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BIOLOGIC THERAPY IN CROHN'S DISEASE: MECHANISMS, TREATMENT OPTIONS AND ADVERSE EFFECTS

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ABSTRACT

Background and aim: Crohn's disease (CD) is a chronic inflammatory bowel disease that can involve any segment of the gastrointestinal tract. It is characterized by a relapsing-remitting clinical course, significantly impairing patients' daily functioning and quality of life. This article reviews the current evidence on biologic therapies for CD and discusses their practical application in primary care settings.
Material and methods: This study was based on an analysis of the guidelines issued by the Polish Society of Gastroenterology and the National Consultant in Gastroenterology, along with the updated B.32 drug program (effective February 2024). Additionally, a systematic review of available scientific literature from the PubMed database was conducted. The article selection process utilized the following search terms: "Crohn's disease," "biological treatment," and "Crohn's disease treatment."
Results: The treatment of Crohn's disease is chronic and initially relies on conventional therapies, including glucocorticosteroids and immunosuppressants. In moderate-to-severe cases, biological medicines are introduced. Currently, five biologic drugs are approved for use in Poland: infliximab, adalimumab, vedolizumab, ustekinumab, and upadacitinib—the first oral biologic approved for CD treatment. Further research is needed to treat Crohn's disease patients more effectively.
Conclusions: The rapid advancement of biologic therapies has significantly improved disease control, reduced reliance on steroids, and enhanced patient outcomes. For primary care physicians, recognizing the typical adverse effects of biologics and differentiating them from CD exacerbations is essential for effective management.

KEYWORDS

Crohn's Disease, Inflammatory Bowel Disease, Biologic Therapy, Quality of Life, Clinical Remission

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Introduction

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract with a steadily increasing worldwide prevalence [1]. According to Ministry of Health data, 22,937 patients in Poland received healthcare services for Crohn's disease between January and October 2021 [2].

The etiology of Crohn's disease remains incompletely understood. Current evidence suggests that both environmental factors and genetic predisposition contribute to disease pathogenesis [3]. The inflammatory lesions predominantly affect the terminal ileum and colon, though any segment of the gastrointestinal tract may be involved. The pathological process originates in the mucosa and may progressively extend transmurally. Disease complications include fistulae, strictures, and abscess formation. Cardinal clinical features typically present as chronic diarrhea, abdominal pain, involuntary weight loss, and associated gastrointestinal symptoms including nausea and emesis. Systemic symptoms such as fever and chills may also occur. CD should be particularly considered in the differential diagnosis of young adults, as the first incidence peak occurs between 16-30 years of age, with a second smaller peak around 50 years [3,4]. Approximately 20-30% of patients develop extraintestinal manifestations, most frequently affecting the joints, skin, biliary tract, and eyes [5].

Notably, no single diagnostic criterion or pathognomonic sign exists for Crohn's disease. Diagnosis requires comprehensive evaluation of clinical presentation combined with laboratory, endoscopic, histopathological, and radiological findings [6,7]. As CD is a progressive condition, early diagnosis and appropriate treatment are essential to prevent irreversible gastrointestinal damage, complications, and disability [8]. The prognosis for complete cure remains poor, with at least 50% of patients eventually requiring surgical intervention. Poor prognostic factors include early disease onset, stricturing or fistulizing phenotype, extensive intestinal involvement, and tobacco use [6].

Recent decades have witnessed substantial therapeutic advances in CD management, primarily through the development of biologic therapies enabled by progress in medical biotechnology [9]. Biologic drugs have revolutionized treatment by inducing remission in patients with moderate-to-severe disease refractory to conventional therapies.

Review Methods

This study was based on an analysis of the guidelines issued by the Polish Society of Gastroenterology and the National Consultant in Gastroenterology, along with the updated B.32 drug program (effective February 2024). Additionally, a systematic review of available scientific literature from the PubMed database was conducted. The article selection process utilized the following search terms: "Crohn's disease," "biological treatment," and "Crohn's disease treatment."

Table 1. Diagnostic tests performed for eligibility for treatment in the drug program for Crohn's disease.

