

Review Article

Adalimumab – General Considerations

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Abstract

Dysregulation of the immune system and overexpression of TNF- α represents the basis of the action of TNF- α inhibitors. Adalimumab, as well as the other tumor necrosis factor alpha (TNF- α) inhibitors, has brought a revolution in the treatment of the immune-mediated inflammatory disease (IMIDs). Over the last two decades, this therapy has made a significant improvement in the quality of life for an ever increasing number of patients. Since its regulatory approval in 2002, adalimumab has shown a remarkable success and, although was the third TNF- α inhibitor that was put on the market, is now the leading agent among the TNF- α inhibitors. This review article discusses about key characteristics of the adalimumab, such as its production, pharmacokinetics, pharmacodynamics, indications, immunogenicity and side effects.

Keywords

- Adalimumab
- Production
- Pharmacokinetics
- Pharmacodynamics
- Indications
- Immunogenicity
- Side effects

ABBREVIATIONS

TNF- α : Tumor Necrosis Factor Alpha; CAT: Cambridge Antibody Technology; tmTNF: Transmembrane TNF- α ; sTNF: Soluble TNF- α ; TNFR1, p55 or CD120a: Type 1 TNF- α receptor; TNFR2, p75 or CD120b: Type 2 TNF- α receptor; kDa: kiloDaltons; Fab: Antigen-binding fragment; Fc: Fragment crystallizable; CDR: Complementarity-determining Region; Fc γ Rs: Fc γ receptors; FcRn: Neonatal Fc receptor; MAK195: Murine Monoclonal Antibody MAK195; PCR method: Polymerase Chain Reaction; CHO: Chinese Hamster Ovary cells; IV: Intravenous Administration; SC: Subcutaneous Administration; c_{max} : Peak Serum concentration; K_d : Dissociation constant; CDC: Complement-Dependent Cytotoxicity; ADCC: Antibody-Dependent Cell-Mediated Cytotoxicity; TIMP-1: The Tissue Inhibitor of Metalloproteinases-1; IMIDs: Immune-mediated Inflammatory Disease; ADA: Anti-drug Antibodies; IRIS: Immune Reconstitution Inflammatory Syndrome; NMSC: Non-Melanoma Skin Cancer; RA: Rheumatoid Arthritis

INTRODUCTION

Adalimumab, the first fully human recombinant IgG1 monoclonal antibody, is a tumor necrosis factor alpha (TNF- α) inhibitor that binds TNF- α with subnanomolar affinity [1]. It was developed through cooperation of the Knoll and Abbot by using Cambridge Antibody Technology (CAT), and approved for the first time in December 2002 by the FDA. It was put on the market by Abbott Laboratories under the trade name Humira®, which means "human monoclonal antibody in rheumatoid arthritis" [1,2]. Humira®, although it was third TNF- α inhibitor on market, became the best selling TNF- α inhibitor, and the best selling biological medical product with annual global sale of nearly 11 billion USD in 2013 [3]. This protein drug, together with other

TNF- α inhibitors, represents one of the most sound stories in the field of pharmaceutical biotechnology that has significantly affected a number of treated patients worldwide.

PHYSIOLOGY OF TUMOR NECROSIS FACTOR ALPHA (TNF- α)

TNF- α is a member of the TNF family ligands and powerful pro-inflammatory cytokine that exerts different immunomodulatory and inflammatory activities [4,5]. TNF- α is expressed in an activated macrophages, lymphocytes, natural killer cells (NK) and various other cell types as a transmembrane TNF- α (tmTNF). This tmTNF is proteolytically cleaved and it is released into extracellular fluids as the soluble TNF- α (sTNF) [5]. Biologically active form of TNF- α is homotrimeric molecular complex that is comprised of three identical monomeric subunits [4]. Both transmembrane and soluble form of TNF- α exist as a homotrimers. A monomeric form of sTNF, which is without clear biological activity, circulates in blood and it is able to congregate with other monomers into active trimeric complexes [4].

