

Therapeutic Effects of Adalimumab Biosimilars on Rheumatoid Arthritis

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Abstract:

Rheumatoid arthritis (RA) is a chronic and autoimmune disease. Adalimumab and its generic drugs exerted an effective therapeutic effect on RA. Adalimumab is a monoclonal antibody against CD20. Adalimumab can specifically bind to tumor necrosis factor TNF- α , prevent TNF- α from binding to TNF- α receptors p75 and p55 on the cell surface, and inhibit the biological activity of TNF- α . This article summarizes several generic drugs, including ABP 501, BI 695501, PF-06410293, SB5, FKB327, LBAL, MSB11022, GP2017, etc. The limitation of the study is that it did not evaluate the quality of the research methods as a criterion for inclusion or exclusion in evaluating generic drugs. This article mainly focuses on the generic drugs of Adalimumab, reflecting the differences and similarities between the Adalimumab group and the generic drug group. In addition, the pharmacokinetics, safety, and efficacy of Adalimumab generic drugs were evaluated in several clinical trials. Future research may focus on generating drugs with higher safety, lower costs, and higher efficacy.

Keywords: Adalimumab; biosimilar; rheumatoid arthritis; pharmacokinetics; clinical trials.

1. Introduction

Rheumatoid arthritis (RA) is a systemic, chronic autoimmune inflammatory disease mainly affecting joints and surrounding soft tissues [1]. Progressive disability, premature death, and high socioeconomic status costs are all associated with RA. The average life expectancy of severe RA patients has been estimated to be shortened by ten years. However, in 2006, the total cost of RA to society was evaluated to be 52 billion dollars in the United States [2]. The prevalence of RA ranges from 0.25% to 1% globally. RA has increased the incidence rate of the elderly for more than 40 years and is related to various age groups. Women are affected two to three times more frequently than men [1]. Thus, the need to study RA is emerging.

Adalimumab is a recombinant, whole human IgG1 monoclonal antibody [2]. The original research drug of Adalimumab, Humira, achieved global sales of \$18 billion in 2017, becoming the best-selling drug in the world. It is also one of the most widely used drugs. Ankylosing spondylitis/axial spinal arthritis, Crohn's disease, non-infectious uveitis, psoriatic arthritis, adolescent idiopathic arthritis, ulcerative colitis, plaque psoriasis, polyarthritis, and purulent sweat gland inflammation have all been approved for treatment with Adalimumab [2]. Its biosimilars have been found promising during clinical applications.

Multiple phase III randomized controlled trials confirmed the treatment of long-term RA by Adalimumab. There is no significant difference between biosimilars and reference drugs, which is the basis for the approval of biosimilars [2]. Many generic drugs of Adalimumab have been shown to establish biological similarity in one indication and have been approved for use in other indications of reference drug holdings without the need for analysis clinical trials. Indications extrapolation reduces the number and scale of required clinical trials, thereby lowering economic costs and potentially increasing accessibility. Multiple biosimilars of Adalimumab have been approved in the European Union and/or the United States. Fujifilm Kyowa Kirin Biology's FKB327 is a clinical trial. A Phase 3 RA trial was released in abstract form by this company; Sandoz's GP2017 conducted a Phase III plaque psoriasis trial in summary form and has undergone regulatory review. Exemptia (India) and CinnoRA (Iran) have also published randomized controlled trials in PubMed [2]. The first Adalimumab biosimilar drug was Anjin's ABP 501, which received FDA approval (named AMJEVITA) and EMA approval, named AMGEVITA/Solymbic, in 2016 and 2017, respectively. ABP 501 is highly comparable to the reference drug in structure, function, and pharmacokinetics. Subsequently, a phase III study was conducted on plaque psoriasis and RA [2]. Current biosimilars in-

clude ABP 501, BI 695501, SB5, GP2017, PF-06410293, LBAL, MSB11022, and FKB327, etc.

This review summarizes the definition, mechanisms, and structure of Adalimumab and its biosimilars. It also addresses the pharmacokinetics, safety, and efficacy of two generic drugs. In addition, this article focuses on the clinical studies of various biosimilars of Adalimumab and compares the biosimilars group with the Adalimumab group. These clinical data not only include safety and efficacy but also the types of experiments, patient types, treatment methods, and outcomes.

