The Immunology of Endometriosis and the Therapeutic Potential of Bispecific Antibodies: A Hypothesis

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Abstract

Endometriosis is a chronic inflammatory disease characterized by the presence of endometrial lesions outside the uterus. Current treatment methods primarily focus on hormone-based therapy or invasive procedures. However, given the crucial role of the immune system in disease initiation and progression, there is an opportunity to explore new treatment approaches. Bispecific antibodies, which bind two different cells using their bivalent arms, have shown promise in treating cancers and autoimmune diseases. This study postulates that, due to the similarities in pathogenesis between endometriosis and the aforementioned diseases, a novel therapeutic method based on this new target could be introduced. This approach could potentially lead to a reduction in the limitations to patients' quality of life. In addition, it is important to highlight that future studies should prioritize the identification of specific binding markers on endometrial cells. This could contribute to the development of new diagnostic tools for the disease. Furthermore, the production of bispecific antibodies that selectively bind to these receptors on immune cells may prove effective in improving the immune response.

Keywords: Endometriosis; CD3; Bispecific Antibody; Monoclonal Antibody; Immunology; Therapy

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Introduction

Endometriosis is a chronic, estrogen-dependent inflammatory disease characterized by the presence of endometrial tissue outside the uterus. Symptoms include pelvic pain, dysmenorrhea, dyspareunia, and infertility. It is important to note that a small number of patients may not experience any symptoms [1]. Despite affecting many women worldwide, the exact cause of endometriosis is not yet fully understood. However, there is substantial evidence suggesting that immunological, inflammatory, genetic, and environmental factors play a significant role in the development of the disease [2].

Nonsurgical diagnostic methods for endometriosis are not completely reliable, often leading to delayed diagnosis and prolonged suffering for patients. However, advancements in imaging techniques such as transvaginal ultrasonography, MRI, and multi-layer CT scans have improved early and less invasive diagnosis in this field. The lesions associated with endometriosis can be classified into three major types: superficial peritoneal lesions (SUP), ovarian endometriomas (OMA), and deep infiltrating endometriosis (DIE). The American Society of Reproductive Medicine classifies the disease into four stages (I, II, III, IV) based on surgical evaluation of size, location, severity, and adhesion [1].

Based on studies, endometriosis has a prevalence rate of 6-10% in women of reproductive age, and up to 30-50% in women with chronic pelvic pain or infertility. It is estimated that there are 176 million women worldwide affected by this disease [3]. Endometriosis is a multidimensional disease that

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affects various aspects of a patient's life, including physical activity, mental health, social well-being, and quality of life. The negative impact of this disease, such as depression and fatigue, can lead to a loss in work productivity, resulting in both health and economic burdens [1-3].

Endometriosis is a multisystem disease that involves interactions between the endocrine and immune systems. It not only affects the gynecological system but also impacts the entire body [4]. Significant changes occur in immune cells, cytokines, and immune-activating pathways. Alterations in macrophage activity and numbers, the activation status of T and B cells, and dysfunctions in NK cell activity all play critical roles in disease onset and progression [5]. For example, these changes can reduce the cytotoxicity of T cells and NK cells, disrupting immune surveillance, which is a significant factor in both implantation and lesion progression, similar to the mechanisms observed in oncology [6, 7].

Understanding the influence of the immune system on the pathophysiology of endometriosis is crucial. From another perspective, the increase in autoantibodies through B cell polyclonization can indicate an autoimmune disease. Additionally, the cytokines and chemokines produced by immune cells contribute to the inflammatory status of the disease, highlighting the importance of understanding the immunological processes [8]. Effectively countering these processes could pave the way for a more comprehensive and personalized approach to patient treatment.

CD3, also known as Cluster of Differentiation 3, represents a collection of proteins that are present on the outer surface of T cells. The CD3 complex consists of several distinct protein subunits, namely CD3 gamma, delta, epsilon, and zeta. These CD3 proteins play a crucial role as constituents of the T cell receptor (TCR) complex, which is responsible for the recognition of specific antigens encountered on pathogens. Upon encountering an antigen, the CD3 complex facilitates the transmission of the signal to the interior of the T cell, thereby initiating a series of intracellular events that ultimately culminate in the activation of the T cell. This activation is a pivotal step in the immune response, empowering T cells to execute their diverse functions, encompassing the elimination of infected cells, regulation of immune responses, and the generation of immunological memory [9].

Studies have shown that CD3 antibodies (Ab) can be used to control and modulate autoimmune diseases such as type 1 diabetes, inflammatory bowel disease, immune-mediated neurological diseases, immune-mediated inflammatory arthritis, organ transplantation rejection, and GVHD [10]. Although endometriosis is not an autoimmune disease, it has autoimmune features and, therefore, CD3 Ab can modulate the disease [11]. Furthermore, endometriosis shares some similarities with tumors, such as inflammation and cell invasion, in which CD3 treatment has been investigated recently, as demonstrated in previous studies. Therefore, there is growing interest in considering this method as a potential treatment for endometriosis.

In conclusion, endometriosis exhibits both pro-inflammatory and anti-inflammatory aspects, which can be modulated by anti-CD3 antibodies. Moreover, unlike current therapeutic approaches, this therapy is selective and targeted, making it a promising choice for treating endometriosis. Consequently, further investigation into the potential of this therapy in endometriosis is warranted, given its multiple beneficial aspects. Despite years of study and research on this matter, treatment methods for endometriosis are still limited. Because it is a chronic inflammatory disease, lifelong management is needed. There are two major treatment goals for endometriosis: pain relief and fertility. Pain management can be achieved through various methods, with surgical intervention and hormone therapy being the most successful approaches [1].

A) Pain Therapy Options:

1. Non-hormonal drugs such as analgesics, NSAIDs, SSRIs, and TCAs.
2. Hormonal drugs like combined oral contraceptives (COC), gonadotropin-releasing hormone agonists (GnRH agonists), progesterone, gonadotropin antagonists, and aromatase inhibitors. However, these drugs have side effects and are ineffective for patients desiring pregnancy. It has been reported that a quarter to a third of patients do not respond to these treatments, are intolerant to them, or have contraindications.
3. Pelvic physiotherapy.
4. Dietary interventions.
5. Psychological treatments, with cognitive-behavioral therapy (CBT) being the most commonly used method.
6. Surgical options, which include conservative surgery (excision of endometrial lesions only) and definitive surgery (removal of endometrial lesions, hysterectomy, and oophorectomy). However, a recent review from the Cochrane Library concluded that the current studies were inconclusive about the effectiveness of laparoscopic surgery in relieving pain [1, 4, 12].

B) Fertility Options:

1. Surgical interventions, which have proven to be successful but have a high recurrence rate if postoperative hormone therapy is excluded. There is also a risk of incomplete lesion excision and various side effects, especially in DIE type, such as postoperative infections, rectovaginal fistula, bowel dysfunction, and neurogenic bladder.
2. Assisted reproductive therapies (ART) [4, 12, 13].

