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REVIEW

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Mega doses of retinol: A possible immunomodulation in Covid-19 illness in resource-limited settings

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Summary

Of all the nutrients, vitamin A has been the most extensively evaluated for its impact on immunity. There are three main forms of vitamin A, retinol, retinal and retinoic acid (RA) with the latter being most biologically active and all-trans-RA (ATRA) its main derivative. Vitamin A is a key regulator of the functions of various innate and adaptive immune cells and promotes immune-homeostasis. Importantly, it augments the interferon-based innate immune response to RNA viruses decreasing RNA virus replication. Several clinical trials report decreased mortality in measles and Ebola with vitamin A supplementation.

During the Covid-19 pandemic interventions such as convalescent plasma, antivirals, monoclonal antibodies and immunomodulator drugs have been tried but most of them are difficult to implement in resource-limited settings.

The current review explores the possibility of mega dose vitamin A as an affordable adjunct therapy for Covid-19 illness with minimal reversible side effects. Insight is provided into the effect of vitamin A on ACE-2 expression in the respiratory tract and its association with the prognosis of Covid-19 patients. Vitamin A supplementation may aid the generation of protective immune response to Covid-19 vaccines. An overview of the dosage and safety profile of vitamin A is presented along with recommended doses for prophylactic/therapeutic use in randomised controlled trials in Covid-19 patients.

Abbreviations: 9-cisRA, 9-cis retinoic acid; ACE-2, angiotensin converting enzyme 2; ACE-I, angiotensin converting enzyme inhibitor; AID, activation-induced cytidine deaminase; ALDH1A, aldehyde dehydrogenase 1A; APCs, antigen presenting cells; ARB, angiotensin-receptor blockers; ARDS, acute respiratory distress syndrome; ATRA, all-trans-retinoic acid; Blimp-1, B lymphocyte-induced maturation protein-1; BMP, Bone morphogenic protein; BRSV, bovine respiratory syncytial virus; Covid-19, coronavirus disease 2019; COX-2, cyclooxygenase-2; CSIF, human cytokine synthesis inhibitory factor; CXCL10, C-X-C motif chemokine ligand 10; CXCL9, C-X-C motif chemokine ligand 9; EBF1, early B cell factor 1; FDA, U.S. Food and Drug Administration; FDCs, follicular dendritic cells; GATA3, G-A-T-A binding protein 3; GCs, germinal centers; GM-CSF, granulocyte macrophage colony stimulating factor; IFNγ, interferon gamma; IL-1, interleukin-1; IL-10, interleukin 10; IL-12, interleukin 12; IL-13, interleukin 13; IL-1β, interleukin 1 beta (leukocytic pyrogen); IL-23, Interleukin 23; IL-4, Interleukin 4; IL-6, interleukin 6; IL-6R, interleukin 6 receptor; IL-8, interleukin 8 (or chemokine [C-X-C motif] ligand 8, CXCL8); ILC, innate lymphoid cells; IP-10, interferon gamma inducible protein 10 kD (or CXCL10); IRF-4, interferon regulatory factor 4; LPS, lipopolysaccharide; LTBP, latent TGF-β binding proteins; LTi, lymphoid tissue inducing cells; MCP-1, monocyte chemoattractant protein-1 (CCL2); MERS-CoV, Middle-East respiratory syndrome coronavirus; MHC, major histocompatibility complex; MIP-1α, macrophage inflammatory protein 1α (CCL3); MMP, matrix metalloproteinases; mTOR signaling pathway, mammalian target of rapamycin *signaling pathway*; NFkB pathway, nuclear factor kappa-light-chain-enhancer of activated B cells; NK cells, natural killer cells; NO, nitric oxide; Pax-5, paired box protein-5; PGE2, prostaglandin E2; PPAR-β, peroxisome proliferator-activating receptor beta; pre-DCs, precursor dendritic cells; RA, retinoic acid; RDA, recommended dietary allowance; RIG-I, retinoic acid inducible gene I; RLRs, RIG-I like receptors; RORγt, retinoic acid receptor-related orphan nuclear receptor gamma (RORγt); RSV, respiratory syncytial virus; RXR, retinoid X receptor; SARS-CoV, severe acute respiratory syndrome associated coronavirus; SARS-CoV-2, severe acute respiratory syndrome associated coronavirus-2 (Cov-2019); STRA6 receptor, signaling receptor and transporter of retinoic acid 6; TGF-β1, transforming growth factor beta 1; Th17 cells, T helper cells type 17; Th1 cells, T helper cells type 1; Th2 cells, T helper cells type 2; TLR, toll-like receptors; TNF-α, tumor necrosis factor-α; Tregs, regulatory T cells.

1 | INTRODUCTION

On 31 December 2019, WHO Country Office in China was informed regarding a pneumonia of obscure etiology. On 30 January 2020, this upsurge of the novel SARS-CoV-2 infections was declared a Public Health Emergency of International Concern, and on 11 February 2020 disease was named Covid-19.[1] Novel infectious disease agents are those newly appearing infectious agents in a human population for whom low or no pre-existing immunity exist, hence, they carry a risk of evolving into a pandemic of severe illness.[2]

Covid-19 patients experience varying degrees of respiratory symptoms, with most having non-serious illness and recuperate without any specific treatment.[3] However, the elderly with comorbid cardio-respiratory, oncological or metabolic conditions like diabetes are at risk of progressive deteriorations.[3] Due to paucity of paediatric Covid-19 patients compared to adults due to unknown reasons, its exact impact on paediatric health is not known.[4] However, there are reports of serious illness and need for intensive care in paediatric patients.[5]

Having faced recent outbreaks of Ebola virus disease, SARS-CoV and MERS-CoV, the scientific community initiated rapid research for potential preventive and curative treatments[6] and clinical trials for the SARS-CoV-2 are emerging at a rate never observed before.[7]

