REVIEW

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Antibody Dependent Enhancement of SARS-CoV-2 Infection in the Era of Rapid Vaccine Development

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ABSTRACT

Background: Antibody dependent enhancement (ADE) is a unique immunopathological phenomenon in which pre-existing immunity to a viral agent accentuate disease severity upon secondary exposure. Multiple viruses have been shown to demsotrate ADE with no clear understanding of the underlying mechansims. Recently, with the emeregence of Sever acute respiratory syndrome-2 (SARS-CoV2) and the need for rapid vaccine prodcution, ADE have emerged as an important issue that need to be assessed. **Objective:** The aim of this study was to review ADE, proposed mechanisms and impact of ADE in the era of rapid SARS-CoV2 vaccine production. **Methods:** Review of existing published literature on ADE and SARS-CoV2 and identify facts that support or otherwise contradict the impact of ADE on SARS-CoV2 vaccination. **Results:** SARS-CoV2 demonstrate high genetic homology to other members of the *Coronaviridae* viral family and animal studies and studies on SARS-CoV, another member of the *Coronaviridae* have been shown to induce ADE. In addition sever SARS-CoV2 infection have been associated with high antibody titer. Yet vaccine efficacy studies and studies on breakthrough infection showed reduced severity in individual with preexisting immunity **Conclusion:** Although evidence exist to support ADE in SARS-CoV2, multiple studies do not support its occurrence, indicating the need for more case control studies to understand the role of high antibody titer and disease severity and compare disease severity in patient with preexisting immunity vs naïve individuals.

Keywords: Enhancement, SARS-CoV2, vaccine, intrinsic, extrinsic.

1. ANTIBODY DEPENDENT ENHANCEMENT (ADE)

Antibody dependent enhancement (ADE) is a unique immunopathological phenomenon, described as early as 1964 (1), in which the presence of non-neutralizing antibodies to a viral agent leads to enhancement of viral replication upon secondary exposure to the virus. This phenomenon requires sensitization to the viral agent by either previous infection with antigenically similar virus, active or passive vaccination. ADE has been associated with production of suboptimal level of neutralizing antibody or production of antibodies with reduced specificity of binding which, instead of neutralizing the virus, cause enhancement of infectivity, increase viral production and increase severity of disease.

Following viral infection, multiple arms of the immune system is activated including cellular and humoral immunity. Antibody production occur following clonal activation of B cells leading to production of polyclonal antibodies directed against multiple viral epitopes. Some antibodies are neutralizing while other are not. On the other hand, vaccination which can be done using whole live attenuated viral vaccine, whole killed inactivated vaccine, subunit vaccine, viral vector vaccine and the most recent mRNA vaccine will not be as effective in producing wide spectrum of antibodies and mostly used to produce a specific neutralizing antibody. Yet selection and preparation of the vaccine need to preserve the conformational antigenic structure and must be evaluated for their efficacy in producing optimal level of neutralizing antibodies. In addition, vaccines must be assessed for their abilities to produce disease enhancing antibodies which can detrimental.

2. MECHANISM OF ADE

Multiple mechanisms have been proposed to explain ADE including IgG and IgM antibody-enhanced entry to macrophage and subsequent replication via Fc receptors, enhancement of C1q complement activation by anti-

body-antigen complexes, induction of conformational changes and affinity to co-receptors and inhibition of antiviral cellular response via inhibition of gene expression (2, 3). Antibodies represent a vital component in mediating these changes, and therefore they are called antibody dependent enhancement. Furthermore, antibodies and Fc receptors need to be of the same phylogenetic class in order to interact together as original studies on fowls antisera against a number of arboviruses induces ADE only in chick embryo cell and not in mouse or rabbit derived cells (1, 4)

In addition, disease enhancement can be explained by broadening the type of cells targeted by the virus via facilitating entry through Fc receptors and complement receptors available on wider range of cells such as the complement mediated entry of parvovirus B19 in to endothelial cells not harboring blood group P antigen commonly targeted by the virus (5)

Two types of ADE have been described, intrinsic and extrinsic. Intrinsic type is caused by enhanced internalization of macrophage tropic virus into the macrophage following Fc receptor binding and phagocytosis leading to inhibition of innate immune response and IL-10 production and increased viral production. Extrinsic ADE, on the other hand, is associated with increased phagocytosis of virus-antibody complexes and increased number of virally infected cells (5-7).

