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MONOCLONAL ANTIBODY THERAPY ROLE IN AUTOIMMUNE DISEASES

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Abstract:

Introduction: *Monoclonal antibody in the management of autoimmune diseases is considered a new and novel treatment strategy for many types of diseases including but not limited to autoimmune diseases, cancers, and demyelinating diseases. It is characterized by high high efficacy and tolerability. Side effects are notable issue when monoclonal are studied. Many have been shown to cause adverse events. These new medications are expensive, we have seen that most of the well-studied monoclonal antibodies are highly effective in many diseases*

Aim of work: *In this review, we will discuss the most recent evidence regarding the role of antibodies in the management of autoimmune diseases.*

Methodology: *We did a systematic search for the role of antibodies in the management of autoimmune diseases using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com).*

Conclusions: *Monoclonal antibody in the management of autoimmune diseases is considered a new and novel treatment strategy for many types of diseases including but not limited to autoimmune diseases, cancers, and demyelinating diseases. Side effects are notable issue when monoclonal are studied. These new medications are expensive, we have seen that most of the well-studied monoclonal antibodies are highly effective in many diseases. There are also hybridized or mutated next-generation monoclonal antibodies that have adverse events and higher tolerability. In this review, we discussed the most recent evidence regarding the role of antibodies in the management of autoimmune diseases.*

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INTRODUCTION:

Monoclonal antibody in the management of autoimmune diseases is considered a new and novel treatment strategy for many types of diseases including but not limited to autoimmune diseases, cancers, and demyelinating diseases. It is characterized by high high efficacy and tolerability. For example: I n multiple sclerosis (MS) and neuromyelitis optica (NMO) spectrum disorders, several monoclonal antibodies have been reported to decrease the number of relapses and modify disease activity. There are many promising antibodies including: the anti-α4 integrin (natalizumab), anti-CD52 (alemtuzumab), anti-CD25 (daclizumab) and anti-CD20 (ocrelizumab). Randomized clinical trials have showed that they effectively decrease the relapses.

Ocrelizumab is the first medication reported to significantly decrease brain volume loss. [1] In NMO, there are no approved monoclonal antibodies so far, however, rituximab, anti-complement C5 (eculizumab), anti-IL-6 receptor (tocilizumab), anti-CD19 (inebilizumab) and non-pathogenic anti-aquaporin 4 (aquaporumab) have been reported to be significantly effective, many monoclonal antibodies are being studied in clinical trials [2]. Aquaporumab is a recombinant human monoclonal antibody. The mechanism behind it lies in the fact that it competitively inhibits the binding of the pathogenic auto-antibody against aquaporin 4 in NMO patients; so, it is supposed to significantly specific with less side effects and adverse events.

Side effects are notable issue when monoclonal are studied. Many have been shown to cause adverse events. It is well established that Natalizumab and rituximab increase the risk of progressive multifocal leukoencephalopathy. [3] While Eculizumab increases the risk of meningococcal infection. Tocilizumab is known to cause intestinal diverticulitis that may lead to intestinal perforation.

These new medications are expensive, we have seen that most of the well-studied monoclonal antibodies are highly effective in many diseases. There are also hybridized or mutated next-generation monoclonal antibodies that have adverse events and higher tolerability. Target molecules of monoclonal antibodies have also been more disease specific. Most of those monoclonal antibodies have not yet been approved for many autoimmune diseases, however, their clinical implications should be considered in each patient, balancing the risks and benefits. [4-5]

In this review, we will discuss the most recent evidence regarding the role of antibodies in the management of autoimmune diseases.

METHODOLOGY:

We did a systematic search for the role of antibodies in the management of autoimmune diseases using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). Our search also looked for their role in demyelinating diseases, the characteristics of, evidence for and notable adverse events of each monoclonal antibody. All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: Monoclonal antibodies, autoimmune disease, multiple sclerosis, rheumatoid arthritis.

DIFFERENT TYPES OF MONOCLONAL ANTIBODY:

1- Natalizumab (Tysabri®):

Natalizumab is considered a humanized IgG4 monoclonal antibody against α4 integrin (CD49d), which is an adhesion molecule. This medication is considered one of the best and most well-studied monoclonal antibody treatment in many diseases especially the treatment of MS. It can block the binding of α4β1-integrin on the surface of lymphocytes to vascular cell adhesion molecule-1 (VCAM1) which is located on the surface of endothelial cells and in this way it prevents the passage of inflammatory immune cells (mainly T cells) through the gut and blood–brain barrier. [6-7] The major role of this medication currently are MS and Crohn's disease. It can be given intravenously once for four weeks.

