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Real-World Use of Biologic and Targeted Therapies in Internal Medicine: An Ambispective Study at Laghouat Mixed Hospital

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Serment d’Hippocrate

« Au moment d'être admise à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité. Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J’interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences. Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire. Admise dans l’intimité des personnes, je tairai les secrets qui me sont confiés. Reçue à l’intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs. Je ferai tout pour soulager les souffrances.

Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément. Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission.

Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés. J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonorée et méprisée si j'y manque ».

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List of Abbreviations:

ACPA: Anti-Citrullinated Peptide Antibodies

ADCC: Antibody-Dependent Cellular Cytotoxicity

AE: Adverse Events

AI: Autoimmune Disease

ANA: Antinuclear Antibodies

ANCA: Anti-Neutrophil Cytoplasmic Antibodies

APRIL: A Proliferation-Inducing Ligand

axSpA: Axial Spondyloarthritis

BAFF: B-cell Activating Factor

BICLA: BILAG-Based Composite Lupus Assessment

BLM: Belimumab

BTLA: B- and T-Lymphocyte Attenuator

BVAS: Birmingham Vasculitis Activity Score

CBC: Complete Blood Count

CDAI: Crohn's Disease Activity Index

CDC: Complement-Dependent Cytotoxicity

CD: Crohn's Disease / Cluster of Differentiation

CD40L: CD40 Ligand

CML: Chronic Myeloid Leukemia

CMV: Cytomegalovirus

COVID-19: Coronavirus Disease 2019

CRP: C-Reactive Protein

Cs DMARDs: Conventional Synthetic Disease-Modifying Antirheumatic Drugs

CTLA-4: Cytotoxic T-Lymphocyte Antigen 4

DAA: Direct-Acting Antivirals

DAS28: Disease Activity Score in 28 Joints

DMARDs: Disease-Modifying Antirheumatic Drugs

EBV: Epstein–Barr Virus

ECLAM: European Consensus Lupus Activity Measurement

EMA: European Medicines Agency

ESR: Erythrocyte Sedimentation Rate

ETP: Therapeutic Patient Education

EULAR: European League Against Rheumatism

FDA: Food and Drug Administration

GCA: Giant Cell Arteritis

GEPA: Eosinophilic Granulomatosis with Polyangiitis

GPA: Granulomatosis with Polyangiitis

GVHD: Graft-Versus-Host Disease

HAS: French National Authority for Health (Haute Autorité de Santé)

HBV: Hepatitis B Virus

HBI: Harvey–Bradshaw Index

HCC: Hepatocellular Carcinoma

HCV: Hepatitis C Virus

HIV: Human Immunodeficiency Virus

HLA: Human Leukocyte Antigen

HPV: Human Papillomavirus

HSV: Herpes Simplex Virus

IBD: Inflammatory Bowel Disease

ICOS: Inducible T-cell Co-Stimulator

IFN: Interferon

IgG1: Immunoglobulin G1

IIM: Idiopathic Inflammatory Myopathies

IL: Interleukin

IMID: Immune-Mediated Inflammatory Disease

ITP: Immune Thrombocytopenic Purpura

IVIG: Intravenous Immunoglobulins

JAK: Janus Kinase

JNK: c-Jun N-terminal Kinase

mAb: Monoclonal Antibody

MAPK: Mitogen-Activated Protein Kinase

MA: Marketing Authorization

MRI: Magnetic Resonance Imaging

mTOR: Mammalian Target of Rapamycin

NF-κB: Nuclear Factor Kappa B

NSAIDs: Nonsteroidal Anti-Inflammatory Drugs

NYHA: New York Heart Association

PAM: Microscopic Polyangiitis

PAN: Polyarteritis Nodosa

PCR: Polymerase Chain Reaction

PD-1: Programmed Cell Death Protein 1

PI3K: Phosphoinositide 3-Kinase

PML: Progressive Multifocal Leukoencephalopathy

PMN: Primary Membranous Nephropathy

RA: Rheumatoid Arthritis

RF: Rheumatoid Factor

RNA: Ribonucleic Acid

RTX: Rituximab

SAE: Serious Adverse Events

SLE: Systemic Lupus Erythematosus

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

SRI-4: Systemic Lupus Responder Index-4

SSc: Systemic Sclerosis

TB: Tuberculosis

TCR-CD3: T-cell Receptor Complex

Tfh: Follicular Helper T Cells

TNF-α: Tumor Necrosis Factor Alpha

TNFR: Tumor Necrosis Factor Receptor

TPO-RAs: Thrombopoietin Receptor Agonists

TYK2: Tyrosine Kinase 2

VZV: Varicella-Zoster Virus

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Annexe N01

THEORETICAL SECTION

1) General Overview of Biotherapy :

Biotherapies represent a major advance in modern medicine. Unlike conventional small-molecule drugs produced through chemical synthesis, biotherapies are complex molecules derived from living cells. They mainly include monoclonal antibodies, fusion proteins, and recombinant proteins designed to specifically target key mechanisms involved in disease processes.

Biotherapy refers to all treatments based on biological substances, most often developed through genetic engineering, with the aim of selectively modulating the pathophysiological pathways involved in various diseases. In contrast to conventional immunosuppressive therapies, biotherapies act specifically on major immune mediators such as cytokines, membrane receptors, or specific immune cell populations (1).

In internal medicine, biotherapies have become a cornerstone in the management of inflammatory, autoimmune, and systemic diseases, particularly in patients who are refractory or intolerant to conventional therapies. Their development has significantly improved disease control, prognosis, and quality of life in many patients.

Among biotherapies, immunotherapy represents a specific category aimed at either stimulating or inhibiting the immune system in order to control inflammatory or autoimmune responses. These therapies mainly act on immune cells and cytokine pathways involved in disease activity (2).

Biosimilars are biological agents developed to be highly similar to an already approved reference biologic. Although they are not exact copies due to the intrinsic complexity of biological molecules, they demonstrate comparable efficacy, safety, and quality to the originator product, while improving treatment accessibility because of their lower cost (1,3).

Overall, biotherapies, immunotherapies, and biosimilars now represent essential therapeutic tools in internal medicine, allowing a more targeted and personalized approach to inflammatory and autoimmune diseases.

2) History of Biotherapy:

One of the major medical advances of the last decades has been the development of biological therapies, based on the use of biologically engineered substances to selectively target pathophysiological mechanisms. Early forms of biological treatment date back to the late nineteenth century with the use of sera and vaccines aimed at modulating immune responses. However, the modern era of biotherapy truly began in the 1970s with the development of monoclonal antibodies (mAbs).

In 1975, Köhler and Milstein introduced hybridoma technology, enabling the production of monoclonal antibodies directed against specific antigens through the fusion of immunized B-lymphocytes with immortalized murine myeloma cells. This breakthrough opened the way for clinical applications of mAbs, although the first murine antibodies were limited by significant immunogenicity and the development of human anti-mouse antibodies.

The first monoclonal antibody approved by the US Food and Drug Administration (FDA) was muromonab-CD3 in 1986, used for the prevention of acute renal transplant rejection. To reduce immunogenicity, chimeric and subsequently humanized monoclonal antibodies were developed during the 1980s and 1990s. Rituximab, approved in 1997 for non-Hodgkin lymphoma, became one of the first major therapeutic successes of targeted antibody therapy. The subsequent development of anti-TNF agents such as Infliximab,

Adalimumab, and Golimumab revolutionized the management of chronic inflammatory and autoimmune diseases.

Further technological advances led to the development of fully human monoclonal antibodies, recombinant fusion proteins, and more recently nanobodies derived from camelid antibodies. Etanercept, one of the first fusion proteins, was approved for rheumatoid arthritis in the late 1990s, while caplacizumab became the first therapeutic nanobody approved in 2019 for acquired thrombotic thrombocytopenic purpura.

Overall, the history of biotherapy reflects the progressive evolution from murine antibodies to highly targeted and less immunogenic biological agents. These advances have profoundly transformed the management of autoimmune, inflammatory, and systemic diseases, particularly in internal medicine, where biotherapies now represent a cornerstone of modern therapeutic strategies (4).

3) Pathophysiological Basis:

3.1) Immune Dysregulation:

Autoimmune and autoinflammatory diseases result from a complex and persistent dysregulation of the immune system involving genetic, environmental, and immunological factors. Autoimmune diseases are mainly characterized by abnormalities of adaptive immunity, with a breakdown of central and peripheral immune tolerance leading to the activation of autoreactive immune cells responsible for tissue damage. (5)

Immune tolerance is established at two levels. Central tolerance mainly relies on the negative selection of autoreactive T lymphocytes within the thymus, whereas peripheral tolerance limits the expansion of autoreactive cells through complementary mechanisms including clonal deletion, immune anergy, and regulatory T-cell induction. Peripheral clonal deletion occurs mainly through activation-induced or restimulation-induced cell death, while immune anergy is mediated by inhibitory co-stimulatory molecules such as CTLA-4 and regulatory immune cells. In addition, dendritic cells and helper T lymphocytes play a key role in maintaining immune homeostasis and regulating adaptive immune responses (6).

During autoimmune processes, these regulatory mechanisms fail, leading to infiltration of autoreactive T lymphocytes into target tissues and activation of inflammatory cascades. Cytotoxic CD8+ T lymphocytes directly destroy target cells, whereas CD4+ T lymphocytes produce pro-inflammatory cytokines and stimulate B lymphocytes. Activated B cells subsequently differentiate into plasma cells and produce autoantibodies directed against self-antigens. These autoantibodies may activate the complement system, induce antibody-dependent cellular cytotoxicity (ADCC), or form immune complexes that deposit within tissues and trigger local inflammation, as observed in systemic lupus erythematosus (7).

In contrast, autoinflammatory diseases are predominantly driven by dysregulation of innate immunity, independently of autoreactive T lymphocytes or autoantibodies. Monocytes, macrophages, and neutrophils play a central role through excessive activation of inflammasomes, resulting in uncontrolled production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α (8).

Overall, chronic inflammation and defective immune regulatory mechanisms contribute to disease persistence and clinical heterogeneity, forming the pathophysiological basis for the development of targeted biotherapies (9).

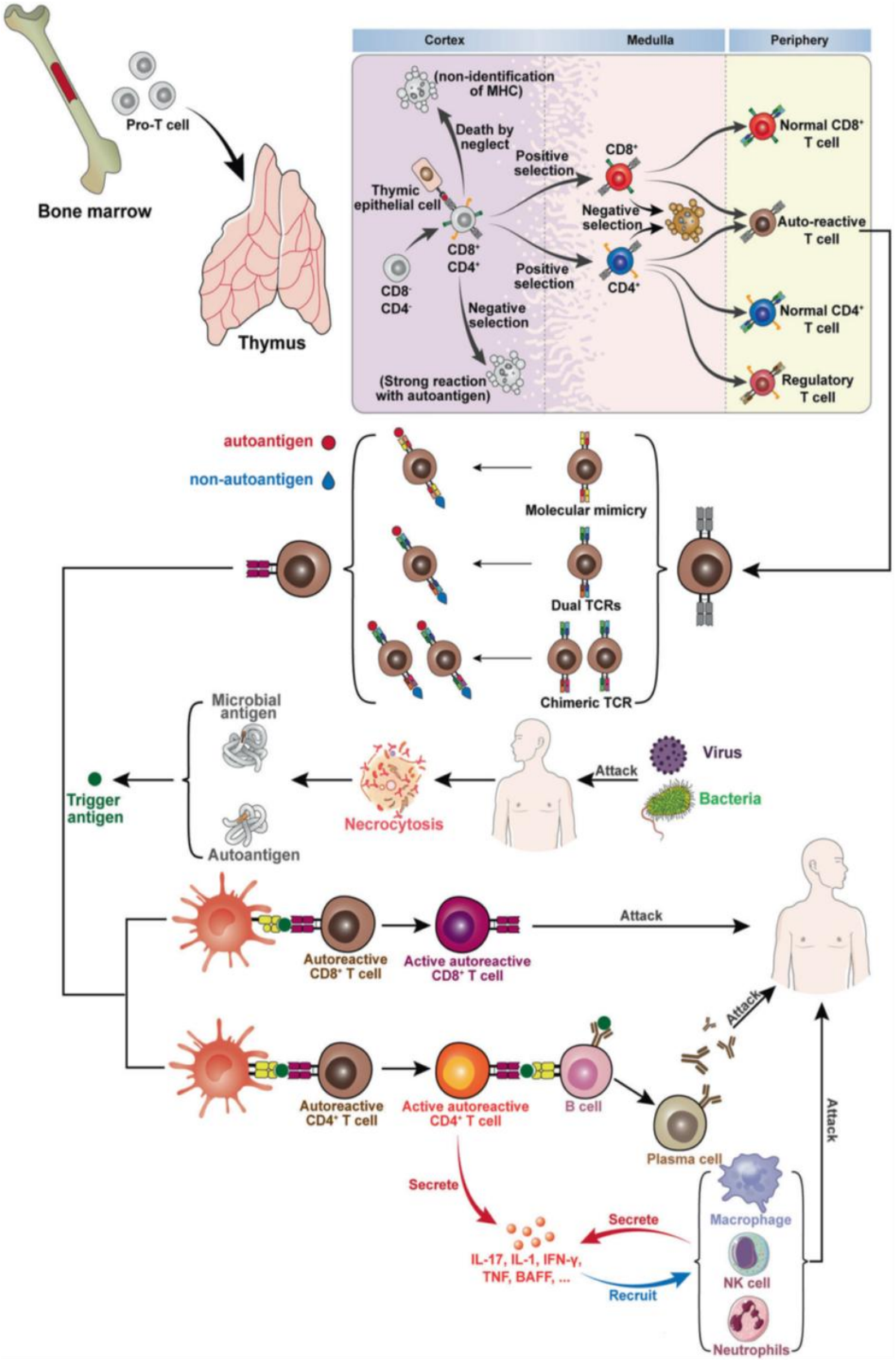


Figure 1 : Diagram illustrating the mechanisms of autoimmune diseases.

3.2) Environmental Triggers:

Immune dysregulation may be initiated or amplified by several environmental factors that contribute to the pathogenesis of autoimmune diseases. Among the proposed mechanisms, molecular mimicry is considered one of the main triggers of autoimmunity. It occurs when exogenous antigens sharing structural similarities with self-antigens activate autoreactive T or B lymphocytes in genetically predisposed individuals (10).

Several infectious agents have been implicated in autoimmune diseases. Epstein–Barr virus (EBV), for example, is capable of stimulating both innate and adaptive immune responses and has been associated with multiple autoimmune disorders, including systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis (11).

Alterations in the microbiota composition involving bacteria, viruses, and fungi within the gut, oral cavity, or skin may also influence immune homeostasis. Dysbiosis can promote abnormal immune activation and local inflammatory responses through microbial translocation and modulation of immunoregulatory metabolic pathways (12).

Lifestyle-related factors such as smoking and Western dietary habits have also been associated with autoimmune diseases, partly through their interactions with the microbiota and immune-regulatory metabolites, thereby contributing to the development and persistence of autoimmunity (13).

3.3) Molecular Signaling Pathways in Autoimmune Diseases :

At the molecular level, autoimmune diseases are driven by dysregulation of several signaling pathways involved in immune activation, lymphocyte survival, and cytokine production. T- and B-cell activation depends on complex interactions between membrane receptors, co-stimulatory molecules, and intracellular signaling cascades (14).

Among the major pathways involved, the CD28–CTLA4 signaling axis plays a central role in T-cell activation and immune regulation. CD28 binding to its ligands CD80 and CD86 promotes T-cell proliferation, survival, and cytokine production through activation of the PI3K–AKT–mTOR pathway. In contrast, CTLA4 negatively regulates this pathway by competing for the same ligands and suppressing excessive immune activation. Therapeutic agents targeting CTLA4 pathways have been investigated in several autoimmune diseases, including psoriasis and juvenile idiopathic arthritis (15).

The ICOS signaling pathway also contributes to T-cell activation, particularly follicular helper T-cell (Tfh) responses involved in autoantibody production through IL-21 and IL-4 secretion. Other inhibitory receptors such as PD-1 and BTLA act as immune checkpoints limiting inflammatory responses and maintaining peripheral tolerance (16).

Another important pathway is the CD40–CD40L interaction, which regulates B-cell activation, germinal center formation, antibody production, and memory B-cell differentiation through downstream activation of NF-κB and other transcription factors. Excessive activation of this pathway contributes to chronic inflammation and tissue damage in autoimmune diseases such as rheumatoid arthritis and Sjögren syndrome (17).

Additional members of the TNF receptor superfamily, including BAFF, APRIL, and OX40–OX40L, are involved in lymphocyte activation, cytokine secretion, and maintenance of inflammatory responses. Genetic

polymorphisms affecting these pathways have been associated with several autoimmune disorders, particularly systemic lupus erythematosus and Sjögren syndrome (18).

Overall, these signaling pathways interact within a highly interconnected immune network responsible for maintaining immune homeostasis. Their dysregulation contributes to chronic inflammation and autoimmunity, providing the rationale for the development of targeted biotherapies aimed at selectively modulating these molecular pathways (19).

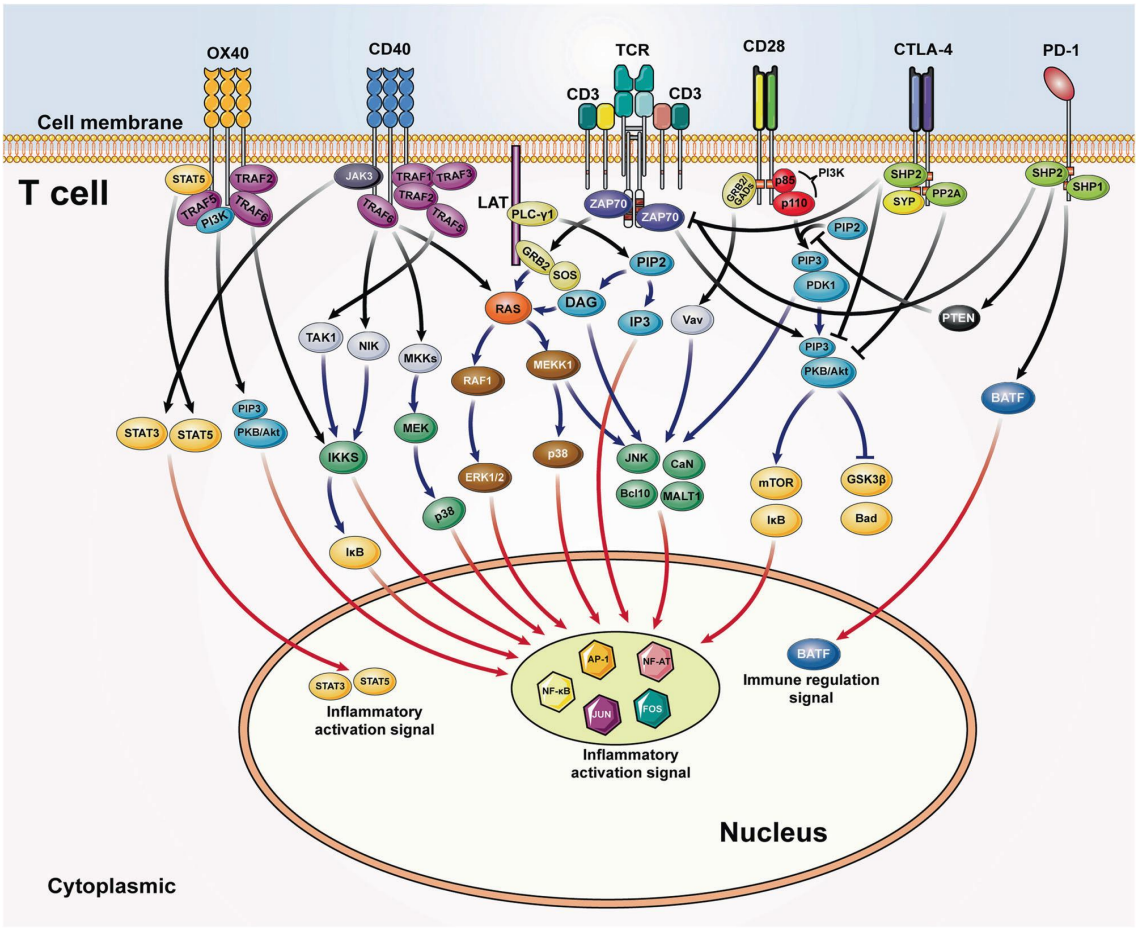


Figure 2: Major molecular signaling pathways and membrane surface markers involved in autoimmune diseases.

3.4) Clinical Consequences:

The combination of lymphocyte dysregulation, autoantibody production, and excessive activation of inflammatory signaling pathways leads to persistent chronic inflammation and progressive tissue damage affecting target organs such as the joints, kidneys, skin, and exocrine glands. These mechanisms are responsible for the clinical heterogeneity and chronic progression observed in autoimmune and systemic diseases (20).

4) Classification of Biotherapies:

Biotherapies can be classified according to their therapeutic target and mechanism of action. They mainly include anti-TNF agents, B-cell–targeted therapies, interleukin inhibitors, JAK inhibitors, and anti-integrin therapies (21).

4.1) Anti-TNF Agents:

Tumor necrosis factor alpha (TNF-α) is a major pro-inflammatory cytokine produced mainly by macrophages, T lymphocytes, neutrophils, and natural killer cells. Through its interaction with TNF receptors (TNF-R1 and TNF-R2), TNF-α activates several intracellular inflammatory pathways including NF-κB, MAPK, and JNK, leading to cytokine production, leukocyte recruitment, and chronic tissue inflammation. Excessive TNF-α activity plays a central role in several chronic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, psoriatic arthritis, and autoimmune uveitis. (4)

The development of anti-TNF therapies has revolutionized the management of these diseases. Currently approved anti-TNF agents include infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol.

A) Infliximab:

Infliximab is a chimeric monoclonal antibody directed against both soluble and transmembrane TNF-α, thereby neutralizing its biological activity.

B) Etanercept:

Etanercept is a recombinant fusion protein composed of the extracellular portion of TNF receptor 2 linked to the Fc fragment of human IgG1. It acts as a soluble receptor that binds circulating TNF-α.

C) Adalimumab:

Adalimumab is a fully human monoclonal antibody targeting TNF-α, characterized by lower immunogenicity compared with chimeric antibodies.

D) Golimumab:

Golimumab is a fully human IgG1κ monoclonal antibody with high affinity for both soluble and transmembrane TNF-α.

E) Certolizumab Pegol:

Certolizumab pegol is a pegylated humanized Fab fragment lacking the Fc region, which reduces complement-mediated cytotoxicity while prolonging plasma half-life (4).

4.2) Anti-CD20 Therapies:

Anti-CD20 therapies selectively target CD20, a transmembrane protein expressed on mature B lymphocytes. Binding of anti-CD20 antibodies induces B-cell depletion through complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and direct apoptosis (22). Available anti-CD20 agents include:

Rituximab (chimeric antibody)

Obinutuzumab (humanized antibody)

Ofatumumab (fully human antibody)

These therapies are used in B-cell lymphomas, chronic lymphocytic leukemia, rheumatoid arthritis refractory to anti-TNF agents, systemic lupus erythematosus, vasculitis, and multiple sclerosis (23).

4.3) Anti-CD52 Therapy:

CD52 is a surface glycoprotein highly expressed on B and T lymphocytes, as well as on monocytes and natural killer cells. Alemtuzumab, an anti-CD52 monoclonal antibody, induces profound lymphocyte depletion through ADCC and complement activation, followed by slow immune reconstitution. This immune "reset" may induce prolonged remission in some autoimmune diseases (24).

Its main indications include :

- Relapsing-remitting multiple sclerosis.
- Chronic lymphocytic leukemia (23).

