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MONOCLONAL ANTIBODY THERAPY FOR OBESITY

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ABSTRACT
Obesity is a complex, multifactorial disease in which the accumulation of excess body fat leads to negative health consequences. Its prevalence continues to accelerate, leading to an unprecedented epidemic that shows no significant signs of slowing anytime soon. An elevated body mass index (BMI) is a risk factor for noncommunicable diseases such as diabetes, cardiovascular disease, and musculoskeletal disorders, leading to a dramatic reduction in quality of life and life expectancy. Since most obese patients find it difficult to achieve and maintain successful long-term weight loss through lifestyle modifications (e.g., diet, exercise, and behavioral therapy), pharmacological approaches to obesity treatment should be considered as adjunctive therapies. Several monoclonal antibodies have been developed that are promising agents for the treatment of obesity.

INTRODUCTION
Obesity is the excessive or abnormal accumulation of body fat or adipose tissue, which impairs health due to its association with the risk of developing diabetes mellitus, cardiovascular disease, hypertension, and hyperlipidemia [1] . It is a significant public health epidemic that has been gradually worsening over the past 50 years. Obesity is a complex disease with a multifactorial etiology. It is the second most common cause of preventable death after smoking. Obesity requires multifaceted treatment strategies and may require lifelong treatment. A 5–10% weight loss can significantly improve health, quality of life, and economic burden for individuals and countries [2] .
Obesity results from an imbalance between daily energy intake and energy expenditure, leading to excessive weight gain. Obesity is a multifactorial disease caused by numerous genetic, cultural, and social factors. Various genetic studies have shown that obesity is highly heritable, and numerous genes have been linked to obesity and weight gain. Other causes of obesity include decreased physical activity, insomnia, endocrine disorders, medications, access to and consumption of excessive amounts of carbohydrates and high-sugar foods, and decreased energy metabolism [3] .
Today, obesity treatment includes dietary modification, behavioral interventions, medications, and surgery when necessary. FDA-approved obesity medications include phentermine, orlistat, liraglutide, semaglutide, diethylpropion, phentermine/topiramate, naltrexone/bupropion, setmelanotide, and phendimetrazine [4] . All of these medications are used for long-term weight management. Orlistat is usually the first choice due to its lack of systemic effects due to limited absorption. However, almost every treatment available today has its limitations and potential side effects. Thus, there is a need to find new therapeutic agents for the treatment of obesity [5] .
Monoclonal antibodies (mAbs) are laboratory-produced molecules designed to mimic the immune system’s ability to fight harmful pathogens and diseased cells [6]. These antibodies are designed to precisely target specific antigens, offering a potent and targeted therapeutic approach to a variety of medical conditions [7]. Monoclonal antibodies have revolutionized medicine by offering highly effective treatments for a variety of diseases. Their specificity and versatility make them invaluable diagnostic and therapeutic tools, providing physicians with powerful options to combat complex medical problems [8]. To date, several mAbs have been developed that are promising agents for the treatment of obesity. Therefore, the aim of this review is to determine the therapeutic potential of mAbs in the treatment of obesity.

General pathogenesis of obesity
Food intake and energy balance
The underlying causes of obesity remain somewhat controversial. Current obesity treatment guidelines are based on the basic physiological principle that fat accumulation is driven by an energy imbalance between calories consumed and expended. The obesity epidemic has been largely fueled by increased energy availability due to the greater availability of highly nutritious, high-calorie foods. Diet and various social, economic, and environmental factors related to the food supply significantly influence a patient's ability to achieve balance [9] . A 13-year study of 3,000 young people found that those who consumed significantly more fast food weighed, on average, approximately 6 kg more and had a larger waist circumference than those who consumed the least fast food. They were also found to be more likely to have weight-related health problems, such as elevated triglyceride levels, and were twice as likely to develop metabolic syndrome [10] . These problems are exacerbated in some individuals who have a genetic predisposition to fat accumulation, which may be driven by significant interactions between homeostatic and reward circuits in the brain. The accumulation of lipid metabolites,

inflammatory signaling, or other mechanisms that disrupt hypothalamic neuronal function may also lead to obesity, which may explain the biological defenses of increased body fat [9] .