In randomized placebo-controlled trials, It was found that it is effective in decreasing the relapses as well as preventing the occurrence of new lesions on MRI [1-2] In addition, another study showed it to be effective in decreasing the progression of disability in patients with MS especially those resistant to IFN-β1a [8]. But it was not effective in preventing the progression of cerebral atrophy [3]. The mechanism is unknown, however, researchers believe that the irreversible axonal damage secondary to demyelination in MS may be prevented by natalizumab.

The most dangerous side effect of natalizumab is progressive multifocal leukoencephalopathy (PML),

especially in patients who have John Cunningham virus (JCV) antibody. [9] The prevelance of PML in patients with natalizumab is estimated to be more than 1 per 1000, which is almost more than one hundred times above the average in normal population.[4] This is why it is extremely recommended to check the JCV antibody before starting natalizumab.

2- Alemtuzumab (Campath®/Lemtrada®)

Alemtuzumab is considered a humanized IgG1 monoclonal antibody, it works against CD52, which presents on the surface of many types of immune cells as well as sperms. Although the specific role of CD52 is unknown, CD52 is suggested to be vital for allowing lymphocytes to move freely by working as an anti-adhesion molecule [10] The exact mechanism is still largely unknown, however, the medication destroys CD52-expressing lymphocytes. This is belived to be due to the IgG subclass of alemtuzumab which is IgG1, this medication can lead to antibody-dependent cell-mediated cytotoxicity (ADCC) as well as complement-dependent cytotoxicity (CDC). It is usualy given intravenously every other day. [11]

There are many non-randomized longitudinal trials that shown alemtuzumab to decrease the recurrence or the relapses episodes in MS [12-13] In addition, there have been many randomized control trials which show it to be better than IFN-β for suppressing the relapse rate in MS [12_14]

The main side effects of it include but not limited to infusion-related reactions can occur in more than ninety percent and infections which is estimated to occur in around seventy percent. One of the reported side effects is increase in the risk of autoimmune thyroid disease [15]. Interestingly, though CD52 is highly present in sperms, no case reports mentioned its effect on quality no infertility.

3- Daclizumab (Zinbryta®)

Daclizumab is considered a humanized IgG1 monoclonal antibody against CD25, which is the α-subunit of the IL-2 receptor present on lymphocytes. Lymphocytes that have both CD4 and CD25 are known as T-regulatory, its function is to suppress Natural killing cell-mediated [16]. By blocking CD25, this medication leads to expansion of immune-regulatory NK cells in comparison to other lymphocytes and is believed to decrease MS plaques [16]. The medication is given subcutaneously once every four weeks.

It was found to decrease the attack rate in MS by around fifty percent in comparison tob the placebo [17]. Recent studies including two randomized control trials compared daclizumab with IFN-β. They concluded that daclizumab is better than IFN-β in decreasing the relapse rate and the new advent of MRI-detectable lesions [18-19] But, it was not better to IFN-β in improving the long-term progressive neurological disability.

The main side effects of this medication are infusion-related reactions and infections, which is similar to other antibodies. It can also lead to severe liver complications in some patients; so, the medication should not be used in patients with hepatic diseases. [20]

4- Rituximab (Rituxan®)

Rituximab is considered a chimeric IgG1 monoclonal antibody works against CD20, which is present on the surface of B cells during the maturation stages. Though the exact mechanism of CD20 is unknown, it is estimated to depress apoptotic death of CD20-expressing B cells in physiological conditions. It stimulated the apoptotic as well as cytotoxic (ADCC and CDC) cell death in CD20-expressing B cells. It is given intravenously in 375 mg m−2 body surface per day every week or four weeks [21]. It could also be loaded at 1000 mg per day once every two weeks for a total of 2 doses [22]. Additional dose might be given six to nine months after the first infusion according to the degree of recovery of blood B-cell levels.

In patients with MS or NMO, it is an off-label use currently, however, there are new promising reports that suggested the its effectiveness in refractory cases.

A randomized controlled trial concluded the effectiveness of rituximab in decreasing the attack rate and volume of MRI lesions in relapsing–remitting MS [23]. In primary progressive MS, a randomized controlled trial that showed that rituximab reduced the MRI lesion volume more than placebo [24] However, The progression of neurological disability, measured with the Expanded Disability Status Scale (EDSS), was not significantly decreased with rituximab but was estimated to be milder in younger patients. Although there is no a randomized blinded active-control trial comparing rituximab with other DMDs in MS, But reports suggested that rituximab is better to fingolimod in decreasing relapses and the formation of new lesions

on MRI in relapsing–remitting MS after the cessation of natalizumab because of the risk of PML [25]

The main side effects of rituximab include but not limited to infusion-related reactions and infections, similarly to other medications. A slight risk of PML has been reported in patients treated with rituximab, though no report showed increasing PML risk in MS patients [26]
Now, there has been no report of MS patients presenting PML with rituximab, however it is better to exclude JCV positivity before starting the treatment. Another relevant side effect of rituximab is reactivation of hepatitis B virus, which may result in severe hepatic failure [27]. So, it is extremely recommended to check for serum positivity for the hepatitis B virus antigen.