4.4) Interleukin Inhibitors :

Interleukin inhibitors constitute a major class of targeted therapies designed to block specific cytokine pathways involved in chronic inflammation and autoimmunity (25).

4.4.1) Anti-IL-1 Therapies:

IL-1 plays a major role in autoinflammatory diseases and acute inflammatory responses.

Main agents:

Anakinra

Canakinumab (26,27).

Indications:

Adult-onset Still disease

Hereditary autoinflammatory syndromes

Severe gout

These agents inhibit innate immune activation and inflammatory cytokine release (28).

4.4.2) Anti-IL-6 Therapies:

IL-6 is involved in systemic inflammation, CRP production, and lymphocyte activation.

Main agent:

Tocilizumab.

Indications:

Rheumatoid arthritis.

Giant cell arteritis (29).

4.4.3) Anti-IL-17 and Anti-IL-23 Therapies:

The IL-17/IL-23 axis plays a major role in psoriatic skin and joint inflammation.

Anti-IL-17 agents :

- Secukinumab.
- Ixekizumab (30).

Anti-IL-23 agents :

- Ustekinumab.
- Risankizumab.
- Guselkumab (31).

Indications :

- Plaque psoriasis
- Psoriatic arthritis
- Ankylosing spondylitis
- Crohn disease

4.4.4) Anti-IL-4 and Anti-IL-13 Therapies :

IL-4 and IL-13 are key mediators of type 2 inflammatory responses.

Main agent :

- Dupilumab

Indications :

- Atopic dermatitis
- Severe asthma
- Nasal polyposis

These therapies reduce IgE production and eosinophilic inflammation (32).

4.5) JAK Inhibitors:

Janus kinase inhibitors (JAK inhibitors or JAKi) are oral small molecules that block intracellular cytokine signaling pathways. Unlike monoclonal antibodies acting extracellularly, JAK inhibitors act inside the cell by inhibiting JAK enzymes (JAK1, JAK2, JAK3, TYK2), thereby preventing activation of inflammatory genes (33).

Main agents include:

- Tofacitinib
- Baricitinib
- Upadacitinib
- Filgotinib

- Abrocitinib

Advantages include oral administration, rapid onset of action, and absence of immunogenicity.

Indications :

- Rheumatoid arthritis
- Psoriatic arthritis
- Ankylosing spondylitis
- Atopic dermatitis
- Alopecia areata
- Inflammatory bowel disease
- Myelofibrosis
- Graft-versus-host disease (34).

4.6) Anti-Integrin Therapies :

Integrins are transmembrane glycoproteins involved in leukocyte adhesion and migration into inflamed tissues. Anti-integrin therapies inhibit leukocyte trafficking and thereby reduce tissue inflammation (23).

These therapies are mainly used in:

- Crohn disease
- Ulcerative colitis
- Certain auto-immune disorders

Main agents include :

- Natalizumab
- Vedolizumab

Anti-integrin therapies offer a more targeted mechanism of action with potentially fewer systemic immunosuppressive effects compared with conventional therapies.

5) Indications in Internal Medicine:

5.1) Rheumatology:

5.1.1) Rheumatoid Arthritis (RA):

Rheumatoid arthritis is a chronic immune-mediated inflammatory disease characterized by pain, swelling, and stiffness of synovial joints, particularly affecting the small joints of the hands and feet. Diagnosis is primarily clinical and supported by inflammatory markers and autoantibodies such as rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA). The 2010 EULAR/ACR classification criteria are widely used for disease classification and early diagnosis (35).

Biotherapies are indicated in patients with moderate-to-severe active disease who show inadequate response or intolerance to conventional disease-modifying antirheumatic drugs (DMARDs), particularly methotrexate.

Main biologic agents include :

- Infliximab
- Etanercept
- Adalimumab

These therapies reduce disease activity, improve functional outcomes, and slow radiographic progression of joint damage (36).

5.1.2) Axial Spondylo arthritis (axSpA):

Axial spondyloarthritis is a chronic inflammatory rheumatic disease characterized mainly by inflammatory back pain, stiffness, enthesitis, arthritis, and dactylitis. Extra-articular manifestations may include anterior uveitis, psoriasis, and inflammatory bowel disease (37).

Biotherapy is indicated in :

- Persistent active disease despite at least two NSAIDs
- Peripheral disease refractory to corticosteroid injections or DMARDs
- Severe enthesitis or dactylitis
- Psoriatic arthritis refractory to conventional treatment

Poor prognostic factors such as elevated CRP or inflammatory lesions on MRI further support biologic initiation (38).

5.2) Systemic Diseases:

5.2.1) Systemic Lupus Erythematosus (SLE):

Systemic lupus erythematosus is a chronic multisystem autoimmune disease characterized by autoantibody production and immune-mediated tissue damage. Clinical manifestations range from mild cutaneous and articular involvement to severe renal, hematological, cardiovascular, and neurological complications. Lupus nephritis remains one of the most severe manifestations (39).

- **Biotherapy Indications**

Belimumab is indicated as add-on therapy in patients with active autoantibody-positive SLE with persistent disease activity despite standard treatment. It is particularly useful in refractory cutaneous and musculoskeletal forms (40).

5.2.2) Systemic Sclerosis (SSc):

Systemic sclerosis is a rare autoimmune disease characterized by fibrosis, vasculopathy, and immune dysregulation, leading to skin and internal organ involvement. Pulmonary and renal complications are major causes of morbidity and mortality. Early diagnosis is essential because severe organ involvement may occur within the first years of disease (41).

- **Biotherapy Indications**

Tocilizumab has received approval in some countries for systemic sclerosis-associated interstitial lung disease, although its use may still require multidisciplinary validation depending on local regulations (42).

5.2.3) Idiopathic Inflammatory Myopathies (IIM):

Idiopathic inflammatory myopathies are a heterogeneous group of systemic autoimmune diseases including dermatomyositis, polymyositis, immune-mediated necrotizing myopathy, antisynthetase syndrome, and overlap myositis. They are characterized primarily by muscle weakness and may also involve the lungs, joints, skin, and heart (43,44).

- **Biotherapy Indications**

Rituximab is mainly used in refractory dermatomyositis and juvenile dermatomyositis (45).

5.2.4) Vasculitis:

Vasculitides are inflammatory diseases affecting blood vessels of various sizes and types. They include large-, medium-, and small-vessel vasculitis such as giant cell arteritis, polyarteritis nodosa, granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (46,47).

- **Biotherapy Indications**

Rituximab is preferentially used in:

- Relapsing disease
- Cyclophosphamide failure or intolerance
- Women of childbearing age
- Pediatric patients
- Patients with previous malignancy (48).

5.2.5) Bechet Disease :

Behçet disease is a multisystem variable-vessel vasculitis involving arteries and veins of all sizes. Clinical manifestations include mucocutaneous lesions, uveitis, neurological involvement, thrombosis, and vascular aneurysms (49).

- **Biotherapy Indications**

Anti-TNF therapies are indicated in:

- Refractory mucocutaneous and articular disease
- Severe ocular involvement
- Neurological disease
- Severe vascular involvement including thrombosis and pulmonary artery aneurysms (50).

5.3) Gastroenterology :

5.3.1) Inflammatory Bowel Disease (IBD) :

Inflammatory bowel disease includes Crohn disease and ulcerative colitis, both characterized by chronic non-infectious gastrointestinal inflammation resulting from immune dysregulation. Clinical manifestations include diarrhea, abdominal pain, rectal bleeding, weight loss, and extra-intestinal manifestations such as arthritis, uveitis, and skin disease (51).

A-Ulcerative Colitis

- Anti-TNF agents including infliximab, adalimumab, and golimumab are indicated in moderate-to-severe active disease refractory to corticosteroids or immunosuppressants.

Vedolizumab is indicated after failure or intolerance of conventional therapy and/or anti-TNF agents (52).

B-Crohn Disease

Infliximab and adalimumab are indicated in moderate-to-severe active disease refractory to conventional therapy in both adults and pediatric patients.

Vedolizumab is mainly used after failure or intolerance of anti-TNF therapy (53).

5.4) Neurology :

- **Multiple Sclerosis (MS)**

Multiple sclerosis is a chronic autoimmune demyelinating disease of the central nervous system predominantly affecting young adults, especially women. It presents with relapsing-remitting, secondary progressive, or primary progressive forms. Clinical manifestations include visual, motor, sensory, sphincteric, and cognitive impairment. Diagnosis is based on clinical findings, MRI, and cerebrospinal fluid analysis according to the McDonald criteria (54,55).

- **Biotherapy Indications**

Natalizumab is indicated in highly active relapsing-remitting multiple sclerosis, particularly in patients with inadequate response to interferon beta or rapidly evolving severe disease. (56)

Ocrelizumab is approved for both relapsing forms of multiple sclerosis and early primary progressive multiple sclerosis (57).

5.5) Hematological Diseases:

5.5.1) Immune Thrombocytopenic Purpura (ITP):

Immune thrombocytopenic purpura is an autoimmune hematological disorder characterized by isolated thrombocytopenia resulting from immune-mediated platelet destruction. Autoantibodies directed against platelet antigens play a central role in disease pathogenesis.

Rituximab is indicated in chronic or persistent ITP refractory to corticosteroids. Thrombopoietin receptor agonists (TPO-RAs) are also widely used as second-line therapy in chronic disease (58).

5.5.2) Chronic Myeloid Leukemia (CML):

Chronic myeloid leukemia is a myeloproliferative neoplasm characterized by the Philadelphia chromosome and the BCR-ABL1 fusion gene, resulting in constitutive tyrosine kinase activation.

Imatinib, a BCR-ABL1 tyrosine kinase inhibitor, represented a major therapeutic breakthrough and remains a cornerstone in the treatment of CML (61).

5.6) Dermatology:

5.6.1) Severe Psoriasis:

Psoriasis is a chronic multisystem inflammatory disease primarily affecting the skin and joints. Its pathogenesis involves genetic predisposition and dysregulated immune activation, with significant physical and psychosocial impact (59).

Several biologic agents are approved for moderate-to-severe psoriasis, including:

- Anti-TNF agents (adalimumab, etanercept, infliximab, certolizumab)
- Anti-IL-12/23 therap y (ustekinumab)
- Anti-IL-23 agents (risankizumab, guselkumab, tildrakizumab)
- Anti-IL-17 agents (secukinumab, ixekizumab)
- Anti-IL-17 receptor therapy (brodalumab)

Treatment selection should be individualized according to disease severity, comorbidities, and patient characteristics (60).

5.7) Other Rare Indications:

5.7.1) Hepatocellular Carcinoma (HCC):

Hepatocellular carcinoma accounts for approximately 90% of primary liver cancers and remains one of the leading causes of cancer-related mortality worldwide. Advances in tumor biology have led to the development of targeted systemic therapies for advanced disease (62).

Sorafenib and lenvatinib, both multikinase inhibitors, are approved first-line systemic therapies for unresectable hepatocellular carcinoma (63).

5.7.2) Primary Membranous Nephropathy (PMN):

Primary membranous nephropathy is a major cause of nephrotic syndrome in adults. The discovery of anti-PLA2R autoantibodies confirmed the autoimmune nature of the disease and provided a highly specific biomarker for diagnosis and disease monitoring.

Rituximab is increasingly used as targeted therapy because reduction in anti-PLA2R antibody levels correlates strongly with clinical remission (64).

5.7.3) Panuveitis:

Panuveitis is a severe inflammatory ocular disease involving the uveal tract and potentially extending to the retina, vitreous, and retinal vessels. Visual prognosis may be significantly affected depending on disease severity and complications.

Biotherapies are indicated in moderate-to-severe forms refractory to corticosteroids or conventional immunosuppressive therapy. Anti-TNF agents, particularly adalimumab and infliximab, are the main biologic therapies used. Tocilizumab and rituximab may be considered in refractory cases (65).

6) Clinical Effectiveness of Biotherapies:

6.1) Evaluation Criteria:

6.1.1) DAS28 Score:

In clinical practice, disease activity in rheumatoid arthritis is commonly assessed using the Disease Activity Score in 28 joints (DAS28), which combines clinical findings, biological inflammatory markers, and patient global assessment.

The DAS28 score allows standardized evaluation of disease activity and therapeutic response, facilitating both daily clinical management and comparison of treatment efficacy across clinical studies.

Score	Formula
Disease activity score (four variables) = DAS4	DAS4 = 0.53938*√(Ritchie) + 0.06465*(swollen joints) + 0.330*ln(ESR) + 0.00722*(general health)
Disease activity score (three variables) = DAS3	DAS3 = 0.53938*√(Ritchie) + 0.06465*(swollen joints) + 0.330*ln(ESR) + 0.224
Modified Disease Activity Score (four variables) = DAS28-4	DAS28-4 = 0.56*√(TJC28) + 0.28*√(SJC28) + 0.70*ln(ESR) + 0.014*(general health)
Modified Disease Activity Score (three variables) = DAS28-3	DAS28-3=[0.56*√(TJC28) + 0.28*√(SJC28) + 0.70*ln(ESR)]1.08 + 0.16

Figure 3: Different versions of the DAS score and their corresponding calculation formulas.

Current DAS28:	Reduction of DAS28:		
	>1.2	>0.6 and ≤1.2	≤0.6
DAS28 ≤3.2	good	moderate	none
3.2 < DAS28 ≤5.1	moderate	moderate	none
DAS28 >5.1	moderate	none	none

Figure 4: European League Against Rheumatism (EULAR) response criteria based on the DAS28 score.

6.1.2) SLEDAI:

The SLEDAI is a global index used to assess disease activity during the previous 10 days and includes 24 items evaluating specific manifestations across 9 organ systems: neurological, musculoskeletal, renal, mucocutaneous, general, cardiac, respiratory, vascular, and hematological systems. The maximum score is 105.

The SLEDAI appears to be sensitive to changes in disease activity over time (106).

Disease activity categories were defined according to SLEDAI scores as follows: no disease activity (SLEDAI = 0), mild disease activity (SLEDAI 1–5), moderate disease activity (SLEDAI 6–10), high disease activity (SLEDAI 11–19), and very high disease activity (SLEDAI ≥ 20) (66).

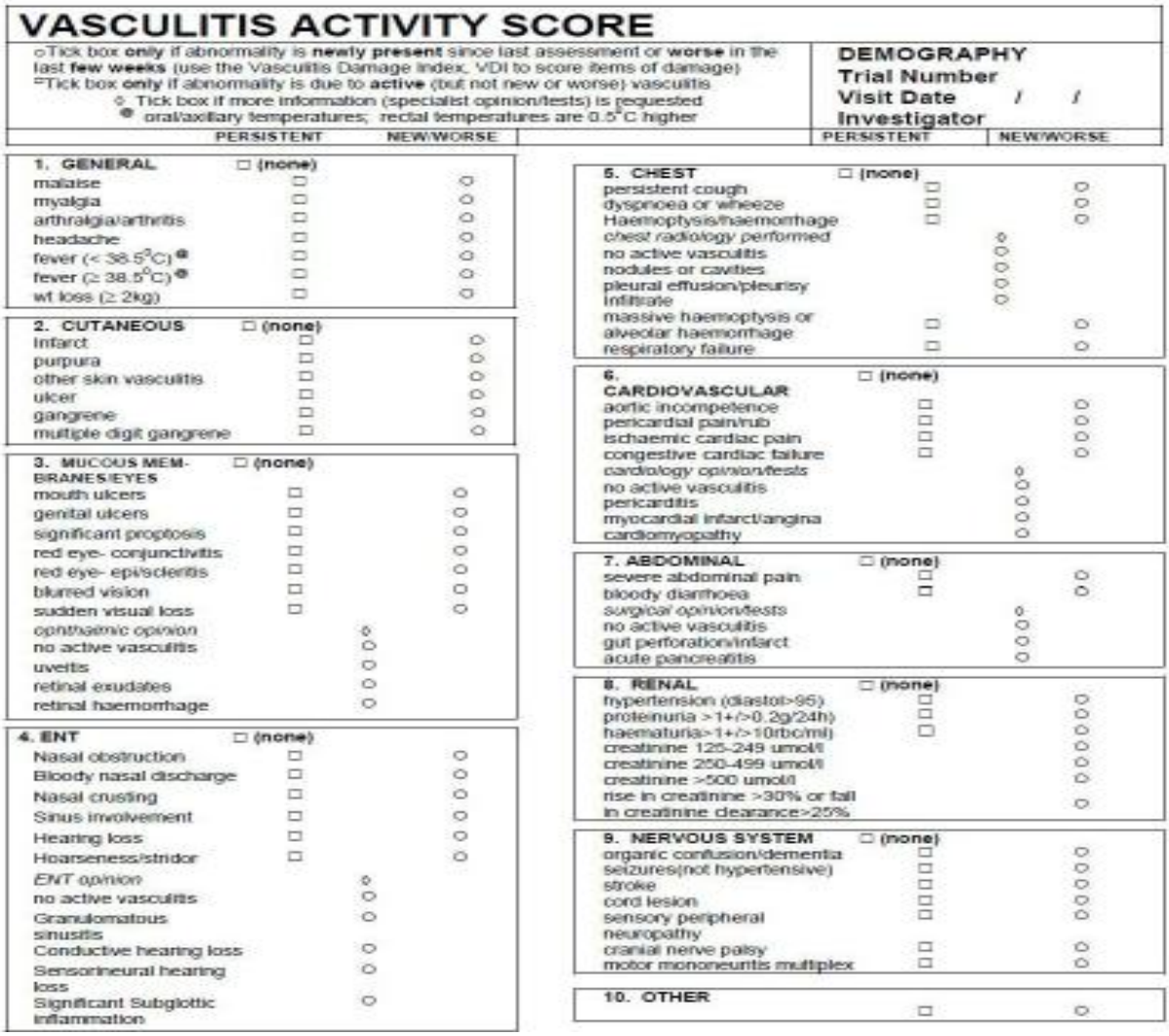
1. Generalized manifestations	Any of the following:	0.5
Fever	Documented basal morning temperature of 37.5°C not due to an infective process	
Fatigue	A subjective feeling of extraordinary tiredness	
2. Articular manifestations	Any of the following:	1
Arthritis	Non-erosive arthritis involving at least 2 peripheral joints (wrist, metacarpophalangeal or proximal, interphalangeal joints).	
Evolving arthalgia	New onset or worsening of specific localized pain without objective symptoms in at least two peripheral joints	
3a. Active muco-cutaneous manifestations	Any of the following:	0.5
Malar rash	Fixed erythema, flat or raised over the malar eminences, and tending to spare the naso-labial folds.	
Generalised rash	Amaculo-papular rash not induced by drugs, that may be located anywhere on the body, and that is not strictly dependent on sun exposure.	
Discoid rash	Erythmatosus, raised patches with adherent keratotic scaling and follicular plugging.	
Skin vasculitis	Including digital ulcers, purpura, urticaria, bullous lesions.	
Oral ulcers	Oral or naso-phayngeal ulcers, usually painless, observed by a physician.	
3b. Evolving mucocutanteous manifestations	If any of the above mucocutaneuous manifestations are new or have worsened since the last observation, add 1 point.	1
4. Myositis*	Confirmed by raised muscle enzymes and/or EMG examination and/or histology.	2
5. Pericarditis	Documented by ECC or rub or evidence of pericardial effusion on ultrasound.	1
6. Intestinal manifestations	Any of the following:	2
Intestinal vasculitis	Evidence of acute intestinal vasculitis.	
Sterile peritonitis	Evidence of abdominal effusion in the absence of infective processes.	
7. Pulmonary manifestations	Any of the following:	1
Pleurisy	Clinical or radiological evidence of pleural effusion in the absence of infective processes.	
Pneumonitis	Single or multiple lung opacities on chest X-ray thought to reflect active disease not due to an infective process.	
Ingravescent dyspnoea	Due to an evolving interstitial involvement.	
8. Evolving neuropsychiatric manifest.*	New appearance or worsening of any of the following:	2
Headache/migrane	Recently developed, persistent or recurrent/ Poorly responsive to the most commonly used drugs, but partially or totally responsive to corticosteroids.	
Seizures	Grand mal or petit mal seizures, Jacksonian fits, temporal lobe seizures, or choreic syndrome, in the absence of offending drugs or known metabolic derangements (e.g. uremia, ketoacidosis, or electrolyte imbalance).	
Stroke	Cerebral infarction or haemorrphage, instrumentally confirmed.	
Organic brain disease	Impairment of memory orientation, perception, and ability to calculate.	
Psychosis	Dissociative features in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis, or electrolye imbalance.	
9a. Renal manifestations*+	Any of the following:	0.5
Proteinuria	At least 500 mg/day.	
Urinary casts	Red cells, haemoglobin, granular, tubular, or mixed casts.	
Haematuria	Microscopic or macroscopic.	
Raised serum creatinine or reduced creatinine clearance		
9b. Evolving renal manifestations	If any of the above renal manifestations are new and have worsened since the last two observations, add 2 points.	
10. Haematologic features	Any of the following:	1
Non-haemolytic anaemia	A Coombs-negative normocytic hypochromic or normochromic anaemia without reticulocytosis.	
Haemolytic anaemia*	A Coombs-positive haemolytic anaemia, with reticulocytosis and elevated LDH, in the absence of offending drugs.	
Leukopenia (or lymphopenia)	Less than 3,500/mm^3 WBC (or 1,500/mm^3 lymphocytes) in the absence of offending drugs.	
Thromocytopenia	Less than 100,000/mm^3 in the absence of offending drugs.	
11. Erythrocyte sedimentation rate		
Raised ESR	>25 mm/h by Westergren or comparable methods, not due to other concomitant pathological process.	1
12a. Hypocomplementaemia	Reduced plasma level of any of the following:	1
C3	By radial immunodiffusion or laser nephelometer.	
CH50	By standardized haemolytic methods.	
12b. Evolving hypocomplementaemia	Significantly reduced level of any of the items mentioned above (plus C4) with respect to the last observation.	1
FINAL SCORE #		

*If this system (or manifestations) is the only involvement present from among items 1-10, add 2 more points. + Excluding patients with end-stage chronic renal disease. #If the final total score is not an integer number, round off to the lower integer for values <6 and to the higher integer for values >6. If the final total score is >10, round off to 10.

Figure 4 : Assessment of lupus disease activity according to the European Consensus Lupus Activity Measurement (ECLAM) (67).

6.1.3) BVAS:

The Birmingham Vasculitis Activity Score (BVAS) is currently the reference tool for assessing disease activity in systemic vasculitis and has been used in major randomized vasculitis trials (107).



