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Review Article

Antibody-Drug Conjugates vs. Traditional Biologics: A Comparative Analysis of Rheumatic Disease Management

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ABSTRACT

The review article deals with the possibility of the use of Antibody-Drug Conjugates (ADCs) for the treatment of rheumatic diseases. The introduction emphasizes the difficulty of chronic autoimmune diseases' management and identifies the shortcomings of the current approach of using Disease-Modifying Antirheumatic Drugs (DMARDs) and biologies. ADCs appear as an attractive solution which links a monoclonal antibody and a cytotoxic component to recognize cancer cells specifically and in so doing minimize systemic toxicity. In the overview of ADCs and traditional biologics these new therapies are compared to traditional biologics with a focus on the major developments in the field of ADC since the 1st ADC approval in 2000. The properties it addresses cover the structural characteristics of ADCs in terms of monoclonal antibodies, cytotoxic components and linkers. The action section is describing how ADCs convey selectively to specific antigens on cancer cells, internalization through endocytosis. This process results in the generation of cytotoxic agents within tumor cells that proclaim apoptosis and are harmless to the other tissues. The problem of a bystander effect, under which released payloads impact non-target cells nearby, is also considered. The review also assesses the effectiveness and safety of approved ADCs in the US FDA: presenting clinical trial results and patients' outcomes. It then considers difficulties in the generation of next-generation ADCs and their further case usage in clinical practice and points out the need for further research to enhance the effectiveness of these therapies for rheumatic diseases. In conclusion, this article seeks to demystify areas of uncertainty and lay a robust background for subsequent investigations that will enhance treatment plans for rheumatic condition patients.

Keywords: Antibody-Drug Conjugates (ADCs), Cytotoxic Payload, Disease-Modifying Antirheumatic Drugs (DMARDs), Monoclonal Antibodies and Rheumatic Diseases.

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INTRODUCTION

Arthritis conditions include a broad group of rheumatic diseases that are chronic autoimmune conditions and which are difficult to manage in clinical practice because of the underlying multifactorial etiology and the diverse patient response to treatment (Huang *et al*., 2024). Although DMARDs and more recently biologic agents, have given significant symptom relief to numerous patients, they have often offered suboptimal relief and safety to others (Rubio *et al*., 2024). ADCs turn into a new treatment principle in the medicinal arsenal because they can be targeted at cancer cells selectively and their action is based on the connection of monoclonal antibodies with cytotoxic agents (Medina *et al*., 2024). It is a distinct approach which in addition to improving the therapeutic index, also works to decrease the toxicity of the therapeutic product when administered systemically, which is in fact one of the challenges of application of conventional treatments (Aggarwal *et al*., 2023).

ADCs can therefore be described as advanced cross between high performing mAbs and highly effective cytotoxicity agents connected using a chemical linker (Medina *et al*., 2024). This advanced biopharmaceutical approach is a method of selectively attacking cancer cells by targeting with mAbs that fix onto antigens located on the cancer cell membrane and delivering lethal medicine. ADCs preserve most healthy cells hence decreasing systemic toxicity and improving the treatment ratio (Huang *et al*., 2024). When attached to the target antigen, ADCs are taken up by endocytosis by the tumor cell and move through the endo-lysosomal pathway. Here the chemical linker is severed for liberating the cytotoxic payload in the cytosol, which leads to cell demise by pathways such as DNA fragmentation or microtubule formation inhibition (Tolcher, 2016). There are two primary types of linkers: cleavable linkers, which release the toxin selectively in the tumor environs due to the properties of tumor cells and non-cleavable linkers, which are endocytosed and released by the action of lysosomal enzymes within the tumor cell. Although

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it seems obvious to unite these three components, mAb, linker and cytotoxin, the fine tuning of the interaction between them is still a great challenge because of the interactions with the tumor integrands and the tumor microenvironment (Criscitiello *et al.*, 2021). Moreover, ADCs may take advantage of the "bystander effect," in which cytotoxic payloads released from targeted cells affect other neighboring non-target cells, so the therapeutic effect of ADC is expanded to various heterogeneous tumor samples. However, first generation ADC formulations were not without developmental issues, however, greater progress has been achieved in overcoming these limitations resulting in several FDA approved ADCs for clinical application after complete preclinical and clinical evaluation (Staudacher *et al.*, 2017; Criscitiello *et al.*, 2021). This paper aims to briefly introduce efficacy and safety evaluation results of FDA-approve ADCs (Table 1) and to provide references for the clinical practice as well as research.

This review article aims to compare the ADCs and traditional biologics regarding rheumatic diseases. The focus of the paper will be on the modality of action of both these methods, clinical trials involving their applicability, the safety profile of the methods and their impact on patient outcome. In addition, possible difficulties in the further development of the next generation ADCs will be explored along with their potential for use in clinical practice in the future. Based on literature reviews from databases including PubMed, Scopus, Web of Science, ScienceDirect, Springer, Taylor and Francis online and Open Athens, this article aims to clarify the existing understanding and provide literature gaps to the future research on management of rheumatic diseases.

Overview of ADCs and traditional biologics

Antibody-Drug Conjugates (ADCs) are considered a qualitative leap forward in targeted cancer therapy that combines properties of biologics and small molecules. The novel anti-cancer agents include monoclonal antibody-drug conjugates, whereby the cytotoxic moiety is conjugated to monoclonal antibodies that selectively bind to tumor-associated antigens with very little harm to the other components of the body. The basic idea of ADCs can be attributed to the concept outlined by Paul Ehrlich and his notion that is known today as 'magic bullet' in where it was envisioned that agents delivering throughputs should be delivered to the diseased cells selectively with no harm or interference to the normal adjacent cells (Khongorzul *et al.*, 2020; Baah *et al.*, 2021). From 2000 when the first ADC, Mylotarg, was approved by the FDA for the treatment of Acute Myeloid Leukemia (AML) to the present, ADC architecture has been changing constantly (Liu *et al.*, 2024).

Since then, the field has grown beyond recognition, today there are 80 plus ADCs in clinical development and several have already received approval for use in different types of cancers (Metrangolo *et al.*, 2024). Figure 1 illustrates the Structure and Key Functions of Antibody-Drug Conjugates (ADCs), highlighting their essential components: a monoclonal antibody that recognizes tumor-associated antigens, a cytotoxic payload which leads to cell death and a linking domain through which the two components are connected.