1.1 | Elevated pro-inflammatory cytokines and severity of illness in Covid-19

A well-coordinated rapid innate immune response with appropriate cytokines is the key defence against an infectious agent but an exaggerated immune dysregulation has potential to produce tissue damage.[8–13] This dysregulated and excessive immune response is called cytokine storm and is a major cause of acute respiratory distress syndrome (ARDS) and multiple organ failure in Covid-19 patients.[14–16]

The most immediate and important defence mounted by the body against viral infections is IFN-I or IFN-α/β production especially in the early stages.[17–19]

After infection, SARS-CoV-2 generates proteins that effectively inhibit the innate immune response, especially RIG-I-dependent immune response.[20,21] Thus, post SARS-CoV-2 infection an insignificant IFN response is mounted for 48 h and in severe cases is followed by a hyper-inflammatory state with release of various pro-inflammatory cytokines like Interleukin (IL) 6, Monocyte Chemoattractant Protein-1 (MCP1), C-X-C motif chemokine (CXCL) 1, CXCL5 and CXLC10.[22]

Clinical data also suggested that severity of Covid-19 is due to an imbalanced activation of the adaptive immune response promoting virus replication.[14] Animal studies suggested that dysregulated immune response was more prominent in older non-human primates and BALB/c mice irrespective of viral titers.[23,24] A positive correlation exists between worsening of Covid-19 symptoms and augmented serum levels of proinflammatory cytokines IL-2R, IL-6, granulocyte colony-stimulating factor, IP-10, MCP-1, macrophage inflammatory protein-1A, and TNF-α, with serum levels of IL-2R and IL-6 being directly proportional to the severity of illness.[14,25] Therefore, treatment of Covid-19 should deal with inflammation and immune-modulatory drugs should be added to the line of treatment for improved prognosis. Dexamethasone decreases inflammation and has now been licensed in Covid-19 patients based on the results of randomised controlled trials.[26] A randomised clinical trial of inhaled interferon-beta also reported clinical benefit in Covid-19 patients.[27]

2 | IMMUNE REGULATION MEDIATED BY VITAMIN A

Anti-inflammatory effects of vitamin A were known since 1928.[28] Dietary vitamin A is absorbed from the gut, transformed into retinyl esters which gets hydrolysed into retinol and gets stored in the hepatic stellate cells of liver.[29] Retinol after binding to retinol binding protein in the liver enters the circulation and its cellular uptake is mediated by receptors such as STRA6 receptor (Signalling receptor and transporter of retinoic acid 6).[30] Retinol gets oxidised into retinal by alcohol dehydrogenase and further to retinoic acid (RA) by retinal dehydrogenase.[29] There are three main forms of RA, the most abundant all-trans-RA (ATRA), 9-cis-RA and 13-cis-RA.[31] RA mediates its immunomodulatory effects by interacting with nuclear receptors such as retinoic acid receptor (RAR), retinoid receptor X (RXR), peroxisome proliferator-activating receptor beta (PPAR-β) and regulates the transcription of several genes including cytokines, chemokines, integrins and genes related to lipid metabolism and glucose homeostasis.[32] RA supplementation has significant impact on functions of various immune cells and mucosal epithelial cells (Figure 1).

2.1 | Dendritic cells

RA promoted the differentiation of murine precursor dendritic cells (pre-DCs) to pre-mucosal DCs to intestinal tolerogenic CD103 + CD11b + DCs with an inherent ability to synthesise RA and promote generation of Il-10 secreting, FoxP3+ regulatory T cells.[33] RA induced expression of gut trafficking receptors α4β7 and CCR9 on these DCs, enable them to promote gut-homing migration of T and B cells.[34] Prostaglandin E2 (PGE2) may inhibit RA synthesis and suppress generation of tolerogenic DCs.[35] Whereas, GM-CSF, IL-4, IL-13 and ligands of TLR-2 and TLR-5 induced the RA synthesis.[36–38] During infections, RA induced the production of pro-inflammatory cytokines by DCs, leading to enhanced number of effector T cells and formation of tertiary lymphoid structures.[34] RA enhanced the expression of MHC class II and CD86 and promoted the maturation, survival of monocyte-derived DCs.[39] While DCs regulate T-cell responses, Follicular DCs (FDCs) located in the germinal centres (GCs) of secondary lymphoid organs regulate B-cell responses. Retinoic acid receptors (RARs) are expressed by FDCs and RA induces expression of chemokines, survival factors and molecules involved in the activation of TGF-β1 (i.e., latent TGF-β-binding proteins (LTBP1, LTBP2 and LTBP3), matrix metalloproteinases (MMP2 and MMP9),

