

Licensed monoclonal antibodies and associated challenges

Amjad Hayat Khan and Esmaeil Sadroddiny*

Department of Medical Biotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, International Campus (TUMS-IC), Tehran, Iran

Abstract.

Monoclonal antibodies (mAbs) are the leading class of targeted therapeutics and remarkably effective in addressing autoimmune diseases, inflammations, infections, and various types of cancer. Several mAbs approved by US food and drug administration (FDA), are available on the market and a number are pending for approval. Luckily, FDA approved mAbs have played a pivotal role in the treatment and prevention of lethal diseases. However, claiming that licensed mAbs are 100% safe is still debatable, because infections, malignancies, anaphylactoid, and anaphylactic reactions are the more frequently associated adverse events. To evaluate benefit to risk ratio of mAbs, it is important for the clinical research staff or physicians to monitor and follow-up the patients who are receiving mAbs doses. It is recommended that patients, physicians, biopharmaceutical companies, and researchers should keep in touch to highlight and resolve antibody-based adverse events. In this review we underscore the associated challenges of mAbs, approved by FDA from 2007–2014.

Keywords: FDA approved mAbs, adverse events of mAbs, antibody-based therapeutics, safety and risks of mAbs, licensed mAbs and associated challenges

1. Introduction

Kohler and Milstein have inaugurated monoclonal antibodies (mAbs) production technology with their seminal work on hybridoma [1]. Further advancement in the field of genomics and proteomics enabled the researchers to develop mouse, chimeric, humanized, and ultimately fully human mAbs. Variable regions of chimeric and complementarity determining regions (CDRs) of humanized mAbs are derived from murine origin. On the other hand, fully human mAbs are derived purely from human sequences. International non-proprietary (INN) names of mAbs ends with suffixes -ximab, -zumab, and -mumab respectively. Table 1 enlist some of the mAbs approved by US food and drug administration (FDA) from 2007–2014.

Target specificity and low toxicity have made mAbs fast and growing class of therapeutics and preventive agents. Amino acid sequences of mAbs have been tailored to reduce the antigenicity and enhance the specificity and functionality. Majority of the mAbs available on the market of US and Europe have been produced in murine myeloma cell lines (e.g. SP2/0, NS0), Chinese hamster ovary (CHO) cells, phage display, and *E. coli* cells [2]. Unfortunately, mAbs derived from mammalian cell lines are expensive, which is the remaining foremost obstacle in the development of new biopharmaceuticals. However, fragment antibodies such as scFv, Fab, and diabodies have been easily produced in yeast, phage display, and *E. coli* at reduced cost [3]. Luckily, antibody-based therapeutics, including, conjugated antibodies, intact antibodies and fragment antibodies have also been licensed for marketing [4].

Mechanism of action of mAbs include, antigen crosslinking, activation of apoptosis, and blockade of ligand-receptors interaction or signalling pathways (Fig. 1). Several mAbs, for instance, eculizumab,

*Corresponding author: Esmaeil Sadroddiny, Department of Medical Biotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, No 88 Italia st., Tehran, Iran. PO Box. 1417755469, Tel.: +98 21 88991118 24; Fax: +98 21 88991117; E-mail: sadroddiny@sina.tums.ac.ir.

Table 1
Monoclonal antibodies approved by FDA from 2007–2014 for various diseases

