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THERAPEUTIC APPLICATIONS OF MONOCLONAL ANTIBODIES: RECENT ADVANCES

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ABSTRACT
Monoclonal antibodies (MAB_S), the most rapidly growing drug class, are developed to improve quality of life of millions of patients suffering from relapsed/inadequate drug response /drug resistant malignant, autoimmune diseases and rare genetic disorders. They are better than conventional pharmacotherapy in terms of potency, dosing, frequency and specificity for their target antigens. MAB_s have revolutionized the treatment of various types of cancer, serious bacterial & viral infections, inflammatory and autoimmune diseases, cardiovascular and many other conditions generally not responding to conventional treatment. New antibody based therapeutics are under clinical development for treatment of diabetes mellitus, diabetic retinopathy, glaucoma, age related macular degeneration, uveitis, HIV/AIDS, asthma/respiratory disorders and Alzheimar's disease. However, their use is associated with some immunogenic, target related and off target adverse effects such as hypersensitivity and these drugs are costly. This review describes therapeutic applications of MAB_S and their new indications in the treatment of various diseases.

KEYWORDS: Monoclonal antibody, cancer, Rheumatoid arthritis, crohn's disease, macular degeneration.

INTRODUCTION
Antibodies, also known as immunoglobulins (Ig_s) are B cells produced molecules composed of 4 polypeptide chains (2 heavy, 2 light) that come together to form characteristic Y shape. The concept of using antibodies for the treatment of disease dates back to the 1890_s, when Emil Adolf Von- Behring discovered that small doses of diphtheria or tetanus toxin produce transferable immunity in animals.[1] In 1960_s structure of antibodies were characterized with the discovery of method of production (Hybridoma technique) of monoclonal antibodies (MAB).[2] In 1986 MAB muromonab-CD3 was approved for treating steroid resistant acute allograft rejection of renal transplant recipients.[3] The first fully human MAB (adalimumab) was approved for treating Rheumatoid arthritis (RA) in 2002.[3] MAB_s can offer benefits over conventional pharmacotherapy in terms of potency, dosing, frequency and specificity for their target antigen. They do not undergo hepatic or renal metabolism and allow less frequent drug interactions. These drugs developed to benefit quality of life of millions of patients worldwide. Mouse derived antibodies were initially used in humans. However patients developed human antimouse antibodies resulting in rapid antibody clearance (loss of efficacy) and hypersensitivity reactions. Therefore, chimeric, humanized and fully human antibodies were developed to reduce immunogenicity.[4] These drugs of large molecule have a higher approval success rate and revolutionized the treatment of cancer, infectious, inflammatory and autoimmune diseases. Most of the recently approved biologics are fully human MAB_s and cancer and immunologic disorders continue to be the focus of investigational therapeutic MAB_s.[5] In addition, MAB_s are being developed for a variety of broad range of indications like diagnostic and evaluation of therapeutic response of a drug, in the treatment of cardiovascular disorders, HIV, asthma, Glaucoma & macular degeneration, plaque psoriasis, for dissolution of blood clot , treatment of drug abuse and for drug delivery etc. Therapeutic antibodies and F_c like fusion proteins rank the most rapidly growing drug class. Novel molecules ie MAB_S and fusion proteins have been entering clinical studies at a rate of over 40 per year since 2007.[6] Some older MAB_s are recently approved for new indications particularly in combination with other drugs. Many new MAB_S are filling the preclinical and clinical pipelines of major pharmaceutical companies.[7] This review describes recent advances in the field of MAB_s particularly role in pharmacotherapy and to emphasize on Mab_s those approved by U S Food & Drug Administration in the year 2015 & 2016 and

MAB_s those are still under clinical phases (I-III) of development.

METHODS

Data collection: The data for present review was collected from internet, online journals and from various internationally recognized peer reviewed journals. Drugs.com-New Drugs Approvals Archives, Jan .to Dec. 2015 and Drugs. com-New drugs Approval Archives Jan to April 2016 have been searched and FDA approved drugs were included in this review.

Therapeutic Uses of monoclonal antibodies (MABs)

MAB_S have a wide range of therapeutic applications. These can be used directly for enhancing immune function of the host. Direct use of MAB_S causes minimal toxicity to the target tissue or host. Following are the uses of MAB_s.

1. MAB_S in treatment of cancer: MAB_s against the antigens on the surface of cancer cells are useful for treatment of cancer. Antibodies bind to cancer cells and destroy them via antibody dependent cell mediated cytotoxicity, complement mediated cytotoxicity & phagocytosis of cancer cells. They also promote apoptosis Leukemia, colorectal cancer, lymphoma, melanoma have been treated with MAB_S. MAB specific to cells of leukemia is used to destroy only residual cells. MAB_S are used in vitro to remove residual tumor cells prior to autologous bone marrow transplantation. Following MAB_S are effective in treatment of cancer.

