treatment is fluoxetine and amitriptyline. Carbamazepine and valproate can be used as mood stabilizers.

Auditory problems: Auditory problems in EVD survivors if left untreated, may lead to hearing loss. An acute labyrinthitis (inflammation of the inner ear) should be treated within 10 days after the onset of its symptoms and can be treated with prochlorperazine. Amoxicillin can be chosen for the treatment of otitis media.

Ocular problems: The commonly reported ocular problems are uveitis, panuveitis, cataracts, retinal and optic nerve disease. For uveitis the recommended treatment is prednisone and cyclopentolate. If uveitis is not resolved or panuveitis is suspected, then systemic corticosteroids (adults) or methotrexate (children) can also be recommended. Triamcinolone acetonide (corticosteroid) and favipiravir (antiviral agent) can be chosen in case of panuveitis.[17]

Other Treatment Options:

Cannabidiol is used to treat arthritis, colitis, ischemia reperfusion, diabetes, and depression.[19] Animal and human studies suggest that cannabidiol reduces inflammation and improves the mental and physical health of patients. Therefore, cannabidiol is considered a potential

treatment for chronic PES. The starting proposed dose of cannabidiol in humans would be 100 mg/day with slow titration up to 600 mg/day.[7] However, a well-designed clinical trial must be performed to determine the efficacy and safety of the proposed cannabidiol treatment.

A double-blind, randomized, and placebo-controlled study (PREVAIL IV) is currently ongoing and conducted to evaluate the antiviral activity of a small molecule, GS-5734 (Remdesivir) developed by Gilead Sciences, for the clearance of persistent Ebola virus in male survivors.[20]

Conclusion

In conclusion, due to lack of an effective treatment for EVD, the prevalence of PES is high. The most commonly reported post-Ebola clinical manifestations that last from 2 weeks to more than 2 years are arthralgia, myalgia, blurred vision, headache, auditory problems, depression, diminished ability to work, and difficulty in sleeping. Long-term follow-up studies for EVD survivors are required to be conducted to evaluate the incidence/severity of PES symptoms and the clinical recommendations for treating these effects. Until an effective vaccine is widely available in affected countries, studies evaluating possible connections between the actual treatments during the infection and the specific PES symptoms may be valuable.

References

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Table 1: Long-term Adverse Effects in Ebola Virus Disease Survivors

Study author	Duration after Ebola Treatment discharge	No of analysed EVD survivors	Long-term Adverse Effects						
			Musculoskeletal	Ocular	Auditory	Abdominal	Neurological	Psychological	Others
Keita MM et al[13]	12 months	33	Muscle and joint pain (33%)	Eye pain or decreased visual acuity (15%)	Ear pain or decreased auditory acuity (12%)	NA	Memory impairment (9%)	Depression (82%), headache (21%) %) and post-traumatic stress disorder (9%),	NA
Pers YM et al[14]	8.8 months	44	Joint pain (98%), low back pain (77%), myalgia (61%), and muscle weakness (42%)	Dry eyes (20%)	NA	NA	NA	Fatigue (84%) and depression (42%)	Morning stiffness (75%), mechanical and inflammatory pain (45%), dry mouth (37%)
Wilson HW et al[9]	12 months	242	Joint pain (48%) and muscle pain (32%)	Eyes problem - NOS (48%)	NA	Abdominal pain (31%)	NA	Headache (63%), sleep disorder (39%), depression (35%), and anxiety (9%)	Unusual tiredness (56%), menstrual problems (53%), chest pain (21%), and testes pain (8%)
Clark DV et al[8]	29 months	49	Arthralgia (73%), Stiffness in joints (56%) and muscle weakness (40%)	Retro-orbital pain (71%) and Blurred vision (61%)	Hearing loss (69%)	Difficulty swallowing (92%)	NA	Fatigue (75%) and difficulty sleeping (67%)	NA
Jagadesh S et al[15]	12 months	27	NA	Disability with blurred vision (44%), near-distance vision (41%), and long-distance vision	Hearing disability (19%)	NA	NA	Disability in cognition (33%), fatigue [3.26 (2.65)][a], anxiety [3.37 (3.49)][a], and depression]5.07	Disability in mobility (Minimal: 85%, Moderate: 67%, and Severe: 15%)

Study author	Duration after Ebola Treatment discharge	No of analysed EVD survivors	Long-term Adverse Effects						
			Musculoskeletal	Ocular	Auditory	Abdominal	Neurological	Psychological	Others
				(26%)				(4.19)][a]	
Rowe AK et al[10]	21 months	29	Arthralgia (62%) and myalgia (47%)	NA	Hearing loss (14%)	NA	NA	NA	Diminished general health (70%) and capability to work (70%)

[a] mean (SD)

NA = not available, SD = standard deviation

Table 2: Long-term Adverse Effects in Ebola Virus Disease Survivors – Case Studies

Study author	Patient's Age	Duration after Ebola Treatment discharge	Long-term Adverse Effects						
			Musculoskeletal	Ocular	Auditory	Abdominal	Neurological	Psychological	Others
Chertow DS et al[16]	34 years	7 months	NA	NA	NA	NA	NA	NA	Fatigue
Kalongi Y et al[11]	31 years	24 months	NA	Blindness of the right eye with an atrophic lesion of the fundus, and ophthalmoplegia	NA	NA	NA	NA	Light facial paralysis
Shantha JG et al[17]	43 years	18 months	NA	Declined visual acuity, cataract development and anterior uveitis	NA	NA	NA	NA	NA

