

Update on the mechanisms of action of anti-TNF- α antibodies and their clinical implications in inflammatory bowel disease

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ABSTRACT

The mechanisms of action of antitumor necrosis factor α (anti-TNF- α) antibodies in the therapy of inflammatory bowel disease (IBD) are not completely understood. Binding of antibodies to transmembrane TNF- α seems to be crucial for the induction of several cellular responses, including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and reverse signaling. However, these processes alone do not fully explain the diversity of responses to anti-TNF- α therapy seen in different patients. Thus, the present review aimed to discuss the current role of anti-TNF- α antibodies in treatment algorithms for IBD as well as the current knowledge on the mechanisms of action of these antibodies, particularly the less well known aspects of anti-TNF- α blockade. We also discussed a complex role of particular macrophage subpopulations, T regulatory cells, and intestinal endothelial cells, as well as presented new data on the clinical relevance of anti-inflammatory responses attributed to the Fc region of anti-TNF- α antibodies.

Introduction Introduction of antitumor necrosis factor α antibodies (anti-TNF- α) has significantly changed the treatment algorithms for inflammatory bowel disease (IBD).¹ Anti-TNF- α agents enabled the new therapeutic goals to be achieved, including mucosal healing and prevention of irreversible structural bowel damage.² However, the exact mechanism by which these new agents exert their effects is not fully understood.³ This knowledge has important practical implications, as it has been estimated that up to 30% to 40% of patients with IBD may not respond to anti-TNF- α therapy.⁴

Although the fundamental role of TNF- α in the pathogenesis of IBD is now well recognized, it appears that binding of TNF- α by anti-TNF- α agents results in the effects that go beyond simple TNF- α neutralization. Here, we briefly present the current place of anti-TNF- α antibodies in the management of IBD and summarize the knowledge on the mechanisms underlying their activity, with emphasis on new data and emerging pathways.

The biology of tumor necrosis factor α There are two main forms of TNF- α : soluble TNF (sTNF) and transmembrane TNF (tmTNF).^{3,5} The sTNF is a 17-kDa molecule released predominantly by macrophages, T cells, and natural killer (NK) cells as a result of proteolytic cleavage of the 26 kDa tmTNF molecule. The process is mediated by TNF- α -converting enzyme. Both sTNF and tmTNF form homotrimers and act through two distinct TNF receptors (TNFR). TNFR1 is expressed constitutively by many cell types and binds mainly to sTNF. In contrast, TNFR2 is induced chiefly in the course of inflammation and immune responses in hematopoietic and endothelial cells and binds mainly to tmTNF. Interestingly, it appears that TNFR2 can also transiently bind sTNF and then release it for interaction with a more affinitive TNFR1, a phenomenon known as ligand passing.⁵

The structure of antitumor necrosis factor α agents

Anti-TNF- α agents certified for use in IBD include either full monoclonal antibodies (infliximab [IFX], adalimumab [ADA], and golimumab [GOL]) or their fragments (certolizumab

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[CER]).⁶ Each antibody consists of 2 heavy (H) and 2 light (L) polypeptide chains. Both L and H chains contain variable (V) and constant (C) domains. The H chain consists of one V domain (VH) and three C domains (CH1, CH2, CH3), whereas the L chain consists of one V and one C domain (VL and CL, respectively).^{3,6} IFX is a monoclonal, chimeric (75% human and 25% murine) immunoglobulin (Ig) G1 antibody, while ADA and GOL are fully human IgG1 antibodies. CER pegol is a humanized (90% of human origin) Fab fragment of IgG4 antibody conjugated to polyethylene glycol (PEG), so that it does not contain the Fc domain. The structure of etanercept (ETA), another TNF-binding molecule, is different in that it is a fusion protein containing extracellular part of TNF receptor 2 (TNFR2/p75) and Fc fragment of IgG1 immunoglobulin.⁶ Curiously, however, ETA shows no significant clinical effect and is not used in IBD.^{5,7} Each antibody contains the Fab region, which is responsible for antigen binding, and the Fc region, which can bind to cell surface receptors or complement proteins and thus exert some effector functions. For detailed characteristics of anti-TNF- α antibodies, the reader is directed elsewhere.^{3,5}

Clinical application of antitumor necrosis factor α antibodies in inflammatory bowel disease