Alemtuzumab is a recombinant DNA derived humanized monoclonal immunoglobulin IgG1 kappa antibody, that targets the cell surface glycoprotein CD-52 (compliment mediated lysis of T & B lymphocytes). It is approved for use in patients with B cell chronic lymphocytic leukemia for several years and has recently become approved in the EU & several other countries for use in adults with active relapsing remitting multiple sclerosis.[8] In phase III trials, it was shown to be more effective than a first line treatment, sc interferon-β-1_a, in decreasing relapse rate in treatment naïve and previously treated patients and in decreasing disability progression. Currently alemtuzumab is approved for treatment of Bcell chronic lymphocytic leukemia in patients who have been treated with alkylating agents and have failed fludarabine therapy. Dose is-iv infusion 12 or 24 mg/day on 5 consecutive days followed by same dose on 3 consecutive days 12 months later. There was an increased risk of autoimmunity & infections associated with alemtuzumab. Infusion related reactions(headache, skin rash, pyrexia, urticaria), infections(UTI, Herpes viral infection, UTI, nasopharyngitis, influenza like illness) and rarely liver toxicity.

Amatuximab: is a antimesothelin MAB for malignant pleural mesothelioma. Mesothelin is a glycosylphosphatidyl inositol(GP-1) anchord membrane glycoprotein which is present in a restricted set of normal adult tissue. Phase I study conducted in 13 patients in USA, iv infusion weekly for 4 of a 6 week than 12.5 to 400mg/$m^{2.}$. A phase II study was conducted in 17 patients, iv infusion weekly for 4 week cycle 50-200mg/m^2. Combination with gencitabine, iv infusion 5 mg/kg for 7 weeks in an 8 week cycle. In patients with MPM, higher amatuximab exposure in combination with chemotherapy was shown to be associated with longer overall survival.[9] However, more future trials are required with different dosage regimens.

Bevacizumab is a humanizedIgG1 MAB that binds to vascular endothelial growth factor and inhibits VEGF from binding to its receptors mainly on endothelial cells. It is antiangiogenic in tumors. It is approved as first line treatment for patients with metastatic colorectal cancer alone or in combination with 5-FU based chemotherapy. It is also approved for treatment of non small cell lung cancer, metastatic kidney cancer & glioblastoma multiforme. Intravitreal injection is used to slow the progression of macular degeneration(off label use). Side effects include delay wound healing, haemorrhage, gastrointestinal perforation. Phase II study with bevacizumab 7.5 mg/kg,iv + irinotecan 175mg/m^2(DNA topoisomerase inhibitor), iv on day 1 and 15 in 30 days cycles for a target of atleast 4 cycles showed promising efficacy and low toxicity compared to historical controls in patients with relapsed chemotherapy resistant SLE.[10] Further investigations are warranted.

Blinatumomab: is a novel bispecific T cell engaging antibody that binds CD-19 antigens on blast cells also binds & activates CD-3/T cell receptor complex causing cell lysis. It is approved in 2015 for treatment of haematological cancers that originate from B cell line.[11] Approved by US FDA in Dec. 2014 for treatment of adults with Philadelphia chromosome(Ph) negative relapsed/ refractory B cell precursor acute lymphoblastic leukemia. It is awaiting approval for this indication in EU & is in phase III clinical development in various countries. Dose- iv infusion 5-90 µg/m^2/ day. Most frequent adverse events are pyrexia, headache, peripheral edema, nausea, febrile neutropenia, hypokalemia & constipation, pneumonia tremor, encephalopathy, infections, staphylococcal bacterimia may occur. Rarely cytokine release syndrome & increased liver enzymes.

Brentuximab vedotin is a recent addition to treatment used in management of patients with Hodgkin's lymphoma. It is an MAB drug conjugate that specifically target CD-30 expression on HRS cells. Antibody binds to CD30 and is internalized releasing the MMAE toxin which inhibit proliferation & induces apoptosis of malignant cell. It is in initial phase I clinical development for patients with Hodgkin's lymphoma & anaplastic large cell lymphoma.[12] Dose 1.8 mg/kg given every 3 weeks. Overall response rate was 75% with a complete response rate 34%. Median progression free survical was 5.6 months. Also for combination ABVD

chemotherapy (BRECADD) regimen, ABVDchemotherapy + brentuximab.

