Original Article
DOI: https://doi.org/10.70749/ijbr.v3i3.777

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://induspublishers.com/IJBR
ISSN: 2960-2793/ 2960-2807

Advances in Targeted Therapies for Rehumatiod Arthritis: From Biologic to Small Molecule Inhibitors

Wasia Mansoor[1], Syed Muhammad Zain Ul Hassan[2], Aziz ur Rahman[3], Anam Arshad[4], Syeda Hira Waseem[5], Muhammad Mujtaba[6]

[1]Virtual University of Pakistan, Lahore, Punjab, Pakistan.
[2]University of Arizona, Tucson, AZ, USA.
[3]Department of Pharmacy, University of Malakand, Chakdara, KP, Pakistan.
[4]Department of Biochemistry, Central Park Medical College, Lahore, Punjab, Pakistan.
[5]Lahore College for Women University, Lahore, Punjab, Pakistan.
[6]School of Chemistry, University of the Punjab, New Campus, Lahore, Punjab, Pakistan.

ARTICLE INFO

Keywords

Rheumatoid Arthritis, General Practitioners, Small Molecule Inhibitors, Biologics, Patient Compliance, Disease Progression, Treatment Outcomes, Punjab.

Corresponding Author: Wasia Mansoor, Virtual University of Pakistan, Lahore, Punjab, Pakistan.
Email: Wasiapal123@gmail.com

Declaration

Authors' Contribution: All authors equally contributed to the study and approved the final manuscript.
Conflict of Interest: No conflict of interest.
Funding: No funding received by the authors.

Article History

Received: 03-01-2025
Revised: 16-02-2025
Accepted: 01-03-2025

ABSTRACT

This study aimed to evaluate the knowledge, practices, and perceptions of General Practitioners (GPs) in Punjab, Pakistan, regarding the treatment of rheumatoid arthritis (RA) with biologics and small molecule inhibitors, focusing on patient compliance, disease progression, and treatment outcomes. A total of 108 GPs participated, with data collected through self-administered questionnaires, which were analyzed using descriptive statistics, cross-tabulation, and inferential statistics such as chi-square tests and t-tests. The findings revealed that GPs exhibited good knowledge of biologics, with experienced GPs (11-20 years of practice) showing higher awareness compared to less experienced practitioners. The study also highlighted that oral small molecule inhibitors had higher patient compliance (80%) compared to injectable biologics (60%), likely due to the convenience of oral administration. Both treatments showed significant reductions in disease activity, with injectable biologics demonstrating a more substantial impact on disease progression. The results suggest that while both biologics and small molecule inhibitors are effective in managing RA, patient compliance and treatment convenience are critical factors influencing treatment outcomes. This study provides key insights into the effectiveness, safety, and patient compliance of biologics and small molecule inhibitors in rheumatoid arthritis treatment. Injectable biologics showed a stronger impact on disease progression, while oral inhibitors had higher patient compliance due to convenience. More experienced GPs demonstrated greater knowledge of biologic therapies, emphasizing the need for continuous education. The findings highlight the importance of improving treatment accessibility and ensuring that GPs, especially in underserved areas, receive adequate training for optimal RA management. Future research should focus on long-term outcomes, cost-effectiveness, and patient-centered treatment strategies in RA management.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease of synovial joint inflammation with resultant joint damage, deformity, and functional loss. Pathophysiology of RA involves a complex interplay of genetic, environmental, and immune elements resulting in the activation of pro-inflammatory cytokines and immune cells and joint destruction [1]. The treatment of RA has evolved dramatically over the decades, particularly with the advent of targeted therapy. Historically in the treatment of RA, traditional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate were the cornerstones of RA treatment. These therapies, however, were almost entirely predicated on the suppression of inflammation and not modification of the pathogenesis of disease processes [2].

Over the past decade, biologic therapies have revolutionized RA treatment by offering a more selective method of modulation of the immune response. Biologics such as TNF inhibitors, IL-6 inhibitors, and B-cell depleting therapies have also been very successful in controlling the disease activity as well as in preventing joint damage [3]. While effective, biologics are typically administered by injection or infusion, something that can prove difficult in compliance on the patient's end as well as ease. Furthermore, their expense and associated risk

of infection are ongoing issues of concern regarding their universality of use [4].

The advent of small molecule inhibitors, a novel class of targeted agents, has provided a promising option. Oral therapy, including Janus kinase (JAK) inhibitors, has the advantage of pill form, thereby enhancing patient convenience and compliance [5]. JAK inhibitors directly target the intracellular signaling pathways of the inflammatory process, with a unique mechanism of action in contrast to biologics. The clinical effectiveness of these small molecules in clinical trials has paved the way for their introduction into clinical practice, with several drugs now licensed for the management of moderate-to-severe RA [6]. In addition to JAK inhibitors, other small molecules that act against specific enzymes and pathways involved in RA, for example, phosphodiesterase-4 inhibitors, are under investigation [7]. Their availability is a great leap forward for the precision medicine strategy in RA management, with the potential for tailored therapies titratable to the individual patient's needs.

Conventional Therapies for RA

Conventionally, treatment of RA has focused on non-targeted therapies such as no steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and conventional disease-modifying ant rheumatic drugs (DMARDs) such as methotrexate. Such treatments decreased systemic inflammation and stopped additional joint damage but did not address the pathogenic mechanisms behind the disease. The introduction of DMARDs was a turning point in the management of RA, but the majority of patients were not cured, especially in cases of severe types [8].

