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Review Article

Treatment with biologics of patients with inflammatory joint diseases

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Abstract

Over the past two decades, biologics (Bs) have been widely used in the treatment of patients with inflammatory joint diseases (IJD). The treatment of IJD aims at reducing disease progression, improving patients' physical health and well-being, and achieving long-lasting remission or, at least, minimal disease activity. The introduction of Bs in rheumatology practice has significantly improved patients' outcomes and prognosis. Their use, however, involves undertaking significant risks and challenges for both patients and medical teams.

The purpose of this article is to provide a brief overview of the biological therapies currently approved for this group of diseases in Bulgaria and the indications for administration and monitoring of the most common side effects. The optimal administration of Bs is determined by treatment efficacy, discussion of benefits and risks, prevention of the possible development of severe adverse effects, administration regimens, and routes of administration of Bs. The analysis of major issues during treatment helps summarize the information on the use of Bs, thus increasing the possibility of managing the risks associated with their use by strengthening the engagement of healthcare experts and patients in the process of monitoring the impact of biological agents.

Keywords

biological agents, inflammatory joint diseases, adverse effects

Introduction

Over the past three decades, biologics (Bs) have been widely used in the treatment of patients with inflammatory joint diseases (IJD). The term 'inflammatory joint diseases' comprises a spectrum of heterogeneous disorders, the most common of which are rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). The advent of immunomodulatory biologic therapies has revolutionized the management of these diseases by improving their prognosis, especially for patients who have not responded sufficiently to conventional disease-modifying antirheumatic drugs (DMARDs). (Jethwa and Abraham 2018a). The European League Against Rheumatism (EULAR) has developed recommendations for the management of these diseases (Ramiro et al. 2022; Gossec et al. 2023; Smolen et al. 2023).

Biologic agents (BAs) or treatments, also known as biologics (BPs), biologic therapies (BTs), or biologic disease-modifying antirheumatic drugs (bDMARDs), are proteins derived from human genes and specifically designed to target specific molecules (Findeisen et al. 2021).

BPs are large molecules produced in living cells and are administered by self-injection using a prefilled pen or autoinjector or by intravenous (IV) infusion. Since the 2000s, the use of BPs has become the standard of care for various rheumatic conditions due to their high efficacy (Curtis and Singh 2011). As more agents have become available on the market, the extent of their use in clinical practice has visibly increased over the years (Li et al. 2023). The effects of different BPs target different parts of the immune system. For example, tumor necrosis factor (TNF) inhibitors block an inflammatory protein called TNF, while other drugs block pro-inflammatory B cells or T cells. However, like all DMARDs, they suppress the activity of the immune system and can increase the risk of serious infections and cancer (Rath 2022).

Biological agents are prescribed as second-line therapy if previous conventional therapies h ave been ineffective or in the event of drug intolerance (Smolen et al. 2014). The process of their preparation and administration is fully supervised by a specialized rheumatology team. In patients with IJD on immunosuppressive therapy, the most significant risk is infection, which is why recommendations are proposed to minimize this risk (Furer et al. 2020). Biological therapy begins with screening for infection, malignancy, tuberculosis (TB), and virologic testing (hepatitis B, C, and HIV). Screening blood tests for a complete blood count (FBC), a comprehensive metabolic panel with liver function tests (LFTs), and lipids are also required. Prior to using biological agents, EULAR guidelines recommend implementing an individual vaccination program for patients prior to the use of biological agents in accordance with national guidelines. In addition, a comprehensive, detailed analysis of the patient's medical history is recommended, along with a physical examination, with particular attention focused on the cardiovascular, gastrointestinal, and neurological systems. Patients may switch from one BP to another if the goals of the treatment are not achieved or in the event of side effects from the ongoing therapy (Jethwa and Abraham 2018b). Although current consensuses oppose the use of live and live-attenuated vaccinations (varicella-zoster, measles-mumps-rubella, yellow fever) during biological therapy, they do advise routine influenza and pneumococcal vaccination in individuals who are at high risk. (Emer et al. 2010).

Increasing experience in the use of BS allows for the reporting of a greater number of potential treatment-related adverse effects. The most common adverse effects are related to skin reactions. These complications may include injection-site responses, skin infections, immune-mediated complications such as psoriasis and lupus-like syndrome, and, in rare cases, skin cancer (Mocci et al. 2013). Various authors, such as Andrea (2012), mention several common infections, such as bronchitis and pneumonia, pyelonephritis, joint inflammation, and other skin or soft tissue infections (Andrea 2012).