Multiple virus families have been associated with ADE in human and animals including *Flaviviridae*, *Retroviridae*, *paramyxoviridae*, and *Cornonaviridae* (table.1). One of the best studies models of ADE is dengue hemorrhagic syndrome/ dengue shock syndrome (DHF/DSS) seen in patients with secondary infection with heterologous dengue virus infection, due to the presence of non-neutralizing antibody (8). Yet its crucial to know that not all secondary dengue infection are associated with DHF/DSS, it is only reported in 0.5-2% of the cases. In addition children who received whole inactivated measle or RSV virus demonstrated more sever disease upon exposure to the agent, due to conformational difference between the vaccine and the virus inducing non-neutralizing antibodies, in comparison to children with past natural infection (9). These conformational changes affect innate immune response via interference with toll-like receptor stimulation and dendritic cell activation (10) . yet this enhancement is not seen with other whole inactivated vaccines. Furthermore, influenza trivalent inactivated vaccine (2008-2009) was observed to be associated with increased risk of medically attended H1N1 infection(11) and extrinsic ADE was suggested by the increased number of infected cell rather that increased viral load in cells treated with human sera (12)

These viruses share some features in that they are RNA enveloped viruses. In fact, disease enhancing antibodies has been linked to surface antigen such as envelope glycoproteins but not internal antigens (13). On the other hand, enhancement in not seen in all patients and therefore critical analysis of the evidence to support or otherwise defer the argument is essential. This review will focus on discussing coronavirus associated ADE in the era of rapid vaccine development to combat the COVID-19 (Coronavirus disease 2019) pandemic.

3. ADE AND SARS-COV2

Coronaviridae is a viral family of enveloped single-stranded RNA viruses characterized by a large genome. The family is subdivided in to *Coronavirinae* and *Torovirinea* subfamilies. *Coronavirinae*, which include human pathogens, is further subclassified in to four genera: alpha, beta, gamma, and delta which include a number of respiratory and enteric viruses. Majority of human infections caused by coronaviruses are mild with the exception of Sever acute respiratory syndrome caused by (SARS-CoV), Middle East respiratory syndrome caused by (MERS-CoV) and more recently Sever acute respiratory syndrome-2 (SARS-CoV2) (18). Despite years of research for MERS-CoV and SARS-CoV vaccine, an efficient and safe vaccine was not produced (19). This can be partly explained by the reduced need to produce vaccines for diseases with limited geographical distribution, but more studies are needed to clarify the challenges faced. Genetic homology of coronaviruses and associated antibody cross reactivity among different members of the family, raises concerns about possibility of disease enhancement by antibodies directed against a specific coronavirus upon exposure to other members of the family. This phenomenon is well described for the four dengue viruses, in which infection with one serotype, leads to enhanced disease severity during infection with another serotype (16). In addition, children born with low titer maternal antibody to dengue develop dengue hemorrhagic fever (20). Furthermore, studies have shown that Zika virus, another member of the Flaviviridae, can induce ADE in patient with previous dengue virus infection (16).

What support ADE in SARS-COV2?

SARS-CoV, MERS-CoV, and SARS-CoV2 demonstrate 82-90% sequence homology (21). Antibodies directed against SARS-CoV2 cross react with SARS-CoV but not MERS-CoV, yet these antibodies were non neutralizing (22, 23). Furthermore, adaptive immune response in the form of reactive CD4 cells were detected in patients with no prior history of SARS-CoV2 infection suggesting cross reactivity with circulating coronaviruses (24). This antigenic similarity between the three most virulent coronaviruses and the presence of non-neutralizing antibodies raises concern of enhancement of infection by other coronaviruses.

Multiple in vitro and in vivo studies supported the possibility of ADE in coronaviruses infection in both animals and humans. In cats, vaccination against feline coronavirus with recombinant spike protein vaccine was associated with sever disease (25). Furthermore, studies on SARS-CoV recombinant vaccine in rodents showed that prior vaccination facilitated the entry of SARS-CoV to non ACE-2 (angiotensin converting enzyme-2) bearing immune B cells, therefore expanding the types of cell targeted by the virus (26). This means antibodies can facilitate the uptake of viruses into new types of cells not bearing the virus receptors allowing more cells to be in-

fected. Although the impact of this broader targets was not linked directly to disease enhancement in human, it could facilitate our understanding of the immunopathological changes seen in sever SARS-CoV infection and other respiratory viruses.

