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REVIEW

Anti-interleukin and associated receptors monoclonal antibodies therapy in autoimmune diseases

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There are nearly 40 approved monoclonal antibodies (mABs) in the U.S. for different diseases. These drugs are increasingly using in different autoimmune diseases, including rheumatoid arthritis (RA), asthma, psoriasis, systemic lupus erythematosus (SLE), atopic dermatitis (AD), multiple sclerosis (MS), and type 1 diabetes (T1D). Several phase 2 and 3 studies reported the clinical improvement due to treating with mABs. However, some adverse events (AEs) such as infections, injection-site reactions are frequently reported. In addition to approved diseases, off-label uses also led to some new results, which may cause reviewing the drug for other diseases. In this review, it was tried to discuss on the role of mABs that target interleukins or their associated receptors in treatment of autoimmune diseases. Moreover, approval statues, efficiency, safety and the possible associated AEs of the mABs on the market, based on the least clinical trials were also discussed.

Keywords: Monoclonal antibody; autoimmune disease; anti-interleukin therapy; interleukin inhibitor.

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Introduction

The commercial development of therapeutic monoclonal antibodies (mABs) commenced about 40 years ago by approving muromonab-CD3 in 1986. Since then, various mABs were approved or currently are in review. About 40 mABs are currently licenced for different diseases and conditions, including cancer, transplantation, infectious disease, chronic inflammation, and autoimmune diseases. Some of these are approved for certain condition, but are also using in treating another disease. For example, rituximab is one of the most-used mABs with a high global sale in 2013, was approved in 1997 for treating non-Hodgkin's lymphoma. However, now it is using in a wide range of diseases such as autoimmune diseases [1]. Corticosteroids are the most commonly and also the effective way to control autoimmune diseases, while these treatments are along with serious adverse effects.

There are several types of autoimmune diseases, which responded to mABs. Rheumatoid arthritis (RA), asthma, psoriasis, systemic lupus erythematosus (SLE), atopic dermatitis (AD), multiple sclerosis (MS), and type 1 diabetes (T1D) are the most common autoimmune diseases that are

trying to be treated with different mABs. Since in these diseases, immune responses are responsible for development of them, suppression of immune system could help to control these diseases. These suppressions may affect B cells or T cells responses. Targeting interleukin (IL)s is used to inhibit aggressive immune responses. In this review, it was tried to evaluate available mABs, which target interleukins or their receptors in order to control autoimmune diseases progression. Approval statues, efficiency, safety and associated adverse events (AEs) of the mABs on the market were also discussed.

Anti-Interleukin and their receptor monoclonal antibodies

IL-1β

Canakinumab

Canakinumab is an anti-IL-1β mAB that binds selectively and with high affinity to human IL-1β and has a long half-life. It was approved for using as monotherapy or in combination with methotrexate (MTX) for treating active systemic juvenile idiopathic arthritis (SJIA) in children 2 years of age and older. A small phase 2 study, which enrolled 23 children ages 4-19 years with active SJIA, introduced canakinumab as a promising therapy for active SJIA [2]. This therapy has demonstrated the steroid-sparing effects. It also claimed that it was generally well tolerated, and few patients experienced injection-site reactions (ISRs). No deaths, macrophage activation syndrome (MAS), or discontinuing the study due to AEs was reported. However, some AEs, including, cough, abdominal pain, vomiting, diarrhea, and pyrexia with mild to moderate in severity were observed. Subsequently, two other phase 3 clinical trials have been carried out to evaluate the efficiency of canakinumab in SJIA patients [3]. In trial 1, 84 SJIA patients, ages 2-19 years, were randomly assigned in a double-blind fashion, to a single subcutaneous dose of canakinumab or placebo. At day 15, canakinumab led to having more adapted JIA ACR 30 response compared to placebo (36 of 43 [84%] vs. 4 of 41 [10%]). In trial 2, it was found that the rate of flare in canakinumab group was significantly lower than placebo. Additionally, in the patients who were treated with canakinumab, the average glucocorticoid dose was reduced or even was discontinued in 33% of patients. Similar to the previously discussed study, infections were more frequently in canakinumab group. In contrast to result of Ruperto *et al*. [2], 5 patients experienced MAS in trial 2 (4 in canakinumab vs. 1 in the placebo). Recently, it was concluded that MAS is independent to canakinumab. Additionally, it could be occurred in SJIA patients with controlled disease by this treatment [4]. Moreover, increasing the risk of infections with canakinumab has been highlighted.

