Proceedings of ICBioMed 2025 Symposium: Computational Modelling and Simulation for Biology and Medicine
DOI: 10.54254/2753-8818/2025.LD26485

The Application of Abatacept in the Treatment of Rheumatoid Arthritis

Shian Wang

Nanjing Tech University, Nanjing, China
wangshihan345@gmail.com

Abstract. Rheumatoid arthritis (RA), as a type of chronic autoimmune disease. It is mainly characterized by invasive synovitis, cartilage destruction, leading to irreversible joint deformity and functional disability. Methotrexate and monoclonal antibody TNF inhibitors (TNFi) have become popular choices for the treatment of RA in recent years. However, these two types of drugs are accompanied by serious side effects and poor tolerance. Therefore, the drugs with significant therapeutic effects, stable safety and long-term use value have become a new direction in the treatment of RA. Abatacept (ABA), as a T-cell inhibitor, has shown good results in this regard and has become a valuable research direction in clinical studies. ABA interrupts T cell-mediated immune responses by inhibiting T cell function without consuming T cells. Activated T cells drive the inflammatory cascade. This causes joint inflammation. Such inflammation leads to irreversible structural damage. Patients with RA experience chronic inflammation. This inflammation occurs specifically in the synovial tissue. The synovial tissue lines the joint capsule. ABA therapy offers a suitable treatment option. It alleviates signs and symptoms of moderate to severe RA. This treatment is intended for adult patients. These patients have shown an inadequate response to at least one prior disease-modifying antirheumatic drug (DMARD). Their condition did not improve sufficiently with that prior DMARD therapy. In addition to introducing the basic pharmacology of abatacept, this article, through the analysis of multiple sets of clinical trial data, has derived the alternative therapy and combination treatment mechanism of abatacept in clinical treatment. Moreover, the clinical data of patients who have been using abatacept for a long time were analyzed to verify its excellent therapeutic effect and safety.

Keywords: Abatacept, Rheumatoid arthritis, disease-modifying antirheumatic drug

1. Introduction

RA is a kind of serious autoimmune sickness. Due to autoimmune disorders, it causes synovitis, which in turn affects the joints and the soft tissues around the joints. As of 2020, the global number of patients had reached 17.6 million, among which the number of female patients was 2.45 times that of male patients and it is predicted that the number of patients may reach 31.7 million by 2050 [1,2]. The onset of RA is significantly influenced by genetic factors, such as citrullinated antibodies regulated by HLA genes, while environmental factors, such as smoking, occupational exposure

DOI: 10.54254/2753-8818/2025.LD26485

(silica dust), microorganisms and mucosal inflammation, also play a certain role in its induction [3,4].

Traditional treatments mainly targeted the immune response mechanism and the production of inflammatory factors, focusing on alleviating inflammatory symptoms before the mid-1980s. Previously, RA was considered to have a good prognosis, with symptoms mainly controlled by aspirin/non-steroidal anti-inflammatory drugs (NSAIDs), but the actual patient outcomes were very poor. As the understanding of its pathogenesis deepened, a turning point emerged when it was found that the long-term effects of traditional DMARDs (gold preparations, penicillamine, etc.) were limited, and the treatment concept shifted to "early intensive treatment ". Since then, the treatment strategy has shifted to controlling disease activity, targeting and inhibiting key pathological links, including pro-inflammatory cytokines and Regarding the immune response to T and B cells, thereby achieving intervention in the disease process of RA. Since then, methotrexate (MTX) has gradually become the first-line preferred drug for the treatment of RA. However, this drug has significant toxic and side effects, and long-term use may lead to drug tolerance. The emergence of ABA, by specifically inhibiting the T-cell activation pathway and demonstrating high safety, offers a new option for the treatment of RA. At present, the core challenges in the treatment of RA lie in three points: First, the diseases themselves vary greatly, but the treatment methods are relatively single; Second, it is necessary to control symptoms in the short term while also taking into account the safety of long-term medication. Thirdly, although there are many innovative therapies, These treatments still face challenges for widespread adoption.

As a recombinant fusion protein, ABA competitive blocks CD28-mediated co-stimulatory signals by mimicking cytotoxic T lymphocyte antigen 4 (CTLA-4), a natural inhibitory molecule with high affinity for CD80/CD86, thereby inhibiting T cell proliferation and the release of inflammatory factors, and interrupting the immune cascade of RA. Clinical studies have shown that ABA has demonstrated significant value in the treatment of RA. This article will introduce the alternative therapy and combination treatment mechanism. These approaches apply to specific patients in clinical practice, who have resistance to both MTX and TNFi. And the article also evaluates the therapy's safety.