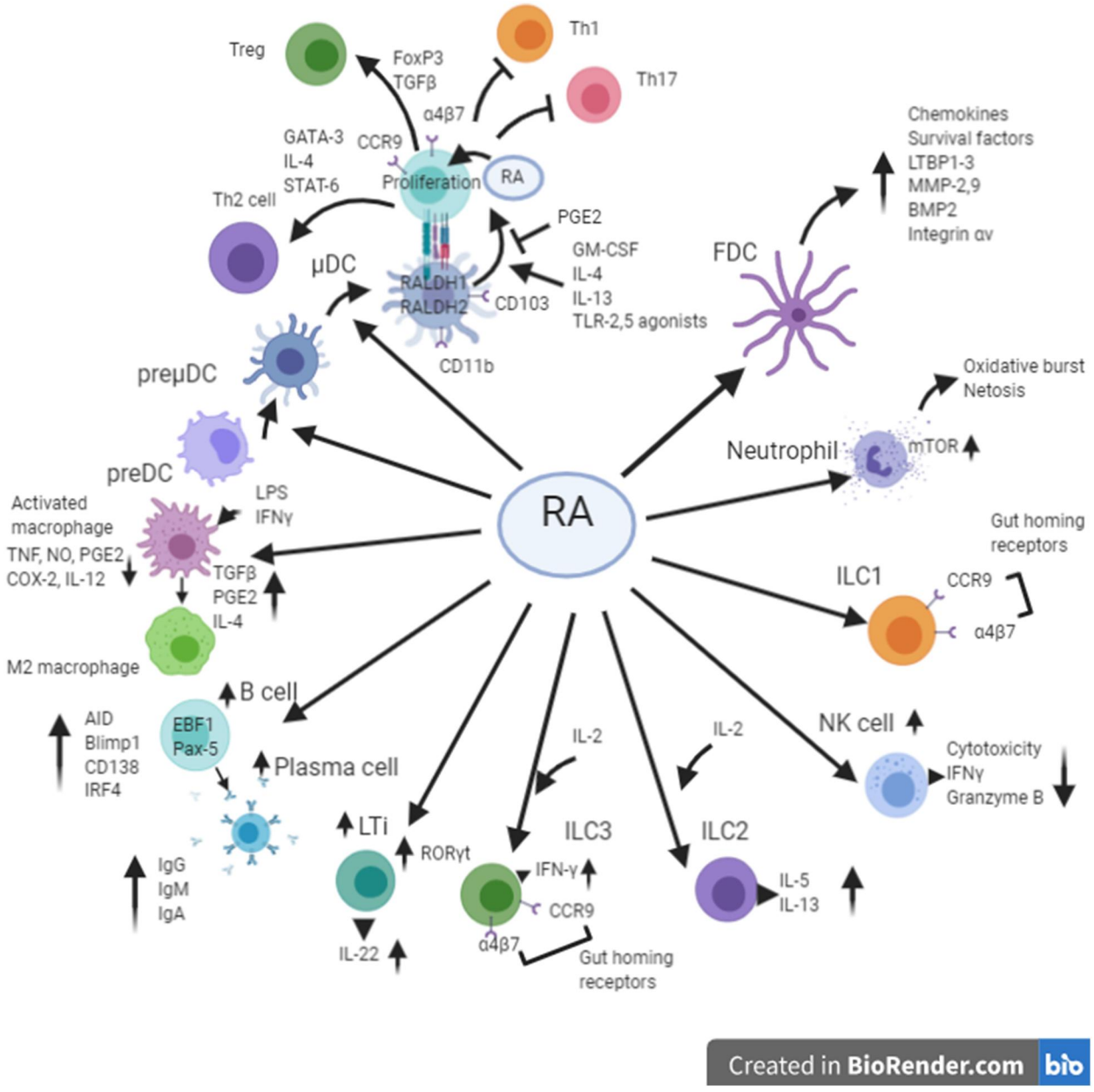

FIGURE 1 Vitamin A directly influences differentiation of immune cell precursors and modulates the functions of various immune cells to strengthen the host-defence and restoration of immune-homeostasis

bone morphogenic protein (BMP2) and integrin αv.[39]; Vitamin A deficiency results in decreased production of these molecules by FDCs leading to reduced numbers of B cells and defective production of IgA + B cells within GCs.[39] Thus, RA influences host's adaptive immune response by regulating gene expression in DCs.

2.2 | Monocytes and macrophages

ATRA suppressed TNF, NO, PGE2, COX-2, IL-12 production in peritoneal macrophages challenged by endotoxin and IFN-γ and human monocytic cell lines.[40–43] RA synergised with TGF-β, PGE2 and IL-4 to polarise macrophages to M2 type and regulate inflammation in mice.[44] Importantly, vitamin A deficient mice are unable to convert monocyte-derived inflammatory macrophages to M2 type during infection.[45] ATRA through activation of the mTOR signalling pathway enhances neutrophil extracellular traps and cytotoxicity.[46]

2.3 | Innate lymphoid cells

RA has an integral role in the immune regulation by tissue resident innate lymphoid cells (ILCs). RA is essential for generation of foetal and adult lymphoid tissue inducing cells (LTi), a subtype of ILC3 via retinoic acid receptor-related orphan nuclear receptor gamma (RORγt).[47,48] Similar to tolerogenic DCs, RA induces the expression

of gut-homing receptors on ILCs 1and 3.[49] Along with IL-2, RA contributes to secretion of IL-5 and IL-13 by ILC2 and IFN-γ by ILCs 1 and 3 in allergic diseases.[50] RA induced IL-22 secretion by ILC3 promoted intestinal tolerance in mice.[47,48]

RA has both inhibitory and activating effects on natural killer cells (NK cells), a circulating subtype of ILC1. IFN-α induced cytotoxicity of NK cells, IFN-γ and Granzyme B release from NK cells are inhibited by ATRA.[50,51] A killer inhibitory receptor of NK cells, CD158b is induced by 13-cis RA.[52] On the other hand, there is a positive correlation between number of NK cells and the retinol levels.[53]

2.4 | B-cells

Deficiency of vitamin A and zinc lead to decreased IgA and mucosal immunity.[54] RA increased early B-cell factor 1 (EBF1) and paired box protein-5 (Pax-5) and increased the number of B cells in the spleen.[55] Formation of antibody secreting plasma cells and immunoglobulin production (IgG, IgM, IgA) is promoted by RA by upregulation of activation-induced cytidine deaminase (AID), B lymphocyte-induced maturation protein-1 (Blimp-1), CD138, interferon regulatory factor 4 (IRF-4).[56–58] These evidences support an integral role of RA in the humoral immune response at the mucosal barriers.