The treatment options mentioned above are chosen based on the patient's situation and priorities. There is growing consideration that personalized, multimodal, and interdisciplinary treatment methods are best due to the mixed phenotypes of pain in patients and the different scattering of lesions. It is worth noting that the rich immune background and diverse effects in both initiating and progressing the disease support the idea that immune therapy can be a new and more comprehensive therapeutic approach for treating patients with endometriosis, resulting in better outcomes and quality of life [1, 13].

Immunology of endometriosis

The immune system in a normal endometrium plays a crucial role in maintaining hemostasis at the endometrial site through its strong interaction with the humoral system. It has two major functions: protection against pathogens and the ability to adapt to an immunosuppressive state to create a tolerant and hospitable environment for embryo implantation [5]. These functions are mediated by hormonal fluctuations. The immune system in the endometrium is composed of three main compartments: endometrial epithelium, innate immune cells, and adaptive immune cells.

The roles of these cells and their changes throughout the menstrual cycle will be further elaborated. The endometrial epithelium serves as the first line of defense by acting as a physical barrier against pathogens that may enter the uterus. However, its role goes beyond this function. It also generates immune-related chemicals like defensins, which not only have immediate antimicrobial effects but also activate other immune cells, like T cells and dendritic cells. This activation occurs through the binding of defensins to C-C chemokine receptor 6 (CCR6). As a result, the endometrial epithelium plays a crucial role in the innate immune system. Furthermore, it produces other immune-related molecules, including macrophage inflammatory protein (MIP)-3α, which also acts as a ligand for CCR6, and secretory leukocyte protease inhibitor (SLPI) [14].

Innate immunity

Macrophages play a crucial role in the immune system by bridging the gap between innate and adaptive immunity. They perform essential functions such as phagocytosis of foreign cells, damaged tissue, and cell debris. Additionally, they act as antigen-presenting cells (APCs) for T cells and contribute to tissue remodeling and repair. Macrophages are primarily found in two locations: the luminal epithelium and sub-epithelial stroma of the functionalis layer, as well as the lymphoid aggregates of the lamina basilaris. During the proliferative phase, macrophages account for approximately 10% of the leukocyte population. Interestingly, their numbers increase during the menstrual phase, suggesting their involvement in clearing damaged cells from the endometrium. These changes in macrophage populations indicate that their regulation is influenced by estrogen and progesterone levels [7, 15, 16].

There are two main types of macrophages: Macrophage 1 and alternatively activated, also known as Macrophage 2. These types have different actions and roles. Macrophage 1 is responsible for antigen presentation and pro-inflammatory responses. It secretes various pro-inflammatory cytokines such as IL-1α, IL-6, IL-8, IL-12, IL-13, TNF-α, reactive oxygen species (ROS), and nitric oxide (NO). Notably, Macrophage 1 can activate Th1 cells, triggering a cascade of inflammatory events. In contrast, Macrophage 2 has anti-inflammatory functions and promotes resolution and tissue repair. It secretes IL-10, TGF-β, angiogenesis factors, VEGF, and coagulation factors, while also possessing the ability to activate Th2 cells. In a normal endometrium, the predominant macrophage phenotype is type 2 [15-19].

Neutrophils are the most frequent circulating leukocytes in the body and play a crucial role in defending against pathogens. In a normal endometrium, the number of neutrophils increases during the secretory and menstrual phases due to their involvement in tissue repair and cyclic vascular proliferation. This is achieved through the secretion of VEGF, a cytokine produced by neutrophils. Another cytokine produced by neutrophils is IFN-γ, which acts as a regulatory cytokine for cellular differentiation and immune response. IFN-γ is responsible for creating a favorable environment for embryo implantation and maintenance [15, 17, 20].

NK cells, also known as natural killer cells, are an essential part of the body's defense system. They have the ability to eliminate stressed cells, viral-infected cells, and neoplastic cells. During the secretory phase, NK cells are the most frequent

leukocytes, increasing in their numbers from 30% to 70%. In the endometrium, these cells, referred to as uNK cells, differ from their counterparts in the blood. uNK cells are characterized by high levels of CD56 and low levels of CD16, while circulating NK cells have the opposite expression (CD56lowCD16high). CD16 expression is associated with NK cell toxicity. Although uNK cells have lower toxicity, they mediate antimicrobial function. Interestingly, the most essential role of these cells is to create a supportive environment for embryo implantation and development. They achieve this by secreting factors such as VEGF, angiotensin II factor, TNF-α, TGF-β, LIF, and IL-2. Any dysfunction or defect in NK cell function can lead to infertility and complications in pregnancy [15, 21].

Dendritic cells (DCs) are antigen-presenting cells (APCs) that play a crucial role in immune responses at mucosal surfaces, including the endometrium. In the endometrium, DCs can be found in both the functionalis layer and basilaris layer. There are two major types of DCs: plasmacytoid DCs, which are responsible for recognizing viruses and secreting interferon-gamma (IFN-γ), and myeloid DCs, which activate T cells. Myeloid DCs go through two phases: an immature phase (iDC) where they recognize antigens, and a mature phase that remains relatively constant, suggesting that mature DCs migrate from remaining tissue. The iDCs play a role in menstruation by producing MMP, IL-6, IL-10, IL-12, MCP-1, RANTES, and TNF-α [15, 19, 22, 23].

Mast cells (MCs) have angiogenic and tissue repair effects. In a normal endometrium, their numbers increase during the secretory and menstrual phases of the cycle, as their main function is the shedding and regeneration of the endometrium. Histological findings have also shown a strong connection between MCs and nerves. Furthermore, MCs have been reported to have neoangiogenic actions [15, 24].

Moving on to adaptive immunity, B lymphocytes are present in lymphocytic aggregates in the basilaris layer. These cells produce antibodies after interacting with antigens and make a significant contribution to the immune system. Notably, their numbers do not show any changes during the menstrual cycle [15, 19, 25].

T lymphocytes are immune cells responsible for cell-mediated immunity and are primarily located in lymphocytic aggregates, which tend to increase during the proliferative phase of the menstrual cycle. These cells can activate other immune cells by secreting various cytokines. There are three major types of T lymphocytes: CD4+, CD8+, and CD4-8-, all of which express CD3 receptors [15]. CD4+ T cells have their own subtypes, with the most essential ones being Th1, which secretes pro-inflammatory cytokines such as IL-2, IL-12, TNF-α, and IFN-γ. Th1 cells also play a role in the differentiation of CD8+ T cells. On the contrary, Th2 cells produce anti-inflammatory cytokines like IL-4, IL-5, IL-6, and IL-10, with their presence being particularly important in pregnancy, especially in the early stages. Additionally, there are Th17 cells that secrete IL-17A and Tregs, which act as potent immunosuppressors, preventing autoimmunity and inducing tolerance [26, 27]. Tregs also secrete IL-10 and TGF-β. CD8+ T cells, also known as cytotoxic T cells, are differentiated via Th1 cells and play a crucial role in eliminating antigens [6, 7, 15, 16, 18, 28].