Tests performed for classification for treatment
1) Peripheral blood morphology; 2) Alanine aminotransferase; 3) Aspartate aminotransferase; 4) Creatinine; 5) C-reactive protein; 6) General urine test; 7) Quantiferon test; 8) HBs antigen; 9) Anti-HCV antibodies; 10) HIV antigenvirus (HIV Ag/Ab Combo); 11) Serum electrolyte concentration; 12) Chest X-ray (up to a maximum of 3 months prior to eligibility); 13) ECG with description (required in adult patients only); 14) Calculation of CDAI in patients over 18 years of age or PCDAI in children; 15) Anti-HBctotal.

Źródło: [14]

Biologic Drugs Used in Crohn's Disease

Until 2024, four main active agents were used in the treatment of Crohn's disease in Poland: infliximab, adalimumab, vedolizumab and ustekinumab. The recent inclusion of upadacitinib in the reimbursement scheme has expanded the available treatment options, representing a significant advancement in the management of this condition [10].

Infliximab and adalimumab are monoclonal antibodies of the IgG1 class that exert their therapeutic effect by inhibiting tumor necrosis factor-alpha (TNF-α), a key mediator of inflammation. As a chimeric antibody, infliximab contains both murine and human components, which increases its immunogenic potential. Consequently, combination therapy with immunosuppressants (azathioprine or mercaptopurine) is often required to prevent the formation of neutralizing antibodies and maintain therapeutic efficacy [11].

Vedolizumab, a humanized monoclonal antibody, targets the α4β7 integrin, thereby inhibiting lymphocyte migration to intestinal tissues. By blocking this gut-specific homing mechanism, vedolizumab selectively reduces the recruitment of immune cells to sites of inflammation.

Ustekinumab exerts its therapeutic effect through binding to the p40 subunit common to both interleukin-12 (IL-12) and interleukin-23 (IL-23), thereby inhibiting their pro-inflammatory activity in immune pathways [6].

Upadacitinib, representing the most recent therapeutic advance, belongs to a distinct pharmacological class as a selective, reversible Janus kinase (JAK) inhibitor. This small-molecule agent may be administered either as monotherapy or in combination with methotrexate [11,12]. Notably, upadacitinib holds distinction as the first orally administered biologic approved for Crohn's disease, potentially offering significant treatment convenience for select patient populations [12].

Table 2. Trade names of biologic drugs used in Crohn's disease.

Infliksymab	Adalimumab	Ustekinumab	Wedolizumab	Upadacytynib
Flixabi Remsima Zessly	Amgevita Yuflyma Hyrimoz Idacio	Stelara	Entyvio	Rinvoq

Źródło: [14]

Crohn's Disease Treatment Program

In Poland, biologic therapy for Crohn's disease is administered exclusively at designated specialist centers, typically through a drug program funded by the National Health Fund. This program is restricted to patients meeting specific clinical criteria, with detailed protocols - including eligibility requirements, necessary diagnostic and monitoring procedures, dosing regimens, and discontinuation criteria - outlined in official Ministry of Health documents.

A significant revision to the therapeutic program was implemented on January 1, 2022, most notably eliminating previous duration limitations (previously set at one or two years). This modification enables more flexible, individualized treatment approaches based on patients' clinical needs [13].

Further program modifications were implemented in 2024, expanding the indications for biologic therapy and incorporating novel therapeutic agents - including upadacitinib - thereby enabling more personalized treatment strategies and broadening the spectrum of available therapeutic options [10].

A. Eligibility Criteria for Treatment Under the Program

Patients with confirmed active Crohn's disease of moderate-to-severe intensity qualify for inclusion in the therapeutic program. Disease severity assessment requires the use of validated clinical indices: the Crohn's Disease Activity Index (CDAI) for adult patients and the Pediatric Crohn's Disease Activity Index (PCDAI) for children aged 6-18 years. Initiation of therapy mandates exceeding established threshold scores: >220 points on the CDAI scale and ≥30 points on the PCDAI. An essential inclusion criterion is documented treatment failure with conventional therapies (corticosteroids and/or immunosuppressants) or the presence of contraindications/intolerance to these agents.

For pediatric and adolescent populations (ages 6-18), only two biologic agents - infliximab and adalimumab - are approved. Other therapeutic options (vedolizumab, ustekinumab, and upadacitinib) are exclusively indicated for adult patients (≥18 years). Ustekinumab therapy requires prior treatment failure with TNF-α inhibitors or documented contraindications/intolerance to anti-TNF agents. Similar restrictions apply to patients with perianal fistulas, where vedolizumab and ustekinumab may only be considered following unsuccessful anti-TNF therapy.