VASCULITIS ACTIVITY SCORE

○Tick box **only** if abnormality is **newly present** since last assessment or **worse** in the last **few weeks** (use the Vasculitis Damage Index, VDI to score items of damage)
□Tick box **only** if abnormality is due to **active** (but not new or worse) vasculitis
◊ Tick box if more information (specialist opinion/tests) is requested
● oral/axillary temperatures; rectal temperatures are 0.5°C higher

DEMOGRAPHY
Trial Number
Visit Date / /
Investigator

	PERSISTENT	NEW/WORSE
1. GENERAL	□ (none)	
malaise	□	○
myalgia	□	○
arthralgia/arthritis	□	○
headache	□	○
fever (< 38.5°C)●	□	○
fever (≥ 38.5°C)●	□	○
wt loss (≥ 2kg)	□	○
2. CUTANEOUS	□ (none)	
infarct	□	○
purpura	□	○
other skin vasculitis	□	○
ulcer	□	○
gangrene	□	○
multiple digit gangrene	□	○
3. MUCOUS MEMBRANES/EYES	□ (none)	
mouth ulcers	□	○
genital ulcers	□	○
significant proptosis	□	○
red eye- conjunctivitis	□	○
red eye- epi/scleritis	□	○
blurred vision	□	○
sudden visual loss	□	○
ophthalmic opinion	◊	
no active vasculitis	○	
uveitis	○	
retinal exudates	○	
retinal haemorrhage	○	
4. ENT	□ (none)	
Nasal obstruction	□	○
Bloody nasal discharge	□	○
Nasal crusting	□	○
Sinus involvement	□	○
Hearing loss	□	○
Hoarseness/stridor	□	○
ENT opinion	◊	
no active vasculitis	○	
Granulomatous sinusitis	○	
Conductive hearing loss	○	
Sensorineural hearing loss	○	
Significant Subglottic inflammation	○	

	PERSISTENT	NEW/WORSE
5. CHEST	□ (none)	
persistent cough	□	○
dyspnoea or wheeze	□	○
Haemoptysis/haemorrhage	□	○
chest radiology performed	◊	
no active vasculitis	○	
nodules or cavities	○	
pleural effusion/pleurisy	○	
infiltrate	○	
massive haemoptysis or alveolar haemorrhage	□	○
respiratory failure	□	○
6. CARDIOVASCULAR	□ (none)	
aortic incompetence	□	○
pericardial pain/rub	□	○
ischaemic cardiac pain	□	○
congestive cardiac failure	□	○
cardiology opinion/tests	◊	
no active vasculitis	○	
pericarditis	○	
myocardial infarct/angina	○	
cardiomyopathy	○	
7. ABDOMINAL	□ (none)	
severe abdominal pain	□	○
bloody diarrhoea	□	○
surgical opinion/tests	◊	
no active vasculitis	○	
gut perforation/infarct	○	
acute pancreatitis	○	
8. RENAL	□ (none)	
hypertension (diastol>95)	□	○
proteinuria >1+/>0.2g/24h)	□	○
haematuria>1+/>10rbc/ml)	□	○
creatinine 125-249 umol/l		○
creatinine 250-499 umol/l		○
creatinine >500 umol/l		○
rise in creatinine >30% or fall in creatinine clearance>25%		○
9. NERVOUS SYSTEM	□ (none)	
organic confusion/dementia	□	○
seizures(not hypertensive)	□	○
stroke	□	○
cord lesion	□	○
sensory peripheral neuropathy	□	○
cranial nerve palsy	□	○
motor mononeuritis multiplex	□	○
10. OTHER	□	○

Figure 5: Vasculitis activity score.

6.1.4) HBI / CDAI:

Crohn's disease (CD) activity is usually assessed clinically using two scoring systems:

The Crohn's Disease Activity Index (CDAI) is the most widely used score in clinical trials; however, its calculation remains complex in daily practice.

The Harvey–Bradshaw Index (HBI) is closely correlated with the CDAI and is easier to use in routine clinical practice (68).

	Valeur
Bien-être général : • bon = 0 • moyen = 1 • médiocre = 2 • mauvais = 3 • très mauvais = 4	
Douleurs abdominales : • absentes = 0 • faibles = 1 • moyennes = 2 • intenses = 3	
Selles liquides : nombre/jour	
Masse abdominale : • absente = 0 • douteuse = 1 • certaine = 2 • certaine avec défense	
Signes extra-digestifs, fistule, fissure anale : 1 point par item présent	
Score (= somme)	

Score < 4 : maladie inactive Score compris entre 4 et 8 : maladie active minime	Score compris entre 8 et 12 : maladie active modérée Score supérieur à 12 : maladie active sévère

Figure 6 : Harvey-Bradshaw Index.

	J1	J2	J3	J4	J5	J6	J7	Somme	Coefficient multiplicateur	Total
Nombre de selles liquides ou molles									2	
Douleurs abdominales : • absente = 0 • légères = 1 • moyennes = 2 • intenses = 3									2	
Bien-être général : • bon = 0 • moyen = 2 • médiocre = 3 • mauvais = 4 • très mauvais = 5									2	
Autres manifestations :										
arthrites ou arthralgies									20	
iritis ou uvéite									20	
érythème noueux, pyoderma, aphtes buccaux									20	
fissures, fistules, abcès anal ou périrectal									20	
autre fistule intestinale									20	
fièvre (> 38° dans la semaine)									20	
Traitement antidiarrhéïque (lopéramine ou opiacés) • non = 0 • oui = 1									30	
Masse abdominale : • absente = 0 • douteuse = 1 • certaine = 5									10	
Hématocrite* : • homme : 47 - Hématocrite • femme : 42 - Hématocrite									6	
Poids* : 100 x (1-Poids actuel/Poids théorique)										
* Le signe doit être conservé donc ajout ou soustraction.										
									TOTAL	

Figure 8: CDAI or Best Index.

6.2) Data from the Literature:

6.2.1) Algerian Study:

According to the Algerian Journal of Allergy and Clinical Immunology 2024, the study aimed to evaluate the effectiveness of biologic therapies in real-life conditions among Algerian patients with rheumatoid arthritis (RA). Five biologic agents are currently used in Algeria for this indication: three anti-TNF alpha agents (adalimumab, etanercept, infliximab), one anti-IL-6 agent (tocilizumab), and one anti-CD20 agent (rituximab).

Results: A total of 42 patients were included; 18 patients (43%) received tocilizumab, 13 (31%) rituximab, and 11 (26%) anti-TNF alpha therapy. Before initiation of biologic therapy, the mean disease duration was 12.3 ± 9.3 years, and the mean DAS28-ESR score was 5.33 ± 1.12.

At weeks 12 and 24 of treatment, a statistically significant improvement in the mean DAS28-ESR score was observed ($p < 0.001$). A EULAR response was achieved in 90.3% and 83% of patients at weeks 12 and 24, respectively; the response was classified as good in 61% of patients at week 12 and 53.7% at week 24. Treatment with tocilizumab was the only independent predictive factor associated with a good EULAR response.

The mean erythrocyte sedimentation rate (ESR) and mean C-reactive protein (CRP) levels decreased after only 12 weeks of biologic therapy. At week 24, the mean CRP level remained as low as that observed at week 12, whereas a slight increase in mean ESR was noted. A reduction in the mean number of tender joints and swollen joints was observed at both 12 and 24 weeks of biologic therapy.

Disease activity improved significantly; the mean DAS28-ESR score decreased markedly at week 12 ($p < 0.001$), and this response was maintained at week 24 ($p < 0.001$). The proportion of patients in remission (DAS28-ESR < 2.6) or with low disease activity ($2.6 \leq$ DAS28-ESR ≤ 3.2) was 61% and 56.1% at weeks 12 and 24, respectively.

A good EULAR response was observed in 61% of patients at week 12 and in 53.7% at week 24. The proportion of patients with a moderate response was 29.3% at both week 12 and week 24, whereas EULAR non-responders accounted for 9.7% at week 12 and 17% at week 24.

Regarding rituximab therapy, a EULAR response was observed in 92.3% of patients at week 12 (good response: 53.8%, moderate response: 38.5%) and in 77% at week 24 (good response: 38.5%, moderate response: 38.5%). Concerning anti-TNF alpha agents, 80% of patients responded at week 12 (good response: 50%, moderate response: 30%), compared with only 60% at week 24 (good response: 40%, moderate response: 20%).

As for tocilizumab, the response was relatively superior compared with the other biologic agents; 94.4% of patients responded to treatment at week 12, and no non-responders were recorded at the end of week 24. A good EULAR response was observed in 72.2% of patients at both week 12 and week 24 (69).

6.2.2) International Studies:

According to a study published in Clinical Reviews in Allergy & Immunology in 2025, the aim of the study was to compare the efficacy and safety of biologic agents in systemic lupus erythematosus (SLE) using a Bayesian network meta-analysis. A comprehensive and systematic search was conducted in electronic databases (PubMed, Medline, Cochrane Library, EMBASE, Web of Science, CNKI, and Wan Fang Data) from 2014 to September 2024.

Only randomized controlled trials with full-text articles involving adult patients with SLE treated with biologic agents compared with standard therapy were included in the study. The main efficacy outcomes were the Systemic Lupus Erythematosus Responder Index-4 (SRI-4) and the BILAG-Based Composite Lupus Assessment (BICLA). A total of 13,712 patients met the inclusion criteria.

The network meta-analysis demonstrated that, compared with standard therapy, telitacicept showed superior efficacy in achieving an SRI-4 response, whereas deucravacitinib and anifrolumab both demonstrated significant BICLA responses in patients with moderate-to-severe SLE. Regarding safety, no statistically significant differences were observed among the different therapeutic options.

Cluster analysis revealed that deucravacitinib had the best efficacy–safety profile. Telitacicept demonstrated the most marked improvement in SRI-4 response; however, it was associated with higher rates of adverse events (AEs) and serious adverse events (SAEs), whereas anifrolumab and deucravacitinib showed advantages in reducing SAEs.

In patients with high baseline interferon (IFN) signatures, type I anti-interferon biologic agents such as anifrolumab and sifalimumab are recommended to maximize clinical benefit. Since indirect comparisons were used, these findings should be interpreted cautiously; therefore, future research should prioritize direct comparative trials to validate the efficacy and safety profiles of these biologic agents (70).

A study conducted by the A. Nasonova Research Institute of Rheumatology and the Department of Rheumatology, Institute of Professional Education, demonstrated that biologic therapy was effective in patients with SLE. It reduced both clinical and immunological disease activity after 3 months of treatment, with a progressive increase in clinical efficacy and a further reduction in immunological activity throughout follow-up.

Rituximab (RTX) and belimumab (BLM) differed in terms of the time required to achieve clinical efficacy and their effects on immunological parameters. The results confirmed the good efficacy of belimumab in patients with articular, cutaneous, and mucosal involvement associated with high immunological activity. Belimumab therapy progressively reduced anti-double-stranded DNA antibody levels and increased serum complement levels, with these effects being more pronounced at month 12.

At the same time, positive changes in the clinical manifestations of SLE were observed as early as the third month of treatment, with a progressive increase in efficacy consistent with previous observations and with results reported from real-world clinical practice. Similarly, according to Collins CE et al., treatment with belimumab in 501 patients with SLE resulted in a slower but progressive development of clinical efficacy after 6 to 12 months of therapy (71).

6.3) Predictive Factors for a Good Response:

Rheumatoid Arthritis:

Good EULAR responders are characterized by:

Younger age, with lower erythrocyte sedimentation rates and fewer swollen joints.

Moderate baseline disease activity, which was strongly associated with a better response compared with high baseline disease activity.

Absence of joint deformities, which increases the likelihood of achieving a good EULAR response.

Absence of previous medical history and comorbidities.

Tocilizumab appears to be more effective compared with other biologic agents such as rituximab and anti-TNF alpha therapies (72).

Crohn's Disease :

Predictive factors associated with a good therapeutic response include:

Recent-onset disease.

Isolated colonic disease.

Absence of previous abdominal surgery.

Young, non-smoking patients.

Endoscopic findings showing ileocolonic ulcerative lesions.

Absence of stenosis.

Elevated CRP levels.

Good treatment adherence.

High blood infliximab concentrations (68).

7) Tolerance and Safety:

7.1) Adverse Effects and Complications:

7.1.1) Infectious Complications:

7.1.1.1) Reactivation of Tuberculosis:

Initiation of anti-TNFα therapy significantly increases the risk of tuberculosis (TB), most commonly due to reactivation of latent infection or previously inadequately treated disease. Because of its central role in both innate and adaptive immunity, TNFα is essential for the formation and structural integrity of the tuberculous granuloma. Neutralization of this cytokine by monoclonal antibodies promotes immune escape of Mycobacterium tuberculosis.

This risk is statistically higher with infliximab than with etanercept, as the latter mainly targets circulating TNF, thereby preserving granulomatous architecture to a greater extent (73).

Clinically, these tuberculosis cases are characterized by their severity and atypical presentation: more than 50% are extrapulmonary and 25% are disseminated. They often occur early, sometimes within the first month of treatment, and these severe forms may be fatal in approximately 10% of cases (74).

7.1.1.2) Viral Infections :

- **Varicella-Zoster Virus (VZV) Infections :**

Varicella-zoster virus (VZV) was rapidly identified as one of the potential complications associated with biologic therapy. VZV is a highly prevalent virus. Primary infection manifests clinically as varicella (chickenpox). After clinical recovery, the virus remains latent for life within sensory ganglia. Disruption of immune balance may lead to viral reactivation, clinically presenting as herpes zoster (shingles).

The classic clinical presentation combines a dermatomal vesicular skin eruption with often severe neuropathic pain, evolving over 1 to 4 weeks and sometimes followed by persistent and disabling post-herpetic neuralgia.

Although herpes zoster is classically limited to the skin, it may extend to severe complications, particularly neurological complications such as meningoencephalitis, or ophthalmological involvement. In patients receiving biologic therapy, the risk of progression to disseminated forms, characterized by multivisceral involvement or generalized rash mimicking varicella, requires increased diagnostic vigilance.

In the general population, the life time risk of developing herpes zoster is estimated at 20–30% (with an annual incidence ranging from 1.85 to 3.9 per 1,000 individuals according to studies), especially in older adults and/or immunocompromised individuals. The risk is even higher in patients with chronic inflammatory diseases because of the impact of immunosuppressive therapies on natural immune defenses.

Among biologic therapies, anti-TNF alpha agents and JAK inhibitors have also been associated with an increased risk of herpes zoster. Furthermore, the excess risk particularly concerns severe forms requiring hospitalization and/or intravenous antiviral therapy (75).

- **Herpes Simplex Virus (HSV) Infections:**

Reactivation of Herpes Simplex Virus (HSV) is frequently reported during biologic therapy. These infections mainly present as recurrent mucocutaneous lesions, without a clearly established increased risk of severe systemic forms or atypical primary infections for most biologic agents. In the absence of an available preventive vaccine, a preemptive treatment strategy using valaciclovir may be considered in patients with recurrent herpes infection before initiation of immunomodulatory therapy (76).

- **Cytomegalovirus (CMV) Infections:**

Cytomegalovirus (CMV) infections are rarely observed with anti-TNF alpha therapy, but their incidence appears to be higher with other classes of biologic therapies. They have been reported with JAK inhibitors, mainly in post-transplant settings, although rarer cases have also been documented with tofacitinib in the treatment of rheumatoid arthritis.

A significantly increased risk, sometimes up to sevenfold higher, has also been described with kinase inhibitors such as idelalisib or dasatinib in specific settings including leukemia or hematopoietic stem cell transplantation.

Regarding therapies targeting lymphocytes, no major risk appears to exist with anti-CD19 or anti-CD20 agents; however, the risk of reactivation with alemtuzumab (anti-CD52) is markedly higher, with a prevalence estimated between 0 and 9.5%. This vulnerability is explained by the profound lymphocyte depletion induced by the treatment, which promotes viral reactivation from latency.

Clinically, CMV reactivation may present as prolonged fever, severe fatigue, or organ involvement such as colitis, hepatitis, or pneumonitis. In the most severe cases, the virus may induce an apparent resistance to the background treatment of the autoimmune disease.

As of 2026, these risks require close monitoring: for high-risk agents such as alemtuzumab, regular monitoring of viral load using PCR is essential. This strategy allows the initiation of targeted preemptive therapy, generally with valganciclovir, to prevent severe complications before the onset of clinical symptoms (77).

- **Hepatitis B Virus (HBV):**

Hepatitis B virus (HBV) represents a major source of complications during initiation of biologic therapy. In adults, progression to chronic infection occurs in only 5% of cases; however, functional cure, defined as HBsAg loss, remains rare. Complete virological cure is exceptional because of the intrahepatic persistence of the viral genome in the form of covalently closed circular DNA (cccDNA).

This viral reservoir exposes immunocompromised patients to a permanent risk of reactivation. Reactivation manifests as necro-inflammatory hepatic cytolysis, which may be extremely severe. Clinically, the following manifestations may be observed :

- Early signs: severe asthenia, nausea, and abdominal pain.
- Cholestatic signs: development of mucocutaneous jaundice.
- Fulminant hepatitis: characterized by acute liver failure with decreased prothrombin levels and hepatic encephalopathy, potentially leading to death in the absence of urgent liver transplantation.

The risk of reactivation depends on the initial serological status and the potency of the immunosuppressive therapy (78).

- **Hepatitis C Virus (HCV):**

Unlike hepatitis B virus, HCV is an RNA virus that does not integrate into the host genome. Therefore, the risk of fulminant reactivation is considerably lower, although not absent, since immunosuppression may alter the balance between viral replication and immune control.

During biologic therapy, particularly with anti-TNF alpha agents or JAK inhibitors, HCV infection may present with:

- Hepatic cytolysis: the most frequent adverse effect, characterized by elevated liver transaminases (ALT/AST). According to studies, this risk of hepatic flare may affect up to 50% of untreated HCV patients.
- Increased viral load: immunosuppression may enhance viral replication, leading to elevated circulating HCV RNA levels. Although often initially asymptomatic, this increase promotes long-term progression of hepatic fibrosis.
- Extrahepatic manifestations: HCV may induce systemic manifestations such as cryoglobulinemia and vasculitis, which may mimic symptoms of the treated autoimmune disease (e.g., rheumatoid arthritis), making differential diagnosis challenging.

The excellent efficacy and safety profile of pangenotypic direct-acting antivirals (DAAs) now justifies systematic treatment of hepatitis C, whether chronic or acute. Viral eradication should be prioritized and, whenever possible, completed before initiation of biologic therapy. If this is not feasible, anti-HCV treatment should be started promptly after biologic therapy initiation (79).

- **Progressive Multifocal Leukoencephalopathy:**

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease caused by reactivation of the JC virus, a member of the polyomavirus family, which is latent in a large proportion of the general population (approximately 80%), mainly within the kidneys, lymphoid organs, and bone marrow.

PML presents with subacute neurological deficits such as confusion and ataxia. Diagnostic confirmation relies on brain magnetic resonance imaging (MRI), demonstrating characteristic demyelinating lesions, combined with lumbar puncture. Cerebrospinal fluid analysis allows detection of JC virus DNA by polymerase chain reaction (PCR).

This complication has mainly been described in patients receiving rituximab, particularly those treated for lymphoma, but also in patients treated with anti-TNF agents or other immunosuppressive therapies. Fortunately, it remains exceptionally rare in patients with rheumatoid arthritis (80).

7.1.2) Neoplasia:

In general, patients with inflammatory rheumatic diseases are at higher risk of developing lymphoproliferative disorders than the general population, independently of their treatment.

Rheumatoid arthritis (RA) is associated with an increased risk of prostate cancer, with a hazard ratio (HR) of 1.66, lung cancer with an HR of 2.24, and non-Hodgkin lymphoma with an HR of 1.75. The risk of lymphoma is particularly associated with the severity and inflammatory activity of RA (81).

A recent meta-analysis showed that the risk of solid malignancies in patients receiving anti-TNF therapy is not increased compared with patients treated with conventional disease-modifying antirheumatic drugs (csDMARDs). Similar findings were observed for abatacept and rituximab compared with methotrexate. This study also demonstrated the absence of cancer recurrence when biologic therapy was introduced after 5 to 13 years of oncological remission in patients with a history of cancer (82).

Anti-TNF agents also do not appear to increase the risk of lymphoma, findings confirmed by a relative risk (RR) of 0.90. Regarding the risk of melanoma under biologic therapies (anti-TNF agents, rituximab, tocilizumab, and abatacept), no increase in risk was observed, with an RR of 1.17.

These findings were confirmed by two additional meta-analyses, one involving anti-TNF agents and the other involving biologic therapies in Europe. There was also no significant increase in the risk of developing a second primary melanoma, with a reported HR of 3.2 (83).

7.1.3) According to Organ System:

- **Neurological (Demyelination):**

Demyelinating syndromes have been reported with all anti-TNF agents. Other neurological complications such as optic neuritis, Guillain–Barré syndrome, and multiple mononeuritis have also been described. Clinical manifestations include paresthesia, visual impairment, confusion, and balance disorders.

The occurrence of such symptoms requires immediate discontinuation of anti-TNFα therapy. Therapeutic management may include high-dose corticosteroids or intravenous immunoglobulins (IVIG). Clinical outcomes are generally favorable, with regression of symptoms, although recovery may occasionally remain incomplete.

Consequently, a history of demyelinating disease constitutes an absolute contraindication to initiation of anti-TNFα therapy (84).

- **Cardiovascular:**

In general, cardiovascular morbidity and mortality are increased in these patients. Disease activity and disease duration exceeding 10 years are independent risk factors for heart failure, associated with an increased risk of hospitalization.

A 28% increase in myocardial infarction risk has been observed in patients treated with anti-TNF agents compared with abatacept. However, a recent meta-analysis comparing anti-TNF agents with conventional DMARDs (cDMARDs) demonstrated a protective effect of anti-TNF therapy, with a reduction in cardiovascular events including myocardial infarction, heart failure, and stroke.

Similar findings have been reported for rituximab and other biologic agents. The contraindication of anti-TNF therapy in heart failure originates from studies initially designed to demonstrate their efficacy in this indication, based on the correlation between TNFα levels and heart failure severity.

Studies involving infliximab and etanercept in patients with heart failure without inflammatory disease failed to demonstrate clinical benefit and instead highlighted deleterious effects. Harmful effects were particularly observed with infliximab at high doses (10 mg/kg).

Therefore, congestive heart failure stage III or IV according to the New York Heart Association (NYHA) classification constitutes a formal contraindication to anti-TNFα therapy (85).

- ❖ **Pulmonary:**

Drug-Induced Pneumonitis:

More than one hundred cases of acute pneumonitis occurring after the second month of treatment and within 15 days following the last infliximab infusion (87% of cases) have been described.

Most drug-induced pneumonitis cases correspond to acute febrile organizing pneumonia, often severe and early in onset. Establishing causality remains difficult because of the frequent coexistence of pre-existing respiratory diseases, concomitant methotrexate prescription, particularly in rheumatoid arthritis, and the absence of drug rechallenge tests.

Anti-TNF agents, mainly used in refractory sarcoidosis, may occasionally induce infectious and non-infectious complications such as granulomatous disorders. These complications are rare; approximately twenty cases of sarcoidosis and sarcoid-like reactions have been reported in the literature, generally occurring late during treatment.

The pathophysiological mechanism underlying anti-TNF-induced sarcoidosis remains unclear. Possible explanations include infectious triggers or the role of interferon-gamma, whose levels are increased in patients treated with anti-TNF agents. In addition, sarcoid-like reactions have also been reported in patients with chronic hepatitis C treated with interferon.

Rare cases of pleuropericarditis related to drug-induced lupus, thromboembolic events associated with antiphospholipid antibodies, and exceptional pulmonary vasculitic nodules have also been reported (86).

- ❖ **Digestive:**

An increased risk of gastrointestinal perforation has been reported with tocilizumab therapy. Weight gain under tocilizumab treatment has also been described (87).

7.1.4) Biological Adverse Effects:

- **C-Reactive Protein (CRP):**

It should be remembered that elevated serum CRP levels may be absent in cases of infection or inflammation in patients treated with tocilizumab. Indeed, IL-6 is a pro-inflammatory cytokine that stimulates hepatocytes to synthesize CRP as well as other acute-phase proteins. Therefore, clinicians should be cautious of falsely reassuring CRP levels in patients receiving tocilizumab (88).

- **Hepatotoxicity:**

Hepatotoxicity associated with anti-TNF therapy is rare and generally mild. It has mainly been described with infliximab, less frequently with adalimumab, and has not been reported with etanercept.

The proposed mechanism involves clearance of immune complexes by hepatic sinusoids with activation of Kupffer cells, leading to free radical production and focal hepatic injury.

Occasional elevations in liver transaminases have also been observed with tocilizumab. In most cases, these abnormalities are transient and without clinical consequences (89).

- **Hypercholesterolemia:**

Hypercholesterolemia involving both LDL and HDL cholesterol levels has been reported with tocilizumab therapy, although apparently without an associated increase in cardiovascular risk Elevated cholesterol levels may occasionally require initiation of statin therapy (90).