There are various theories regarding the pathophysiology of endometriosis. One theory, known as coelomic metaplasia, suggests that endometriosis originates from coelomic epithelial cells in the mesoderm, specifically from a pair of Müllerian ducts. Another theory, the embryonic rest theory, proposes that the Wolffian duct, in addition to the Müllerian duct, can also be a source of endometriosis. Additionally, there are two stem cell-based theories: the endometriosis stem cell recruitment theory and the bone marrow-derived stem cell theory. Both of these theories are based on the multipotent feature of stem cells. However, the most widely accepted hypothesis worldwide is Sampson's retrograde menstruation theory. This theory suggests that endometriosis results from endometrial cells regurgitating into the peritoneal cavity during menstruation. Although retrograde menstruation is a common phenomenon experienced by almost all women at least once in their lifetime, endometriosis only occurs in about 10% of this population. This indicates the involvement of other factors such as epigenetics, endocrine, and immune factors [1, 20, 29].

From an immunological standpoint, studies have identified several roles that contribute to immuno-escape and survival, invasion and attachment, and lesion growth and proliferation. During retrograde menstruation in a normal peritoneal cavity, immune cells like NK cells and macrophages recognize and diminish endometrial cells. However, in endometriosis, changes in the immune system lead to the survival and growth of lesions. These changes include decreased phagocytic activity of macrophages, dysfunction in NK cell cytotoxicity, and aberrations in the I-CAM and FAS-FAS-L pathways. Consequently, resident and recruited immune cells secrete cytokines and angiogenic factors, promoting lesion growth and proliferation, thereby furthering the development of the disease [11, 22].

Macrophages play a crucial role in the development and progression of endometriosis. Previous studies have reported an increase in the number of macrophages in both peritoneal fluid and the site of

the lesion. Surprisingly, these numbers do not change in response to hormonal fluctuations. During the early stages of endometriosis, the numbers of type 1 macrophages are further increased in response to the inflammatory environment. However, as the disease progresses, type 2 macrophages become dominant due to their angiogenic, fibrotic, and proliferative actions [7, 15, 18, 20, 30].

Phagocytosis in these macrophages is activated through two main routes: CD36 and MMP-9 [31]. Unfortunately, both pathways are suppressed by increased PGE2 production caused by the upregulation of COX-2 and SIRP-α production by endometrial cells. Additionally, other contributing factors include iron overload due to increased lysis of RBC cells, increased expression of CD200 on endometrial cells and CD200 receptor on macrophages, and decreased Annexin A2 receptor on macrophages [11, 22, 32, 33].

Furthermore, macrophages not only have decreased phagocytic activity, but they also play a crucial role in promoting the survival and growth of lesions. They produce potent angiogenic factors, such as VEGF and FGF-2, which further enhance lesion proliferation. Moreover, by secreting IL-8, macrophages recruit neutrophils to the site, contributing to lesion proliferation. Additionally, the secretion of IL-4, IL-6, and TNF-α by macrophages induces fibro genesis and worsens the inflammatory state of the disease [18, 19, 22, 30].

Interestingly, macrophages have also been observed to interact with nerve fibers, causing nerve growth, regeneration, and sensitization. This interaction implicates macrophages in the pain symptoms experienced by endometriosis patients. Notably, Greaves et al. have established that this connection is regulated by estradiol [18, 34].

Neutrophils play a crucial role in the pathogenesis of endometriosis. Elevated neutrophil numbers and increased infiltration have been observed, which can be attributed to the presence of IL-8 in plasma and peritoneal fluid, as well as HNP 1-3 and ENA-78 in the local environment of endometriosis. Notably, these increases are primarily seen in the early stages of the disease, suggesting their involvement in disease initiation. A study utilizing anti-granulocyte receptor-1 (Gr-1) showed that early depletion of neutrophils led to reduced lesion growth. Neutrophils contribute to lesion growth and angiogenesis through the secretion of VEGF, CXCL9, and CXCL10. Additionally, they recruit more neutrophils by producing IL-8, thereby further augmenting the inflammatory state with the production of IL-17A and IL-6 [7, 11, 17, 22, 24].

Natural Killer (NK) cells are essential for maintaining normal endometrial homeostasis. However, their numbers do not significantly change in the context of endometriosis. Instead, the reduced cytotoxic activity of NK cells plays a pivotal role in diminished immune surveillance, allowing lesions to survive. Various theories exist regarding this dysfunction, including the impact of cytokines such as IL-6, IL-10, IL-12, IL-15, and TGF-β. Furthermore, increased expression of KIRs such as KIR2DL1, NKG2A, LILRB1, and LILRB2, alongside decreased expression of KARs like NKG2D and NKP44, contribute to defective NK cell activity. It has been proposed that intraperitoneal injection of IL-2 can activate and revive the cytotoxicity of NK cells [16, 18, 21, 31, 32].

The role of dendritic cells (DCs) in endometriosis is not yet fully understood. However, studies on mice models have proven that depletion of these cells decreases lesion size, suggesting that they contribute to endometriosis growth, probably via secreting IL-10 [23, 35]. Recently, there has been evidence that the frequency of mannose receptor (MR) BDCA1+ dendritic cells increases. These cells are known for removing dead endometrial cells, inducing inflammation, and supporting the disease. The total number of these cells does not show significant change, although immature dendritic cells increase, indicating a decrease in mature cells. This disturbance in antigen presentation promotes the existence of the disease [15, 19].

The two subtypes of T lymphocytes exhibit distinct alterations in endometriosis. CD8+ T cells demonstrate a decrease in cytotoxicity, which contributes to lesion growth and immune invasion. Studies suggest that this feature can be restored with IL-2 treatment [36]. However, there is conflicting evidence regarding the frequency of these cells, with some studies reporting an increase while others report a decrease. Despite this discrepancy, it is well-established that the decrease in cytotoxic activity contributes to lesion survival [15, 16].

CD4+ T cells comprise different subtypes. Studies on cytokines in endometriosis have revealed an increase in Th2 byproducts, such as IL-4 and IL-10, suggesting a shift towards Th2 cells [37]. These proliferative factors promote disease progression. Another subtype, Th17, has also been found to be elevated in endometriosis, with enhanced production of IL-17A. This cytokine is known to augment inflammation and angiogenesis, thereby promoting disease progression [38].

Tregs, another important subtype of CD4+ cells, possess potent immunosuppressive properties and regulate the immune response. In endometriosis, there is an increase in the local environment, indicating a localized role of these cells. It is hypothesized that Tregs thrive in an estrogen-dominant environment, characteristic of endometriosis due to overexpression

of estradiol receptors and progesterone resistance. The increase in Tregs leads to immune escape and survival of the lesion by suppressing other immune cells, such as T cell activation and proliferation, NK cells, and macrophages. Additionally, Tregs have been implicated in infertility and chronic pain in patients [22, 26, 39].

