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Immunopharmacological Interventions in Select Disease Conditions

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Abstract

Purpose: Medical practitioners have grappled with the challenge encountered with management of several diseases especially diseases that cannot be cured but can only be managed. In the course of therapy, some patients stop getting positive results from previously efficacious drug while adverse effects of some drugs become unbearable in time. This study aims at bringing together immunotherapeutic approaches that could be researched upon, and presented for clinical trials for the betterment of patients' lives.

Materials and Methods: SALSA, a simple and rational framework (Search, Appraisal, Synthesis and Analysis) was adopted in the study. Only studies on immunology and immunotherapy were included. By applying the framework of SALSA, the first step was to search or to identify relevant and related studies. For this purpose, different search engines that include Google Scholar, Web of Science and Scopus were used. Different key words such as immunology, immunotherapy, immune response, hypertension, diabetes, tumour, etc. were used in the search for relevant studies. After downloading the studies, a manual appraisal was done to remove irrelevant and duplicated ones. In the end, 105 studies that align with our research objectives were selected and reviewed.

Findings: Hypertension was ranked the third factor for disability-adjusted life years by World Health Organisation. For over 40 years, the role of immune system in the genesis of HTN has been firmly established by investigations from around the world. Researchers have pinned inflammation as central to the pathology of Type 1 disease. Type 2 diabetes has more recently been linked to inflammation too. Natural Killer cells along with some others have the ability to kill tumour cells. Since the immune system has been implicated in the pathogenesis of these diseases, any therapy that would target the immune system may ameliorate and prevent disease progression and the usual complications that ensue later.

Unique Contribution to Theory, Practice and Policy: Further investigations utilising well-designed and statistically powered clinical studies should be done to ascertain necessary information, especially safety profile on the reviewed immunomodulators.

Keywords: *Immunology, Immunotherapy, Immune Response, Hypertension, Diabetes, Tumour*

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INTRODUCTION

Diseases are deviations from the normal state of an organism that disrupts the typical structure or function of the organism, often leading to specific signs and symptoms (Hostad et al., 2020). It can be caused by various factors like infections, genetic errors, physiological processes, environmental factors, psychological stress, etc. (Khan et al., 2015; Morse, 2024). Diseases are classified based on the body system affected, underlying cause and the type of pathological change. Diseases are broadly categorized into: Infectious and non-infectious diseases. While infectious diseases are broadly classified into viral, parasitic, bacterial, and fungal, non-infectious diseases are grouped into deficiency, hereditary and physiological diseases.

Ability for medical practitioners to diagnose various diseases and proffer treatment approaches with high success rates has improved over the years. Several approaches can be explored to cure or mitigate diseases including holistic care, disease management, immunotherapies. Immunotherapy encompasses various treatments designed to regulate or temper the immune response (Karlitepe et al., 2015).

Immunotherapy harnesses the abilities of the immune system to target disease-causing cells and respond adequately (Ramamurthy et al., 2020). This approach offers several advantages, including the potential for long-lasting remission and reduced side effects compared to conventional drugs. This treatment approach can also be individualised (Goetz and Schork, 2018). Immunotherapy is laden with so much potential benefits which are yet to be fully harnessed. Researchers are therefore constantly developing new immunotherapeutic approaches for managing several diseases effectively (Ramamurthy et al., 2020). This study reviews the immunopharmacological interventions that could be harnessed for the treatment of hypertension, diabetes, and cancer.

Problem Statement

Medical practitioners have grappled with the challenge encountered in providing treatment for several diseases, especially diseases that cannot be cured but can only be managed. In the course of therapy, tolerance sets in for some patients while adverse effects of some drugs become unbearable in time. Immunotherapy harnesses the abilities of the immune system to target disease-causing cells and respond adequately. Since the body's immune system is targeted, several drawbacks of traditional drugs are navigated, even though immunotherapy in itself is not totally free of downsides. This approach offers several advantages, including the potential for long-lasting remission and reduced side effects compared to conventional drugs which are yet to be fully harnessed. This study aims at bringing together immunotherapeutic approaches that could be researched upon, and presented for clinical trials for the betterment of patients' lives.