Antibody name	Target	Format	Drug class	Company	Indication	Year
Stelara (Ustekinumab)	IL-12/-23	Human	Immune-suppressant	Janssen Cilag	– Plaque psoriasis	2009
Simponi (Golimumab)	TNF- α	Human	Immune-suppressant	Centocor Ortho Biotech	– RA – Psoriatic arthritis – Ankylosing spondylitis	2009
Cimzia (Certolizumab pegol)	TNF- α	Humanized Fab fragment	Immune-suppressant	UCB	– Crohn's disease – Active RA	2008
Benlysta (Belimumab)	BLyS	Human	Immune-suppressant	GSK/Human Genome Sciences	– SLE	2011
ABthrax (Raxibacumab)	PA of <i>B. anthracis</i>	Human	Anti-infection	GSK	– Inhalational anthrax	2012
Arzerra (Ofatumumab)	CD20	Human	Anti-cancer	Genmab/GSK	– CLL – MS – RA	2009
Yervoy (Ipilimumab)	CTLA4	Human	Anti-cancer	Bristol-Myers Squibb	– Metastatic melanoma	2011
Gazyva TM (Obinutuzumab)	CD20	Humanized	Anti-cancer	Genentech	– LLC	2013
Perjeta (Pertuzumab)	HER2	Humanized	Anti-cancer	Genentech	– HER2 ⁺ breast cancer	2012
Adcetris (Brentuximab vedotin)	CD30	Chimera	Anti-cancer	Seattle Genetics	– Hodgkin's lymphoma (HL)	2011
Kadcyla (Ado-Trastuzumab emtansine)	HER2 ⁺	Humanized	Anti-cancer	Genentech/Roche	– Breast cancer	2013
Soliris (Eculizumab)	C5 complement protein	Humanized	Blood disorders	Alexion	– Paroxysmal nocturnal haemoglobinuria	2007
Ilaris (Canakinumab)	IL-1 β	Human	Anti-inflammatory	Novartis	– Gout	2009
Prolia (Denosumab)	RANK ligand	Human	Anti-bone loss	Amgen	– Osteoporosis	2010

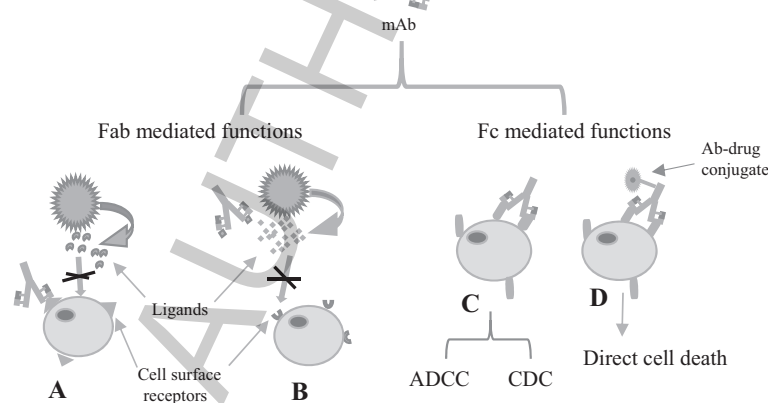


Fig. 1. Mechanism of action of monoclonal antibodies (mAbs). A and B; Fab portion of the mAb binds the ligand and/or receptors thus blocking the receptor-ligand interaction, and inhibit signaling pathways. C; Immune mediated responses e.g. ADCC and CDC. D: direct cell death by the release of drug after internalization by the target cell (apoptosis).

denosumab, and ustekinumab are involved in antagonism by targeting the ligands, cell surface receptors, thereby, inhibiting signalling pathways [5]. Such functions are performed by the Fab portion and independent of the Fc portion of the antibody. Likewise, mAbs;

such as, ofatumumab, ado-trastuzumab emtansine, and obinutuzumab have the potentiality to elicit immune-mediated effector functions, for example, antibody dependent cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), or antibody dependent phagocyto-

sis [6]. Luckily, now antibodies have also been used as a vehicles for carrying effector moieties; such as, enzymes, toxins, radionuclides, cytokines or even DNA molecules to the target cells. Antibody portion of the antibody drug conjugates (ADCs), track and bind to the respective tumor antigen, the cell internalize and degrade the conjugated antibody inside the lysosomes or endosomes. Consequently, releasing the attached potent drug which cause death of the cell [7]. For example, brentuximab vedotin antibody conjugated to an antitubulin agent, monomethyl auristatin E (MMAE), targets the CD-30 surface antigen of leukemic cells is an example of ADCs. MMAE impedes cell division by interfering the formation of tubulin [8]. Further research is needed to diversify the structure of mAbs and bring more efficient and inexpensive with no or less adverse events mAbs-based therapeutics to the market. This review aims to discuss and report the challenges observed in patients who were receiving mAbs during clinical trials, approved by FDA from 2007–2014.