Furthermore, in human, COVID19 is found to be less sever in pediatric age group indicating key role of the immune system in the pathogenesis of sever disease(27)

In addition, studies on the association of SARS-COV2 antibody titer and disease severity indicated that disease severity was directly related to high total anti-spike protein antibodies (28, 29), and that high IgG is detected in patient with critical illness (30). furthermore, IgM antibodies level was higher in sever COVID-19 in comparison to mild COVID-19 (22, 23). One study on 113 patient found direct association between high anti-receptor binding domain (RBD) antibodies and disease severity (31). Another study on 10 children with multisystem inflammatory disease (MIS-C), a serious complication of COVID-19, demonstrated that anti-RBD was significantly higher in MIS-C than in children with COVID-19, Kawasaki disease and controls (p value <0.001)(32). in comparison with dengue virus enhancement, which is one of the most wildly studied model of ADE, high neutralizing antibody titers were actually associated with disease protection and ADE were observed in a narrow range of antibody titer (33, 34)

What is against ADE in SARS-COV2?

Despite multiple studies suggesting possible role of ADE in sever SARS-COV2 infection and post-vaccination, one study in UK demonstrated that administration of convalescent sera to COVID19 patient was safe with no evidence of ADE, yet no control group was included in the study (35). Studies on breakthrough infections among individual who received COVID-19 vaccine showed that most cases are asymptomatic or mild disease with few persistence infection (36, 37) and case control studies showed that disease severity, and hospitalization is less in vaccinated versus unvaccinated (38, 39). Thus, neither previous infection, not active/passive immunization against SARS-CoV2 have been shown to be directly associated with enhanced disease severity in human.

4. CONCLUSION

Coronaviruses have demonstrated the ability to induce antibody enhanced infection in animals and in-vivo and with the emergence of novel coronaviruses, and the need for vaccines, assessment of the safety and efficacy of the vaccine is needed. Although multiple studies have correlated high SAR-CoV2 antibody titer with severity, the role of these antibodies in disease enhancement have not been explained. Furthermore, high neutralizing antibody titer have always been correlated with protection in other virus models and the need to better characterize the types and role of these SARS-CoV2 high antibodies is highly needed. Studies on breakthrough infections did not support the possibility of ADE nor does studies on the use of monoclonal antibodies. Further studies therefore are needed to characterize the role of high antibodies titer in sever COVID-19 and further explore the immunopathological basis of severe illness.

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REFERENCES

1. Hawkes RA. Enhancement of the Infectivity of Arboviruses by Specific Antisera Produced in Domestic Fowls. Aust J Exp Biol Med Sci. 1964; 42: 465-482.
2. Mitchell WM, Robinson WE, Montefiori DC. Antibody-dependent enhancement of viral infectivity. I. An ineffective response. Infectious diseases newsletter (New York, NY). 1988; 7(8): 59-60.
3. Sauter P, Hober D. Mechanisms and results of the antibody-dependent enhancement of viral infections and role in the pathogenesis of coxsackievirus B-induced diseases. Microbes and infection. 2009; 11(4): 443-451.
4. Kliks SC, Halstead SB. Role of antibodies and host cells in plaque enhancement of Murray Valley encephalitis virus. J Virol. 1983; 46(2): 394-404.
5. Taylor A, Foo S-S, Bruzzone R, Vu Dinh L, King NJC, Mahalingam S. Fc receptors in antibody-dependent enhancement of viral infections. Immunological reviews. 2015; 268(1): 340-364.
6. Halstead SB, Mahalingam S, Marovich MA, Ubol S, Mosser DM. Intrinsic antibody-dependent enhancement of microbial infection in macrophages: disease regulation by immune complexes. The Lancet infectious diseases. 2010; 10(10): 712-722.
7. Narayan R, Tripathi S. Intrinsic ADE: The Dark Side of Antibody Dependent Enhancement During Dengue Infection. Front Cell Infect Microbiol. 2020; 10: 580096-.
8. Guzman MG, Alvarez M, Halstead SB. Secondary infection as a risk factor for dengue hemorrhagic fever/dengue shock syndrome: an historical perspective and role of antibody-dependent enhancement of infection. Archives of virology. 2013; 158(7): 1445-1459.
9. Polack FP. Atypical measles and enhanced respiratory syncytial virus disease (ERD) made simple. Pediatr Res. 2007; 62(1): 111-115.
10. Ubol S, Halstead SB. How Innate Immune Mechanisms Contribute to Antibody-Enhanced Viral Infections. Clinical and vaccine immunology. 2010; 17(12): 1829-1835.
11. Skowronski DM, De Serres G, Crowcroft NS, Janjua NZ, Boulianne N, Hottes TS, et al. Association between the 2008-09 seasonal influenza vaccine and pandemic H1N1 illness during Spring-Summer 2009: four observational studies from Canada. PLoS Med. 2010; 7(4): e1000258.
12. Dutry I, Yen H-l, Lee H, Peiris M, Jaume M. Antibody-Dependent Enhancement (ADE) of infection and its possible role in the pathogenesis of influenza. BMC Proc. 2011; 5(Suppl 1): P62-P.
13. Porterfield JS. Antibody enhanced viral growth in macro-