In addition to SJIA patients, those with RA may also benefit from canakinumab. A phase 2 placebo-controlled study had been carried out, which demonstrated that addition of canakinumab could improve therapeutic responses among active RA patients [5]. Although some few ISRs were observed, no safety concerns were raised with canakinumab therapy. Furthermore, no unusual or opportunistic infections were observed in canakinumab group.

Gevokizumab

Gevokizumab is another mABs, which targets IL-1β and has not been approved so far. It has a suitable half-life of (about 23 days), which leads to have a monthly infusion. Recently, two distinct randomized, double-blind, placebo-controlled, phase 2 studies associated with the effects of gevokizumab on insulin production in subjects with well-controlled T1D have just finished (NCT01788033, NCT00998699). We are looking forward to the results of these two trials. Recently, two patients with severe, recalcitrant geralized pustular psoriasis (GPP) were treated with the 60 mg gevokizumab subcutaneously every 4 weeks for a total of 3 injections [6]. No significant AEs were observed, and both patients showed the substantial initial clinical response to gevokizumab.

IL-2R

Daclizumab

Daclizumab is a humanized mAb of immunoglobulin (Ig)G1 subtype that blocks the interaction of IL-2R (CD25) with IL-2. Primarily, its usage was limited to prevention of organ transplant rejections. Recently, U.S. food and drug administration (FDA) has accepted biologics license application for zinbryta (daclizumab high-yield process) for treatment of MS. In 2004, the results of a phase 2 open label baseline-to-treatment trials of daclizumab in 10 MS patients with the incomplete response to interferon-beta (IFN-β) therapy and high brain inflammatory and clinical disease activity were reported [7]. The results of that study demonstrated a significant improvement in several clinical outcome measures. In 2007, a phase 2 trial in relapsing-remitting MS was completed, which demonstrated daclizumab can be effective in reducing lesions and improving clinical scores [8]. Recently, the result of a phase 3 clinical trial involving 1841 patients with relapsing–remitting MS were published [9]. The effect of daclizumab compared to IFN-β1a was evaluated, and it was found that daclizumab high-yield process was more effective. However, the rates of

infection, rash, and abnormalities on liver-function testing were higher with daclizumab. In the overall, transient thrombo-cytopenia, skin rashes, lymphadenopathy, infections, elevation of liver function tests (LFTs), and ISRs are the most frequently AEs of daclizumab administration.

Basiliximab

Basiliximab is a chimeric mouse-human mAB that similar to daclizumab targets IL-2R of T cells. It was approved in 1998 for prevention of kidney transplant rejection. In addition to that, treatment of patients with psoriasis was reported in different studies [10-12]. In the majority of these studies, no AE was observed. However, in a study, a marked but transient myalgia of the upper limbs after the infusions was reported [10].

IL-4R

Dupilumab

Dupilumab is a human mAB, which targets IL-4Rα and causes blocking of IL-4 related to IL-13 signaling. Although this mAB has not been approved, its effectiveness for treatment of AD and asthma was reported. So far, 3 studies on the role of this drug in the treatment of AD have been conducted, which were reported promising results [13-15]. Interestingly, this therapy leads to lower rate of infection. Dupilumab was also found as a new therapeutic option in patients with moderate to severe asthma [16]. Nasopharyngitis, nausea, ISRs, and headache are the possible dupilumab associated AEs. In addition to AD and asthma, according to our study on the critical role of IL-4 in pemphigus [17], in a very recently published study of author, dupilumab was introduced as a new therapy in pemphigus [18].

IL-5/IL-5R

Mepolizumab

Mepolizumab is a very recently approved mAB in the U.S. for treatment of patients with severe asthma and an eosinophilic phenotype (≥ 12 years old) that binds to IL-5 with high affinity. Looking for the benefit of this treatment for severe refractory eosinophilic asthma patients, several clinical trials have been carried out (reviewed by Keating [19]). Additionally, there are several ongoing studies of mepolizumab in severe refractory eosinophilic asthma. Although mepolizumab showed an acceptable tolerability profile across clinical trials, some AEs were reported that the most frequently of them are nasopharyngitis, headache, upper respiratory tract infection, and ISRs.