2. Adverse events related with licensed mAbs

2.1. Autoimmune diseases

Immune system has the potentiality to differentiate between self and non-self proteins and ensure host protection. Occasionally, the immune system loses its ability to differentiate between friends from foe, leading to autoimmune diseases. The ultimate results of autoimmune diseases is the malfunctioning of tissues or organs, could lead to further severe debilitation or even death. Genetics, age, gender, reproductive status, hormones, diet, environmental factors, and pathogens (bacteria, viruses and parasites) all are assumed to be responsible for autoimmune diseases [9]. For instance, plaque psoriasis is an autoimmune disease of the skin. Signs and symptoms include; redness of the skin, irritation, and appearance of silver white patches on scalp, knees, elbows, and lower back. Interleukin 12 and 23 (IL-12/23) are involved in the immuno-pathophysiology of psoriasis. In January 2009, ustekinumab (Stelara; Janssen Cilag), a human anti-interleukin-12/23 mAb was approved by the European Commission for the treatment of plaque psoriasis. It binds to the shared, p40 subunit of the IL-12/23 with high affinity. In clinical trials it was observed that 45 mg and 90 mg dose of ustekinumab after every 12 weeks, significantly reduced signs and symptoms of psoriasis, and skin lesions. More than 90% pa-

tients who were receiving the antibody, revealed excellent results. Nevertheless, injection site reactions were observed both in placebo and patients receiving ustekinumab, suggesting that it has no significant link with the antibody dose. Moreover, glucose abnormalities, malignancies, serious infections, and heart attack were also observed, yet, further studies have been suggested to find their relationship with ustekinumab [10]. Small portion of the patients developed anti-ustekinumab antibodies. Similarly, the incidence of hyperglycaemia, mild to severe adverse events; for instance, infections and malignancies were also observed in small and large population studies. However, statistical data suggested that the adverse events were insignificant and were not associated with ustekinumab treatment. No evidence of cardiovascular diseases and infection i.e. mycobacterium and salmonella were reported. Results of double blind-placebo-controlled trail, (PHOENIX 1 and 2) conducted for one and half years, have revealed that there is no major adverse events associated with the ustekinumab therapy [11,12]. However, it is clear from studies that IL-12/23 produced by antigen presenting cells i.e. Langerhans cells of the skin, play an important role in the activation of naïve and memory CD4⁺ T-cells, and natural killer cells, thus, promoting cellular immunity [13]. Indeed, IL-12/23 provide resistance to a wide range of pathogens and protection against tumors [14,15].

Similarly, golimumab (Simponi; Centocor Ortho Biotech), an anti-tumor necrosis factor- α (TNF- α), fully human mAb was approved by FDA in April 2009, for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis [16]. RA, ankylosing spondylitis, and PsA target joints, are chronic autoimmune inflammatory diseases, occurring due to the overproduction of TNF- α . It was demonstrated that subcutaneously administered golimumab at a dosage of 50 mg or 100 mg with methotrexate (MTX) after four weeks interval, significantly reduced signs and symptoms of RA in MTX-naïve patients [17]. Other studies have also revealed that golimumab is effective for addressing PsA and ankylosing spondylitis [18,19]. Assessment of the efficacy and safety profile of golimumab showed that it is safe and effectual; however, mild injection site reactions were observed in small population. Moreover, basal cell malignancy and prostate cancer were also reported in some patients, receiving 100 mg dose. Anti-golimumab antibodies were also observed rarely in small population. Moreover, mild to severe but asymptomatic-rise in the level of transaminase was more common. Interestingly,

transaminase level aberrations were observed more frequently only in patients who previously received isoniazid for latent tuberculosis, demonstrating no relation with golimumab [17,18]. Moreover, the incidence of serious adverse events and infections was low in all groups. Yet, in 100 mg golimumab with MTX group, the frequency of infection was more than other treatment groups [17]. Furthermore, the incidence of mild nausea and pneumonia was more in treatment group than placebo, yet, it did not lead to discontinuation of the golimumab. Unfortunately, small population studies precluded the interpretation of data properly [20]. Although no unexpected golimumab-related concerns were observed in clinical studies, conducted for one and half years. Conversely, TNF- α , an important cytokine play a critical role in coordinating various arms of the immune system along with providing resistance to a variety of infectious pathogens [21]. Blockade of TNF- α with golimumab in long term treatment would make the patients susceptible to infections and other complications.