B lymphocytes undergo polyclonal activation, as evidenced by the increased anti-endometrial antibodies in the peritoneal fluid. This further promotes inflammation at the local level. Although some studies report no change in B cell numbers [25], this growth may contribute to the increased autoimmune comorbidities associated with the disease and infertility in patients. Additionally, B cells produce IL-6 and IL-17, which support inflammation, angiogenesis, and modulate the immune response [15, 30].

CD3, also known as Cluster of Differentiation 3, is a group of proteins located on the surface of T cells and plays a crucial role in their ability to recognize antigens and pathogens. CD3 is composed of four subunits: gamma (γ), epsilon (ε), zeta (ζ), and delta (δ). These subunits come together to form γ-ε, δ-ε, and ζ-ζ heterodimers and homodimers, each of which possesses both extracellular and intracellular domains. Notably, the ζ-ζ homodimer has a very short extracellular domain and a long intracellular domain.

In an α-β T cell, the ratio of TCRαβ:CD3δε:CD3γε:CD3ζζ is 1:1:1:1. Interestingly, anti-CD3 antibodies can activate T cells without the presence of MHC class molecules. Furthermore, CD3 subunits remain constant in αβ T cells, unlike TCR, whose subunits are variable. These two characteristics support the claim that anti-CD3 therapy is a promising and novel therapeutic approach [9].

TCR alone cannot initiate the T cell signaling process because it has short cytoplasmic tails on each of the two chains, which lack immune-receptor tyrosine-based activation motifs (ITAMs). ITAMs are phosphorylated by Src family kinases such as LCK and FYN, initiating T cell activation. Phosphorylated ITAMs serve as docking sites for tyrosine kinases like ZAP70, which further propagates the signaling cascade. It's worth noting that δ, ε, and γ chains each have one ITAM, while the ζ chain has three ITAMs, emphasizing the role of CD3 in TCR signaling and activation.

There are two primary categories in the classification of anti-CD3 antibodies: anti-CD3 monoclonal antibodies (mAbs) and anti-CD3 bispecific antibodies (BsAbs). CD3 mAbs can be

Table 1. Cytokine or chemoreactant alteration and their function in endometriosis

Cytokine or chemoreactant	levels	Produced by	function
IL-1	↑↑	Activated Monocytes and Macrophages, Endometrial and Mesenchymal cells	Increases VEGF/ICAM-1/RANTES(40-42)
IL-2	↓↓	Activated T cells	Activating factor for T,B lymphocytes, NK cells, macrophages and monocytes(41, 43, 44)
IL-6	↑↑	Macrophages, Monoctytes, Fibroblast, Endometrial stromal and epithelial cells	Decrease NK cell cytotoxicity, protection of Endometrial implants by increasing haptoglobin(45-49)
IL-8	↑↑	Neutrophils,Monocytes,Macrophages,NK cells,Lymphocytes,Endometrial epithelial cells	Recruitment of neutrophils, proliferation of Endometrial stromal cells(50-54)
IL-10	↑↑	Th2, B cells,Macrophages,DC	Anti-inflammatory, Immune mediator, proliferative factor(16, 55, 56)
TNF-α	↑↑	Monocytes and Macrophages, Endometrial and Mesenchymal cells	Pro-inflammatory factor, Induces IL-8 production, alongside IL-8 supports adhesion of lesion(16, 22, 41)
VEGF	↑↑	Macrophages,Monocytes,T cells, Neutrophils, Endometrial stromal cells	Angiogenesis and vascular growth(22, 57-59)
RANTES	↑↑	Endometrial stromal cells, also its production is induced by IL-1β	Potent immune chemoreactant of Eosinophil,Macrophage,Monocyte and T cell, Involved in Immune cell recruitment(22, 60, 61)
TGF-β	↑↑	Tregs, Th1, Peritoneal mesothelial cells	Suggested to be responsible for dysfunction of NK cell cytotoxicity(16, 62, 63)
MCP-1	↑↑	Fibroblasts,Leukocytes,Epithelial cells	Recruitment of Monocytes, Inducing Macrophages to produce growth factors and cytokines(22, 64, 65)

Table 2. Immuno-based therapies used for endometriosis

Classification	Drug name	evidence	downfall
COX2/PGE2 Pathway	NSAID (naproxen, diclofenac)/Selective COX inhibitors (celecoxib, rofecoxib and valdecoxib)	NSAID→decrease pain celecoxib reduced lesion in mice (33, 66-68)	NSAID→no effect on infertility rofecoxib, valdecoxib→ side effects including myocardial infraction
Anti TNF-α	pentoxifylline, leflunomide, etanercept, infliximab, and recombinant human TNF binding protein-1 (r-hTBP-I).	pentoxifylline→reduced growth in rats r-hTBP1→reduced lesion in baboons and rats (33, 69)	infliximab→failed to relieve pain
NFkB pathway	BAY 11-7085,SN-50,PDTC,Curcumin,Nobiletin,Andrographolide	Experimental models shows decrease in lesion size(32, 33, 70-72)	In preclinical stage
CD47 pathway	CD47SIRPa	Improved phagocytic activity of Macrophages(32, 73, 74)	In preclinical stage
NK cell activation	Oral probiotics/Helixor/IL-2	In animal models increased cytotoxicity and reduced lesion size(75, 76)	In preclinical stage
Anti-Angiogenesis and Neuroangiognesis	sunitinib, SU6668, SU5416, sorafenib and pazopa,Dopamin agonists (bromocriptine, cabergoline and quinagolide)	Experimental models shows decrease in lesion size(33, 77-79)	In preclinical stage
IL-12	-	Inhibition of lesion development and improvement of NK cell cytotoxicity in animal model(80)	In preclinical stage
IL-37	-	Inhibition of lesion development in mice(81)	In preclinical stage
Interferon	INF α/INF β	IFN-2β reduced lesion in rats(32, 82)	In preclinical stage
Statins	Atorvastatin	Reduced expression of inflammatory genes like MCP-1(83)	In preclinical stage
Mesenchymal stem cells	-	Decreased IL-1β,IL-1R,IL-10,TNF-α in horse endometrial models(84, 85)	Increase in IL-6,IL-8
Anti-IL-6	Tocilizumab	Lesion regression in rats(86)	In preclinical stage
Anti-IL-6,IL-8	Pyrvinium pamoate	Suppression of gene expression in vitro (87)	In preclinical stage
DNA methylation inhibitor	5'-aza-deoxycytidine (AZA)	Inhibition of DNA methylation in vitro(88)	Toxic to hematopoietic and gastrointestinal system
EMT regulators	isoliquiritigenin, fucoidan, melatonin and 3,6-dihydroxyflavone	Inhibition of cell migration in murine endometrial cell lines(89-92)	In preclinical stage
Antioxidants	Naringenin,curcumin,NAC	Experimental models shows decrease in lesion size(33, 93-95)	In preclinical stage
Vaccine	BCG	Decrease in lesion numbers, inhibition of implantation, improved immune surveillance,activation of cytotoxic NK cells,increased Macrophage type 1 in animal model(96-98)	In preclinical stage
MC stabilizers	palmitoyl ethanolamide and levonorgestrel-releasing intrauterine system (LNG IUS)	Experimental models shows decrease in lesion size(99)	In preclinical stage