2. The pathogenesis of RA

The core of RA lesions mainly involves the synovial tissue presenting structural characteristics similar to secondary lymphoid tissue, as well as the proliferation and activation of synovial fibroblasts accompanied by immune cell infiltration. The lymphoid organ structure formed by synovial tissue is a key which will activate and differentiate T cells and B cells. The autoantibodies produced and the activated T cells further mediate the immune attack on joint tissues, ultimately leading to joint destruction. The early pathogenesis of RA is closely related to the $CD4^+$ T cell activation pathway driven by citrullination. Under the combined effect of genetic susceptibility (such as polymorphisms of specific HLA gene loci) and environmental factors (such as smoking and occupational exposure), specific proteins in the body undergo citrullination modification. These citrullinated proteins, as autoantigens, are taken up and processed by Antigen-presenting cells (APCs), and then classified by Major histocompatibility complex Class II. MHC-II) molecules are presented to the cell surface. $CD4^+$ helper T cells are activated by specifically recognizing the MHC-II/ citrullinated peptide complex through their T cell receptor (TCR) [5]. CD4+ helper T cells (Th) undergo differentiation. They form two distinct subsets: Th1 cells and Th17 cells.Th17 cells also have two types: pathogenic and non-pathogenic. In RA pathogenic Th17, pathogenic Th17 cells release pro-inflammatory factors such as interleukins (ILs, such as IL-17A, IL-17F and IL-22),

DOI: 10.54254/2753-8818/2025.LD26485

Among them, IL-22 plays a key role in the pathogenesis of RA [6, 7]. IL-22 aggravates the inflammatory response by inducing the proliferation of synovial fibroblasts and the production of chemokines [8].

Meanwhile, B cells are activated and differentiate into plasma cells when presenting proteins to T cells, generating Anti-citrullinated protein antibody (ACPA). Antibodies bind to Fc receptors expressed by myeloid immune cells, activating the complement system, and inducing the release of the inflammatory factor tumor necrosis factor -α (TNF-α), thus forming an inflammatory cytokine storm [9]. This process leads to synovitis and pannus, which in turn activates osteoclasts to release proteases that attack cartilage joints and bone tissue, ultimately causing joint deformity and functional disorders.

3. The mechanism of ABA in the treatment of RA

The etiology of RA indicates that T-cell-mediated inflammation plays a significant role in the pathogenesis of RA. The activation of T cells requires antigen-specific first signals, which are mediated by MHC through TCR on APCs, and antigen-non-specific second signals, which are mediated by co-stimulatory molecules expressed on both types of cells [10, 11]. Among them, CD28 on T cells binding to CD80 and CD86 on antigen-presenting cells is regarded as the most important co-stimulatory signal in the process of T cell activation [12].

ABA, as a costimulatory molecule that inhibits T cell activation, is a CTLA-4. The binding affinity of CTLA-4 for CD80/CD86 is 270 to 2800 times that of CD28 [13]. By competing with CD28 to bind to CD80/CD86, ABA inhibits CD28-mediated co-stimulatory signals and simultaneously transmits the inhibitory signals to T cells, thereby blocking T cell activation, proliferation and cytokine production. This mechanism effectively intervenes in the immunopathological process of RA.

4. Clinical applications of ABA

ABA is often used in combination with MTX in clinical treatment. ABA is a CTLA-4 fusion protein that reduces the production of inflammatory factors by blocking the CD80/CD86 co-stimulatory signal, while MTX is an antimetabolite that reduces the proliferation of inflammatory cells by inhibiting folic acid synthesis. Their different mechanisms can play a synergistic role. Both are administered intravenously. Their dosage is adjusted according to patient body weight. The standard dosage is approximately 10 mg per kilogram. Actual administered doses follow specific weight categories: Patients weighing under 60 kg receive 500 mg. Patients weighing between 60 kg and 100 kg receive 750 mg. Patients weighing over 100 kg receive 1000 mg [14].

Ruperto, N et al. conducted data from two 2-year clinical trials of two injection methods of ABA in children about 2-17 years old [15]. These two trials respectively evaluated patients who were unresponsive or intolerant to MTX, and they were treated with ABA + MTX or ABA monotherapy. Researchers evaluated the treatment outcomes through JIA-ACR70, disease inactivity (ID), and JADAS27-CRP (low activity LDA≤3.8, ID≤1.9). The results showed that during the treatment period of up to 2 years, the children who received ABA + MTX combined treatment (n = 310) and those who received ABA monotherapy (n = 99) demonstrated similar improvements in efficacy, with both the JIA-ACR response rate and the JADAS27-CRP score decreased. Moreover, this therapeutic effect is not related to whether the patient has used biological agents or MTX before, and the therapeutic effect can be observed in all cases. Therefore, the patient did not achieve the expected therapeutic effect in MTX treatment. ABA monotherapy has demonstrated good efficacy and

DOI: 10.54254/2753-8818/2025.LD26485

tolerance, whether administered subcutaneously or intravenously. The therapeutic effect of ABA is not affected by whether MTX is used in combination or not. Therefore, for patients who are intolerant to MTX, ABA monotherapy is an effective treatment option.