The role of anti-TNF- α agents in therapeutic algorithms for IBD has significantly evolved over the past 20 years. Initially, IFX was administered only to patients with symptoms of active disease (the so called episodic treatment) and when all other pharmaceuticals (mesalamine, steroids, thiopurines) had failed to produce a desired effect (a step-up strategy).^{1,2,8} However, subsequent clinical trials have demonstrated that all TNF- α antagonists should rather be used in a continuous manner, starting with the induction period and then followed by the maintenance therapy.^{2,4,8} D'Haens et al⁹ were the first to suggest that very early application of anti-TNF- α agents, even just after the diagnosis (a top-down strategy), could lead to better long-term therapeutic outcomes and a significant change in the known natural history of IBD, with irreversible intestinal damage occurring despite seemingly optimal immunosuppressive treatment.

In recent years, a trend for more personalized use of TNF- α antagonists has emerged. It was triggered by defining predictors of a disabling disease, which included age younger than 40 years at diagnosis, the presence of perianal lesions, deep colonic ulcerations, and extensive small bowel involvement, as well as the need for early use of steroids, the habit of smoking, and the history of significant weight loss.^{4,10} When these criteria are met, a top-down or an accelerated step-up approach should be implemented.^{4,10} In the latter, conventional nonbiological drugs are used initially for a strictly defined short period of time (eg, steroids for 1–2 weeks, thiopurines for 8–12 weeks), but if they fail or produce serious

side effects, the biological therapy is strongly recommended.^{2,4,10}

Also an ongoing anti-TNF- α therapy could be made more effective and safe if it was individualized and precisely controlled. This could be achieved by therapeutic drug monitoring, which involves the accurate measurements of anti-TNF- α trough levels (TLs), that is, the serum concentrations of a drug just before the administration of the next dose, and the titers of neutralizing antidrug antibodies.^{2,4,6,10} In this respect, Vermeire et al¹⁰ have proposed an algorithm of when to perform anti-TNF- α drug monitoring. In each case, TLs should be assessed after the induction therapy has been completed. If TLs are high, the maintenance treatment can be started, but if not, one should consider increasing the dose or reducing the interval between the subsequent doses. In patients on maintenance treatment, TLs should be measured if signs of reduced drug responsiveness appear.¹⁰ If TLs are still detectable, imaging and/or endoscopy should be performed in order to confirm or exclude the presence of active inflammation. If the former is the case, the anti-TNF- α therapy should be discontinued and replaced by a different regimen (eg, by anti-integrin antibodies). In the latter scenario, other potential causes of the symptoms (eg, stenosis, bacterial overgrowth, irritable bowel syndrome) should be searched for. On the other hand, if TLs are undetectable, the patient ought to be tested for the presence of antidrug antibodies. If these are present, a switch to a different TNF- α blocker is recommended, and if not, the ongoing therapy should be optimized by shortening the intervals between the doses, by increasing the doses, or by adjusting the associated immunosuppressive treatment.^{2,4,6,10}

These recommendations need to be supported by further prospective clinical trials, the optimization of effective serum drug concentrations, the use of more reliable assays to measure TLs and detect antidrug antibodies, as well as by a thorough assessment of the pharmacoeconomic aspects of therapy.^{2,10} Nevertheless, there is no doubt that therapeutic drug monitoring is the future of personalized anti-TNF- α therapy for IBD.

The list of anti-TNF- α antibodies used in the therapy of IBD is presented in [TABLE 1](#).

Mechanisms of action of antitumor necrosis factor α antibodies: what do we know?

As indicated above, the pharmacokinetics of TNF- α antagonists impacts significantly on the treatment efficacy. At the molecular level, anti-TNF- α antibodies bind first to their target molecules: tmTNF and sTNF. Both IFX and ADA can bind the monomeric and homotrimeric forms of TNF- α . Moreover, one TNF- α homotrimer can react with three IFX molecules and one molecule of either IFX or ADA is capable of binding two TNF- α homotrimers at the same time.^{3,5} This cross-linking phenomenon allows the therapeutic molecule to form a cascade of complex interactions

TABLE 1 Antitumor necrosis factor α (anti-TNF- α) antibodies used in the therapy of Crohn disease (CD) and ulcerative colitis (UC)

