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Immunotherapy will be More Promising Tool than Antimicrobial Therapy in Future: A Review

Rishav Kar[1]

[1]Department of Microbiology, Ramakrishna Mission Vivekananda Centenary College, Rahara, Kolkata, India
rishavkar07[at]gmail.com

Abstract: ***Today we are living in antimicrobial treatment era where in treatment of infectious diseases chemical based anti-microbial agents are used. These chemical compounds cure the infection primarily but they show various other negative effects on our health. Not only that, multidrug resistance is another worst result of using anti-microbial drugs indiscriminately. In this situation immunotherapies will show the path further. Many immunology based methods are now practically used in treatment of infections and many are still under research. The two main problems i.e. multidrug resistance and side effects of chemical drugs can be solved by immunotherapies. In this article some infections, drugs along with their side effects are shown in one hand and in other hand several immunotherapies are discussed with their recent applications. This will point out the drawbacks of antimicrobial therapy and the need of development and advancement of immunotherapy in future, which will be more promising.***

Keywords: Antimicrobial therapy, multidrug resistance, immunotherapy

1. Introduction

Infectious diseases are always being a great matter of health concern. From the very beginning of the evolution of humans we are continuously fighting with some of the pathogenic invisible organisms i.e. microbes or sometime visible infectious agents that cause severe life threatening diseases or mild infections sometimes. In this battle if we the humans won then there is no problem but if the infectious agent overruled us then actually the disease flourished. We have a well organized and specialized system in our body that fights day and night with those foreign infectious invaders, i.e. immune system. Immune system comprised of many specialized immune cells that are always stands to protect us just like the military-men standing on the border to protect us. But most interesting thing is that, if we have such developed immune system in the one hand, then in the other hand microbial agents have gather a great experience in course of time**.** They also have some strategies to defeat our immune cells. These infectious agents can be categorized into four major categories which infect humans most commonly; these are bacterial agents, fungal agents, protozoan agents and viral agents. Once they successfully infects us and consequently disease occurs we used various antibiotics, anti-fungal, anti-protozoan and anti viral drugs respectively for treatment. But these chemical drugs used in treatment of such diseases have various negative impacts on our health. In this article one disease from each group and the drugs along with their side effects are discussed. This study will show the significance of the advancement of immunological research and importance of various immunological therapies in treatment of such infection rather than commonly used chemical drugs.

Tuberculosis- infection by a bacterial agent

The bacterium:

These are fairly large non-motile, aerobic, bacilli. Rods are 2-4 micrometer in length and 0.2-0.5 um in width. Most interestingly these bacteria cannot be categorized on the basis of their Gram character. They have a thick layer of mycolic acid on their cell wall which makes it impermeable to Gram stains. These are actually acid fast bacteria and can be identified by Ziel-Neelsen staining. Two media are used to grow *Mycobacterium tuberculosis* (MTB) i.e. Middlebrook's medium and the Lowenstein-Jensen medium. Tb bacteria have very slow generation time of about 15 to 20 hours hence it needs about 4 to 6 weeks to get visual colonies on agar plate which are small and buff colored.

The disease:

TB is one of the most common airborne bacterial infection caused by M. Tuberculosis. Almost every organ is susceptible to TB but most typically lungs are infected. The bacterium is exposed to the air from the patients as very small water droplets commonly known as droplet nuclei. Coughing, sneezing, shouting or singing of people with the pulmonary or laryngeal TB are the ways by which these droplets can be spread in the outer environment. Tuberculosis can be transmitted by inhalation of those droplet nuclei which ultimately reaches the alveoli of the lungs. Immediately after entering into the lung cells the bacteria are ingested by alveolar macrophages that cause destruction or inhibition of a greater proportion of the inhaled tubercle bacilli. Remaining of the bacteria within the macrophages stats multiplication and consequently released upon death of the macrophages. Released tubercle bacilli spread via the bloodstream or lymphatic channels to any a part of the body tissues or organs mostly lungs, larynx, lymph nodes, spine, bone or kidneys.

Treatment:

A number of antibiotics are potentially used in treatment of tuberculosis infection; many of those drugs are listed below along with their side effects.