Cetuximab is a humanized chimeric MAB that target epidermal growth factor receptor (EGFR). Binding of cetuximab to EGFR inhibits tumor cell growth by various mechanisms including increase apoptosis, decrease Kinase activity & matrix metalloproteinase. It is indicated for metastatic colorectal cancer along with radiation therapy, in head & neck cancer. It may be given in combination with irinotecan or alone in patients who cannot tolerate irinotecan. It is also given for head & neck cancer.[6] Standard dose is a single loading dose of 400mg/m^2, iv followed by weekly dose of 250mg/m^2 for duration of treatment. Human anti-mouse antibody developed in approximately 4% patients treated with cetuximab. Other side effects are rash, pruritis, diarrhea, cardiopulmonary arrest, interstitial lung disease& hypomagnesemia.

Daratumumab injection: is a first in class humanized $IgG1_k$ MAB that target the CD-38 epitope and approved by FDA on 16.11. 2015 for treatment of multiple myeloma. Daratumumab(iv) was recently approvedby FDA in 2016 via an accelerated approval programme in the USA for patients with multiple myeloma who are received atleast 3 prior lines of therapy including a proteosome inhibitor(PI) and an immunomodulatory agents and who are double refractory to a PI and an immunomodulator.[13] It is in preregistration for this indication in the EU & Canada. In a phase IItrial in patients with previously treated relapsed/ refractory multiple myeloma, monotherapy with daratumumab 16mg/kg achieved an overall response rate of approximately 30 %.

Dintuximab is anIgG1 human/mouse chimeric switch variant murine MAB $14G_2a$, binds to GD_2 and induces antibody dependent cell mediated cytotoxicity & complement dependent cytotoxicity. The US FDA has recently approved use of dinutuximab combination therapy for high risk neuroblastoma in paediatric patients. Marketing authorization application is under regulatory review in the EU and phase I –III development is underway in several countries.[14]

Elotuzumab injection: is a humanized IgG1 MAB approved as combination therapy with lenalidomide and dexamethasone for relapsed/refractory multiple myeloma in the USA (approved by FDA in 2016 in the USA).[15] It binds to cell surface receptor signaling lymphocytic activation molecule F7 (SLAMF7) which is selectively expressed on myeloma cell and NK cells leading to antibody dependent cellular cytotoxicity and direct natural killer cell activation. Dose- 17.5 ml/day/kg, iv at a dose of 0.5ml/kg to 5.8ml/day/kg at a dose of 20ml/kg twice the recommended dose. Adverse events include pyrexia, constipation, cough, peripheral neuropathy, upper respiratory tract infection, pneumonia & decrease in appetite.

Ipilimumab: Target cytotoxic T lymphocyte associated protein-4(CTLA-4) receptor, indicated for reduced risk of melanoma.[16] Approved by FDA on 13.5.2016 in combination (ipilimumab+pembrolizumab) for treatment of melanoma.Combinationof ipilimumab+nivolumab has yielded higher response rate, greater tumor shrinkage and longer progression free survival than either monotherapy alone. Ipilimumab has been or is being studied in over 50 clinical studies of patients with a variety of cancers including prostate, pancreatic, lung, brain, breast, colorectal and renal cancer, as well as lymphoma & chronic myeloid leukemia During induction phase dose is 10mg/kg, iv every 21 days for 4 cycles. In the maintenance phase, starting at weeks 24, 10 mg/kg every 12 weeks until week 156 or progression. Side effects-Immune related events, skin toxicity and gastrointestinal adverse effects.

Necitumumab: Humanized IgG MAB directed against EGFR, which is expressed in a variety of solid tumors. It is approved as a part of combination therapy with gemcitabin & cisplatin in USA as Ist line treatment of metastatic squamous non small cell lung cancer.[17] Dose -800mg, iv, on day Ist & 8 of a 3 week cycle. It is in phase II clinical development for colorectal cancer in Belgium & Spain. Side effects include skin rash, vomiting, diarrhea.

Nivolumab a fully humanized MAB against programme cell death receptor-1.It is approved for new indications ie FDA expends approval for use to treat lung cancer on 4.3.2015. & for metastatic renal cell carcinoma on 23.11.2015. In phase II clinical development with previously treated relapsed patients. Nivolumab+ ipilimumab was given extended FDA approval on 23 Jan 2016 for treatment of unresectable or metastatic melanoma.[18]

Obinutuzumab: Humanized & glycoengineered type II & CD20 MAB, for iv treatment of B cell malignancy.It induces direct cell death. It is approved in the US for use in combination with chlorambucil for first line treatment of chronic lymphocytic leukemia & has been failed for approval in EU. The MAB is in phase III development worldwide.[19] It also indicated for follicular lymphoma (approved by FDA on 26 Feb 2016). In a multinational phase III study in this patient population, obinutuzumab plus chlorambucil significantly prolonged progression free survival compared with chlorambucil alone and iv rituximab. It is given iv 1000 mg on day1, 8 & 15 of cycle 1 and day1 of cycles 2-6. First infusion 100-900 mg on day 1& 2 respectively. Side effects include leucopenia, anemia, thrombocytopenia, neutropenia and infusion related reactions.

