



Review

# Past, Present and (Foreseeable) Future of Biological Anti-TNF Alpha Therapy

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**Abstract:** Due to the key role of tumor necrosis factor-alpha (TNF- $\alpha$ ) in the pathogenesis of immunoinflammatory diseases, TNF- $\alpha$  inhibitors have been successfully developed and used in the clinical treatment of autoimmune disorders. Currently, five anti-TNF- $\alpha$  drugs have been approved: infliximab, adalimumab, golimumab, certolizumab pegol and etanercept. Anti-TNF- $\alpha$  biosimilars are also available for clinical use. Here, we will review the historical development as well as the present and potential future applications of anti-TNF- $\alpha$  therapies, which have led to major improvements for patients with several autoimmune diseases, such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), psoriasis (PS) and chronic endogenous uveitis. Other therapeutic areas are under evaluation, including viral infections, e.g., COVID-19, as well as chronic neuropsychiatric disorders and certain forms of cancer. The search for biomarkers able to predict responsiveness to anti-TNF- $\alpha$  drugs is also discussed.

**Keywords:** monoclonal antibody; TNF- $\alpha$ ; TNF- $\alpha$  inhibitors; biomarker; biosimilar agents; inflammation; COVID-19



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## 1. Introduction: History of Biologics

One of the main breakthroughs of the past 50 years in medicine has been the development of biologics. The invention of hybridoma technology goes back to 1975, when Kohler and Milstein [1] developed this method to produce antigen-specific monoclonal antibodies (mAbs) by hybridizing B cells from immunized animals with immortalized mouse myeloma cells [1].

mAbs may exert two types of therapeutic effects: first, by binding an antigen, they can neutralize its biological functions; second, by opsonizing target cells, they may induce an effective Fc receptor-mediated immune response.

In 1986, the first murine mAb (muromonab CD-3) was approved by the USA Food and Drug Administration (FDA) for preventing acute kidney transplant rejection [2]. This drug selectively binds to the  $\epsilon$  chain of the TCR-CD3 complex expressed on the surface of T lymphocytes, blocking their proliferation and differentiation and consequently leading to an immunodepression state. Although this was the first step toward the introduction of mAbs in clinical use, hybridoma technology exhibited several disadvantages. In particular, patients treated with murine mAbs produced a neutralizing anti-mouse antibody that reduced the efficacy of the mAbs and accelerated their clearance [3]. The overcoming of this hindrance was the development of genetic engineering techniques through which chimeric murine-human mAbs were generated [4]. In particular, in 1984, Boulianne and colleagues developed chimeric mAbs by fusing the murine variable domain of antigen-binding fragment (Fab) regions with human  $\mu$  and  $\kappa$  domains of the fragment crystallizable (Fc) region [4]. In 1994, the first chimeric mAb (abciximab) received FDA approval as

an antiplatelet therapy in patients with cardiovascular diseases [5], and in 1997, the anti-CD20 mAb, rituximab, was approved by the FDA to treat patients with non-Hodgkin lymphoma [6]. Then, abciximab and rituximab were also approved by the European Medicine Agency (EMA) in 1997 and 1998, respectively [7,8]. On the other hand, infliximab (Remicade) was the first chimeric anti-TNF- $\alpha$  mAb for the treatment of Chron's disease [9]. The use of Remicade was then extended to other therapeutic areas, including RA (in combination with methotrexate), ankylosing spondylitis, psoriatic arthritis, ulcerative colitis, pediatric Crohn's disease, plaque psoriasis and pediatric ulcerative colitis.

A further and highly significant improvement in the pharmacology of mAbs was achieved with the production of humanized mAbs that were developed by transplanting murine hypervariable segments of the complementary-determining regions (CDRs) into a human Ab structure [10–12]. In 1997, the anti-IL-2 receptor (daclizumab) was the first humanized mAb that received FDA approval for preventing renal transplant rejection [13]. Then, it was also approved by the EMA in 1999 [14]. Humanized anti-TNF- $\alpha$  mAbs include adalimumab, golimumab and certolizumab. Humanized mAbs are less immunogenic than murine and chimeric mAbs [11]. However, humanized mAbs still showed some limits. In fact, their production was hard work and expensive. In order to bypass these limitations, fully human mAbs were developed in the early 1990s, using display technologies (phage display and yeast display libraries) [15–17].

Another innovative approach to obtain fully human mAbs is based on transgenic animals that are genetically modified by inserting human immunoglobulin genes into their genome sequence deprived of immunoglobulin loci. Hence, plasma B cells of transgenic animals can produce fully human mAbs after exposure to a specific antigen [18,19]. Although this technology was developed in 1994, the first human mAb based on transgenic mice technology (i.e., panitumumab) was only approved by the FDA and EMA in 2006 and 2007, respectively, to treat patients with colorectal cancer harboring epidermal growth factor receptor (EGFR) mutations [20].

The advent of these new technologies propelled interest in the production of recombinant Fc-fusion proteins, which are characterized by the Fc domain of the Ab conjugated with another protein such as an enzyme, cytokine or a receptor through a peptide linker, therefore increasing the stability and half-life of the bound protein and prolonging its biological effects [21]. The first Ab fusion protein, etanercept, was approved by the FDA and EMA for clinical use in patients with RA in 1998 and 2000, respectively. It comprises the Fc region of Ab conjugated with TNF-receptor 2 (TNFR2) [22]. The approval of etanercept opened up the way to the development of several recombinant protein methodologies based on the fusion of various proteins to different antibody regions, including single-chain variable fragments (scFvs), heavy-chain Abs (hcAbs), single-chain Abs (scAbs) and antigen-binding fragments (Fabs) [23].

The development of these Abs was based on the discovery of Abs with only two heavy chains (containing a single variable domain referred to as a VHH or nanobody) in the serum of camelids (alpaca, llama and camel) in 1993 [24]. Although the nanobodies have a low molecular weight (14 kDa) and bind very well to the antigen, the binding is unstable [25]. Through the development of bioengineering, the VHH from hcAbs can be isolated, maintaining the binding properties of the original hcAbs. Once isolated, a fusion of nanobodies may be generated, either by direct chemical bonding creating a 25 kDa bivalent structure or by binding to human Fc chain fragments, creating human-compatible 50 kDa structures. The bivalent nanobodies quickly proved to be very stable at high temperatures and able to bind to specific epitopes not easily accessible by conventional mAbs [26].