Environment and lifestyle

Family history, lifestyle, and psychological factors all influence the tendency to become obese. The likelihood of becoming obese may be influenced by nature and nurture, enhanced by family genetics (a tendency to accumulate fat) [11] , or lifestyle (poor diet or exercise) [12] . A child with one obese parent has a threefold risk of becoming obese as an adult, while when both parents of a child are obese, that child has a 10-fold risk of future obesity. A cross-sectional observational study of 260 children (139 girls, 121 boys, aged 2.4 and 17.2 years) found that family history of cardiometabolic disease and obesity are critical risk factors for the severity of obesity in childhood [13] .

Gut microenvironment and microbiome

Knowledge of the gut microbiome has grown substantially in recent years, as has understanding of its complex relationship with disease. For example, obesity is associated with an altered gut microenvironment that supports a greater diversity of viral species than in lean hosts. This environment is more susceptible to the formation of pathogenic variants that can cause more severe disease [14] . Increasing evidence shows that changes in the gut microbiome cause changes in host weight and metabolism. For example, compared with individuals with a normal gut microbiota, germ-free male mice (those without gut microbiota) had 42% less total body fat, even while consuming 29% more food per day. However, after colonizing the cecum with microbes, these mice increased total body fat by 57%, decreased lean body mass by 7%, and decreased daily food intake by 27% [15] . A subsequent study showed that these changes were the result of a decreased metabolic rate with a concomitant increase in adipose tissue deposition, as capillary density in the distal villi of the small intestine increased by 25% after microflora colonization. Similar results were also obtained in female mice [14] .

Genetic factors

Genetic causes of obesity can be generally classified as follows: 1) Monogenic causes, which result from mutation of a single gene, mainly localized in the leptin-melanocortin pathway. Many genes, such as AgRP (agouti-related peptide), PYY (orexogenic) or MC4R (melanocortin-4 receptor), have been identified for monogenic obesity, disrupting the appetite and weight regulation system, hormonal signals (ghrelin, leptin, insulin) are perceived by receptors located in the arcuate nucleus of the hypothalamus [16] . 2) Syndromic obesity is severe obesity resulting from abnormalities in the development of the nervous system and other organ/system malformations. It can be caused by changes in a single gene or a larger chromosomal region spanning several genes [17] . 3) Polygenic obesity is caused by the cumulative contribution of many genes. Furthermore, some obese people gain excess weight due to multiple genes they carry, and these genes cause them to prefer food and thus consume more calories. The presence of these types of genes can lead to increased calorie intake, increased hunger, decreased control over overeating, decreased satiety, an increased tendency to accumulate body fat, and an increased tendency toward a sedentary lifestyle [1 8] .

Currently used drugs for the treatment of obesity and their disadvantages

Orlistat (Xenical)

Orlistat causes weight loss by inhibiting lipases in the mucosal lining of the stomach, small intestine, and pancreas, thereby preventing the breakdown of triglycerides into fatty acids and their absorption in the intestine [1 9]. The side effects of orlistat are mainly limited to the intestine. Side effects, experienced by more than 20% of participants taking orlistat for 2 years, include fecal incontinence, oily discharge, and fatty stools. In one study, the discontinuation rate was 8.8% in the treatment group and 5.0% in the placebo group. Other potential side effects of orlistat include an increase in oxalic acid in the urine, which may cause kidney stones; decreased effectiveness when taken with cyclosporine or thyroid hormone medications; and, when taken by patients prescribed warfarin, decreased absorption of vitamin K causes changes in blood clotting [2 0].