Reslizumab

Reslizumab is an IL-5 inhibitor and leads to prevention from interacting of this cytokine with its receptor (IL-5Rα). The reslizumab biologics license application was accepted for standard review by the FDA [20]. At the time of this manuscript, there are different completed phase 2 and 3 trials of reslizumab in eosinophilic asthma patients in addition to two currently ongoing (NCT02452190, NCT02501629).

As a pilot study, Leckie *et al.* [21] conducted a small double-blind, randomized, multicenter trial and suggested that reslizumab can be safely used in severe steroid-treated asthma. As the other attempt, in 2011, a phase 2 multi-center randomized placebo-controlled trial revealed that reslizumab could lead to a significantly greater reduction in sputum eosinophils, improvements in airway function as well as a trend toward greater asthma control compare to patients, who were receiving placebo [22]. This drug was generally well tolerated, but some AEs, including nasopharyngitis, fatigue, and pharyngolaryngeal pains were observed. Subsequently, two other phase 3 trials on effect of this drug in uncontrolled asthma patients confirmed the high ability of reslizumab for treating asthma [23,24]. It seems that 3.0 mg/kg, once every 4 weeks be a favorable dose of reslizumab.

Benralizumab

The same as mepolizumab and reslizumab, benralizumab could prevent interaction of IL-5 with IL-5R. It binds to the IL-5Rα which is expressed on eosinophils and basophils. This action made it an attractive option for use in the management of asthma. Benralizumab is in phase 3 study of patients with asthma, which its results for benralizumab in severe asthma are expected in 2016 [20]. In 2014, a phase 2b, randomised, double-blind, placebo-controlled, dose-ranging study, includes 324 eosinophilic individuals and 282 non-eosinophilic individuals, ages 18-75 [25]. As the results, it was suggested that 20 mg and 100 mg of benralizumab with a special protocol (two subcutaneous injections every 4 weeks for the first three doses, then every 8 weeks, for 1 year) can reduce asthma exacerbations in adults with uncontrolled eosinophilic asthma. In issue of AEs, no clinically relevant differences between benralizumab and placebo were observed. The effectiveness of this drug was also demonstrated in a phase 2 clinical trial, which randomized 110 patients with asthma [26]. The reduction in the rate and severity of exacerbations was reported as the benefit of 1 dose of benralizumab. Headache, dizziness, cough, pyrexia, bronchitis, anxiety, muscle spasms, and hyperhidrosis are considering as the possible AEs of treatment with benralizumab. Furthermore, several ongoing controlled clinical trials are investigating the efficacy and safety of the benralizumab in the treatment of adult asthmatic patients

with different levels of asthma severity (NCT02322775, NCT02075255, NCT02258542, and NCT01928771)

IL-6/IL-6R

Olokizumab

Olokizumab is considered as another biological agent for blocking IL-6 signaling pathways. It is a humanized mAB that targets IL-6 and can cause improvement of RA. In a randomized, double-blind, placebo-controlled study, includes 38 RA patients, who were followed for 12 weeks [27]. Subcutaneous administration and intravenous olokizumab at the dose of 3 mg/kg and 0.1 mg/kg, respectively were compared to the placebo group. It was observed that single-dose subcutaneous administration of olokizumab markedly reduced free IL-6 levels as well as suppression of C-reactive protein (CRP) in RA patients. A phase 2 clinical trial elevated efficiency and safety of olokizumab in moderate-to-sever RA patients, who did not respond to treatment with tumour necrosis factor (TNF) inhibitors [28]. The results of the study demonstrated that olokizumab caused improvements in efficacy variables compare placebo.