In 2019, the first bivalent nanobody directed against the A1 domain of the von Willebrand factor (caplacizumab) received FDA and EMA approval to treat patients with acquired thrombotic thrombocytopenic purpura (aTTP) [27,28]. Three years later, ozoralizumab was approved in Japan for patients with RA [29]. It is a trivalent bispecific nanobody that has a high binding affinity with both human TNF- $\alpha$  and human serum albumin [30].

Currently, different nanobody therapies are investigated in the clinical setting. It appears likely that as the breadth of nanobody targets is expanded, their utility as diagnostics or therapeutics will grow as well.

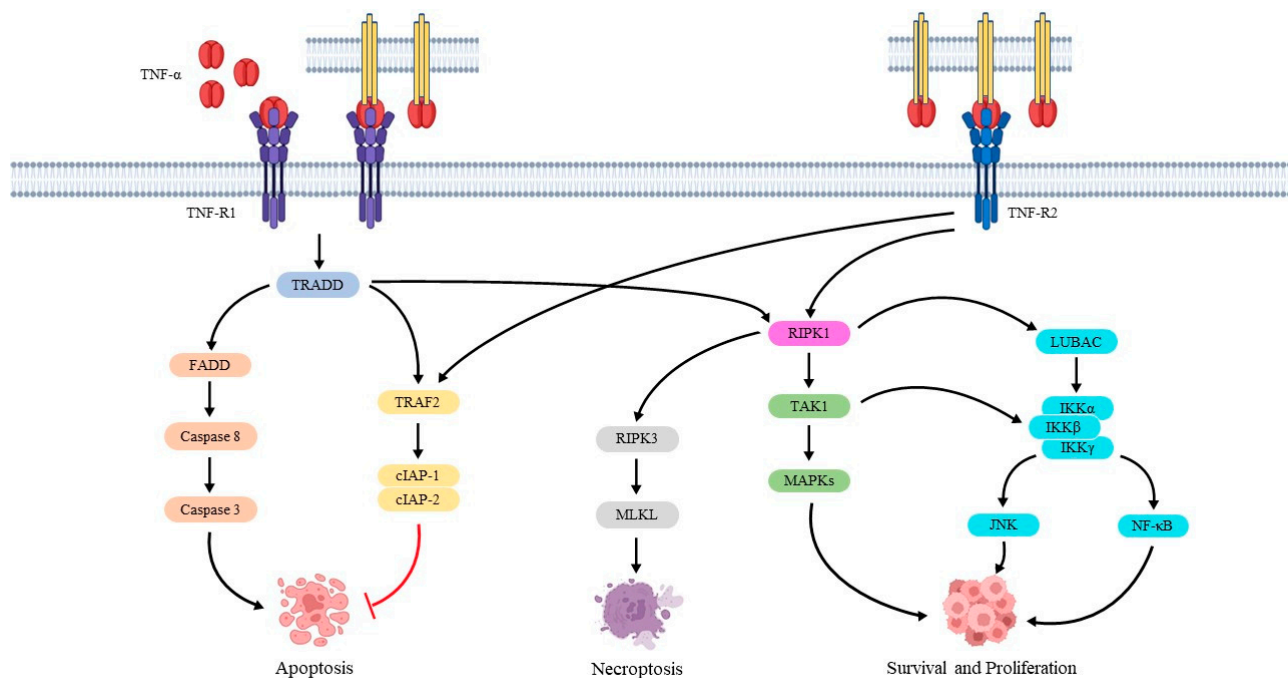
In the present review, we will discuss the historical development, as well as the present and potential future applications of all five FDA-approved biological anti-TNF- $\alpha$  agents (infliximab, adalimumab, etanercept, golimumab and certolizumab), which have led to major improvements for patients with RA and other autoimmune diseases, such as ankylosing spondylitis, Crohn's disease, ulcerative colitis and psoriasis. More recently, other therapeutic areas are under evaluation, including viral infections, e.g., COVID-19, neuropsychiatric disorders and cancer [31].

The search for biomarkers for predicting anti-TNF- $\alpha$  responsiveness is also discussed.

## 2. Tumor Necrosis Factor-Alpha

The tumor necrosis factor-alpha (TNF- $\alpha$ ) gene is located in chromosome 6. It consists of four exons, and it encodes for a pro-inflammatory and immunomodulatory transmembrane protein made up of 233 amino-acid residues [32]. TNF- $\alpha$  is expressed as a transmembrane precursor by macrophages but also by CD4<sup>+</sup> T cells, mast cells, neutrophils and NK cells. When these cells are activated, TNF- $\alpha$  is cleaved and released by a metalloprotease enzyme known as a TNF- $\alpha$ -converting enzyme (TACE) to generate its soluble form of 157 amino-acid residues, which promotes inflammation. The binding of TNF- $\alpha$  with its receptors triggers several events, including the production of cytokines, expression of adhesion molecules, releasing of pro-coagulatory substances and production of the synthetase nitric oxide. In addition, TNF- $\alpha$  increases the expression of other pro-inflammatory cytokines (i.e., interleukin-1 (IL-1), IL-6 and IL-8), suppresses lipoprotein lipase in adipocytes and stimulates hepatocytes to produce acute phase proteins which sustain systemic inflammation [33,34]. The effects of TNF- $\alpha$  are mediated by binding to two different receptors (TNF-R1 and TNF-R2). TNF-R1 is the main mediator of TNF- $\alpha$  action, and it is expressed on the surface of several cell types [35]. TNF-R1 is activated by both soluble and transmembrane TNF- $\alpha$  forms, whereas transmembrane TNF- $\alpha$  activates TNF-R2 which is expressed on the surface of lymphocytes [36,37]. These receptors have similar cysteine-rich extracellular domains, although they have different intracellular domains (ICD) [38]. In the ICD of TNF-R1, there is a death domain (DD) which recruits an adaptor protein known as the TNF receptor-associated death domain (TRADD) [39]. TRADD is recognized by other adaptor proteins, including receptor-interacting protein kinase 1 (RIPK1) and TNF-R-associated factor 2 (TRAF2). These proteins make the complex I that has a key role in cell survival and proliferation. In particular, TRAF2 binds and activates the cellular inhibitor of apoptosis protein-1 (cIAP-1) and 2 (cIAP-2), which exerts a ligase activity. RIPK1 binds and activates TGF $\beta$ -activated kinase 1 (TAK1) and the linear ubiquitin chain assembly complex (LUBAC), promoting the activation of the c-Jun N-terminal kinase (JNK), mitogen-activated protein kinases (MAPKs) and nuclear factor  $\kappa$ B (NF- $\kappa$ B) signaling pathways via an inhibitor of  $\kappa$ B kinase (IKK) complex activation [40,41]. However, TRADD can also bind the Fas-associated death domain (FADD) producing complex II. This complex recruits and activates procaspase 8, which triggers the proteolytic cleavage of procaspase 3 and starts the apoptotic process [42]. In addition, the phosphorylated RIPK3 with RIPK1 can phosphorylate and activate the mixed lineage kinase domain-like protein (MLKL), inducing inflammatory and necroptosis. On the other hand, TNF-R2 lacks the DD domain. Hence, it can only promote cell survival and proliferation through the activation of MAPK, NF- $\kappa$ B and JNK pathways (Figure 1) [37,43].