- **Cytopenia:**

Transient neutropenia, particularly at treatment initiation and without increased infectious risk, has been described with tocilizumab, anti-TNF agents, and secukinumab.

Rare cases of cytopenia, especially late-onset neutropenia, have been reported with rituximab and have been associated with infections (91).

- **Hypogammaglobulinemia:**

Hypogammaglobulinemia is a recognized adverse effect of rituximab therapy. It is associated with an increased risk of infection, particularly when baseline IgG levels are below 6 g/L before treatment initiation (92).

7.1.5) Cutaneous Adverse Effects:

- **Infusion Reactions:**

Injection-related reactions vary according to the route of administration (intravenous or subcutaneous) and the biologic agent used.

With infliximab, two types of reactions have been described. Acute reactions occurring within 24 hours (approximately 20% of cases) manifest as pruritus, flushing, or urticaria. These reactions are usually controlled by slowing the infusion rate and generally do not recur.

Delayed reactions occur between3 day and 14 day (approximately 2.5% of cases) and may include rash, pruritus, facial edema, fever, arthromyalgia, and sicca syndrome. Management relies on paracetamol, antihistamines, or corticosteroids depending on severity.

With abatacept, the incidence of infusion reactions is approximately 2%, without treatment discontinuation in reported cases. Rituximab may induce reactions from the first infusion because of B-cell lysis.

Tocilizumab may induce reactions within 24 hours of administration, including rash, headache, or elevated pressure (93).

- **Injection Site Reactions:**

According to one study, these reactions occur in approximately 20% of patients receiving adalimumab and 37% of those treated with etanercept. They are less frequent with other biologic agents but have also been reported with golimumab and certolizumab.

These reactions manifest as localized erythema, with or without associated pruritus and edema. They usually resolve spontaneously over time, although topical ice application or anti-inflammatory treatment may occasionally be required.

Rotation of injection sites helps prevent these reactions. These manifestations do not justify treatment interruption or discontinuation (94).

7.1.6) Other Reactions:

Severe cutaneous reactions such as Stevens–Johnson syndrome and DRESS syndrome have been reported with anti-TNF agents.

Psoriasiform eruptions, presenting as guttate, plaque-type, palmoplantar, or pustular psoriasis, have also been reported with anti-TNF therapy, either occurring de novo or through worsening of pre-existing psoriasis. Plaque-type and palmoplantar forms are the most common.

These reactions have been reported more frequently with infliximab, appearing on average between 10 and 31 months after treatment initiation. Similar reactions have also been described with tocilizumab and rituximab.

The pathophysiology may involve increased type I interferon production by dendritic cells in predisposed individuals. In moderate forms involving less than 5% of body surface area, treatment modification is generally unnecessary, and local therapy or methotrexate may be added if involvement exceeds 5% of body surface area.

In more severe cases, switching anti-TNF therapy or even changing the therapeutic class should be considered (95).

7.2) Biological Monitoring:

7.2.1) Pre-Therapeutic Infectious Assessment:

It is essential to evaluate the immune status of patients as soon as an inflammatory disease is diagnosed.

To identify infectious or immunological risks before initiation of immunosuppressive therapy or biologic treatment.

Systematic Investigations:

- **Hematological and Biochemical Tests:**

Complete blood count (CBC)

C-reactive protein (CRP)

Liver function tests

Serum protein electrophoresis

Serum creatinine

Blood electrolyte panel

Viral Serologies

Hepatitis B virus (HBV): HBsAg, anti-HBs antibodies, anti-HBc antibodies; viral DNA testing if HBsAg is positive

Hepatitis C virus (HCV) and HIV serologies

Epstein–Barr virus (EBV), cytomegalovirus (CMV), and varicella-zoster virus (VZV) serologies in the absence of documented previous varicella infection

- **Autoimmune Screening:**

Antinuclear antibodies (ANA) and anti-native DNA antibodies, particularly because of the risk of drug-induced lupus, especially with anti-TNF agents

Chest Imaging

Chest radiography, mandatory before initiation of anti-TNF therapy

- **Tuberculosis Screening:**

Tuberculin skin test (TST): considered positive if induration is > 5 mm or in the case of tuberculin conversion after BCG vaccination

Interferon-gamma release assays (IGRAs): QuantiFERON-TB® or T-SPOT.TB® according to current recommendations

- **Other Investigations:**

Beta-hCG testing in women of childbearing age

Special Situations

Stool culture and parasitological examination in cases of parasitic exposure risk, particularly after travel

Strongyloidiasis serology in patients returning from endemic areas

Urine culture (ECBU) in patients with a history of recurrent urinary tract infections

Serum cholesterol and magnesium levels when cyclosporine therapy is used

Gynecological Consultation

Cervical smear test to rule out human papillomavirus (HPV) infection

- ✓ **Important Notes:**

Tuberculosis screening is mandatory before any anti-TNF therapy and should ideally be performed before initiation of any immunosuppressive treatment.

Performing this assessment early facilitates interpretation of subsequent results and allows appropriate management (96).

- **Monitoring of Hematological and Hepatic Parameters:**

Monitoring the tolerance of associated disease-modifying therapies includes regular assessment of complete blood count, liver transaminases, serum creatinine, and renal clearance.

The frequency of monitoring and the biological parameters to be evaluated depend on patient characteristics such as age and comorbidities, as well as the possible concomitant use of conventional therapy in association with biologic treatment (96).

Biothérapies / Biologie	Anti-TNF	Abatacept	Rituximab	Tocilizumab
Hémogramme	M1, M3 puis trimestriel ; infliximab : à chaque perf.	Trimestriel	Trimestriel	Mensuel
Transaminases	M1, M3 puis trimestriel ; infliximab : à chaque perf.	Trimestriel		Mensuel (1er trimestre) puis trimestriel (si normales)
DPIg			Avant chaque chaque cycle ou si infection	
Phénotypage lymphocytaire			Pas de suivi systématique	
Bilan lipidique				2e ou 3e perf.
* *Un dosage des lymphocytes B circulants peut être utile dans l'évaluation du risque infectieux en cas de traitement itératif.*				

Table 12 : Biological monitoring of patients by drug.

7.3) Practical Recommendations:

- **Vaccination before Initiation of Biologic Therapy:**

Before updating vaccination status, it is essential to reconstruct the patient's previous vaccination history through direct patient questioning, information from relatives, possible contact with the primary care physician and/or specialists involved in the patient's management, as well as careful review of the medical records and vaccination booklet. Serological testing should be guided by this assessment.

Before administering vaccines, previous vaccine tolerance should also be verified. It is strongly recommended that this evaluation and vaccination update be performed before initiation of treatment for two main reasons:

- Vaccine efficacy is unquestionably better in patients not receiving immunosuppressive therapy.
- Live vaccines are contraindicated in immunocompromised patients and therefore cannot be administered to patients already receiving immunosuppressive therapy, including corticosteroid therapy >10 mg/day prednisone equivalent for more than 2 weeks or pulse corticosteroid therapy within the previous 3 months, or biologic therapy.

In the case of vaccination with a live vaccine, a minimum interval of 4 to 6 weeks (depending on the vaccine) is required before initiation of immunosuppressive treatment. Conversely, after discontinuation of immunosuppressive therapy, a delay of 3 months is necessary before administration of a live vaccine.

If vaccination updates could not be completed before treatment initiation, for example because urgent therapy was required in a severely ill patient, vaccination should be performed as soon as possible after treatment initiation. Indeed, although reduced, vaccine immunogenicity persists in patients receiving immunosuppressive therapy.

Whenever possible, vaccination should preferably be completed before initiation of immunosuppressive treatment.

The main live vaccines include:

- Bacillus Calmette–Guérin (BCG)
- Measles–Mumps–Rubella (MMR)
- Varicella vaccine
- Herpes zoster vaccine
- Rotavirus vaccine
- Yellow fever vaccine
- Oral poliomyelitis vaccine (97).

Vaccin	Moment de réalisation par rapport au début du traitement immuno-suppresseur	Indication	Modalités vaccinales	Rappels
Grippe injectable	Avant/après	**Tout patient sous immuno-suppresseurs**	1 injection	Tous les ans
Pneumocoque	Avant/après	**Tout patient sous immunosuppresseurs**	Vaccin conjugué 13-valent Puis 2 mois plus tard : vaccin non conjugué 23-valent	Si antécédent de vaccin 23-valent : attendre 1 an pour vaccin 13-valent, 5 ans pour vaccin 23-valent Si antécédent de vaccination complète (vaccin conjugué 13-valent puis vaccin 23-valent) : vaccin 23-valent tous les 5 ans
Hépatite B	Avant/après	**À proposer systématiquement si sérologie négative Vérifier taux ac anti-HBs**	**schéma renforcé à discuter (40 µg à M0, M1 , M2, M6)**	
Human Papilloma Virus (HPV)	Avant/après	Idem population générale : femmes ≤ 19 ans, homosexuels < 26 ans	**Si pratiqué sous immunosuppresseurs : Schéma 3 doses : M0, M2, M6**	
Diphtérie, tétanos, poliomyélite	Avant/après	Idem population générale		**Tous les 10 ans**
Vaccins vivants :				
Rougeole, oreillons, rubéole (ROR)	**4 semaines avant, si non vacciné**	À proposer systématiquement si non vacciné		
Varicelle	**Au moins 6 semaines avant si sérologie négative 2 doses à 4 semaines d'intervalle**	**À proposer systématiquement si sérologie négative**		
Fièvre jaune	**4 semaines avant, si non vacciné**	**À proposer si susceptible de voyager, même si pas de projet immédiat**		

Table 2: Vaccination specificities in patients receiving immunosuppressive therapy regarding vaccine indications and administration modalities (97).

- **Prevention of Opportunistic Infections:**

- **Prevention of Parasitic Infections.**

- **Prevention of Pneumocystis jirovecii Pneumonia:**

Cases of Pneumocystis jirovecii pneumonia are frequently reported in the literature, although this condition remains rare in this patient population. Given the potentially severe adverse effects associated with prophylactic therapy, prophylaxis is recommended mainly for patients receiving triple immunosuppressive therapy, including at least one calcineurin inhibitor or an anti-TNF-α antibody.

Prophylaxis is primarily based on trimethoprim-sulfamethoxazole (80/400 mg: 1 tablet daily or 160/800 mg: 1 tablet three times weekly), which is considered the most effective regimen. Atovaquone, dapsone, or aerosolized pentamidine may be considered as alternative therapies (98).

- **Prevention of Herpes Virus Infections (CMV, HSV, VZV, EBV):**

Although reactivation of latent CMV infection is common in patients receiving immunosuppressive therapy, progression to severe tissue-invasive disease is very rare. Given the toxicity of anti-CMV treatments, routine preventive antiviral therapy is not recommended for these patients.

For patients with a history of ocular, oral, or genital HSV infection, anti-HSV prophylaxis should be considered. To prevent recurrent herpetic infections in immunosuppressed patients, daily administration of a single dose of valaciclovir (500 mg) is recommended because of its ease of use.

Prevention of VZV infection concerns only patients with no history of varicella and no previous vaccination. Post-exposure prophylaxis includes administration of specific anti-VZV immunoglobulins, or polyvalent immunoglobulins if unavailable, within 96 hours (or at most within 10 days) following exposure.

These patients should be monitored carefully, as immunoglobulins do not completely eliminate the risk of infection.

Primary Epstein–Barr virus (EBV) infection may lead to lymphoma, mainly involving the gastrointestinal tract, particularly in patients receiving thiopurines such as azathioprine or 6-mercaptopurine. However, because this situation is rare, prophylactic antiviral therapy is not routinely required.

For patients with negative EBV serology, anti-TNF-α therapy may be preferred over thiopurines in order to reduce this risk (99).

- **Influenza Prevention:**

Apart from vaccination, which is strongly recommended for all patients, chemoprophylaxis with oseltamivir should be considered in any unvaccinated patient who has been in contact with an individual infected with influenza. This prophylaxis should be initiated as soon as possible after exposure (100).

- **Prevention of Hepatitis B:**

All patients eligible for immunosuppressive therapy should undergo hepatitis B serological screening.

Vaccination should be proposed to all non-vaccinated patients. If previous HBV exposure is identified by serology, prophylactic therapy with tenofovir or entecavir should be considered. This decision depends on the risk of reactivation, which is related to both the serological profile and the type of immunosuppressive therapy used. Recommendations may vary between academic institutions.

It appears reasonable to initiate antiviral treatment in all patients positive for HBs antigen. This treatment should be continued for up to six months after completion of immunosuppressive therapy.

If HBV DNA is detected, initiation of immunosuppressive treatment should ideally be delayed until viral replication becomes undetectable.

For patients with negative HBs antigen and positive anti-HBc antibodies, the risk of viral reactivation is considered very low. Monthly monitoring of liver function tests and HBV DNA should initially be performed, followed by monitoring every three months thereafter. Antiviral treatment should only be considered if viral reactivation occurs.

Coinfection with hepatitis Delta virus should also be investigated in HBsAg-positive patients (101).

- **Prevention of Bacterial Infections:**

Patient education is essential in order to avoid high-risk situations:

- Salmonella infections: avoid raw meat, raw eggs, and unpasteurized milk.
- Clostridium difficile infections: unnecessary antibiotic use should be avoided, and hospital hygiene protocols should be strictly followed when immunosuppressed patients are hospitalized in units affected by C. difficile infection.
- Listeria monocytogenes infections, especially in patients receiving anti-TNF-α antibodies: avoid raw meat, raw vegetables, smoked fish, and unpasteurized milk and cheese.
- Nocardia species infections, particularly in patients receiving anti-TNF-α antibodies: gardening activities should be avoided (101).

Prevention of Tuberculosis:

Although available data remain limited, these precautionary measures should also be considered for other biologic therapies such as anti-IL-12/IL-23 antibodies and anti-α4β7 integrin agents.

Strict vigilance is required in all patients receiving immunosuppressive therapy, as reactivation of latent tuberculosis may also occur.

If latent tuberculosis is diagnosed, prophylactic treatment with isoniazid alone for 9 months or a combination of isoniazid and rifampicin for 3 months is recommended.

Anti-TNF-α therapy should only be initiated after at least three weeks of tuberculosis prophylaxis, except in emergency situations requiring earlier treatment initiation (102).

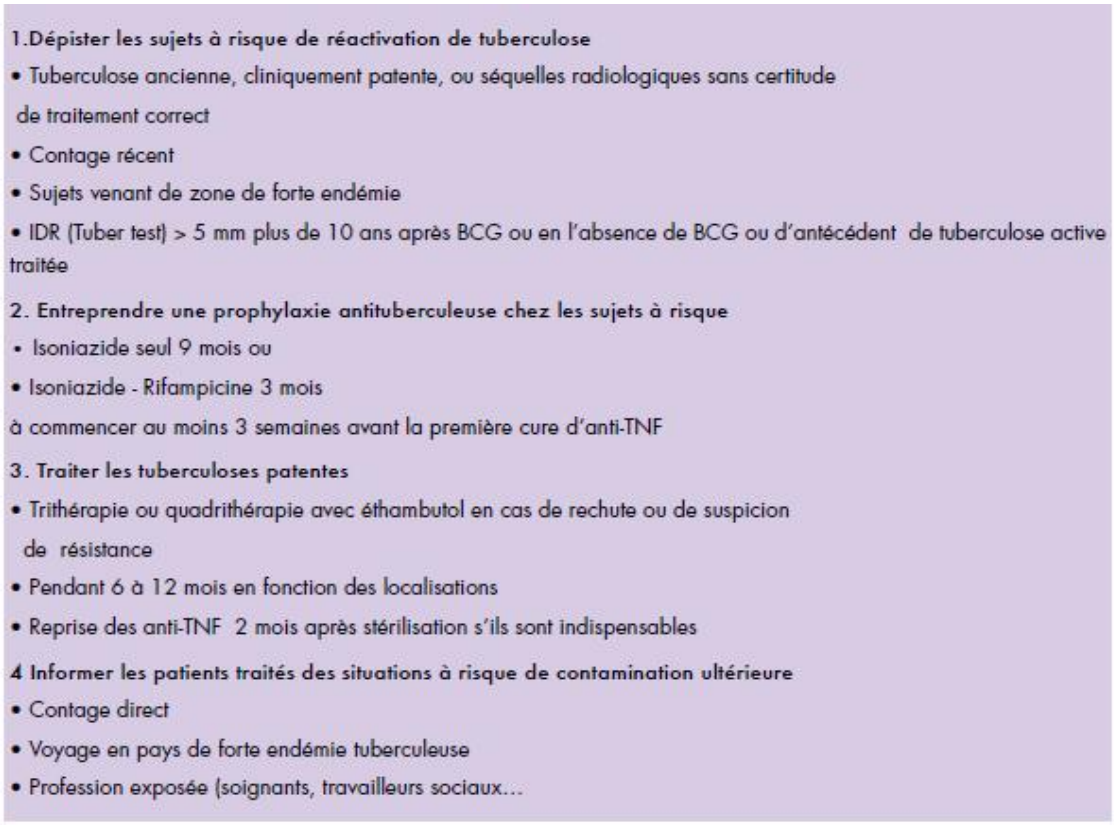


Figure 9 : Screening, prevention, and management of tuberculosis occurring during anti-TNF therapy (102).

8) Practical and Organizational Aspects:

8.1) Access in Algeria:

The introduction of biologic therapies has profoundly transformed the management of chronic inflammatory and autoimmune diseases such as rheumatoid arthritis, inflammatory bowel diseases, and certain systemic disorders (103). These treatments, mainly including monoclonal antibodies and targeted therapies, are characterized by high efficacy (104), but also by high costs and specific organizational requirements.(105)

In Algeria, biologic therapies are generally available and used in specialized hospital departments, particularly in internal medicine, rheumatology, gastroenterology, and oncology units. Their prescription is strictly supervised by specialists because of the need for regular clinical and biological monitoring of patients. Studies conducted in Algerian hospital centers show that these treatments are now integrated into routine clinical practice, although real-world data remain limited.

From an organizational perspective, access to biologic therapies depends heavily on the public healthcare system. Their availability is influenced by importation procedures, public procurement systems, and budgetary constraints. At the international level, the World Health Organization emphasizes that access to innovative biologic drugs remains unequal, particularly in middle-income countries, because of economic and structural barriers.

The high cost of biologic therapies represents a major obstacle to accessibility. Even when these treatments are covered by the public healthcare sector, their financial impact on healthcare systems limits their widespread diffusion. In this context, the introduction of biosimilars represents an essential strategy to improve access to biologic therapies by providing therapeutic alternatives with comparable quality at lower cost.

According to an analysis of the Algerian regulatory framework, the country has made progress in the adoption of biosimilars, relying on recommendations from the European Medicines Agency, the U.S. Food and Drug Administration, and the World Health Organization, although it still lacks a fully autonomous national regulatory framework. This evolution could progressively improve accessibility to biologic therapies.

Finally, inequalities in access persist between regions because of the concentration of specialized healthcare structures within major university hospital centers. This results in disparities in patient management according to geographical location.

8.2) Logistical Constraints:

- **Importation, Delays, and External Dependence:**

Many active pharmaceutical ingredients, bioproduction equipment, reagents, and related materials are imported. This results in long supply delays influenced by currency fluctuations, customs barriers, and bureaucratic procedures.

Delays in approval of innovative drugs, particularly biologic therapies, mean that several years may pass between international approval and availability in Algeria.

- **Limited Local Industrial Capacity:**
  Although Algeria has increased local production of conventional medications, local production of biologic therapies remains limited. Insufficient infrastructure, inadequate equipment, and limited access to cell culture materials remain major challenges.

There is also a shortage of specialized technical expertise and trained personnel for production, handling, storage, and distribution.

- **Internal Transportation:**

Transportation between suppliers, warehouses, and hospitals is sometimes poorly organized because of road conditions, long distances, inadequate transportation means, and limited reliability. These issues are particularly important for biologic products.

Risks include cold chain interruption during transport, lack of suitable vehicles, overloading, and poor insulation.

- **Equipment Maintenance:**

Freezers, ultra-low-temperature freezers, temperature monitoring systems, and backup generators must be reliable and adequately maintained.

In many hospitals, preventive maintenance remains insufficient, while spare parts and technical support services may be unavailable or delayed.

- **Financial Constraints:**

Biologic therapies are often very expensive because of production costs, importation of reagents and raw materials, and specialized transportation expenses.

Hospital and national healthcare budgets must allocate resources for these therapies; however, budgetary limitations and competing healthcare priorities reduce opportunities for innovation.

- **Traceability and Quality Assurance:**

Biologic products require strict traceability, including batch identification and monitoring of storage conditions.

Documentation systems, whether computerized or manual, must therefore be robust and reliable.

- **Geographical Accessibility:**

Hospitals located in rural or remote areas are generally less well equipped, and supply delays may be considerably longer.

Patients are sometimes required to travel to major urban centers to access costly or specialized therapies.

- **Awareness and Training:**

Healthcare professionals and hospital pharmacists must be trained in biologic therapies, including storage conditions, administration techniques, and management of adverse effects.

Lack of adequately trained personnel may lead to errors such as improper storage or incorrect handling.

8.3) Importance of Therapeutic Patient Education:

Therapeutic patient education (TPE) plays a central role in the management of patients receiving biologic therapies. These treatments, often complex and used in chronic systemic diseases, require adequate patient understanding to ensure both efficacy and safety.

TPE improves therapeutic adherence by explaining administration procedures, dosage regimens, and the importance of strict treatment compliance. Better adherence directly contributes to reducing therapeutic failure and disease relapse.

In addition, biologic therapies expose patients to an increased risk of adverse effects, particularly infectious complications. Patient education helps raise awareness regarding early warning signs such as fever, infections, and skin reactions, encouraging prompt medical consultation and thereby reducing severe complications.

TPE also promotes patient empowerment by making patients active participants in their own care. It facilitates disease self-management, improves quality of life, and reduces treatment-related anxiety.

Finally, in resource-limited settings such as Algeria and similar countries, TPE contributes to optimizing the use of costly biologic therapies by limiting unjustified treatment interruption and inappropriate use.

Conclusion

Biologic therapy currently represents a major therapeutic breakthrough in the management of inflammatory and autoimmune diseases in internal medicine. Its development is based on a better understanding of immunopathological mechanisms, particularly immune system dysregulation, molecular signaling pathways, and interactions with environmental factors. This targeted therapeutic approach has led to the emergence of several treatment classes, including anti-TNF agents, B-cell and T-cell inhibitors, anti-interleukin therapies, JAK inhibitors, and anti-integrin agents, each with specific clinical indications.

In routine clinical practice, biologic therapies have profoundly transformed the management of numerous chronic diseases such as rheumatoid arthritis, systemic lupus erythematosus, vasculitis, and inflammatory bowel diseases. These therapies have demonstrated significant efficacy in controlling disease activity, reducing disease progression, preserving organ function, and improving patients' quality of life.

However, despite these major benefits, the use of biologic therapies remains associated with important limitations, including the risk of infectious and immunological adverse effects, the need for strict clinical and biological monitoring, as well as organizational and economic constraints. These challenges highlight the importance of rational prescribing, careful patient selection, and individualized long-term follow-up.

Furthermore, disparities in accessibility, particularly in resource-limited settings, emphasize the need to strengthen healthcare organization, improve professional training, optimize therapeutic patient education, and facilitate access to biosimilars in order to ensure broader and more equitable use of these innovative therapies.

Thus, biologic therapy has become a true therapeutic revolution in internal medicine. Nevertheless, its optimal use requires thorough scientific knowledge, continuous vigilance, multidisciplinary collaboration, and constant adaptation to both clinical realities and healthcare system constraints (110).