Anti-TNF- α antibody	Indications	Dosage	Route of administration	Rates of clinical improvement ^a	Rates of the most relevant adverse events
infliximab	CD UC	5 mg/kg body weight at weeks 0, 2, and 6, and then every 8 weeks	intravenously	CD: 65%–88% for induction and 43%–64% for maintenance therapy ^{61–63} UC: 60%–70% for induction and 35%–50% for maintenance therapy ^{64,65}	serious infections: 3%–5% infusion reactions: 10%–40% paradoxical psoriasis/psoriasiform dermatitis: 1%–20% malignancies: <1% ^{55,70,71}
adalimumab	CD UC	160 mg at week 0, 80 mg at week 2, and then 40 mg every 2 weeks	subcutaneously	CD: 50%–60% for induction and 40%–50% for maintenance therapy ⁶⁶ UC: 50%–55% for induction and 20%–30% for maintenance therapy ^{65,67}	serious infections: 3%–6% injection site reactions: 10%–20% paradoxical psoriasis/psoriasiform dermatitis: 1%–20% malignancies: <1% ^{55,70,72}
certolizumab pegol	CD	400 mg at weeks 0, 2, and 4, and then 400 mg every 4 weeks	subcutaneously	35%–64% for induction and 23%–67% for maintenance therapy ^{68,69}	serious infections: 2%–3% injection site reactions: 2%–3% malignancies: <1% ⁶⁹
golimumab	UC	200 mg at week 0, 100 mg at week 2, and then 50 mg (<80 kg body weight) or 100 mg (\geq 80 kg body weight) every 4 weeks	subcutaneously	50%–55% for induction and 28%–56% for maintenance therapy ^{65,73}	serious infections: 3%–5% hypersensitivity reactions: 2%–3% malignancies: <1% ⁷³

a The percentages can significantly differ between studies due to high heterogeneity in the definitions of clinical improvement after anti-TNF- α therapy.

with its target. Subsequent effects depend on whether anti-TNF- α antibodies bind to sTNF or tmTNF, that is, on whether the drug inhibits signaling from TNF receptor or whether it acts as a ligand for tmTNF.^{3,5} On the one hand, binding of sTNF and tmTNF by anti-TNF- α antibodies blocks stimulation of TNFR1 and TNFR2, which results in the inhibition of proinflammatory pathways leading to decreased cytokine release and reduced inflammatory cell infiltration. On the other hand, ligation of tmTNF by anti-TNF- α antibodies can trigger at least 3 phenomena: 1) antibody-dependent cellular cytotoxicity (ADCC); 2) complement-dependent cytotoxicity (CDC); and 3) reverse signaling.^{3,5}

During ADCC, the Fab fragment of an anti-TNF- α antibody binds tmTNF on the target cell, while the Fc fragment binds the Fc receptor on effector cells (eg, NK cells) and promotes the secretion of cytotoxic molecules (granzyme B, perforins) that destroy target cells. During CDC, the Fc fragment activates the complement, which leads to the formation of the membrane attack complex and target cell death. ADCC and CDC can be induced by IFX, ADA, and GOL, but not by CER.³ This is because CER does not contain the Fc region that is crucial for the initiation of these responses. However, both IFX, ADA, and CER can launch reverse signaling, during which binding of an anti-TNF- α agent initiates several responses in tmTNF-bearing target cells.^{3,5,11} These include suppression of cell growth and cytokine release, and induction of apoptosis. These processes seem to be crucial for the clinical efficacy of anti-TNF- α agents in IBD, since ETA that cannot bind tmTNF is ineffective in both Crohn disease (CD) and ulcerative colitis (UC).^{3,5} Molecular

pathways underlying these phenomena have recently been extensively reviewed.³

Mechanisms of action of antitumor necrosis factor α antibodies: what is new? The role of macrophages

While it is clear that T cells play a key role in the pathogenesis of IBD and as such are effectively targeted by anti-TNF- α antibodies, recent studies have pointed to a significant contribution of other cell types, including monocytes and macrophages.^{12,13} Intestinal biopsies from IBD patients show increased presence of macrophages in the inflamed tissue.^{14,15} Activation status of these macrophages can be inferred from increased expression of hemoglobin-haptoglobin scavenger receptor CD163 and elevation of its soluble form (sCD163) in plasma.^{16–18} A rapid decrease in sCD163 levels has been observed after administration of anti-TNF- α antibodies, but not after prednisone, suggesting a specific effect of anti-TNF- α therapy on macrophage activation in IBD.¹⁹ This effect is thought to be mediated via apoptosis induced by binding of anti-TNF- α agents to tmTNF on monocytic cells.²⁰ Suppression of macrophage activity can also be linked to the modulating effect of TNF- α blockers on cytokine–extracellular matrix interactions.

