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Surveillance of Adverse Events of Biologic Therapy in Patients with Rheumatologically Diseases and Oncological Diseases

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ABSTRACT

Background: Systemic rheumatic diseases (SRDs) cause long-term disability and affect both physical and mental health, leading to major challenges in daily life and work. New biologic treatments have improved outcomes in SRDs and cancer, but they require careful monitoring, and need to be tailored to each patient for the best results.

Aim of the work: To compare between side effects and the most common toxicities associated with biological therapies in patients with rheumatological diseases and oncological diseases.

Patients and methods: This cross-sectional observational cohort study included a total of 75 patients, who were classified into two groups. Group A consisted of 18 patients with rheumatological diseases who are receiving biological therapy, while Group B included 57 patients with oncological diseases undergoing treatment with biological therapy.

Results: Rheumatologic patients were commonly males (66.7%), had lower RBCs (3.9 million/μL), and longer treatment duration (15 vs. 6 months), with 77.7% showing regression. Oncologic patients had higher urea (47 mg/dL), more GI symptoms (5.3–7.0%), and greater disease progression (35.1%) with 3% mortality.

Conclusion: This study compares biologic therapy in rheumatological and oncological illness, with better outcomes in the rheumatological group, including fewer progression rates and more regression. The oncological group experienced increased adverse events and increased mortality. Some positive responses were seen in patients with oncology, whereas rheumatological diseases were generally more treatable. Continuous monitoring is essential to improve the safety and effectiveness of the treatment in both groups.

Keywords: Biologic therapy**,** Oncological diseases**,** Rheumatological diseases**,** Side effects**,** Toxicity.

INTRODUCTION

Even in nations with advanced healthcare systems, systemic rheumatic disorders (SRDs) significantly impact all societies financially and socially and are a leading cause of disability worldwide. In addition to physical impairment and decreased activity, SRDs have a significant mental impact because they make it difficult for people to fulfill their professional, social, and family responsibilities, all of which increase the prevalence of anxiety disorders and lower quality of life. SRDs are one of the primary causes of long-term dysfunction and absenteeism in the working population, which includes those between the ages of 19 and 65[(1)].

In the field of chronic immune-mediated disorders (IMD), the introduction of biologic medicines has transformed treatment strategies and results, resulting in symptom alleviation and a halt to the course of the disease. Although oral immunosuppressants or biologic monotherapy help the majority of IMD patients achieve sufficient disease management, some individuals do not react, which poses a treatment challenge [(2)].

Anti-cytokine biologics, such as tumor necrosis factor inhibitors (TNFi), interleukin (IL)-1 inhibitors (IL-1i), IL-6 inhibitors (IL-6i), IL-17 inhibitors (IL-17i), IL-12/23 inhibitors (IL-12/23i), and IL-23 inhibitors (IL-23i), are used to treat rheumatoid arthritis (RA) and psoriatic arthritis (PsA). B-cell depleting agents and T-cell co-stimulation inhibitors (CTLA4-Ig) are also used. Biologic treatments are administered in a sequential manner in clinical practice, and they are switched when there is therapeutic resistance or intolerance [(3)].

The increased use of biological medications to treat inflammatory rheumatic disorders has forced rheumatology departments to adjust in order to provide high-quality care. Due to the known hazards associated with these pricey medications, careful monitoring and a thorough assessment of the advantages and disadvantages are necessary. Multidisciplinary teams must deliver high-quality healthcare in order to guarantee patient safety and compliance. Implementing techniques that improve care delivery, particularly in SRDs, which are lifelong conditions, depends critically on how patients feel about their treatment [(1)].

Treatment involving natural chemicals produced by the body or generated in labs is known as biological cancer therapy. These treatments either target cancer cells directly or assist the immune system in combating cancer. These consist of immunoconjugates, gene therapy, cytokine treatments, cancer vaccines, oncolytic viruses, monoclonal antibodies, adoptive cell transfer, and targeted therapies. This strategy is in line with the new precision oncology paradigm, which employs next-generation sequencing (NGS) to find uncommon mutations and customize treatment plans for each patient[(4)]. Molecules that target genetic abnormalities in tumor suppressor and oncogene genes are crucial for cancer treatment. Classic examples include osimertinib, which was licensed in 2017 for non-small cell lung cancer with the EGFR T790M mutation; vemurafenib, a BRAF serine/threonine kinase inhibitor used in melanoma; and imatinib, a BCR-ABL tyrosine kinase inhibitor used in chronic myeloid leukemia [(5)].

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The current study's objective was to evaluate the most frequent toxicities and side effects linked to biological therapy in patients with cancer and rheumatological conditions.