An abnormal production of TNF- $\alpha$  is associated with several chronic, immunoinflammatory diseases, such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), psoriasis (PS), psoriatic arthritis (PsA) and autoimmune uveitis [44–48].



**Figure 1.** Signaling pathways of TNF- $\alpha$ .

### 3. TNF- $\alpha$ Blockers

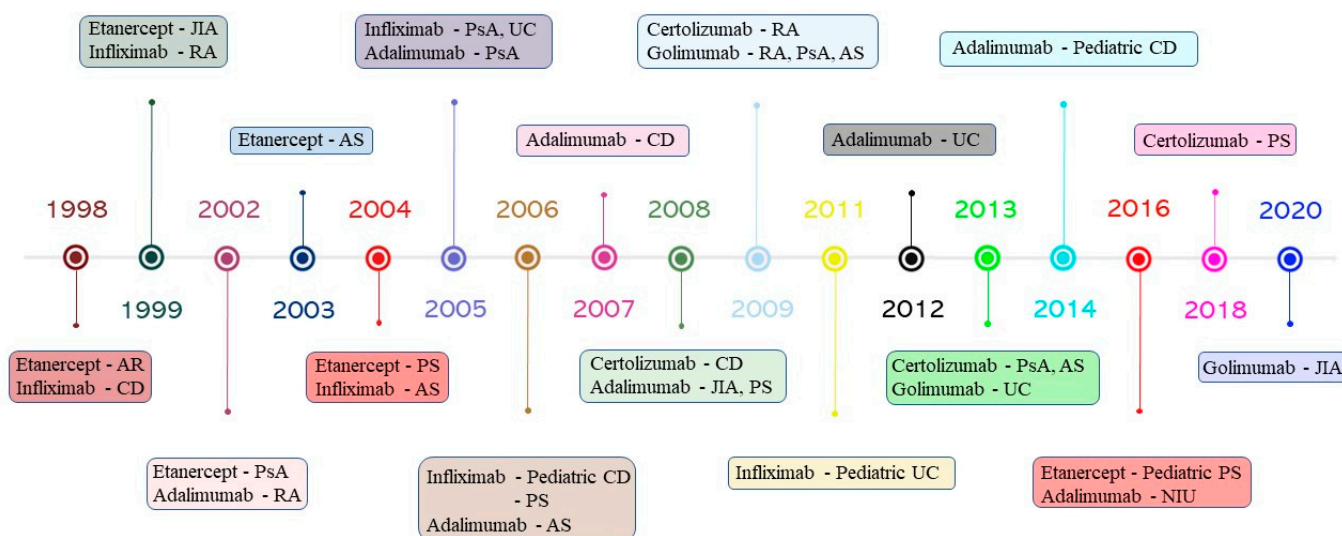
To date, five anti-TNF- $\alpha$  drugs have been approved: infliximab (Remicade), adalimumab (Humira), golimumab (Simponi), certolizumab pegol (Cimzia) and etanercept (Enbrel). Several studies have demonstrated the efficacy and safety profiles of these agents in different diseases. In particular, Burr and colleagues demonstrated that patients with severe ulcerative colitis treated with infliximab (10 mg/kg) showed superior endoscopic improvement compared with the placebo group (with a response rate of 0.61) [49]. Another group reported that 60% of patients with uveitis treated with adalimumab or infliximab showed a visual acuity improvement and a central macular thickness decrease of 112.70  $\mu\text{m}$  [50]. Moreover, Liu and colleagues observed greater efficacy of TNF- $\alpha$  inhibitors than the placebo in patients with ankylosing spondylitis [51]. Finally, Fleischmann and colleagues demonstrated that the addition of TNF- $\alpha$  inhibitors to methotrexate in RA patients with an inadequate response to methotrexate could be associated with a greater likelihood of achieving the American College of Rheumatology 70% response criteria at 6 months compared to the addition of sulfasalazine and hydroxychloroquine [52].

Overall, these studies highlight that the use of TNF- $\alpha$  inhibitors is safe and well tolerated in a large percentage of patients suffering from various diseases.

#### 3.1. Infliximab

Infliximab is a chimeric mAb, generated by Vilcek and Le [53], consisting of murine variable regions from the murine anti-TNF- $\alpha$  hybridoma A2 and human IgG1 constant regions. It binds both transmembrane and soluble TNF- $\alpha$  with high affinity, hindering the binding with their receptors and neutralizing their biological effects [54]. Infliximab was first approved by the FDA in 1998 for treating patients with Crohn's disease (CD) [9]. Subsequently, it has received approval for the treatment of RA, ankylosing spondylitis (AS), psoriatic arthritis (PsA) and psoriasis (PS) patients (Figure 2) [55]. The approval was based on the results from a randomized double-blind study conducted on 108 patients, which showed that infliximab at 5 mg/kg resulted in a response rate of 81% [56]. However, infliximab administration is associated with the manifestation of severe adverse events, including pneumonia, hepatotoxicity, lymphoma and the reactivation of the tuberculosis [57].





**Figure 2.** Timeline of the approval of TNF- $\alpha$  blockers in autoimmune diseases. AR, rheumatoid arthritis; CD, Crohn's disease; AS, ankylosing spondylitis; PsA, psoriatic arthritis; PS, psoriasis; UC, ulcerative colitis; NIU, non-infectious uveitis; JIA, juvenile idiopathic arthritis.