The architecture of an ADC typically comprises three main components: a monoclonal antibody, a linking moiety and a cytotoxic agent. The mAb is expected to bind with preferred antigens present on the outer membranes of target cancer cells that are internalized by endocytosis (Lucas *et al.*, 2021). Once inside the cell the lysosomes release the cytotoxic drug in the cell the drug then binds to cellular factors such as DNA or microtubules creating a cell cycle arrest and apoptosis (Trybus *et al.*, 2023). This mechanism not only drives up the therapeutic gain but also minimizes side impacts that are did by most conventional chemotherapeutic agents. From this work, the linker used is one of the critical determinants of the stability and potency of ADCs. Linkers should be stable in circulation so as not to release the drug on circulation but should also be cleavable within target cells for optimal drug delivery (Ponziani *et al.*, 2020). Several linker technologies have been devised over the years and they range from cleavable linkers which break in response to specific cellular conditions. For instance, protease-sensitive linkers can increase the bystander effect by allowing the next active drug molecules into neighboring cells, hence improving the therapeutic performance (Metrangolo *et al.*, 2024). Nevertheless, ADCs exist with numerous challenges that affect their application in clinic. One concern is immunogenicity when monoclonal antibodies are of murine or chimeric origin. The recent changes to fully humanized antibodies reduce some of these concerns, thus minimizing the immune reactions and enhancing the patient compliances (Fu *et al.*, 2022).

Furthermore, the advancement in new payloads has also increased the therapeutic window of ADCs. Novel agents for example Pyrrolobenzodiazepines (PBDs) and immunomodulatory drugs are currently under investigations for their potentially enhanced cytotoxicity while still being safe (Hartley *et al.*, 2021).

Extensive research has shown that the application of ADCs can be highly effective

Compared to other forms of treatment. For example, trastuzumab emtansine (T-DM1), one of the ADCs targeting of HER2-positive breast cancer, has a longer progression-free survival rate than other conventional therapies. Moreover, recent trials have highlighted the effectiveness of ADCs in treating various malignancies beyond breast cancer, including hematological cancers and solid tumors (Ballantyne *et al.*, 2013). Further identification of dosing regimens and selection of targets of tumor antigen expression will see ADCs as fundamental parts of targeted cancer therapy.

The ability to achieve post-attachment toxin release and remove the antibody armory depends on numerous factors that influence ADCs' effectiveness and toxicity in clinical trials.

Table 1: Overview of FDA-approved ADC drugs.

ADC (Company)	Trade Name	Target Antigen	Payload	Approved Date	Indications	References
Pfizer/Wyeth	Gemtuzumab ozogamicin	CD33	Calicheamicin	2017	Relapsed acute myeloid leukemia.	(Theocharopoulos *et al.*, 2020)
Seagen Genetics	Brentuximab vedotin	CD30	MMAE (microtubule inhibitor)	2011	Relapsed Hodgkin lymphoma, systemic anaplastic large cell lymphoma.	(Chen *et al.*, 2013)
Pfizer/Wyeth	Inotuzumab ozogamicin	CD22	Calicheamicin	2017	Relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia.	(Wu *et al.*, 2024)
Genentech/Roche	Trastuzumab emtansine	HER2	DM1 (microtubule inhibitor)	2013	HER2-positive metastatic breast cancer.	(Hunter *et al.*, 2020)
AstraZeneca	Moxetumomab pasudotox	CD22	Immunotoxin	2018	Relapsed or refractory hairy cell leukemia.	(Abou and Ravandi, 2019)
Genentech/Roche	Polatuzumab vedotin	CD79	MMAE (microtubule inhibitor).	2019	Relapsed or refractory diffuse large B-cell lymphoma.	(Theocharopoulos *et al.*, 2020)
Astellas/Seagen Genetics	Enfortumab vedotin	Nectin-4	MMAE (microtubule inhibitor).	2019	Locally advanced or metastatic urothelial cancer after PD-1/PD-L1 therapy and platinum therapy.	(Rajagopal *et al.*, 2024)
AstraZeneca/Daiichi Sankyo	Trastuzumab deruxtecan	HER2	DXd (topoisomerase I inhibitor).	2019	Unresectable or metastatic HER2-positive breast cancer.	(Perez *et al.*, 2021)
Immunomedics	Sacituzumab govitecan	Trop-2	SN-38 (topoisomerase I inhibitor).	2020	Metastatic triple-negative breast cancer after two prior therapies.	(McGuinnes *et al.*, 2021)
GlaxoSmithKline	Belantamab mandolin	BCMA	MMAF (microtubule inhibitor).	2020, withdrawn	Relapsed or refractory multiple myeloma.	(Shang *et al.*, 2008)
ADC Therapeutics	Loncastuximab tesirine	CD19	Tesirine	2021	Large B-cell lymphoma	(Xu *et al.*, 2022)
Seagen Inc	Tisotumab vedotin	Tissue factor	MMAE (microtubule inhibitor).	2021	Recurrent or metastatic cervical cancer.	(Heitz *et al.*, 2023)
ImmunoGen	Mirvetuximab soravtansine	FRα	DM4	2022	Platinum-resistant ovarian cancer.	(Heo *et al.*, 2023)

Core of this concerns is the identification of target antigens that should be highly displayed on the cancer cells without being in relatively normal tissues to avoid side effects (Fu *et al.*, 2022). This specificity not only improves the therapeutic index but also facilitates the internalization of the ADC and realizes the targeting of toxic payloads. Alike, the characteristics of the cytotoxic payload are relevant; the payload should be highly toxic to the target cancer cells and at the same time should have stability in circulation. Another factor-the Drug-to-Antibody Ratio (DAR); higher DARs can lead to improved potency but at the expense of increased toxicity; necessary optimization is required during the development of the therapeutic agent (Fu *et al.*, 2022; Nejadmoghaddam *et al.*, 2019). However, the linker technology connecting the antibody and payload needs to be stable in bloodstream and facilitate drug release once internalized. Designing clinical trials also plays a role in the success of ADCs; addition of biomarker throughout patient selection and the knowledge of resistance also goes a long way to determine outcomes (Metrangolo *et al.*, 2024). Together, they define the complexity of ADC design process and the idea that further development of these agents may require a multidisciplinary proximal regarding their utilization in oncology (Lucas *et al.*, 2018) (Figure 2). Key performance indicators for ADC influence is aimed to demonstrate what aspects make ADC efficient and safe, with more attention to how target, drug-to-antibody ratio, a choice of payload, the linker and a tumor microenvironment affect the result.

Mechanism of action

Mechanism of Action of Antibody-Drug Conjugates (ADCs)

The mechanism of action of Antibody-Drug Conjugates (ADCs) is based on the interaction of the antibody portion of the ADC with certain antigens on the membranes of cancerous cells. This is an inherent part of ADC functioning since it is the only way to achieve target cells' selective uptake, which eliminates side effects typical for most chemotherapeutic drugs (Drago *et al.*, 2021). As a result of their precise targeting, ADCs can deliver highly toxic payloads into tumor cells, but this agent is not toxic to other cells in the body unlike chemotherapy. After binding to the target antigen, ADCs are taken into the cell with the use of endocytosis by receptor-mediation. This internalization results in the formation of endosomes containing the conjugate. The best described mechanism for this process is Clathrin-dependent endocytosis where small regions on the cell membrane, known as Clathrin-coated pits, assist in the internalization of the ADC-antigen complex (Khongorzul *et al.*, 2020). After internalization, these re-arranged endosomes become part of late endosomes where it undergoes further development and later fuses with Lysosome where the cytotoxic drug is to be released.