Name of Drugs	Description	Side effects
Amikacin	An aminoglycoside used in treatment of gram negative and some gram positive bacteria.	Electrolyte abnormalities, nephrotoxicity, vestibular toxicity/ ototoxicity.
Aminosalicylic acid	An aminosalicylate drug used to induce remission in ulcerative colitis.	Gastrointestinal problems following oral administration, including anorexia, nausea, epigastric pain, abdominal distress, and diarrhea.
Capreomycin	An aminoglycoside antibiotic used as an adjunct drug in tuberculosis.	Electrolyte abnormalities, eosinophilia, vestibular toxicity/ ototoxicity.
Pretomanid	Part of a three-drug regimen used for the treatment of extensively drug-resistant and multidrug-resistant pulmonary tuberculosis.	Peripheral neuropathy, acne, anemia, nausea, vomiting, headache, increased trans-aminases, dyspepsia, decreased appetite, rash, pruritus, abdominal pain, pleuritic pain, increased gamma-glutamyltransferase, lower respiratory tract infection, hyperamylasemia, hemoptysis, back pain, cough, visual impairment, hypoglycemia, abnormal loss of weight, and diarrhea.
Rifabutin	An antibiotic used to treat *Mycobacterium avium* complex disease in patients with HIV.	Reddish/orange discoloration of body fluids including urine, tears, saliva, nausea, vomiting, heartburn, abdominal cramps, loss of appetite, discomfort near the ribs on the right upper abdomen, jaundice.

Esophageal candidiasis- infection by a fungal agent

The fungus:

Candida albicans is an opportunistic pathogen which will cause the disease. It's the commensal microflora of the skin, oral, GIT, vagina, and therefore the tract. C. albicans could be a fungus just like yeast it's soft-wall exterior to its cell. The morphology seems globular to oval, gram-positive and 5 um in diameter. Reproduce asexually by budding, and is comparatively bigger than the dimensions of bacteria. Sabouraud culture media comprising antibiotic that allowed for Candida spp. isolation. After 3 days after incubation of Candida spp at 25°C, it forms false hyphae and true hyphae. The blastoconidia are formed in like clusters along the length of the hyphae. Terminal chlamydoconidia could also be formed with extended incubation. Candida albicans could ferment glucose and do ferment other sugars for the creation of ethanol one among the more well-known characteristics. candida could be a dimorphic fungus; that has the power to configure two forms. The yeast hyphal form that has the power to invasive the membrane and non-invasive form don't form hyphae. C. albicans display various morphological structures following diverse environmental statuses; so forms include budding yeast (blastospores), pseudohyphae, true hyphae, and chlamydospores and every one can distinguish C. albicans from another Candida non albicans spp.C. albicans form germ tube, that's a primary step within the yeast-hyphal transition. Nevertheless, the capacity to assume several forms could also be related to the pathogenicity. **(Ali R. Hameed et al., 2018)**

The disease:

Esophageal candidiasis is an infection of the esophagus — the tube that connects the mouth to the stomach. it's caused by an overgrowth of Monilia albicans. Candida causes health problems only if there's an overgrowth. Esophageal candidiasis is an AIDS-defining illness. Like most of the conditions related to AIDS. Candidiasis within the esophagus can cause difficulty swallowing, pharyngitis and sometimes a sense of hurting, just behind the breastbone**.**

Treatment:

A number of anti-fungal drugs are potentially used in treatment of this infection; many of those drugs are listed below along with their side effects.

Name of drugs	Description	Side effects
Anidulafungin	An antifungal used in the treatment of several types of candida infections.	Nausea, headache, reversible elevation of liver function, dyspnea.
Caspofungin	An echinocandin used to treat a variety of fungal infections.	Nephrotoxicity or hepatotoxicity, fever, flushing, nausea, headache, vomiting, and infusionrelated Phlebitis, eosinophilia.
Fluconazole	A triazole antifungal used to treat various fungal infections including candidiasis.	Allergic reactions**,** sudden wheezing, difficulty in breathing or tightness in the chest, swelling of eyelids, face or lips, itching all over the body, reddening of the skin or itchy red spots, skin rash, severe skin reactions such as a rash that causes blistering.
Voriconazole	A triazole compound used to treat fungal infections.	Stomach upset, nausea, vomiting and loss of appetite, abdominal pain, diarrhea, and headache.