Another TNF- α antagonist, certolizumab pegol (Cimzia; UCB), a pegylated humanized Fab' fragment mAb was approved by FDA in April, 2008 for the treatment of Crohn's disease [22]. Unlike other mAbs, certolizumab pegol has no Fc region, precluding the induction of CDC and ADCC. Certolizumab pegol at a dosage of 200 mg or 400 mg with MTX significantly reduced the signs and symptoms of RA [23]. Studies have confirmed that certolizumab pegol is more effective and efficient than the infliximab [24]. Safety assessment have revealed that like other anti-TNF- α blocking agents, the chance of serious adverse events like TB, fungal and opportunistic infections, and bacterial sepsis do exist. However, the incidence of TB was more in patients who were suffering from latent TB, therefore, it is recommended to perform TB test before taking certolizumab pegol. During clinical studies serious infections, cancer, and injection site reactions were seen in low rates [22,23]. Indeed, PEGylation has significantly improved the circulating half-life along with reducing the immunogenicity of certolizumab pegol, resulting in minimizing the adverse events [25]. Certolizumab pegol is more advantageous, efficient and less immunogenic than the full length mAbs bearing Fc region, inducing cytotoxicity.

Systemic lupus erythematosus (SLE), an organ specific autoimmune disease, mostly affect heart, joints, skin, brain, lungs, liver, kidneys, blood vessels, and nervous system. B-cell differentiate into antibodies producing cells, regulating immune system. Currently

it has been demonstrated that B-cells hyperactivity is involved in the pathogenesis of SLE [26]. B-lymphocyte stimulator (BLyS) also known as B-cell activating factor, responsible for the survival and selection of B-cells, is an ideal target for addressing SLE. Belimumab (Benlysta; Human Genome Sciences/ GSK), BLyS antagonist mAb was licensed in March 2011, for the treatment of SLE [27]. Clinical studies reported a significant depletion of BLyS bearing B-cells without worsening the overall conditions of the patients [28]. The rates of serious adverse events reported in clinical trials were approximately same in all groups with slight variations, yet, differences were insignificant. In belimumab group, more frequently reported adverse events included, nausea, diarrhea, and upper respiratory tract infections (URTI). Infusion reactions and hypersensitivity were more frequently observed during first or second infusion [29]. Infections and malignancies especially, non-Hodgkin's lymphoma, cervical cancer, lung cancer, bronchial carcinoma, and hepatobiliary cancer have also been shown to be associated with immunosuppression in SLE [30,31]. The level of IgG and IgM slipped down below normal in patients, receiving belimumab. Although opportunistic infections were rare, but still, infection followed by cardiovascular disease was the main cause of death. Furthermore, spontaneous abortion was observed but there was no pattern of malignancy [29,32]. Indeed, immune system keep the body healthy and strong by combating with the invading microbes. Nevertheless, in case of addressing autoimmune diseases, immune system is suppressed showing no evidence of serious adverse events in short term. However, in long term immunosuppression might lead to severe infections, malignancies, or other complications.

2.2. Anti-infective

Every moment in our life, we are exposed to a number of microbes, such as, viruses, bacteria, fungi and protozoa. Usually when innate and adaptive immune arms fail to combat the invading microbes then antibiotics, antiviral and antifungal drugs are used. Occasionally, despite of the existing drugs, infections continue to worsen, thereby, leading to morbidity and mortality. Indeed, the shocking increase in the incidence of resistant microbes, such as; bacteria, AIDS virus (HIV), severe acute respiratory syndrome, and avian influenza entail new strategies to combat infections.