2.5 | T lymphocytes

Polarisation to T-helper cell 2 response is promoted by RA, RXR agonists and 9-cisRA by inducing IL-12 secretion from APCs and IL-4 expression in naive T cells.[29,59,60] Repression of RORγt by RA favours differentiation to Th1 over the Th17 cells.[61] ATRA induces TGF-β-dependent anti-inflammatory immune responses by increasing T-regulatory cells (Tregs) and inhibits induction of pro-inflammatory cells (Th-17) and this anti-inflammatory phenomenon happens by ATRA induced Foxp3 activation through nuclear RAR.[62] ATRA is not only essential for Treg formation and regulating immunity but also fundamental to provide stability to Tregs in pro-inflammatory environments, where IL-6 and IL-21 induce transformation of already present Tregs into inflammatory Th-17 augmenting inflammation.[62] This phenomenon of T-cell differentiation is dependent on ATRA concentration; if the concentration is above a certain threshold Tregs are formed but at the lower concentrations, ATRA favours Th-17 cell differentiation.[29,63] RA induced inhibition of IL-23 and IL-6 signalling blocks differentiation of naïve T cells to Th17 cells.[64] To summarise, RA balances the differentiation of T-helper cell subsets to maintain immune homeostasis.

2.6 | Impact of RA on pulmonary mucosal immune response

Though the role of oral vitamin A supplementation in asthma is controversial owing to Th2 upregulation, RXR agonist alleviated allergic airway inflammation.[65,66] Importantly, there is increased asthma incidence in children with deficiency of vitamin A and lower retinoid concentrations correlated with severe asthma.[67,68] In murine model of ovalbumin-induced pulmonary inflammation, RA administration led to induction of Tregs in the lung besides decreased eosinophilic infiltration.[69] ATRA downregulated Th2 and Th17 cells by inhibiting GATA3 and RORγt in the lung.[70] Akin to tolerised DCs in the gut, lung resident macrophages coexpress TGFβ and retinal dehydrogenases and induce Tregs in airways.[71] Vitamin A regulated IL-6, MCP-1 and IL-10 expression in respiratory epithelial and macrophage cells infected with lipopolysaccharide (LPS) or Sendai virus is suggestive of increased elimination of pulmonary pathogens.[72] The three plausible mechanisms are augmentation of anti-inflammatory cytokine production by antigen presentation cells, increased production of virus-specific IgA, and reduction in the pathogen replication by inducing senescence in epithelial cells. Borderline vitamin A levels cause impairment of epithelial integrity.[73] Reduced numbers of cilia in ciliated cells of the pulmonary tract and the olfactory cells were also associated with deficiency of vitamin A.[74] Therefore, optimal levels of vitamin A are critical to sustain epithelial barrier integrity in order to face off the pathogen challenges.

3 | IMPACT OF VITAMIN A SUPPLEMENTATION ON INFECTION ASSOCIATED MORTALITY: EARLY DAYS

Vitamin A is a nutrient well studied in relation to immune function with its link to immunity deduced as early as in 1931.[75] Earlier reports showed that the infection outcome of malnourished dogs was improved with butter intake and that the deficiency of vitamin A increased the susceptibility of rats to infections.[28,76] In the early 1930s, Ellison concluded a positive impact of supplementation of vitamin A with decreased mortality in children suffering from measles.[77] The next decade saw 30 more clinical trials to study the impact of vitamin A supplementation on other infection-related mortalities and morbidities.[77,78] In 1960s a turning point came with the review by Scrimshaw et al., rekindling attention to interaction between infection and nutritional needs, and postulated that 'no nutritional deficiency in the animal kingdom is more consistently synergistic with infection than that of vitamin A'.[79] E.V. McCollum, a renowned biochemist, stated that 'Vitamin A builds fences that keep germs out'.[80] Trials of vitamin A supplementation suggest a positive impact of this intervention on mortalities and morbidities in patients suffering from measles and related pneumonias, HIV infection, malaria and diarrhoea.[81] These studies also informed that vitamin A mediated immune-modulation will vary based on the infectious agent and immune responses of the host involved.[82]

3.1 | Clinical impact of vitamin A in the infections mediated by RNA viruses: Implications for Covid-19

The double-stranded RNA formed within cells by viral pathogens is primarily sensed by pattern recognition receptors including retinoic acid inducible gene I (RIG-I) and RIG-I-like receptors (RLRs).[83] These

receptors induce NFkB pathway leading to alpha/beta interferon production. Thus, vitamin A directly induces the most immediate innate antiviral immune response within infected cells. Vitamin A derivatives inhibit growth of many RNA viruses including murine norovirus,[84] mumps,[85] Ebola[86,87] and measles.[88] In vitro studies of HIV replication in different model systems found conflicting results with addition of retinoids.[89,90] Addition of ATRA improved the clinical response in patients suffering from hepatitis C virus infection.[91]

The clinical impact of supplementation with mega doses of vitamin A in measles and Ebola are discussed in depth.

3.1.1 | Measles

In the past, measles has been a disease with not only a high secondary attack rate but also with high case fatality rate.[92] With improvement of vaccination coverage cases of measles have progressively decreased but are not infrequent even at places with high vaccine coverage.[93]

Measles is associated with depressed serum retinol levels and retinol supplementation results in augmentation of these levels.[94–97] The plausible reasons for the low levels of retinol in patients could be lack of mobilization of hepatic stores and/or enhanced consumption. Interestingly, the seriousness of measles is directly related to the level of hyporetinemia.[98] Markowitz et al., emphasized that children under 2 years with hyporetinemia are at a higher risk of mortality.[96]

A meta-analysis of eight trials (n = 2574 participants) analysed the impact of vitamin A supplementation on morbidity and mortality in patients suffering from measles[99] (Tables 1 and 2).[77,94,100-105] These trials not only varied in their durations but also had a difference in the age groups of participants, dosages, formulations used (oil- or water-based) and were done in communities with dissimilar measles-related fatality rates.