Cvetkovski et al. proposed a combined treatment approach based on the mechanism by which rituximab and ABA inhibit T cell activation [16]. Both have inhibitory effects on CD2/CD58 and CD28/B7 respectively, thus forming a dual blockade. It can almost completely inhibit the proliferation of T cells and enhance the clearance of memory T cells. Researchers used a bidirectional mixed lymphocyte response (MLR) model to evaluate and compare the efficacy of rituximab monotherapy, ABA monotherapy, and the combination of rituximab and ABA. Study results demonstrated the combination therapy's profound effect. It inhibited CD4/CD8 T cell proliferation by over 95%. The therapy also nearly eliminated memory T cells. This combined treatment approach covers $CD28^{-}/CD2^{+}$ or $CD28^{+}/CD2^{-}$ T cells, reducing immune escape and lowering the risk of activated T cells attacking bone and joint. However, the strong inhibitory effect of combined medication on T cells and the weakening of the enrichment effect of regulatory T cells (Treg) pose certain therapeutic risks.

In addition, for patients who do not respond to TNF-α antagonists, ABA treatment has a significant therapeutic effect. Alisson P et al. compared the efficacy of rituximab (RTX), ABA, and tocilizumab (TCZ) in RA patients who failed TNFi treatment through systematic reviews and network meta-analyses (NMA). This study integrated data from 19 randomized controlled trials (RCTs), involving a total of 7,835 patients [17]. After adjusting for confounding factors(study duration, the TNFi usage rate etc) in the control group. The results of statistical analysis indicated that ABA demonstrated superiority over tocilizumab about an ACR70 response rate (relative risk RR=2.22), while its efficacy was similar to that of rituximab. Based on the efficacy analysis after adjusting for confounding factors, for RA patients with TNFi resistance, ABA can be considered preferentially over tocilizumab. However, it should be noted that during the medication period, combination with TNFis (such as infliximab and etanercept) should be avoided to prevent the condition from worsening [18].

In the treatment of RA, TNF has been proven to increase the risk of severe infection. Salliot, C et al. evaluated the infection risk of ABA through a meta-analysis. This analysis included five RCTs, involving a total of 1,960 patients treated with ABA and the placebo group was approximately half the size of the ABA group [19]. By using the fixed effects model and the Mantel-Haenszel method. The combined odds ratio (OR)of severe infection and its 95% confidence interval (95% CI) between the ABA group and the placebo group can be calculated. The result was OR=1.35, 95%CI:0.78-2.32. Among them, the incidence of severe infection in the ABA group was 2.5%, and that in the placebo group was 1.8%. The result of two groups is similar. So there is no obvious risk of infection for ABA. Compare the high/low dose ABA group with the placebo group, the statistical results showed that different doses of ABA did not significantly increase the risk of infection. The safety of ABA is a stable guarantee in clinical practice. By analyzing the existing RCT data, ABA does not pose a serious infection risk to RA patients. Whether in the overall analysis or dose-stratified analysis, the risk was comparable to that of the placebo group. Through the study indicate the ABA is stable, clinical trials usually exclude high-risk patients with severe comorbidities or a history of severe infection, and the follow-up period is relatively short. Therefore, careful monitoring is still needed in the long-term application of clinical treatment, especially for patients with comorbidities or those using glucocorticoids concurrently.

DOI: 10.54254/2753-8818/2025.LD26485

5. Conclusion

This article expounds the application value of ABA in the treatment of RA. As a CTLA-4 fusion protein, ABA effectively inhibits T cell activation, proliferation and the release of pro-inflammatory factors by competitively binding to CD80/CD86 with high affinity and blocking the co-stimulatory signal of CD28, thereby precisely intervening in the immunopathological process of RA.

At the clinical application level, this article, based on multiple key clinical research data, indicates that ABA monotherapy provides an effective alternative for MTX intolerance. And people failed in TNFi treatment, ABA (especially compared with tocilizumab) demonstrated significant efficacy. In addition, the combination of ABA and MTX has a synergistic potential, and the possibility of "double blocking" the T-cell activation pathway when combined with rituximab. Moreover, research and analysis have shown that ABA does not significantly increase the risk of severe infection compared with placebo, providing strong support for its long-term safety.