For instance, inhalational anthrax, a rare and lethal form of anthrax is caused by *Bacillus anthracis*, a

Gram positive bacterium, forming dormant spores that are resistant to harsh environmental conditions. Raxibacumab (ABthrax[®]; GSK) mAb was approved in December 2012, under the Animal Efficacy Rule, against protective antigen (PA) of *Bacillus anthracis* for addressing inhalational anthrax. It is not feasible and ethical to perform clinical trials in humans. Therefore, efficacy trials were conducted in rabbits and monkeys, because pathogenesis is same both in humans and animals. Raxibacumab binds with the protective antigen with high affinity and specificity, blocking its binding with receptors. It was observed that 40 mg/kilogram single dose of raxibacumab has prolonged the survival rate in rabbits and monkeys considerably, suffering from symptomatic inhalational anthrax [33]. Besides, raxibacumab was also effective in human; however, infusion reactions such as rash, urticaria, pruritus have been reported during clinical trials. According to the label included in the product; infusion reactions, pain in extremities, drowsiness, urinary tract infection, URTI, headache, and nausea are associated with raxibacumab. Furthermore, its efficacy has not been evaluated in pregnant women, nursing mothers and pediatrics.

2.3. Anti-cancer

Cancer is the leading cause of death and is increasing globally, especially in economically developed countries. Approximately 12.7 million new cancer cases and 7.6 million deaths due to cancer occurred in 2008 [34]. Since the last few decades, constant research on cancer enabled the scientists to understand cancer pathogenesis and develop innovative antibody-based therapeutics. Currently two types of mAbs, i.e. naked and conjugated antibodies are available on the market for the treatment of cancer.

2.3.1. Naked antibodies

Naked antibodies are the most common form of antibodies used for cancer therapy and the term “naked” refers to the fact, that there is no drug or radiolabeled material attached to them. For example, chronic lymphocytic leukemia (CLL), characterized by the abnormal proliferation of B-lymphocytes. The progressive accumulation of monoclonal B-lymphocytes lead to leukocytosis, lymphadenopathy, hepatosplenomegaly, bone marrow failure, recurrent infection and sometimes autoimmune diseases [35]. Ofatumumab (Arzerra; Genmab/GSK), a fully human cytolytic CD20 mAb was approved in October 2009, for the treat-

ment of CLL. Ofatumumab is used as an alternative therapy for patients who were resistant to rituximab. Unlike rituximab, ofatumumab targets a different epitope of B-cells i.e. CD20, enhancing ADCC and CDC [36]. The most common adverse events observed during efficacy studies included; neutropenia, pneumonia, pyrexia, anemia, dyspnea, infusion reactions, and URTI. Rate of infusion reactions were more with first infusion, however, reduced with subsequent infusions [36,37].

Another humanized anti-CD20 glycol engineered mAb, obinutuzumab (Gazyva[™]; Genentech) was licensed in November 2013. Glycol engineered antibodies have improved ADCC and thereby, augmenting immune mediated target cell death. It is recommended in combination with chlorambucil for the treatment CLL in naïve patients. Studies compared rituximab and ofatumumab with obinutuzumab on the base of CDC, ADCC, antibody-dependent cell mediated phagocytosis, and internalization. It was observed that obinutuzumab is superior in inducing direct cell death [38]. Most frequently occurred adverse events related to obinutuzumab in combination with chlorambucil included; infusion reactions, neutropenia, thrombocytopenia, leukopenia, and anemia. Like ofatumumab, infusion reactions were more frequent, yet, reduced with subsequent infusions. Furthermore, approximately 13% recipients were found positive for anti-obinutuzumab antibodies [39]. Indeed, obinutuzumab significantly reduces B-cells, thereby, could lead to serious fungal, bacterial, and new or reactivated viral infections; for example, hepatitis B virus (HBV) reactivation and progressive multifocal leukoencephalopathy (PML).