phages. Immunol Lett. 1985; 11(3-4): 213-217.
14. de Swart RL, van den Hoogen BG, Kuiken T, Herfst S, van Amerongen G, Yüksel S, et al. Immunization of macaques with formalin-inactivated human metapneumovirus induces hypersensitivity to hMPV infection. Vaccine. 2007; 25(51): 8518-8528.
15. Prabhakar BS, Nathanson N. Acute rabies death mediated by antibody. Nature. 1981; 290(5807): 590-591.
16. Dejnirattisai W, Supasa P, Wongwiwat W, Rouvinski A, Barba-Spaeth G, Duangchinda T, et al. Dengue virus sero-cross-reactivity drives antibody-dependent enhancement of infection with zika virus. Nature immunology. 2016; 17(9): 1102-1108.
17. Kuzmina NA, Younan P, Gilchuk P, Santos RI, Flyak AI, Ilinykh PA, et al. Antibody-Dependent Enhancement of Ebola Virus Infection by Human Antibodies Isolated from Survivors. Cell reports (Cambridge). 2018; 24(7): 1802-15.e5.
18. Payne S. Family Coronaviridae: Viruses. 2017: 149-158. doi: 10.1016/B978-0-12-803109-4.00017-9.
19. Dhama K, Sharun K, Tiwari R, Dadar M, Malik YS, Singh KP, et al. COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics. Hum Vaccin Immunother. 2020; 16(6): 1232-1238.
20. Simmons CP, Chau TNB, Thuy TT, Tuan NM, Hoang DM, Thien NT, et al. Maternal antibody and viral factors in the pathogenesis of dengue virus in infants. The Journal of infectious diseases. 2007; 196(3): 416-424.
21. Naqvi AAT, Fatima K, Mohammad T, Fatima U, Singh IK, Singh A, et al. Insights into SARS-CoV-2 genome, structure, evolution, pathogenesis and therapies: Structural genomics approach. Biochimica et Biophysica Acta (BBA)–Molecular Basis of Disease. 2020; 1866(10): 165878.
22. Wang J, Zand MS. The potential for antibody-dependent enhancement of SARS-CoV-2 infection: Translational implications for vaccine development. Journal of clinical and translational science. 2020: 1-4.
23. Wang Y, Zhang L, Sang L, Ye F, Ruan S, Zhong B, et al. Kinetics of viral load and antibody response in relation to COVID-19 severity. J Clin Invest. 2020; 130(10): 5235-5244.
24. Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, Moderbacher CR, et al. Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals. Cell. 2020; 181(7): 1489-501.e15.
25. Kadkhoda K. COVID-19: are neutralizing antibodies neutralizing enough? Transfusion (Philadelphia, Pa). 2020; 60(7): 1602-1603.
26. Kam YW, Kien F, Roberts A, Cheung YC, Lamirande EW, Vogel L, et al. Antibodies against trimeric S glycoprotein protect hamsters against SARS-CoV challenge despite their capacity to mediate FcgammaRII-dependent entry into B cells in vitro. Vaccine. 2007; 25(4): 729-740.
27. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 Infection in Children. New England Journal of Medicine. 2020; 382(17): 1663-1665.
28. French MA, Moodley Y. The role of SARS-CoV-2 antibodies in COVID-19: Healing in most, harm at times. Respirology (Carlton, Vic). 2020; 25(7): 680-682.
29. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody Responses to SARS-CoV-2 in Patients With Novel Coronavirus Disease 2019. Clin Infect Dis. 2020; 71(16): 2027-2034.