Within the lysosomes, proteolytic enzymes digest the linker that links the antibody and the toxic moiety. Such cleavage is necessary to allow the release of the drug within the cytoplasm to perform its influence on the cellular functions (Khongorzul *et al.*, 2019). The released drug most often inhibits certain cellular processes like DNA synthesis or microtubule assembly which cause apoptosis or programmed cell death (Drago *et al.*, 2021). For instance, some ADCs employ microtubule disrupting agents that arrest cell cycle and others directly damage DNA.

Further, ADCs can also bring about a bystander effect that can bring about harm to other neighboring cancer invasive cells by the cytotoxic agent which is released from the targeted cells. This heuristic amplifies the overall therapeutic effect by targeting not only the cell surface expressing the antigen of interest, but

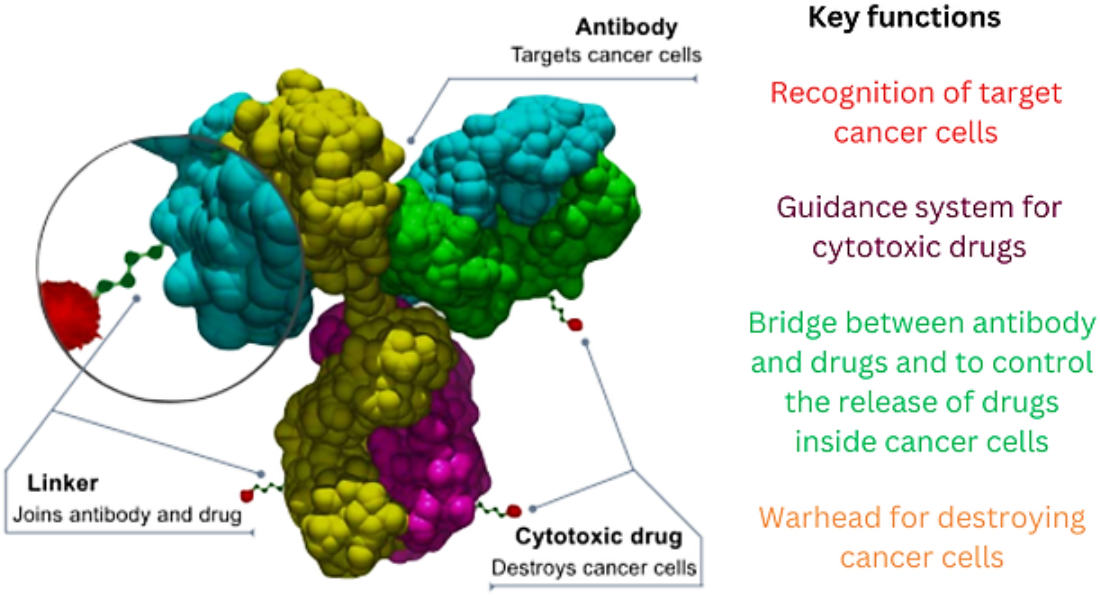

Figure 1: Structure and Key functions of ADCs.

also others in the vicinity. These are common in heterogeneous tumors where all the tumor cells may not have high density of target antigen (Staudacher *et al.*, 2017). The design of an effective ADC involves careful consideration of its three main components: the monoclonal antibody, the linker and the cytotoxic payload, therefore, forming the basis for ADC creation. It should preferentially bind with an antigen that is abundantly distributed in cancer cells; this is because the antibody targeting is selective. Ideally, the linker should be resistant in circulation so that it would not immediately release the drug while at the same time, cleavable once in the lysosome environment. Last but not least, the choice of a powerful payload is vital to gain enough therapeutic effect (Riccardi *et al.*, 2023).

The ADSs development mechanism of action is a complex procedure that aims at improving targeted cancer treatment. It starts with the ADC attachment to specific antigens on the surface of cancer cells and is essential for internalization of the ADC complex. After this binding, the ADC follows the receptor mediated endocytosis and once entrapped within the cell; it forms early endosome which then matures into a Late endosome and fuses with lysosomal (PhD AR, 2022). The ADC then enters lysosomes where it is also degraded thus releasing the cytotoxic part of the molecule. This payload can then intercalate, insert, or groove in DNA structures and inhibit microtubule polymerization leading to apoptosis (programmed cell death) in cancer cells. Furthermore, certain released payloads may exert a bystander effect on neighboring cancer cells thus increasing the general therapeutic effectiveness of the ADC (Peters *et al.*, 2015). In a detailed manner the mechanism of action of Antibody-Drug Conjugates (ADCs) is illustrated in Figure 3. In the top right area, the primary core mechanism that is represented is the fact that ADCs selectively bind to proteins expressed on the surface of cancer cells, which lead to receptor meditation and endocytosis of the ADC and internalization of the cytotoxic payload into the cancer cell. One of the boxes in the lower left corner illustrates how the antibody part of ADC acts to modulate immune effector cells to destroy tumor cells: this includes CDC, ADCC and ADCP. Last but not the least, in the lower right quadrant, one gets to see that the antibody component remains functional to frustrate the working of the target and by so doing, reduce downstream signaling and eventual tumor growth.

Mechanism of Action of Traditional Biologics

The mechanism of action of traditional biologics is a critical area of study in pharmacology, particularly due to their role in treating various inflammatory diseases. These biologic drugs primarily work by blocking certain inflammatory signaling molecules including, for example, the Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6), or by altering the activity of immune cells. In comparison with ADCs which are aimed at targeted therapy, the so-called first-generation biology acts systemically and affects more pathways belonging to the immune system. Biologics are products of living cells and are consequently macromolecules characterized by intricate modes of efficacy. Most of them are directed against certain proteins responsible for initiation of inflammation; for example, TNF antagonists interfere with the action of TNF-α, a cytokine that is central to systemic inflammation and associated with autoimmune diseases (MORROW and Felcone, 2004). These drugs inhibit the effects of TNF-α hence minimizing inflammation in diseases like rheumatoid arthritis by also halting joint erosion. In the same manner, IL-6 inhibitors block another cytokine that plays a part in the inflammatory processes, as an illustration of the ways through which biologics may selectively intervene on inflammatory signaling networks. Turn also some biologics can affect the activity of specific cytokines that are released from the cells, but other biologics can directly alter the function of specific immune cell types such as T cells or B cells, which are major actors in the immune response (BMD, 2024). Figure 4 illustrates Traditional Biologics.