History of Immunology

Immunology is the study of the immune system. Immunology has its origins in the study of how the body protects itself against infectious. It deals with the response of an organism to antigenic challenge and its differentiation of "self" from "non-self" (Köhl, 2006). It is concerned with immunity. Immunity describes a state of having sufficient biological defences against infection, disease, or other unwanted biological invasion. Humans have been interested in the concept of immunity for ages (Silverstein, 1989).

Thucydides, an Athenian, was probably the first to describe in writing, the concept of immunity. In 430 BC, he described that when a plague hits Athens, "the sick and the dying were tended by the pitying care of those who had recovered, because they knew the course of

the disease and were themselves free from apprehensions; for no one was ever attacked a second time, or not with a fatal result" (Gherardi, 2006).

The first clinical description of immunity is probably *Kitab fi al-jadari wa-al-hasbah* (*A Treatise on Smallpox and Measles*) written by the Islamic physician, Al-Razi, in the 9th century and translated in 1848 (Al-Razi, 2003). However, Louis Pasteur's Germ theory of disease – "many diseases are caused by the presence and actions of specific micro-organisms within the body" (Worboys, 2008) was the background that provided understanding of how bacteria caused disease and ability to resist further infections after a first exposure (Gherardi, 2006).

The concept of immunity from disease dates back at least to Greece in the 5th century BC. Thucydides noted that individuals who recovered from diseases which at that time was called plague became exempted from further assault. In 1774, Benjamin Jesty inoculated his wife with the vaccinia virus while in 1796, Edward Jenner inoculated James Phipps and both became exempted from future occurrence. Robert Koch and Louis Pasteur were instrumental to the establishment of the germ theory of disease. Metchnikoff discovered the place of *phagocytosis* in Immunity while Paul Ehrlich predicted the existence of antibodies and receptors (Greenberg, n.d.). The chemistry of antigen-antibody reactions and immunoglobulin molecule was uncovered in the 1950s. In 1986, *T helper subsets* were discovered. Later studies identified CD40 ligand on activated T-cell as a critically important molecule that provides co-stimulation to Bcells (Greenberg, n.d.).

Further discoveries about the human immune system, development of several vaccines and immunopharmacological disease management strategies continue to evolve. Understanding these historical milestones lays the foundation for the development of contemporary immunopharmacological agents aimed at modulating immune responses in disease

Immunomodulation

Immunomodulation describes the manipulation of the immune system by way of enhancement, suppression or induction of tolerance to achieve a desired effect. Immunomodulators are classified into:

Immunosuppressants

These are drugs that lower or inhibit immune response. They are usually employed in organ transplantation and autoimmune diseases (Rang et al., 2007). They include: Calcineurin inhibitors, antiproliferative and antimetabolite drugs, glucocorticoids and antibodies.

Immunostimulants

They activate and increase response of the immune system where necessary, for example, in infections, immunodeficiency and cancers. They include: Levamisole, Thalidomide, Bacillus Calmette Guerin and Recombinant Cytokines.

Tolerogens

Tolerogens induce tolerance and make the immune system non-responsive to antigen. Tolerance is the state of non-responsiveness of the immune system to antigen. Tolerogenic therapy aims to induce immune tolerance where there is pathological or undesirable activation of the normal immune response.

The approaches used to induce tolerance include: Costimulatory blockade, donor cell chimerism and soluble human leukocyte antigen. Specific antigens provided in a variety of forms have the ability to induce immunologic tolerance in preclinical models of diabetes, arthritis and multiple sclerosis.

Some Disease Conditions and Immunopharmacological Management Approaches

Hypertension

Hypertension (HTN) is one of the most common diseases that plagues mankind. It is diagnosed when the systolic and diastolic blood pressure is not below 140 and 90 mmHg respectively. It occurs in 25-43% of the world population and has been placed as the most viable killer disease (Rodriguez-Iturbe et al, 2001). The WHO reports in 2002 that high blood pressure (HBP) is ranked the third factor for disability-adjusted life years. HTN is a risk factor for cardiovascular disease and stroke which is the leading killer disease accounting for about 10 million deaths annually (WHO, 2023). HBP has been a menace for decades if not centuries, yet efforts to contain it, though highly supportive, have not brought complete hope to humans. The role of immune system in the genesis of HTN has been firmly established by investigations from around the world (Rodriguez-Iturbe et al., 2001; Harrison et al., 2011).