TNF- α perform its biological action by binding to type 1 (TNFR1, p55 or CD120a) and type 2 (TNFR2, p75 or CD120b) receptors. They are expressed as the trimeric glycoproteins on almost all known cell types with type 1 receptors having more ubiquitous distribution and type 2 being expressed primarily on cells of hematopoietic origin [6]. These receptors express different properties, with type 1 generating proinflammatory and type 2 mostly immunomodulatory effects. By interacting with its cognate receptors, TNF- α can activate a number of secondary proteins that elicit different signaling processes inside the cell. These activated proteins include transcription factors, protein kinases, phospholipases, mitochondrial proteins

and caspases [6]. By acting in this way, TNF- α mediates in cell proliferation, differentiation, cytokine production or signaling process of apoptosis [4]. It remains to be entirely explained which homeostatic mechanisms regulate these processes [7].

TNF- α INHIBITORS

TNF- α inhibitors are biological products that specifically bind to TNF- α and block its interaction with both TNF- α receptors, thus inhibiting its biological effect [8]. Structurally, the group of TNF- α inhibitors contains three monoclonal antibodies, soluble fusion protein and pegylated Fab fragment. Currently, five approved TNF- α inhibitors are infliximab (Remicade[®]), adalimumab (Humira[®]), golimumab (Simponi[®]), certolizumab pegol (Cimzia[®]) and etanercept (Enbrel[®]) [9].

Infliximab is a chimeric IgG1 monoclonal antibody consisting of a human constant region and murine variable region (Table 1). Since it contains a mouse-derived sequence, it has a greater tendency to immunogenicity when compared with the fully human antibodies. Adalimumab and golimumab are fully human IgG1 monoclonal antibodies that inhibit TNF- α . Certolizumab pegol is monovalent humanized IgG4 Fab fragment that is chemically linked to polyethylene glycol in order to improve its pharmacokinetical properties. It doesn't contain an Fc region and therefore the risk of an activation of Fc-mediated effects, such as complement-dependent cytotoxicity (CDC) or antibody dependent cell-mediated cytotoxicity (ADCC), is greatly reduced [81]. Etanercept is a recombinant soluble fusion protein between the TNFR2 extracellular region and the Fc fragment of human IgG1 [10,11].

STRUCTURE OF ADALIMUMAB

Adalimumab is the first fully human recombinant IgG1

monoclonal antibody [12]. Its structure resembles all features of IgG class of human immunoglobulin. It is a heterodimeric protein that consists of 1330 amino acids and has a large molecular weight of approximately 148 kDa [7,13]. It is made of four polypeptide chains, two identical heavy chains (49 kDa) and two identical light chains (24 kDa), each of them comprising of constant and variable domains [14,15]. The light chain contains one variable (V_L) and one constant domain (C_L), while heavy chain contains one variable (V_H) and three constant domains (C_{H1} , C_{H2} , C_{H3}) [16]. Functionally, the IgG molecule contains two identical antigen-binding fragment (Fab) and the fragment crystallizable (Fc). Fab fragment of adalimumab contains hypervariable or complementarity-determining region (CDR) that binds to the TNF- α with high affinity and specificity. On the other hand, Fc fragment can bind to different receptors on the surface of the cell, such as Fc γ receptors (Fc γ Rs) or neonatal Fc receptor (FcRn), and C1q subunits of complement [14,15,17].

DEVELOPMENT AND PRODUCTION OF ADALIMUMAB - PHAGE DISPLAY TECHNOLOGY

Adalimumab is produced by recombinant DNA technology using in vitro selection technologies, such as phage display. Adalimumab was the first fully human monoclonal antibody that was created by the phage display and approved for therapy [2].

Phage display, introduced in 1985 by Smith [18], represents an adjustable platform technology that involves manipulation of bacteriophage DNA in order to produce a fusion of a protein with one of the phage coat proteins [19]. By this way, the antibody variable regions are shown on the surface of the phage, thus giving the phenotype that can be used to discover the genotype of the recombinant antibody clone [20]. Phage display technology relies on the antibody libraries whose collection of antibody

Table 1: TNF- α inhibitors with their generic names, trade names and year of approval [9,78-80].

TNF- α inhibitor					
Generic name	Infliximab	Etanercept	Adalimumab	Golimumab	Certolizumab pegol
Trade name	Remicade [®]	Enbrel [®]	Humira [®]	Simponi [®]	Cimzia [®]
Year of approval	1998	1998	2002	2009	2009

Table 2: Indications for use of adalimumab and date of regulatory approval [45-59,65].