Malaria- infection by a protozoan agent

The protozoa:

The most liable pathogen for the bulk of this particular disease is Plasmodium falciparum. It is one of the most the predominant species in tropical Africa, eastern Asia, Oceania and therefore the Amazon basin of South America. Life cycle of P. falciparum (and other Plasmodium species) involves several stages in both human and mosquito hosts. Following the bite of an infected female Anopheles mosquito, sporozoites injected from the insect's salivary glands enter the bloodstream and travel quickly to the liver. After that the invasion of hepatocytes ensues and an 8 to 12 days period of time enables the asexual replication to get many daughter merozoites. Infected hepatocytes then rupture consequently releasing merozoites into the circulation, thus commencing the blood stage of the infection during which clinical malaria may develop.

The disease:

Malaria is an acute febrile illness with period of time of seven days or longer. Malaria parasites are transmitted from person to person through Anopheles mosquitoes. When a mosquito bites, blood containing the parasites is taken into the mosquito's gut. Over a period of 10 or more days, the parasites undergo a fancy development, the mature parasite eventually coming to reside within the mosquito's salivary glands, ready for transmission to a replacement person when it bites again. In the next human host the pathogen first infects the hepatocyte cells then it undergoes for rapid replication. Duration of this phase is for minimum of five days after that it infects red blood cells. Foremost serious symptoms of malaria which includes cerebral malaria initiated by parasitized blood cells blocking blood capillaries within the brain. Malaria includes various other symptoms like fever, chills, headache, muscular aching, weakness, vomiting, cough, diarrhea and abdominal pain, acute kidney failure, pulmonary oedema, generalized convulsions, circulatory collapse, followed by coma and death.

Treatment:

A number of anti-malarial drugs are potentially used in treatment of this infection; many of those drugs are listed below along with their side effects.

Name of drugs	Description	Side effects
Atovaquone	An antimicrobial indicated for the prevention and treatment of Pneumocystis jirovecii pneumonia (PCP) and for the prevention and treatment of Plasmodium falciparum malaria.	Rash, itching, sudden wheezing, tightness of the chest or throat, or difficulty breathing or low blood pressure, swollen eyelids, face, lips, tongue or other part of the body, headache feeling sick and being sick (nausea and vomiting), stomach pain diarrhea.
Proguanil	A medication indicated for prophylaxis and treatment of Plasmodium falciparum malaria.	Rash, itching, sudden wheezing, tightness of the chest or throat, or difficulty breathing or low blood pressure, swollen eyelids, face, lips, tongue or other part of the body, headache feeling sick and being sick (nausea and vomiting), stomach pain diarrhea.
Quinine	An alkaloid used to treat uncomplicated Plasmodium falciparum malaria.	Tinnitus, impaired hearing, rashes, headache, nausea and disturbed vision, gastrointestinal symptoms, oculotoxicity, CNS disturbances, cardiotoxicity

Influenza- infection by a viral agent

The virus:

Influenza viruses are highly variable RNA viruses that may affect birds and mammals including humans. There are currently three species of those viruses, designated influenza A, B and C. All these viruses are widespread among them Influenza A are quite common in wild aquatic birds i.e. their natural hosts. Poultry are readily infected and a limited number of viruses have adapted to circulate in people, pigs, horses and dogs. Within the mammals to which they're adapted, influenza A viruses usually cause respiratory illnesses with high morbidity but low mortality rates. These viruses contain two highly variable surface antigens, the hemagglutinin (HA) and neuraminidase (NA) proteins, which are wont to classify them into subtypes.

The disease:

Epithelial cells of the upper tract (nose and throat) are mainly infected by this virus. In case of severe infection the virus can enter into the lungs consequently cause pneumonia. The respiratory tract's first line of defence could be a protective layer of mucus. The virus NA protein can traverse this enabling the virus particle to achieve the vegetative cell surface. The virus then uses its HA protein to connect to a receptor on the host cell's semipermeable membrane and is taken into the host cell by endocytosis. The protein core contains the viral RNA and also the viral polymerase used for replication of its own genome, is released into the cytoplasm and moves into the nucleus of the host. Inside the host cell viral RNA is replicated. The ribosomes of the host are hijacked to translate proteins from the viral mRNAs. New copies of the RNA genome are shuttled out of the nucleus and goes up to the cytomembrane where they combine with the newly made viral protein; ultimately bud out of the cell's cell membrane, acquiring their outer

envelope within this process. Finally, using the NA protein to chop themselves off from the infected cells, the new virions move away to infect other cells. Being an extremely contagious virus, it can transmitted from one person to another person by the droplets expelled during sneezing and coughing or by direct contact, for instance by touching virus-contaminated surfaces like door handles and after that touching the own eyes or nose.