Transposition of lymphocytes from rats with unilateral renal infarction caused HTN in recipient rats (Okuda and Gruman, 1967). A study showed reduced blood pressure when the immune system of rats that had partial renal infarction was suppressed (White and Grollman, 1964). Blood pressure normalized when thymus gland of hypertensive mice was removed (Svendsen, 1976).

B lymphocytes are also involved in HTN. Angiotensin (Ang) type I receptor (AT1R) antibodies are found in humans suffering from secondary malignant HTN (Fu et al., 2000). Malignant HTN is a medical emergency. It is defined by extreme HBP that develops rapidly, capable of causing organ damage. Malignant hypertension describes a person whose blood pressure is higher than 180/120 and with multiple complications, e.g., renal allograft rejection (Dragun et al., 2005). Depletion of B cells attenuates blood pressure increase caused by Ang II infusion. Kriska et al (2012) found that mice lacking 12/15 lipoxygenase are markedly resistant to HTN caused by nitro L-arginine methyl ester (L-NAME). And on adoptive transfer of wild-type macrophages to these animals, hypertensive response to L-NAME was restored.

Mice lacking T and B cells developed blunted HTN but hypertensive response and vascular dysfunction observed in WT mice were restored by adoptive transfer of T cells (Rodriguez-Iturbe et al., 2001; Vinh et al., 2010).

Mycophenolate mofetil lowers blood pressure in Dahl salt-sensitive rats (Tian, 2007) and in rats with lead induced HTN (Bravo, 2007). Mycophenolate mofetil has been shown to reduce blood pressure in humans with psoriasis and rheumatoid arthritis (Herrera et al., 2006). This is significant since Neimann et al. (2006) wrote that HTN is common in rheumatoid arthritis and severe psoriasis respectively. Decrease in leakage of T cells into the kidney in various hypertensive models have lowered blood pressure (Nava et al., 2003). Incidence of HTN in AIDS patients (with reduced CD4 cells) was reported to be markedly lower than is seen in non-infected population and administration of highly active antiretroviral therapy for 2 years increased rate of HTN incidence to the rate found in the control population (Seaberg et al., 2005). This collaborates previous work done to show the role of CD4+ cells in HTN (Dzielak, 1992).

Virtually all cell types that are involved in immunity have been implicated in HTN. Norlander et al. (2018) showed that mice lacking the recombination-activating gene, which doesn't have both T and B cells, develop blunted HTN with preserved vascular endothelial function at the challenge with Ang II or DOCA and salt. Abatacept and mycophenolate mofetil are T-cell modulating agents. Epelerone, a mineralocorticoid receptor antagonist, prevented IFN-γ production by CD8+ T cells in HTN (McCurley et al., 2012). Etanercept, a Tumour necrotic

factor (TNF) - α antagonist was shown to prevent HTN and reduce renal injury in experimental animals (Guzik et al., 2007). In fact, each cell type discussed is a potential target for future therapy.

These drugs could be used in essential HTN, HTN unresponsive to circular drugs and in patients with aggressive end organ damage (Norlander et al., 2017). They can also be used in newly diagnosed cases or severe HTN and particularly malignant HTN. Short term treatment with immunomodulating drugs in emergency situations and briefly afterwards may prove useful.

Diabetes

Diabetes is a metabolic disorder marked by impaired ability to produce or respond to insulin and maintain normal glucose levels. Two types are common - Type 1 and Type II diabetes. Type 1 diabetes is an autoimmune disease. Here, the immune system attacks insulin-producing beta cells in the pancreas until the pancreas is incapable of producing insulin. Insulin injection becomes necessary to compensate for the death of the beta cells. Type 1 diabetes patients therefore depend on insulin for survival. In type 2, the amount of insulin produced by the pancreas is not sufficient to meet the body's needs, or the body cells are resistant to it. The body compensates by producing more insulin. Over time, this becomes burdensome on the beta cells and could lead to their destruction (diabetes.co.uk, the global diabetes community, 2019). Type II is the most prevalent form of the disease and since obesity which is a risk factor has become a worldwide epidemic, its prevalence has increased (American Diabetes Association, 2003; Meddah et al., 2009). Four hundred and fifteen million people are reported diabetic (International Diabetes Federation, 2015) and it is predicted to increase to 642m people in 2040. This poses a threat to homosapiens (Tiwari, 2015). Some factors are known to be implicated in the development of diabetes. The aetiology is unclear but it is thought to be caused by a combination of genetic and environmental/lifestyle factors. In Type 1, a virus might set off the immune system attack.