It becomes especially useful in chronic inflammatory diseases, which have immunomodulation disorder as the primary cause. Also, the ADCs tend to be more targeted than the traditional biologics in cancer therapy; while ADCs deliver cytotoxic agents directly to target cancer cells using specific targeting techniques, traditional biologics commonly work on larger immune processes. This broader effect can be beneficial in conditions where many mediators of inflammation are involved such as in diseases with multiple causes, on the other hand the involvement of other immune functions can lead to side effects. Thus, in addition to the actions biologics poses unique challenges, such as production and administration, not common to typical chemical drugs. They are large molecules produced from biological processes, such as recombinant DNA technology, which often present challenges in their production methods because they are sensitive to environmental factors and require complex procedures that add up to the costs and regulatory obligations over the small molecules (Biologics vs. Biosimilars, 2024). These mechanisms have large clinical significance; biologics have reassorted the management of some autoimmune diseases through principles that can effectively address inflammatory procedures inherent to the diseases. However, they should not be used freely; biologics for instance can lead to suppression of immune system and thus lead to the development of other complications such as infections. Hence, there is need to exercise good patient selection when using these therapies and to also closely monitor the patients (https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers, 2023). With biologic therapies still under investigation about how the agents really work, additional effective treatments are being launched which might be individualistic in strategy. The emergence of biosimilars that are biological products highly like existing products also has potential for developing cost-effective treatments and have similar therapeutic effects. In conclusion, traditional biology is a marked

improvement in the management of inflammatory diseases since normalizes individual mediators and/or organ function through immunomodulation. In this context, they differ from more specific therapeutics, such as ADCs, owing to their global effects on immune routes. Thus, as knowledge about their action grows, it should be possible to optimize use of the therapeutic potential of these drugs, expanding the range of treatment possibilities for patients with chronic inflammation and simultaneously alleviating certain difficulties posed by present-day treatments (Biologics, 2024).

Comparative efficacy of Antibody-Drug Conjugates (ADCs) and traditional biologics in rheumatic diseases

The management of rheumatic diseases has also changed over the last few decades mainly by the development of biological agents. The standard format of biologics has had a considerable impact on patient outcomes-TNF inhibitors and IL inhibitors, for example. However, their effectiveness is mainly compromised by irregular response among the patients in question and development of resistance. In this regard, ADCs are an innovative approach of treatment comprising monoclonal antibodies which target and link with cancer cells and a cytotoxic drug.

ADCs are built to deplete poisonous compounds specifically on the cancer-bearing cells with minimal effect on all other body parts. Such a targeted approach reduces side effects and effectively increases the therapeutic ratio of the drug. The basic ADC design can be described as a monoclonal and a cytotoxic drug covalently connected to a stable linker. ADCs target specific antigens on the target cells and once bound, are internalized in the target cell releasing the cytotoxic agent within the targeted cell. This mechanism enables the specific targeting of certain dead cells, which is something especially helpful in immune-mediated pathologies, like RA and SLE (Huang *et al.*, 2024).

These ADCs have confirmed effective outcomes in rheumatic diseases in current clinical trials. For example, brentuximab vedotin is a SOM recognizes that is equally effective in the treatment of hematological malignancies that express CD30 positive cells and it is currently under trial as a treatment for

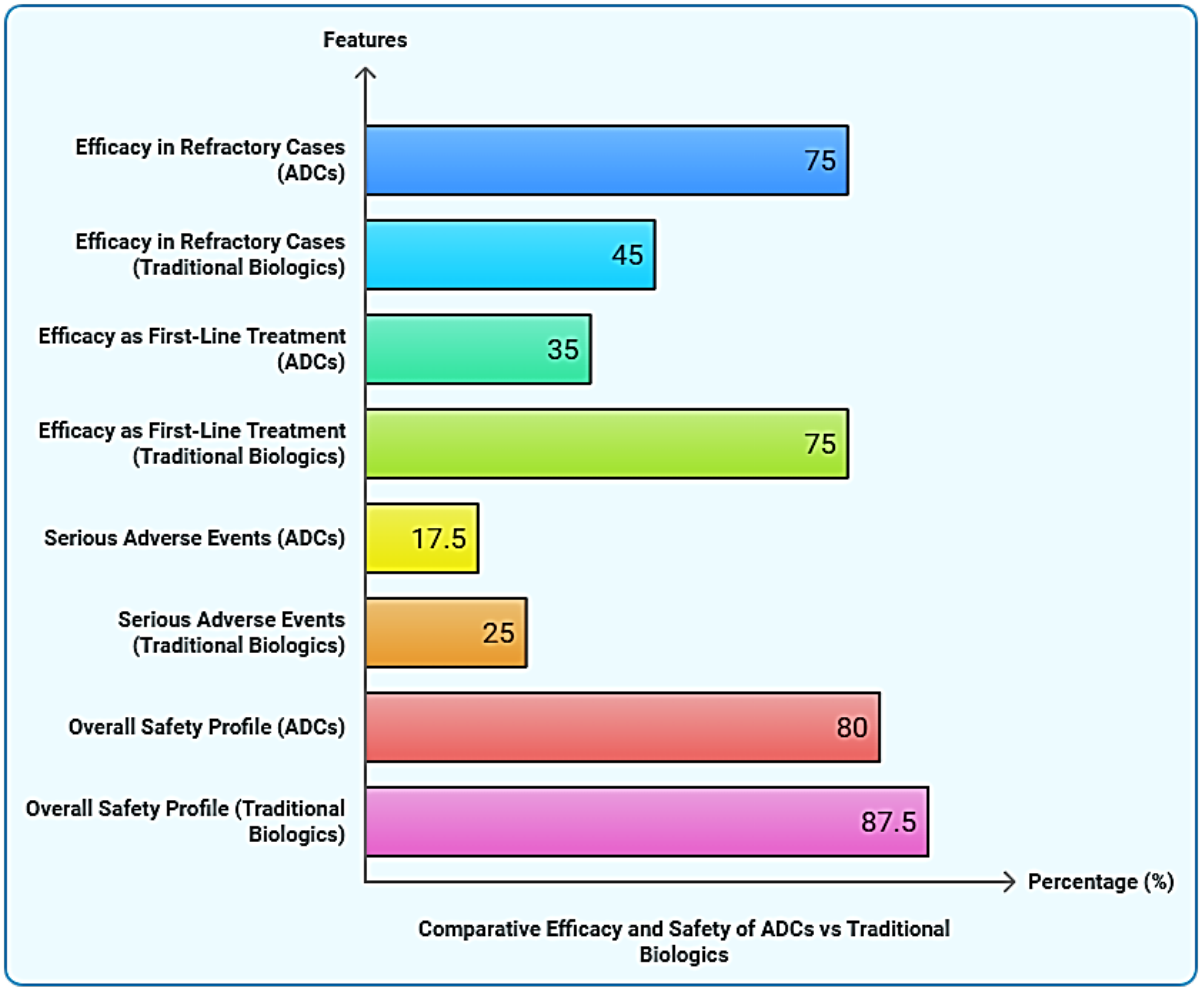

Figure 5: comparative efficacy and safety profiles of Antibody-Drug Conjugates (ADCs) and traditional biologics in treating rheumatic diseases.

Table 2: Comparative overview factors regarding Antibody-Drug Conjugates (ADCs) and Traditional Biologics.