Disorder	Date of approval	
	USA	Europe
Rheumatoid arthritis	2002	2003
Psoriatic arthritis	2005	2005
Plaque psoriasis	2008	2007
Polyarticular juvenile idiopathic arthritis	2008	2008
Ankylosing spondylitis	2006	2006
Adult Crohn's disease	2007	2007
Pediatric Crohn's disease	2014	2012
Ulcerative colitis	2012	2012
Hidradenitis suppurativa	2015	2015
Uveitis	2016	2016
Behçet disease	2013 (approved in Japan)	

genes encrypts antibodies of unknown properties [2]. The library members that have preferred binding affinity and specificity are isolated in vitro by binding to an immobilized receptor in a process called panning [2,13]. Given that these libraries include a vast repertoire of antibodies (theoretically more than 10^{10} of individual clones) [2], several rounds of in vitro selection may be needed in order to gain antibody of desired affinity and specificity. When preferred antibody is obtained, the final step is to discover its coding gene sequences [13].

Adalimumab was developed through cooperation of Knoll and Abbot by using Cambridge Antibody Technology (CAT) with the aim to reduce the immunogenicity of the chimeric antibodies by eliminating all mouse-derived sequences [13,21,22]. The template for the production and isolation of adalimumab was murine monoclonal antibody MAK195 that mediate strong TNF inhibition [2]. This murine antibody was used for guided selection of human antibody variable domains that would bind with high affinity to a similar epitope on TNF- α [2]. The murine heavy and light chains are cloned and paired with the repertoire of human light and heavy chains. Further, the obtained mouse-human hybrid antibody libraries are panned by using human TNF- α as the receptor in order to enhance the hybrid's binding affinity for human TNF- α [13,19]. Desired human variable domains are subjected to additional sequence modification in the complementary determining region by PCR method [2,13,19]. High affinity human antibody variable domain is connected with DNA sequence of human constant regions and via expression vector inserted into Chinese Hamster Ovary cells (CHO) that are producing the completely human antibody that is highly specific for the TNF- α [23].

PHARMACOKINETICS OF ADALIMUMAB

Administration

Adalimumab and other monoclonal antibodies have inadequate oral bioavailability and need to be administered parenterally due to their large size, limited membrane permeability and vulnerability towards gastrointestinal proteolytic activity. Adalimumab was firstly administered intravenously (IV) [23]. Following studies showed that subcutaneous (SC) administration had similar plasma concentrations and safety profiles [1]. Due to lack of clinically important dissimilarity among the two approaches of administration on one hand, and convenience of the SC administration on the other, the latter was adopted as the standard way of adalimumab administration [1].

Adsorption

Although subcutaneous administration is the standard way of adalimumab application, the mechanism of adsorption that follows SC administration is not completely elucidated [14,15]. It is assumed that after SC administration, diffusion of the monoclonal antibodies is facilitated by the lymphatic system [14,15]. Because of the slow drainage of the lymph fluid into the vascular system, the resulting adsorption process into the systemic circulation is also very slow, with a corresponding slow increase in plasma concentration [15]. Subcutaneously administered antibodies may undergo presystemic elimination due to combination of interaction with phagocytic cells in lymph

nodes, endocytosis and subsequent lysosomal degradation and soluble peptidase activity in the interstitial space [15]. In healthy adults, a single subcutaneous dose of 40mg of adalimumab resulted with peak serum concentration (c_{max}) of $4.7 \pm 1.6 \mu\text{g/ml}$ that was achieved at 131 ± 56 hours with average bioavailability of 64% [24].

Distribution

Because of its high molecular weight and hydrophilic structure, adalimumab, as well as other monoclonal antibodies, has a relatively small volume of distribution of 5 to 6 liters. Despite the fact that monoclonal antibodies are mainly distributed in extracellular fluid, they can penetrate into cells [14,24]. This is likely due to fluid phase endocytosis, which is an important way of penetration of antibodies into vascular endothelial cells, and receptor-mediated endocytosis via Fc γ R on the membrane of immunological cells [14,24].