NA = not available

Table 3: Summary of Long-term Adverse Effects

PES symptoms	Range of frequency
Arthralgia	33% of 33- 98% of 44
Difficulty in swallowing	92% of 49
Fatigue	75% of 49- 84% of 44
Depression	35% of 242- 82% of 33
Morning stiffness	75% of 44
Retro-orbital pain	71% of 49
Diminished ability to work	70% of 29
Diminished general health	70% of 29
Auditory problems	12% of 33- 69% of 49
Difficulty in sleeping	39% of 242- 67% of 49
Headache	21% of 33- 63% of 242
Myalgia	32% of 242- 61% of 44
Blurred vision	44% of 27- 61% of 49
Unusual tiredness	56% of 242
Menstrual problems	53% of 242
Mechanical and inflammatory pain	45% of 44
Muscle weakness	40% of 49- 42% of 44
Near-distance vision	41% of 27
Dry mouth	37% of 44
Long-distance vision	26% of 27
Chest pain	21% of 242
Dry eyes	20% of 44
Decreased visual acuity	15% of 33
Severe disability in mobility	15% of 27
Anxiety	9% of 242
Memory impairment	9% of 33
Post-traumatic stress disorder	9% of 33
Testes pain	8% of 242
Cataract development and anterior uveitis	1 patient
Ophthalmoplegia	1 patient
Blindness of the right eye with an atrophic lesion of the fundus	1 patient
Light facial paralysis	1 patient

Table 4: WHO-Recommended Treatments for Post-Ebola Syndrome in Ebola Virus Disease Survivors

Long-term adverse effects	Treatment	Dose	Frequency
Musculoskeletal problems			
Arthralgia, tenosynovitis, and Myalgia	First line: Paracetamol	Adults: 1 g Children: 15 mg/kg	Adults: TID Children: TID
	Second line: NSAIDs		
	Ibuprofen	Adults: 200-400 mg Children: 10 mg/kg	Adults: TID Children: TID
	Diclofenac	50 mg	BD or TID
	Naproxen	250-500 mg	BD
	Others: Meloxicam, piroxicam, celecoxib, and etodolac extended release	NA	NA
	Ranitidine (for patients > 60 years old)	150 mg	BD
	Omeprazole	Adults: 20 mg Children: As per body weight <10 kg: 1-2mg/kg; 10-20 kg: 10mg; >20 kg: 20mg	QD
Arthritis	First line: NSAIDs (as given above)	As given above	As given above
	Second line: Adults: Prednisone Children: Methotrexate	Adults: 20 mg Children: Refer to a specialist	Adults: Daily for 7 days
Ocular problems			
Ocular surface disease	Artificial tears	NA	NA
Uveitis	Prednisone	1% eye drops	Every 1-2 hours for 7 days
	Cyclopentolate	1% eye drops	1 drop 4 times a day for 7 days
Panuveitis	Adults: Corticosteroids Children: Methotrexate	Adults: 20 mg Children: Refer to a specialist	Adults: Daily for 7 days
Refractive error	Corrective lenses	NA	NA
Auditory problems			
Acute labyrinthitis	Prochlorperazine	Adults: 5-10 mg Children: As per body weight Under 10 kg: Not recommended 10-13 kg: 2.5 mg 13-18 kg: 2.5 mg 18-39 kg: 2.5 mg or 5mg	Adults: 3-4 times daily Children: 10-13 kg: QD or BD 13-18 kg: BD or TID 18-39 kg: TID (2.5 mg) or BD (5 mg)
Otitis media	Amoxicillin	Adults: 250 mg Children: 40-90 mg/kg (as per weight) If over 40 kg, use adult dose	Adults: TID for 10 days Children: BD or TID for 10 days
Abdominal problems	Paracetamol	As given above	As given above
	H_2 blockers (Ranitidine)	As given above	As given above
	Omeprazole	As given above	As given above

Long-term adverse effects	Treatment	Dose	Frequency
Neurological problems			
Headache: Infrequent or less severe	First line: Paracetamol	As given above	As given above
	Second line: Ibuprofen	As given above	As given above
Headache: More moderate to severe	Promethazine (concomitant NSAIDs)	12.5-25 mg	Every 4-6 hours
	Metoclopramide (concomitant NSAIDs)	10 mg	Every 8 hours
Headache: Very severe	Propranolol	40 mg, 80 mg (If headache persists)	BD
	Amitriptyline	10-25 mg	Each night
Peripheral neuropathy	Amitriptyline	As given above	As given above
Tremor	Propranolol	As given above	As given above
Seizures	First line: Phenytoin	100 mg, 400 mg (as needed)	Nightly
	Second line: Carbamazepine	200 mg, 1600 mg/day (as needed)	BD
Psychological problems			
Moderate-severe depressive disorder	Psychoeducation	NA	NA
	Psychosocial support	NA	NA
	Counselling	NA	NA
	Amitriptyline	25–50 mg (Adults)	Bedtime
	Fluoxetine	Adult:10 mg, 20 mg (after 1 week) Adolescents: 10 mg	QD
	Carbamazepine	200 mg	BD
	Valproate	400 mg	BD

BD = twice a day, NA = not available, NSAID = nonsteroidal anti-inflammatory drugs, QD = once a day, TID = three times a day