Comparison Factor	Antibody-Drug Conjugates (ADCs)	Traditional Biologics	References
Mechanism of Action	Targeted delivery of cytotoxic drugs via monoclonal antibodies to specific antigens.	Broad immunomodulatory effects through various mechanisms.	(Huang *et al.*, 2024)
Target Specificity	High specificity for tumor cells or disease-related antigens.	Variable specificity; often targets immune pathways.	(Fu *et al.*, 2022)
Payload Type	Cytotoxic drugs linked to antibodies.	Biological agents such as proteins, enzymes, or antibodies.	(Next-Generation Antibodies, 2024)
Therapeutic Window	Enhanced due to selective targeting, reducing off-target toxicity.	Limited by broader action and potential side effects.	(Criscitiello *et al.*, 2021)
Efficacy in Cancer	Proven efficacy in various cancers, with ongoing research for other diseases.	Established efficacy primarily in autoimmune diseases.	(Deslandes *et al.*, 2014)
FDA Approvals	Over 14 ADCs approved, with more in clinical development.	Numerous biologics approved across multiple indications.	(Redefining *et al.*, 2024)
Immunogenicity	Lower immunogenicity with fully humanized antibodies.	Higher potential for immunogenic reactions depending on the agent.	(Baah *et al.*, 2021)
Clinical Application	Primarily in oncology, expanding into autoimmune and inflammatory diseases.	Widely used in rheumatology, dermatology and oncology.	(Huang *et al.*, 2024)
Development Timeline	Rapidly evolving field with continuous advancements in technology.	Established field with a wealth of historical data.	(Huang *et al.*, 2024)
Production Complexity	Complex manufacturing processes involving antibody engineering and linker technology.	Generally simpler production processes for recombinant proteins.	(Fu *et al.*, 2022)
Cost of Treatment	Often high due to complex manufacturing and development.	Variable; can be high depending on the biologic.	(Deslandes *et al.*, 2014)
Resistance Mechanisms	Potential for resistance through antigen loss or mutation.	Resistance can occur through various pathways, including receptor downregulation.	(Paci *et al.*, 2020)
Administration Route	Typically intravenous; some may be subcutaneously administered.	Various routes including subcutaneous, intravenous and intramuscular.	(Bittner *et al.*, 2018)
Side Effects	Generally fewer off-target effects but can include specific toxicities related to the payload.	Common side effects include infections, allergic reactions and infusion reactions.	(Donaghy *et al.*, 2016)
Combination Therapies	Often used in combination with other therapies for enhanced efficacy.	Frequently combined with DMARDs or other biologics.	(Dale *et al.*, 2007)
Research Focus	Increasing focus on expanding indications beyond oncology.	Ongoing research into new targets and combinations.	(Islam *et al.*, 2022)
Linker Technology	Advanced linker technologies (cleavable vs. non-cleavable) enhance delivery.	Linker technology not applicable; relies on direct biological activity.	(Sheyi *et al.*, 2022)
Patient Selection	Requires specific biomarkers for optimal efficacy.	Broader patient selection criteria based on disease type.	(Carden *et al.*, 2010)
Long-term Outcomes	Ongoing studies to assess long-term efficacy and safety.	Established long-term data available for many biologics.	(Nast *et al.*, 2015)

autoimmune diseases (Klener *et al.*, 2019). Likewise, other ADC candidates for rheumatic disease treatment are under investigation concerning their immunomodulatory properties or direct pathogenic cell cytotoxic effects. These developments show the promise that ADCs have for helping the unmet needs of patients with rheumatological diseases especially those who have not responded well to biologic therapies (Wainwright *et al.*, 2022).

A comparison of the efficacy demonstrated in ADC clinical trials with that of traditional biologics shows the following differences. Research has established that ADCs might demonstrate somewhat superior response levels in specific patient groups,

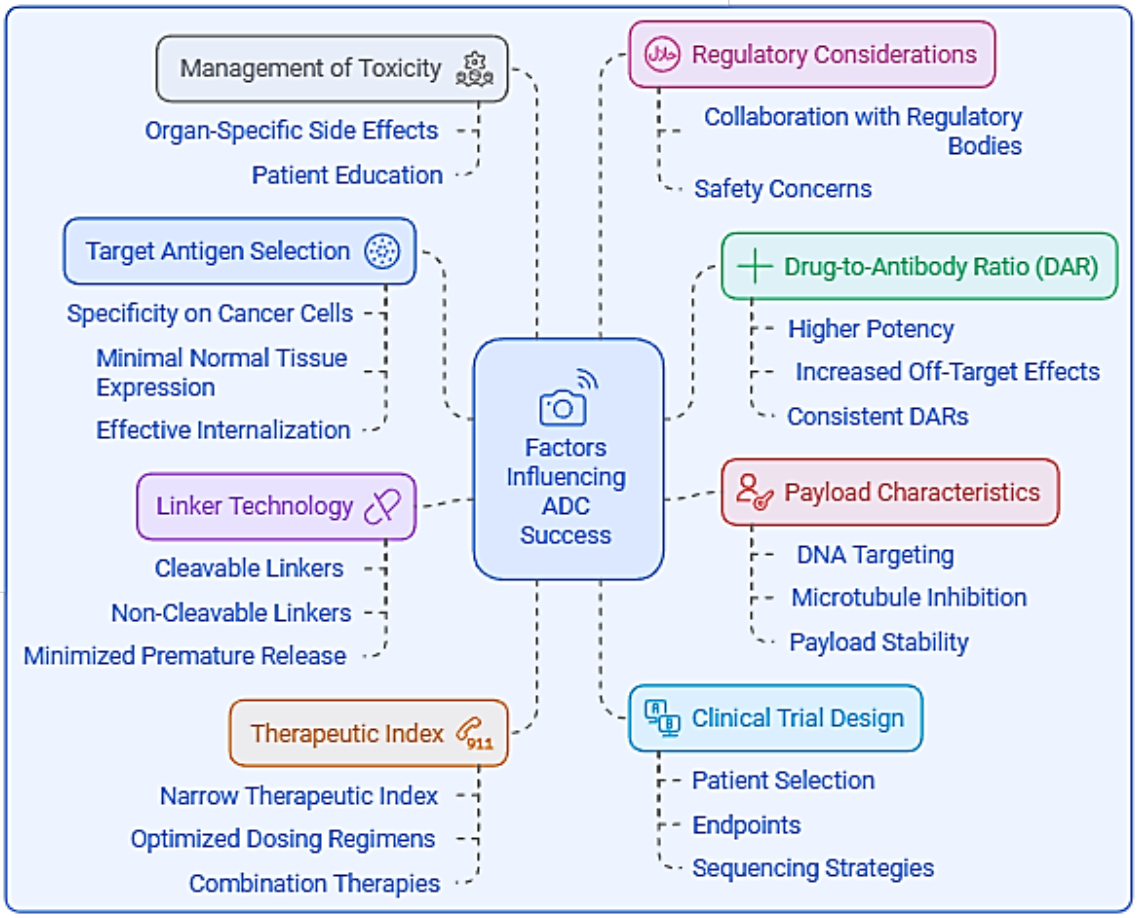

Figure 2: Factors Influencing ADC Success.