Ofatumumab is a human IgG1 MAB directed against a different epitope on CD20.It binds to all B cells, causes B CLLcell lysis and mediate antibody dependent cytotoxicity. It is indicated for treatment of recurrent or progressive chronic lymphocytic leukemia (Received

revised FDA approval as extended on 19.1.2016). Side effects- risk of hepatitis –B virus activation.[16]

Osimertinib is an oral IIIrd generation EGFR tyrosine kinase inhibitor that is being developed for treatment of non smallcell lung cancer. Granted accelerated approval(in Nov. 2015)in the USA for treatment of patients with metastatic EGFR T790M. Received accelerated approval in EU also & is in phase III development on I and II line and adjuvant treatment for advanced EGFR in several countries. Phase I clinical trial in patients with advanced solid tumors are also being conducted.[20] Dose 80mg once daily untill unacceptable toxicity or disease progression. Side effects include diarrhea, dry skin, rash, pneumonitis, nail toxicity, cardiomyopathy, QTC prolongation.[20]

Panitumumab is a fully human Ig G2 kappa light chain MAB. It is approved for treatment of EGFR expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine, oxaliiptin & irinotecan containing chemotherapy regimens.[21] Dose-6mg/kg, iv given once every 2 weeks. It binds to EGFR, activates kinases, inhibit cell growth, induces apoptosis. This is Ist FDA approved MAB produced from transgenic mice expressing human immunoglobulin gene loci. Some dermatological and infusion related toxicity, rash, pulmonary fibrosis & electrolyte abnormalties observed in patients treated with panitumumab.

Pembrolizumab: Humanized MAB against Programme cell death receptor protein. Approved for new indications ie advanced non small cell lung cancer on 2.10.2015 and for advanced melanoma on 18.12 2015 by FDA.[22]

Ramucirumab is a fully human IgG1 MAB that inhibits VEGF receptor2. Approved for treatment of advanced or metastatic gastric cancer, gastroesophageal junction, adenocarcinoma in patients who experience disease progression after fluropyrimidin or platinum containing chemotherapy.[23] Dose 8mg /kg, iv over 60 min. Every 2 weeks. Ramucirumab+FOLFIRI- indicated as II line treatment of metastatic colorectal cancer (FDA approved on 24.5. 2016).[24]

Rituximab: is a Chimeric-human MAB IgG1 that targetingCD-20 antigen on B lymphocytes. It was first develop to treat haematological malignancy & is indicated for aggressive non Hodgkin lymphoma in both the USA & Europe[6]. Mechanism of action includes complement mediated lysis, antibody dependent cell cytotoxicity and induction of apoptosis in malignant lymphocytes. It is also approved for the treatment of chronic lymphocytic leukemia, rheumatoid arthritis(in combination with methotrexate). Rituximab may also be very useful in autoimmune diseases such as multiple sclerosis & SLE[6]. Rituximab plus lenalidomide is useful for Mantle cell lymphoma.[25]

Trastuzumab emtansine is an antibody conjugate consisting of humanized antihuman epidermal growth factor-2 linked to potent microtubule inhibitor DMI. It was recently approved for use in patients with HER-2 positive unresectable or metastatic breast cancer.[26] Dose is 3.6 mg/kg, iv every 3 weeks.

2. MAB_s as anti-inflammatory and immunosuppressive agents

Abatacept: is a recombinant fusion protein composed of extracellular domain of Cytotoxic T lymphocyte associated antigen 4. It binds to CD80/86 then CD-28 and blocks activation of T cells & lead to cytokine release. Approved for rheumatoid arthritis (RA) & juvenile idiopathic arthritis.[27] Side effects include Infections, Tuberculosis. Contraindicated along with other anti TNF drugs.

Adalimumab: Human IgG1 MAB, approved for use in patients with RA, psoriatic arthritis(PA), ankylosing spondylitis(AS), plaque psoriasis and crohn's disease.[28] Adalimumab blocks TNFα receptors on cell surface, it does not bind TNF –β. It lysis cells expressingTNFα in the presence of compliment. It reduces level of C reactive protein, ESR, serum IL-6, matrix metalloproteinase,MMP-1 &MMP-3. Approved for new indication- for moderate to severe Hidradenitis on 10.9. 2015.