PRACTICAL SECTION

INTRODUCTION

Over the last two decades, biologic and targeted therapies have profoundly transformed the management of inflammatory, autoimmune, systemic, and immune-mediated diseases. By specifically targeting key molecular and cellular pathways involved in immune dysregulation, these therapies have significantly improved disease control, reduced organ damage, and enhanced the quality of life of patients suffering from chronic and complex diseases.

Initially developed for rheumatologic and oncologic indications, biologic therapies are now increasingly used in internal medicine for a wide spectrum of diseases including systemic lupus erythematosus, vasculitis, inflammatory myopathies, Behçet disease, inflammatory bowel disease, autoinflammatory disorders, and several rare immune-mediated diseases. Their use has progressively expanded with the development of new therapeutic targets and targeted synthetic therapies such as Janus kinase inhibitors.

Internal medicine occupies a central position in the management of these complex multisystem diseases, particularly in referral centers where patients often present with severe, refractory, overlapping, or rare conditions requiring multidisciplinary management and prolonged follow-up. In this context, biologic and targeted therapies represent a major therapeutic advancement but also introduce new clinical, infectious, organizational, and economic challenges.

Despite the increasing use of biologic therapies worldwide, real-world data concerning their utilization in North African countries, particularly in Algeria, remain limited. Most available data originate from randomized clinical trials conducted in highly selected populations and may not fully reflect daily clinical practice, especially in resource-variable settings where accessibility, therapeutic monitoring, infectious risk, and treatment availability may differ significantly from international reference centers.

In Algeria, and particularly in Southern regions, few studies have evaluated the real-life use of biologic and targeted therapies in internal medicine departments. Data regarding the prevalence of biologic therapy use, the profile of treated diseases, therapeutic strategies, tolerance, infectious complications, adherence, and patient satisfaction remain poorly documented.

Therefore, this ambispective real-world study was conducted in the Department of Internal Medicine of Laghouat Mixed Hospital with the aim of providing an overview of biologic and targeted therapy utilization in routine clinical practice over a 53-month period. Beyond the descriptive epidemiological aspect, this work also aims to better characterize the diseases treated, the therapeutic patterns used, the safety profile, and the clinical outcomes observed in our local context.

Primary Objective

- To determine the prevalence of biologic and targeted therapy use in the Department of Internal Medicine of Laghouat Mixed Hospital and within the population of Laghouat Province during the study period.

Secondary Objectives

- To describe the epidemiological and clinical profile of patients receiving biologic or targeted therapies.
- To identify the main diseases and indications treated with biologic therapies in the Internal Medicine Department.
- To describe the different biologic and targeted therapeutic agents used in routine clinical practice.
- To evaluate therapeutic response and clinical outcomes under biologic therapies.
- To assess tolerance and adverse effects associated with biologic and targeted therapies.
- To analyze infectious complications occurring during treatment.
- To evaluate treatment adherence and patient satisfaction.
- To identify factors associated with therapeutic response, adverse effects, and infectious complications.
- To provide real-world data regarding the use of biologic therapies in an Internal Medicine Department in Southern Algeria.

PATIENTS

AND

METHODS

1) Type of study:

This was an ambispective observational single-center cohort study conducted in the Department of Internal Medicine at Laghouat El AkidLotfi General Hospital.The study combined both retrospective and prospective components.

2) Study area and period:

This study included patients undergoing biologic therapy. These patients were managed in the Department of Internal Medicine at the LAGHOUAT El Akid Lotfi General Hospital during a five-year study period running from January 2020 to December 2025.

3) Study population:

- A total of 136 patients receiving biologic or targeted therapies were initially identified through the hospitalization data base of the Department of Internal Medicine.
- All patients receiving biologic therapy regardless of the indication were screened for eligibility.
- After verification of inclusion criteria and exclusion of unusable or highly incomplete records, 125 patients were finally included in the study.

Inclusion criteria:

- Age ≥ 18 years;
- Follow-up in the Department of Internal Medicine;
- Exposure to biologic or targeted therapy for at least 3 months;
- Available medical records ;
- Informed consent.

Exclusion criteria:

- Patients with missing key outcome data despite medical record review and telephone follow-up;
- Patients lost to follow-up with insufficient evaluable data;
- Patients who declined participation during telephone contact;
- Duplicate records or unusable files.

4) Data collection methodology

Data collection was performed using a standardized study form developed specifically for this work.The methodology included three complementary steps:

1. Identification of eligible patients:

Patients receiving biologic therapies were identified through:

- Hospitalization data bases ;
- Internal medicine department registries ;
- Archived medical records.

2. Retrospective data extraction :

Clinical and therapeutic data were retrospectively extracted from archived medical records.

The following variables were collected :

- Sociodemographic characteristics ;
- Underlying diseases;
- Comorbidities;
- Previous conventional treatments ;
- Type of biologic therapy ;
- Associated therapies ;
- Biological and clinical follow-up data;
- Infectious complications ;
- Adverse effects.

3. Prospective telephone assessment:

Whenever possible, patients were directly contacted by telephone in order to:

- Complete missing information ;
- Assess treatment adherence ;
- Evaluate treatment satisfaction ;
- Clarify adverse events and infectious complications;
- Identify accessibility and follow-up constraints.

For patients who could not be reached by telephone, analyses were based exclusively on available hospital records. (Annexe I).

4. Ethical considerations:

This study was conducted in accordance with the principles of the Declaration of Helsinki. Patient confidentiality and anonymity were respected throughout the study. Oral informed consent was obtained whenever direct telephone interviews were performed.

5. Statistical analysis :

Statistical analyses were performed using Python-based statistical analysis tools, including the pandas, scipy, statsmodels, and matplotlib libraries.

Qualitative variables were expressed as frequencies and percentages, whereas quantitative variables were expressed as means ± standard deviation (SD) when appropriate.

A descriptive analysis was initially conducted to characterize the study population, indications for biologic and targeted therapies, therapeutic modalities, clinical response, adverse effects, infectious complications, adherence, and patient satisfaction.

Subsequently, an exploratory analytical analysis was performed to identify factors potentially associated with:

- favorable clinical response ;
- occurrence of adverse effects ;
- occurrence of infectious complications.

Comparisons between categorical variables were performed using Chi-square test or Fisher's exact test when appropriate according to expected frequencies.

An exploratory multivariate logistic regression analysis was additionally conducted to evaluate factors potentially associated with favorable clinical response. Variables included in the model were selected according to their clinical relevance and data availability.

Graphical representations were generated using matplotlib.

Only evaluable patients were included in each specific analysis according to the available-case analysis principle.

A p-value < 0.05 was considered statistically significant.

RESULTS

To our knowledge, this study represents one of the first real-world evaluations of biologic and targeted therapy utilization in an Internal Medicine department in Southern Algeria.

Study flowchart:
A total of 136 patient records were initially identified.
After exclusion of incomplete files, unavailable data, and patients lost to follow-up, 125 patients were included in the final analysis.
The number of evaluable patients varied depending on the studied parameter:
103 patients for comorbidity analysis;
97 patients for clinical response assessment;
93 patients for infectious complications;
90 patients for adherence and satisfaction evaluation.

1) Prevalence:

1.1) Hospital prevalence of biotherapie:

= Number of hospitalized patients receiving biotherapy **/** Total number of patients hospitalized in the Internal Medicine Department of Laghouat Mixed Hospital during the study period.

1.2) Overall Prevalence in Laghouat Province (Wilaya):

= Number of patients using biotherapy **/** Total population of Laghouat Province.

Conditions	**Number of cases**	**Hospital prevalence (%)**	**Overall prevalence (%)**
Number of patients using biotherapy	125	1.84	0.017
Total population of Laghouat Province	750000		
Total number of patients hospitalized during the study period	6758		

Table 13 : The prevalence of biotherapy in the Internal Medicine Department of the Mixed Hospital of Laghouat Province, as well as in the overall population of the province, over a 53-month period.

Descriptive analysis

1) Epidemiological characteristics :

1.1) Age:

The mean age of the patients was 43.04 ± 14.28 years, ranging from 18 to 86 years.

The study population was predominantly composed of young and middle-aged adults.

1.2)Sex:

The study population included 60 men (48%) and 65 women (52%), with a sex ratio of 0.92.

A slight female predominance was observed in the study population.

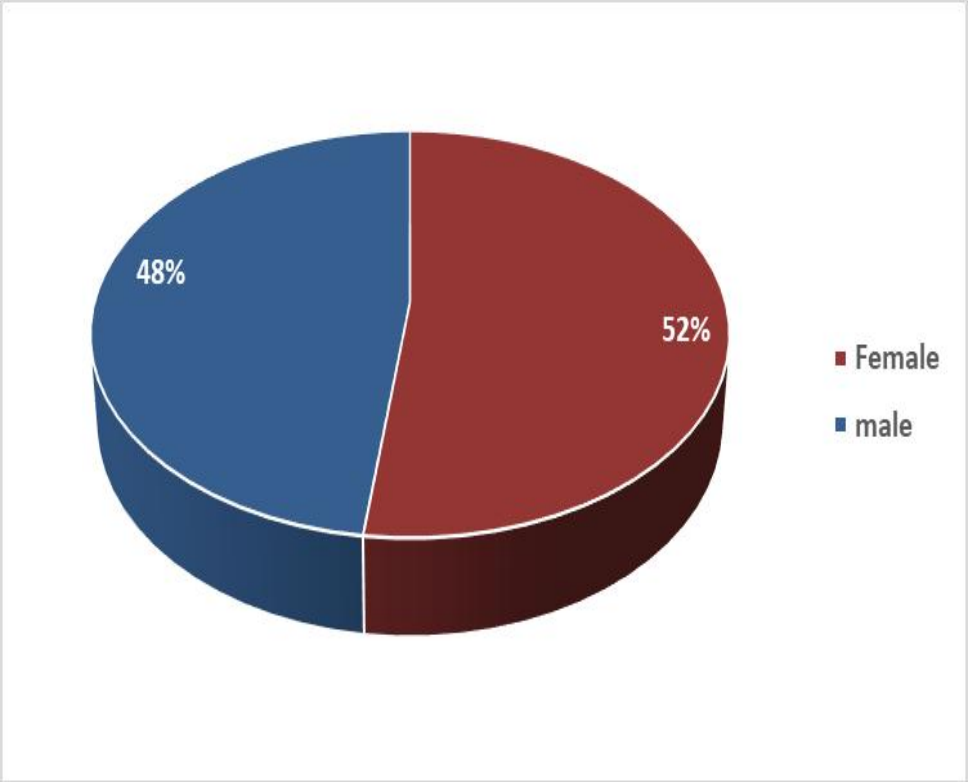


Diagram 1 : The distribution of patients by sex

1.3) Comorbidities:

Comorbidity analysis was available for 103 patients.
The majority of patients had no associated comorbidities, representing 71 patients (68.9%).
Most patients did not present associated comorbidities.
Among patients with comorbid conditions, the most frequent were:

- Hypertension : 8 cases ;
- Ankylosing spondylitis : 7 cases ;
- Hypothyroidism : 3 cases ;
- Diabetes mellitus : 2 cases ;
- Uveitis : 2 cases.

Combined comorbidities were less frequent:

- Hypertension + diabetes mellitus : 3 cases ;
- Hypertension + ankylosing spondylitis : 1 case ;
- Hypertension + diabetes mellitus + ankylosing spondylitis : 1 case.

Other isolated comorbidities included :

- Celiac disease
- Cirrhosis
- Non-cirrhotic portal hypertension ;
- Osteoporosis
- Polycythemia vera.

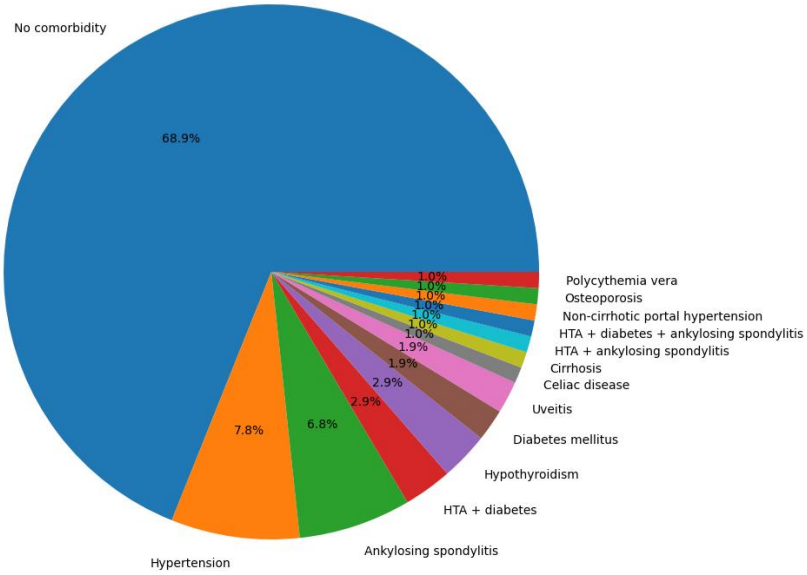


Diagram 2: Distribution of comorbidities

Comorbidities	Number of patients
Diabete	**2**
Ankylosing spondylitis	**7**
Celiac disease	**1**
Cirrhosis	**1**
HTA	**8**
HTA Ankylosing spondylitis	**1**

HTA diabete Ankylosing spondylitis	**1**
HTA diabete	**3**
Hypothyroidism	**3**
no comorbidity	**71**
Non-cirrhotic portal hypertension	**1**
Osteoporosis	**1**
Polycythemiavera	**1**
Uveitis	**2**

Table 4: Number of patient with comorbidities

2) Indications for biologic therapy:

Indications for Biologic therapies were prescribed for a broad spectrum of diseases, reflecting the heterogeneity of indications encountered in internal medicine.

Inflammatory bowel diseases represented the main indications:

- Crohn's disease : 47 cases (37.6%) ;
- Ulcerative colitis : 15 cases (12.0%).

Overall, inflammatory bowel diseases accounted for 62 cases (49.6%) and represented the most frequent indication for biologic therapy.

Hematological diseases included :

- Chronic myeloid leukemia : 18 cases (14.4%) ;
- Immune thrombocytopenic purpura : 2 cases (1.6%) ;
- Evans syndrome : 1 case (0.8%).

Overall, hematological diseases accounted for 21 cases (16.8%).

Neurological diseases included:

- Multiple sclerosis : 10 cases (8.0%);
- Neuromyelitis optica spectrum disorder: 1 case (0.8%);
- Optic neuritis: 1 case (0.8%).

Neurological diseases represented 12 cases (9.6%).

Rheumatologic diseases included :

- Ankylosing spondylitis : 5 cases (4.0%) ;
- Rheumatoid arthritis : 3 cases (2.4%) ;
- Osteoporosis: 2 cases (1.6%).

Overall, rheumatologic diseases accounted for 10 cases (8.0%).

Systemic autoimmune diseases included :

- Behçet disease : 2 cases (1.6%) ;
- Antisynthetase syndrome : 1 case (0.8%) ;
- Takayasu arteritis : 1 case (0.8%) ;
- Dermatomyositis : 1 case (0.8%) ;
- Polymyositis : 1 case (0.8%) ;
- Systemic lupus erythematosus : 1 case (0.8%) ;
- Renal vasculitis : 1 case (0.8%) ;
- IgG4-related disease : 1 case (0.8%) ;
- Refractory sarcoidosis : 1 case (0.8%) ;
- Overlap syndrome : 1 case (0.8%).

Systemic autoimmune diseases represented 11 cases (8.8%).

Other indications included :

- Refractory psoriasis : 2 cases (1.6%) ;
- Extensive psoriasis : 1 case (0.8%) ;
- Idiopathic panuveitis : 2 cases (1.6%) ;
- Vogt–Koyanagi–Harada disease: 1 case (0.8%);
- Extramembranous glomerulonephritis : 2 cases (1.6%) ;
- Hepato cellular carcinoma : 1 case (0.8%).

Other indications accounted for 9 cases (7.2%).

Commentary:

Inflammatory bowel diseases constituted nearly half of all indications for biologic therapy in the present cohort, with Crohn's disease representing the leading indication. Hematological and neurological diseases represented the second and third most frequent groups, respectively. In contrast, systemic autoimmune and rheumatologic diseases accounted for a smaller proportion of indications. Overall, these findings highlight the wide therapeutic spectrum of biologic therapies in internal medicine practice.

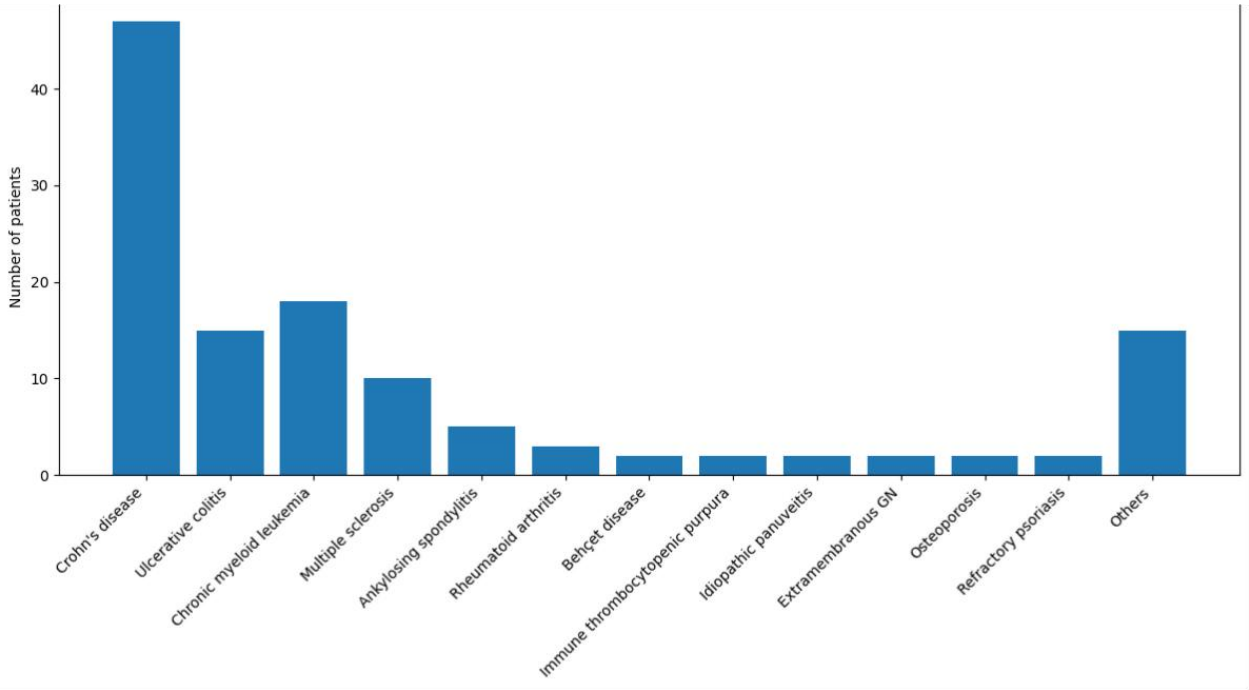


Diagram 3: distribution of indications for biological therapy

Disease	Number of patients
Ankylosing spondylitis	5
Antisynthetase syndrome	1
Becet disease	2
chronic myeloid leukima	18
Crohn's disease	47
dermatomyositis	1
Evans syndrome	1
Extensive psoriasis	1
extramembranous glomerulonephritis	2
hepatocellular carcinoma	1
Idiopathic panuveitis	2
IgG4-related disease	1
Immune Thrombocytopenic Purpura	2
MS disease	10
MS disease Neuromyelitis optica	1
optic neuritis	1
osteoporosis	2
Overlap syndrome	1
polymyositis	1
Refractory psoriasis	2
refractory sarcoidosis	1

Renal vasculitis	**1**
Rheumatoid arthritis	**3**
Systemic Lupus Erythematosus	**1**
takayasu arteritis	**1**
Ulcerative colitis	**15**
Vogt-Koyanagi-Harada disease	**1**

Table 5 : Distribution of medical indications for biotherapy (Internal Medicine vs. Other Specialties)

3) Previous conventional treatments:

The distribution of treatments shows a predominance of azathioprine (44 patients; 35.2%) and corticosteroids (41 patients; 32.8%). Together, they represent the most commonly used therapies in the cohort.

5-aminosalicylic acid was prescribed in 14 patients (11.2%), while NSAIDs were used in 6 patients (4.8%). Interferon beta and methotrexate were each used in 4 patients (3.2%).

Colchicine, cyclophosphamide, and sulfasalazine were each reported in 2 patients (1.6%). Hydroxychloroquine, ciclosporin, and mycophenolate mofetil were each used in 1 patient (0.8%).

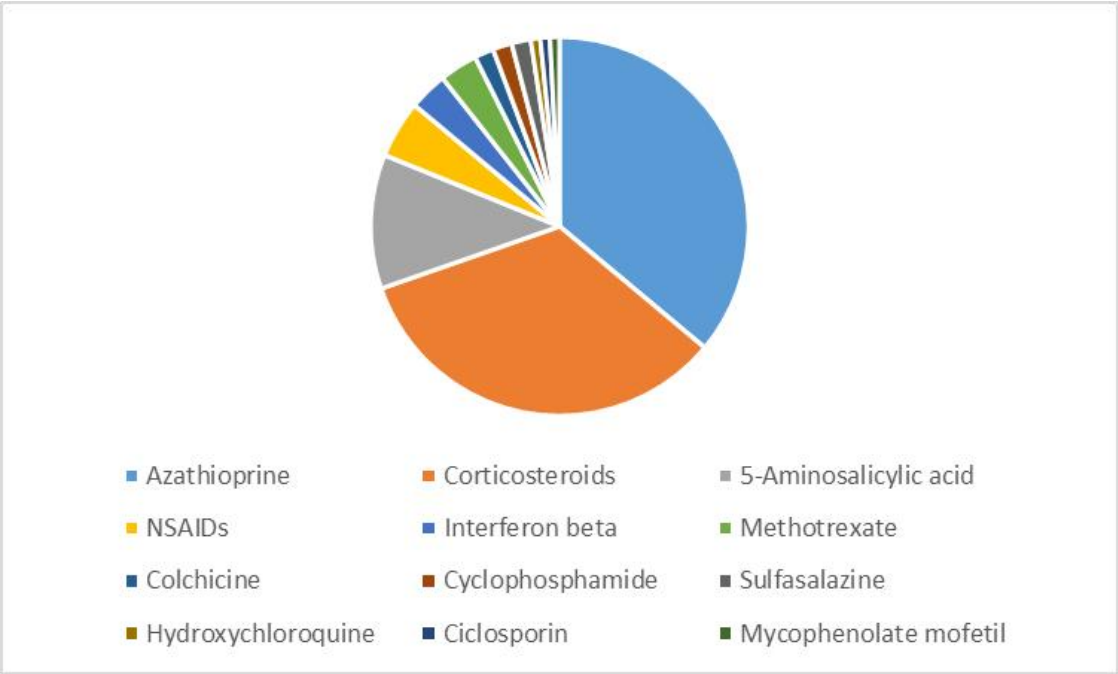


Diagram 4: conventional systemic treatments used prior to biotherapy initiation.

Commentary:

Azathioprine and corticosteroids were the most frequently used conventional therapies before initiation of biologic treatment. Overall, most patients had previously received immunosuppressive or anti-inflammatory therapies prior to escalation to biologic agents.

4) Biologic therapy:

4.1) First-line biologic therapy:

Adalimumab was the most frequently prescribed biologic therapy, accounting for 45 patients (36%).Infliximab was prescribed in 32 patients (25.6%).

Othe rtherapies included:

- Imatinib: 18 patients (14.4%);
- Rituximab: 14 patients (11.2%);
- Natalizumab: 7 patients (5.6%);
- Etanercept: 4 patients (3.2%);
- Denosumab: 2 patients (1.6%);
- Romiplostim: 2 patients (1.6%);
- Sorafenib: 1 patient (0.8%).