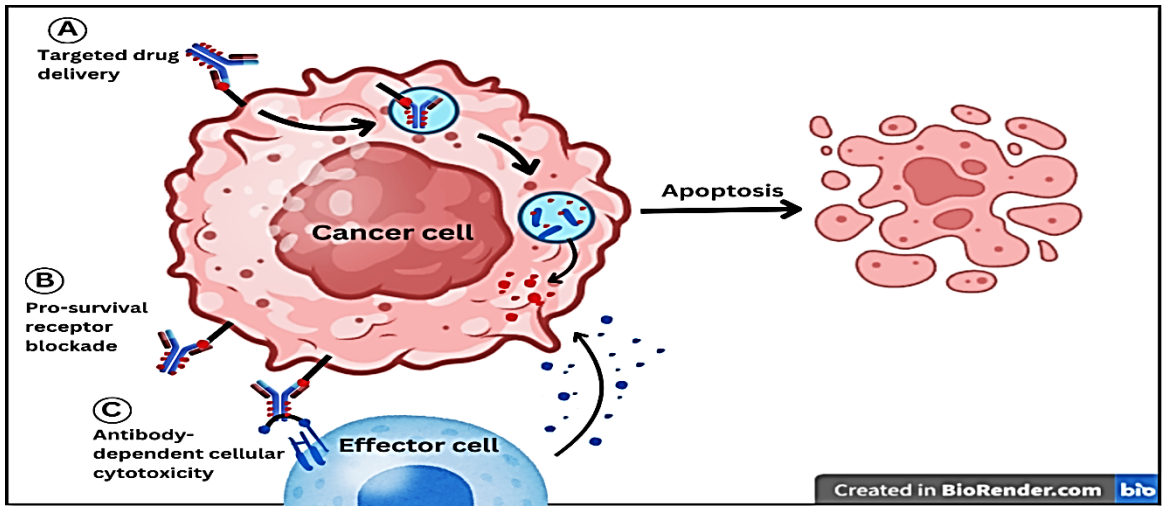

Figure 3: Mechanism of action of the ADC.

because of the uniqueness of the delivery systems used (Trail *et al.*, 2018). For example, a recent meta- analysis revealed that the patients who were treated with ADC therapy had significantly better improvements in the outcome reflected by disease activity scores compared to that in patients receiving anti-TNF agents. Nevertheless, more direct comparisons between the two modalities are still sparse at present indicating the requirement for further research to make direct conclusions concerning the effectiveness of both the treatment methods (Mazhar *et al.*, 2020).

This relation indicates that the therapeutics of current ADCs can be improved through the development of subsequent generations of antibodies. These new strategies include bispecific antibodies and innovative linker technologies to help with enhancing the targeting and minimizing immunogenicity (Vezina *et al.*, 2017). Furthermore, there are ongoing trials with regards to the varied payloads where other molecules may hold comparable or even superior cytotoxicity, immunomodulatory activity. These technologies may help place ADCs at the foundation of the next-generation treatment for the rheumatic diseases, especially for patients whose rheumatic diseases are not well controlled with other therapies (Chang *et al.*, 2023). Table 2 gives an outline comparison of Antibody-Drug Conjugates (ADCs) and Traditional Biologics based on the factors which include. All the presented factors explain the specifics as well as the working and use of these two types of therapeutic agents in the treatment of diseases such as cancer and autoimmune diseases.

Figure 5 illustrates the comparative therapeutic effectiveness and safety of Antibody-Drug Conjugates (ADCs) and traditional biologics in the treatment of rheumatic diseases are presented. They are both used for the purposes of enhancing the patient's

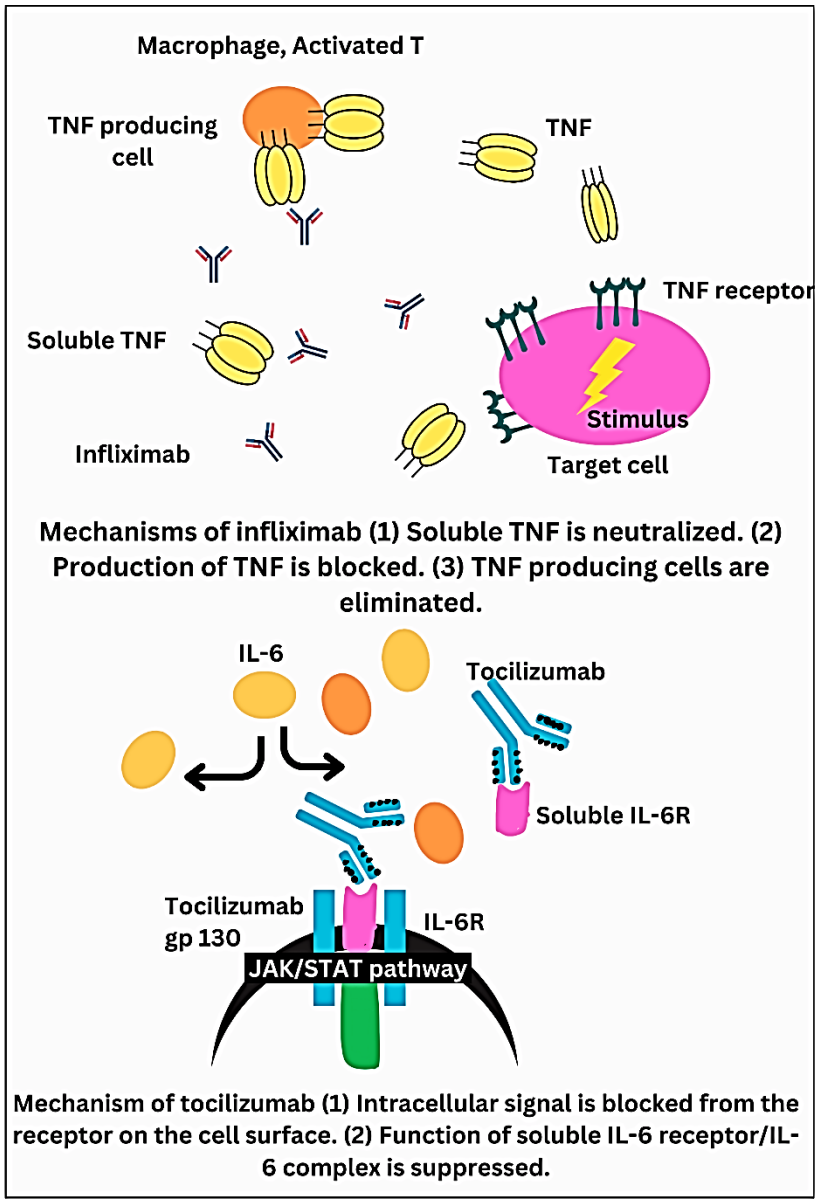

Figure 4: Mechanisms of action of traditional biologics.