2. Mechanisms of Adalimumab and Its Biosimilars

2.1 Structure of Adalimumab

Adalimumab is composed of the antigen-binding region Fab and the crystallizable region Human IgG1 Fc [1]. The structure of Adalimumab is different from other types of antibodies in the heavy chain Fc region, such as infliximab, Golimumab, Certolizumab, and Certolizumab. TNFR1 is present on the cell surface and specifically binds to tumor necrosis factor. After binding with TNFR1 and tumor necrosis factor, information is transmitted to the nucleus, followed by the production of pro-inflammatory factors by the nucleus, which is the mechanism of inflammation. Adalimumab is a tumor necrosis factor blocker that can specifically bind to TNFR1, thereby blocking the binding of tumor necrosis factor and TNFR1, thereby blocking the signaling pathway and ultimately preventing the production of inflammatory factors (Figure 1) [2].

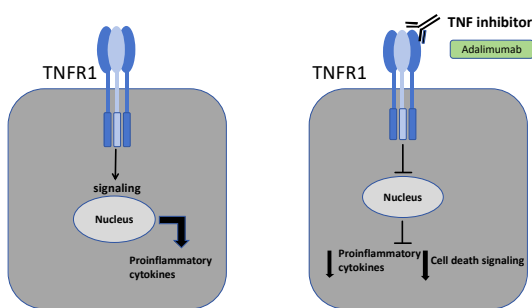


Fig. 1 Molecular mechanisms of Adalimumab through tumor necrosis factor receptor (TNFR1). Adalimumab binds to and inhibits TNFR1, which in turn regulates gene expression, followed by blocking the production of pro-inflammatory factors. Figure credit: original.

2.2 Pharmacokinetics, Safety, and Efficiency of ABP 501

There are many similarities between biosimilar ABP 501

and reference drugs [3]. By evaluating the inhibition of TNF α -induced cell apoptosis rate, it was found that ABP 501 can pair with sTNF α . The inhibitory ability of induced pro-inflammatory signal transduction is highly similar to that of Adalimumab [3]. Moreover, repeated dose toxicology research was using ABP 501 in a crab-eating monkey model. ABP 501 showed protective effects, such as reduced number and size of mesenteric lymph nodes, axillary lymph nodes, as well as tonsil germinal centers [3]. In addition, clinical trials showed that the adverse symptoms of medication use are mild to moderate, with the most common adverse reactions being headache, oropharyngeal pain, nasopharyngeal inflammation, sinus congestion, and nausea [3]. More than one patient developed sepsis but was eventually cured, and no deaths were reported in this study. It can be seen that although there are some adverse reactions, the safety of ABP 501 is very high.

2.3 Pharmacokinetics, Safety, and Efficiency of SB5

SB5 is a biosimilar to Adalimumab. For RA, psoriatic arthritis, and ankylosing spondylitis, adults were injected with 40mg every week, and pediatric patients over two years old were injected according to different body weights [4]. In addition, for Crohn's disease, adults have 160 mg on the first day; On the 15th day, 80 mg; Starting from the 29th day, 40 mg per week [4]. For ulcerative colitis and plaque psoriasis, adults need 160 mg on day 1, 80 milligrams on day 15, 40 milligrams every week starting from day 29, and a first dose of 80 mg every week, followed by 40 milligrams every week starting from one week after the initial dose [4]. It is worth noting that the use of SB5 in combination with abaloprol and anabaizhila increases the risk of severe infection, and the most prevalent adverse reactions include infection, injection site reactions, rash, and headache [5].

No significant difference was found between SB5 and Adalimumab in randomized controlled trials regarding the safety, showing an equivalent of the safety of the biosimilar. In clinical trials, there were no deaths reported in the SB5 group. At the same time, there were two deaths reported in the Adalimumab group, both of which were not related to drug research, and there were no adverse reactions observed when switching from ADL to SB5 at week 24 [5]. Most adverse reactions are mild or moderate. Overall, the safety of SB5 drug therapy is relatively high. Clinical equivalence studies have shown that SB5 and ADL drugs have the same efficacy in treating patients with moderate to severe RA [5]. At week 24, the treatment rates of SB5 and ADL drugs were 72.4 and 72.2, respectively, and converting ADL to SB5 did not reduce the

treatment rate. In week 52, 77.8% and 73.4% of people achieved ACR20 remission after using SB5 and ADL [5]. In summary, SB5 and ADL have similar safety and efficiency.

3. Clinical Applications of Adalimumab Biosimilars

A variety of Adalimumab biosimilars have been applied in clinical trials, including ABP-501, BI 695501, SB5, FKB327, PF-06410293, HLX03, etc., and showed therapeutic effects (Table 1).