Adalimumab and Infliximab represented the most frequently used molecules.

Anti-TNF agents represented the most frequently prescribed biologic therapies.

Molecule	Number of patients
Adalimumab	45
Denosumab	2
Etanercept	4
Imatinib	18
Infliximab	32
Natalizumab	7
Rituximab	14
Romiplostim	2
Sorafenib	1

Table 6: Distribution of patients according to the type of biotherapy administered

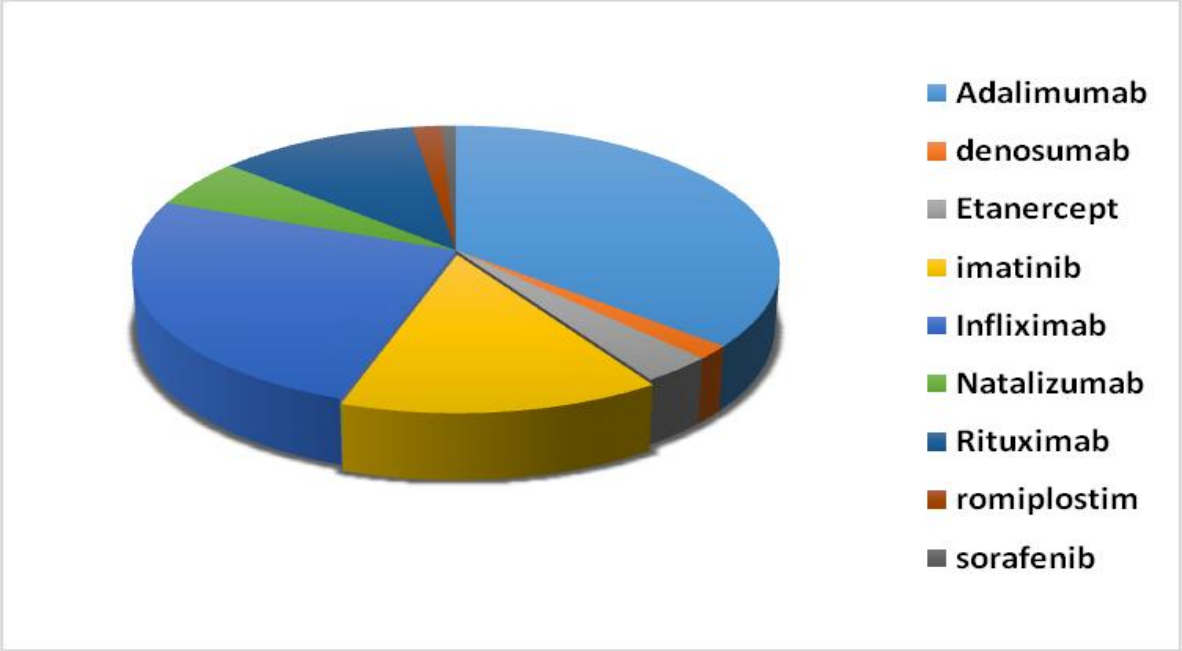


Diagram 5: distribution of patients according to the type of biotherapy administered

4.2) Second-line therapy:

Second-line biologic therapy analysis was available for 100 patients.

Most patients did not require switching therapy, representing 86% of cases.

Among patients requiring second-line therapy:

- Infliximab was used in 11 cases;
- Adalimumab in 2 cases ;
- Ocrelizumab in 1 case.

MOLECULE	Numbers of used as a second-line treatment
Adalimumab	**2**
Infliximab	**11**
No molecule used as a second-line treatment	**86**
Ocrelizumab	**1**

Table 7: Profile of biologic therapies used as second-line treatment in patients

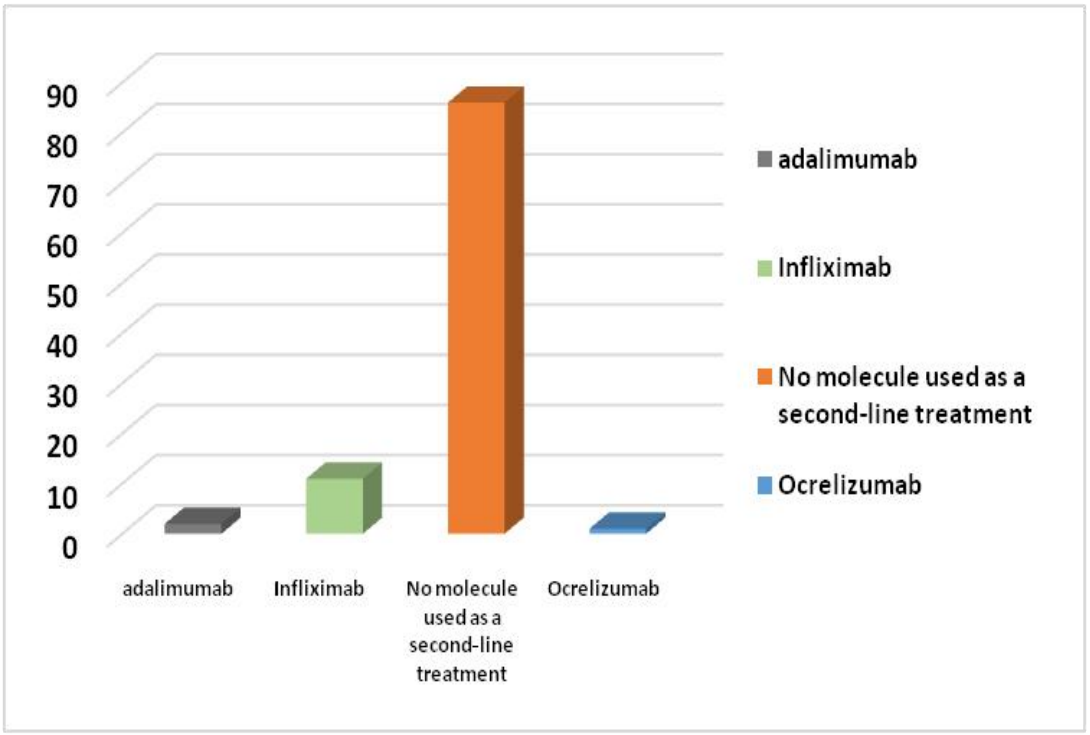


Diagram 6: Distribution of patients according to biologic molecules used as second-line treatment

4.3) Associated treatment :

Among the 89 evaluable patients, 40 patients (44.9%) received at least one associated treatment, whereas 49 patients (55.1%) did not receive any concomitant therapy.

Azathioprine was the most frequently prescribed associated treatment, used in 7 patients (7.9%), followed by corticosteroids in 4 patients (4.5%).

NSAIDs were prescribed in 2 patients (2.2%).

Methotrexate, 5-aminosalicylic acid, colchicine, hydroxychloroquine, and sulfasalazine were each reported in 1 patient (1.1%)

Commentary

More than half of the evaluable patients did not receive any associated treatment. Among concomitant therapies, azathioprine and corticosteroids were the most frequently prescribed agents.

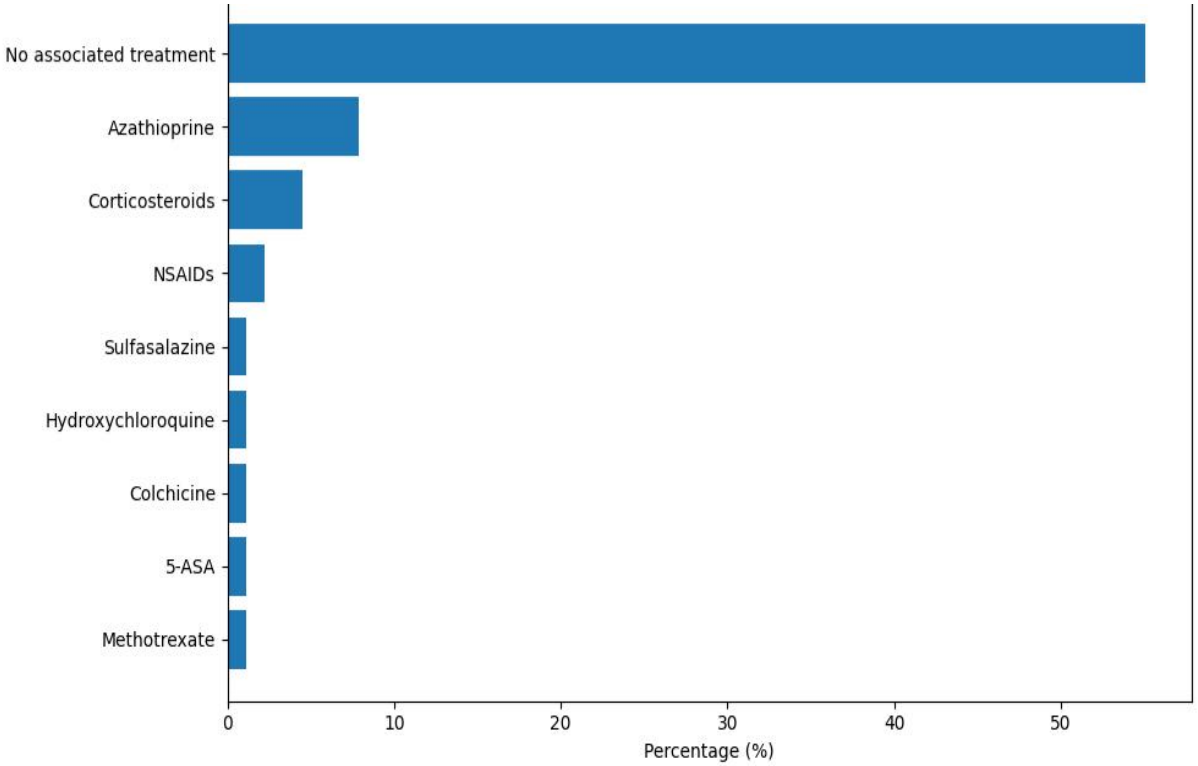


Diagram 7: distribition of associated treatments

5) Clinical response:

Clinical response assessment was available for 97 evaluable patients.

A favorable clinical response was observed in 87 patients (89.7%).

Partial clinical improvement was observed in 3 patients (3.1%).

Seven patients (7.2%) showed no clinical improvement.

Overall, these results demonstrate a high therapeutic response rate.

Most evaluable patients showed a favorable clinical response to treatment.

Clinical improvement	Number of patients
No	**7**
partial clinical improvement	**3**
Yes	**87**

Table 8 : Distribution of patients according to clinical response

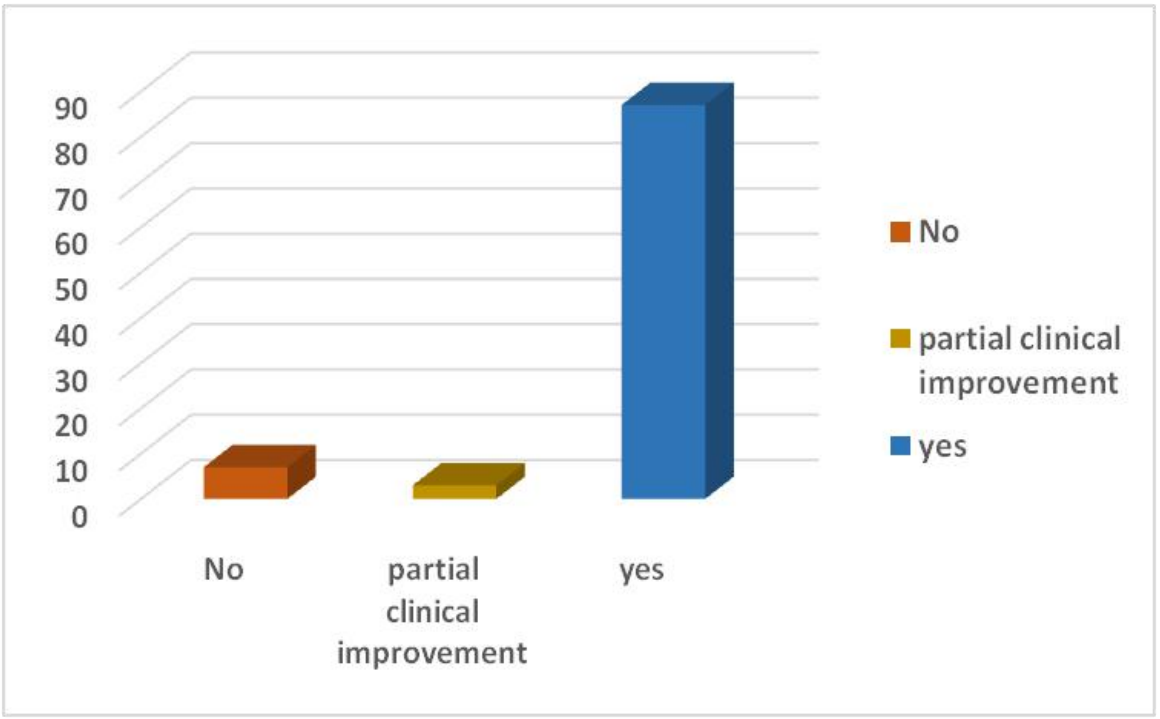


Diagram 8: Distribution of patients according to clinical response

6) Tolerance and side effects of biotherapies:

6.1) Side effects:

Adverse effect evaluation was available for 95 patients.

Adverse effects were reported in 14 patients, representing approximately 15% of evaluable patients.

Adverse effects were observed in a minority of evaluable patients. Three deaths were recorded during the study period.

Side effects	Number of patients
No	**81**
Yes	**14**

Table 9 : Number of patients according to clinical response

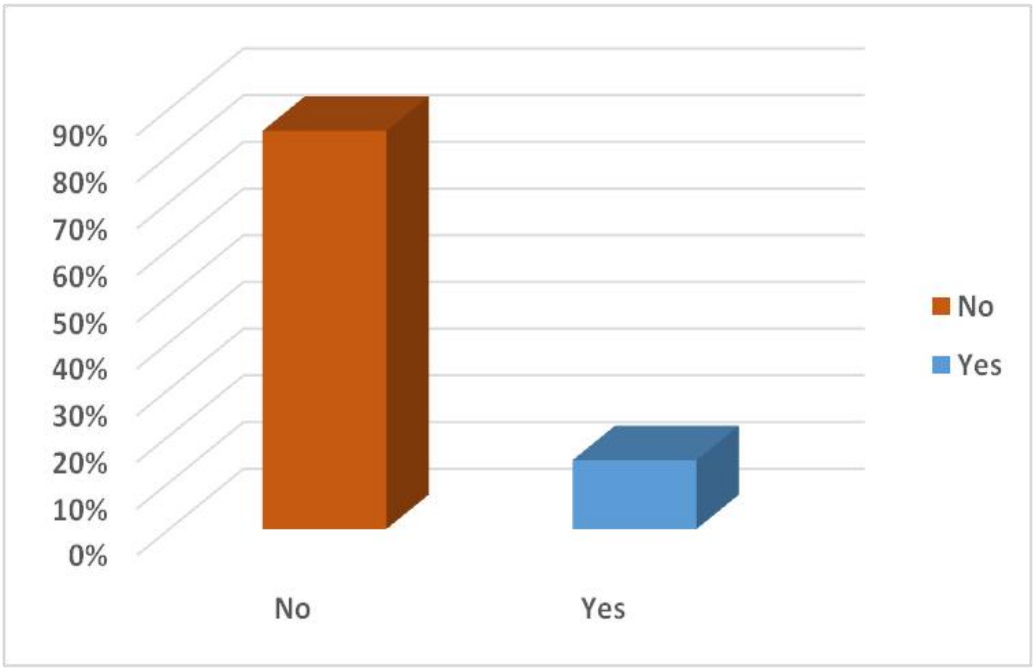


Diagram 9: Distribution of patients according to the occurrence of adverse effects

6.2) Tolerance according to biologic therapy:

- **Adalimumab:**

Among the 41 patients treated with Adalimumab, adverse effects were reported in 7 cases (17.1%).

Reported adverse events included :

- Thrombocytopenia ;
- Pancytopenia in 2 cases ;
- General symptoms such as asthenia and fever in 3 cases.

- **Infliximab:**

Twenty-nine patients received Infliximab.

Adverse effects were observed in 5 patients (17.2%), including:

- Cutaneous reactions such as rash and eczema in 2 cases;
- One psychiatric adverse effect ;
- Other non-specific general symptoms.
- **Rituximab:**

Among the 13 patients treated with Rituximab, one patient (7.7%) developed an allergic reaction.

- **Denosumab:**

One patient developed lung cancer during follow-up, reported as an adverse event.

Other biologic therapies

Natalizumab was prescribed to 6 patients, Etanercept to 4 patients, and Romiplostim to 1 patient, with no reported adverse effects.

- **Commentary:**

Adverse effects were observed in a minority of evaluable patients. Adalimumab and Infliximab were associated with the highest number of reported adverse events, whereas other biologic therapies demonstrated favorable overall tolerance profiles.

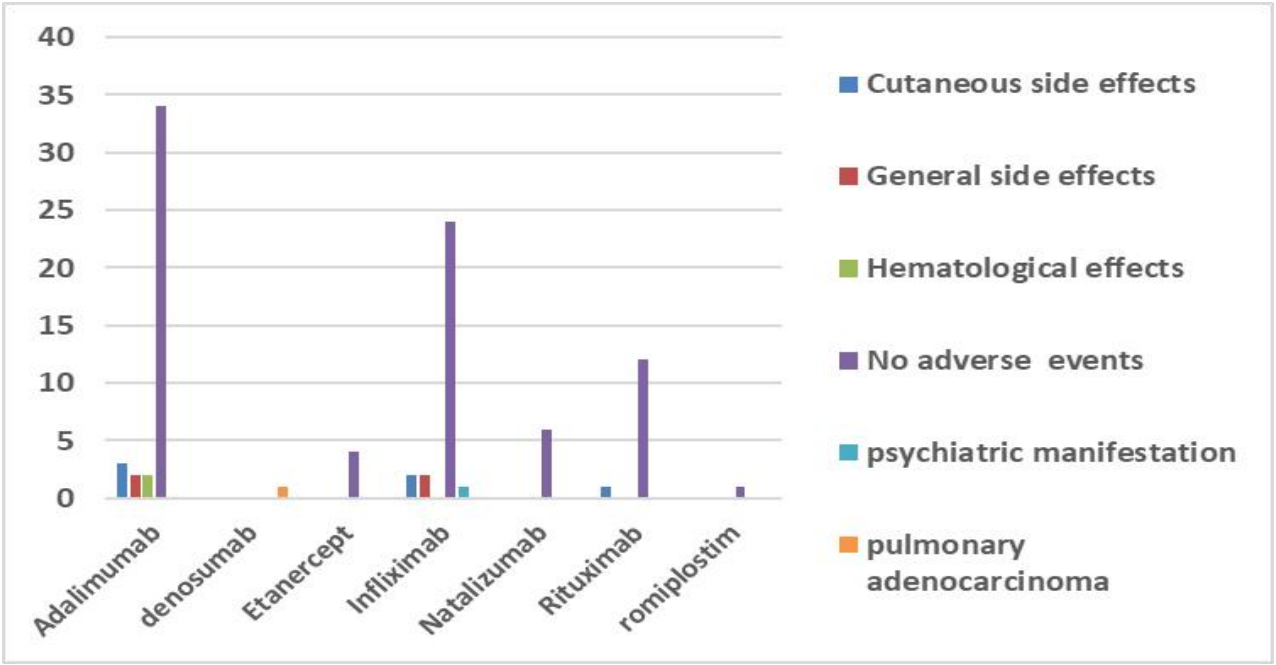


Diagram 10: Profile of adverse effects according to biologic therapies

6.3) Infectious complications:

Infectious complication analysis was available for 93 evaluable patients.
The majority of patients did not experience infectious complications, representing 82 patients (88.2%), whereas infections were reported in 11 patients (11.8%).

6.4) Distribution of infectious complications:

The analysis of infectious events showed that urinary tract infections were the most frequent infectious complication, reported in 6 cases.
Biological infectious syndromes were observed in 4 cases.

Overall, infectious complications appeared relatively infrequent in the studied population.

Commentary:

Most evaluable patients did not develop infectious complications. Urinary tract infections represented the most frequently reported infectious events.

Infections	Number of patients
No	**82**
Yes	**11**

Table 10 : Distribution of patients with or without infections

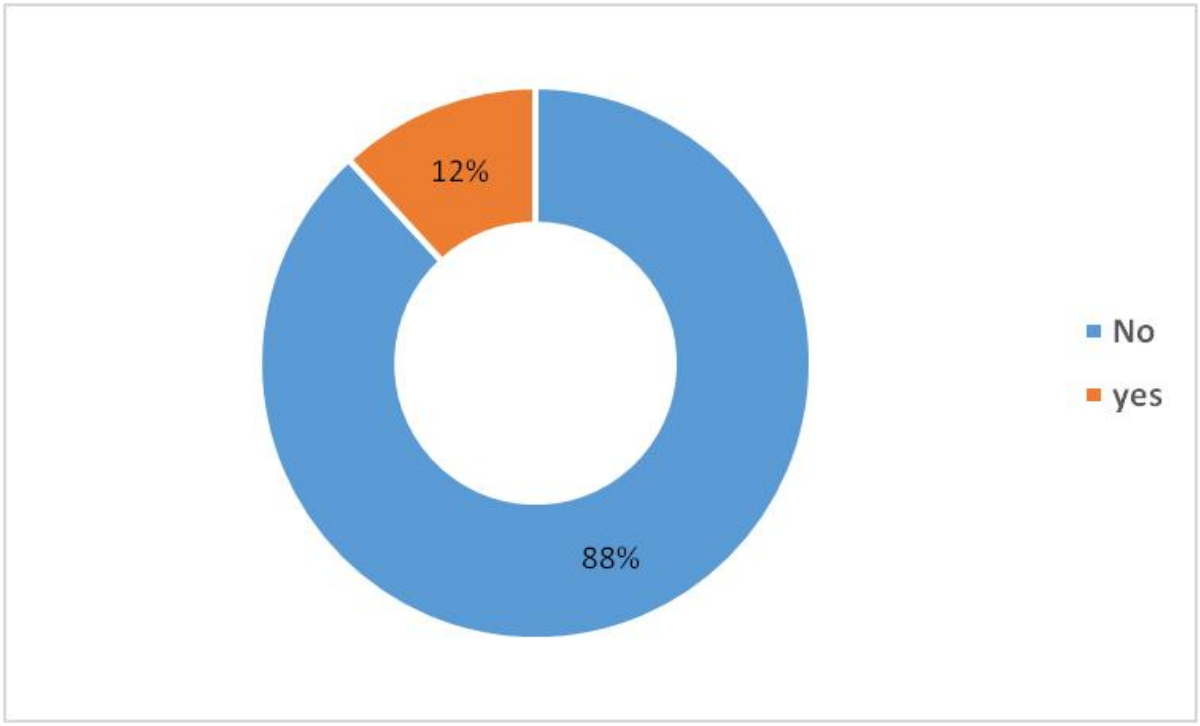


Diagram 11: Distribution of patients with or without infections

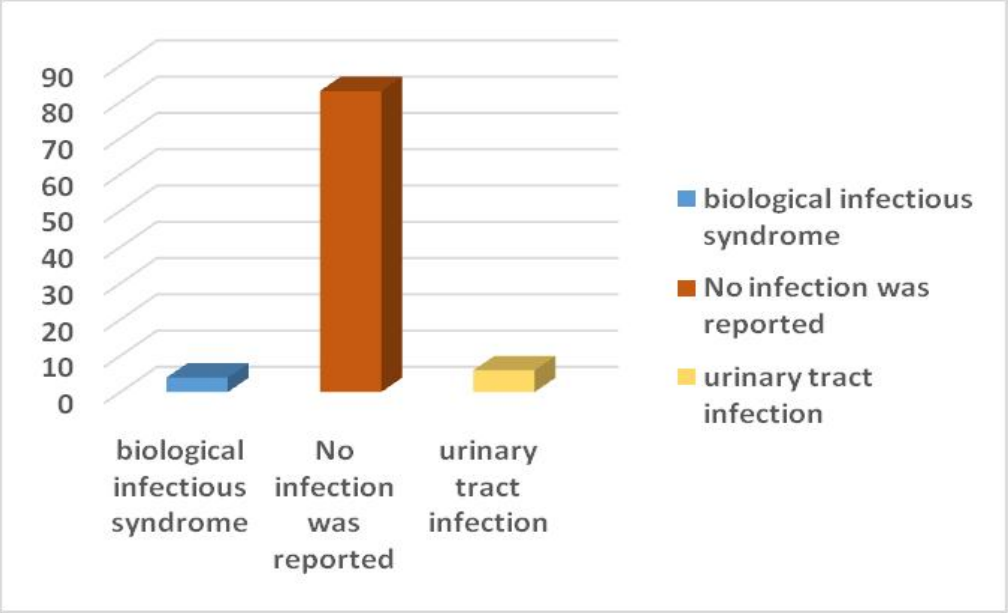


Diagram 12: Distribution of infectious complication

7) Adherence:

Adherence evaluation was available for 90 patients.