A recent proteomic analysis has revealed significantly reduced tenascin C levels in patients with UC who responded to anti-TNF- α therapy.²¹ This effect was associated with downregulation of monocyte chemoattractant CCL2 and reduced monocyte expression of CD14 and CD86. Tenascin C is an extracellular matrix glycoprotein capable of activating Toll-like receptor-4 signaling and inducing monocyte-recruiting chemokines.^{22,23} Thus, it has been suggested

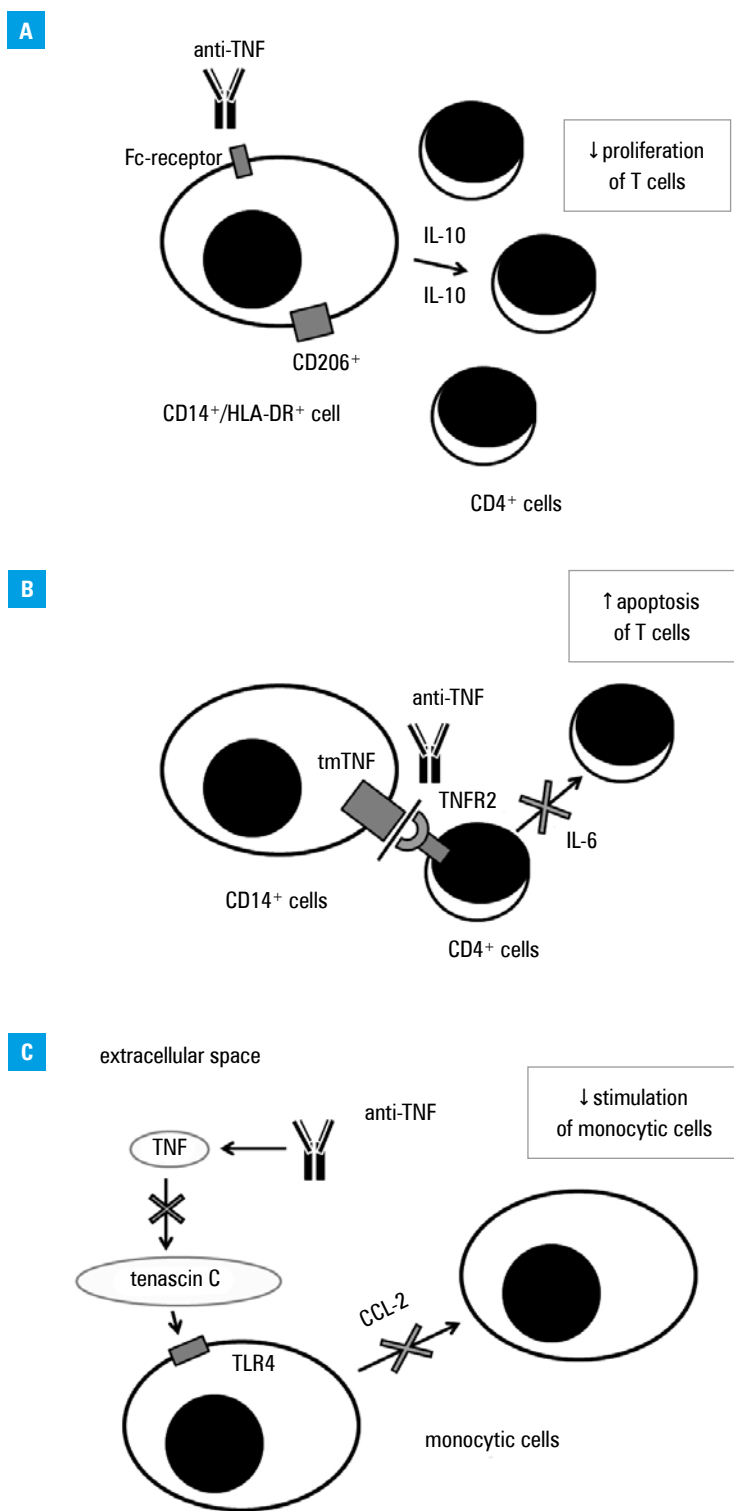


FIGURE 1 The role of macrophages in the mechanisms of action of antitumor necrosis factor α (anti-TNF- α) antibodies. **A** – In the presence of CD4⁺ T cells, anti-TNF- α agents containing the Fc fragment induce the CD14⁺ and HLA-DR⁺ monocytic cells in an Fc-dependent manner. These cells exhibit anti-inflammatory properties, expressing regulatory macrophage marker CD206 and producing interleukin 10 (IL-10), which downregulates proliferation of T cells. **B** – anti-TNF- α antibodies neutralize transmembrane TNF (tmTNF) on CD14⁺ macrophages, which prevents from binding of tmTNF to TNF receptor 2 (TNFR2) on CD4⁺ T cells. In consequence, the TNFR-2-dependent production of interleukin 6 (IL-6) is decreased, which sensitizes T cells to proapoptotic signals. **C** – anti-TNF- α antibodies modulate the function of tenascin C, an extracellular matrix glycoprotein, which is induced in inflammatory conditions. Tenascin C activates Toll-like receptor 4 (TLR4) on monocytes, which promotes monocyte-recruiting chemokines. The decrease of tenascin C levels after administration of an anti-TNF- α agent downregulates the monocyte chemoattractant CCL2 and reduces stimulation of monocytes.

that successful response to IFX could be linked to tenascin C-mediated reduction in monocyte activation.¹⁹

However, given large functional heterogeneity of macrophages, their role in anti-TNF- α -induced responses may be more complex. For example, it has been demonstrated that anti-TNF- α antibodies can induce regulatory macrophages with immunosuppressive properties, and that the interaction between anti-TNF- α antibodies and macrophages is the sine qua non for apoptosis of T cells in inflammatory infiltrates in IBD.^{24,25}