Sirukumab

Sirukumab is a human anti-IL-6 mAB that similar to other IL-6 signaling blocker cloud prevent interaction of IL-6 with its receptor. This drug has been or is being evaluated as a treatment for RA in several studies. In a phase 2 study by Smolen *et al*. on evaluation of safety and efficacy of subcutaneous sirukumab active RA patients despite MTX theray, 36 patients were randomised to placebo or sirukumab [29]. Moreover, in the second part of that study, 151 patients were randomised to sirukumab (four different subcutaneous doses/regimens) or placebo. Although there were no significant differences between four sirukumab groups, all of them led to significantly more efficacious improvement than placebo. Infections were considered as the most common AE, but no dose effect associated with AEs was observed among the four sirukumab groups. In addition to the efficiency of sirukumab on RA patients, there is a paucity of data to support the possible role of this anti-IL-6 in those with SLE [30]. Regardless to those with cutaneous lupus erythematosus (CLE), 15 patients with SLE were randomized to 4 infusions of placebo or 10 mg/kg sirukumab every 2 weeks. As the conclusion, treatment with intravenous sirukumab infusions was generally well tolerated in SLE patients. In general, this treatment may be along with some AEs, including infections, gastrointestinal disorders, elevation of LFTs, pharyngolaryngeal pain, headache, ISRs.

Tocilizumab

Tocilizumab is a humanized mAB that acts as an anti-IL-6R. FDA has been approved this drug for treatment of RA and SJIA in 2010 and 2011, respectively. However, there is a paucity of data to support the possible effect of tocilizumab in treatment of other autoimmune diseases, including SLE and MS. In RA patients, tocilizumab could be used as the monotherapy or in combination with MTX or disease-modifying antirheumatic drugs (DMARDs). Evidence of successfully treatments of RA and SJIA patients with tocilizumab are not rare. Indeed, there are plenty of proofs to confirm the efficiency of this drug in treatment of RA and SJIA. The recommended dosage of intravenous dose of tocilizumab by FDA, regardless of monotherapy or in combination with MTX or DMARDs, is 4 mg/kg once 4 weeks [31] followed by an increase to 8 mg/kg every 4 weeks, based on clinical response. However, the dose of subcutaneous administration depends on body weight of patients. 162 mg every other week is recommended for patients less than 100 kg weight, which could be followed by an increase to weekly administration, depending on clinical response. For those above 100 kg weight, 162 mg once week is recommended. The most frequently AEs are infections, nasopharyngitis, headache, hypertension, increased alanine aminotransferase (ALT), and ISRs.

Different studies have suggested that tocilizumab could be a suitable therapy in those with SLE. In 2010, an open label, dose-escalating, phase 1 study, containing 16 (1 was excluded) patients with mild-to-moderate SLE were treated bi-weekly for 12 weeks [32]. This study was the first phase 1 clinical trial showing the efficacy of tocilizumab on SLE patients. A significantly improvement in disease activity was recorded in 8 of 15 patients (53%). In another study, an astonishing outcome due to intravenously administration of tocilizumab as the dose of 8 mg/kg once every 4 weeks was reported [33]. It is noteworthy that before starting treatment, the level of IL-6 markedly increased (1160 pg/ml). Administration of tocilizumab also let the tapering of prednisolone from 15 mg/d to 5 mg/d. Makol *et al.* [34] commenced tocilizumab for a SLE patient, who did not respond to several therapies. After revealing the high level of IL-6, this therapy was started and resulted in achieving remission in addition to tapering corticosteroid therapy.

The off-label use of tocilizumab is not limited to SLE. There are some case reports of treatment MS patients with this mAB. In one of these cases, despite the lack of respond to IFN-β, blocking IL-6 signaling pathway by tocilizumab was found as a promising therapy, which induced a clinical and radiological stabilization [35]. In the other case, a patient with both MS and RA was commenced on tocilizumab at 8 mg/kg every 4 weeks [36]. This caused complete remission of

MS at the second of administration, which lasted for more than 5 years.

Sarilumab

Sarilumab is a fully human anti-IL-6Rα mAb, which recently has been appeared as a novel therapeutic option for treatment of RA. There are different evidences that this antibody could inhibit IL-6 signaling in a dose dependent manner [37-39]. A 12-week phase 2 study conducted by Huizinga *et al.* [40] evaluated safety and efficiency of sarilumab in different subcutaneous protocols. That study includes 306 patients with active RA who were randomised to receiving placebo or sarilumab (five different subcutaneous doses/regimens). Firstly, it was found that the ability of sarilumab in improvement signs and symptoms of RA was higher than placebo. Secondly, sarilumab at the dose of 150 mg and 200 mg every other week were introduced as the most favorable protocols. Analogous to the other IL-6 signaling blockers, the most common AE was infections. In a recently phase 3 study, efficiency and safety of sarilumab in combination with MTX in RA patients were evaluated [41]. That study has been used sarilumab with the dose of 150 mg or 200 mg every 2 weeks. According to 53 weeks sarilumab, it was concluded that it caused the statistically significant improvements in comparison to placebo. In addition to infections, elevation in ALT and total cholesterol levels was more frequently in sarilumab group.