Among evaluable patients:

- 89 patients (98.9%) were classified as adherent;
- 1 patient was non-adherent.

These findings demonstrate excellent overall treatment adherence.

Most evaluable patients were classified as adherent to treatment.

Adherence	Number of patients
Good adherent	**89**
No adherent	**1**

Table 11: Patient distribution by adherence status

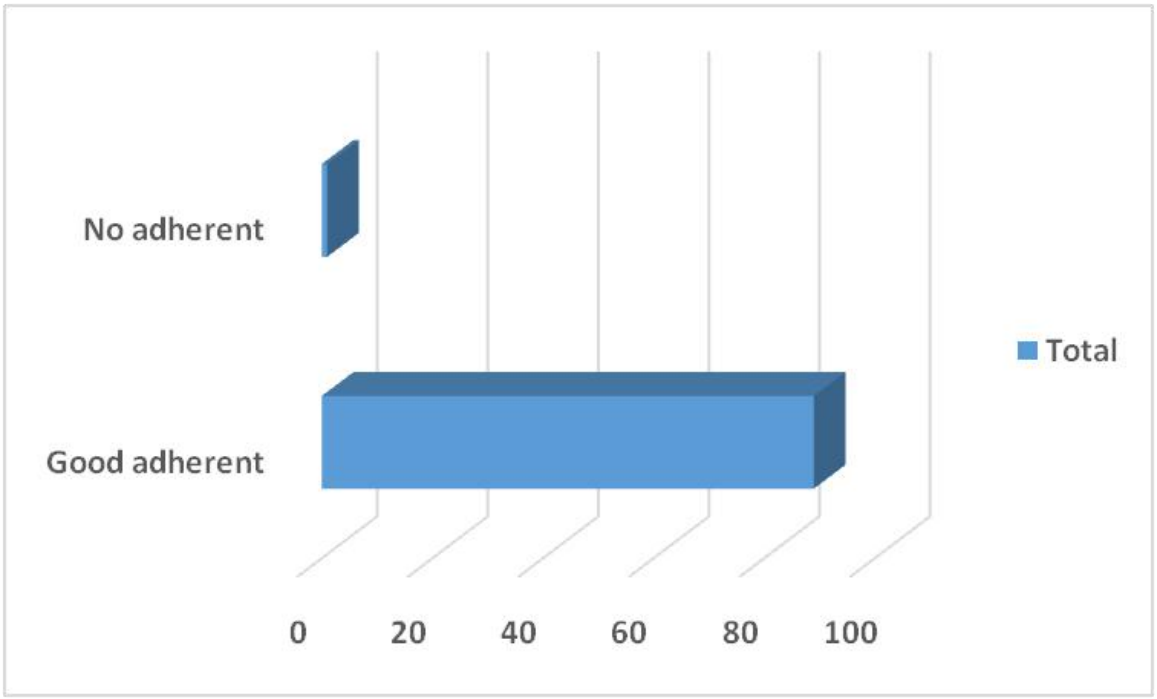


Diagram 13: Patient distribution by adherence status

8) Patients satisfaction:

Patient satisfaction assessment was available for 90 patients.

Overall:

- 80 patients were very satisfied ;
- 8 patients were moderately satisfied ;
- 2 patients were not satisfied.

The global satisfaction rate (very satisfied + moderately satisfied) reached 97.8%.

A high level of patient satisfaction was observed across the different biologic therapies.

Adalimumab and Infliximab were associated with the highest satisfaction rates.

Étiquettes de lignes	Number of Patient satisfaction
Moderately satisfied	8
Not satisfied	2
verysatisfied	80

Table 12 : Patient distribution by satisfaction level

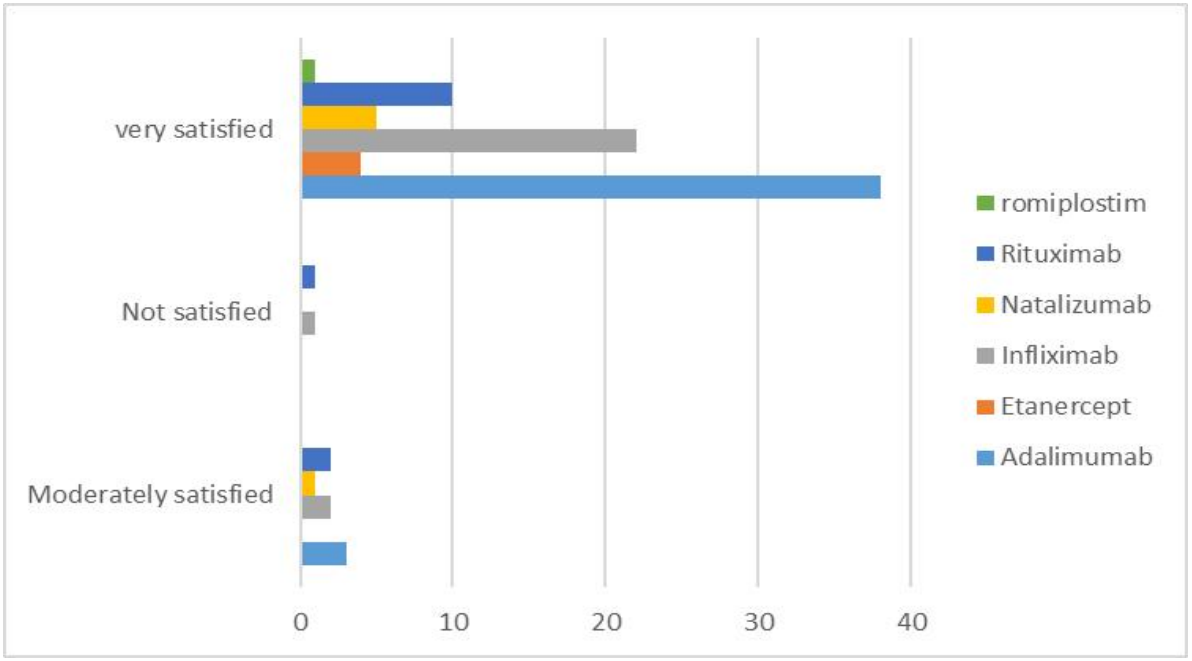


Diagram 14: Distribution of satisfaction level according to biologic therapy type

Analytical Section

1) Factors associated with clinical response:

Clinical response appeared high in both anti-TNF and non-anti-TNF groups, with no statistically significant difference between therapeutic groups ($p > 0.05$).

Variable	Statistical test used	Responders n (%)	Partial/non-responders n (%)	p-value
Sex	**Chi-square test**			**>0.05**
Female		**High majority**	**Minority**	
Male		**High majority**	**Minority**	
Disease category	**Chi-square test**			**>0.05**
Inflammatory bowe ldiseases		**High majority**	**Minority**	
Other indications		**High majority**	**Minority**	
Therapeutic group	**Chi-square test**			**>0.05**
Anti-TNF therapies		**High majority**	**Minority**	
Non-anti-TNF therapies		**High majority**	**Minority**	
Comorbidity status	**Chi-square test**			**>0.05**
No comorbidity		**High majority**	**Minority**	
At least one comorbidity		**High majority**	**Minority**	
Associated treatment	**Chi-square test**			**>0.05**
With associated treatment		**High majority**	**Minority**	
Without associated treatment		**High majority**	**Minority**	

Table 13: Factors associated with clinical response

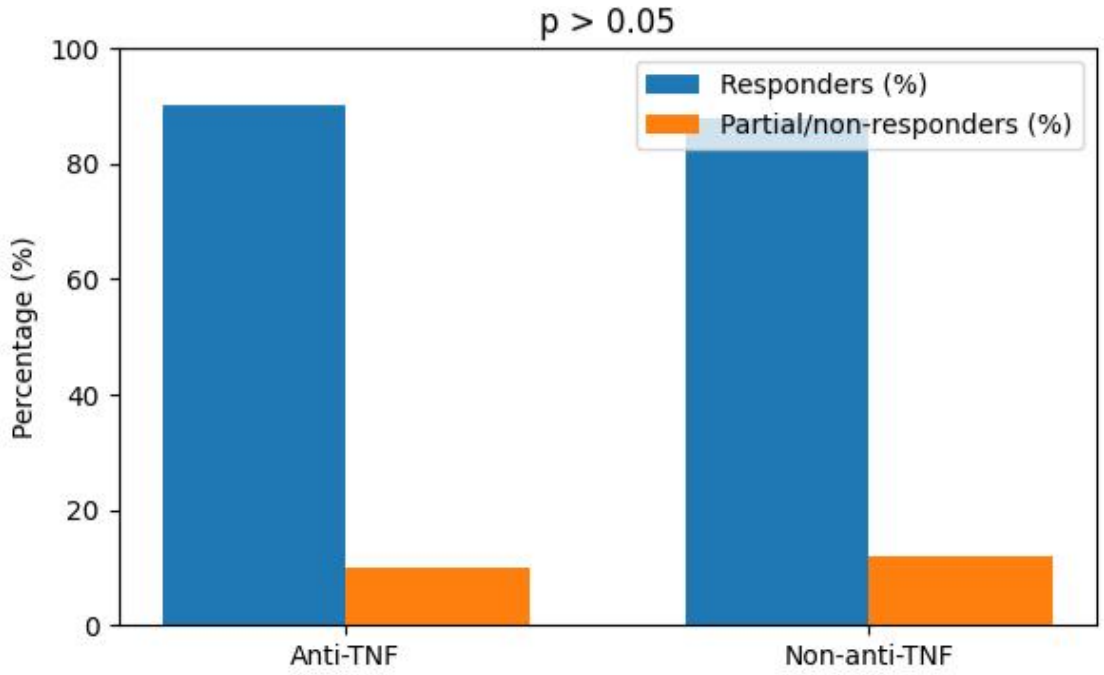


Diagram 15: clinical response according to therapeutic group

Commentary

Chi-square test analysis did not demonstrate any statistically significant association between clinical response and sex, disease category, therapeutic group, comorbidity status, or associated treatment use (p > 0.05).

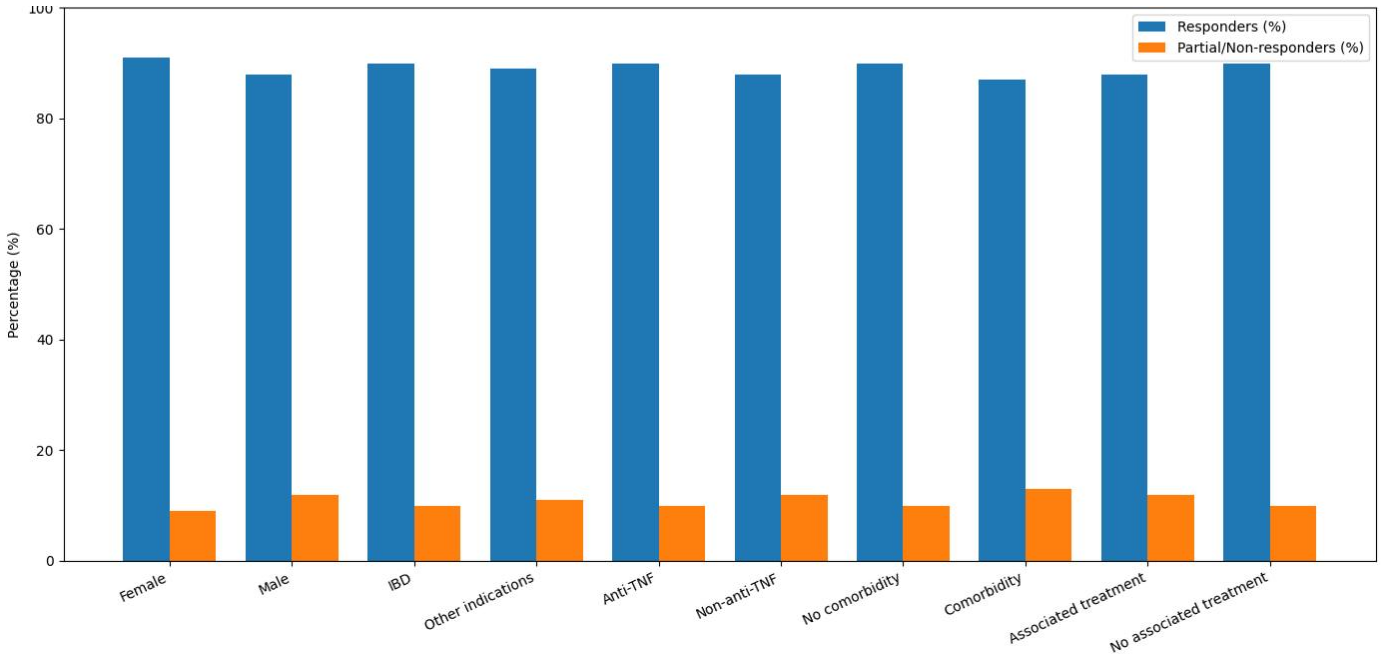


Diagram 16 : clinical response according to analyzed factors

2) Factors associated with adverse effects:

Adverse events were observed in a minority of patients and appeared numerically more frequent among anti-TNF-treated patients; however, the difference was not statistically significant (p > 0.05).

Variable	Statistical test used	Patients with adverse effects n (%)	Patients without adverse effects n (%)	p-value
Sex	**Chi-square test**			**>0.05**
Female		**Minority**	**Majority**	
Male		**Minority**	**Majority**	
Disease category	**Chi-square test**			**>0.05**
Inflammatory bowel diseases		**Minority**	**Majority**	
Other indications		**Minority**	**Majority**	
Therapeutic group	**Chi-square test**			**>0.05**
Anti-TNF therapies		**Slightly higher frequency**	**Majority**	
Non-anti-TNF therapies		**Lower frequency**	**Majority**	
Comorbidity status	**Chi-square test**			**>0.05**
No comorbidity		**Lower frequency**	**Majority**	
At least one comorbidity		**Slightly higher frequency**	**Majority**	
Associated treatment	**Chi-square test**			**>0.05**
With associated treatment		**Slightly higher frequency**	**Majority**	

Without associated treatment		**Lower frequency**	**Majority**	

Table 14: Factors associated with adverse effects

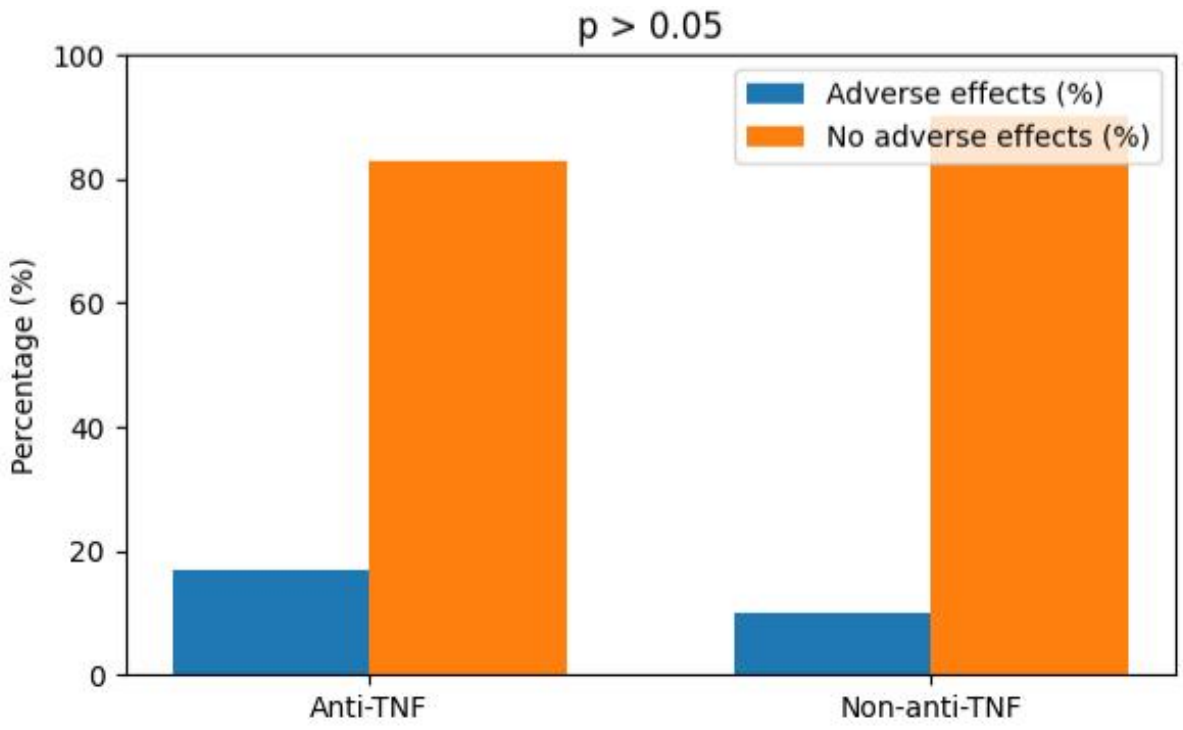


Diagram 17: adverse effects according to therapeutic group

Commentary

Adverse effects were observed in a minority of evaluable patients. No statistically significant association was identified between adverse effect occurrence and sex, disease category, therapeutic group, comorbidity status, or associated treatment use ($p > 0.05$).

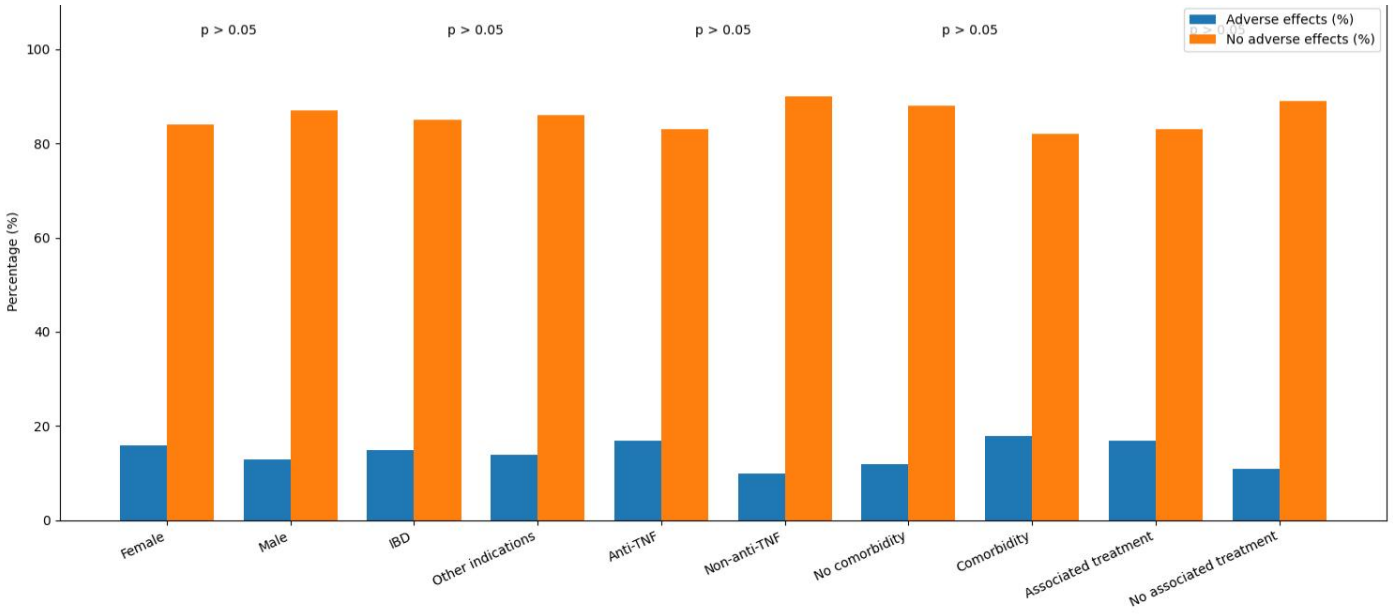


Diagram 18: adverse effects according to analyzed factors

3) Factors associated with infections:

Infections appeared more frequent among patients receiving associated treatments, although no statistically significant association was identified (p > 0.05).

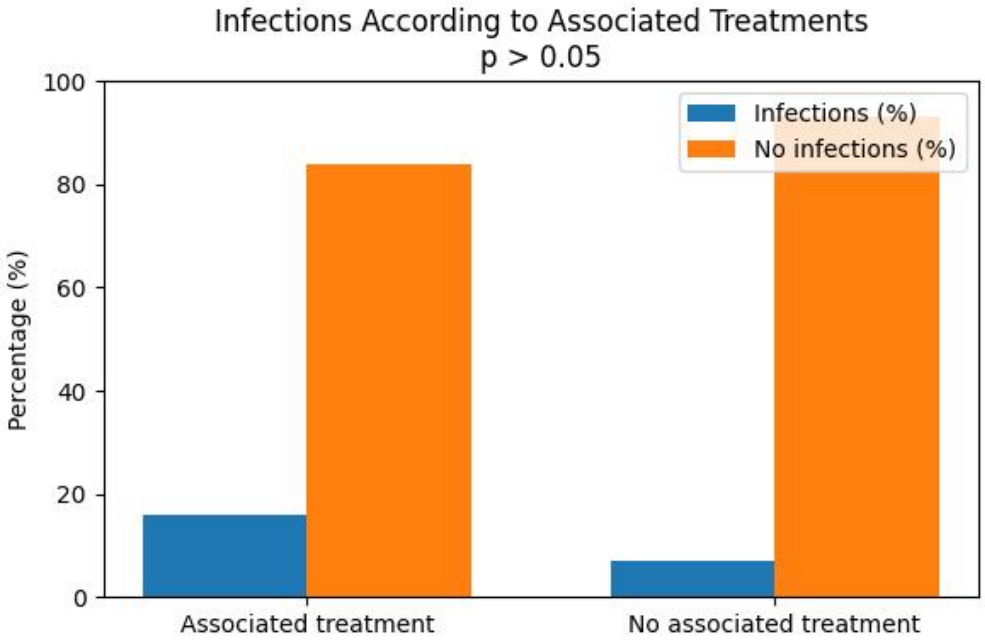


Diagram 18: infections according to associated treatments

Variable	Statistical test used	Patients with infections n (%)	Patients without infections n (%)	p-value
Sex	**Chi-square test**			**>0.05**
Female		**Minority**	**Majority**	
Male		**Minority**	**Majority**	
Disease category	**Chi-square test**			**>0.05**
Inflammatory bowel diseases		**Minority**	**Majority**	
Other indications		**Minority**	**Majority**	
Therapeutic group	**Chi-square test**			**>0.05**
Anti-TNF therapies		**Slightly higher frequency**	**Majority**	
Non-anti-TNF therapies		**Lower frequency**	**Majority**	
Comorbidity status	**Chi-square test**			**>0.05**
No comorbidity		**Lower frequency**	**Majority**	
At least one comorbidity		**Slightly higher frequency**	**Majority**	
Associated treatment	**Chi-square test**			**>0.05**
With associated treatment		**Slightly higher frequency**	**Majority**	
Without associated treatment		**Lower frequency**	**Majority**	

Table 15: Factors associated with infections

Commentary

Most evaluable patients did not develop infectious complications during follow-up. No statistically significant association was identified between infection occurrence and sex, disease category, therapeutic group, comorbidity status, or associated treatment use ($p > 0.05$).