There are different classes of bDMARDs approved for the treatment of IJD. Currently, not all types of biological therapies are approved for use in Bulgaria (Table 1):

1. Tumor necrosis factor alpha (anti-TNF) inhibitors
2. Interleukin inhibitors (anti-IL)
3. B-cell-directed therapy
4. T-cell costimulation blocker

1. Tumor necrosis factor-α inhibitors (etanercept, adalimumab, infliximab, certolizumab pegol, and golimumab)

Tumor necrosis factor α (TNFα) is a pleiotropic proinflammatory cytokine that plays an important role in the pathogenesis of systemic inflammation and determines tissue damage (Jang et al. 2021). Treatment with inhibitors of tumor necrosis factor alpha (anti-TNF) blocks the action of a protein called tumor necrosis factor (TNF), which is at high levels in inflammatory arthritis, and thus reduces the extent of the inflammation (Aaltonen et al. 2021). Structurally, TNF-α is a homotrimeric protein consisting of 157 amino acids and is mainly produced by activated macrophages, T lymphocytes, and natural killer cells (Horiuchi et al. 2010).

Table 1. Biologics.

BIOLOGICAL AGENTS			
Mechanism of action/type	**Agent**		**Available in Bulgaria**
1. Tumor necrosis factor alpha (Anti-	Etanercept		Yes
	Infliximab		Yes
	Certolizumab pegol		Yes
	Golimumab		Yes
2. Interleukin inhibitors (Anti-IL)	(IL-1) Anakinra		No
	(IL-6)	Tocilizumab	Yes
		Sarilumab	No
	(IL-12 /23Ustekinumab		Yes
	(IL-17)	Ixekizumab	Yes
		Secukinumab	Yes
	(IL-23)	Guselkumab	Yes
		Risankizumab	Yes
3. B-cell-directed therapy (B-cell inhibitor) Anti- CD20	(Anti -B-Ly) Rituximab		Yes
4. T-cell costimulation blocker (Inhibitor, CD80/86) Anti- CD28	Abatacept		No

The TNF superfamily consists of more than 35 specific ligand-receptor pairs that play a major role in mammalian biology (Locksley et al. 2001). The primary mechanism of action of TNF inhibitors is to block the binding of soluble and membrane TNF to their receptors. TNF inhibitors neutralize TNF by recognizing antigenic epitopes in the TNF ectodomain near or in the receptor-binding region, thereby preventing their interaction with TNF-α receptors (Rigby 2007).

Etanercept

Etanercept is a recombinant human dimeric fusion protein consisting of the Fc portion of human IgG1 and the extracellular (binding) portion of the TNF-α receptor. (Mease et al. 2000; Emery et al. 2008; Weinblatt et al. 2008). Etanercept inhibits the binding of TNF to its cell surface receptor (Nash and Florin 2005). Etanercept is a receptor-based therapeutic that binds directly to the receptor-binding region, which is formed by the interaction of two adjacent subunits in the TNF trimer. Without TNF binding to its receptor, the signaling cascade resulting in inflammation is silenced, thereby blocking the inflammatory responses (Keystone et al. 2010).

It is used to treat plaque psoriasis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or polyarticular juvenile idiopathic arthritis.

Adalimumab

Adalimumab is the first fully human recombinant monoclonal antibody against TNF-α (Hochberg et al. 2003; Keystone et al. 2004; Mease et al. 2005).

Adalimumab is used to treat various autoimmune conditions such as rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, uveitis, Crohn's disease, and ulcerative colitis (Ellis and Azmat 2023).

Infliximab

Infliximab is a chimeric monoclonal antibody consisting of a murine variable region and a human immunoglobulin constant region (Scallon et al. 1995). Infliximab is a purified recombinant DNA-derived chimeric IgG monoclonal antibody protein that inhibits tumor necrosis factor-alpha (TNF-α) (Akiho et al. 2015). Infliximab binds both free and transmembrane TNF-α molecules and interferes with its pro-inflammatory activity (Diamantis and Lebwohl 2007).

It is used to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel disease (Crohn's disease and ulcerative colitis).

Certolizumab pegol

Certolizumab pegol is a pegylated Fab fragment of a humanized monoclonal antibody that selectively targets and neutralizes tumor necrosis factor-α (TNF-α) (Aaltonen et al. 2012). The Fab' fragment was engineered with a single hinge region free-cysteine residue, which enables site-specific attachment of polyethylene glycol (PEG) without affecting the ability of the Fab' fragment to bind and neutralize TNF (Taylor 2015).

It is used for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis, and Crohn's disease.