Metabolism and elimination

Unlike the vast number of small molecule drugs, metabolism of monoclonal antibodies does not occur through renal excretion or biliary metabolism, except in pathological conditions [14]. The metabolism and elimination of monoclonal antibodies occur through intracellular catabolism by lysosomal degradation to amino acids [15]. Cellular uptake of monoclonal antibodies is possible by fluid phase endocytosis and receptor-mediated endocytosis. Receptor-mediated endocytosis represents interplay of receptor on the surface of the cell and Fc or Fab fragment of the antibody. Consequential endocytosis results in lysosomal degradation of monoclonal antibody [15]. Fluid phase endocytosis occurs in endothelial cells covering blood vessels. It happens throughout the body and it is not constrained to a particular organ [15]. However, FcRn-mediated recycling of IgG immunoglobulins, rescues from lysosomal degradation nearly two third of the IgG molecules [15]. Thankfully to this salvage pathway, adalimumab has relatively long plasma half-life ($t_{1/2}$) of 10-20 days [7,17]. Influence on the adalimumab clearance rate has several different factors, like immunogenicity and the formation of anti-adalimumab antibodies [14,16], concomitant administration of medications such as methotrexate [16], genetic variants such as polymorphisms in genes encoding FcRn [15], high concentrations of rheumatoid factors [16], and others.

PHARMACODYNAMIC OF ADALIMUMAB

Adalimumab binds to both soluble and transmembrane form of TNF, although for the transmembrane form with lower affinity [25]. By binding to TNF- α , adalimumab prevents its binding to both types of its receptors and thereby influences downstream processes that are regulated by TNF- α [26]. Adalimumab binds to TNF- α with relatively high affinity, with dissociation constant (K_d) values between $7.05 \times 10^{-11} \text{M}$ to $10 \times 10^{-10} \text{M}$ [27]. Structural comparisons show that there is extensive overlap of binding sites amid the TNF- α receptor and the Fab fragment of adalimumab. The result of adalimumab binding to TNF- α is the steric hindering of TNF- α and the prevention of ligand binding to the receptor. In sum, adalimumab occupies the binding site of TNF- α and competitively inhibits the binding to the TNF- α receptor [27].

Trimeric TNF- α molecule shows dynamic nature which is

manifested by the continuous dissociation of trimeric TNF- α complex into TNF- α monomers, which can reassociate depending on overall concentration of TNF [28,29]. Being constituted of two antigen-binding fragments, adalimumab has a bivalent nature and is able to concurrently interact with two neighbouring TNF- α protomers and interfere with dissociation of the trimeric TNF- α complex. Therefore, adalimumab can, by suppressing TNF- α monomer exchange, stabilize TNF- α in its trimeric form [28].

HIGHER ORDER COMPLEX STRUCTURES

Given that biologically active form of TNF- α is trimer, it provides three epitopes for a bivalent molecule of adalimumab. Considering this multivalency, adalimumab is likely to form higher order complex structures and aggregations with TNF- α [30]. According to Kohno et al. [31], adalimumab and trimeric TNF- α could create higher order complex structures with molecular weight in a range between 4000 and 14 000 kDa, indicating an existence of a wide range of complex sizes and stoichiometries [31]. Santora et al. [32], showed that adalimumab formed stable complex of molecular weight of 598 kDa upon overnight incubation with TNF- α [32]. Using X-ray crystallography and electron microscope techniques, new insights about higher order complex structures have been obtained [30]. Wide range of higher order complex structures that consist of 1:1, 1:2, 2:2 and 3:2 complexes have been shown between adalimumab and trimeric TNF- α . The largest complex constitutes of three adalimumab molecules and two TNF- α trimer. It can emerge from the 2:2 complex by binding another adalimumab molecule that would bridge the two opposing trimer of TNF- α [30]. This 3:2 complex might be the most stable because it is the major form present upon extended incubation and all binding epitopes of adalimumab and TNF- α are fully occupied [30,32]. Creation of large molecular complexes between TNF- α and adalimumab may have several consequential effects, such as higher stability of complex between adalimumab and sTNF, slower dissociation of sTNF from the adalimumab in the complex, faster clearance of complexes from the circulation and bigger probability to induce „outside to inside“ signaling by the tmTNF [17].