Naltrexone/bupropion

Bupropion is a norepinephrine and dopamine reuptake inhibitor used to treat depression and smoking cessation. It activates proopiomelanocortin (POMC), a neuropeptide that reduces appetite when its concentration increases in the hypothalamus, and complements dopamine activation, which is lower in obese patients. Naltrexone is a mu-opioid receptor antagonist used to treat opioid and alcohol dependence. Naltrexone suppresses the appetite-enhancing effects of beta-endorphin, which is mediated by cannabinoid-1 receptor activation. Concomitant use of bupropion and naltrexone has a synergistic effect on appetite suppression [21]. The primary side effect of naltrexone/bupropion is nausea, which in some patients is severe enough to require discontinuation of the drug. Naltrexone/bupropion should be used with caution in elderly patients and is not recommended for individuals over 75 years of age. Its pharmacokinetics in patients with impaired liver and kidney function have not yet been adequately studied. When using naltrexone/bupropion, the presence of emotional or psychological disorders should be considered. Patients with emotional or psychological disorders taking antipsychotics or antidepressants should exercise caution due to the potential for drug interactions and an increased risk of seizures [22].

Phentermine/topiramate

Phentermine suppresses appetite by increasing epinephrine secretion in the hypothalamus and has been approved for short-term use in the treatment of obesity. Topiramate is a gamma-aminobutyric acid agonist, glutamate antagonist, and carbonic anhydrase inhibitor that is used to treat epilepsy and prevent migraine, although its mechanism for treating obesity is unclear

[23]. However, it has a weight-loss effect by increasing satiety, increasing energy expenditure, decreasing caloric intake, and taste abnormalities. Many of the side effects of topiramate are related to inhibition of carbonic anhydrase activity, including metabolic acidosis, hypokalemia, renal calculi, angle-closure glaucoma, myopia, and anhidrosis. Associated symptoms should be closely monitored, and the drug should be discontinued immediately if symptoms occur. The use of phentermine/topiramate increases the risk of depression, anxiety, sleep disturbances, suicidal thoughts, and difficulty concentrating [24] . There are also no large-scale studies on the safety and effectiveness of phentermine/topiramate in relation to cardiovascular disease, although patients with recent cardiovascular disease are advised not to take this drug. Because this drug was approved by the FDA contingent on further follow-up studies, including an assessment of long-term cardiovascular safety, a more accurate assessment of long-term safety will be possible once these results become available [25] .

Liraglutide (Saxenda)

Glucagon-like peptide-1 (GLP-1), which is secreted from the intestine in response to carbohydrates and fats digested after a meal, reduces calorie intake by increasing satiety. Liraglutide is 97% identical to human GLP-1 but has a longer duration of action [26]. The main side effects of liraglutide are gastrointestinal symptoms such as nausea, diarrhea, constipation, and vomiting, and it is recommended to gradually increase the dose to reduce the incidence of these adverse events. Due to the delayed gastric emptying caused by liraglutide, the effect of other drugs may be affected. In addition, the use of liraglutide may cause gallstones and, rarely, acute pancreatitis; it should not be used in patients with a history of pancreatitis. Since there are concerns regarding the use of liraglutide and medullary thyroid cancer and multiple endocrine neoplasia, it should not be used in patients with a past history or family history of these conditions [27] .

developments in monoclonal antibodies for the treatment of obesity

Bimagrumab

Bimagrumab is a human monoclonal antibody that binds to the activin receptor type II (ActRII). ActRII blockade prevents the binding of natural ligands that negatively regulate skeletal muscle growth and, in animal models, promotes brown adipose tissue differentiation and activity [28] . In a small, 48-week phase 2 study in adults with type 2 diabetes and obesity, bimagrumab (10 mg/kg up to 1200 mg, intravenous infusion every four weeks) resulted in a 20.5% loss of fat mass compared with 0.5% in the placebo group (7.5 kg vs. 0.2 kg, respectively) and a 3.6% increase in lean mass compared with a loss of 0.8% in the placebo group (+1.7 kg vs. -0.4 kg, respectively), as well as improved glycemic control. The increase in muscle mass is noticeable, as negative energy balance and weight loss are usually associated with a decrease in muscle mass. The mechanism of fat mass reduction is unknown. Diarrhea and muscle cramps were the most common side effects [2 9] .