Infliximab and adalimumab may be administered to patients with fistulizing disease irrespective of CDAI scores. The program also permits treatment continuation for patients who have undergone small bowel resection, regardless of current disease activity.

Program enrollment requires comprehensive diagnostic evaluation to assess health status and identify potential contraindications. Mandatory screening includes testing for active infections (tuberculosis, HIV, HBV, and HCV) and anti-HBc antibody assessment. Additionally, recent chest radiography (obtained within three months prior to qualification) must be available. Identification of any significant safety concerns constitutes grounds for exclusion from biologic therapy under the program [14].

B. Exclusion Criteria from the Program

Prior to initiating biologic therapy, a thorough assessment must confirm the absence of contraindications that could compromise patient safety or treatment efficacy. Identification of any such exclusionary factor precludes program enrollment.

The main contraindications include hypersensitivity to any of the preparations used in the program, active infections - viral, bacterial or fungal - with a severe course, as well as serious comorbidities. This includes, in particular, cardiopulmonary insufficiency (e.g., moderate or severe heart failure, chronic obstructive pulmonary disease), renal and liver dysfunction of significant severity, and neurological diseases such as demyelinating syndrome or other symptoms suggestive of it. Exclusion criteria also include alcohol dependence and its complications, including toxic liver damage, and any progressive liver disease regardless

of etiology. Another major limitation is a diagnosis of malignant neoplasm within the last five years preceding eligibility for the program. Exceptions include cervical cancer in situ and skin cancers other than melanoma.

Furthermore, patients experiencing Crohn's disease complications necessitating therapeutic strategy modification - particularly those requiring radical surgical intervention - are excluded from biologic treatment under the program. Notably, surgical management of fistulas, when clinically warranted, may be performed concurrently with biologic therapy.

Particular consideration applies to pregnant and lactating women. While biologics are not standard therapy in this population, the program permits their use in clinically justified cases. Such decisions must be evidence-based, following current clinical guidelines from recognized scientific societies, including the European Crohn's and Colitis Organisation (ECCO) and the Polish Society of Gastroenterology.

Additionally, women of childbearing potential must be counseled regarding the requirement for effective contraception during treatment and for a defined period following therapy cessation. The duration of required contraception varies by agent: six months post-infliximab, five months post-adalimumab, fifteen weeks post-ustekinumab, and eighteen weeks post-vedolizumab. These precautions are implemented to mitigate teratogenic risks and ensure optimal safety for both patients and potential fetuses [14].

C. Laboratory tests in patients with CD on biologic therapy

Laboratory tests play a crucial role in the diagnosis, qualification for biologic therapy (Table 1), and monitoring of Crohn’s disease (CD). In diagnostically challenging cases, the assessment of ASCA (anti-Saccharomyces cerevisiae antibodies) and ANCA (anti-neutrophil cytoplasmic antibodies) can be valuable. A serological profile of ASCA+/ANCA– supports a diagnosis of CD, whereas the reverse (ASCA–/ANCA+) is more indicative of ulcerative colitis [6].

During the active phase of CD, inflammatory changes occur in the gastrointestinal tract. The primary laboratory marker of inflammation is C-reactive protein (CRP); however, its levels do not always correlate with disease activity. Consequently, fecal calprotectin—a more sensitive and specific inflammatory marker—is increasingly utilized, particularly for assessing large intestine involvement, and has become a valuable tool in disease monitoring [15].

It should be noted, however, that calprotectin is not specific to CD. Elevated levels may also occur in ulcerative colitis, infections, diverticulitis, gastrointestinal malignancies, active rheumatic diseases, or with the use of non-steroidal anti-inflammatory drugs (NSAIDs) [16]. Nevertheless, calprotectin testing offers a non-invasive alternative to repeated ileocolonoscopies for evaluating mucosal inflammation, contributing to its growing clinical adoption [17].

Additionally, blood tests often reveal anemia and thrombocytosis (reactive hyperplasia), resulting from chronic inflammation, blood loss, iron malabsorption, and intestinal dysbiosis. Chronic inflammation may also lead to nutrient malabsorption and malnutrition, underscoring the importance of monitoring total protein and albumin levels. Due to the potential coexistence of primary sclerosing cholangitis (PSC)—particularly in colonic CD—regular assessment of cholestasis markers, primarily alkaline phosphatase (ALP), is also recommended [6].