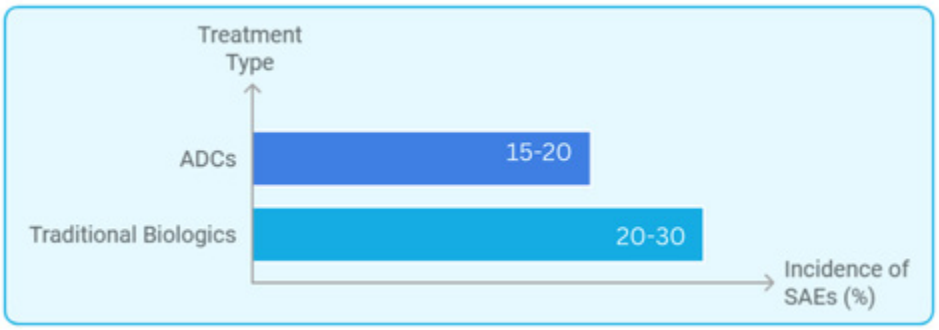

Figure 6: Comparison of Serious Adverse Events (SAEs) in ADCs vs Traditional Biologics.

quality of life yet bring characteristics that affect its usage in practice.

Patient outcomes in rheumatic disease treatments

ADCs, conventional biologics are designed to enhance patient prognosis by providing optimal control of disease and reducing severity and occurrence of comorbidities related to rheumatic diseases. Conversely, the population type that will benefit from each therapy may be vastly different.

Antibody-Drug Conjugates (ADCs)

The benefits accrued to rheumatic disease patients, especially with rheumatoid arthritis involve clinical effectiveness, quality of life and other self-reported parameters. Biologics and ADCs consequently have dominated treatment procedures and therefore enhanced these outcomes. The assessment of treatment efficacy is often rated by disease activity checks such as the Disease Activity Score (DAS28) and functional ability tests, like the Health Assessment Questionnaire (HAQ). For instance, it was evidenced that after receiving treatment in specialized centers, the remission rates have increased significantly to 58,5%, in contrast to 20,8% (Heckert *et al.*, 2024). Furthermore, Best and IMPROVED investigations indicate that an immediate treat-to-target management style produces a healthy end position and simple disease activity while over time it preserves substantially no structural changes (Fujii *et al.*, 2024).

Quality of life is another component of the patients that is very important in the judgment of the outcomes. Changes in functional capacity are well demonstrated by HAQ that have demonstrated considerable changes to current therapeutic regimens (Ajeganova *et al.*, 2017). Biologic DMARDs also provide better disease control, functional disability than so-called non-DMARDs. Moreover, according to surveys, most patients enjoy higher quality of life because of the successful management of their disease, using activity indices for scheduling and revising the control and treatment mode (Lin *et al.*, 2020). Self-report data are important in all phases of RA therapy to gain a comprehensive view of the condition (Nikiphorou *et al.*, 2016). These reflect patient accounts of their condition, treatment satisfaction and general wellbeing. Numerous case reports and observational studies indicate that at least 20%-50% of patients with RA can enter remission in the best-case scenario, pointing up the need for early diagnosis and treatment initiation (Hashimoto, 2024). These outcomes include but are not limited to age, comorbidities and the timing of treatment initiation. Altogether, advancement of RA therapeutic management could significantly enhance clinical effectiveness and possibility of better quality of life for many patients. The current work showed that understanding individual differences can provide significant insight on how better to approach treatment to achieve the most favorable outcomes for patients with RA (Bucala *et al.*, 2019).

Traditional Biologics

Small molecule biologics are a significant part of the treatment of rheumatic diseases, especially rheumatoid arthritis, because they are safer than traditional Disease Modifying Antirheumatic Drugs (DMARDs) and physicians have substantial clinical experience using them. These agents include Tumor Necrosis Factor (TNF) inhibitors and interleukin inhibitors have potential benefits in the treatment of numerous rheumatic conditions. This has been practiced in better disease management, overall quality of life and even patient survival rates (Golhen *et al.*, 2022). For example, available research show that individuals taking the conventional biologics have their disease activity scores significantly reduced while their ability to function is enhanced in ways that are very useful in their day-to-day activities. The safety of these biologics has also been described over many well-controlled RCTs. Like all immunosuppressants, there are known side effects of prednisone including open sores, increased risk of infections and possible malignancies yet the overall serious side effects do not pose as much of a threat to the patient when compared to those who are untreated (Kamata *et al.*, 2020). This good safety profile is one among the factors that makes traditional biologics to be considered as the initial choice of treatment. In addition, the therapies have been used for a long time and clinicians get to learn about the effects as well as the side effects of the therapies across all population of patients (Ozen *et al.*, 2019). Thus, established biologics present a reliable approach to the treatment of rheumatic diseases, as their efficacy is proven and their safety is attainable. They still enjoy a well-fixed place

in the therapeutic arsenal and new evidence further strengthens their utility in enhancing various patient profiles in RA and other rheumatic diseases (Fiorillo *et al.*, 2024).

Safety profiles

The safety profile of Antibody-Drug Conjugates (ADCs) is generally considered favorable, particularly when compared to traditional biologics. SAEs were observed in 15 to 20% of the patients under ADCs and the overall incidences are comparatively lower than those reported with conventional biologics (Bhushan *et al.*, 2024). This reduced incidence is explained by the fact that ADCs are developed to selectively deliver cytotoxic agents to cancer cells avoiding health endangering tissues. Such targeting reduces side impacts greatly, which increases the general tolerance level for patients who are under treatment.

Figure 6 shows the breakdown of serious adverse events of ADCs and other traditional biologics in treating different diseases including cancer and autoimmune diseases. Together, the data demonstrate that the safety profile of the two therapeutic classes is indeed significantly divergent and is a function of the mechanism of action of the drugs and the kaleidoscope of responses among patients. On the other hand, upon evaluation traditional biologics display a more pronounced SAE profile, ranging within 20-30% (Kurki *et al.*, 2021). Nevertheless, these therapies have a significantly enhanced risk profile while at the same time retaining a high level of safety. When it comes to the side effects, it was established that 85-90% of patients treated with classical biologics mentioned that the side effects are easily manageable due to long years of clinical practice and monitoring. This long history seems to enable healthcare providers to prevent or be in a better position to handle possible adverse effects, thus create an impression of safety in use of these drugs (Klener *et al.*, 2019). The reason for the comparatively safe profile of ADCs is rooted in the design of these drugs. An ADC can therefore be described as a monoclonal antibody conjugated with a cytotoxic drug through a chemical linker. The antibody section selectively targets and attaches to the antigens that are present on the cell membrane of target cell and ultimately leads to internalization of the cytotoxic portion within the cancer cells. They direct the anticancer drug to tumor cells without affecting the rest of the body-a common cause of toxicity related to conventional chemotherapy drugs (Wong *et al.*, 2007). Furthermore, developments in ADC technology area linkers and cytotoxic payloads available for use in ADC design. Current ADCs apply stable linkers that do not break in the bloodstream releasing the cytotoxic component only after internalization by the target cell. This innovation goes even further and reduces the probability of off-target toxicities and broadens the therapeutic ratio for improved therapeutic outcomes (Abdollahpour *et al.*, 2019).