IL-12/IL-23

Ustekinumab

Because of binding of ustekinumab to the shared p40 subunit of both IL-12 and IL-23, it results in blocking of their cognate receptors. It is a human IgG1, which was approved by FDA to treat moderate-to severe plaque psoriasis, in 2009. Subsequently, it licensed as a treatment of adults with active psoriatic arthritis), alone or in combination with MTX. Meng *et al*. [42] performed a systematic review of studies related to randomized controlled trials of ustekinumab to evaluate efficiency, safety and dose-dependency of ustekinumab compared to the placebo. In the overall, that study includes 11381 patients from 9 associated studies between 1990 and 2013. It was concluded that those who were treated with ustekinumab, experienced a significant improvement within 12 weeks, based on several factors, including psoriasis area and severity index (PASI) physician's global assessment (PGA) and dermatology life quality index (DLQI). Efficiency did not differ significantly in two dosages of 45 mg and 90 mg at the end of 12 weeks. Additionally, despite the more response of patients to ustekinumab, no significant difference between AEs due to this mAB (at the dose of 45 mg or 90 mg) and placebo were seen. Although the first line treatment for active psoriatic arthritis is TNF inhibitors, ustekinumab could be an alternative therapy for this disease. The higher efficiency of ustekinumab than placebo in treatment of psoriatic arthritis at the end of week 24 was concluded in various studies (reviewed by McKeage [43]). There are controversial results associated with treatment of AD patients with ustekinumab. In 2012, an adult with AD was treated with ustekinumab [44]. Two weeks after the ustekinumab administered in a single dose of 45 mg, a substantial clinical improvement was observed. One year later, another successfully treatment of severe refractory AD in an adolescent patient with ustekinumab was reported [45]. The first signs of clinical improvement were appeared 1 month after the first ustekinumab administration in a single dose of 45 mg. After the subsequent administrations, the disease was completely controlled without any ustekinumab associated AE. Conversely, two adult cases with AD, who did not respond to ustekinumab, were reported [46]. Indeed, initiation of ustekinumab at the dose of 45 mg caused no improvement. In another interesting case, treatment with ustekinumab was started in a patient with severe psoriasis refractory to conventional systemic treatments and childhood history of atopy (AD, asthma, seasonal rhinitis) [47]. Surprisingly, this treatment led to exacerbation of AD, but remission of psoriasis. Recently, ustekinumab therapy in patients with psoriasis and MS indicated the possible capability of this drug for treatment of MS [48]. However, Longbrake and Racke do not believe to efficiency of ustekinumab for treating MS [49]. Using the ustekinumab may be along with infections, headache, ISRs, and development of anti-ustekinumab antibodies.

Briakinumab

Briakinumab is a fully human, IgG1 mAB and similar to ustekinumab and targets the shared p40 subunit of IL-12 and IL-23. In early 2011, this antibody had its approval application withdrawn in the U.S. and Europe to conduct further analysis and clinical trials in and it has never been resubmitted for approval. Despite the withdrawing of briakinumab, the results of clinical trials in phase 2 and 3 imply to its efficiency to treat plaque psoriasis (reviewed by Traczewski and Rudnicka [50]). In a phase 3 study, includes 347 patients with moderate to severe psoriasis, who were treated with briakinumab, etanercept or placebo, outcomes after 12 weeks were compared between these groups [51]. A superior efficacy of briakinumab to both placebo and etanercept were reported. In another comparative study, 317 moderate to severe psoriasis patients were randomized to receive briakinumab or MTX. Although serious infections and cancers were reported more frequently in briakinumab group, it showed a higher efficacy than MTX [52]. Although this antibody was previously investigated in some

autoimmune diseases, such as RA and MS, there is no recommendation for using that in these diseases [53]. Between the studies, infection, non-melanoma skin cancers, major adverse cardiovascular events, ISRs, nasopharyngitis, and hypertension were observed in patients, who were treated with briakinumab.