D. Treatment Protocol in the Drug Program

The initial phase of biological treatment for Crohn’s disease (CD) follows an induction regimen. After administering the first remission-inducing doses, the therapeutic response is assessed using the Crohn’s Disease Activity Index (CDAI). If the patient fails to achieve an adequate response during the induction period, continuation of therapy with the same agent and qualification for maintenance treatment is not justified [6].

Each biologic agent has a distinct dosing regimen (see Table 2 for biologic and biosimilar drugs registered in Poland and Table 3 for dosing schedules). Within the drug program, switching to another biologic agent or escalating therapy is permitted in cases of non-response or loss of response. According to the program’s guidelines, biologic drugs may be used for CD treatment as long as a clinical response is maintained [14].

Treatment continuation is evaluated at least once every 12 months using the CDAI [6]. Discontinuation of therapy is warranted in cases of:

- Adverse drug reactions related to the biologic agent,
- Complications requiring alternative specific treatment [11, 12, 18–20].

If clinical remission is achieved with biologic therapy, these agents should be continued as maintenance treatment. Regular monitoring is essential to assess treatment effectiveness and identify potential complications. In cases of secondary loss of response to maintenance therapy, treatment intensification should be initially considered,

followed by potential switching to a biologic agent with a different mechanism of action if needed. Any change of biologic drug requires re-induction therapy according to current clinical guidelines [6].

The measurement of drug concentrations and neutralizing antibodies can aid in therapeutic decision-making. This approach has been most extensively documented for anti-TNF agents. For vedolizumab and ustekinumab therapies, treatment intensification decisions are primarily based on clinical symptoms, typically involving a reduction of the dosing interval. This strategy has been shown to lower the average treatment cost for patients compared to standard dose escalation protocols [21, 22].

Table 3. Biologic treatment regimens in Crohn's disease.

Infliksymab	**Induction therapy:** 5 mg/kg i.v., with subsequent infusions at 5 mg/kg 2 and 6 weeks after the first dose. Lasts 6 weeks. **Maintenance treatment:** 1. infusion of 5 mg/kg i.v. every 8 weeks 2. infusion of 5 mg/kg i.p. if disease symptoms recur
Adalimumab	**Induction therapy:** 160 mg s.c., with 80 mg s.c. 2 weeks after the first dose. Lasts 12 weeks. **Maintenance treatment:** 40 mg every 2 weeks s.c.
Ustekinumab	**Induction therapy:** - ≤ 55kg 260 mg i.v. - >55kg to 85kg 390 mg i.v. - >85 kg 520 mg i.v. Lasts 8 weeks. **Maintenance treatment:** 90 mg i.v. 8 weeks after the i.v. dose, then 90 mg i.v. every 12 weeks thereafter
Wedolizumab	**Induction therapy:** 300 mg i.v., followed at 2 and 6 weeks after the first dose Lasts 10 weeks. **Maintenance treatment:** 300 mg i.v. every 8 weeks

Źródło: [14]

Possible Side Effects of Drugs

Patients enrolled in the drug program receive continuous care at designated therapy centers, where subsequent drug doses are administered. For subcutaneous or oral formulations, medications are dispensed for self-administration at home following proper training. These centers also conduct follow-up evaluations and manage treatment-related complications. However, outside the clinical setting, patients frequently consult primary care physicians or specialist clinics. Consequently, familiarity with the most common adverse effects of biologic therapies remains essential for routine medical practice.

Biologic agents may induce both class-wide adverse effects and substance-specific reactions. The most frequently reported adverse events for subcutaneous formulations include nasopharyngitis, injection-site reactions, headache, arthralgia/myalgia, abdominal discomfort, nausea, and vomiting [11,12,18-20]. Due to the risk of hypersensitivity reactions (including anaphylaxis), patients require post-administration monitoring to ensure early intervention for potential severe reactions. Cutaneous manifestations - particularly psoriasis-like eruptions associated with infliximab therapy - also represent common complications [11].

Biologic therapy increases susceptibility to infections, including tuberculosis and severe systemic infections (e.g., septicemia). While less frequent, potential oncologic risks include non-melanoma skin cancers and lymphoproliferative disorders. Additionally, patients require monitoring for neuropsychiatric manifestations such as mood disorders, insomnia, and depressive symptoms during treatment [11,12,18-20]. TNF-α inhibitors (particularly infliximab and adalimumab) demonstrate higher adverse effect profiles, predominantly infection-related risks encompassing both de novo infections and reactivation of latent viral infections [23].