PATIENTS AND METHODS

This six-month cross-sectional observational cohort study was undertaken from April to October 2023 in order to assess the frequency and nature of adverse events (AEs) among patients who were administered biologic therapies for rheumatological and cancer conditions. The study was performed at Menoufia University Hospital, more specifically in two specialized departments: the Rheumatology Unit of the Internal Medicine Department and the Clinical Oncology and Nuclear Medicine Department.

A total of 75 adult patients (aged ≥18 years) who were receiving intravenous or subcutaneous biologic therapies participated in the study. The patients were divided into two groups: Group A consisted of 18 patients with systemic rheumatic diseases, and Group B consisted of 57 patients with different oncological diseases. The inclusion criteria required the patients to have an established diagnosis and to be naïve or to have undergone previous treatment with biologics. Excluded were patients with biologic contraindications, patients in other simultaneous clinical studies, patients missing essential follow-up visits, or pregnant or breastfeeding women.

Recruitment of patients was carried out based on outpatient and inpatient clinic visits and review of medical records. For each patient who was registered, the complete clinical and demographic data were collected, such as gender, age, disease type, comorbidities, full blood count, liver function tests and kidney function tests. Oncology patients had the cancer type and stage recorded, which were pertinent for making decisions regarding treatment as well as evaluating risks with biologic therapies.

The trial employed a wide range of biologic agents particular to the disease under treatment. Seven types of biologics were employed: tumor necrosis factor (TNF) inhibitors (e.g., adalimumab, golimumab, infliximab), monoclonal antibodies (e.g., rituximab, daratumumab), immune checkpoint inhibitors (e.g., atezolizumab), and proteasome inhibitors (e.g., bortezomib). The drugs were administered according to standard dosage regimens, either as monotherapy or in combination with other medications such as methotrexate or chemotherapy. For instance, rituximab was employed at 1000 mg IV every two weeks for RA and 375 mg/m² weekly for B-cell lymphoma. Adalimumab was typically given as 40 mg subcutaneous injection every two weeks. Other treatments such as bortezomib and daratumumab were administered in multi-drug regimens for lymphoma and multiple myeloma. The treatment histories, including the number and types of previous biologic drugs received and why they were stopped, were recorded diligently. Evaluation of treatment response was a key component of the study. For patients with rheumatologic diseases, treatment response was defined as good response, primary nonresponse, secondary loss of response, or inadequate response. This was based on disease activity score changes, inflammatory markers, and clinical findings. Response to oncological therapy was assessed based on the RECIST 1.1 criteria, which categorize responses as Complete Response (CR), Partial Response (PR), Stable Disease (SD), or Progressive Disease (PD), based on target lesion size, change in non-target lesions, and appearance of new metastatic lesions. This allowed reproducible, standardized measurement of treatment response in many types of cancer.

Systematic monitoring of adverse events was conducted during the six-month follow-up period. All patients had at least three follow-up visits initial, mid-study, and end-study at approximately every two months. During these visits, clinicians assessed for a broad range of possible AEs for biologic therapy. Written AEs included dermatologic side effects (e.g., rashes, photosensitivity), gastrointestinal side effects (e.g., nausea, diarrhea), endocrine disease (e.g., thyroid disease), musculoskeletal symptoms (e.g., arthralgia), hematologic consequences (e.g., anemia, leukopenia), infectious and immunological complications, and neurological signs such as headache or peripheral neuropathy. The adverse events were investigated thoroughly to identify their relationship with the used biologic treatment.

Ethical approval:

The approval for the research was obtained from the Institutional Review Board (IRB) of the Faculty of Medicine, Menoufia University (approval number 3/2022INTM22), ensuring adherence to ethical guidelines for human subject research in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Ethical considerations were observed in the course of the study. Informed consent was obtained from all the subjects with awareness of the study purposes, procedures, and dangers. Confidentiality was maintained by de-identifying individual information and limiting data access to those research staff who had been authorized. Patients were explicitly informed of their right to withdraw at any moment without impairing their treatment. Design and procedures of the study were entirely in line with ethical research protocols on human subjects and aligned with the standards of the endorsing IRB.

Statistical Analysis

SPSS version 29 (IBM Corp., Armonk, NY) was used to analyze the data. Variables were summarized as frequencies and percentages.