Another well-known type of cancer is melanoma that originates in the melanocytes and is considered an aggressive type of skin cancer. Despite of continuous rise in metastatic melanoma worldwide, no medication had been approved for its treatment. Luckily, in March 2011, FDA licensed ipilimumab (Yervoy; Bristol-Myers Squibb) mAb, targeting cytotoxic T-lymphocyte-associated antigen4 (CTLA-4), found on the surface of T-cell, for the treatment of metastatic melanoma [40]. During clinical trials it has been demonstrated that ipilimumab administration at 10 mg/Kg in combination with dacarbazine improved survival rates. Safety profile of ipilimumab plus dacarbazine revealed that immune-related adverse events, such as, dermatologic (pruritus and rash), gastrointestinal (enterocolitis and diarrhea), and hepatic do existed. Moreover, total 14 deaths occurred, yet, 7 were related

to immune-related adverse events. Increase in the alanine aminotransferase and aspartate aminotransferase level was also seen [41,42]. The role of ipilimumab during pregnancy, nursing mothers, and pediatrics need to be studied. Hence, ipilimumab should not be given to children under 18.

In June, 2012 pertuzumab (Perjeta; Genentech), human epidermal growth factor 2 (HER2) antagonist humanized mAb plus trastuzumab and docetaxel for the treatment of HER2-positive metastatic breast cancer was approved by FDA [43,44]. It binds to the dimerization site on the HER2, blocking the binding of HER2 with ligand-activated HER receptors, hence, arrest cell growth and survival. Pertuzumab and trastuzumab in combination with docetaxel blocked HER signalling pathway efficiently, thereby, demonstrated best anti-tumor activity [45]. However, mild to severe adverse events were also observed, among which diarrhea, rash, mucosal inflammation, dry skin, and febrile neutropenia were more common [44]. Although cardiac toxicity was observed in previous studies, however, in the current study no such event was observed [46].

2.3.2. Antibody-drug conjugates

Conventional therapeutic drugs do not selectively target tumor cells, which may damage healthy tissues and organs. Antibodies are target specific, hence, ideal vehicles for drug delivery (toxic drugs) to the target sites. Diverse linkers are used for conjugation of antibodies to a wide range of cytotoxic drugs. Following crosslinking with the antigen on the surface of tumor cells, ADC is internalized and processed, releasing the conjugated drug, consequently, the drug kills the cells by the cytotoxic mechanism. ADC is a successful and potent class of cancer therapeutics. Cytotoxic agents used in ADCs are 1000 times more potent than the currently available chemotherapeutics. Brentuximab vedotin (Adcetris; Seattle Genetics), an ADC was licensed by FDA in August 2011, for the treatment of Hodgkin's lymphoma. Brentuximab vedotin is composed of an anti-CD30 chimeric mAb and an effective antimicrotubule agent monomethylauristatin E connected by a protease cleaver linker. CD30 is an ideal target of brentuximab vedotin, because its expression is more on malignant cells as compared to the normal cells [47]. However, the most common adverse events related to the brentuximab vedotin therapy included; peripheral sensory neuropathy, which was resolved after the completion of the treatment or reducing the dose [48]. It has been confirmed by research that microtubule inhibitor induce neuropathy also [49].

The incidence of manageable neutropenia and infusion reactions were also observed. The outcomes of infusion reactions were chills, nausea dyspnea, pruritus, and cough. Moreover, higher rates of infusion reactions were observed in patients who produced antagonist antibodies to brentuximab vedotin. Thrombocytopenia and hyperglycemia of various grades were also seen. Besides, infrequent but serious progressive PML due to John Cunningham virus also occurred. Due to this adverse event FDA mandated the black box warning [47,50].