But it is also necessary to know that not all ADCs have the same safety profile. It is important to bear in mind that individual ADCs may exhibit certain toxicities due to the components and action profiles of the latter (Sun *et al.*, 2024). For example, certain ADCs may readily cause certain side effects or effects such as low blood cell count or nausea, diarrhea and so on (Nguyen *et al.*, 2023). It is therefore important to develop awareness and preventive measures for these theoretical toxicities to allow patients the best chances of improvement (Jordan *et al.*, 2010). On the other hand, traditional biologics also have associate risks, which have been noted below; Despite that, they are pleased with acceptable tolerance profiles but are associated with life-threatening complications arising from immuno suppression such as infections or hypersensitivity. The control of such risks is usually performed through careful patient enrollment and patient monitoring within the course of the treatment (Schneider *et al.*, 2021).

Adverse effects

Adverse Effects of Antibody-Drug Conjugates (ADCs)

ADCs are approved cancer treatments that have been described as antibody–drug conjugates, which are engineered to pinpoint and eliminate cancerous cells while sparing normal cells. Nonetheless, like their selective targeting, ADCs are associated with a set of side effects, mainly attributed to cytotoxic components of the molecule (Fu *et al.*, 2022). Some side effects are immediate and require reactions during Infusions, for instance, fever, chills, or rashes while others are delayed and include cytopenia, neutropenia, or thrombocytopenia due to the toxicity of the cytotoxic agents on bone marrow. The improvement demonstrates that the overall incidence of Treatment related AEs is rather high, overall studies show that a vast majority of patients experience at least one AE. More severe adverse reactions can result from the premature release of such cytotoxic agents into the bloodstream to cause hematotoxicity, hepatotoxicity, or gastrointestinal manifestations such as nausea and diarrhea farther from the tumor site (Zhu *et al.*, 2023). There is evidence that certain specific classes of ADC's cause specific toxicities: topoisomerase inhibitors of Alopecia and Myelosuppression, microtubule inhibitors of peripheral neuropathy. Moreover, the bystander effect when non-targeted cells are affected by released toxins is a major problem of managing such therapies. A potentially manageable safety profile has been attributed to ADCs based on the accumulating clinical data. The longevity of the procedures is yet unknown and therefore it becomes prudent to continue conducting evaluation and research in order to inform them of the impact of these therapies in the lives of patients. In view of the gradually increasing use of ADCs in the management of cancer, one cannot overemphasize the importance of recognizing these potential side effects to be in a position to guide the choice of therapy as well as provide care for the patient (Li *et al.*, 2023).

Adverse Effects of Traditional Biologics

SAs the current study will establish, traditional biologics offer some therapeutic benefits for different inflammatory and autoimmune

diseases; however, such medications cause numerous side effects that are potentially fatal (ADC Toxicities, 2024). These include relative sterility, changes in immune system function which can lead to increased rates of life-threatening infections such as tuberculosis. Ten main AEs that occurred in at least 20% of the study population were injection site reactions characterized by pain, swelling and erythema at the site of administration of biologics (Li *et al.*, 2023). Additionally, there may be a possibility of malignancies; one research has found out that some of the biologic agents have been associated with increased propensity of developing cancers, especially lymphomas and skin cancers, albeit the connection between biologics and these types of cancers remains somewhat contentious. This risk also differs by class, for example, TNF inhibitors are associated with a greater risk of serious infection than, for example, IL-6 inhibitors. Patients with opportunistic infections are at a higher frequency while TNF inhibitors require surveillance. These side effects can be also expressed as systematic reactions, for example, influenza-like, headaches, gastrointestinal reactions of various severity including nausea. However, they continued with worry over the permanent health consequences of its use and over other possible chronic conditions that might be associated with its use. Therefore, further investigation is crucial for the elucidation of the effects of biologic treatments in patients in the long term. Consequently, screening for TB, HIV and other opportunistic infections is recommended periodically and close surveillance for any sign of malignancy in patients receiving traditional biologics (Singh *et al.*, 2011).

CONCLUSION

Therefore, the comparison of the specific area of interest, ADCs and traditional biologics establishes the respective benefits and drawbacks inherent in each therapeutic strategy in the treatment of rheumatic diseases. ADCs appear to be a novel class of targeted treatment, which has the pharmacological advantage of higher effectiveness due to the targeted delivery of cytotoxic agents to cancer cells with minimal damage to the rest of the body. The present mechanism that is targeted in this approach not only makes the treatment efficacious, but also minimizes the toxicities that are related to standard therapies. On the other hand, conventional biologics although have vast efficiency in managing immune and inflammatory reactions as a class tend to exhibit systemic toxicity like higher propensity to infections and malignancy. It would therefore be appropriate to base the further choice between ADCs and traditional biologics more on the considerations of individual patients, disease and treatment-related characteristics. It therefore requires continued investigation to better characterize the safety and effectiveness of ADCs in other patient groups as well as in different contexts. With our current knowledge of these therapies, it remains crucial to look at other novel ways in which treatment schedules can be manipulated for better utilization and thus enhance patient care in rheumatic diseases. Finally, patient-specific strategy that includes comparative analysis of the mechanisms of action, side effects and other features of available therapeutic agents will be crucial for resistant epilepsy treatment improvements.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ADCS: Antibody-Drug Conjugates; **RA:** Rheumatoid Arthritis; **SLE:** Systemic Lupus Erythematosus; **DMARDS:** Disease-Modifying Antirheumatic Drugs; **MABS:** Monoclonal Antibodies; **AML:** Acute Myeloid Leukemia; **ADCs:** Antibody-Drug Conjugates; **Mabs:** Monoclonal Antibodies; **IGG:** Immunoglobulin G; **ADCC:** Antibody-Dependent Cell-Mediated Cytotoxicity; **CDC:** Complement-Dependent Cytotoxicity; **ADCP:** Antibody-Dependent Cellular Phagocytosis; **MBC:** Metastatic Breast Cancer; **TOPO 1:** Topoisomerase 1.

AUTHOR CONTRIBUTIONS

The authors confirm their contributions to the paper as follows: study conception and design by Mujibullah Sheikh; data collection by Pranita S. Jirvankar; analysis and interpretation of results by Mujibullah Sheikh, Pranita S. Jirvankar; draft manuscript. All the authors reviewed the results and approved the final version of the manuscript.

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