Attention is also being directed to the immune system as being involved in the pathogenesis of this disease condition (Pollack et al., 2016). Researchers have pinned inflammation as central to the pathology of Type 1 disease. Type 2 diabetes have more recently been linked to inflammation too. If chronic inflammation is implicated in the pathophysiology of type 2 diabetes (Hotamisligil et al., 1993; Maedler et al., 2002), then use of drugs that target inflammation and immune system may ameliorate diabetes, and prevent disease progression and the usual complications that ensue later in the process of time.

Inflammation markers are shown to be involved in diabetes (Tooley et al., 2012; Vogel et al., 2017; Wahid et al., 2018). During prediabetic phase, effector T cells target B cells (Tooley et al., 2012). By the time 70 to 90 % of total B cell mass is lost, clinical presentation ensues (Tooley et al., 2012). In type 1 diabetes, there is cell-mediated autoimmune destruction of the pancreatic cells leading to complete or almost complete insulin deficiency, usually caused by autoimmunity. Rate of B cell destruction is higher in children than in adults (American Diabetes Association, 2010).

Inflammation has been tagged central to the pathology of the pancreatic islet in type 1 diabetes. Growing evidence also suggests that inflammation is involved in type 2 diabetes. Since both type 1 and type 2 diabetes has been linked to immune cells and inflammation, targeting host immune system may ameliorate diabetes, prevent its progression, thereby forestalling vascular complications (Pollack et al., 2016).

The following drugs that target the immune system have hyperglycaemia effect:

Salsalate

It is a non-acetylated salicylate, a prodrug of salicylate with better pharmacokinetics. Independent clinical trials have demonstrated that salsalate improves glycaemia, inflammatory parameters, insulin sensitivity (Goldfine et al., 2008; Goldfine et al., 2010) and reduces insulin clearance. Diabetic patients recorded reduced fasting and post challenge glucose levels after 2 weeks of treatment with high (4.5 g/d) and standard (3.0 g/d) doses of salsalate. This result supports targeting of inflammation and NF-kappaB as a therapeutic approach in type 2 diabetes (Goldfine et al., 2008). Studies show that it is well tolerated though there is a small increase in LDL cholesterol level and a reversible increase in urinary albumin secretion (Pollack et al., 2016). There's need for further studies to ascertain its long-term safety.

Anti-TNF-α

TNF- α is involved in type 2 diabetes (Hotamisligil et al., 1993). TNF- α is a proinflammatory cytokine; therefore, it is expected that antagonism of TNF- α will enhance at least the quality of life of diabetes patients. Some studies did not corroborate this hypothesis (Dominguez et al., 2005); while some showed improved glycaemia and reduced risk for developing diabetes when TNF- α antagonists are administered to non-diabetic subjects with inflammatory diseases (Pollack et al., 2016). Well-designed clinical studies on TNF antagonism in type 2 diabetes patients will address the uncertainty around TNF- α antagonism.

Anti-IL 1B

Interleukin *1 beta* (*IL*-1β) is a cytokine protein that is encoded by the *IL1B* gene in humans. It is a pro-inflammatory cytokine that is highly involved in host immune response and resistance (Dinarello, 1996). It plays a central role in the pathogenesis of type 2 diabetes (Banerjee and Saxena, 2014). Studies reveal that IL-1B-receptor antagonist (anakinra) and IL-1B- specific antibodies (devokizumab, canakizumab and LY21891020) have beneficial effects on metabolic parameters including decreased HbA1c and enhanced insulin sensitivity (Cavelti-Weder et al., 2012; Sloan-Lancaster et al., 2013). Anakinra produced a sustained decrease in HbA1c, C-reactive protein (CRP), IL-6 levels, proinsulin to insulin ratio, while enhancing C-peptide secretion. This indicates improved B-cell function (Larsen et al., 2009). Anakinra was well tolerated though there is need for daily injection. Humanized IL-1B antibodies make room for monthly injections hence minimising the previous concerns of daily need for injection.