The cumulative analysis of the data derived from all the high quality studies suggested no significant effect of retinol supplementation on risk of dying due to measles-related complications (RR 0.83; 95% CI 0.51 to 1.34). Importantly, when the data belonging exclusively to patients requiring hospitalization due to measles was analysed, those who received 2 megadoses of vitamin A showed a statistically significant (64%) decrease in their risk of mortality (RR 0.40; 95% CI 0.19 to 0.87). This impact was most evident in children less than 2 years of age where an 83% reduction in risk of mortality (RR 0.21; 95% CI 0.07 to 0.66) was observed. Need of hospitalization being a measure of severity, it was concluded that the impact of retinol supplementation was most significant in sick children.[99]

Impact of solitary dose of retinol was assessed in populations with lower measles-related fatality rate (<6%) but influence of the two dose regimen was assessed on populations having higher measles-related deaths (>10%). Areas with higher measles-related mortality have greater potential to show a positive impact of retinol supplementation, therefore, it cannot be concluded whether two-dose retinol supplementation has greater impact on measles mortality compared to single dose. In mild cases of measles, solitary dose supplementation of oil based retinol preparation resulted in 70% augmentation in serum retinol levels.[103]

Since aqueous formulations or retinol are more rapidly absorbed they result in higher serum retinol levels. However, oil-based preparations are economical, easily accessible and more stable. When the data of studies that were based on supplementation of two doses of retinol was stratified for preparations used, it was found that aqueous preparations resulted in 81% decrease in the risk of mortality (RR 0.23; 95% CI 0.06 to 0.89).[99] During assessment of effect of retinol supplementation on anti-measles antibody titres, it was concluded that there was a dose-dependent increase in titres.[81,106,107]

In an immunocompetent person where measles is a novel virus, like an unimmunised adult, it can cause severe pneumonia and ARDS. There are case reports of adult patients having severe measles and timely mega dose vitamin A supplementation has been used as an adjunct therapy with favourable results in many cases.[108–111] During a measles epidemic in China, 55 out of 58 children with measles pneumonia, lacked a history of measles vaccination. About 20% of measles pneumonia evolved into ARDS and three patients expired. Thus, it was concluded that lack of immunity was associated with severe infection.[112]

As per WHO recommendation, paediatric populations residing in areas of high prevalence of vitamin A deficiency and suffering from measles, should receive oral retinol supplementation (100,000 IU in infancy and 200,000 IU after infancy) for two consecutive days.[99]

3.1.2 | Ebola

Aluisio et al., studied the impact of mega doses of retinol to adults suffering from Ebola virus disease during the West African epidemic.[113] Supplementation with 200,000 IU of retinol on day 1 and/or 2 within the first 48 h of admission resulted in 16.9% decrease in mortality. Authors inferred that early mega dose retinol supplementation has potential to reduce mortality due to Ebola virus disease.[113]

4 | IMPACT OF VITAMIN A ON ACE-2, RECEPTOR FOR SARS-CoV-2

Physiologically, ACE-2 degenerates vasoconstrictive angiotensin II to vasodilator angiotensin (1–7).[114] SARS-CoV-2 attaches to ACE-2 enzyme to enter host cells with an affinity around 10- to 20-fold higher than SARS-CoV, and is a plausible reason for higher transmission rates in COVID-19.[115,116] It was hypothesised that increased cellular ACE-2 levels may increase chances of severe SARS-CoV-2 infection in the host.[117] Since, ATRA supplementation upregulated ACE-2 enzyme, American Nutrition Association issued a caution against the use of vitamin A and its derivatives in amounts that exceed the recommended dietary allowance (RDA).[118–120]

On the other hand, downregulated ACE-2/angiotensin (1–7) may play an integral role in inflammatory mechanisms leading to tissue injury

TABLE 1 Summary of clinical trials of vitamin A supplementation in measles patients (children)

Author	Country	Total, case and control	Settings	Age group	Vit A def.	Type of trial	Dose of vitamin A	Preparation of vitamin a	Outcome measures	Mortality outcome	Risk of bias
Ellison 1932[77]	England	*N* = 600, 300 each in two hospital wards	Hospital	Children	Data not provided	Controlled trial	300 Carr and Price units for 7 to 12 days	Oil based	Death	Case = 11 Placebo = 26	High risk
Barclay 1987[99]	Tanzania	*N* = 180 Case = 88 Placebo = 92	Hospital	Children	91%	Randomized clinical trial using a random number table	200,000 IU two doses on consecutive days	Oil based	Death Death < 2 years	Case = 6 (7%) Placebo = 12 (13%) *P* = 0.13 Case 46 = 1 Placebo 42 = 7 *P* < 0.05	Low risk
Hussey 1990[100]	South Africa	*N* = 189 Case = 92 Placebo = 97 With complicated measles	Hospital	<13 years of age	92%	Randomized, double-blind trial	Either 200,000 IU retinyl palmitate given orally for 2 days or a placebo, within 5 days of the onset of the Rash	Water based	Death	Case = 2 Placebo = 10 *P* = 0.046	Low risk
Coutsoudis 1991[93]	South Africa	*N* = 60 Case = 29 Placebo = 31 with complicated measles	Hospital	4 to 24 months	90%	Randomized, placebo-controlled, double-blind trial	54.5 mg < 12 months or 109 mg > 12 months of retinyl palmitate dropsTwo doses on consecutive days on admission and on day 8 and 42.	Water based	Death	Case = 0 Control = 1 *P* > 0.05	Low risk
Ogaro 1993[101]	Kenya	*N* = 294	Hospital	>5 years	30% had Vit A level >20 mcg/dl	Randomized, double-blind trial	50,000 IU to infants <6 months, 100,000 IU to infants 6 to 12 months200,000 IU to children >12 monthsSingle dose on admission	Oil based	Death	Overall case fatality rate was 2.7%*P* > 0.05	Low risk
Rosales 1996[102]	Zambia	*N* = 200 With acute measles Case = 90 Placebo = 110	Community	Children	Data not provided	Randomized, double-blind, placebo-controlled clinical trial	200,000 IU to children100,000 IU for infantsSingle dose	Oil based	Death	Case = 6 Placebo = 7*P* > 0.05 Case fatality rate of 6.5%	Low risk
Dollimore 1997[103]	Ghana	*N* = 946	Community	6 to 90 months	Data not provided	Randomized, placebo-controlled, double-blind trial	100,000 IU infant 6 to 11 months 200,000 IU older childrenEvery 4 months for 2 years	Oil based	Death	Total death 151 (15.7%) Case = 15.4% Placebo = 14.5%	Low risk
Kawasaki 1999[104]	Japan	*N* = 105 Case = 47 Control = 58	Hospital	5 months to 4 years	Data not provided	Randomized controlled trial	Oral vitamin A (100,000 IU) supplementation Single dose	Oil based	Death	Case = 0 Control = 0	Low risk