30. Qu J, Wu C, Li X, Zhang G, Jiang Z, Li X, et al. Profile of Immunoglobulin G and IgM Antibodies Against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020; 71(16): 2255-2258.
31. Garcia-Beltran WF, Lam EC, Astudillo MG, Yang D, Miller TE, Feldman J, et al. COVID-19-neutralizing antibodies predict disease severity and survival. Cell. 2021; 184(2): 476-488.e11.
32. Rostad CA, Chahroudi A, Mantus G, Lapp SA, Teherani M, Macoy L, et al. Quantitative SARS-CoV-2 Serology in Children With Multisystem Inflammatory Syndrome (MIS-C). Pediatrics. 2020; 146(6).
33. Katzelnick LC, Gresh L, Halloran ME, Mercado JC, Kuan G, Gordon A, et al. Antibody-dependent enhancement of severe dengue disease in humans. Science. 2017; 358(6365): 929-932.
34. Clapham HE, Rodriguez-Barraquer I, Azman AS, Althouse BM, Salje H, Gibbons RV, et al. Dengue Virus (DENV) Neutralizing Antibody Kinetics in Children After Symptomatic Primary and Postprimary DENV Infection. J Infect Dis. 2016; 213(9): 1428-1435.
35. Roberts DJ, Miflin G, Estcourt L. Convalescent plasma for COVID-19: Back to the future. Transfusion medicine (Oxford, England). 2020; 30(3): 174-176.
36. Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, et al. Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. New England Journal of Medicine. 2021; 385(16): 1474-1484.
37. Chandan S, Khan SR, Deliwala S, Mohan BP, Ramai D, Chandan OC, et al. Postvaccination SARS-CoV-2 infection among healthcare workers: A systematic review and meta-analysis. J Med Virol. 2022; 94(4): 1428-1441.
38. Tenforde MW, Self WH, Adams K, Gaglani M, Ginde AA, McNeal T, et al. Association Between mRNA Vaccination and COVID-19 Hospitalization and Disease Severity. JAMA. 2021; 326(20): 2043-2054.
39. Abou Ghayda R, Lee KH, Han YJ, Ryu S, Hong SH, Yoon S, Jeong GH, Yang JW, Lee HJ, Lee J, Lee JY, Effenberger M, Eisenhut M, Kronbichler A, Solmi M, Li H, Jacob L, Koyanagi A, Radua J, Park MB, Aghayeva S, Ahmed MLCB, Al Serouri A, Al-Shamsi HO, Amir-Behghadami M, Baatarkhuu O, Bashour H, Bondarenko A, Camacho-Ortiz A, Castro F, Cox H, Davtyan H, Douglas K, Dragioti E, Ebrahim S, Ferioli M, Harapan H, Mallah SI, Ikram A, Inoue S, Jankovic S, Jayarajah U, Jesenak M, Kakodkar P, Kebede Y, Kifle M, Koh D, Males VK, Kotfis K, Lakoh S, Ling L, Llibre-Guerra J, Machida M, Makurumidze R, Mamun MA, Masic I, Van Minh H, Moiseev S, Nadasdy T, Nahshon C, Ñamendys-Silva SA, Yongsi BN, Nielsen HB, Nodjikouambaye ZA, Ohnmar O, Oksanen A, Owopetu O, Parperis K, Perez GE, Pongpirul K, Rademaker M, Rosa S, Sah R, Sallam D, Schober P, Singhal T, Tafaj S, Torres I, Torres-Roman JS, Tsartsalis D, Tsolmon J, Tuychiev L, Vukcevic B, Wanghi G, Wollina U, Xu RH, Yang L, Zaidi Z, Smith L, Shin JI. The global case fatality rate of coronavirus disease 2019 by continents and national income: A meta-analysis. J Med Virol. 2022 Jun; 94(6): 2402-2413. doi: 10.1002/jmv.27610.