Diacerein

Diacerein has anti-inflammatory, anti-catabolic and pro-anabolic effects on cartilage and synovial membrane. It is used in osteoarthritis. (Pavelka et al., 2016). It decreases levels of IL-1B through an unknown mechanism. Diacerein administration improved insulin secretion and HbA1c levels while reducing IL-1B and TNF- α levels (Ramos-Zavala et al., 2011) in drug naïve patients with type 2 diabetes.

Chloroquine/hydroxychloroquine

Apart from their function as antimalarial, these drugs have anti-inflammatory effects. The anti-inflammatory effect come from increased expression of p21, inhibition of T cell and IFN-γ-producing Th1 cells (Oh et al., 2016). They reduce incidence of diabetes (Chen et al., 2015). Chloroquine increases insulin levels in humans by increasing insulin secretion and inhibiting its degradation (Tiwari, 2015). Hydroxychloroquine inhibited insulin degradation in rat hepatocytes (Emami et al., 1999) and lowered HbA1c and LDL cholesterol levels in with type 2 diabetic patients (Quatraro et al., 1990; Shojania et al., 1999).

CTLA4-Ig

Abatacept (CTLA4-Ig) binds CD80 and CD86 preventing their interaction with CD28 and hence inhibiting co-stimulation and T cell activation. Treatment of non-obese diabetic (NOD) mice with human CTLA4-Ig was effective in preventing loss of islet grafts (Londrigan et al., 2010). Treatment of patients with monthly injections of abatacept for 2 years resulted in 59% higher C-peptide response and decreased glycosylated haemoglobin levels, but these were not sustained. It has a favourable safety profile. This is a good approach for future combination therapies.

Since progression of diabetes has been linked to inflammation/immune involvement, more detailed and sustained researches and trials to find immunomodulatory drugs that can reduce progression of disease, obliterate or at least delay the complications seen in diabetes should be encouraged.

Cancer

Cells are the basic units of the human body. Cells grow and divide to make new cells as the need arises. Cells die when they get too old or damaged with new ones replacing them. Cancer begins when there is an interference of this orderly process; cells grow uncontrollably and may form a mass (tumour). A cancerous tumour is malignant while a benign tumour can grow but will not spread. Cancer has been ranked the second major cause of death in the United States (Siegel et al., 2015). Cytotoxic T lymphocytes, NK cells, macrophages and dendritic cells have the ability to kill tumour cells. Under normal conditions, the activity of these cells should inhibit proliferation and differentiation of tumour cells (Kozlov, 2016). The immune system protects and defends the body. It is a collection of reactions that the body makes in response to damaged cells or infection (Candeias and Gaipl, 2016). The immune system is pivotal in the maintenance of the integrity of an organism. Besides the protection against pathogens, it is strongly involved in cancer prevention, development and defence (Candeias and Gaipl, 2016). Avoiding immune detection and elimination is the hallmark of cancer (Hanahan and Weinberg, 2011).

During the early stages of tumour development, innate and adaptive immunity work together to recognize and eliminate the more immunogenic cancer cells (Teng et al., 2015), long before they become clinically apparent. This first phase is called elimination phase.

Tumour cell variants that were not destroyed in the first phase enters into the next phase: equilibrium phase, where their outgrowth is prevented by immunologic mechanisms. Those that finally dodge immune recognition and destruction, progress from the equilibrium to the escape phase, where they become clinically apparent. Tumours escape due to changes in their response to immunoselection pressures, increased tumour-induced immunosuppression or immune system deterioration (Schreiber et al., 2011).

Over the past two decades, these three mechanisms of tumour escape have been the subjects of intense investigation, with the aim of developing new cancer immunotherapies (Dunn et al., 2004; Vesely et al., 2011).