3.1 ABP 501

Scientists conducted a randomized, double-blind, active-controlled equivalence study and found that there was no significant difference in the various indicators between ABP501 and Adalimumab. In the clinical treatment of moderate to moderate RA, the percentage of patients who achieved ACR20, ACR50, and ACR75 (ACR is the ratio of urine microalbumin to creatinine, and its clinical significance is to measure early renal injury and measure 24-hour urine albumin excretion) after receiving ABP501 and Adalimumab was very similar in the experimental data of phase 3, confirming that the efficacy of these two drugs is high. Moreover, ABP 501 has a high level of safety, with 2.3% of patients experiencing injection site reactions, lower than Adalimumab (5% of patients experiencing injection site reactions) [3].

3.2 BI 695501

Scientists conducted a phase III, randomized controlled double-blind trial to compare whether multiple conversions between BI 695501 and Adalimumab RP lead to akin safety and pharmacokinetics [6]. On the first day, 80 mg of Adalimumab RP was used for treatment, and every other week (EOW) from 2 to 12 weeks, 40 mg was subcutaneously injected (SC). Under the premise of SC treatment in all cases, the treatment of the switching group was first to take BI 695501 40mg in weeks 14 and 16, then took Adalimumab RP 40mg in weeks 18 and 20, and finally inject BI695501 40mg EOW into the patient in weeks 22-48. The continuous processing group was treated with Adalimumab RP 40 mg EOW between 3-12 months [6]. Finally, at week 32, the ratio of patients with PASI75 (severity index and psoriasis area) remission was similar between the two groups, and the proportion of patients with sPGA response ≤ 1 was highly similar between the two groups [6]. Less than 5% of patients in both groups experienced severe treatment-emergent adverse events (TEAEs). No patients died after randomization treatment.

3.3 SB5

A phase III, double-blind, randomized, parallel-group

study was performed to evaluate the safety, efficacy, and immunogenicity of SB5 and ADL. This study included 544 patients with moderate to severe RA who received the treatment of methotrexate (MTX) [7]. The results showed that the ACR20 remission rates in the SB5 and ADL groups were 72.4% and 72.2%, respectively, with similar probabilities and a rate difference of 0.1%. By week 24, 40.7% of patients in the ADL group and 35.8% in the SB5 group experienced TEAEs (Level 1 or Level 2 treatment-related adverse events). Especially, 10.1% and 11.7% of patients were related to the study drug, respectively. One patient with Escherichia coli urinary tract infection (0.4%) was present in the SB5 group, while two patients with bronchopneumonia and Staphylococcal sepsis (0.7%) were present in the ADL group. Patients reporting injection site reactions were similar between the SB5 group and the ADL group [7]. Additionally, in terms of efficacy, key clinical equivalence studies conducted in patients with moderate to severe RA have been proved that SB5 and ADL have equal efficacy [5].

3.4 FKB327

The DB study is a phase III, parallel, randomized, active comparative control, 6-month equivalence study. For adult RA patients, the dose of Adalimumab is 40 mg/0.8 mL or 40 mg/0.4 mL, administered subcutaneously every week using a disposable pre-loaded syringe or pen; FKB327 is delivered at the same dosage and in the same manner. In this regard, adult participants with moderate to severe, poorly controlled RA despite receiving MTX for \geq three months [8]. In the 24th week, according to the judgment of the researchers, patients who completed the DB study and had clinical reactions and no serious adverse events (AEs) were qualified for admission to OLE and were re-randomized. Approximately 66% of patients continued to receive the same treatment, and one-third switched to alternative treatment during the second phase. Subsequently, from week 30 to week 76, all patients received FKB327 treatment and were followed up for an additional four weeks. Overall, 328 patients (90.04%) of the RP group and 333 patients (90.7%) of FKB327 group finished the research [8]. In terms of safety, the incidence of TEAE in patients receiving FKB327 treatment is numerically lower than that in patients receiving RP treatment (1.707 and 2.075 events per patient-year, respectively) [8].

3.5 PF-06410293

An optional, open-label, single-arm sub-research was performed. Adult patients with insufficient response to MTX and diagnosed with active RA ≥ 4 months participated in the main study [9]. The patient received a subcutaneous injection of ADL-PF 40 mg at weeks 52 and 54 and then

received six doses of ADL-PF 40 mg every two weeks (weeks 56-66). The first injection training will be conducted in the 56th week. No deaths, ISR, or permanent discontinuation of treatment due to TEAE was reported during the sub-study period [9]. During the sub-study, the most commonly reported TEAE was viral upper respiratory tract infection (5 [10.0%] patients). Two patients reported all other TEAEs. A total of 17 patients (34.0%) reported a total of 20 TEAEs. During the sub-study, 3 cases (6.0%) of SAE (tonsillitis, RA flare, and pelvic fracture) were reported [9].