TABLE 2 Summary of clinical trials suggesting impact of Vitamin A supplementation on morbidity of measles patients

Author	Condition	Case	Placebo group	*p*-Value
Hussey 1990[100]	Recovery from pneumonia	6.3 days	12.4 days	<0.001
	Recovery from diarrhoea	5.6 days	8.5 days	<0.001
	Croup	13 patients	27 patients	0.03
	Herpes stomatitis	2 patients	9 patients	0.08
	Intensive care	4 patients	11 patients	0.13
	Hospital stay in days	10.6 days	14.8 days	0.01
	Adverse outcome (death, pneumonia ≥ 10 days, diarrhoea ≥ 10 days, post measles croup, transfer to ICU)	25 patients	52 patients	<0.001
Coutsoudis 1991[93]	Recovery in <8 days	28/29 (98%)	11/31 (65%)	0.002
	Pneumonia episodes	5	6	-
	Recovery from pneumonia in days	3.8 ± 0.40	5.7 ± 0.79	<0.05
	Integrated morbidity score	0.60 ± 0.22	4.12 ± 1.13	-
Ogaro 1993[101]	Progression to croup grade III	4/119	0/116	-
Rosales 1996[102]	Measles-associated pneumonia	63/90 patients	68/110 patients	0.42
	Failure to improve from pneumonia at 1 week	37	36	0.96
	Failure to improve from pneumonia at 2 weeks	32	30	0.41
	Failure to improve from pneumonia at 3 weeks	4	10	0.31
	Failure to improve from pneumonia at 4 weeks	0	12	0.005
Kawasaki 1999[104]	Pneumonia	23/37 patients	9/52 patients	>0.05
	Laryngitis	12/37 patients	9/52 patients	>0.05
	Duration of cough	7.2 ± 1.6 days	9.2 ± 1.8 days	<0.05
	Fever	6.8 ± 1.4 days	8.3 ± 1.1 days	>0.05
	Hospitalization	5.5 ± 1.7 days	5.9 ± 1.5 days	>0.05

and explain various Covid-19 manifestations like hypokalemia, vasoconstriction[121] and development of acute respiratory distress syndrome (ARDS).[122] Importantly, 175 admitted, critically ill patients with SARS-CoV-2 infection, showed increased potassium loss concomitant with ACE-2.[123] Murine models of SARS-CoV showed a decreased concentration of ACE-2 in cells through internalization and degradation, and that was positively correlated with the lung damage.[124,125] It was inferred that by upregulating the vasodilator angiotensin 1-7, ACE-2 may protect against VILI (virus induced lung injury).[124]

In the beginning of pandemic, it was observed that many Covid-19 patients with cardiac comorbidities on ACE-1/ARB (angiotensin-receptor blockers) drugs, had adverse outcomes.[126] Since, use of ACE inhibitors or ARB is also associated with upregulation of ACE-2 expression, concerns were raised for their continuation during SARS-CoV-2 infection.[127–129] However, an earlier systematic review and meta-analysis had inferred an association of use of ACE inhibitors with a significant reduction in risk of pneumonia and pneumonia-related mortality.[130] Hospitalised hypertensive patients suffering from SARS-CoV-2 infection, taking ACE-I or ARB showed lesser mortality (3.7%) compared to others (9.8%) who were on different drugs.[131] The older people on ACE inhibitors were at almost 40% lower risk for Covid-19 hospitalization. However, the younger patients or the group with ARBs did not show any such alteration in risk for hospitalisation.[132] BRACE CORONA trial on patients on chronic ACE I/ARB therapy showed no significant difference in hospital stay and day 30 mortality outcomes with discontinuation versus continuation of therapy.[117] Therefore, many regulatory bodies and professional societies advised for continuation of treatment with ACE-1 and ARB medications in patients suffering from Covid-19.[133–135] With these evidences in the support of benefits extended by upregulated ACE-2, it is likely that vitamin A induced upregulation of ACE-2 may benefit Covid-19 patients.

5 | VITAMIN A: IMPLICATIONS FOR COVID-19

Animal studies evaluating serum retinol levels suggest that despite higher levels in the liver, serum levels decline with age.[136] Studies in older individuals and diabetics suggest vitamin A deficiency.[137–139]

In aged mice and in humans over the age of 65, activation of the aged innate immune system leads to dysregulated inflammation. There is aggravated basal inflammation associated with lack of effective innate and adaptive immune responses to the newly encountered pathogens or vaccine antigens.[10]

All three viral illnesses measles, Ebola and Covid-19 are suspected to have jumped species from other animals to humans,[140–142] have multisystem involvement and severe courses in naïve geriatric population compared to young adults.[143,144] (Figure 2).

Despite adequate retinol stores, hyporetinemia may occur during an infection, probably due to slower speed of mobilization of stores than required to keep the levels in normal range.[168,148] Use of mega dose, therefore, has been proven to be useful in hospitalized patients with measles and Ebola.