### 3.2. Etanercept

Etanercept is a recombinant Fc-fusion protein that comprises two human TNF-R2 conjugated with the CH2 and CH3 domains of the Fc region of human IgG1, which mimics soluble TNF-R activity [58]. It was approved by the FDA for clinical practice in patients with RA in 1998 [22]. It was further approved for the treatment of juvenile idiopathic arthritis (JIA), PsA, AS and PS (Figure 2). The approval was based on the results from a randomized double-blind study conducted on 234 patients with RA. The patients were randomly assigned to receive a placebo or two doses of subcutaneous injections of etanercept (10 or 25 mg) for six months. Overall, 40% of patients treated with etanercept at 25 mg showed a significant improvement, with a 50% American College of Rheumatology (ACR) response, compared to 4% of the placebo group [59]. Etanercept is less immunogenic than infliximab; however, it produces unstable complexes due to the presence of a conformational hindrance as a result of the absence of a hinge region in its Fc region, resulting in it being weaker than other blockers [60]. In addition, it is not specific to TNF- $\alpha$  but can also recognize and bind other members of the lymphotoxin family, such as TNF- $\beta$ , which is a cytokine involved in the regulation of bowel immune cells [61]. Furthermore, it should be noted that long-term administration of etanercept causes severe infections and sepsis that may lead to hospitalization or death. To prevent the risk of infections, it is administered along with methotrexate or prednisone, but the clinical use of etanercept is not recommended for patients with active infections [62].

### 3.3. Adalimumab

In 2002, adalimumab, a fully human mAb generated using phage display technology, was approved by the FDA to treat patients with RA [63]. Subsequently, it was approved for the treatment of PsA, AS, CD, JIA, ulcerative colitis (UC) and non-infectious uveitis (NIU) (Figure 2) [64]. The efficacy and safety of adalimumab have been substantiated by the results gained from a randomized, double-blind, placebo-controlled trial. Of the 120 RA patients recruited, 89 received ascending doses of adalimumab, and 31 received a placebo. Overall, adalimumab at 10 mg/mL showed a response rate of 100%, which was significantly higher than the other groups, while no adverse events were observed compared with the placebo group [65]. Adalimumab induces a strong complement-mediated cytotoxicity and is less immunogenic than infliximab due to the absence of murine variable domains of the immunoglobulin Fab [47]. However, patients treated with adalimumab manifested several

adverse events, including thrombocytopenia, leukopenia, malignancies and a reactivation of the tuberculosis, with an odds ratio of 14.6 [66].

### 3.4. Golimumab

Golimumab is a fully human mAb produced using Medarex's UltiMab transgenic mouse platform, in which human IgG genes are inserted into the genome of engineering mice. It has a bivalent Fab region, which can bind the soluble and transmembrane form of TNF- $\alpha$  proteins with a higher affinity than infliximab and adalimumab, reducing both the circulating TNF- $\alpha$  protein levels and the binding of TNF- $\alpha$  with its receptors [67]. In comparison with other TNF- $\alpha$  blockers, it was less immunogenic than [68]. Golimumab reduces serum levels of IL-6, IL-8, serum amyloid A, serum amyloid P and ferritin and inhibits the cell surface expression of adhesion molecules, including E-selectin, intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) [69]. In 2009, golimumab received FDA approval for the treatment of RA, PsA and AS [64]. More recently, it was also approved for the treatment of UC and JIA in 2013 and 2020, respectively (Figure 2). The approval was based on the results of the multicenter, randomized, double-blind, placebo-controlled GO-AFTER trial [70].

### 3.5. Certolizumab Pegol

In 2008, certolizumab pegol was approved by the FDA to treat patients with CD [71]. Its efficacy and safety were proven by the results obtained from a randomized, double-blind, placebo-controlled trial conducted on 662 patients with CD [71]. It was further approved for the treatment of RA, PsA, AS and PS (Figure 2). It is a single Fab fragment of humanized IgG1 mAb conjugated to two 20 kDa polyethylene glycol chains that increase the drug's half-life [72]. Furthermore, it is capable of binding both soluble and transmembrane TNF- $\alpha$  forms, neutralizing the binding with their receptors [73]. Certolizumab pegol lacks the Fc region which may trigger the complement-mediated cytotoxicity, so it does not produce cellular lysis by inducing natural killer cell activity [74].

## 4. Adverse Events after TNF- $\alpha$ Blocker Use

The toxicity profile of TNF- $\alpha$  blockers is acceptable; however, patient surveillance continues to be warranted. Common side effects range from gastrointestinal to behavioral disturbances. Rarely, patients may also experience symptoms, such as fatigue, myalgia, nausea and anorexia which often disappear after the discontinuation of therapy [75–77]. Furthermore, several researchers have reported the role of anti-TNF- $\alpha$  agents in the development of different serious side effects, including infections, malignancies, autoimmune diseases, in particular systemic lupus erythematosus, Guillain-Barre syndrome and multiple sclerosis [78–80].

### 4.1. Infections

For years, researchers have been trying to understand whether patients treated with TNF- $\alpha$  blockers are at a greater risk of developing serious infections than the general population, reaching conflicting results. The discrepancies among the different studies could be related to several factors, such as the duration of the treatment and follow-up, the patients' prior therapies, and the severity of the disease [81–83]. The respiratory system is the site mostly affected by infections in these patients. In particular, the blockade of TNF- $\alpha$  can cause reactivation of latent tuberculosis [84]. To reduce the risk of the reactivation of tuberculosis, current guidelines recommend screening for latent tuberculosis before starting treatment with TNF- $\alpha$  blockers [85]. However, none of these recommendations provide indications for choosing the correct biological treatment according to the specific risk associated with each patient [86]. Attention should also be paid to the possibility of the reactivation of the hepatitis B virus (HBV) during treatment with anti-TNF- $\alpha$ . The vaccination of children has proven very useful when it is administered before the onset of immunosuppressive therapy [87,88]. In this regard, in 2011, the task force of the Euro-

pean League Against Rheumatism (EULAR) published recommendations regarding the vaccination of adults and children with rheumatic diseases [89].