Some anticancer drugs with immunomodulatory effects:

Thalidomide and its Derivatives

These are mostly used in multiple myeloma since it has direct tumouricidal effects on myeloma cells via cell cycle arrest and anti-angiogenic properties (Moreau, 2017; Pan and Lentzsch, 2012). Subsequent research showed that it also has immunological effects (Zeldis et al., 2011). Thalidomide, over the years, has become a highly effective therapy for treating leprosy and

multiple myeloma. Several mechanisms have been proposed to explain the anticancer effects of thalidomide, including antiangiogenic and immunomodulatory activities (Zhang et al., 2005). At present, evidence suggests that thalidomide may induce vessel maturation (Wang et al., 2016). Lenalidomide, a derivative of thalidomide, can suppress residual myeloma cells. FDA has approved it for maintenance therapy of post-transplant myeloma patients.

Anthracyclines

These drugs beyond their already known mechanism of action have been reported to induce immunomodulatory effects on various cancer cells by enhancing the cell surface expression of calreticulin and the subsequent release of high mobility group box1 (HMGB1), ATP, through CD91, Toll-like receptor 4 and P2X purinoreceptor 7, respectively and take up cancer cell (Hodge et al., 2013). Multiple mechanisms have also been proposed for the cytostatic and cytotoxic actions of anthracyclines, including free radical formation, lipid peroxidation, and direct membrane effects (Szuławska and Czyz, 2006)). Doxorubicin or mitoxantrone showed cancer regression in mouse immunization experiments (Fucikova et al., 2016), through CRT expression which is important for a good prognosis and HMGBI secretion (Lu et al., 2015). Some others elicit their immunomodulating actions through immunogenic cell death. Such drugs can be used in combination with other cancer drugs.

Hypomethylating Agents

These are analogues of pyrimidine nucleosides (which are incorporated into RNA or DNA) and they impair DNA methylation by inhibiting DNA methyl transferase (Schroeder et al., 2018). It also enhances expression of cancer-specific antigens and MHC molecules, hence predisposing cancer cells to death by cytotoxic T lymphocytes' action. Azacitidine or decitabine have been approved for treatment of myelodysplastic syndromes and acute myeloid leukaemia (Matsushita et al., 2014).

Monoclonal Antibodies

Monoclonal antibodies (mAbs) can target molecules on the T-cell surface and mediate tumour regression (Khalil et al., 2015). Under immunomodulatory mAb therapy, we have Immune checkpoint blockade (CTLA-4, PD-1 axis) and T-cell co-stimulation (T-cell antigen 4-1BB homologue Ox 40), CD19-targeted CAR-T-cell therapy).

Immune Checkpoint Blockade

Immune checkpoints are molecules that induce or inhibit T-cell activation (Wieder et al., 2018). Checkpoint inhibitor therapy is a form of cancer immunotherapy that targets key regulators of the immune system, which tumours can use to protect themselves from attacks by the immune system.

CTLA-4

CTLA-4 is crucial for regulatory T (Tregs) cell to exert maximal immune-suppressive function (Read et al., 2005). Inhibition of CTLA-4 signalling provides immune therapy that significantly improves the survival of patients with metastatic solid cancers (Wieder et al., 2018). At the immunological synapse, T cells acquire effector function with an antigen-presenting cell (APC). T-cell receptor first recognizes an antigen peptide presented in the context of an MHC molecule on the surface of an APC. Secondly, T-cell receptor CD28 binds with CD80 or CD86 on the APC. Then the T-cell inhibitory CTLA-4 receptor is moved to the cell surface to bind CD80 or CD 86 more strongly (Walunas et al., 1994; Krummel et al., 1995). In a study, some patients were given Ipilimumab alone, gp100 peptide vaccine alone while others were given both. Overall survival of patients in the ipilimumab group was better than those in the peptide

vaccine group, while there were no additional advantages observed in the combination group. Results were sustained even after treatment with ipilimumab had ended (Hodi et al., 2010). Since these drugs do not target the tumour itself but modify patients' immune system to control tumour progression even after withdrawal of such drugs, it therefore implies that when once immune-checkpoint blockade is successful, immune response is sustained, and drug administration can cease (Khalil et al., 2015). Ipilimumab was approved by the Food and Drug Administration (FDA) of the US for the treatment of metastatic melanoma in 2011 (Khalil et al., 2015), though combination of ipilimumab with other therapeutic options may spread its wings of approval for management of other tumour types.