5- Ocrelizumab (Ocrevus®)

Ocrelizumab is considered a humanized IgG1 monoclonal antibody that works against CD20, similar to rituximab and ofatumumab. Due to the fact that ocrelizumab has more human derived polypeptides than rituximab does, ocrelizumab is supposed to have less risk of allergy response than rituximab.

This medication can be given intravenously once every twenty four weeks for ninety six weeks. A recent randomized control study compared the effectiveness of ocrelizumab and IFN-β in relapsing–remitting MS.[28] Ocrelizumab was better than IFN-β in suppressing the relapse rate and new advent of active MRI-detectable lesions. Additionally, , the progression of disability at twelve and twenty four weeks from initiating the medication was estimated to be milder in the ocrelizumab group than in the IFN-β group. Ocrelizumab is considered the first medication that has shown statistically significant improvement in progressive neurological disability. It has also been shown to be effective in primary progressive MS. In a randomized controlled study on primary progressive MS, it was better than placebo in reducing the relapse rate, MRI-detected lesion volume and rate of brain volume loss [29] When considering these results, we could conclude that ocrelizumab is the first medication to suppress the irreversible progression of neurological disability and brain atrophy in MS.

The main side effects are similar to other monoclonal antibodies: infusion-related reactions and infections, but the rate of infusion-related reactions was estimated to be around thirty five percent which is considered low for a monoclonal antibody [28] In addition, the rate of dangerous side effects was expected not to be higher in the ocrelizumab group than in the placebo [29]. In conclusion, ocrelizumab is one of the best and most effective as well as tolerable monoclonal antibodies.

6- Ofatumumab (Arzerra®)

Ofatumumab is considered a human IgG1 monoclonal antibody that work against CD20, similar to rituximab and ocrelizumab. The polypeptides of this medication are entirely from humans, this lead to the fact that allergy are less than expected among the monoclonal antibodies. As of 2016, this medication is only approved for chronic lymphocytic leukemia. This medication is often given intravenously once every week for the first 8 doses and once every four weeks for another four doses. [30]

Unfortunately, there are no clinical trial study the effectiveness of ofatumumab in MS and the medication is still at an experimental stage. But, due to its highly safety and tolerability, this medication might be a choice for the management of MS in the near future.

The main side effects of ofatumumab include infusion-related reactions and infections, as with other monoclonal antibodies. There's also a risk of hepatitis B virus, which can cause liver failure.

MONOCLONAL ANTIBODY THERAPIES IN PREGNANCY:

Monoclonal antibodies in general are not contraindicated in pregnancy and are not considered to increase the rate of miscarriage at present. But, it is important to know that an IgG antibody can pass through the placenta in the third trimester of pregnancy [31] Additionally, the fact that antibodies increase the risk of spontaneous abortion in the first trimester of pregnancy is not yet established. It is critical to take into consideration when giving monoclonal antibodies during the pregnancy. However, aquaporumab has been reported to decrease AQP4-Ab-mediated miscarriage and fetal death by competitively blocking the binding of the pathogenic AQP4-Ab that causes placentitis [32]

Considering these facts, at present, the usage of a monoclonal antibody in pregnant women must be considered in a personalized case by case method, calculating the risk to benefit ratio for the women and fetus.

SPECIAL EMPHASIS ON RITUXIMAB IN RHEUMATIC DISEASES:

Recently, Ritixumab (RTX) is a well-established biologic agent for the management of some rheumatic autoimmune diseases such as refractory rheumatoid arthritis (RA)[33]and anti-neutrophil cytoplasmic antibodies (ANCAs)-associated vasculitis (AAV). [34]

1- RTX in RA

Rheumatoid arthritis (RA) is a long-term autoimmune disorder that primarily affects joints. The first randomized placebo-controlled trial on long-standing active RA was done in 2004, it demonstrated that a single course of two infusions of RTX, alone or in combination with either cyclophosphamide or continued methotrexate, showed statistically significant improvement in clinical response at weeks twenty-four and forty eight week. Its efficacy and safety plus methotrexate, with or without glucocorticoids, in patients with active RA who did not respond to disease-modifying antirheumatic drugs (DMARDs) were examined in the DANCER study. Both RTX doses (ie, 500 mg or 1,000 mg on days 1 and 15) were strongly effective and very well tolerated. [35]