The ABA introduced in this article offers a unique and effective treatment option for RA. It has especially solved the problem of "single therapy" for patients who have insufficient or intolerant responses to traditional DMARDs or TNFi. Meanwhile, its excellent safety data takes into account the demand for long-term medication safety. These findings provide crucial references for optimizing the treatment pathways for patients with refractory RA.

Of course, the research also has certain limitations. For instance, the clinical trials cited usually exclude high-risk individuals with severe diseases or a history of serious infections in the past, and the follow-up period is relatively limited. Its long-term safety (especially the risk of rare adverse events and malignant tumors) still requires further verification through larger-scale and longer-term real-world studies.

Future research on ABA should focus on in-depth exploration of the optimal dosage of ABA, the frequency of administration, and the combination strategy with other biological agents to enhance efficacy and convenience. And comprehensively study the stability of ABA, attempt to predict the efficacy or adverse reactions of ABA, and achieve more precise individualized treatment. At the same time, evaluate the potential of ABA in other autoimmune diseases and reveal more clinical medicinal value of ABA.

References

[1] Black, R. J., et al. (2023). Global, regional, and national burden of rheumatoid arthritis, 1990–2020, and projections to 2050: A systematic analysis of the Global Burden of Disease Study 2021. The Lancet Rheumatology, 5(10), e594–e610.
[2] Gill, T. K., et al. (2023). Global, regional, and national burden of other musculoskeletal disorders, 1990–2020, and projections to 2050: A systematic analysis of the Global Burden of Disease Study 2021. The Lancet Rheumatology, 5(11), e670–e682.
[3] Ruscitti, P., et al. (2024). Recent advances and evolving concepts in Still's disease. Nature Reviews Rheumatology, 20(2), 116–132.
[4] Cho, M. H., et al. (2024). Rheumatoid arthritis and risk of lung cancer: A nationwide cohort study. Journal of Thoracic Oncology, 19(2), 216–226.
[5] Mellado, M., et al. (2015). T cell migration in rheumatoid arthritis. Frontiers in Immunology, 6, 2015.
[6] Wang, B., et al. (2017). Increased expression of Th17 cytokines and interleukin-22 correlates with disease activity in pristane-induced arthritis in rats. PLOS ONE, 12(11), e0188199.
[7] Lotfi, N., et al. (2019). Roles of GM-CSF in the pathogenesis of autoimmune diseases: An update. Frontiers in Immunology, 10, 2019.
[8] Ikeuchi, H., et al. (2005). Expression of interleukin-22 in rheumatoid arthritis: Potential role as a proinflammatory cytokine. Arthritis & Rheumatism, 52(4), 1037–1046.

DOI: 10.54254/2753-8818/2025.LD26485

[9] Kurowska, W., et al. (2017). The role of anti-citrullinated protein antibodies (ACPA) in the pathogenesis of rheumatoid arthritis. Central European Journal of Immunology, 42(4), 390–398.
[10] McInnes, I. B., & Schett, G. (2017). Pathogenetic insights from the treatment of rheumatoid arthritis. The Lancet, 389(10086), 2328–2337.
[11] Sawcer, S., et al. (2011). Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. Nature, 476(7359), 214–219.
[12] Kunkl, M., et al. (2020). T helper cells: The modulators of inflammation in multiple sclerosis. Cells, 9(2), 482.
[13] Glatigny, S., et al. (2019). Abatacept targets T follicular helper and regulatory T cells, disrupting molecular pathways that regulate their proliferation and maintenance. The Journal of Immunology, 202(5), 1373–1382.
[14] D'Agostino, M.-A., et al. (2017). Body mass index and clinical response to intravenous or subcutaneous abatacept in patients with rheumatoid arthritis. Clinical Rheumatology, 36(12), 2655–2665.
[15] Ruperto, N., et al. (2023). Abatacept as monotherapy and in combination with methotrexate in patients with juvenile idiopathic arthritis: Analysis of 2 phase III trials. The Journal of Rheumatology, 50(11), 1471–1480.
[16] Cvetkovski, F., et al. (2023). Siplizumab combination therapy with belatacept or abatacept broadly inhibits human T cell alloreactivity in vitro. American Journal of Transplantation, 23(10), 1603–1611.
[17] Pugliesi, A., et al. (2023). Compared efficacy of rituximab, abatacept, and tocilizumab in patients with rheumatoid arthritis refractory to methotrexate or TNF inhibitors agents: A systematic review and network meta-analysis. Advances in Rheumatology, 63(1).
[18] Fleischmann, R., et al. (2019). Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: Results of a phase III, double-blind, randomized controlled trial. Arthritis & Rheumatology, 71(11), 1788–1800.
[19] Salliot, C., Dougados, M., & Gossec, L. (2009). Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: Meta-analyses of randomised placebo-controlled trials. Annals of the Rheumatic Diseases, 68(1), 25–32.