When large amounts of vitamin A are ingested, this overwhelms the absorptive capacity of intestines leading to formation of large amounts of retinoic acid.[148,149] This may be the reason for its dose-dependent protective immunomodulatory and antiviral effects, which in turn may influence disease severity. Combination of retinoic acid with simvastatin (an oral antilipemic agent) supplementation in animal models of ARDS exerted anti-inflammatory and pro-repair effects on respiratory tracts.[149,150] This anti-inflammatory and pro-repairing effect might be of help in ARDS related to Covid-19.

5.1 | Dosage and safety profile of vitamin A. How much is not too much?

Table 3 shows the RDA[150,151] of vitamin A for different age groups and its reported therapeutic doses used for measles, Ebola, supplementation in ocular manifestations of vitamin A deficiency and acne.

Red flags have been raised regarding vitamin A supplementations in view of the possibility of acute and chronic intoxication.[152] It is recommended that children are more vulnerable and doses around 20 times RDA in the paediatric population and 100 times RDA in adult population, over a period of hours or a few days carries risk of acute intoxication.[153] However, much larger doses than RDA have been used for various infections,[94,100,101,113] deficiency[154] and inflammatory conditions[156] (Table 3).

WHO recommends prophylactic routine supplementation of children with vitamin A 100,000 IU (<1year) and 200,000 IU (>1 year to 5 years) to decrease ocular complications of vitamin A deficiency and mortality and morbidity due to childhood infectious illnesses in this vulnerable age group,[157] which is many times the RDA.

Therapeutic vitamin A supplementation depends on the age group and disease condition and vitamin A is tolerated well across various doses with occasional reversible side effects. When vitamin A is given for measles in children there is transient anorexia, nausea, vomiting with some headache and in infancy bulging fontanelles which resolve without sequelae.[154,155] Acute retinoid toxic effects include dry lips, cheilitis, and dry oral, ophthalmic, and nasal mucosa.[157,158]

Doses much higher than the RDA were used by Kligman et al.[156] for acne, a chronic inflammatory skin condition. Kligman et al., started their study by supplementing 100,000 IU daily for 3 months and in view of absence of satisfactory results augmented it to 200,000 IU daily for 3-4 months and since most had persistence of inflammatory acne doses were increased to 300,000 IU daily, most remitted and if required in some cases dose was increased to 400,000–500,000 IU. They reported that to be effective serum retinol levels need to be higher than normal range and recorded dryness of skin and mucous membranes in most cases while frequent headaches in some cases.

Owing to the difference observed in the therapeutic effects of vitamin A supplementation between one dose and two doses, the two-dose regimen was recommended for measles. Compared to a large cumulative decrease in mortality in children with measles[99] (64%), the difference in the mortality in adult patients suffering from Ebola[113] who received megadose vitamin A was smaller that is 16.9%. The impact on mortality in paediatrics was also more prominent in the younger age group.[99] This may be due to the difference in dosage requirement of adults and children to achieve a certain threshold concentration of retinoic acid to realise the immunomodulatory effect of vitamin A.

Therefore, the potential benefits of the proposed intervention can be explored by assessing serum retinol levels of Covid-19 patients for hyporetinemia. The possibility of a randomised control trial to supplement sick patients suffering from Covid-19 with mega doses of vitamin A, should then be explored as a cost effective, readily available, easy to administer medication with minimal reversible side effects, to assess its impact on mortality, morbidity, hospital stay, ICU stay.[99] An open label randomised clinical trial is underway to study the effect of oral and aerosolized 13-cis-retinoic acid (isotretinoin) treatment as adjunct therapy in sick adult Covid-19 patients.[159] The study will not only assess the impact of this intervention on lung injury score but also on various other hematological, virological, immunological, molecular parameters and clinical outcomes.

6 | THE WAY FORWARD

In early 1930s, when many researchers investigated the potential benefits of convalescent serum therapy, the Ellison's attempt to supplement children suffering from measles with large doses of vitamin A significantly decreased the measles-related mortality and morbidity.[160] During Covid-19 pandemic again convalescent plasma therapy has been explored as a potential therapy along with various antivirals, monoclonal antibodies, immunomodulators and drugs.[7] However, most of these therapies have issues associated with their efficacy, safety and importantly are unaffordable/need sophisticated health care establishments for implementation. Appropriate mega doses of vitamin A may hold benefits for Covid-19 patients especially in resource-limited settings and should be directly considered for