It has been demonstrated that anti-TNF- α antibodies can reduce T-cell proliferation during mixed lymphocyte reaction only in the presence of cells combining the features of regulatory and M2-type macrophages.²⁴ Interestingly, this population of macrophages emerged only upon treatment with anti-TNF- α agents containing Fc fragment (IFX, ADA, and CER-IgG), and when co-cultured with CD4⁺ cells. Moreover, these macrophages expressed a number of costimulatory molecules, Fc receptor, and the regulatory macrophage marker CD206. They exhibited strong anti-inflammatory properties as assessed by the inhibition of T-cell responses and the increased production of anti-inflammatory interleukin (IL) 10.²⁴ Importantly, mucosal healing after administration of IFX was found to occur only in those IBD patients in whom a significant induction of regulatory macrophages was observed.²⁶ This effect was even more pronounced in patients receiving a combination therapy with azathioprine.

The above data may collectively suggest that anti-TNF- α antibodies can induce—in a Fc region-dependent manner—macrophages resembling M2 type and regulatory macrophages that then act to dampen inflammation and promote wound healing. More recently, it has been reported that induction of such macrophages in response to anti-TNF- α therapy is related to effective cellular autophagy, which may be impaired in some individuals with a polymorphism (Thr300A-la) in the essential autophagy gene, autophagy related 16-like 1 (*ATG16L1*).²⁷ This gene variant has been shown to confer an increased risk for the development of CD through the effects on cytokine production and antibacterial autophagy.²⁸

Another new concept of macrophage involvement in anti-TNF- α -induced responses has been proposed by Atreya et al.²⁵ These authors have shown that macrophage tmTNF interacts with TNFR2 on T cells, which results in the activation of TNF receptor-associated factor 2 and nuclear factor kappa-B pathway. This leads to increased IL-6 production and increased resistance to apoptosis. The authors postulated that by targeting tmTNF on CD14⁺ macrophages, anti-TNF- α antibodies block the interaction between tmTNF and TNFR2 on T cells and sensitize them to proapoptotic signals.

The new concepts on the role of monocytes/macrophages in the mechanisms of action of TNF- α blockers in IBD are summarized in **FIGURE 1**.