IL-13

Lebrikizumab

Lebrikizumab is a humanized mAB that targets IL-13 and it is undergoing evaluation in different phase 3 studies of asthma patients. It was not approved so far, but it may be submitted by the end of 2016, if it shows the promising results in ongoing phase 3 trials. This drug has been tested in mild asthmatics and uncontrolled asthmatics, which was reviewed by Jose Maselli *et al*. based on the latest studies [54]. In overall, the results of different reviewed studies demonstrated that lebrikizumab is promising and safe therapy in asthma. However, unexpected safety issue is warned for future studies. Although the ISRs and incidence of musculoskeletal events were observed in lebrikizumab treated patients, Maselli *et al*. concluded that the reported rates of AEs are similar compared to placebo.

Tralokinumab

Tralokinumab is a human IgG4 mAB, currently in clinical development for the treatment of severe and uncontrolled asthma. Different phase 1 and 2 studies found tralokinumab as an effective treatment with favorable outcomes for uncontrolled, severe asthma (reviewed by Baverel *et al*. [55]). Worsening asthma, ISRs, bronchitis, sinusitis, and injection-site pruritus were seen in patients treated with tralokinumab.

IL-17

Brodalumab

Brodalumab is a mAB that inhibits the IL-17R receptor with the emerging roles in treating psoriasis disease. Brown *et al.* reviewed all the phase 2 studies associated with the efficiency of anti-IL-17 agents for treatment of psoriasis. In respect to brodalumab, it was introduced as a mAB that leads to the higher degree of improvement in individuals with psoriasis compare to placebo. In general, the recorded AEs in brodalumab groups were more frequently than placebo groups. The most common reported AEs were nasopharyngitis, upper respiratory tract infection, arthralgia, and injection-site erythema. A phase 3 study evaluated the effects of briakinumab on quality of life and work productivity measures in patients with moderate to severe psoriasis. A total of 1465 patients were received briakinumab every 4 weeks, every 12 weeks, or placebo and were monitored through weeks 12 and 52. A significantly clinical improvement compared to placebo was reported. Additionally, patients benefit from administration of briakinumab every 4 weeks more than every 12 weeks [56].

Despite the satisfactory result of using brodalumab in psoriasis patients, it seems that this agent in not a suitable treatment for RA patients. Martin *et al.* tested different doses of brodalumab subcutaneously or intravenously in MTX-resistant RA patients, but no evidence of a clinical response was found [57]. The relatively same study was also performed by Pavelka *et al*. [58], which led to failure of achievement any meaningful clinical efficacy.

IL-17A

Ixekizumab

Ixekizumab is a humanized IgG4 mAB, which binds the IL-17A homodimer, thereby blocking the binding of IL-17A to the IL-17R. Several phase 1, 2 and 3 clinical trials evaluated the efficacy, safety and tolerability of ixekizumab in patients with psoriasis, which recently were reviewed comprehensively by Dyring-Andersen *et al.* as an expert review article. In conclusion, ixekizumab was identified as a promising drug for treating psoriasis. Regardless to similar AEs to placebo, mild ISRs and neutropenia were the most common in ixekizumab groups. In issue of using ixekizumab in RA patients, as the first attempt, in a phase 1 study the safety, tolerability and efficiency of this biological agent were evaluated [59]. This study demonstrated that the combination of ixekizumab to oral DMARDs improved signs and symptoms of RA, with no strong adverse safety issue. In another study, the results of a phase 2 clinical trial revealed that ixekizumab could improve RA signs and symptoms in both inadequate responders to TNF Inhibitors group as well as RA patients, who were naive to biologics treatments [60]. Additionally, no unexpected safety concern was observed.