PD-1 Axis

This is another inhibitory receptor expressed on the surface of APC and malignant cells when they are primed. PD-1 ligation inhibits signalling downstream of the TCR (Chemnitz et al., 2004; Parry et al., 2005) and also it ligates to CD 80 expressed on T cells as another mechanism of T-cell suppression. PD-1 ligands present within tumours can cause T-cell suppression and intratumural PD-L1 expression and this cause's poor prognosis in some tumour types such as lung, ovarian/colon cancer etc. Two anti-PD-1 mAbs, pembrolizumab and nivolumab were administered for clinical trials. Forty percent of the patients responded positively. This value is encouraging when compared to 12% got with ipilimumab monotherapy (Robert et al., 2015). Nivolumab therefore was approved in 2015 for squamous-cell lung cancer that is refractory to platinum-based therapy (Brahmer et al., 2015). Now, it is also used to treat patients with other types of advanced-stage non-small cell lung cancer while pembrolizumab is used in patients with PD-L1- positive non-small-cell lung cancer (NSCLC) (U.S. Food and Drug Administation, 2015).

T-Cell Co-Stimulation

T-Cell Antigen 4-1BB Homologue (4-1BB)

4-1BB is expressed on T cells, natural killer cells and monocytes (Bartkowiak and Curran, 2015). Engagement of 4-1BB by its ligand or an agonistic antibody promotes T cell proliferation, cytokine production and cytolytic effector functions and protects lymphocytes from programmed cell death (Wallach and Kang, 2018). Stimulation of T cells by 4-1BBL, a cognate ligand expressed on dendritic cells, results in proliferation and upregulation of the anti-apoptotic proteins, Bcl-2-like protein 1 (Bcl-XL) and Bcl-2-related protein (Bfl1) (Lee, 2002). These proteins protect T cells from activation-induced cell death (Shuford et al., 1997). Curran et al (2011) showed that 4-1BB activation with CTLA-4 blockade enhances tumour rejection by increasing T cell infiltration, proliferation and cytokine production.

Glucocorticoid-Induced TNFR-Related Protein (GITR)

This is another co-stimulatory receptor which is expressed by TREG cells (Schaer, Cohen and Wolchok, 2010). Its activation augments T cell proliferation, cytokine production and resistance to T_{REG}-cell mediated suppression (Valzasina et al., 2005; Ronchetti et al., 2007). It has been established that anti-GITR agonist mAbs induced melanoma tumour immunity in mice by altering regulatory T-cell stability and intra-tumour accumulation (Cohen et al., 2010). G1TR ligation was found to disrupt T_{REG}-cell lineage stability and impart T-effector function (Schaer et al., 2013). Clinical trials of many anti-G1TR antibodies both in monotherapy and in combination with PD1 and CTLA-4 antibodies are ongoing.

CD40

The ligand for CD40, CD40Lis expressed by CD4+Tcells. This ligand enables APC to activate T cells. After ligation, dendritic cells upregulate MHC class II and secrete proinflammatory cytokines, such as IL-12. CD40 is important for immunoglobulin class switching (Kawabe et al., 1994) on B cells. MAbs whose effect is on CD40 expressed on tumour cells, have been developed (Burington et al., 2011).

OX40

OX40 ligand, OX40L is expressed on immune cells (Baumann et al., 2004). OX40 engagement on T cells promotes proliferation, survival and secretion of cytokines associated with type 1 and type 2 T helper cell responses (Arestides et al., 2002). Ligation of OX40 exerts antitumour activity and confers immunological memory manifested as resistance to tumour rechallenge (Pan et al., 2002) in preclinical models. A phase 1 trial (Curti et al., 2013) result showed that mAb targeting OX40 given as monotherapy has antitumour activity in patients with melanoma or RCC.