administered orally, nasally, and intravenously. When administered intravenously, mAbs bind to the epsilon chain of the CD3-TCR complex on the surface of T cells. Subsequently, this complex undergoes a process known as antigenic modulation, during which it is either internalized or shed from the T cell surface. This leads to T cells losing their ability to recognize antigens, rendering them antigen-blind. Simultaneously, mAbs induce signaling through the CD3-TCR complex, resulting in T cell anergy (expressing $CD4^+$, $CTLA4^+$, $PDL1^+$) or triggering apoptosis. Apoptotic T cells and macrophages that ingest apoptotic bodies produce TGF-β, which can induce $FoxP3^+$ expression in $CD4^+$ T cells, further suppressing effector T cells. Both TGF-β and $CD4^+FoxP3^+$ T cells exert an inhibitory effect on effector T cells, while also inducing a shift in antigen-presenting cells, such as dendritic cells, toward a tolerogenic phenotype. Consequently, mAbs lead to the depletion of pathogenic T cells [100, 101].

Monoclonal antibodies (mAbs) maintain their integrity when administered orally and can pass through the stomach to be absorbed by the intestinal epithelium. Once they reach the lamina propria, these mAbs interact with the CD3/TCR complex on

T cells. This interaction between mAbs and $CD4^+$ T cells in the lamina propria has an important effect: it triggers the upregulation of latent membrane-bound TGF-β by the $CD4^+$ T cells. This conversion of $CD4^+$ T cells into a specialized subset known as Th3 cells is significant because Th3 cells play a crucial regulatory role in the immune system. The regulatory function of Th3 cells primarily relies on the action of TGF-β. However, IL-10 can also contribute to the establishment of a tolerogenic microenvironment. This microenvironment inhibits effector T cells, promotes the induction of Tregs, and supports the development of tolerogenic dendritic cells. This cascade of events, in turn, supports the generation of specific subsets of Tregs, including IL-10-producing Tr1 cells and $FoxP3^+$ Tregs [10].

In contrast to intravenous administration, oral administration of mAbs does not lead to antigenic modulation, T cell depletion, or T cell proliferation. Nasal administration of mAbs is facilitated by the action of TGF-β and IL-10. This phenomenon has been linked to an increase in the production of IL-10 by $CD4^+CD25\text{-}LAP^+$ regulatory T cells and a simultaneous reduction in the production of IL-17 and IL-21 by $CD4^+ICOS^+CXCR5^+$ follicular T helper cells. The establishment of nasal tolerance hinges on the development of IL-10-secreting LAP^+ T cells.

The in vivo stimulation of IL-10-secreting regulatory T cells, also known as Tr1 cells, through nasal anti-CD3 mAb administration is contingent upon the presence of IL-27-secreting dendritic cells in the upper respiratory tract. This process is regulated by the transcription factors AHR and c-maf. In summary, oral administration of mAbs primarily relies on TGF-β, while nasal administration predominantly depends on IL-10. This targeted approach using mAbs can effectively prevent and reverse the progression of autoimmune diseases by selectively targeting pathogenic T cells while preserving the integrity of regulatory T cells [100].

OKT3 marked a significant milestone as the initial murine mAb capable of recognizing CD3 on the surface of human T cells. However, its use was marred by issues of immunogenicity and side effects, including cytokine release syndrome. Subsequently, mAbs underwent humanization, which involved incorporating specific complementarity-determining regions crucial for antigen recognition into an IgG framework. As a result, it is worth noting that some antibody clones are now exclusively derived from human sources, such as Foralumab.

In Table 3, we provide a concise overview of the preclinical and clinical utilization of CD3 modulators, elucidating their effects and functions in vivo [100, 101].

Bispecific antibodies can be classified into two major groups based on their morphology: IgG-like and non-IgG-like. Non-IgG-like antibodies consist only of the Fab region. In contrast, IgG-like antibodies possess both the Fab and Fc regions, resulting in a higher molecular weight, reduced penetration capabilities, and an extended half-life compared to their non-IgG-like counterparts.

BsAbs possess two distinct arms, offering more diverse functions in antibody-based therapeutic methods compared to mAbs. Various types of BsAbs exist, including BiTE, ScFv, crossmab, fab-scFv-Fc, triomab, and others. CD3 bispecific antibodies play three major roles: engaging immune cells to eradicate tumor cells, delivering payloads to tumors, and blocking tumor signaling pathways. BsAbs exhibit the capability to connect two T-regs without necessarily binding to TAAs or CD3. They can even bind two antibodies together. Additionally, they can deliver payloads such as radioimmunotherapy and antibody-drug conjugates [102].

Blinatumomab (CD19×CD3), an FDA-approved BiTE antibody, is utilized in the treatment of ALL [103]. CD3-BsAbs function by simultaneously binding to a TAA located on cancer cells and to CD3 on T cells (CD3xTAA). This interaction between the two cell types enables the formation of an immunological synapse, triggering T-cell activation. As a result, cytokines with inflammatory properties and cytolytic molecules are released, effectively eliminating tumor cells. CD3-BsAbs are highly effective because any T-cell can act as an effector cell, regardless of its TCR specificity. This is possible due to the unique feature of these BsAbs, where TCR signaling is initiated through the CD3 pathway, instead of relying on the antigen-binding domain of the TCR [104].

While this therapeutic approach has shown promise, it faces challenges. Studies suggest that the FcR component of anti-CD3 antibodies primarily contributes to CRS and significant side effects. Consequently, recent advancements have led to the engineering of anti-CD3 antibodies without the FcR component. Additionally, there are other hurdles and limitations in anti-CD3 therapy, such as potential hypersensitivity to dosage and a narrow therapeutic window. Some studies indicate that a single injection of antibodies may be insufficient, and in certain cases, continuous drug administration for up to 28 days may be required, which can impact the patient's quality of life [105]. Another significant challenge in bispecific antibodies is identifying a specific marker on the target lesion to avoid harming normal body cells[104].