3.6 HLX03

A randomized, double-blind, actively controlled, parallel-group research was conducted to evaluate the therapeutic effect of HLX03. The study enrolled 262 patients with moderate to severe plaque psoriasis. The participants were given HLX03 or Adalimumab treatment (starting from 80 mg, then 40 mg maintaining) for 48 weeks [10]. At week 16, the improvement rates of PASI in the HLX03 group and Adalimumab group were 83.5% and 82.0%, respectively. HLX03 and Adalimumab showed comparable safety. The incidence of TEAEs in the HLX03 group was 89.3% (117/131), while in the Adalimumab group it was 94.6% (123/130) [10].

3.7 MSB11022

Adult patients with active but clinically stable moderate to severe chronic plaque psoriasis previously received systemic psoriasis treatment or phototherapy. The initial dose of MSB11022, or reference Adalimumab, is the subcutaneous injection of 80 mg, followed by an injection of 40 mg every two weeks starting from 1 week after initial administration. At week 16, patients with a PASI improvement of $\geq 50\%$ from baseline (PASI 50) are eligible to enter the extended period [11]. The final result was that at week 16, the remission rates of PASI 75 in the MSB11022 group and the Adalimumab group were 89.7% and 91.6%,

with a treatment difference of -1.9%. In terms of safety, as of week 66, the incidence of serious adverse events, injection site reactions allergic reactions caused by TEAEs, and treatment interruption were similar in all three treatment groups [11].

3.8 GP2017

GP2017 began to be used for steroid resistance in 5 patients (17.2%), steroid dependence in 16 patients (55.2%), prevention or treatment of postoperative recurrence in 4 patients (13.8%), failure/intolerance to azathioprine in 2 patients (6.9%), indication for related rheumatic or skin diseases in 1 patient (3.4%), and perianal disease in one patient (3.4%) [12]. For the efficacy of GP2017, at the start of treatment, 17.2% of patients were in clinical remission, more than half of patients had mild disease activity, and 27.6% of patients had moderate to severe activity. After half-years, the number of patients with improved symptoms increased by five, the number of patients with mild activity increased by one, and the number of patients with moderate to severe activity remained unchanged. After 12 months, 58.6% of patients were in remission, and 31.0% of patients showed mild activity. Notably, the number of patients with moderate to severe activity decreased to one [12].

Among patients using other Adalimumab analogs, at the beginning of GP2017, 60% of patients had clinical remission, 30% of patients showed mild activity, and 10% of patients showed moderate to severe activity. After six months of conversion to GP2017 treatment, 70% of patients were in clinical remission, 20% of patients showed mild activity, and 10% of patients showed moderate to severe activity. After one year of conversion, 70% of patients had clinical remission, and the number of patients with mild to moderate to severe symptoms decreased [11]. In terms of safety, 11 patients experienced adverse reactions, but none of them were very severe [12].

Table 1. Effects of Adalimumab biosimilars

Biosimilars	Rate of TEAE (Level 1 or Level 2 treatment-related adverse events)	Reference
ABP 501	63.7% of patients experienced ≥ 1 TEAE	[3]
BI 695501	67 patients (56.8%) in the switching group (from Adalimumab to BI 695501) experienced at least one TEAE	[6]
SB5	35.8% experienced TEAE	[7]
FKB327	208 patients (32.2%) experienced TEAEs	[8]
PF-06410293	218 patients (43.2%) reported 446 full cause TEAEs	[9]
HLX03	The incidence of TEAE in the HLX03 group was 89.3% (117/131)	[10]
MSB11022	78.3% experienced TEAEs	[11]
GP2017	11 patients (15.2%) experienced side effects	[12]

4. Conclusion

In summary, RA is a chronic autoimmune disease and a top priority for medical research. Adalimumab and its biosimilars have been shown to target this disease. The structure of Adalimumab is composed of the antigen-binding region Fab and the crystallizable region Human IgG1 Fc. The two generic Adalimumab drugs, ABP 501 and SB5 showed similar safety, efficacy, and pharmacokinetics to Adalimumab, indicating a potential clinical application to substitute Adalimumab. Through clinical trials, the differences in data, safety, and efficacy between the Adalimumab group and multiple generic drug groups in the treatment of RA are compared. The importance of this study lies in the thorough study of the advantages and potential risks of Adalimumab generic drugs. Future research is required to explore the advantages and risks of generic Adalimumab further in the future, assisting in developing more effective and safer Adalimumab biosimilars.

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