Alefacept is an engineered protein consisting of CD-2 binding portion of leukocyte function associated antigen-3(LFA-3) fused to a human IgG1 Fc region. It inhibits activation of T cell by binding to cell surface CD-2/LFA-3 interaction. It is approved for treatment of plaque psoriasis.[6] Alefacept reduces total circulating T cells especially CD-4 & CD-8memory effector subsets that predominate in psoriatic plaques. Drug should be discontinued if CD-4 lymphocyte levels fall below 250 cells/µl.

Alemtuzumab: Humanized MAB has recently been approved in the EU& other countries for treatment of multiple sclerosis. In phase III trial it was shown to be more effective than first line treatment interferon β/a in decreasing relaps rate.[8]

Certolizumab pegol: is a recombinant humanized Fab fragment that binds to TNF-α. It is coupled to 40kDa polyethylene glycol. It neutralizes activity of TNF-α without cell lysis. It is indicated for crohn's disease and RA.[6] In the EU, certolizumab pegol is indicated for severe active axial spondyloarthritis comparising ankylosing spondylitis, for adults with active psoriatic arthritis. In the US it is indicated for active AS or active PSA. 200mg every 2 weeks or 400mg every 4 weeks for 12-24 weeks was effective in improving clinical sign & symptoms of disease, reducing inflammation in joints and spine.

Etanercept: Dimeric fusion protein composed of IgG1 constant region fused to TNF receptor. It binds to both TNF-α and β and reduces TNF –α mediated inflammation. It is approved for RA, polyarticular juvenile idiopathic arthritis, AS & psoriatic arthritis.[6] It may be used in combination with methotrexate in patients with arthritis. It is given sc twice weekly.

Golimumab: Human IgG MAB that binds to soluble and membrane associated TNF-α. It is an intect human IgG1 and does not lyse cells expressing membrane associated TNF-α. It is indicated for patients with RA, AS & psoriatic arthritis.[6] It may be given sc injection only once per month (because of long half life).

Infliximab is a human-mouse chimeric IgG1 MAB possessing human Fc regions &murine variable regions. It is approved for use in crohn's disease, maintenance of ulcerative colitis, RA, AS, plaque psoriasis & psoriatic arthritis.[6] Infliximab dyyd injection – a TNF blocker biosimilar to infliximab approved by FDA on 5.4.2016. for crohn's disease, ulcerative colitis, RA, AS. plaque psoriasis & psoriatic arthritis. It is given iv.[24]

Ixekizumab injection: Humanizes IL-17A antagonists approved by FDA on23.3. 2016. for plaque psoriasis.[29]

Natalizumab: is a humanized IgG4 MAB that binds to α-4 subunit of α-4 β 1 & α-4 β 7 integrins expressed on surface of all leukocytes except neutrophils and inhibits the α4 mediated adhesion of leukocytes to their cognate receptors. It is indicated for patients with multiple sclerosis & crohn's disease who cannot tolerate or had inadequate response to conventional treatment.[6]

Rituximab a chimeric- murine- human MAB IgG1 that binds to CD-20 on normal and malignant B-lymphocytes. It is also useful in autoimmune diseases such as SLE and multiple sclerosis. Rituximab is an effective & safe treatment of relapsed elderly patients with resistant autoimmune haemolytic anemia.[30]

Secukinumab: Humanized MAB againstIL-17A. First global approval in Japan on 26 Dec. 2014 for treatment of psoriasis and psoriatic arthritis in adults. In the USA and EU secukinumab was approved by FDA in early 2015 for treatment of patients with moderate to severe plaque psoriasis. It is also being investigated for AS & RA.[31]

Tocilizumab: is a recombinant humanized Ig G1 that binds to soluble and membrane associated IL-6 receptors. It inhibits IL-6 mediated signaling on lymphocytes suppressing inflammatory process It is indicated for treatment of RA in refractory patients with anti TNF.[6] It may be used alone or in combination with methotrexate or other DMARD. Side effects – risk of infections.

Ustekinumab: is a human IgG1 MAB that binds to P-40 subunit of IL-12 & IL-23 cytokines. It blocks IL-12 & IL-23 from binding to their receptors and blocking signal for their cognate receptors. It is indicated for patients with moderate to severe plaque psoriasis.[32] Recently, received approval in adults with active psoriatic arthritis (under phase III). Dose is 45 or 90 mg, sc, it was significantly more effective than placebo after 24 weeks.