Hypothesis

The effect of the immune system on endometriosis has two distinct yet interconnected aspects that support

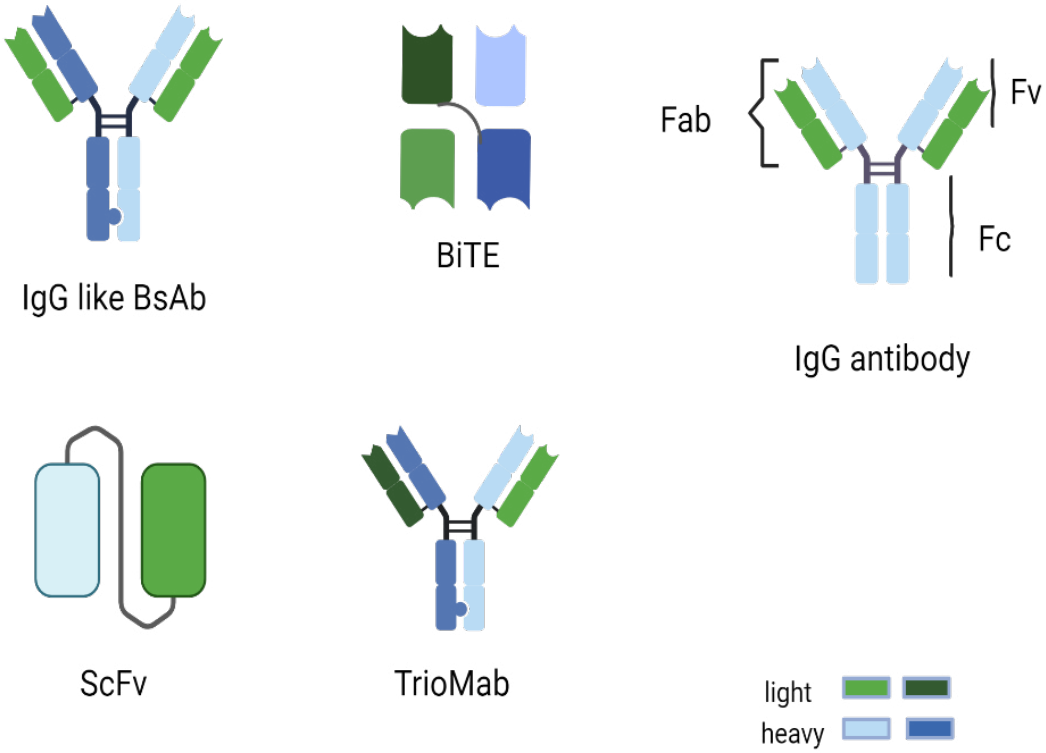

Fig 1. example of current BsAbs and their subbraches in trials

Table 3. Summary of CD3 modulators and their effects in clinical or preclinical use

Name	Target	Type of T cell modulator	In vivo effect
OKT3	human	Anti-CD3 antibody	Utilized in the prevention of acute rejection in transplant procedures(100, 106), for the management of autoimmune conditions, and for the eradication of $CD3^+$ lymphoblastic leukemia populations in vivo.(107) In addition, modified versions of OKT3 are employed to augment the populations of T cell adoptive therapy in ex-vivo(108, 109)
145-2C11	mouse	Anti-CD3 antibody	The induction of immune tolerance in vivo and the promotion of tolerance towards syngeneic pancreatic islet grafts in preclinical models of diabetes are observed.(110)
G4.18	mouse	Anti-CD3 antibody	Promotes immunotolerance in vivo in preclinical animal models of MS (111, 112)
Teplizumab	human	Anti-CD3 antibody	Delays the onset, diminishes the level of activity of autoreactive T cells, and induces Tregulatory cells(113-117)
Otelixizumab	human	Anti-CD3 antibody	Utilized in the therapeutic intervention of type 1 diabetes—promotes preservation of the βcells mass in the pancreas(118)
Visilizumab	human	Anti-CD3 antibody	Applied in the therapeutic intervention of severe corticosteroid-refractory ulcerative colitis(119)
Blinatumomab	human	Anti-CD3 antibody	Applied in the therapeutic intervention of acutelymphocytic leukemia(103, 120)
Tebentafusp	human	gp100 peptide-HLA-A*02:01 directed T cell receptor (TCR) CD3 T cell engager ImmTAC	Applied in the therapeutic intervention of uvealmelanoma and malignant melanoma(121, 122)

each other: pro-inflammatory and anti-inflammatory responses. Moreover, endometriosis can be compared to both cancer and autoimmunity. It has previously been mentioned that the abnormal immune response to ectopic endometrial tissue contributes to the survival and progression of endometriosis. Similarly, to autoimmune diseases, where an exaggerated and dysregulated immune response leads to disease manifestations, endometriosis exhibits a similar pattern. For instance, polyclonal activation of B cells and excessive production of anti-endometrial antibodies have been observed. Notably, a significant proportion of these antibodies shares similarities with autoimmune diseases such as Crohn's disease, rheumatoid arthritis, and psoriasis, which may contribute to the high comorbidity rates seen in patients.

Anti-CD3 therapy, initially indicated for organ rejection and autoimmunity, has shown promising results in regulating the immune status of individuals with endometriosis through deactivation and inhibition of pathological T cells, thus supporting the hypothesis of its potential in managing endometriosis. Furthermore, studies have demonstrated that Anti-CD3 antibody treatment can help regulate the pro-inflammatory state associated with endometriosis. This is particularly advantageous because endometriosis is a chronic inflammatory disease. The use of Anti-CD3 antibodies provides a way to modulate the activity of overactive immune cells, offering a potential therapeutic approach.

On the other hand, despite being a benign disease, endometriosis shares similarities with cancer in terms of cellular invasion, proliferation, production of new blood vessels, immune evasion, and reduced apoptosis. Notably, similar gene mutations involved in encoding metabolic and detoxification enzymes have been observed in both endometriosis and ovarian carcinoma. These mutations may also play a role in the progression of endometriosis to cancer [123]. Furthermore, mutations in tumor suppressor genes such as PTEN have been identified in both endometriosis and ovarian cancer, further supporting the connection between endometriosis and cancers [124].

In this context, a different type of CD3 antibody known as bispecific anti-CD3 antibodies has been introduced for the treatment of cancers. These antibodies offer a more target-specific and beneficial approach to dismantling cancer cells. Currently, only two bispecific antibodies have been approved for treating patients, while other models are still at a preclinical level. However, it is hypothesized that these antibodies can potentially diminish ectopic lesions and restore immune cytotoxic capabilities by binding effector T cells to specific target antigens. This opens up fascinating possibilities for the removal of endometrial lesions without resorting to invasive procedures [102, 125].

In this paper, we hypothesize that considering the similarities between endometriosis and autoimmune diseases, as well as cancers, along with the increasing usage and success of antibody therapy in these diseases, presents a novel and optimistic approach to treating endometriosis. This approach offers benefits compared to current therapeutic approaches.