#### 4.2. Demyelinating Disorders

Among the neurological manifestations associated with biological TNF inhibitors, headaches and behavioral disturbances are the most common [75]. However, a wide range of more severe neurological disorders has been associated with TNF- $\alpha$  inhibitors, including Guillain–Barre syndrome, peripheral neuropathies, multiple sclerosis, optic neuritis and acute transverse myelitis [90,91]. A retrospective study showed that IBD patients treated with TNF- $\alpha$  blockers showed a 43% increase in the incidence of multiple sclerosis versus patients who did not receive these agents [92]. The demyelination of the central and peripheral nervous system was reported more frequently after 17 months of treatment, although the causal association with anti-TNF- $\alpha$  therapy is still uncertain [92,93]. Indeed, the use of TNF- $\alpha$  inhibitors in patients with multiple sclerosis has showed a worsening of the disease [94–96]. To date, there are no guidelines for the management of patients who manifest this complication, and only the suspension of TNF- $\alpha$  inhibitors and the administration of high-dose corticosteroids are recommended [97].

#### 4.3. Drug-Induced Lupus

Another adverse effect of TNF- $\alpha$  inhibitors is the onset of induced iatrogenic lupus (ATIL, anti-tumor necrosis factor-alpha-induced lupus). Many people who develop ATIL show variable symptoms, such as skin rashes, thrombocytopenia, leukopenia, pericarditis, pneumonia and rarely, hemolytic anemia [98,99]. These symptoms often occur in association with elevated serum levels of antinuclear antibodies and double-stranded DNA antibodies, which decrease within a few months after withdrawal of treatment. The pathogenetic mechanism by which anti-TNF- $\alpha$  leads to the development of ATIL is not yet clear. However, this appears to be due to the suppression of Th1 cytokine production, driving the immune response towards the production of IFN- $\alpha$  [100]. Furthermore, anti-TNF- $\alpha$  therapy may inhibit cytotoxic T cells, leading to a reduction in the elimination of autoantibody-producing B cells [101].

Although all anti-TNF- $\alpha$  were reported to potentially induce ATIL, several studies have shown that the onset of ATIL occurs mainly in patients taking infliximab and, in some cases, after treatment with etanercept and adalimumab [102–104]. In particular, the Vigibase dataset has reported that more than 30% of all ATIL cases were due to TNF- $\alpha$  inhibitors (12.2% infliximab, 10.7% adalimumab and 8.0% etanercept) [105]. More recently, Dai and colleagues have reported an increased ATIL incidence in CD patients treated with infliximab compared with the adalimumab group (with an incidence rate of 4.5 and 0.2%, respectively) [106].

Nowadays, it is still unclear whether TNF- $\alpha$  inhibitors play a role in the exacerbation of systemic lupus erythematosus. In order to ensure an accurate diagnosis, it is recommended that a thorough immunological screening is always performed before starting the treatment with TNF- $\alpha$  inhibitors.

#### 4.4. Malignancy

The risk of malignancy associated with the use of TNF- $\alpha$  inhibitors is still widely debated. In fact, treatment-induced suppression of the immune system may increase the risk of cancer development. According to Bongartz and colleagues, high doses of infliximab or adalimumab increases by 3.3-fold the risk of malignancy in RA patients compared with placebo groups. However, this study did not analyze any person–year incidence rate [107]. In contrast, Burmester and colleagues showed no significant differences in cancer risk in RA patients treated with adalimumab [108].

Recently, an increased risk of cancer, especially for non-melanoma skin cancer and lymphoma, was described in patients taking anti-TNF- $\alpha$  agents compared with the control population [109,110]. In particular, an Icelandic case-control study suggests that RA and PS

patients taking TNF- $\alpha$  inhibitors have an increased risk of developing in situ squamous cell carcinoma but not invasive squamous cell carcinoma or basal cell carcinoma [109]. Regarding lymphoma, an American case-control study showed that earlier use of etanercept increases the risk of non-Hodgkin lymphoma (NHL) three times [110].

Although these studies have reported an increased cancer risk in patients taking TNF- $\alpha$  blockers, no definitive conclusions can be drawn, as many studies have not confirmed this trend [111–113]. A possible explanation of these conflicting results may arise from several biases in the studies. In particular, an increased risk of lymphoma in patients with systemic inflammatory diseases taking TNF- $\alpha$  inhibitors could be a result of the disease process and not the effect of immunosuppressive therapy [114]. Furthermore, the increased risk of cancer could be due to other immunosuppressant drugs that are given together with TNF- $\alpha$  inhibitors. In fact, a higher rate of malignancies was found among IBD patients treated with the combination of TNF- $\alpha$  inhibitors and thiopurine (azathioprine or 6-mercaptopurine) compared to those treated without thiopurine (standardized incidence ratios of 6.0 vs. 2.5, respectively) [115]. Additionally, the patient's family history should be investigated to identify the possible predisposition to cancer. Finally, the follow-up period should be sufficiently extended to better evaluate the effective incidence of the neoplasm. Overall, it is recommended that patients who have already had cancer take TNF- $\alpha$  inhibitors with caution.

In light of the enormous interest attracted by immune checkpoint inhibitors (ICI) in the treatment of cancer and the frequent occurrence of immune-related adverse events (irAEs) associated with their use, it has also been debated whether the use of biological TNF inhibitors may impact the pharmacological response to ICI and the development of irAEs. Emerging clinical and preclinical evidence suggests that at least short courses of TNF inhibitors are safe for the treatment of irAEs in patients with cancer undergoing ICI therapy. Data from preclinical studies also propose that TNF inhibition might augment the antitumor effect of ICI therapy while simultaneously ameliorating irAEs [31,116].

#### 4.5. Development of Anti-Drug Antibodies (ADA)

The clinical data indicate that not all patients respond to TNF- $\alpha$  blocker therapy. In fact, the use of these agents is associated with a lack of clinical response in about 30–40% of naïve patients (primary therapeutic failure) [117]. It is also known that some patients responding to TNF- $\alpha$  blockers at the beginning of the therapy may lose sensitivity to these drugs at later phases (secondary treatment failure) [117]. The current evidence suggests that the development of anti-drug antibodies (ADA) is one of the most important factors that can account for secondary failure [118]. ADA can block the therapeutic action of the respective anti-TNF- $\alpha$  drug. Indeed, neutralizing ADA bind the drug to prevent it from interacting with its molecular target, while non-neutralizing ADA facilitate drug clearance, resulting in the reduction in drug concentrations below the levels needed to carry out the expected therapeutic effect [119]. Moreover, the production of ADA can lead to the development of adverse reactions. Indeed, it has been observed that the development of ADA specifically against TNF- $\alpha$  antagonists has been associated with acute infusion reactions, which usually occur within 24 h of TNF- $\alpha$  inhibitor administration [120]. Conversely, no association was highlighted among the ADA directed against anti-TNF- $\alpha$  drugs and delayed hypersensitivity reactions occurring 3 to 12 days after the infusion.