RESULTS

The study included 75 patients, categorized into those

with rheumatological diseases (18 patients, 24%) and oncological diseases (57 patients, 76%). Among the rheumatological group, ankylosing spondylitis was the most common condition, affecting 15 patients (83.3%). In the oncological group, NHL was the predominant disease, reported in 31 patients (54.4%) **(Table 1).**

Table 1: Distribution of rheumatological and oncological diseases among study participants

Disease (N=75)		n (%)
Rheuma-tological (n=18)	Ankylosing Spondylitis	15 (83.3%)
	SLE	3 (16.7%)
Oncological (n=57)	CML	3 (5.3%)
	HCC	6 (10.5%)
	Multiple Myeloma	17 (29.8%)
	NHL	31 (54.4%)

Abbreviations: *CML, Chronic Myeloid Leukemia; HCC, Hepatocellular Carcinoma; NHL, Non-Hodgkin Lymphoma; SLE, Systemic Lupus Erythematosus. Data are presented as frequency (percentage).*

Cytopenias were common in both groups, with anemia being the most frequent: 94.4% of rheumatological patients and 82.5% of oncological patients were affected. Gastrointestinal (GIT) symptoms were generally infrequent across both groups. The majority of patients reported no symptoms: 83.3% in the rheumatological group and 80.7% in the oncological group. Among those with symptoms, diarrhea and its combinations were more prevalent in oncological patients (5.3–7.0%), while mild vomiting with fever and its combinations occurred in 5.6% of rheumatological patients **(Table 2).**

Table 2: Frequency of cytopenias and gastrointestinal symptoms in patients treated with biological therapies

Variable	Rheumato-logical Diseases (n=18)	Oncological Diseases (n=57)
Cytopenia		
– Anemia	17 (94.4%)	47 (82.5%)
– Leucopenia	1 (5.6%)	13 (22.8%)
– Thrombocytopenia	9 (50.0%)	25 (43.9%)
GIT Symptoms		
Vomiting	0 (0.0%)	2 (3.5%)
Mild Vomiting + Fever	1 (5.6%)	0 (0.0%)
Diarrhea	0 (0.0%)	3 (5.3%)
Diarrhea + Vomiting	0 (0.0%)	3 (5.3%)
Mild Fever + Diarrhea	1 (5.6%)	0 (0.0%)
Mild Vomiting + Fever + Diarrhea	1 (5.6%)	0 (0.0%)
Vomiting + Nausea + Diarrhea	0 (0.0%)	4 (7.0%)

Data are presented as frequency (percentage).

In the rheumatological group, adalimumab was the most commonly used biologic therapy, administered to 12 patients (66.7%). NSAIDs were frequently prescribed in this group, with 12 patients (66.7%) using them. In contrast, the oncological group had a more diverse range of biologic therapies, with Rituximab being the most common (22 patients, 38.6%), followed by Bortezomib (17 patients, 29.8%). Chemotherapy was the predominant non-biologic treatment in the oncological group, administered to 35 patients (61.4%), while NSAIDs were used in only 1 patient (1.8%) **(Table 3).**

Table 3: Types of biological therapies and other drugs used in rheumatological and oncological diseases

Variable	Rheumatological Diseases (n=18)	Oncological Diseases (n=57)
Type of Biologic		
Adalimumab	12 (66.7%)	0 (0.0%)
Atezolizumab	0 (0.0%)	6 (10.5%)
Bortezomib	0 (0.0%)	17 (29.8%)
Daratumumab	0 (0.0%)	3 (5.3%)
Golimumab	3 (16.7%)	0 (0.0%)
Infliximab	0 (0.0%)	9 (15.8%)
Rituximab	3 (16.7%)	22 (38.6%)
Other Drugs Other than Biologics		
Chemotherapy	0 (0.0%)	35 (61.4%)
Chemotherapy + PPI	0 (0.0%)	4 (7.0%)
Insulin + Methotrexate	2 (11.1%)	0 (0.0%)
Methotrexate	3 (16.7%)	0 (0.0%)
NSAID	12 (66.7%)	1 (1.8%)

Abbreviations: NSAID, Nonsteroidal Anti-Inflammatory Drug; PPI, Proton Pump Inhibitor.
Data are presented as frequency (percentage).

In the rheumatological group, the most common outcome was complete regression, observed in 14 patients (77.7%). No partial responses or deaths were reported in this group. In the oncological group, complete regression was also the most frequent outcome, seen in 24 patients (42.1%), followed by progressive disease in 20 patients (35.1%), and death in 2 patients (3.5%) **(Table 4).**

Table 4: Clinical outcomes and responses to biological therapies in rheumatological and oncological diseases

Outcome	Rheumatological Diseases (n=18)	Oncological Disease (=57)
PD	3 (16.7%)	20 (35.1%)
Complete Regression	14 (77.7%)	24 (42.1%)
PR	0 (0.0%)	2 (3.5%)
SD	1 (5.6%)	9 (15.8%)
Died	0 (0.0%)	2 (3.5%)