Treatment:

A number of anti-viral drugs are potentially used in treatment of this infection; many of those drugs are listed below along with their side effects.

Name of drugs	Description	Side effects
Amantadine	A medication used to treat dyskinesia in Parkinson's patients receiving levodopa, as well as extrapyramidal side effects of medications.	Dizziness, headache, lethargy, ataxia, dysarthria, Oedema peripheral, Livedo reticularis.
Oseltamivir	A neuraminidase inhibitor used in the prophylaxis and treatment of influenza.	Cyanosis, difficulty of breathing, hyperpnea, hypopnea, irregular breath, respiratory failure, respiratory arrest, cardiorespiratory arrest, and death.
Rimantadine	An RNA synthesis inhibitor used to prevent influenza A infection.	Aagitation, dizziness, fatigue, headache, impaired concentration, insomnia, mental depression, tinnitus, dyspnea, abdominal pain, anorexia, diarrhea, dry mouth, dyspepsia, nausea, vomiting and rash.

Implications of immunotherapy in treatment of infectious diseases:

Immunotherapy is a kind of therapeutics that deals with the immune system and the immune cells of individuals. Immune system of human can able to produce antibody against almost all infectious invaders There are a number of methods by which our immune cells can either destroy the pathogen directly or neutralize the toxic material secreted by the pathogen thus protecting us indirectly. Most important thing is that once a particular invader is recognized by our immune cells the necessary information about the foreign particle is stored in the memory cell our immune system. This helps to elicits response much faster in case of future infection. Furthermore as this therapeutic approach is comprised of our own system hence there are no chances of side effects unlike chemical drugs. Antibody therapy has been effective against a variety of diverse microorganisms. Here various immunotherapies and their implications discussed-

Monoclonal antibodies in treatment:

Monoclonal Antibody (MAb) therapy has been studied and developed for the treatment of the many infectious diseases. A number of mechanisms including inhibition of microbial attachment, agglutination, viral neutralization, toxin neutralization, and antibody directed cellular cytotoxicity, complement activation, and opsonization are shown by the antibodies hence they can be thought as potential antimicrobial agents. Like chemical drugs some antibodies target directly the pathogen and in other hand some neutralize the toxic substance produced by the pathogen. There is a report that some MAbs against poliovirus are neutralizing only at fever temperatures, this points that they know at what physiological condition they have to take their action. The flexibility of antibody-based therapies is illustrated by the flexibility of digoxin-binding antibodies to reverse digoxin toxicity and up to date attempts to treat septic shock by employing MAbs that bind cytokines**.**

Cytokine therapy in treatment:

Cytokines are protein mediators involved in essentially all important biological processes including immunity, cell proliferation and inflammation, wound healing and repair, cell migration, fibrosis and angiogenesis. Neutralization of suppressive cytokines like TGF-b and IL- 10 has shown promising leads to treatments of the many infectious diseases. IL-10 is expressed by diverse cell types like dendritic cells (DCs), monocytes and/or CD4C T cells, and its up-regulation is related to disease progression during chronic infections further as poor prognosis in cancer patients. For example in case of promoting human kala-azar, by restricting Th1 cell-type responses or neutralizing parasitized tissue macrophages IL-10 is responsible and it is also responsible for compromising responsiveness to chemotherapy. IL-10 has been also shown to be a negative regulator of the response, in case of *M. tuberculosis* infection and contributing to chronic infection. Not only that, IL-10 impaired fungal clearance as demonstrated by *Cryptococcus neoformans* infections, the leading explanation for fatal mycosis in HIVC individuals.

T-cell therapy in treatment:

These bsAbs (bispecific antibodies) comprise anti-Env and anti-CD3 arms which simultaneously bind to HIV-infected cells and CD3-expressing polyclonal T cells, subsequently inducing CD8C T lymphocyte elimination of HIV-infected CD4C T cells in vitro, reducing virion levels ex vivo and mediating clearance of latent HIV reservoirs from resting CD4C T cells. BiTEs (bi-specific lymphocyte engagers) that focus on the HIV-1 envelope protein gp120 and CD4 are recently described as another potent antiviral activity in vitro and ex vivo. Furthermore to HIV, bsABs are developed to

redirect effector T cells to HBV- and human cytomegalovirus (HCMV)-infected cells, in vitro.