Maneiro and colleagues showed up to a four-fold increased risk of infusion reactions in ADA-positive patients compared with ADA-negative patients [121]. Infliximab showed the greatest immunogenic power among the currently usable TNF- $\alpha$  inhibitors due to the presence of murine regions in its molecular structure. Indeed, a recent meta-analysis has determined that 25% of infliximab-treated patients develop ADA [122]. Moreover, a recent study suggests that etanercept is the less immunogenic biological TNF- $\alpha$  inhibitor [123]. In clinical studies, the presence of anti-etanercept ADA in the serum of patients treated with this drug was found in only 1.2% of cases [122]. However, it appears that the presence



of ADA has not been associated with significant reductions in the therapeutic efficacy of etanercept, even in long-term studies [124,125].

To avoid the immunogenic effects of TNF- $\alpha$  inhibitors, two therapeutic approaches are available: one is to switch to a second TNF- $\alpha$  inhibitor or agents with different mechanisms of action; another alternative strategy may be the use of immunosuppressive agents in combination with TNF- $\alpha$  inhibitors. In particular, several studies have shown that the co-administration of immunosuppressants (azathioprine, glucocorticoids and methotrexate) reduces immunogenicity and increases the serum levels of TNF- $\alpha$  inhibitors [121,122,126–129]. However, the mechanisms underlying these effects are not yet fully understood. Therefore, it would be necessary to monitor the patient and detect the presence of ADA in serum as soon as possible.

Although numerous studies have shown that the development of ADA can be associated with a loss or reduction of the therapeutic action of TNF- $\alpha$  inhibitors, these data should be considered with considerable caution. In fact, the presence of ADA cannot be considered a condition necessarily associated with the loss or reduction of efficacy of the respective biotechnological drug, as some patients who develop ADA against a specific TNF- $\alpha$  inhibitor show a good persistence of therapeutic response to treatment with the same agents [119]. The development of immune tolerance could play a key role in this mechanism. Notably, several studies have shown that one-third of patients show a transient ADA response with serum ADA levels decreasing over time [130–132].

Overall, the mechanisms underlying the development of ADA and their effects on therapeutic efficacy are not fully understood yet. Further studies are needed to identify possible biomarkers that could predict the development of ADA in patients after treatment with TNF- $\alpha$  inhibitors.

#### 4.6. Other Adverse Events

Based on several clinical studies, TNF- $\alpha$  inhibitors seem to play a key role in the evolution and development of various pathologies. Indeed, there are post-marketing reports of the worsening of congestive heart failure (CHF) in patients treated with these agents. In particular, a randomized study suggests that infliximab increases the risk of hospitalization in patients with CHF [133]. Similar results were obtained in other clinical studies evaluating the role of etanercept [134]. Furthermore, there have been also rare cases of de novo onset of CHF in patients without pre-existing cardiovascular disease [135].

Regarding the role of TNF- $\alpha$  inhibitors in pregnancy, there is no evidence to suggest that treatment with these drugs, before or during pregnancy, is associated with increased risks of preterm births, congenital anomalies or poor pregnancy outcomes [136,137]. However, a prospective study revealed that treatment with TNF- $\alpha$  inhibitors in combination with thiopurines in pregnancy increases the risk of neonatal viral infections [138].

Finally, some adverse events may be induced by interactions between TNF- $\alpha$  inhibitors and other drugs. Although, most studies have observed no clinically relevant drug interactions, some evidence suggests that TNF- $\alpha$  inhibitors may affect cytochrome p450 (CYP450) activity [139]. In particular, the effect of TNF- $\alpha$  inhibitors could involve the restoration of CYP450 with direct effects on plasma concentration and the pharmacological activity of co-administered drugs which are metabolized by CYP450. Furthermore, a clinical study has demonstrated that etanercept in combination with cyclophosphamide was associated with a higher incidence of malignant solid tumors compared with standard therapy alone in patients with Wegener's granulomatosis [140].

Drug interactions should be considered as one of the possible causes of any adverse events. When unexpected clinical responses occur, the physician should determine the serum concentrations of the drugs and adjust the dosage until the desired effect is obtained. If the dosage adjustment is ineffective, it should be replaced with one that does not interact with the other agent.

## 5. Perspectives on Future Applications of TNF- $\alpha$ Blockers

### 5.1. TNF- $\alpha$ Blockers in COVID-19 Disease

During viral infections, inflammation plays a key role in the fight against viral agents. However, TNF- $\alpha$  can also lead to excessive activation of immune cells and a hyperproduction of other pro-inflammatory cytokines, damaging different organs [141]. Recently, the role of TNF- $\alpha$  has been investigated in SARS-CoV-2 disease (COVID-19). The spike glycoproteins of SARS-CoV-2 recognise and bind to angiotensin-converting enzyme-2 (ACE-2) receptors that are expressed on the surface of alveolar, cardiac, endothelial and hematopoietic cells [142]. Then, the spike-ACE-2 complex internalizes into cell cytoplasm and allows the increase in TACE enzymatic activity [143]. Soluble TNF- $\alpha$  is secreted already in the early stages of the infection, underlying the “cytokine storm”, which results in hyperinflammation and tissue damage [144]. Although TNF- $\alpha$  plays a primary role in the onset of the cytokine cascade, anti-TNF agents are not yet clinically approved for the treatment of COVID-19 disease. However, observational studies have suggested that the administration of TNF- $\alpha$  blockers seems to be promising in patients with severe disease [145,146].

In particular, the Inflammatory Bowel Disease Registry (SECURE-IBD) has reported the beneficial effects of TNF- $\alpha$  blockers for treating patients with inflammatory bowel disease (IBD) affected by COVID-19. In particular, among 2307 IBD patients treated with anti-TNF- $\alpha$  monotherapy before and during COVID-19 disease and 2088 patients receiving sulfasalazine/mesalazine treatment, 8% were hospitalized and <1% died in the anti-TNF- $\alpha$  group, while 20% were hospitalized and 3% died in the other group [147].