To elaborate, bispecific antibodies can be used to modify cytotoxic T cells, enabling them to recognize and eliminate target-specific cells that were previously unrecognizable. This approach enhances the immune response in the body and helps counteract the immune invasion associated with ectopic lesions, such as those seen in endometriosis. In these lesions, the cytokines produced can lead to the deactivation or loss of antigen-binding abilities in cytotoxic cells. Through the proposed treatment method, cytotoxic T cells are able to bind to the lesion and induce its lysis. Furthermore, the target-specific properties of these antibodies minimize the side effects of therapy.

Additionally, bispecific antibodies can be used to deactivate cytokines and signaling pathways. For example, a newly designed bispecific antibody named ZW25 has been developed to target the HER2 and HER3 pathways. These pathways are known to activate the MAPK/PI3K/mTOR pathway, which is involved in cell development and resistance to immune cytotoxicity. Studies have shown that the hyperoxidative environment in endometriosis activates kinase pathways, including the MAPK/PI3K/mTOR pathway, which promotes disease progression [28, 126]. Therefore, targeting these kinase pathways with bispecific antibodies presents an exciting field of targeted therapy for endometriosis.

Furthermore, bispecific antibodies have also been used to deactivate cytokines, reducing disease symptoms and their effects on the body. For instance, the bispecific antibody ABT122 targets IL-17 and TNF-α, which decrease important cytokines involved in the pathogenesis and microenvironment of endometriosis [127, 128].

Bispecific antibodies not only activate T cells but also stimulate NK cell cytotoxicity by binding to CD16-positive NK cells and specific targets. This enhances the cytotoxic state [105]. Furthermore, bivalent antibodies that target CD3 can cause crosslinking between T cells, resulting in T cell lysis. This can be used to deactivate hyperactivated T cells in the endometriosis microenvironment, such as Tregs that contribute to an immunosuppressive state that promotes disease survival.

The suggested bispecific antibody binds to a specific receptor on immune cells, such as the CD3

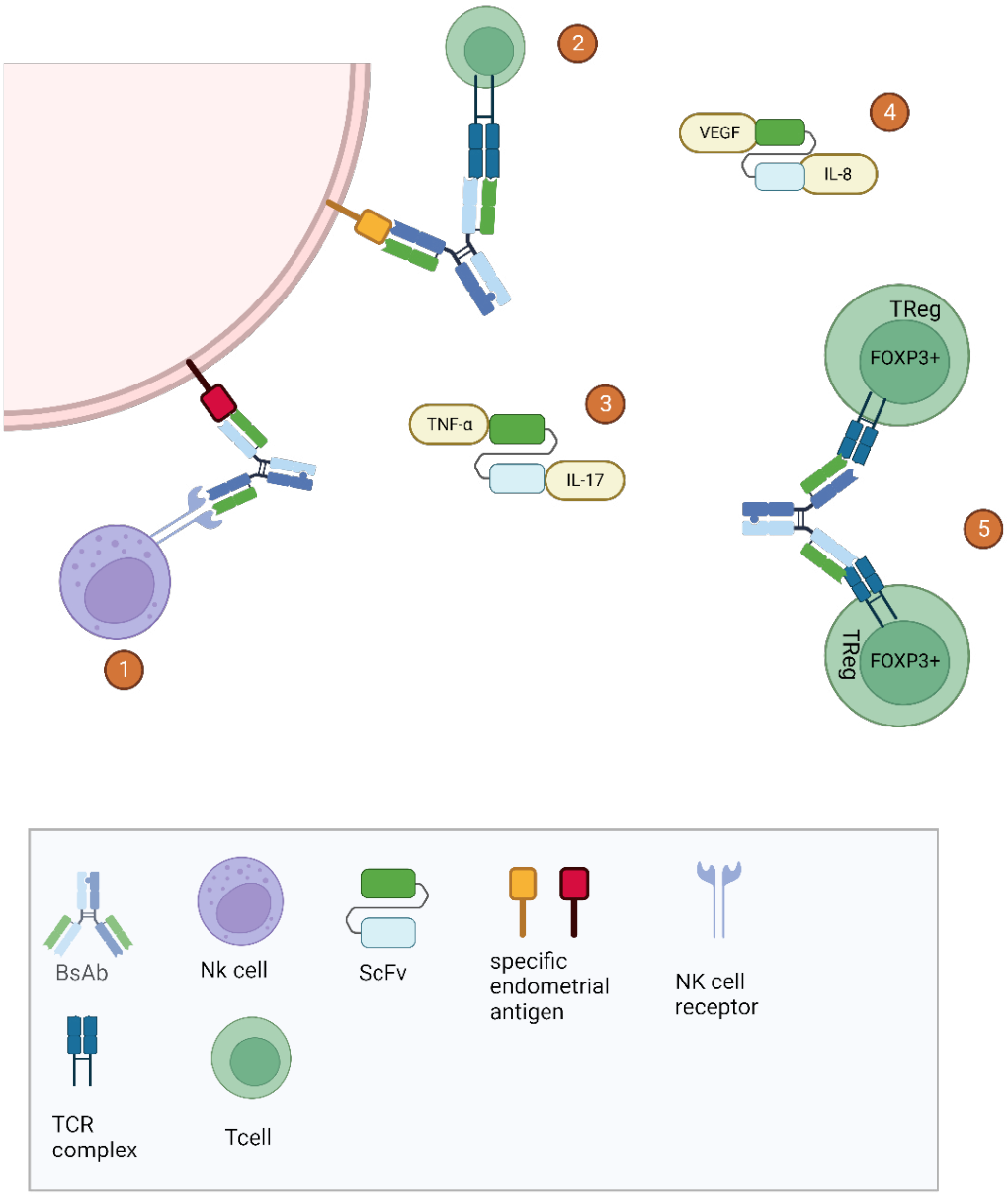

Fig. 2. 1)bispecific antibody binding CD16+ NK cells to endometrial specific markers. 2)bispecific antibody binding cytotoxic T cells to endometrial specific marker 3,4) ScFv simultaneously blocking the function of two cytokines 5) bispecific antibody biding two FPXP3+ T regs and inhibiting immunosuppressive function

region on T cells, using one of its Fab regions. Simultaneously, the other end of the antibody binds to a specific marker on endometrial lesions, triggering a chain reaction of lysis targeting the ectopic lesion. If the antibody also contains an Fc tail region, it has the additional capacity to attract other immune cells, such as NK cells and macrophages, to the region, thereby maximizing the cytotoxic effect.

Another pathway to improve treatment involves utilizing bispecific antibodies to bind to Tregs via FOXP3-positive receptor cells within the immune microenvironment of endometriosis. This approach promotes better recognition of cells and reduces the immunosuppressive properties associated with endometriosis.