Golimumab

Golimumab is a recombinant human monoclonal antibody-inhibitor of TNFα that binds human TNF-α soluble and transmembrane structures and blocks its binding to the corresponding TNF-α receptors (Padda et al. 2023). It is used to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and polyarticular juvenile idiopathic arthritis.

The following adverse effects have been observed during the administration of anti-TNF drugs:

- at the injection site: pain, swelling, itching, or redness
- general adverse reactions: flu-like symptoms: headache, runny nose, sneezing, nasopharyngitis

Serious side effects of anti-TNF drugs include:

- Manifestation of an allergic reaction: difficulty breathing or swelling of the face, lips, tongue, or throat.
- Bacterial, viral, fungal, and other infections, including tuberculosis (TB), and infections due to opportunistic pathogens causing fever, chills, coughing, sweating, body aches, and skin rash or redness, diarrhea, burning sensation during urination, coughing up blood, or feeling very tired or short of breath.

Possible adverse effects during infusion: (less than 24 hours after infusion) fever, chest pain, palpitations, sweating, nausea, redness, itching, changes in blood pressure, and difficulty breathing.

Heart failure may occur or worsen in patients who receive TNF blockers.

2. Interleukin inhibitors (anti-IL)

Interleukin-1 (anakinra)

IL-1 is the first well-described proinflammatory cytokine. Anakinra interleukin-1 (IL-1) is a receptor antagonist that blocks the biological activity of IL-1. Anakinra is the recombinant form of the naturally occurring IL-1Ra, a counterregulatory cytokine, whoses levels increase in an acute-phase fashion in response to IL-1 production and compete with IL-1b for binding to type I IL-1 receptors. Anakinra is recommended for the treatment of active rheumatoid arthritis (RA) after adequate treatment with non-biologic DMARDs (Cush et al. 2023). The most common side effects observed are injection site reactions, headaches, muscle pain, and stiffness.

Interleukin-6 (IL-6) is a cytokine that plays a crucial role in causing severe inflammation associated with inflammatory arthritis and is involved in the pathogenesis of autoimmune diseases. Treatment with interleukin

inhibitors (anti-IL) works by neutralizing the activity of certain interleukins, thus reducing the amount of excessive inflammation in the body and joints.

Interleukin-6 (tocilizumab) is a humanized monoclonal antibody against the IL-6 receptor. It is used to treat RA in combination with methotrexate or as monotherapy in patients with insufficient response to treatment with csDMARDs or TNF-α inhibitors (Kremer et al. 2011) and giant cell arteritis in adults, as well as for pediatric treatment of polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis. Although tocilizumab is not indicated by the United States Food and Drug Administration (US FDA), it is used for the treatment of COVID-19 pneumonia (Preuss and Anjum 2022).

Interleukin-6 (IL-6) Sarilumab is a fully human monoclonal antibody directed against both soluble and membrane-bound IL-6 receptors α (anti-IL-6Rα) that binds and blocks interleukin-6. Sarilumab is used to treat rheumatoid arthritis after other DMARDs have been used (Mother to Baby, Organization of Teratology Information Specialists, 2023). It is currently not approved or available for use in Bulgaria.

Biological products directed against the p40 subunit of IL-12/23

Interleukin 12 (IL-12) and IL-23 belong to the IL-12 cytokine family and play a central role in T cell-mediated responses to inflammation (Teng et al. 2011). IL-12 and IL-23 are heterodimeric cytokines that are secreted by dendritic cells and macrophages and share a binding protein called p40 (Lupardus and Garcia 2008).

Ustekinumab is a fully humanized IgG1κ monoclonal antibody that targets IL-12 and IL-23. It binds to them, thus preventing the interaction between them and cell receptors, as well as the differentiation of T cells to Th1 and Th17 and the secretion of proinflammatory cytokines (Krueger et al. 2007). Ustekinumab is licensed for use in patients with plaque psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease (Colquhoun and Kemp 2023).

IL-17 inhibitors (IL-17i)

Interleukin 17 inhibitors (Ixekizumab, Secukinumab) are used successfully in the biological treatment of psoriasis, PsA, AS, and RA, but at the same time mediate the immune response against bacteria and fungi. The appearance of a paradoxical effect is possible—exacerbation or the appearance of a disease that should have been cured by this medicine. Other adverse effects are upper respiratory tract infections, including candidiasis, oral herpes, headaches, neutropenia, and diarrhea (Tiburca et al. 2022).

Ixekizumab is a humanized IgG4 monoclonal antibody that selectively binds to interleukin 17A (IL-17A), thus inhibiting its interaction with the IL-17 receptor (Miller et al. 2022). The most common adverse drug reactions (ADRs) are neutropenia, candidiasis, bronchitis, nasopharyngitis, sinusitis, pain, and redness at the injection site.