Secukinumab

Secukinumab is a novel human IgG1 mAB that targets IL-17A and received marketing approvals for treatment of psoriasis in US in 2015. It selectively binds to the free IL-17A, inhibiting its interaction with the IL-17R. FDA has been approved it for treating moderate to severe plaque psoriasis in not responder adults to medication applied directly to the skin. Furthermore, it was recommended that it be injected once a week for five consecutive weeks followed by an injection once every four weeks. Several phase 2 and 3 studies have been or is being evaluated this drug for patients with moderate to severe plaque psoriasis. In a recently meta-analysis, 8 randomized controlled trials (RCTs) with a

Table 1. Therapeutic monoclonal antibodies available for treating autoimmune diseases

Target	mAB	Molecular format	Associated autoimmune diseases	First FDA approval year	Most frequently reported AEs
IL-1β	Canakinumab	Human IgG1	SJIA (aged ≥2 years) and RA	2009	Infections, abdominal pain, ISRs, and MAS.
	Gevokizumab	Humanized IgG2	T1D	N/A	N/A
IL-2R	Daclizumab	Humanized IgG1	MS	1997	Transient thrombo-cytopenia, skin rashes, lymphadenopathy, infections, elevation of LFTs, and ISRs.
	Basiliximab	Chimeric IgG1	Psoriasis	1998	Myalgia.
IL-4Rα	Dupilumab	Human IgG4	AD, asthma, and pemphigus	N/A	Nasopharyngitis, nausea, ISRs, and headache.
IL-5	Mepolizumab	Humanized IgG1	Severe eosinophilic asthma (aged ≥12 years)	2015	Nasopharyngitis, headache, upper respiratory tract infection, and ISR.
	Reslizumab	Humanized IgG4	Severe eosinophilic asthma	N/A	Nasopharyngitis, fatigue, and pharyngolaryngeal pain.
IL-5Rα	Benralizumab	Humanized IgG1	Eosinophilic asthma	N/A	Headache, dizziness, cough, pyrexia, bronchitis, anxiety, muscle spasms, and hyperhidrosis.
IL-6	Olokizumab	Humanized IgG4	RA	N/A	Headache, infection, decreased white blood cells, and abnormal LFTs.
	Sirukumab	Human IgG1	RA	N/A	Infections, Gastrointestinal disorders, elevation of LFTs, pharyngolaryngeal pain, headache, and ISRs.
IL-6R	Tocilizumab	Humanized IgG1	RA, SJIA (aged ≥2 years), SLE, and MS	2010	Infections, nasopharyngitis, headache, hypertension, increased ALT, and ISRs.
	Sarilumab	Human IgG1	RA	N/A	Infection, high ALT, and high total cholesterol levels.
IL-12/IL-23	Ustekinumab	Human IgG1	Psoriasis	2009	Infections, headache, ISRs, development of anti-ustekinumab antibodies.
	Briakinumab	Human IgG1	Psoriasis	N/A	Infection, nonmelanoma skin cancers, major adverse cardiovascular events, ISRs, nasopharyngitis, and hypertension.
IL-13	Lebrikizumab	Humanized IgG4	Asthma	N/A	The ISRs, musculoskeletal events.
	Tralokinumab	Humanized IgG4	Asthma	N/A	Worsening asthma, ISRs, bronchitis, sinusitis, and injection-site pruritus.
IL-17R	Brodalumab	Human IgG2	Psoriasis	N/A	Nasopharyngitis, upper respiratory tract infection, arthralgia and injection-site erythema.
IL-17A	Ixekizumab	Humanized IgG4	Psoriasis and RA	N/A	Nasopharyngitis, upper respiratory infection, headache, neutropenia, and mild ISRs.
	Secukinumab	Human IgG1	Psoriasis	2015	Infections, neutropenia, and exacerbations of crohn's disease.
IL-23	Guselkumab	Human IgG1	Psoriasis	N/A	Infections.
	Tildrakizumab	Humanized IgG1/k	Psoriasis	N/A	Bacterial arthritis, lymphedema, melanoma, stroke, epiglottitis, and knee infection.

IgG, immunoglobulin G; SJIA, systemic juvenile idiopathic arthritis; T1D, type 1 diabetes; MS, multiple sclerosis; AD, atopic dermatitis; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; N/A, not applicable; ISRs, injection-site reactions; MAS, macrophage activation syndrome; LFTs, liver function tests; ALT, alanine aminotransferase

total of 3213 psoriasis cases were included [61]. It was revealed that in addition to significantly higher and more rapid clinical improvement, there were no meaningfully differences in emerge AEs between secukinumab and placebo group. In a very recently review study, based on phase 2 and 3 studies, secukinumab was introduced as a superior to the TNF inhibitor etanercept for treatment of plaque psoriasis [62]. Additionally, this drug was found to be effective in treating patients with psoriatic arthritis. Moreover, some AEs, including infection, neutropenia, and worsening of crohn's disease were warned.