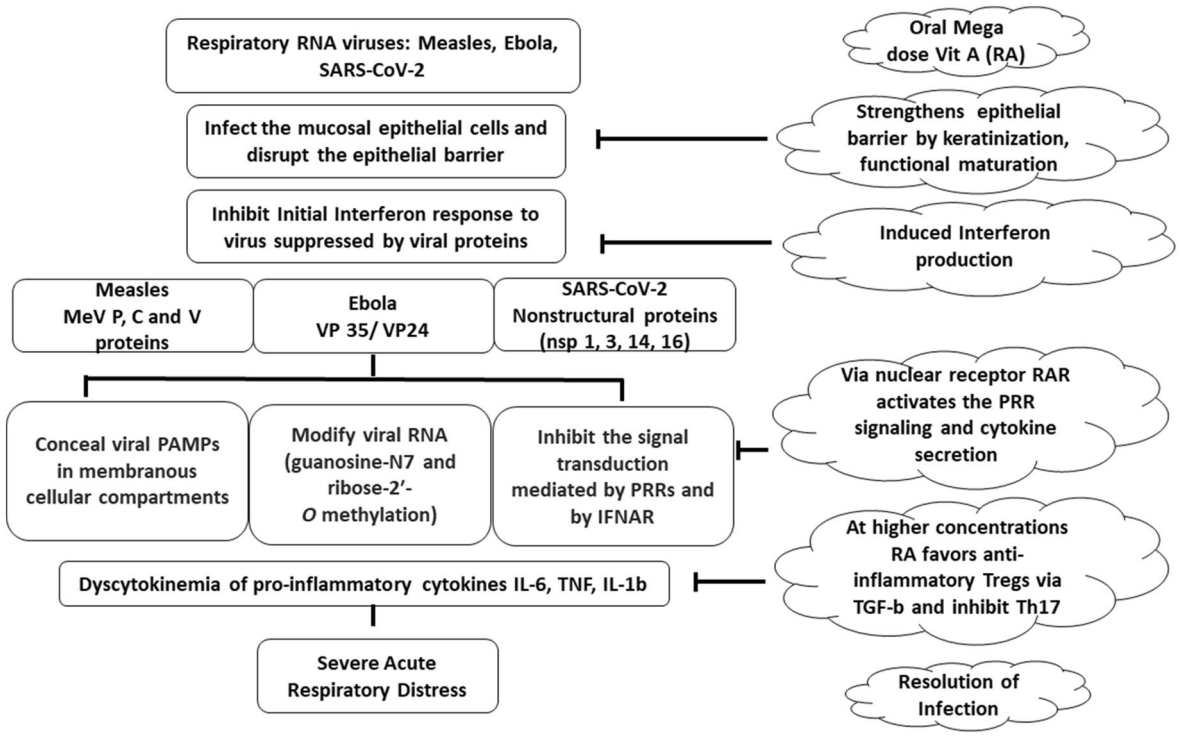

FIGURE 2 The commonalities in the mechanisms of pathogenesis in Measles, Ebola and SARS-CoV-2 viral infections and the possible advantages vitamin A can offer at each step of immune response.[8,145–147]

randomized controlled trials to assess their efficacy. Its use may be explored in following ways:

6.1 | As a potential therapeutic intervention

Moderate to severe cases: Since adults are known to tolerate higher doses, larger doses 300,000–500,000 IU may be used for supplementation during acute and critical phase of illness in attempt to achieve the desired immunomodulatory effect.

Mild cases: Supplementing the usual mega dose of 200,000 IU of vitamin A for 2 days is expected to mediate augmentation in specific IgG1 levels. This may not only decrease their chances of complications, but may also increase the efficacy of their plasma for convalescent plasma therapy. Loss of IgG response over the period of convalescence is also a cause of concern[161] and vitamin A supplementation may be useful during this period.

6.2 | As a potential prophylactic intervention

Health care providers should be offered either monthly mega dose or advised daily supplementation of RDA. This is in view of the reports of children with normal serum retinol levels undergoing milder courses with measles compared to children with vitamin A deficiency.

Adult asymptomatic contacts should be offered 1–2 mega doses to augment their innate immune response to viral antigens.

6.3 | As an adjuvant along with Covid-19 vaccine

Vitamin A enhanced IgA production by the stimulated B cells, with support from respiratory epithelial cells as well as mucosal dendritic cells synthesising RA.[162] Measles vaccination at 9 months of age is routinely accompanied by mega dose of vitamin A supplementation (100,000 IU). This has been shown to increase the protective immune response induced by the vaccine.[163]

Dietary vitamin A supplemented calves (3300 U/kg of dry matter of diet) showed higher serum retinol concentration, more robust IgG1 response to intramuscular inoculations of bovine coronavirus vaccine.[164] Interestingly, these immunised and vitamin A supplemented calves showed an enhanced ratio of IgG1 to IgG2. Immune response to mucosal BRSV vaccine was impaired in vitamin A deficient calves and was not protected against bovine RSV challenge.[165] IgA response to influenza vaccine in vitamin A deficient mice was strengthened by oral supplementation with RA.[166] Role of RA as an adjuvant was emphasised in both adult and neonatal mice.[167,168] Owing to this adjuvant-like ability, vitamin A, may be worthy for consideration of co-administration along with vaccine trials in future.

TABLE 3 RDA of Vitamin A for different age groups and its reported therapeutic doses used for measles, Ebola, supplementation in ocular manifestations of vitamin A deficiency and acne

Age group	RDA (in mcg)[150,151]	RDA (in IU) (1 mcg = 3.33 IU)[150,151]	Daily dose used in Ebola (in IU) (two doses on consecutive days)[113]	Daily dose used in measles (in IU) (two doses on consecutive days, Day 0, 1)[100,101,108-111] Day 0, 1, 8, 42[93]	Daily dose in ocular manifestation of vitamin A deficiency (in IU)[152] Day 0, 1, 14	Daily dose used in acne (in IU) (for 12 weeks)[153]
Men	600	2000	200,000 (100 times RDA approx.)	200,000 (100 times RDA approx.)	200,000 (100 times RDA approx.)	500,000 (250 times RDA approx.)
Women	600	2000	200,000 (100 times RDA approx.)	200,000 (100 times RDA approx.)	200,000 (100 times RDA approx.)	300,000 (150 times RDA approx.)
Infants	350	1150		100,000 (100 times RDA approx.)	100,000 (100 times RDA approx.)	Not known
Children 1–6 years	400	1350		200,000 (150 times RDA approx.)	200,000 (150 times RDA approx.)	Not known
Children 6-16 years	600	2000		200,000 (100 times RDA approx.)	200,000 (100 times RDA approx.)	Not known

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CONFLICT OF INTEREST

All the authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Ish K. Midha conceived the idea for the review and prepared the draft. Nilesh Kumar and Amit Kumar contributed to the draft with respect to role of vitamin A in recognition of RNA viruses and impact of Vitamin A on ACE-2 and prognosis of Covid-19 patients respectively. Taruna Madan contributed to the draft for immune-modulatory role of vitamin A and preparation of the figures.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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