Overall, adverse events and side effects were balanced between the bimagrumab and placebo groups, although more patients in the bimagrumab group experienced transient increases in pancreatic and liver enzymes, which generally resolved after the first dose of bimagrumab. The etiology of these increases is unclear but may be related to the mobilization of triglycerides and amino acids from adipocytes as a new metabolic equilibrium is achieved during early dosing of bimagrumab. Further studies are needed to determine whether weekly administration of the available subcutaneous formulation can alleviate these transient increases, allowing a new steady state to be reached more gradually [28] .

Mibavademab

Mibavademab is a fully human monoclonal antibody that binds to the membrane leptin receptor (LEPR) with nanomolar affinity and activates the receptor without competing with the endogenous ligand leptin. LEPR exists as multiple isoforms and is highly expressed as an active form in the nucleus of the arcuate pars hypothalamus and as an inactive form in a wide range of peripheral tissues [30] . In humans, membrane-bound LEPR undergoes ectodomain shedding, which is detected in the circulation as soluble LEPR (sLEPR). Mibavademab binds to sLEPR, although with lower affinity than to active membrane-bound LEPR [31] . In non-clinical studies, treatment with mibavademab resulted in significant weight loss, elimination of hyperphagia, and improvement in glycemic control and insulin resistance in obese leptin-deficient mice. Mibavademab also reversed metabolic dysfunction and liver steatosis in a mouse model of lipodystrophy [30] .

In a recent first-in-human phase I study, single escalating doses and multiple doses of mibavademab were administered to healthy lean or overweight participants and healthy overweight or obese participants (stratified by BMI and baseline leptin levels), respectively. Repeated treatment with mibavademab resulted in weight loss over 12 weeks in overweight or obese participants with low baseline leptin levels (<8 ng/mL), but had no consistent effect on weight in those with higher baseline leptin levels (>10 ng/mL) [32] . The results of this study indicate that mibavademab is generally well tolerated at the doses tested, with no observed immunogenicity in lean, overweight, and obese individuals. The study supports the concept of baseline weight loss with mibavademab treatment when basal leptin levels are sufficiently low. Mibavademab is a promising agent for the treatment of conditions with defective leptin signaling or leptin deficiency given its low immunogenic potential, long half-life, and demonstrable pharmacological effect observed in preclinical models and in low-leptin obesity [33] .

Nimacimab

Nimacimab is a first-in-class humanized monoclonal antibody that acts as a negative allosteric modulator to inhibit CB1 signaling in the periphery. CB1 inhibition has demonstrated antifibrotic, anti-inflammatory, and metabolic mechanisms of action with the potential to address a wide range of diseases, such as obesity, chronic kidney disease, and steatohepatitis associated with metabolic dysfunction. A phase 2 human clinical trial is currently underway. Weight loss, safety, and tolerability; neuropsychiatric and cognitive assessment; and body composition changes using dual-energy X-ray absorptiometry will be assessed soon [34] .

Monoclonal antibodies to glucose-dependent insulinotropic polypeptide

Glucose-dependent insulinotropic polypeptide (GIP) plays an important role in stimulating nutrient absorption and storage. Recently, a monoclonal antibody to GIP was developed that reduced weight gain in mice. A specific monoclonal antibody to GIP was shown to effectively reduce weight gain in mice fed a high-fat diet while simultaneously reducing fat deposition [35] . Furthermore, the monoclonal antibody to GIP could effectively induce consistent linear weight loss in obese wild-type mice without any change in food intake. Finally, the monoclonal antibody to GIP could prevent weight gain in hyperphagic mice without any effect on food intake. The results of these studies support the hypothesis that reducing GIP signaling appears to affect body weight without suppressing food intake and may provide a useful method for the treatment and prevention of obesity [36] .

What advantages does monoclonal antibody therapy have over other obesity treatments?

Safety and effectiveness

Monoclonal antibodies have gained significant clinical acceptance, with more than 20 mAbs currently in clinical use and the projected market value expected to reach $300 billion by 2025 [37]. Several promising mAbs for the treatment of obesity are currently in preclinical and clinical trials and have already demonstrated their effectiveness.