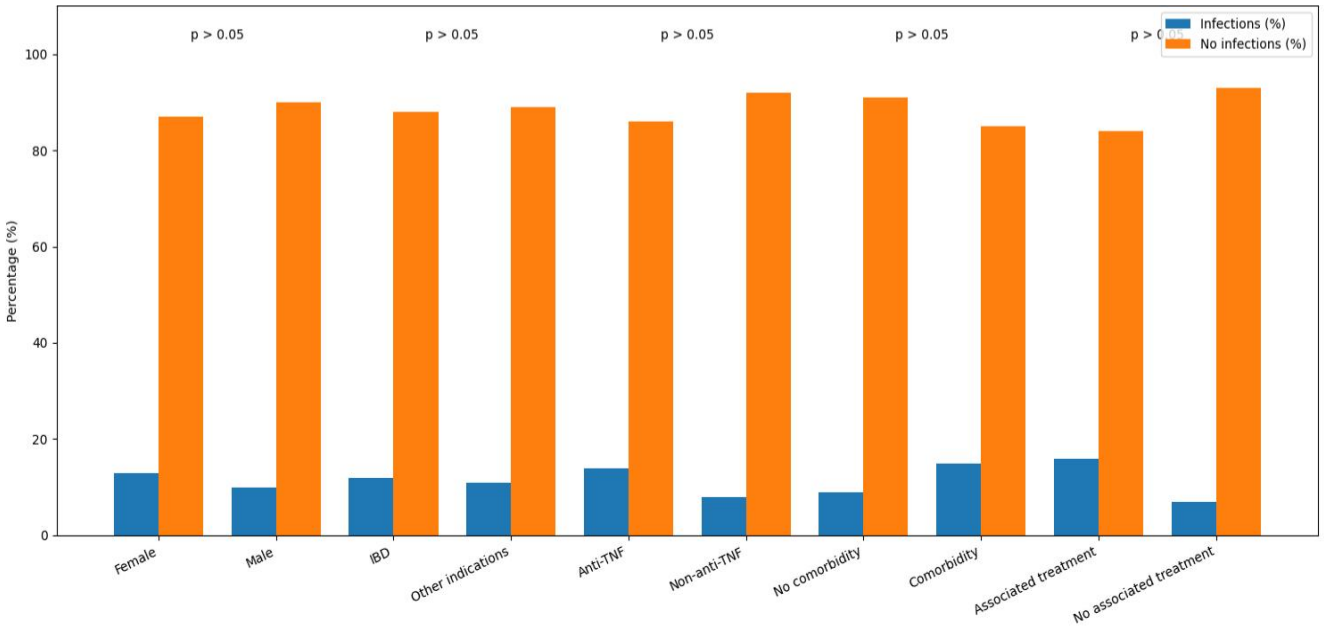


Diagram 18: infections according to analyzed factors

4) Exploratory Multivariate Analysis:

An exploratory multivariate logistic regression analysis was performed to identify factors potentially associated with favorable clinical response. The dependent variable was clinical response (responder versus partial/non-responder). The following variables were included in the model: sex, anti-TNF therapy exposure, associated treatment use, comorbidity status, and age.

Variable	Odds Ratio (OR)	95% CI	p-value
Female	**0.21**	**0.04–1.15**	**0.072**
anti_TNF	**2.58**	**0.52–12.71**	**0.245**
associated_treatment	**2.49**	**0.49–12.59**	**0.269**
Comorbidity	**1.15**	**0.17–7.89**	**0.885**
age_num	**1.02**	**0.97–1.08**	**0.439**

Table 16: Exploratory multivariate logistic regression analysis

No independent factor was significantly associated with favorable clinical response in the exploratory multivariate analysis ($p > 0.05$ for all variables).

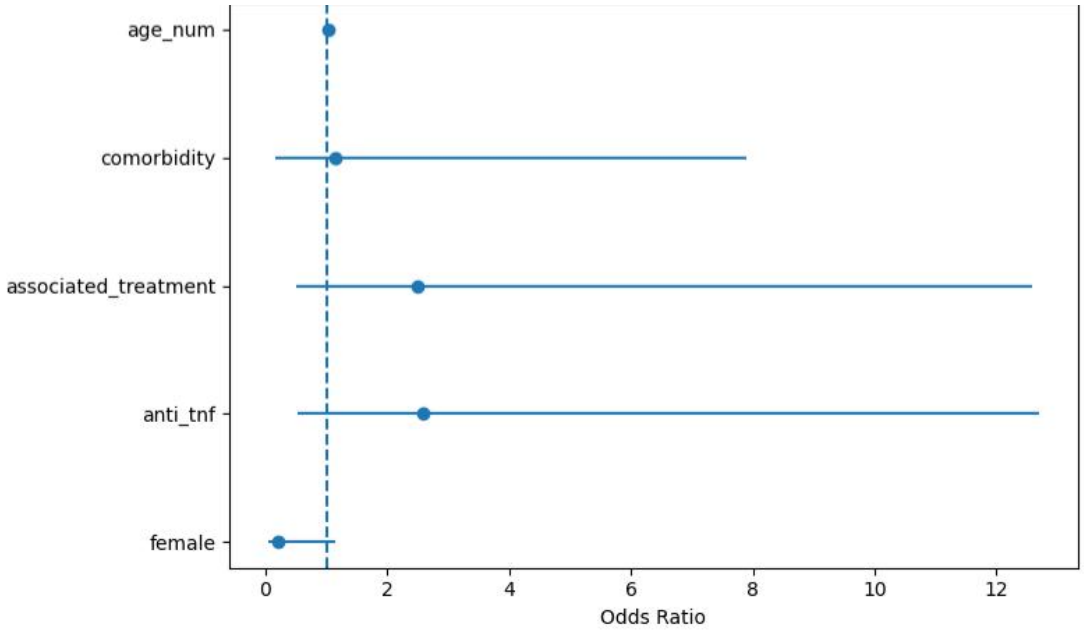


Diagram 19: exploratory multivariate logistic regression

The limited sample size and the relatively small number of non-responders may have reduced the statistical power of the multivariate model.

Discussion

This ambispective single-center study provides a real-world overview of the use of biologic and targeted therapies in the Department of Internal Medicine of Laghouat Mixed Hospital over a 53-month period. A total of 125 patients received biologic or targeted therapies during the study period, allowing evaluation of prevalence, indications, efficacy, tolerance profile, infectious complications, adherence, and factors associated with therapeutic response in routine clinical practice.

Over the last two decades, biologic and targeted therapies have profoundly transformed the management of chronic inflammatory and autoimmune diseases. Their increasing use reflects major advances in the understanding of immune dysregulation and molecular inflammatory pathways (1,2). While most available data originate from Europe and North America, North African and Algerian real-world data remain limited. Our study therefore contributes one of the first regional overviews from southern Algeria regarding the use, efficacy, and safety of biologic therapies in Internal Medicine practice.

One of the important findings of our study concerns the prevalence of biologic and targeted therapy use. During the study period, the hospital prevalence reached 1.84% among 6758 hospitalized patients, whereas the overall prevalence in Laghouat Province was estimated at 0.017% within a population of approximately 750,000 inhabitants. Although these figures remain relatively low compared with prevalence rates reported in high-income healthcare systems, they nevertheless illustrate the progressive integration of biologic and targeted therapies into routine Internal Medicine practice in Algeria (108,109).

Several factors may explain this relatively limited prevalence, including high treatment costs, reimbursement difficulties, delayed referral to specialized centers, limited therapeutic availability, and unequal healthcare access between regions. Similar disparities have been described in developing countries and low-resource healthcare systems where access to advanced therapies remains heterogeneous because of economic and organizational limitations (108,109). In addition, biologic therapies are often reserved for severe, refractory, or advanced diseases after failure of conventional immunosuppressive treatments. Consequently, the observed prevalence likely underestimates the true therapeutic needs of the population.

The demographic profile of our cohort was characterized by a relatively young population with a predominance of female patients. This female predominance is consistent with the epidemiology of several autoimmune and systemic inflammatory diseases such as systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis, which predominantly affect women (35,39,41). The female-to-male ratio observed in our cohort further supports the autoimmune and inflammatory nature of the diseases treated in our department. In addition, the relatively young mean age of the population may partly explain the limited burden of cardiovascular and metabolic comorbidities observed in our cohort.

Most patients did not present major associated comorbidities. Among those with comorbid conditions, hypertension, diabetes mellitus, hypothyroidism, and spondyloarthritis were the most frequent. Although the global comorbidity burden remained moderate, these conditions remain clinically relevant because they may influence treatment tolerance, infectious susceptibility, and long-term prognosis under biologic therapy.

The spectrum of diseases observed in our cohort reflects the diversity commonly encountered in Internal Medicine practice. Inflammatory bowel diseases represented the leading indications for biologic therapy, particularly Crohn’s disease and ulcerative colitis, followed by hematological, neurological, rheumatological, dermatological, and systemic autoimmune diseases. Comparable observations have been reported internationally, where biologic therapies are increasingly used across multiple immune-mediated inflammatory diseases because of their targeted mechanisms of action and favorable efficacy profile compared with conventional immunosuppressive therapies (1,2).

The predominance of inflammatory bowel diseases may be explained by the central role currently played by anti-TNF therapies in moderate-to-severe Crohn’s disease and ulcerative colitis. Previous studies demonstrated that anti-TNF agents significantly reduce disease activity, hospitalization rates, corticosteroid

dependence, and surgical requirements in inflammatory bowel diseases (51,53). In our cohort, adalimumab and infliximab were the most frequently prescribed biologic agents, in agreement with current international recommendations.

The predominance of anti-TNF therapies probably reflects several combined factors including earlier availability in Algeria, broader physician familiarity, wider international experience, and better accessibility compared with newer targeted therapies. Economic and organizational considerations also likely contributed to this therapeutic distribution. In many low- and middle-income healthcare settings, access to newer biologic molecules remains limited by cost, delayed reimbursement procedures, restricted hospital availability, and unequal regional distribution (108,109). Consequently, older biologic classes such as anti-TNF agents continue to dominate routine practice despite the progressive emergence of newer therapies.

The progressive introduction of biosimilars may represent a major opportunity for Algeria and similar healthcare systems. Biosimilars could potentially reduce treatment costs, improve accessibility, and facilitate earlier therapeutic initiation for patients with severe inflammatory diseases. Several international studies demonstrated comparable efficacy and safety profiles between biosimilars and originator biologic agents, supporting their integration into routine practice (110,111). Nevertheless, long-term pharmacovigilance and real-world surveillance remain essential.

Before biologic initiation, azathioprine and corticosteroids represented the most frequently prescribed conventional therapies. This finding reflects the persistent central role of conventional immunosuppressive strategies before escalation toward biologic therapy. Similar therapeutic approaches are recommended internationally, where biologic agents are generally introduced after failure, intolerance, or corticosteroid dependence under conventional treatments (10,11).

Regarding therapeutic efficacy, most evaluable patients demonstrated a favorable clinical response. Among the 97 evaluable patients included in response analysis, responders largely predominated over partial or non-responders regardless of therapeutic group. Clinical response appeared globally high in both anti-TNF and non-anti-TNF groups without statistically significant differences between therapeutic classes ($p > 0.05$). These findings remain consistent with numerous international studies demonstrating the efficacy of biologic therapies in chronic inflammatory and autoimmune diseases (12,14).

The favorable response rates observed in our cohort may reflect both the efficacy of these therapies and careful patient selection with regular clinical follow-up. In many Algerian settings, biologic therapies remain reserved for severe, refractory, or advanced disease because of accessibility limitations. Consequently, several patients included in our cohort had prolonged exposure to corticosteroids or conventional immunosuppressive therapies before biologic initiation, which may partly explain the marked clinical improvement observed after escalation toward targeted therapies.

Our exploratory analytical analyses did not identify statistically significant associations between clinical response and sex, disease category, therapeutic group, comorbidity status, or associated treatment use ($p > 0.05$). Similarly, exploratory multivariate logistic regression analysis did not identify independent predictors of favorable response. Female sex showed a tendency toward lower odds of favorable response (OR = 0.21; 95% CI: 0.04–1.15), while anti-TNF exposure numerically appeared associated with better response (OR = 2.58; 95% CI: 0.52–12.71), although these findings did not reach statistical significance.

Several explanations may account for the absence of statistically significant associations. First, the relatively limited sample size reduced statistical power. Second, the marked heterogeneity of diseases included in the cohort may have diluted disease-specific therapeutic effects. Third, several clinically relevant variables such as disease duration, baseline severity, immunogenicity, therapeutic drug monitoring, and socioeconomic factors were not systematically available. Similar methodological limitations are frequently reported in retrospective and real-world observational studies evaluating biologic therapies (17,18).

Despite the absence of statistical significance, anti-TNF therapies numerically appeared associated with slightly higher response rates. These trends remain clinically plausible and biologically coherent given the major role of TNF-alpha in several inflammatory diseases commonly encountered in Internal Medicine.

Treatment tolerance in our cohort was globally satisfactory. Adverse effects were reported only in a minority of evaluable patients, in agreement with previously published observational studies (81,83). Among the 93 evaluable patients included in safety analyses, most patients did not experience major adverse effects or severe infectious complications during follow-up. Hematological adverse effects such as thrombocytopenia and pancytopenia were mainly observed under adalimumab therapy, whereas infliximab was associated with cutaneous manifestations and isolated psychiatric symptoms. Rituximab was associated with isolated allergic reactions.

Exploratory analyses evaluating factors associated with adverse effects did not identify statistically significant associations with sex, disease category, therapeutic group, comorbidity status, or associated treatment use ($p > 0.05$). Nevertheless, adverse effects numerically appeared slightly more frequent among patients receiving anti-TNF therapies and concomitant immunosuppressive treatments. These findings remain biologically plausible given the immunomodulatory effects associated with combined therapeutic strategies.

One patient developed lung cancer during denosumab exposure. However, current literature does not support a clear increase in overall solid malignancy risk under most biologic therapies. Several meta-analyses demonstrated no significant increase in cancer risk among patients treated with anti-TNF therapies compared with conventional disease-modifying therapies (81,83). Consequently, the malignancy observed in our cohort cannot be directly attributed to biologic therapy.

Infectious complications represented one of the major safety concerns evaluated in our study. Overall, infectious events remained relatively infrequent, with urinary tract infections representing the most common infectious complication. Among the 93 evaluable patients included in infectious analyses, the majority remained free of infectious complications throughout follow-up. These findings are particularly interesting considering that Algeria remains an intermediate tuberculosis burden country.

Anti-TNF therapies are known to increase susceptibility to infections, particularly tuberculosis and opportunistic infections, because of their effects on granuloma integrity and cellular immunity (73,74). However, the relatively low infection rate observed in our cohort may reflect the implementation of systematic pre-therapeutic infectious screening, vaccination strategies, careful patient selection, and close clinical monitoring.

Exploratory analyses did not identify statistically significant predictors of infectious complications ($p > 0.05$). Nevertheless, infections numerically appeared more frequent among patients receiving concomitant immunosuppressive therapies and among patients with comorbidities. Similar findings have been reported in observational cohorts evaluating biologic therapies, where corticosteroid exposure, combination immunosuppressive therapy, diabetes mellitus, and chronic comorbid conditions were associated with increased infectious risk (73,74,97,98).

Treatment adherence in our population was globally favorable. Among the 90 evaluable patients included in adherence and satisfaction analyses, most patients demonstrated good therapeutic adherence and reported subjective clinical improvement. This observation is particularly interesting in the Algerian context where access to biologic therapies remains difficult in several regions. Similar observations have been reported in real-world studies showing that patients experiencing significant clinical improvement under biologic therapies generally demonstrate better long-term adherence (64,65).

Patient satisfaction was also globally favorable. Most patients reported acceptable tolerance, improvement in daily activities, and better overall quality of life under biologic therapy. These findings remain consistent with

previous studies demonstrating improved patient-reported outcomes and quality of life under biologic therapies (22,35,51,63).

One of the major strengths of our study lies in its real-world design. Although randomized controlled trials remain essential, real-world studies better reflect the complexity, heterogeneity, and multisystemic nature of diseases encountered in routine Internal Medicine practice (63,65). Another important strength is the broad diversity of diseases included in the cohort, illustrating the expanding role of Internal Medicine in advanced immunomodulatory therapies and complex multisystem diseases.

However, several limitations should be acknowledged. First, the monocentric design may limit the generalizability of the results. Second, the relatively limited sample size reduced statistical power, particularly for subgroup and multivariate analyses. Third, the heterogeneity of included diseases and therapies may have diluted disease-specific associations. Fourth, missing data were unavoidable because of the ambispective design and incomplete medical records. Finally, several clinically relevant variables such as baseline severity scores, therapeutic drug monitoring, immunogenicity markers, socioeconomic factors, and standardized quality-of-life assessments were not systematically available. Similar methodological limitations are frequently reported in retrospective and real-world observational studies evaluating biologic therapies (17,18).

Despite these limitations, our study provides one of the first real-world overviews of biologic and targeted therapy use in Internal Medicine practice in southern Algeria. It highlights the progressive integration of these therapies into routine management of inflammatory and autoimmune diseases while emphasizing the importance of structured monitoring, infectious screening, therapeutic education, and multidisciplinary follow-up.

Beyond its descriptive contribution, our work reflects the progressive transformation of Internal Medicine practice in Algeria toward precision medicine and advanced immunomodulatory therapies. The increasing integration of biologic and targeted therapies into routine practice will probably require the development of multidisciplinary expert networks, national registries, pharmacovigilance structures, therapeutic education programs, and standardized monitoring protocols adapted to local healthcare realities.

Future multicenter studies involving larger cohorts would be useful to better characterize long-term efficacy, predictors of therapeutic response, infectious risk factors, pharmacoeconomic aspects, biosimilar utilization, and healthcare accessibility challenges associated with biologic and targeted therapies in Algeria. The establishment of national registries could also improve long-term pharmacovigilance, therapeutic surveillance, and real-world outcome assessment in immune-mediated diseases.

Conclusion

In conclusion, this ambispective real-world study provides one of the first overviews of biologic and targeted therapy utilization in an Internal Medicine department in Southern Algeria. Our findings highlight the progressive integration of advanced immunomodulatory therapies into routine Internal Medicine practice, particularly in the management of complex inflammatory, autoimmune, systemic, and rare diseases.

Despite organizational and accessibility challenges, biologic and targeted therapies demonstrated globally favorable clinical efficacy, acceptable tolerance, and relatively limited severe infectious complications in our cohort. Anti-TNF therapies remained the most frequently prescribed agents, reflecting both their broad therapeutic indications and their greater accessibility in our setting.

Beyond its descriptive contribution, this work also underlines the evolving role of Internal Medicine as a specialty increasingly involved in multidisciplinary management, precision medicine, and advanced therapeutic decision-making for complex immune-mediated diseases.

Our study further emphasizes the importance of strengthening infectious surveillance, therapeutic education, pharmacovigilance, and structured monitoring strategies in patients receiving biologic therapies, particularly in countries where infectious diseases such as tuberculosis remain endemic.

Finally, these findings support the need for larger multicenter national studies and collaborative registries in order to better characterize biologic therapy use, optimize therapeutic accessibility, improve long-term safety monitoring, and further develop personalized medicine approaches adapted to the Algerian healthcare context.

Recommendations
&
Perspectives

1) Recommendations:

Based on the findings of our study, several recommendations may be proposed in order to optimize the use of biologic and targeted therapies in Internal Medicine practice in Algeria.

First, strengthening early diagnosis and referral pathways for chronic inflammatory and autoimmune diseases appears essential in order to improve timely access to biologic therapies. Delayed diagnosis and therapeutic escalation may contribute to disease progression, irreversible organ damage, and poorer functional outcomes.

Second, systematic pre-therapeutic evaluation should be reinforced before initiation of biologic therapy, particularly regarding infectious screening for tuberculosis, hepatitis B and C, HIV infection, and vaccination status. Given the infectious risks associated with immunosuppressive therapies, standardized screening protocols and close monitoring strategies remain fundamental.

Third, multidisciplinary collaboration between internists, gastroenterologists, rheumatologists, neurologists, dermatologists, infectious disease specialists, and pharmacists should be encouraged in order to optimize therapeutic decision-making and long-term patient follow-up.

Fourth, therapeutic education programs should be developed to improve patient adherence, treatment understanding, early recognition of adverse effects, and long-term therapeutic outcomes. Patient awareness remains a key element in the success of biologic therapies.

Finally, improving access to biologic and targeted therapies in peripheral regions and optimizing reimbursement policies may contribute to reducing therapeutic inequalities within the Algerian healthcare system.

2) Perspectives:

This study opens several perspectives for future research and clinical development in Algeria.

The establishment of multicenter national registries would allow larger-scale evaluation of biologic therapies, including long-term efficacy, safety, infectious complications, treatment persistence, biosimilar use, and pharmacoeconomic impact.

Future prospective studies involving homogeneous disease-specific cohorts would also be useful to better identify predictive factors of therapeutic response and adverse effects. Integration of validated disease activity scores and patient-reported outcome measures could further improve therapeutic assessment.

Additional research should focus on therapeutic drug monitoring, immunogenicity, biosimilar implementation, and cost-effectiveness analyses in the Algerian context. Such studies could contribute to more individualized therapeutic strategies and optimized healthcare resource allocation.

Finally, the progressive development of personalized medicine, biomarkers, pharmacogenomics, and artificial intelligence-assisted therapeutic monitoring may significantly improve the future management of inflammatory and autoimmune diseases treated with biologic and targeted therapies.

ANNEXES

ANNEXE N01:

Biologic Therapy Study Form in the Department of Internal Medicine:

1. Demographic data:

• Age: --- years • Sexe: Male □ Female □

• Wilaya of residence: ---------- • Scio-economic level: Good □ Medium □ Low □

2. Clinical data:

•Main pathology: Crohn's disease □ Ankylosing spondylitis □ Ulcerative colitis □ others: ----------

• Date of diagnostic: --------- • Comorbidities: HTA □ Diabetes □ Dysthyroïdism □ others: ---------

• Previous treatments before biotherapy:

• the initial activity before biotherapy: Active □ No active □

3. Biotherapy:

• The molecule used: ---------- • Date of initiation of biotherapy: / /

• The method of administration: subcutaneous □ intravenous □

• Molecule used as a second-line treatment: ---------- • The cause of the molecule change: ….

• Associated treatments: …….

4. Clinical and biological follow-up :

• Clinical improvement: Yes □ No □ • Adverse events: Yes □ No □ If yes, which ones? : ----------

• Infections: Yes □ No □ If yes, which ones?: ----------

• Adherence: Good adherent□ Non-adherent □

• Patient satisfaction: very satisfied □ Moderately satisfied □ Not satisfied □

5. Access barriers :

• Availability: available □ Non-available □ if a shortage occurs, what is the duration? :----------

• Constraints related to biological monitoring: Administrative conflicts □ Daily life constraints □ Economic constraints □ Psychological and social constraints□ nothing

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