The role of regulatory T cells and immunosuppressive mechanisms

One of the key events in chronic immune-related diseases, including IBD, is silencing of immunosuppressive mechanisms, which leads to an imbalance that promotes proinflammatory pathways.²⁹ The clinical relevance of these processes has recently been demonstrated in patients with CD treated with mongersen.^{30,31} Mongersen is an oral Smad7 antisense oligonucleotide, and the rationale for its use in CD is that it inactivates Smad7, a transforming growth factor β 1 (TGF- β 1) inhibitor. TGF- β 1 is a potent immunosuppressive mediator and IBD has been shown to reduce TGF- β 1 activity owing to increased expression of Smad7.²⁹ In a double-blind phase 2 trial, mongersen was found to be significantly more effective than placebo in inducing clinical response and remission in active CD.³⁰ Interestingly, it appears that also IFX is capable of enhancing TGF- β 1 secretion. By binding to tmTNF on monocytes, it induces reverse signaling that promotes TGF- β 1 secretion, which in turn can be responsible for immune cell apoptosis.^{32,33}

More recently, Derer et al³⁴ have described a novel TGF- β 1-related pathway that can be induced by IFX and CER. By analyzing transcriptional signatures elicited by IFX and CER in myelomonocytic cells, they have identified growth and differentiation factor 1 (GDF-1) as being downregulated by TNF- α blockers. GDF-1 is a member of the TGF- β superfamily that is upregulated in CD and acts to promote inflammatory IL-6. Ligation of tmTNF by anti-TNF- α agents induces TGF- β 1 through reverse signaling, which then results in downregulation of proinflammatory GDF-1 and IL-6.

These data support the concept that anti-TNF- α agents can directly promote the function of immunosuppressive cell populations, such as regulatory T cells (T_{regs}). It has been proposed that the infusion of autologous T_{regs} may be an attractive therapeutic option for selected patients with active CD.^{35,36} It has also been suggested that anti-TNF- α agents act partially by increasing the number and promoting the function of T_{regs} . In this respect, Guidi et al³⁷ have recently shown that anti-TNF- α therapy increased the number of peripheral regulatory CD4⁺CD25⁺FOXP3⁺ T cells in patients responding to treatment, but not in nonresponders. T_{regs} are likely to contribute to sustained clinical remission following anti-TNF- α therapy, as it has been observed that the loss of response to anti-TNF- α agents is associated with a decrease in the percentage of FoxP3⁺ T cells.³⁸

The exact mechanisms linking anti-TNF- α agents to T_{regs} are poorly defined. The data available so far are often conflicting and limited mainly to the clinical setting of rheumatoid arthritis and psoriasis.³⁹ On the one hand, anti-TNF- α therapy in rheumatoid arthritis was associated with reduced apoptosis of T_{regs} .⁴⁰ On the other hand, however, a clear suppressive effect of anti-TNF- α therapy on FoxP3⁺ T_{regs} was shown.^{39,41} Therefore, further studies focused precisely on IBD are

needed to explore the nature of interactions between anti-TNF- α and T_{regs} .

The role of Fc receptors

As indicated earlier, Fc receptors are important for the action of anti-TNF- α antibodies through their involvement in ADCC and CDC. While this aspect may be important for IFX, ADA, and GOL, it does not apply to CER, which is registered for use in CD but does not contain the Fc fragment and is incapable of inducing such reactions.³ This raises a question of the real clinical significance of Fc-mediated pathways.

A recent study by McRae et al⁴² has shed new light on this issue. The authors have modified an IgG2c anti-TNF- α antibody, which normally binds with high affinity to the Fc receptors, and generated an IgG1 isotype antibody with greatly diminished binding capacity. Then, the therapeutic efficacy of both antibodies was compared in murine models of IBD and arthritis. It turned out that both antibodies were similarly effective in reducing collagen-induced arthritis. However, only IgG2c antibody exerted anti-inflammatory effects in T-cell transfer-induced colitis, which suggested that Fc receptor-mediated responses were essential for the therapeutic effect. This observation is to some extent in line with the clinical data showing that CD patients treated with CER are less likely to achieve mucosal healing when compared with IFX or ADA.⁴³ Moreover, clinical remission rates induced by CER appear to be less convincing than those for IFX and ADA.⁴⁴ Thus, it can be speculated that seemingly weaker anti-inflammatory properties of CER when compared with Fc-containing anti-TNF- α antibodies could be related to its inability to invoke Fc receptor-mediated responses.