Despite their effectiveness, monoclonal antibodies may be associated with adverse effects, including immunogenicity, hypersensitivity reactions, and other toxicities [38]. However, the overall safety profile of monoclonal antibodies appears favorable, with a large study of monoclonal antibody treatment finding that only 0.2% of patients experienced any adverse effects [39]. Of particular note is the safety and efficacy of monoclonal antibodies in immunocompromised patients, who may be more susceptible to drug interactions or contraindications to other treatments [37].

High specificity

One of the main advantages of monoclonal antibody therapy over conventional small-molecule drugs is their high specificity, which ensures precise action, and their long half-life, which allows for infrequent administration [40] . Furthermore, molecular engineering technologies have made it possible to fine-tune the structure of monoclonal antibodies for specific therapeutic actions and minimize immunogenicity, thereby improving the risk-benefit ratio. This is reflected in the current approval rates: approximately 20% compared to 5% for new chemical compounds [40] .

Integration with immunotherapy and gene therapy

The integration of monoclonal antibodies with immunotherapy and gene therapy represents a cutting-edge approach in modern medicine, introducing innovative strategies to improve therapeutic outcomes. Immune checkpoint-based immunotherapies function by either blocking or stimulating pathways to enhance the immune system's ability to recognize and fight diseases. When combined with monoclonal antibodies, these immunotherapeutic regimens demonstrate increased efficacy, leading to improved patient responses and outcomes. Furthermore, gene therapy has attracted attention as an alternative route for the production of mAb therapeutics, offering a promising solution to bypass the challenges associated with traditional mAb production and administration [41]. Gene therapy involves the delivery of genes encoding the mAb of interest, thereby facilitating in vivo production within the body's cells. This innovative approach eliminates the need for traditional mAb production and purification processes, potentially reducing costs and increasing the availability of these vital treatments [42]. The convergence of mAb, immunotherapy, and gene therapy is opening new horizons in personalized and targeted treatment across a wide range of diseases. By leveraging the complementary strengths of each approach, researchers and clinicians are advancing toward more effective and optimized therapeutic interventions, which hold enormous promise for the future of medicine.

DISCUSSION

The global prevalence of obesity has nearly tripled since 1975 and continues to grow exponentially. Obesity has become the number one lifestyle-related risk factor for premature death. Therefore, public health policies aimed at reducing and treating obesity are essential [43] . The WHO Global Action Plan for the Prevention and Control of Noncommunicable Diseases outlines strategies to prevent further increases in the prevalence of obesity, but progress has been slow [44] . However, despite identifying the underlying causes and modulating factors of obesity, the challenge remains in translating them into effective action.

Several monoclonal antibodies are currently in clinical and preclinical trials, and they have already demonstrated efficacy in the treatment of obesity. Looking ahead, it is already clear that this therapy has great potential [45] . However, there are also challenges related to scalability of production, availability, and equitable access to treatment, highlighting the need for continued innovation and collaboration. Nevertheless, the remarkable trajectory of monoclonal antibodies is a testament to human innovation and dedication to advancing healthcare, paving the way for a future in which targeted and effective treatments bring hope and healing to patients worldwide.

CONCLUSIONS

In conclusion, the evolution of monoclonal antibodies has been a transformative journey in modern medicine. Beginning with their discovery and the subsequent development of technologies such as hybridoma and recombinant DNA, monoclonal antibodies have emerged as powerful therapeutic agents with diverse applications across a wide range of medical fields. Their precise targeting capabilities and mechanisms of action have revolutionized the treatment landscape for many diseases. Today, monoclonal antibody therapy is also being considered a promising approach for treating obesity. Bimagrumab, mibavademab, and nimacimab have demonstrated promising results in preclinical and clinical trials, demonstrating that these drugs can

effectively promote weight loss with minimal side effects. Thus, this area is highly promising and warrants further exploration.

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Conflict of Interest
The authors declare no conflict of interest.

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