Additionally, the MIRROR study revealed that RTX dose escalation from two doses of five hundred mg to 2 doses of one thousand mg did not improve the symptoms. Retreatment strategy from week twenty four supported a sustained suppression of disease activity through to week 48. Further studies in patients with RA with inadequate response to antitumor necrosis factor (anti-TNF) therapies revealed that a single course of RTX correlated with methotrexate therapy provided significant improvements in disease activity and progression of radiological damage. A sustained clinical efficacy was better maintained after two courses of RTX about 6 months apart. [36]

An open-label prospective study (RESET) was done in 2012 confirmed that RTX is an effective management option for patients who not responding to a single TNF-α inhibitor. [37] The MIRAR study and real-life data indicate that switching to RTX is a safe option for patients with RA who failed on TNF antagonists. [38]

2- RTX in systemic lupus erythematosus (SLE)

Since B cells has a vital role in SLE, targeted B cell therapies proposed in these patients. [39] B cell depletion therapy based on RTX is not approved for SLE, however it is used to manage early onset and refractory disease. Initially RTX has was not designed for SLE patients, however many studies showed its use in SLE patients who are refractory to conventional treatments. It was found that RTX is a recommended option in SLE nephritis. [40]

Recently, RTX is used for more severe cases with the aim to achieve disease control rather than corticosteroid-sparing strategy in patients with lupus nephritis. Additionally, probably due to its efficacy in idiopathic autoimmune hemolytic anemia and idiopathic thrombocytopenia purpura (ITP), RTX is also used in patients with SLE complicated by thrombocytopenia and hemolytic anemia. RTX is less used in cases of cutaneous and musculoskeletal SLE involvement. The efficacy of RTX in mucocutaneous manifestations is not obvious, while RTX seems to be effective in articular manifestations. [41]

RTX was reported to be an effective in anti-phospholipid syndrome secondary to SLE in the prevention of recurrent thrombotic events [42] A new study showed that a single infusion of RTX was as effective as multiple doses with a reduction in cost therapy. [43]

3- RTX in Sjögren syndrome (SS)

Sjogren's syndrome is a disorder of your immune system identified by its two most common symptoms — dry eyes and a dry mouth. The condition often accompanies other immune system disorders, such as rheumatoid arthritis and lupus.

Recently, management of SS depends on symptomatic and supportive measures. As B cells has a major role in SS pathogenesis, RTX has been reported to be largely useful. A meta-analysis published in 2016 evaluated more than 270 subjects (145 RTX and 131 placebo) from four RCTs. They concluded no significant change in regard to lacrimal gland function,by Schirmer test, while an improvement in salivary gland production and fatigue were described at twenty four weeks was noted.

Another study reported on forty-one patients with SS an improvement at 120 weeks in unstimulated saliva flow rate and a decrease in labial salivary gland lymphocytic infiltration as assessed by focus score in patients treated with RTX in comparison to patients

treated with conventional therapies.

RTX has been shown to be effective at six months as assessed by both the SS responder index and ultrasonography. [44] According to recently published SS treatment recommendations, RTX should be used in selected patients who have not responded to conventional therapies for sicca syndrome and for some extra-glandular manifestations. [45]

AUTOANTIBODIES AND VACCINATIONS:

RTX was reported to affect vaccine immunogenicity, so it is important to consider the right timing of vaccines in relation to RTX administration. Because of that it is better results in terms of humoral response are reported six months or more after RTX dosing.

Vaccinations should be considered at least four weeks before RTX administration. Especially, a significant humoral response impairment has been studied for influenza and pneumococcal vaccinations. However, no data are available on the effects of RTX on hepatitis B virus (HBV), human papilloma virus or yellow fever vaccines.

Screening serologies for HBV and hepatitis C virus (HCV) is a must. In patients with HBsAg and anti-HBc negativity, vaccination is recommended to be given before RTX.in contrast to, patients who are HBsAg and/or anti-HBc positive should be referred to a hepatologist for further consideration.

CONCLUSIONS:

Monoclonal antibody in the management of autoimmune diseases is considered a new and novel treatment strategy for many types of diseases including but not limited to autoimmune diseases, cancers, and demyelinating diseases. Side effects are notable issue when monoclonal are studied. These new medications are expensive, we have seen that most of the well-studied monoclonal antibodies are highly effective in many diseases. There are also hybridized or mutated next-generation monoclonal antibodies that have adverse events and higher tolerability. In this review, we discussed the most recent evidence regarding the role of antibodies in the management of autoimmune diseases.

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