Vedolizumab: Humanized MABα-4 β7 integrin receptor antagonist, has been approved in the EU, Norway, Iceland and Liechtenstein for treatment of ulcerative colitis & crohn's disease.[33]

Basiliximab is a chimeric mouse- human IgG1 that binds to CD-25, IL-2 receptor α- chain on activated lymphocytes. Act as IL-2 antagonist blocking IL-2 from binding to activated lymphocytes. It acts as immunosuppressive and used for prophylaxis of acute renal transplant rejection and may be used as part of immunosuppressive regimen along with glucocorticoids and cyclosporine-A.[6]

Belatacept: A fusion protein composed of Fc fragment of human Ig G1 linked to cytotoxic T lymphocyte associated antigen-4 & inhibit T cell activation. Belatacept was approved by US FDA & European Medical Agency as first line immunosuppressive for kidney transplantation (Nephroprotective).[34]

Daclizumab is a human IgG1, binds to α subunit of IL-2 receptors. It is used for prophylaxis of acute renal transplant rejection and may be used as part of an immunosuppressive along with glucocorticoids & cyclosporine.[6]

Muromonab: CD-3 is a murine MAB against Tcell surface protein OKT-3 directed againstCD-3 molecule on the surface of human T cells. In vitro muromomab-CD3 blocks killing by cytotoxic human T cells and several other T cell functions. It is useful in the treatment of renal transplant rejection. It is more effective in reversing acute rejection than did glucocorticoids. Muromomab-CD3 is approved for treatment of acute allograft rejection & steroid resistant acute cardiac and hepatic transplant rejection.[6] Gaint cell myocarditis is an inflammatory myocardial disease. Immunosuppression is an effective treatment for some cases. Muromomab CD-3 is a short acting & effective agent.[6]

RATG (Rabbit antithyromyglobulin) is a preparation of rabbit polyclonal antibody against T lymphocytes and suppress autoimmune response. RATG has been widely used as immunosuppressive for aplastic anemia, for prevention of bone marrow, kidney & heart transplantation.[35]

3. MAB$_s$ in cardiovascular disorders

Abciximab is a Fab fragment of murine- human MAB that binds to integrin GPIIb/ IIIa receptor on activated

platelet and inhibit fibrinogen, Von Wille brand factor and other adhesion molecules from binding activated platelets. Thus preventing platelet aggregation. It is indicated as an adjunct to percutaneous Coronary Intervention (PCI) for prevention of cardiac ischemic complications.[36]

Alirocumab is a human MAB that target protein convertase subtilisin kexin type-9(PCSK9). PCSK-9 inhibitor prevents binding of LDL to receptor & increase hepatic uptake of LDL-C. It is indicated for familial hypercholesterolemia or clinical atherosclerosis to reduce additional LDL-C. It is approved in Europe and has been recommended for same indication in US by FDA advisory board. FDA has approved alirocumab as an adjunct to diet & maximally tolerated statin therapy for adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiac disease who require additional lowering of LDL-C[4].

Bococizumab: is a humanized MAB binding PCSK9 which may be a potential therapeutic option for reducing LDL-C level in patients with hypercholesterolemia. In a 24 week multicenter, double blind placebo controlled dose ranging study(NCTO 1592240), sc bococizumab 50, 100, 150, mg or 28 days placebo or bococizumab 200 & 300 mg showed significant reduction in LDL-C.[37]

Evolocumab injection: Humanized MAB targeting PCSK9. It is indicated for familial hypercholesterolemia, in patients with atherosclerosis, heart disease who require additional lowering of LDL-C. Approved by FDA on 27.9.2015.[4]

Erlizumab is in phase II clinical development for lowering LDL-C. Other Anti PCSK9 (AMG145, REGN727)[4]

ALX0081, ANTIGEN ($_V$ WF) nanobody indicated for thrombosis. It is in Phase I clinical development.[4,36]

MLN1202, antigen (CCR_2) humanized antibody indicated for atherosclerosis. It is in phase II trial.[4,36]

TB-402, antigen (Factor VIII) human antibody, indicated for deep vein thrombosis and atrial fibrillation. It is in phase I clinical study.[4,36]

Sheep polyclonal digoxin immune Fab - Indicated for treatment of digoxin toxicity.[4,36]

Canakinumab: IL1β antibody, being tested in MI, stroke& cardiovascular death in patients with increased CRP.[38]

Gevokizumab: IL1β antibody, being tested for acute coronary syndrome.[39]