The above notion may be supported by genetic studies suggesting the existence of association between a polymorphism in the *IgG Fc γ -receptor IIIa* gene and the therapeutic response to anti-TNF- α agents in CD.^{45,46} By contrast, Wojtal et al⁴⁷ has suggested that the Fc receptor CD64 could be connected to reduced responsiveness to IFX in IBD. The study detected increased expression of interferon γ (IFN- γ) in the inflamed colonic tissue from nonresponders, which could lead to increased transcription of the *CD64* gene. Subsequent binding of IFX-TNF complexes to CD64 can promote transcriptional activation of several proinflammatory mediators, including granulocyte-macrophage colony-stimulating factor, IL-6, and monocyte chemoattractant protein 1. It is not clear, however, whether this is a cause or a consequence of unresponsiveness to IFX.⁴⁷ Nevertheless, it is reasonable to hypothesize that the upregulation of some types of Fc receptors is linked to decreased efficacy of anti-TNF- α therapy in a proportion of IBD patients.

The role of endothelial cells

Immune-mediated angiogenesis and increased vascular permeability are crucial phenomena in IBD, since they enable

recruitment of proinflammatory cells from bloodstream to the site of disease.⁴⁸ Moreover, vascular endothelial cells (ECs) serve as a potent source of cytokines engaged in a complex crosstalk between innate and adaptive immunity in the intestines.^{48,49} It has been shown that anti-TNF- α agents have a significant impact on these processes. It has been observed that an early decrease in lymphocyte infiltration after administration of TNF- α blockers in patients with rheumatoid arthritis and psoriasis is related to downregulation of adhesion molecules on ECs and immune cells rather than to an increase in lymphocyte clearance via apoptosis.⁵ Several studies have also detected the alterations in serum levels of angiogenesis-regulating peptides following anti-TNF- α therapy.⁴⁸⁻⁵⁰ Moreover, we have demonstrated that initial serum levels of vascular endothelial growth factor (VEGF) in patients with CD may be of predictive value for response to anti-TNF- α treatment.⁵⁰ In this respect, Rutella et al⁵¹ have analyzed the release of VEGF by cultured mucosal extracts obtained from patients with CD before and after IFX administration, as well as by cultured human intestinal fibroblasts stimulated with TNF- α in the presence or absence of IFX. They showed that IFX decreased both the mucosal angiogenesis and VEGF production by human intestinal fibroblasts. Moreover, the administration of IFX prevented the VEGF-dependent migration of intestinal microvascular EC in vitro.

These observations support the view that anti-inflammatory properties of anti-TNF- α agents are at least partly related to their effects on ECs. An intriguing observation has recently been reported by Prattichizzo et al.⁵² Analyzing the effect of ADA on senescence of ECs, they have noticed that although inhibition of TNF- α activity by ADA did not delay replicative cell senescence, it did reduce an augmented IL-6 release that is typically associated with the senescent phenotype. The mechanism of this effect is unclear and these observations need to be verified, as ECs have not been typically viewed as a major source of TNF- α .

Understanding the mechanisms of action of anti-tumor necrosis factor α antagonists: clinical implications By identifying mechanisms triggered by anti-TNF- α agents, it has become important to understand how this knowledge impacts on clinical practice.

Firstly, it was possible to explain why not all TNF- α antagonists were effective in IBD. In this respect, the ability to bind tmTNF seems to be of importance, while the significance of sTNF- α neutralization remains unclear.^{3,5} Intriguingly, we have recently shown that the levels of serum sTNF- α can even significantly increase during successful therapy with IFX and ADA in CD.⁵³

Another implication of basic research is that it can be helpful in predicting clinical response to therapy. By using confocal laser endomicroscopy, Atreya et al⁵⁴ detected a correlation between high numbers of tmTNF-positive cells in the mucosa

of CD patients and better short-term outcomes of anti-TNF- α treatment. Moreover, this clinical response was sustained over 1 year and associated with mucosal healing as assessed by endoscopy. On the other hand, we have found that patients with the greatest increase in sTNF- α over the course of the induction anti-TNF- α therapy were significantly more likely to experience a successful long-term response to treatment.⁵⁴

Although anti-TNF- α antibodies seem to have an acceptable safety profile, possible side effects are still a matter of concern.⁵⁵ The most common adverse events are infections (eg, tuberculosis). An increased risk for these complications is usually attributed to a loss of normal TNF- α functions in host defense.⁵⁵ There are also conflicting reports on the increase in the frequency of several malignancies (skin melanoma, non-melanoma skin cancer, lymphoma). It is thought, however, that this risk may be related to the concomitant use of immunosuppressants rather than to the anti-TNF- α therapy itself.^{55,56} Nevertheless, an increased vigilance for the occurrence of such complications is warranted. Another important adverse effect, an infusion allergic reaction, is linked to the murine component of IFX antibody.⁵