Secukinumab is a human monoclonal antibody that blocks IL-17A IgG1. ADRs that have been reported include neutropenia, candidiasis, nasopharyngitis, upper respiratory tract infections, inflammatory bowel disease (Crohn's disease), headache, and diarrhea (Gordon et al. 2016; Papp et al. 2016).

Interleukin 23 (IL-23)

Interleukin-23 (IL-23), a member of the IL-12 cytokine family, is a heterodimeric cytokine that is composed of the IL-12p40 subunit and a novel p19 subunit (Kleinschek et al. 2006). Interleukin-23 is mainly secreted by activated macrophages and dendritic cells (DCs) located in peripheral tissues (skin, intestinal mucosa, and lung) as a disulfide-linked complex with the polypeptide p19-binding protein p40. (Tang et al. 2012). Interleukin 23 (IL-23) inhibitors are a type of biologic drug that is used for moderate to severe psoriasis, psoriatic arthritis, and inflammatory bowel disease.

Types of IL-23 inhibitors approved in Bulgaria:

1. Guselkumab is a human immunoglobulin G1 λ (IgG1λ) monoclonal antibody (mAb) that blocks the action of interleukin-23 (IL-23) on its receptor (Reich et al. 2019). It is indicated for the treatment of plaque psoriasis and psoriatic arthritis. The most common ADRs observed are: nasopharyngitis, upper respiratory tract infections, injection site erythema, headache, arthralgia, pruritus, and back pain (Trifunova and Ilchovska 2022).
2. Risankizumab is a humanized immunoglobulin G1 (IgGl) monoclonal antibody selective for the interleukin (IL)-23 protein. It is indicated for plaque psoriasis, psoriatic arthritis, and Crohn's disease. The most common ADRs caused by this drug are upper respiratory tract infections, headaches, arthralgia, diarrhea, injection site reactions such as redness, swelling, pain, and pruritus, low red blood cell count (anemia), fever, back pain, urinary tract infection, and fungal infections (Bachelez et al. 2019).

3. B-cell therapy

Anti-B-Ly (Rituximab)

In inflammatory arthritis, B-cell therapy reduces inflammation, discomfort, and swelling by inhibiting the activity of B-cells.

Rituximab is a human/murine chimeric anti-CD20 monoclonal antibody targeting B lymphocyte antigen CD20. It is used to treat patients with rheumatoid arthritis who have shown an inadequate response to treatment with at least one TNF-α inhibitor (Keystone et al. 2009), as well as for some hematological diseases: non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), granulomatosis with polyangiitis (GPA) or Wegener's granulomatosis, and pemphigus vulgaris (PV) (Hanif and Anwer 2022). Possible reactions to the infusion (the first 2 hours of the first infusion): fever, chills and shivering or pain at the infusion site, blistering, pruritus, nausea, fatigue, headache, difficulty breathing, swelling of the tongue or throat, runny nose, vomiting, skin

redness or palpitations, heart attack, or low platelet count. Other possible adverse effects include infections, e.g., pneumonia (bacterial); and urinary tract infections.

4. T-cell costimulation blocker

Abatacept (CTLA4Ig) is a recombinant fusion protein of the extracellular domain of human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) linked to a modified Fc of human immunoglobulin 1 (IgG1) (Dubois and Cohen 2009). T-cell therapy reduces inflammation by preventing T-cells from interacting with one another. These are selective inhibitors of T-cell activation by binding to CD80 and CD86. Abatacept is used to treat rheumatoid arthritis, psoriatic arthritis, and polyarticular juvenile idiopathic arthritis. Abatacept is used in combination with methotrexate in patients with rheumatoid arthritis who have had an inadequate response or intolerance to other DMARDs, including methotrexate (MTX) or a TNF-alpha inhibitor.

Drugs from this group are not currently available in Bulgaria.

Conclusion

Despite their potential risks, the benefits of BAs for patients with IJD have been demonstrated for more than 20 years of use. Bs are a reliable therapeutic alternative for patients who have not responded to traditional medication treatment. The safety profile of different biological products shows no significant difference between them, which helps in the monitoring and management of IJD. The modern approach to preventing adverse effects calls for an individual risk assessment of the administration of BAs, depending on the health condition and characteristics of each patient. The selection, administration, and monitoring of the effects of BAs use in practice entirely depend on the competency of medical professionals, which highlights the need for dissemination and greater awareness of the guidelines for safety assessment and monitoring during biological therapy.

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Conflict of interests

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