4. MAB_s in asthma/ respiratory diseases

Mepolizumab injection: IL-5 antagonist MAB (Ig G1-kappa). Approved by the FDA on 4.11.2015 for treatment of asthma (as add on, in severe eosinophilic asthma).[40]

Omalizumab: Anti IgE recombinant humanized MAB, blocks binding of IgE to high affinity Fc receptor on basophil and mast cells. Approved for treatment of allergic asthma refractory to inhaled corticosteroids.[41]

Palivizumab: MAB binds to fusion protein of respiratory syncytial virus preventing infection in susceptible cells in the airways. It is used in neonates at risk for this viral infection and reduces the frequency of infection & hospitalization by about 50%.[6]

Reslizumab injection: IL-5 antagonist(IgG-4-kappa). Approved by FDA on 23.3.2016 as add on therapy for asthma and for maintenance & treatment of eosinophilic asthma.[6,24]

5. MAB_S in ophthalmology

Aflibercept: Targeting GD-2 glycolipid found on surface of tumor cell, was recommended for use in neovascular age related macular degeneration (NAMD) in 2013. On25.3.2015,it was approved for new indication like macular edema, macular degeneration & diabetic retinopathy.[42]

Bevacizumab: HumanizedIgG1 MAB that binds to VEGF and inhibits its binding to receptors on endothelial cells(antiangiogenic). First line agent for metastatic colorectal cancer. Off label use- intravitreal injection to slow the progression of neovascular macular degeneration. Neovascular glaucoma have been treated off label with bevacizumab. Used on a week or monthly basis for maintenance therapy.Side effects include risk of bleeding, infections and cerebral vascular accidents.[43]

Pegaptinib: Pegylated oligonucleotide a selective VEGF antagonist, it inhibiting binding of VEGF to its receptors. VEGF induces angiogenesis, increases vascular permeability& inflammation. All of which thought to be contribute to the progression of neovascular macular degeneration. It is given intravitreous injection(0.3 mg once every 6 weeks) to slow macular degeneration. Side effects should be monitoredlike elevation of IOP, & endophthalmitis. Rarely anaphylaxis or anaphylactoid reactions.[44]

Ranibizumab: Recombinant human IgG1 Fab that binds to VEGF-A receptors, prevents new blood vessel formation by blocking VEGF from binding to its receptors. It is used as intra-vitreal injection in patients with age related macular degeneration and sudden loss of vision due to macular edema following retinal vein occlusion. Approved by FDA on 6.2.2015 for new indications ie diabetic retinopathy, macular edema /degeneration.[45]

Eculizumab: Completed phase II study in USA for NAMD.[46]

Lampalizumab: In phase III clinical development for age related macular degeneration.[46]

RN6G: Antiamyloid MAB β40 &β42. It is under phase I clinical development for age related macular degeneration and primary open angle glaucoma.[47]

6. MAB_S in Blood disorders

Caplacizumab: Anti Von Willebrand factor immunoglobin (nanobody) for acquired thrombotic thrombocytopenic purpura (TTP). It induced faster resolution of the acute TTP episodes than placebo. Platelet protective effect of caplacizumab was maintained during treatment period. Side effects include increased bleeding tendency.[48]

Idarucizumab: Humanized Fab (fragment) MAB, approved by FDA on 16.10. 2015 for control of bleeding caused by anticoagulant dabigatran.[49]

Von Willebrand factor recombinant) Approved by FDA on 8.12 2015, to control bleeding episodes in patients with Von Willebrand's disease.[16]

7. MAB_s for HIV treatment: Recent advances have led the discovery of human MAB that are broadly neutralizing across many HIV-1 subtypes. These target multiple different epitops on the HIV envelop.[50] CD4 binding site specific.

bNAb—VRCO1, 3BNC 117 has shown antiviral activity in human. V3 glycan dependent bNAb, PGT-121, V2glycan dependent antibodies- CAP 256, PGDM 1400.[50]

8. In destroying disease causing organisms: MAB_s promote efficient opsonization of pathogenic bacteria (by coating with antibody) and enhance phagocytosis. MAB_s were found to protect chimpanzees against certain viral (hepatitis-B virus) and bacterial (E.Coli, H. influenza, Streptococcus sp. & Pseudomonas) infections.[51]

9. Miscellaneous uses of MAB_s

Bevacizumab a recombinant humanized anti-VEGF MAB. It is indicated for the treatment of cholangiopathy in Hereditory Hemorrhagic Telangiectasia (HHT). HHT is an inherited vascular dysplasia characterized by telangiectasia & visceral arteriovenous malformation, may lead to portal hypertension, biliary ischemia & high output cardiac failure. Uncurable condition, only liver transplantation is needed. Bevacizumab is effective in reducing bleeding & liver disease in HHT. It has also been used off label by intravitreal injection to slow the progression of neovascular macular degeneration.[52]