From the pathophysiological point of view, the most intriguing adverse effect is the development of other inflammatory conditions, such as anti-TNF-induced psoriasis, lupus, autoimmune hepatitis, or vasculitis.^{55,57,58} Since these events develop in the course of therapy with the most potent anti-inflammatory drugs, this phenomenon is called a paradoxical inflammation. Data on paradoxical psoriasis, which is the most common adverse event in this group, suggest that the inhibition of TNF- α stimulates uncontrolled secretion of INF- γ by plasmacytoid dendritic cells, which is followed by the recruitment of T cells and the production of IL-12 and IL-23, which initiate the proinflammatory cascade in the skin.⁵⁸ Stopping anti-TNF- α therapy and adding another immunosuppressant (eg, methotrexate or cyclosporin) or an antibody against IL-12 and IL-23 (ustekinumab) can usually dampen the drug-induced inflammation, although there are also cases of paradoxical anti-TNF-driven psoriasis that are resistant to this therapy.⁵⁸

Conclusions The prevalence of IBD and hospitalization rate for both UC and CD are still increasing.⁵⁹ That is why, there is a need to use potent anti-inflammatory drugs, with known and predictable clinical efficacy and acceptable safety profile, in order to prevent gastrointestinal damage and other metabolic complications of uncontrolled inflammation in the course of the disease.⁶⁰ There is a growing body of evidence that anti-TNF- α agents have the strongest potential to heal the gastrointestinal tract in IBD. Although our understanding of the mechanisms underlying anti-TNF- α blockade has significantly increased, there are still many important questions to be answered. In this review, we have highlighted some

issues that relate to biochemical and structural properties of anti-TNF- α agents to their target cells and clinical efficacy. Several other clinical implications, such as predicting therapeutic outcomes or explaining surprising adverse events, have been also presented. This line of investigation may help elucidate the discrepancies in clinical response to anti-TNF- α agents between different patients. The current trend of individualized anti-TNF- α therapy based on drug TLs and the appearance of drug-neutralizing antibodies may provide valuable data on how pharmacokinetics impacts on molecular pathways.^{6,74} Such a back-translational approach will hopefully allow clinicians to use this class of drugs more effectively and safely in patients with IBD.

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Mechanizmy działania przeciwciał przeciwko TNF- α w nieswoistych zapaleniach jelit i ich implikacje kliniczne – aktualny stan wiedzy

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SŁOWA KLUCZOWE

komórki
regulatorowe T,
makrofagi, nieswoiste
zapalenia jelit,
przeciwciała
przeciwko TNF- α ,
receptory Fc

STRESZCZENIE

Mechanizmy działania przeciwciał neutralizujących czynnik martwicy nowotworów α (*antitumor necrosis factor α* – anty-TNF- α), stosowanych w terapii nieswoistych zapaleń jelit, nie są w pełni poznane. Kluczowe znaczenie może mieć wiązanie błonowej formy TNF- α , które skutkuje aktywacją szeregu mechanizmów, takich jak kaskada układu dopełniacza, reakcje cytotoksyczności zależnej od przeciwciał czy procesów odwrotnej sygnalizacji komórkowej. Niemniej jednak procesy te nie tłumaczą w pełni różnorodnej odpowiedzi klinicznej na terapię anty-TNF- α u poszczególnych pacjentów. Celem niniejszej pracy jest przedstawienie aktualnego miejsca przeciwciał anty-TNF- α w algorytmach terapeutycznych nieswoistych zapaleń jelit, a także stanu wiedzy dotyczącego mechanizmów działania tej grupy leków, ze szczególnym uwzględnieniem mniej znanych aspektów molekularnych blokady anty-TNF- α . Omówiono złożoną rolę poszczególnych subpopulacji makrofagów, regulatorowych komórek T oraz komórek śródbłonki naczyń przewodu pokarmowego, a także zaprezentowano nowe dane na temat znaczenia procesów aktywowanych przez fragment Fc przeciwciał anty-TNF- α w indukowaniu odpowiedzi przeciwzapalnej.

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