Another well-known type of cancer for which ADC is used is breast cancer. It is the most frequent cancer diagnosed among women in the US. In about 25% of the breast cancer patients, overexpression of HER2 on tumors have been reported [51]. Despite of trastuzumab and pertuzumab FDA approved anti-HER2 antibodies, breast cancer was still a major dilemma. Therefore, in February, 2013 a humanized anti-HER2 ADC, Ado-trastuzumab emtansine (Kadcyla; Genentech/Roche) was approved by FDA for the treatment of breast cancer. Genentech and ImmunoGen developed and licensed trastuzumab emtansine conjugate, composed of Genentech's trastuzumab antibody linked to ImmunoGen's anti-mitotic agent, mertansine (MD1), which interrupt the process of mitosis; consequently, promoting apoptosis. The most common adverse events observed during clinical trials included; thrombocytopenia, hepatotoxicity leading to high level of aspartate aminotransferase and alanine aminotransferase. In most of the patients thrombocytopenia was managed, only 2% discontinued the Ado-trastuzumab emtansine dosage. Other frequently occurred adverse events included; fatigue, nausea, pain in muscles, headache and constipation. Besides, very rare frequency of cardiovascular diseases and pneumonitis associated with the drug were also observed [52–54].

2.4. Blood disorders

Paroxysmal nocturnal haemoglobinuria (PNH), an acquired clonal stem cells blood disorder characterized by intravascular hemolysis and haemoglobinuria. Glycosylphosphatidylinositol (GPI) anchor, a complement regulatory protein is present in the membrane of the red blood cells (RBCs), protecting RBCs from complement system. In case of susceptible cells, these proteins are absent due to mutation in X-linked phosphatidylinositolglycan class A (*PIGA*) gene, resulting in complement based destruction of the RBCs [55]. Bone marrow transplantation was the only cure, but it was

unsafe and significantly effective only in young population with a sibling blood donors [56]. Eculizumab (Soliris; Alexion), an anti-C5 complement protein mAb was approved by FDA, in March 2007, for the treatment of PNH. Eculizumab is harmless, well tolerated, and effective, thus, reduced hemolysis significantly and improved anemia. Mild to moderate adverse events with eculizumab therapy included; headache, nasopharyngitis, back pain and nausea. Back pain and headache were more frequent in the eculizumab treatment group. However, the issue of headache was resolved with medications. Renal failure was also observed both in the population of Japan and US during clinical trials. Although no cases of infections were observed except meningococcal sepsis, but later on it was confirmed that the patients were previously vaccinated with meningococcal vaccine and it was not related to eculizumab and recovered soon [57–59]. It is clear from the above discussion that eculizumab may reactivate *N. meningitidis*, hence, before starting eculizumab treatment it is recommended to avoid taking *N. meningitidis* vaccine at least 2 weeks prior to treatment.

2.5. Anti-inflammatory

Gout is an inflammatory disease, caused by the increase level of uric acid, leading to the deposition of monosodium urate crystals (MSU) in tissues, especially in joints. Experimental studies on animals have revealed that MSU induce a cascade of pathways, leading to the formation of inflammasome that in turn convert proIL-1 to mature IL-1 β . Consequently, activation of IL-1 β increases the recruitment of neutrophils to the inflammation site, resulting in inflammatory reactions. Hence, blockade of IL-1 β with inhibitors is an ideal strategy for addressing gout [60]. Canakinumab (Ilaris; Novartis), an anti-IL-1 β human mAb, was approved by FDA in June 2009, for the treatment of gout. Canakinumab was effectual in patients who did not respond to non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids. Moreover, it provided potent and long lasting suppression of inflammation [61]. The safety data revealed no immune-related adverse events; nevertheless, infrequent mild injection site reactions have been reported. Additionally, infections were more frequent in children. None of the patient developed an infection of the vaccinated antigen. In clinical trials, canakinumab therapy for addressing RA, diabetes mellitus, and gout did not show any adverse events except a very rare infection [62–64]. Among the canakinumab recipients case of benign

neoplasm (lipoma) has also been seen [64]. However, like other cytokines antagonists, canakinumab could also promote the incidence of infections and malignancies, hence, clinical trials on large population for extended duration are required to highlight the risks of infections and malignancies.