Denosumab: Human IgG2 MAB specific for human RANKL(Receptor Activator Nuclear Factor kappa –B) legend, it inhibits maturation of osteoclast(responsible for bone resorption). It is indicated for postmenopausal women with osteoporosis.[6]

Eculizumab: Humanized IgG MAB that binds C5, inhibiting its cleavage into C5a & C5 b(anti C5 MAB). Approved for patients with paroxysmal nocturnal haemoglobinuria (PNH) and dramatically reduces the need for RBCtransfusion and prevents symptoms like anemia, fatigue, thrombosis, haemoglobenemia by inhibiting intravascular haemolysis due to RBC lysis. Side effects include increased risk of meningococcal infection in patients receiving eculizumab.[6]

Obiltoxaximab Injection: MAB Anthrax Antitoxin, approved by FDA on18.3.2016. It is indicated for Anthrax prophylaxis and prevention and treatment of inhalation Bacillus anthracis. Raxibacumab is also B. anthracis toxin for inhalation anthrax.[53]

Omalizumab: Humanized recombinant anti IgG, anti Ig E MAB that bind Fc region of IgE, prevent binding on Fc ER1on mast cells & basophils. Free IgE leads to reduction in mast cells, basophil degranulation & histamine release. It is used in patients with chronic urticaria, reduces itching, numbers & size of hives and increase patient's health related quality of life. Dose 300mg every 4 weeks for 12-24 weeks. It is also approved for treatment of allergic asthma in adult and adolescent patient refractory to inhalational corticosteroids.[41]

Mouse anti-methamphetamine MAB: Anti methamphetamine MAB can reduce pharmacological effects of methamphetamine in rodent models of methamphetamine abuse. Mouse anti-methamphetamine MAB was selected and tested for preclinical study. This antibody was then converted in to a chimeric anti-methamphetamine MAB suitable for human use. In a phase I clinical study it proved safe with a half life of 18 days. Treatment- once every 3 weeks to aid in the protection from relapse.[54]

Siltuximab: Anti IL-6 chimeric MAB. First drug approved for treatment multicenteric Castleman's disease (MCD) in the US & EU having gained approval under the FDA priority review programme. MCD is a rare lymphoproliferative disorder with high morbidity that is caused by dysregulation of IL-6 production. It is not a malignant disease.[55]

Antibodies in ongoing phase 3 studies

AIN-457: a human Ig G1 MAB that target IL-17A in being evaluated in 3 ongoing phase3 studies in patients with various types of uveitis .It is given iv in a dose 10mg/kg once at base line & once 3 week later and patient were evaluated for9 months. Response criteria were met by 73%.[6]

Bapineuzumab: is a humanized Ig G1 MAB that target the N-terminus of amyloid beta and is currently being evaluated in 7 phases. Of these, 3 are extension study.[6] Evaluated for mild to moderate Alzheimer's disease.

Epratuzubab: is a humanized Ig G1 MAB that target CD-22on B cells. The MAB is being evaluated for patients with SLE.[6]

Otelixizumab: a humanized IgG1 MAB targets CD-3 on T cells It is undergoing evaluation in the phase 3DEFENP-1 study as a treatment for patients with newly diagnosed type 1 diabetes mellitus.[6]

Pagibaximab: is a chimeric Ig G1 MAB developed for the prevention of staphylococcal sepsis in very low birth weight neonates MAB targets lipoteichoic acid (component of staphylococcus cell wall). Dose10-90 mg/kg for 1-3 doses than weekly for 3 weeks. It is currently being evaluated in a phase 2b/3 study.[6]

Solanezumab: a humanized IgG1 MAB target soluble amyloid- beta is undergoing evaluation as a treatment for mild to moderate Alzheimer's disease.[6]

Teplizumab: is a humanized IgG1 MAB that target CD3 and has been engineered to have reduced binding to FcR. The 4 arm controlled phase 2/3 study (PROTÉGÉ study) in children and adults with recent onset type 1 diabetes is ongoing.[6]

CONCLUSION

MAB_s are established therapy for various diseases. However, they are genrally used to improve quality of life in patients with advanced malignant diseases, mainly as add on therapy or in combination with chemotherapy to prolong survival or if conventional drugs fail and in various autoimmune disorders. MAB_s are rapidly growing therapeutics and are being developed for a broad range of indications. However, new technologies and development of biosimilars will make these promising drugs more accessible and economical for common man.

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