In addition, the Global Rheumatology Alliance (GRA) registry has reported the beneficial effects of TNF- $\alpha$  blockers for treating COVID-19 patients with RA. On 12 April 2021, 1388 patients with RA received TNF- $\alpha$  inhibitors at the onset of COVID-19. Of these, 103 patients (7.4%) were hospitalized with ventilation, and only 36 (2.6%) died. Notably, treatment with other drugs (rituximab and Janus kinase inhibitors) has shown a higher probability of developing a severe disease than treatment with TNF- $\alpha$  inhibitors [148]. No associations between abatacept or interleukin 6 inhibitors and COVID-19 severity were observed [148].

Overall, these data have shown that the clinical use of TNF- $\alpha$  blockers is significantly associated with a lower COVID-19-related hospitalization rate compared with other drugs. However, further studies are needed to better define an immune profile of both the disease course and therapy with TNF- $\alpha$  antagonists. For instance, some data show that the use of TNF- $\alpha$  inhibitors seems to be associated with a mild humoral response to the SARS-CoV-2 vaccines and a faster lowering of the antibody titre compared with patients treated with other drugs [149,150]. Furthermore, it would be interesting to investigate the timing of the intervention to prevent the onset of the cytokine storm observed in severe COVID-19 cases.

### 5.2. Inflammation and Neuropsychiatric Disease

Several studies have recently demonstrated that a persistent inflammatory state plays a predominant role in the pathogenesis of psychiatric and neurodegenerative diseases [151–155]. In fact, the peripheral immune system is able to influence brain functions. This is supported by several studies which have suggested that patients with diseases associated with systemic inflammation often also have behavioral disorders [156]. Although the blood–brain barrier (BBB) selectively regulates the passage of substances to the brain, cytokines are capable of crossing it [157]. Furthermore, pro-inflammatory mediators can also be produced in the brain by resident cells, including astrocytes, microglia cells and oligodendrocytes [158]. High serum and cerebrospinal fluid levels of pro-inflammatory markers (IL-1 $\beta$ , IL-6, TNF- $\alpha$  and MIF) have been found in patients with major depression, bipolar disorder and schizophrenia [159–163].

Other studies have shown how TNF- $\alpha$  is positively associated with the severity of depressive symptoms [164]. In addition, the use of antidepressants reduces the release of circulating inflammatory factors, increasing the release of endogenous antagonists of pro-inflammatory cytokines, such as IL-10 [165,166]. Moreover, Benedetti and colleagues

reported a relationship between some pro-inflammatory cytokines (TNF- $\alpha$ , IL-8 and IFN- $\gamma$ ) and white matter integrity. In particular, these molecules were significantly associated with a decrease in the integrity of the white matter (fractional anisotropy) and an increase in the permeability of the myelin sheath (radial and average diffusivity) [167].

#### TNF- $\alpha$ Blockers in Neuropsychiatric Disease

Based on the studies described above, several studies have recently focused on evaluating TNF- $\alpha$  inhibitors as potential therapeutics for behavioral disorders, obtaining encouraging results. Indeed, some studies have reported a significant reduction in anxiety and depressive-like behaviour and an improvement in cognitive function in murine models after anti-TNF- $\alpha$  treatment [168,169]. In line with these pre-clinical studies, similar results were obtained in numerous clinical trials [170,171]. In particular, a randomized, double-blind clinical trial revealed that patients with bipolar disorders treated with infliximab are affected by a depletion in leptin levels [172]. Moreover, the same group observed that infliximab treatment significantly reduces glutamate levels in patients with bipolar disorders [173]. Moreover, the results of these two trials suggested an increase in global cortical volume and an improvement in cognitive functions in bipolar patients after infliximab administration. However, a randomized, double-blind, placebo-controlled trial showed a significant reduction in symptom severity only in bipolar patients with a history of childhood physical abuse after 12 weeks of treatment with infliximab [174]. Furthermore, another group demonstrated that infliximab exhibits only short-lived antidepressant effects in patients with bipolarity [175]. Finally, a systematic review showed a reduction of depressive symptoms only in patients with high protein C reactive (PCR) and TNF- $\alpha$  levels. However, no statistically significant effects were found between the infliximab and placebo groups with low levels of inflammatory markers [176].

Although TNF- $\alpha$  inhibitors are unable to cross the BBB due to their molecular weight, they can bind to peripheral TNF- $\alpha$ , also reducing its levels and the overall activated immune cells in the brain parenchyma [177]. To bypass this hindrance, several strategies have been investigated. In particular, intracranial injections of infliximab have shown a reduction of A $\beta$  and tau pathology and a rapid cognitive improvement in neurological dysfunction [178–180]. More recently, TNF- $\alpha$  inhibitors were fused with other mAbs acting as a BBB molecular “Trojan horse” (human insulin receptor or transferrin receptor mAbs) [181–183]. These mAbs undergo receptor-mediated transport across the BBB via the endogenous receptors, introducing the engineered TNF- $\alpha$  inhibitors into the brain [184].

Overall, although no data on the role of other TNF- $\alpha$  inhibitors are available, these studies highlight that the use of TNF- $\alpha$  as an adjunctive antidepressant therapy exhibits only partial positive results in a small group of patients with behavioral disorders. In addition, a recently study demonstrated that the use of TNF- $\alpha$  inhibitors could be a potential risk factor for the development of a manic episode in patients with or without psychiatric disorders [185].

#### 5.3. Ongoing Trials Using TNF- $\alpha$ Blockers

The therapeutic use of anti-TNF- $\alpha$  has led to important advances for patients with several chronic inflammatory diseases. However, there are still autoimmune/immunoinflammatory diseases for which there is still no evidence of the efficacy of TNF- $\alpha$  inhibitors.

Numerous clinical trials are ongoing for the evaluation of TNF- $\alpha$  blockers in a wide range of disorders that may be characterized by an abnormal production of pro-inflammatory cytokines (Table 1). Most notably, Phase 2–3 trials are evaluating the use of TNF- $\alpha$  blockers in vasculitis patients suffering from Behcet’s disease, Takayasu’s arteritis, Wegener’s granulomatosis and giant cell arteritis for Pemphigus Vulgaris, as well as for the prevention of graft vs. host disease.

**Table 1.** Ongoing clinical studies on future applications of TNF- $\alpha$  blockers registered at <https://clinicaltrials.gov> (accessed on 2 January 2023).