CD19-Targeted CAR-T-Cell Therapy

CAR T cell therapy has so much focused on targeting CD19 since this antigen is well expressed on B cells but not on haematopoietic stem cells, thus its potential for "on target-off tumour" toxicity is limited. CD19 targeted CAR T cells are used to treat diseases from B-cell acute lymphoblastic leukaemia, chronic lymphocytic leukaemia and non-hodgkin lymphomas.

Checkpoint Blockade plus Co-Stimulation

This is an appealing anti-tumour approach. Such researches are ongoing and may bring us great advancement in cancer immunotherapy. An example is:

CAR-T-Cell Therapy

Chimeric antigen receptor T cells are genetically engineered to produce artificial T-cell receptors for use in immunotherapy. They are engineered to give T cells the new ability to target a specific protein. Here, T cells are taken from a patient's blood and changed in the laboratory so they will attack cancer cells. Then the gene for chimeric antigen receptor (CAR) that binds to a certain protein on the patient's cancer cells is added. The special receptor is called a chimeric antigen receptor (CAR) (Lee et al., 2015; Turtle et al., 2015). Large numbers of the CAR T cells are grown in the laboratory and given to the patient by infusion. CAR T-cell therapy is being studied in the treatment of some types of cancer. The mechanism of action is by selection and expression of tumour-infiltrating lymphocytes or through gene transfer of a synthetic TCR or a chimeric antigen receptor into cells.

CD19-Targeted CAR-T-Cell Therapy

CAR T cell therapy has so much focused on targeting CD19 since this antigen is well expressed on B cells but not on haematopoietic stem cells, thus it's potential for "on target-off tumour" toxicity is limited. CD19 targeted CAR T cells are used to treat diseases from B-cell acute lymphoblastic leukaemia, chronic lymphocytic leukaemia and non-hodgkin lymphomas. For B-cell acute lymphoblastic leukaemia, high overall response rates, complete remission rates, minimal residual disease negativity and comparable toxicity have been reported (Lee et al., 2015; Turtle et al., 2015). The use of CAR T cell therapy in patients with chronic lymphocytic leukaemia showed modest results though not as efficacious as CAR T cell use for B-ALL patients (Park et al., 2012) while for non-Hodgkin lymphoma, the use of cyclophosphamide-conditioning therapy before CART cells achieved a complete response in more than 50% of

patients. Administration of CAR T cell without the conditioning therapy did not show any sustained remission (Kochenderfer et al., 2014).

In conclusion, treatment of cancer started with chemotherapy in the 1940s. It attacks all rapidly dividing cells that it can locate within the body and effectively kills the cells, whether cancerous or not. Attack on healthy cells therefore causes some of the notorious side effects.

Immunotherapy is not without drawbacks. It can cause the immune system to attack organs of the body, desired effect takes longer time than chemotherapy to achieve, there could be increased infection risk following immunosuppression and or cytokine storm due to overstimulation of immune system. Moreover, immune system may become overactive resulting in side effects ranging from minor inflammations to major conditions like autoimmune disorders and just like chemotherapy, resistance could develop.

Effects with chemotherapy lasts as long as the drug remains in the body but immunotherapy can provide long-term protection against cancer and since it takes advantage of one's own immune system to recognise and remember cancer cells, it has the potential to effectively treat all cancer types. This factor alone makes immunotherapy a potentially universal answer to cancer. The induction of immunologic memory is an added advantage. More research on immunotherapy is recommended to make it applicable to all tumour types (McClurkey, 2016).

CONCLUSION AND RECOMMENDATIONS

Conclusion

Several diseases plague the Homo sapiens specie, especially, as they advance in age. Some diseases are becoming resistant to long-standing therapeutic approaches. The role of the immune system in the pathogenesis of many diseases has now been established. The review provides a new understanding of these diseases, offering great insight on other approaches that could be harnessed in the fight for freedom from the clutches of these deadly diseases.

Recommendations

Each cell type involved in immune response is a potential target for future therapy to complement currently used therapeutic agents. Further investigations utilising well-designed and statistically powered clinical studies should be considered since most of the immunomodulators reviewed need a better and detailed study for distinct safety profile and mechanism of action.

When these remarkable results observed in clinical trials are translated into clinical practice, the once dreaded diseases will lose their grip of fear on patients.

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