ADALIMUMAB AND THE TMTNF-EXPRESSING CELLS

Regarding the effect of adalimumab on tmTNF-expressing cells, adalimumab can induce lysis or apoptosis of TNF-expressing cells over several different mechanisms [5,33]. As IgG1 immunoglobulin, Fc fragment of adalimumab owns C_H2 domain that activates C1q subunit of the complement, thus initiating classical complement pathway with subsequent formation of membrane attack complex. This complement-dependent cytotoxicity (CDC) leads to the lysis of the targeted cell [5,33-36]. On the other hand, C_H2 and C_H3 domains have an important role in connecting Fc fragment of adalimumab with Fc receptors of NK cells, thus stimulating them to secrete granzyme B and perforin, which results in antibody-dependent cell-mediated cytotoxicity (ADCC) [5,33-36]. Another mechanism that can cause inhibition of TNF-expressing cells is "reverse" or "outside-to-inside" signaling [5,33]. Binding of adalimumab or some other TNF- α inhibitor may induce cell cycle arrest and apoptosis of TNF-expressing cell, thus having an anti-inflammatory response. This

mechanism, non-related to CDC and ADCC, is caspase-dependent and it has been shown that is able to induce apoptosis of activated monocytes [37,38].

Different studies showed that adalimumab has diverse effect in different immune-mediated inflammatory disease. Administration of adalimumab provoked a reduction in acute phase reaction, observable from decrease in levels of C-reactive protein and fibrinogen [12]. Decrease in levels of IL-1, IL-6 and mRNA IL1 β have been observed after a single dose of adalimumab in patients with RA [39]. Further, concentration reduction of cartilage and synovial remodeling markers and macrophage colony-stimulating factors have been reported [40]. In addition, a decrease in the level of oxidative stress has been observed [41] as well as a decrease of the leukocyte migration into the inflamed joints [42]. An increase in activity of the tissue inhibitor of metalloproteinases-1 (TIMP-1) has been reported, which could decrease the level of matrix metalloproteinases (MMP) activity and therefore contribute to the healing of the damaged tissue [43]. Adalimumab also restored the normal chemotactic activity of neutrophil function, and caused a decrease of activation antigen CD69 expression on the neutrophils [44].

APPROVED INDICATIONS FOR ADALIMUMAB

Adalimumab was first approved in December 2002 for the treatment of rheumatoid arthritis, and since then the indications for its application have been extended to several other disorders. Among available TNF- α inhibitors, adalimumab has the widest range of indications and had obtained a regulatory endorsement in a variety of immune-mediated inflammatory disease (IMIDs). These include rheumatoid arthritis [45], psoriatic arthritis [46], plaque psoriasis [47], polyarticular juvenile idiopathic arthritis [48], ankylosing spondylitis [49], adult Crohn's disease [50,51], pediatric Crohn's disease [52,53], uveitis [26,54], ulcerative colitis [55,56], hidradenitis suppurativa [57] and Behçet disease (approved only in Japan) [58,59]. In patients that have one IMID, higher risk of developing another disorder from this group has been observed [60-64]. Adalimumab, as a multi-indication drug, can be appropriated for the treatment of combined and co-occurring disorders, thus diminishing drug burden [4] (Table 2).

ADALIMUMAB AND IMMUNOGENICITY

Adalimumab, as well as all other monoclonal antibodies on the market, provokes certain level of immunogenicity [66-68]. Several different factors may impact on immunogenicity, such as genotype [69], concomitant use of medications such as methotrexat [70], dose, duration of the therapy as well as the status of the patient's immune system [15]. Subcutaneous application, which is the standard regime of adalimumab administration, is mainly more immunogenic than intravenously because of the smaller volumes used, slower distribution and greater interindividual variability of drug exposure [65,71]. Anti-drug antibodies (ADA) can be divided on neutralizing and non-neutralizing antibodies [15,72]. Neutralizing antibodies have high affinity to the complementarity-determining region (CDR) of monoclonal antibody and binding to them results in neutralisation of the targeted antibody activity. On the other hand, non-neutralizing antibodies don't affect the activity after they are bind to the monoclonal antibody [15]. However,

formation of the ADA, regardless of their effect on the activity of the monoclonal antibody, may have an effect on pharmacokinetics due to increased clearance of the antibody-ADA complexes [15].