NCT Number	Interventions	Conditions	Phases
NCT03371095	Infliximab	Behcet's Disease and Vasculitis	Phase 3
NCT03180957	Adalimumab	Dupuytren's Disease	Phase 2
NCT02457585	Infliximab	Takayasu's Arteritis	Phase 2
NCT01730495	Etanercept	Chronic Fatigue Syndrome and Myalgic Encephalomyelitis	Phase 2
NCT01423591	Infliximab	Polymyalgia Rheumatica	Phase 3
NCT00753103	Infliximab	Wegener's Granulomatosis, Renal Limited Vasculitis and Microscopic Polyangiitis	Phase 2
NCT00726375	Etanercept	Acute Graft vs. Host Disease	Phase 3
NCT00604864	Infliximab	Endometriosis	Phase 2
NCT00368264	Infliximab	Lupus Erythematosus Systemic and Lupus Nephritis	Phase 2/Phase 3
NCT00329823	Etanercept	Hidradenitis Suppurativa	Phase 2
NCT00305539	Adalimumab	Giant Cell Arteritis	Phase 3
NCT00228839	Infliximab	Graft vs. Host Disease	Phase 1
NCT00203359	Etanercept	Alzheimer's Disease	Phase 1
NCT00203320	Etanercept	Alzheimer's Disease	Phase 1
NCT00135720	Etanercept	Pemphigus Vulgaris	Phase 2
NCT00031551	Etanercept	Stomatitis	Phase 2

## 6. The Search for Biomarkers

Although TNF- $\alpha$  blockers are the main therapeutic option for patients with immune-mediated inflammatory diseases, they are characterized by high costs and immunosuppressive activity. Moreover, 40% of patients treated with them do not respond or show a loss of response over time [118]. For these reasons, many researchers have focused on identifying potential biomarkers that allow us to predict the patient's response to treatment. Increased serum granulocyte-macrophage colony-stimulating factor (GM-CSF) levels have been found in 87.5% of RA patients responding to one of the TNF- $\alpha$  inhibitors [186]. In addition, Nguyen and colleagues showed that low pre-albumin and S100A12 levels associated with high platelet factor 4 (PF4) levels in pre-treatment could be good predictors for responses to infliximab, etanercept and adalimumab in patients with RA [187]. Another group observed a high number of myeloid-related protein 8 (MRP8) and MRP14-infiltrating macrophages in the synovium of RA patients responding to infliximab [188], whereas a meta-analysis demonstrated that an increased number of inflammatory plasma cells and macrophages, together with elevated tissue levels of the trigger receptor expressed on myeloid-1 cells (TREM-1), the chemokine type 2 receptor (CCR2) and the chemokine ligand 7 (CCL7) could be predictive of the failure of anti-TNF therapy in CD patients [189]. Furthermore, transcriptome analyses regarding patients with CD suggested a significant down-regulation of the K(lysine)-acetyltransferase 2B (KAT2B) gene, both in the tissues and peripheral blood mononuclear cells (PBMCs) in non-responders to anti-TNF therapy [190]. Recently, a systematic review regarding PsA or PS patients has reported that several single nucleotide polymorphisms (SNPs) could be predictive of a favorable response to anti-TNF- $\alpha$  treatment [191].

Finally, some studies have also shown that genetic variants could influence the response to TNF- $\alpha$  blockers. In particular, it was found that the presence of the IFN- $\gamma$  Grs2069705C allelic variant in patients with RA resulted in a better responsiveness to TNF- $\alpha$  inhibitors compared with patients harboring the wild-type allele [192]. Moreover,

Sazonovs and colleagues revealed that the expression of the HLA-DQA1\*05 variant was associated with anti-drug antibody generation in CD patients treated with infliximab and adalimumab [193].

Unfortunately, to date, no biomarker for anti-TNF responsiveness has been validated due to the heterogeneity of the results obtained. Hence, further studies using independent and large cohorts are needed.

## 7. Conclusions

Anti-TNF- $\alpha$  therapy has paved the way for a revolution in the approach to treating chronic inflammatory diseases. In fact, they represent the first biotechnological drugs used in rheumatology after the failure of conventional synthetic drugs, such as methotrexate, sulfasalazine and mesalazine. The efficacy and safety of these biological agents have been confirmed in various fields, and novel potential applications range from psychiatric and neurological disorders to viral infections, such as COVID-19. Novel TNF- $\alpha$  blockers are also currently under development, including AVX-470, L19TNFa, Ozoralizumab, 99mTc and XPro1595. Despite considerable progress, there is still an area of unmet need, for instance, cases in which the therapeutic response is insufficient or in which there are specific clinical conditions of patients or the need to control specific aspects of the disease. This explains the wide range of drugs available and the attention of the reference guidelines to the specificities of the patient, focusing on the increasingly tailored therapy. Due to this, a great effort is being made in the identification of biomarkers to be used as prognostic tools in patients eligible for treatment with TNF- $\alpha$  inhibitors. Secondly, biotechnological therapy is burdened by the high direct costs of the drug. The lack of patent protection for the first TNF- $\alpha$  inhibitors has allowed the introduction of economically affordable biosimilars, such as ABP 501 (Amjevita- Amgen Inc., Thousand Oaks, CA, USA), ABP 710 (Avsola- Amgen Inc., Thousand Oaks, CA, USA), BI 695501 (Cyltezo- Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany), CHS-1420 (Yusimri- Coherus BioSciences Inc., Redwood City, CA, USA), CT-P13 (Inflectra- Celltrion Healthcare, Lake Forest, IL, USA), FKB327 (Hulio- Mylan Inc., Canonsburg, PA, USA), GP2017 (Hyrimoz- Sandoz, Basilea, Switzerland), PF-06410293 (Abrilada- Pfizer Inc., New York, NY, USA), PF-06438179 (Zessly- Sandoz GmbH, Kundl, Austria), SB2 (Flixabi- Samsung Bioepis, Incheon, Republic of Korea), SB4 (Brenzys- Samsung Bioepis, Incheon, Republic of Korea) and SB5 (Imraldi- Biogen-Samsung Bioepis, Incheon, Republic of Korea). The availability of biosimilar agents has allowed a drastic and important reduction in pharmacological expenditure, making TNF- $\alpha$  blockers widely available and accessible to the population. To date, they are an integral part of the biological therapies available. However, although biosimilars are approved on the basis of similar mechanisms of action, efficacy and safety with their reference products, many clinicians remain hesitant to suggest biosimilars as a viable treatment option due to the nocebo effect that could occur in patients following the switch to biosimilars. For this reason, it is necessary that clinicians have full and complete knowledge of the scientific principles that support these agents, their clinical development, approval and safety monitoring.

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