Hepatotoxicity, characterized by elevated liver enzymes, may develop during biologic therapy. For patients receiving adalimumab, monitoring creatine kinase levels is recommended when reporting muscle

cramps [19]. Additionally, these treatments may induce antinuclear (ANA) and anti-double-stranded DNA (anti-dsDNA) autoantibodies, potentially increasing the risk of drug-induced lupus erythematosus [23].

Newer biologic agents such as vedolizumab and ustekinumab appear to demonstrate a more favorable safety profile compared to TNF-α inhibitors, though their relatively recent introduction limits long-term safety data [24]. The most frequently reported adverse effects for vedolizumab include infectious complications, predominantly rhinosinusitis and pneumonia [18,25]. Initial concerns regarding potential association with progressive multifocal leukoencephalopathy (PML) have been mitigated by post-marketing surveillance - as of 2020, only one confirmed case was documented in a high-risk patient with concurrent HIV infection and prolonged immunosuppressive therapy [26].

The most frequently reported adverse effects of ustekinumab therapy include mild upper respiratory tract infections and transient hypersensitivity reactions, occasionally accompanied by pyrexia [27]. While severe complications are uncommon, the potential for anaphylactic reactions remains clinically relevant [20].

Upadacitinib – the newest oral agent in this class – demonstrates a safety profile comparable to other biologics. However, as a relatively recent therapeutic option, its safety requires ongoing surveillance [28]. Current reports indicate common occurrences of upper respiratory infections, acne, cough, pyrexia, nausea, cephalgia, and neutropenia [12,29,30]. Laboratory abnormalities may include elevated cholesterol levels, hepatobiliary enzyme elevations, increased creatine kinase activity, weight gain, and less frequently, hypertriglyceridemia. Serious infections such as pneumonia, oral candidiasis, and viral reactivations (particularly herpes zoster) have been documented [12,28-31]. Post-marketing reports of non-melanoma skin cancers underscore the need for regular dermatologic monitoring in high-risk patients [12,28].Some patients developed anemia during treatment [28]. All adverse drug reactions should be reported using the official adverse event reporting form available on the Ministry of Health website: https://www.gov.pl/web/zdrowie/zasady-zglaszania-dzialan-niepozadanych. Importantly, both drug hypersensitivity reactions and severe infections constitute criteria for therapy discontinuation under the drug program [14].

Conclusions

The contemporary management of Crohn's disease focuses on achieving well-defined therapeutic targets encompassing both clinical and endoscopic remission. The availability of biologic agents in Poland through the national drug program is essential for attaining these treatment goals. These advanced therapies represent a crucial option for patients who have demonstrated inadequate response to conventional treatments, including immunosuppressants and glucocorticosteroids. Biologic drugs provide an evidence-based therapeutic approach, fully aligned with current medical knowledge and consistent with both national and international guidelines for Crohn's disease management.

Disclosure

Author's contributions:

Conceptualization: Karolina Paks, Monika Pelczar, Zuzanna Gajda; Methodology: Karolina Paks, Monika Pelczar, Zuzanna Gajda; Software: n/a Check: Natalia Musialik, Monika Pelczar, Zuzanna Gajda; Formal analysis: Karolina Paks, Monika Pelczar, Natalia Musialik; Investigation: Karolina Paks, Monika Pelczar, Zuzanna Gajda, Bartosz Brzychcy, Karolina Brzychcy, Barbara Starosta, Ewa Jench; Resources: Maciej Magiera, Monika Pelczar, Zuzanna Gajda, Barbara Starosta; Data curation: Karolina Paks, Monika Pelczar, Zuzanna Gajda, Bartosz Brzychcy; Writing - rough preparation: Karolina Paks, Monika Pelczar, Ewa Jench; Writing - review and editing: Karolina Paks, Karolina Brzychcy, Natalia Musialik, Maciej Magiera; Visualisation: Bartosz Brzychcy, Karolina Brzychcy, Barbara Starosta, Maciej Magiera; Supervision: Karolina Paks, Ewa Jench, Zuzanna Gajda, Ewa Jench, Karolina Brzychcy, Barbara Starosta; Project administration: Natalia Musialik, Karolina Brzychcy, Barbara Starosta; Receiving funding: not-applicable.

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