In concordance with hitherto mentioned, the presence of anti-adalimumab antibodies is related to the subtherapeutic concentrations of adalimumab, and therefore with the risk of loss of response to the treatment [67,73-76]. According to the meta-analysis conducted by the Thomas et al [66], the frequency of the anti-adalimumab antibodies in the management of autoimmune disease is 14.1% [66]. However, the reported frequency of the anti-adalimumab antibodies among patients shows considerable variation between different studies, and varies from below 5% and up to above 80% [77]. Although the characteristics of the studied population, such as type of disease, therapeutic regimen, concomitant treatment with immunosuppressants and duration of follow-up period, have an effect on the level of antibodies, this magnitude of the discrepancies is likely to be caused by the considerable diversity of analytical assays used for evaluation of anti-adalimumab antibodies [77]. The titre of the ADA can vary depending on the type of assay and can be perplexed by the existence of the circulating TNF- α inhibitor [65, 77].

ADALIMUMAB AND SIDE EFFECTS

Although representing a specific treatment, adalimumab and other TNF- α inhibitors can provoke different side effects, some of which may be severe or life-threatening [81,82]. Adalimumab is overall well tolerated, with lower than 10% of the patients ceasing the therapy because of the side effects in trials with rheumatoid arthritis [12]. Some adverse reactions associated with the use of adalimumab include injection site reactions, infections, malignancies and neurologic events.

Injection site reactions represent the most common adverse reaction of the treatment with adalimumab. Among trials with rheumatoid arthritis, injection side reactions developed in 20.3% patients treated with adalimumab, compared to 13.8% of patients treated with placebo [12].

Patients treated with adalimumab may experience psoriasiform skin lesions [83-85]. Furthermore, the appearance of paradoxical hidradenitis suppurativa has also been reported [86,87]. These adverse effects might occur because of cytokine dysregulation due to adalimumab therapy [86].

During the pivotal trials, the rate of infections was only slightly higher in adalimumab treated group when compared with placebo treated group [12]. Infections of upper respiratory and urinary tract, rhinitis and bronchitis are the most commonly reported [12]. The rate of serious infectious events, such as cellulitis, pneumonia, gastrointestinal tract abscess and gastroenteritis, can vary across therapeutic indications, and are most commonly seen in patients with rheumatoid arthritis and Crohn's disease [88]. Rate of tuberculosis, arising mostly as the result of the reactivation of the latent tuberculosis, greatly decreased after the introduction of routine tuberculosis screening prior to initiation of the adalimumab [12]. Opportunistic infections during adalimumab therapy are rare events, with deep fungal infections, nocardiosis, cytomegalovirus and herpes zoster infections being the most commonly reported [88]. If severe infection does appear and the cessation of the adalimumab therapy is needed,

immune reconstitution inflammatory syndrome (IRIS) may occur after withdrawal of adalimumab [89-91].

The overall rate of malignancy in adalimumab clinical trials seems to be similar to the rates expected in the reference population [88]. Although the rate of lymphoma in RA patients treated with adalimumab is higher when compared to the general population, it is within the anticipated range when compared with the RA patients that were not treated with adalimumab [88]. It appears that risk for non-melanoma skin cancer (NMSC) as well as for melanoma might be increased in patients on adalimumab therapy in certain therapeutic indications, however this needs to be further explored [88].

Regarding the connection of the adalimumab exposure and neurological diseases, there are several reports of multiple sclerosis among patients treated with adalimumab [92,93]. The expression rate of the multiple sclerosis among patients treated with adalimumab is similar to the rate in the general population. However, the expression of neurologic signs among patients on adalimumab may represent an increased risk of developing multiple sclerosis when compared with the general population. The clear influence of adalimumab and other TNF- α inhibitors on demyelinating conditions needs to be fully elucidated [12].

CONCLUSION

In conclusion, considering all above mentioned, adalimumab represents valuable agent in the treatment of the number of chronic conditions that arise from immune-mediated inflammatory pathogenesis. Its identicalness in structure and function as naturally occurring human IgG₁, convenient way of administration, commendable features of pharmacokinetics as well as pharmacodynamics, the widest range of approved indications among TNF- α inhibitors, explain the staggering success of adalimumab on a demanding and developing market of the monoclonal antibodies.

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