IL-23

Guselkumab

Guselkumab is a human IgG1 mAB in that specifically blocks IL-23. There are limited studies associated with this mAB. In 2014, a phase 1 study evaluated the safety, tolerability, and clinical response of guselkumab in patients with moderate to severe plaque psoriasis for the first time in human [63]. That study includes 24 patients, who were randomized to receive a single dose of placebo or guselkumab in four different doses (10 mg, 30 mg, 100 mg, or 300 mg). The results of that study implied to advantage of guselkumab compare to placebo. Patients, who were received a higher dose (300 mg), achieved the greatest percentage of improvement in PASI (75%). In contrast, those in the

placebo group did not improve. Despite the small sample size of that study, it was concluded that guselkumab alone could be considered as a promising therapy for psoriasis. In general, guselkumab was well tolerated. However, 13 of 20 (65%) and 2 of 4 (50%) in the combined guselkumab and placebo groups, respectively, experienced at least 1 AE, which the most common of them was infections. Recently, in phase 2 trial, the efficiency of guselkumab with different doses, adalimumab, and placebo in patients with moderate to severe plaque psoriasis [64]. The results demonstrate that guselkumab led to significantly higher improvement compare to adalimumab and placebo ($P<0.05$ and $P<0.02$, respectively). It was reported that guselkumab at the dose of 100 mg every 8 weeks was more effective than the other protocols.

Tildrakizumab

Tildrakizumab is a humanized anti-IL-23p19 mAB, which is evaluating for treatment of plaque psoriasis. In contrast to ustekinumab and briakinumab, this mAB does not target the p40 subunit of IL-23. Thus it only leads to blockage of IL-23 signaling without affecting IL-12. The results of a phase 2b randomized, double-blind, trial, which was conducted in 355 adults with chronic plaque psoriasis demonstrated that tildrakizumab is superior to placebo [65]. It also was generally safe and well tolerated. During the study, bacterial arthritis, lymphedema, melanoma, stroke, epiglottitis, and knee infection was recorded as the possible tildrakizumab-related serious AEs.

Discussion

Despite the advanced in medical sciences, treating of autoimmune diseases remained a controversial topic. Generally, corticosteroids are considered as the effective treatment, but with numerous serious side effects. During the last decade, several studies have been conducted to find the alternative therapies with least side effects. Between the new introduced treatments, mABs was known as the effective treatments for different autoimmune conditions, including RA, psoriasis, asthma, AD, MS, T1D, and SLE. Majority of the mABs are safety and could remit the patients with various autoimmune diseases. Development of mABs by the biopharmaceutical industry in the recent years has far exceeded expectations. The large number of mABs are using in different autoimmune diseases. With increasing in late stage clinical trials, several mABs will be entered regulatory review or receive marketing approvals for treating autoimmune diseases. The mABs, which could be used in various autoimmune diseases, were summarized in table 1.

Off-label using of mABs in not approved diseases is not rare. It was proved that mABs that were approved for a certain disease also could be used in other diseases. For example, daclizumab, which was approved to preventing of organ transplant rejections in 1997, was also approved for treatment after a long time. Additionally, some other mABs, such as dupilumab demonstrated promising results in treatment of AD and asthma patients. It seems that this drug could be approved in a few years. Based on similarity in molecular mechanisms in autoimmune diseases, the possible suitable mABs could be speculated. For example, considering the similarity in asthma, AD, SLE, and pemphigus, which are known as the T helper (Th)2 dominant diseases, approved mABs in each of these diseases could be a possible therapy in another one. Recently, based on these similarities, dupilumab was introduced as the possible treatment of pemphigus disease. Since the majority of studies on pemphigus reported the decline in Th1 cells, it seems that targeting cytokines, which are considered as the Th1 promoter, does not improve pemphigus. Thus, failure of ustekinumab therapy in the pemphigus patient could be explained [66].

Most of the mABs, did not demonstrate serious AEs in treated patients. However, some AEs are similar in most of the studies associated with treating patients with autoimmune diseases with mABs, such as infections, headache, and ISRs. Close monitoring of the patients for the opportunistic infections during and after treatment with mABs is strongly recommended.

Conflicting interests

The author has declared that no competing interests exist.

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