There is an alternative approach to utilizing bispecific antibodies (BsAbs) for treating endometriosis. This involves using BsAbs as carriers for existing drugs like GnRH agonists, aromatase inhibitors, as well as antibodies and cytokines such as anti-IL-6, IL-8, IL-12, IL-37, rofecoxib (selective COX inhibitors), pentoxifylline (anti-TNF-α), and others. BsAbs can also play a role in radioimmunotherapy and antibody-drug conjugates, exemplified by brentuximab vedotin, used in treating Hodgkin lymphoma and systemic anaplastic large

cell lymphoma. In this context, BsAbs deliver their payload directly to the tumor by binding to tumor-associated antigens (TAA), with one arm binding to a specific drug, antibody, or cytokine. Subsequently, the internalization of the drug allows for its targeted impact on tumor cells [104].

Limitations and concerns

It is important to acknowledge the current limitations and roadblocks in using targeted therapy for endometriosis. Firstly, the antibodies need to have a specific target on the lesion, but current studies have not identified one for endometriosis cells. Further research is needed to address this issue, which could also impact the early diagnosis of the disease.

Secondly, the endometriosis lesion closely resembles the normal endometrium, which can lead to a counter reaction in the body. One suggested method to decrease this outcome is the use of a new technology named condition-activated biotech bispecific antibodies. These antibodies bind to the target in a specific environment [129]. The hyperoxidative and estrogen-dominant environment of the endometriosis lesion can act as this special factor in activating the antibody.

It has been reported in studies that functional bispecific antibodies binding to cytotoxic T cells were reduced in the presence of Treg cells [130], which are increased and activated in endometriosis [131]. Methods such as using antiestrogen drugs like aromatase inhibitors and GnRH agonists, which decrease the estrogen-dominant environment stimulating Tregs [22], or anti-CTLA4 therapy like PLGAs, which has proven useful in mouse models, can be employed to address this issue.

Additionally, preventing cytokine release syndrome may be achieved through low initial dosages in combination with subsequent high doses, corticosteroids, and antihistamine premedication [128, 131].

Lastly, the challenge of any immune modulatory therapy is finding the lowest effective dosage without promoting harmful systemic immune reactions. This phenomenon can be prevented by extracting certain T cells from the subject's blood, reengineering them in vivo, and then injecting them back into the patient. This treatment method, known as armed T cell therapy, has shown great improvement in this field.

We also suggest combining this method with other factors such as IL-2, which increases T cell and NK cell cytotoxicity and acts synergistically to improve targeted effects. Another example is combining it with anti-TNF-α, which can decrease the angiogenesis and proliferation of the endometriosis lesion for better cytotoxic outcomes [102, 105].

These new therapeutic methods offer an astonishing and novel approach to endometriosis, which can act as a supplementary way in comparison to the current treatment methods, while acknowledging the stated limitations in curing patients.

Conclusion

In conclusion, while current treatment methods for endometriosis have shown effectiveness, they have certain limitations that prevent a complete restoration of patients' reduced quality of life. Bispecific antibody therapy, predominantly utilized in cancer treatment, offers a novel and potentially improved therapeutic approach. This method is based on a specific target and can be further customized for each patient, thus enhancing treatment capabilities. Therefore, it establishes a promising avenue for future research in this field.

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Conflict of interest

The authors declare no conflict of interest.

Abbreviation

MRI: magnetic resonance imaging
%: percentage
T cell: T lymphocyte cell
B cell: B cell lymphocyte
NK cell: natural killer cell
CD: cluster differentiation
TCR: T cell receptor
Abs: anti-bodies
GVHD: graft versus host disease
BsAbs: bispecific antibodies
mAbs: monoclonal antibodies
NSAIDs: non-steroidal anti-inflammatory drugs
SSRI: selective serotonin receptor inhibitor
TCA: tricyclic antidepressants
GnRHa: gonadotropin release hormone agonists
SUP: superficial peritoneal lesions
ONA: ovarian endometriomas
DIE: Deep infiltrating endometriosis
ART: assisted reproductive therapies
CCR6: C-C chemokine receptor 6
MIP: macrophage inflammatory protein
SLPI: secretory leukocyte protease inhibitor
APC: antigen presenting cells
ROS: reactive oxygen species

NO: nitric oxide
IL: interleukin
TNF: tumor necrosis factor
TGF: tumor growth factor
α: alpha
β: beta
Th1: T helper 1
Th2: T helper 2
VEGF: vascular endometrial growth factor
IFN-γ: interferon- gamma
uNK: uterus natural killer cells
LIF: leukemia inhibitory factor
DC's: dendritic cells
MMP: matrix metalloproteinase
MCP-1: monocyte chemoattractant protein-1
RANTES: regulated on activation normal T cell expressed and secreted
iDC: immature dendritic cells
MC: mast cells
T reg: T regulatory cells
+: positive
-: Negative
Th17: T helper 17
I-CAM: intercellular adhesion molecule 1
FAS: Fas-cell surface death receptor
FAS-L: Fas-cell surface death receptor ligand
PEG2: prostaglandin E2
COX-2: cyclooxygenase 2
SIRP-α: signal regulatory protein alpha
RBC: red blood cells
FGF2: fibroblast growth factor 2
HMP: human neutrophil peptide
ENA-78: epithelial neutrophil-activating peptide 78
CXCL: chemokine ligand
KIR: killer inhibitory receptor
KAR: killer activating receptor
KIR2DL1: killer cell immunoglobulin-like receptor
NKG2A: cluster differentiation 159
LILRB: leukocyte immunoglobulin-like receptor
NKP44: natural cytotoxicity triggering receptor 2
NKG2D: natural killer group 2D
BDCA1+: Blood Dendritic Cell Antigen 1
NFkB: nuclear factor kappa B
EMT: epithelial-mesenchymal transition
BCG: basil Calmette-guerin
ε: epsilon
ζ: zeta
δ: delta
MHC: major histocompatibility complex
ITAMs: immune-receptor tyrosine-based activation motifs
Lck: lymphocyte-specific protein tyrosine kinase
FYN: tyrosine specific phospho- transferase
ZAP70: Zeta-chain-associated protein kinase 70
CTLA-4: cytotoxic T lymphocyte-associated antigen
PDL: program death ligand
FOXP3: forkhead box P3
TAA: tumor-associated antigen
Tr1: T regulatory 1
LAP: lymphocyte activation products
ICOS: inducible T cell costimulatory or CD278
OKT3: Ortho Kung T-Cell 3
AHR: aryl hydrocarbon receptor
C-MAF: proto-oncogene C musculoaponeurotic fibrosarcoma
IgG: human immunoglobulin g
Fab: fragment antigen binding
FcR: fragment crystallizable region receptor
ScFv: single-chain variable fragment
BiTEs: bispecific T cell engager
FDA: food and drug administration
CRS: cytokine release syndrome
ALL: acute lymphoblastic lymphoma
MS: multiple sclerosis
immTAC: immune mobilizing monoclonal T cell receptors against cancer
PTEN: Phosphatase and TENsin homolog
HER: human epidermal growth factor receptor
MAPK: mitogen-activated protein kinase
PI3K: phosphoinositide 3-kinase
mTOR: mammalian target of rapamycin
PLGA: Poly (lactic-co-glycolic acid)

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