Abbreviations: *PD, Progressive Disease; PR, Partial Response; SD, Stable Disease.Data are presented as frequency (percentage).*

DISCUSSION

In our current study, biologic treatments were assessed in a group of 75 patients divided into two broad categories: rheumatological and oncological. Disease distribution was highly diverse between the two groups, with the rheumatological being 24% and oncological being 76%. Within the rheumatological category, ankylosing spondylitis was the most prevalent diagnosis by far, and Non-Hodgkin Lymphoma (NHL) was most prevalent in the oncological category. This makes sense with the modern-day treatment trends whereby biologic therapies specifically monoclonal antibodies and checkpoint inhibitors are becoming central in the management of hematological malignancies [6,7]. On the other hand, despite how biologics have transformed rheumatologic disease management, especially in rheumatoid arthritis and spondyloarthropathies, traditional Disease-Modifying Antirheumatic Drugs (DMARDs) remain significant [8,9].

The most important findings of this study were the high prevalence of hematologic adverse effects (cytopenias) among patients treated with biologics. Anemia was found to be overwhelmingly prevalent among both groups, even though to a slightly greater degree in rheumatology patients (94.4%) than in oncology patients (82.5%). Its pathogenesis differs by disease category: anemia of chronic disease (ACD) is common in autoimmune diseases due to chronic inflammation-induced damage in erythropoiesis [10], while in oncology, anemia is commonly exacerbated by the chemotherapy-induced myelosuppression or bone marrow invasion by tumor cells [11]. Thrombocytopenia was also present in both groups but more likely due to immune-mediated platelet destruction in autoimmune illness and cytotoxic damage in cancer therapy. Leucopenia, however, was much more common in the oncology group (22.8% vs. 5.6%), a consequence of the immunosuppressive effects of cancer treatment [12].

Notably, gastrointestinal AEs were relatively rare but had varied trends. Diarrhea and diarrhea combinations were encountered only in oncology patients and are best explained by mucosal toxicity to chemotherapy [13]. On the other hand, minor events such as fever and vomiting with or without immune activation or minor drug reaction were encountered only among the rheumatologic group and are consistent with expected reactions to immunomodulators such as methotrexate or TNF inhibitors [14].

The length of treatment and disease also underscores the divergent paths in rheumatological versus oncological care. The rheumatological patients maintained longer median disease courses (30 months) and courses of biologic therapy (15 months) compared to oncology patients (11 months and 6 months, respectively). This most likely indicates the chronicity of autoimmune illness, where long-term disease control measures are needed, in contrast to cancer therapy, which is often more aggressive but of limited duration [15].

These therapeutic differences were also evident in the biologic treatments. The rheumatologic patients were treated most commonly with adalimumab (66.7%), also often in association with NSAIDs (66.7%) and methotrexate, following standard protocols for managing diseases such as ankylosing spondylitis and rheumatoid arthritis [16,17]. On the contrary, rituximab was most frequently used as a biologic among the oncology group (38.6%), namely for NHL and other B-cell malignancies, testifying to its long-established efficacy in such contexts [18]. Other drugs specifically oncology-specific like bortezomib and daratumumab were also used extensively, testifying to the pluralistic biologic landscape in cancer treatment.

Despite all these complexities, clinical outcomes recorded a more favorable response pattern in the rheumatologic group. An astonishing 77.7% of them experienced complete regression of disease, and no deaths were reported. In comparison, only 42.1% of the patients with complete tumor regression in oncology, 35.1% experienced progressive disease, and a paltry 3.5% died throughout the course of the study. These findings underscore the relative amenability and treatability of chronic inflammatory diseases when contrasted with the often virulent and heterogeneous course of cancer [19,20].

Ultimately, this comparison addresses the universal clinical reality: while biologic drugs have revolutionized both fields, their impact and application are inherently different. Rheumatologic disease is best treated with prolonged and early biologic therapy that can yield remission and control of the disease for the long term [21]. Oncological treatments are still plagued by recurrence, relapse, and mortality even after the identification of targeted biologics [22,23]. The disparity in results also serves to underscore the imperative for individualized treatment strategies, careful monitoring of side effects, and ongoing innovation with biologic therapy to maximize patient results in both fields.

CONCLUSION

This study highlights the benefits and risks of biologic therapies in treating both rheumatological and oncological diseases. The rheumatological group showed more favorable outcomes, with lower disease progression and higher regression rates, while the oncological group had a higher mortality rate and more adverse events. Despite some positive responses in oncology, rheumatological diseases appeared more manageable overall. Ongoing surveillance and personalized monitoring are essential for optimizing treatment and minimizing risks in both groups.

DECLARATIONS

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