Vaccine:

Following the invention of Edward Jenner's smallpox vaccine in 1796 vaccination, especially against viral infections, has been the leading practice of infection prevention. Vaccination represents the primary kind of host-directed immunotherapy to be introduced and includes various categories. Principal of most vaccines is to introduce a non-infectious version of a disease-causing microbial pathogen into a personal thus providing a higher stimulus for the activation of disease-specific T cells and also the development of immunological memory. Those memory-immune cells are able to rapidly kill microbes at present and also reduce the chance of infection in future. Vaccination shows a great response in treatment of smallpox and it also reduces the disease burden of various infectious microbes like rabies, typhoid, cholera, hepatitis etc. But still it needs improvement to treat cancer and chronic infectious diseases like human immunodeficiency virus (HIV).

2. Conclusion

It is very clear from the information already shown in this article that each and every antimicrobial chemical have some adverse effects on our health. Moreover indiscriminate use of such chemical based antimicrobial drugs fetching a situation in which most of the pathogens become multi-drug resistance. Most of the presently available drug will become use less day by day. Many researchers are trying to re-modifying those chemical drugs for re-purposing but that is not the solution because after sometime they will also become useless as the pathogen will show resistance against them. Here the importance of immunotherapy and the need of advancement in immunological research will come. Some immune therapies are already practically used in treatment but we need to expand this field much greater for better future aspects. Because the immune therapies are deals with the immune system of the patient hence there is a very little chance of side effects, apart from that no question of resistance will arise while we are using immunology based methods for treatment. It seems like a biological agent can handle other biological agent more efficiently than a chemical agent could handle. With the advancement in immunology research it will become more promising tool than antimicrobial drugs in future.

References

[1] Anastasia Koch and Valerie Mizrahi (2018), "Mycobacterium tuberculosis" Trends in Microbiology Vol XX.
[2] Houben, R.M.G.J. and Dodd, P. J. (2016)T he global burden of latent tuberculosis infection: are estimation using mathematical modeling. PLoS Med. 13, e1002152.
[3] Abdimajid Ahmed Mohamed, Xin-liang Lu, and Faycal Awaleh Mounmin (2019), "Diagnosis and Treatment of Esophageal Candidiasis: Current Updates" Canadian Journal of Gastroenterology and Hepatology Volume 2019, Article ID 3585136, 6 pages.
Dolton MJ, Ray JE, Chen SC, Ng K, Pont LG, McLachlan AJ. (2012) Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. Antimicrob Agents Chemother. 2012: 56: 4793
[4] Kristin L. Andrejk, Romana C. Mayer, Stephanie Kovacs, Emma Slutskerd, Emily Bartlette, Kathrine R. Tan, Julie R. Gutman (2019), "The safety of atovaquone-proguanil for the prevention and treatment of malaria in pregnancy: A systematic review" Travel Medicine and Infectious Disease 27 (2019) 20–26.
[5] *Sanjeev Krishna* and *Nicholas J. White (1996), "*Pharmacokinetics of Quinine, Chloroquine and Amodiaquine Clinical Implications*"* Clin. Pharmacokinet. 1996 Apr ; 30 (4): 263·299
[6] Essien EE, Ette EI, Thomas WOA, et al. Chloroquine disposition in hypersensitive and non-hypersensitive subjects and its significance in chloroquine-induced pruritus. Eur J Drug Metab Pharmacokinet 1989; 14: 71-7
[7] Krammer, F. and Palese, P. (2015) Advances in the development of influenza virus vaccines. Nat. Rev. Drug Discov. 14, 167–182.
[8] Farrukee, R. and Hurt, A.C. (2017) Antiviral drugs for the treatment and prevention of influenza. Curr. Treatm. Options Infect. Dis. 9, 318–332
[9] Morens DM, Taubenberger JK, Fauci AS. The persistent legacy of the 1918 influenza virus. N Engl JMed2009; 361(3):225–9.
[10] Siao, K.T., Pypendop, B.H., Stanley, S.D. & Ilkiw, J.E. (2011) Pharmacokinetics of amantadine in cats. Journal of Veterinary Pharmacology and Therapeutics, 34, 599–604.
[11] Dadachova, E., and Casadevall, A. (2014). Radio labeled antibodies for therapy of infectious diseases. Microbiol. Spectr. 2:0023. doi: 10.1128/microbiolspec. AID- 0023-2014