2.6. Anti-bone loss

Bone remodeling is a bone resorption and ossification phenomenon, occurring throughout the life. Receptor activator of nuclear factor kappa- β ligand (RANKL), osteoprotegerin (OPG), and receptor activator of nuclear factor kappa- β (RANK) are the key players in regulating bone remodeling pathway. RANKL, a cytokine and a key mediator in the differentiation, activation, and survival of osteoclast cells is responsible for the elevated incidence of bone resorption as compared to bone formation. Abnormal osteoclastogenesis act as gatekeeper in osteoporosis, leading to elevated bone fragility [65]. Indeed, RANKL is an ideal target to reduce osteolytic bone disease and promote regeneration of bones. In June 2010, FDA approved denosumab (Prolia; Amgen), a fully human anti-RANKL antibody, inhibiting the crosslinking of RANKL with RANK. Consequently, lowering the frequency of bone resorption, thereby, increasing bone density. Denosumab is efficacious and relatively safe for the treatment of osteoporosis [65,66]. Safety profile of denosumab demonstrated that adverse events were similar both in placebo and treatment group. Moreover, osteonecrosis of jaw, hypocalcemia, and anti-denosumab antibodies were not observed [67,68]. RANK and RANKL, belonging to the tumor necrosis factor superfamily and expressed by diverse lymphoid cells. Therefore, their inhibition might lead to the progression of malignancies or increase the risk of infections.

3. Discussion

Tailored mAbs with enhanced specificity, affinity, and reduced immunogenicity is the outcome of genetic engineering. These modifications paved the way to the successful development and approval of chimeric, humanized, and fully human mAbs. Usually, when conventional medicines fail to elicit an effective response, mAbs are the method of choice. mAbs down regulate immune system of the body either by neutralizing the cytokine storm or cause depletion of the B and T-cells.

Licensed mAbs currently available on the market are either chimeric, humanized or fully human. Unluckily, rodent derived mAbs, including, chimeric and humanized are relatively immunogenic as compared to the fully human mAbs. However, saying that fully human mAbs are 100% safe is inconclusive, since, they also exhibit immunogenicity [69,70].

Effective immune response is the outcome of interaction between innate and adoptive immune system through a cascade of chemical mediators called cytokines. Cytokines are produced by innate immune arm in response to pathogen interaction. For instance, TNF- α is involved in necrosis of tumor cells and inducing host defense against infections [71]. Similarly IL-12/23 are responsible for stimulating mucosal immune response and overcoming viral infections, whereas, IL-1 β triggers the release of other cytokines, consequently, it is considered as the “master cytokine” [72,73]. Cytokines form a central coordinating network of soluble circulating molecules and have a critical role in the initiation and regulation of autoimmune diseases [74]. A significant improvement has been made in down-regulating cytokine for addressing plaque psoriasis, RA, Crohn’s disease, and PNH. However, inhibition of cytokines critically affect the defense system, thereby, raising the risks of serious infections, cardiovascular disease, malignancy, and multiple sclerosis [75]. Another important component of the immune system is the complement proteins that link innate and adoptive immune response, providing integrated defense to pathogen [76]. Targeting C5 complement protein, cell surface receptors (BLyS, CD20, and CD30) of B-cells, and CTLA-4 found on the surface of T-cells, would result in subduing the immune arms of the body. Hence, down-regulating the immune mediated responses, make the patient susceptible to viral, fungal, bacterial infections and malignancies. Immunosuppression also increases the risk of reactivation of old or latent infections. Moreover, infusion reactions; such as, anaphylactic or anaphylactoid reactions are also the outcomes of mAbs therapy [77]. Therefore, long term studies for extended duration and follow-up of patients are needed to find the risks of malignancies, infections, and infusion reactions, linked with mAbs therapy in the long run.

Finally, it is concluded that prior starting antibody dosage, both physicians and patients ought to know the related adverse events, otherwise, mild disease would cause serious adverse events and sometimes life threatening infections and malignancies. In order to identify and manage adverse events associated

with a specific mAb, it is noteworthy, to keep patients under close observations. Further evaluation of adverse events of mAbs dosage entail correspondence among patients, physicians, biopharmaceutical companies, and researchers.

Acknowledgement

This review is the outcome of financially non-supported in house study and the authors declare no conflict of interest.

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