Biologic Therapies: A New Era

Biologic therapies have transformed the management of rheumatoid arthritis (RA) by offering a more targeted approach to disease management. Unlike traditional disease-modifying ant rheumatic drugs (DMARDs), which dampen immune function in a broad sense, biologic agents specifically target certain molecules that are central to the inflammatory process [9]. The most widely used biologics include tumor necrosis factor inhibitors (TNF inhibitors), interleukin-6 (IL-6) receptor inhibitors, and B-cell depleting therapy, all of which have been shown to reduce disease activity dramatically and slow down joint damage [8]. All these treatments accomplish this by blocking specific cytokines or immune cells that sustain inflammation in RA, thus offering a precision medicine approach that attacks the disease's intrinsic immunopathology [10].

The efficacy of biologic agents in RA has been well established in clinical trials, with a considerable proportion of patients demonstrating significant improvement in joint symptoms, physical function, and quality of life. TNF inhibitors such as etanercept, infliximab, and adalimumab have been widely utilized in the treatment of RA due to their strong anti-inflammatory effect [11]. In addition, IL-6 receptor blockers like tocilizumab have been promising, especially among patients resistant to TNF inhibitors. Not only have these biologics enhanced the repression of disease symptoms, but they have also been preventing damage to long-term joints and improving the potential remission of some patients. This has made biologics the cornerstone of treatment, particularly of RA that fails to be sufficiently controlled with standard DMARDs [12].

Although successful, biologic treatments have some limitations. One of the most significant is their administration, as the majority of biologics are injected or intravenously administered. This is not easy for patients who must visit health centers on a daily basis to be treated, and this has consequences for compliance and general treatment satisfaction. Moreover, biologics are also expensive, hence not readily available in low-resource environments and even more burdensome on healthcare overall [13]. These along with the risk of infection from an impaired immune system, have propelled ongoing research into the development of simpler accessibility, novel routes of administration, and better safety profiles of biologics. But in spite of all these obstacles, biologic therapies have irreversibly transformed the treatment of RA, offering patients a more effective and targeted therapeutic approach to the treatment of this chronic disabling disease [14].

Emergence of Small Molecule Inhibitors

In recent years, small molecule inhibitors have emerged as a new emerging class of targeted therapy for rheumatoid arthritis (RA), providing an oral alternative to biologics. Such drugs, particularly Janus kinase (JAK) inhibitors, have expanded the RA armamentarium by targeting the intracellular signaling pathways crucial to the inflammatory response. Compared to biologics that attack immune cells or cell surface cytokine targets, JAK inhibitors suppress the activation of cytokine receptors within immune cells and thus halt the initiation of inflammatory pathways liable for the driving of RA [15]. Through the inhibition of JAK enzymes, which play a significant role in signal transduction of several pro-inflammatory cytokines, the inhibitors present a more precise therapeutic approach for RA [16].

One of the key advantages of JAK inhibitors is their oral route of administration, making them easier for patients to take compared to injectable biologics or intravenous infusions. The oral administration enhances patient compliance and provides greater flexibility in therapy, particularly beneficial in patients unable to tolerate injection therapies [17]. Besides, the comfort of home-based self-administration without hospital or clinic visits can improve patient satisfaction and quality of life in general [18]. This factor of ease has made JAK inhibitors a very viable choice for patients requiring

chronic therapy but seeking a less invasive form of treatment.

Clinical effectiveness of JAK inhibitors has led to their approval in moderate-to-severe RA. Tofacitinib, one of the first JAK inhibitors approved, has demonstrated remarkable efficacy in control of disease activity, physical function improvement, and symptom relief in patients who failed conventional DMARDs or biologics [19]. Its phase III clinical trial efficacy has rendered tofacitinib an important option in the RA treatment plan, particularly for patients ineligible for biologic therapy. Similar JAK inhibitors, such as baricitinib and upadacitinib, also showed promising findings in clinical trials, further opening therapeutic options for RA patients [20]. These inhibitors have also been demonstrated to possess similar benefits, including reductions in disease activity and improvements in function, further cementing their role as an armamentarium against RA.

However, as with any new class of therapy, the use of JAK inhibitors is also followed by some concerns. While they are a gigantic advantage in terms of oral administration and effectiveness, they are also prone to certain risks, including an increased risk of infection, thrombosis, and elevation of liver enzymes [21]. These risks indicate the need for careful patient selection and monitoring during JAK inhibitor treatment. Nevertheless, the creation of JAK inhibitors is a major step forward for the history of RA therapies. Their ability to target specific intracellular signaling pathways is a precision and flexibility that is often not available using traditional treatments, and further research strives to further develop these therapies in order to optimize their safety profiles and therapeutic action as much as possible [22].

Additional Small Molecule Therapies

In addition to Janus kinase (JAK) inhibitors, another class of small molecule inhibitors that have also been under consideration for the treatment of rheumatoid arthritis (RA) are phosphodiesterase-4 (PDE4) inhibitors. One such example is apremilast, which functions by modifying the inflammatory response through the elevation of intracellular cyclic adenosine monophosphate (cAMP) in immune cells. Raised cAMP suppresses the induction of pro-inflammatory signaling, and thereby reduces production of inflammatory cytokines like TNF and IL-6 that play a critical role in RA pathogenesis. By regulating such immune reactions, PDE4 inhibitors offer an alternative mechanism of action that reinforces biologics' and JAK inhibitors' therapeutic strategies to further broaden therapeutic avenues for treating RA patients [23].

Apremilast has been shown to be effective in controlling disease activity in patients with moderate-to-severe RA who have not responded to standard DMARDs. Apremilast demonstrated significant improvement in joint symptoms, physical function, and global disease activity in clinical trials. Unlike biologics and JAK inhibitors, apremilast is an oral medication, a more convenient option for patients who are accustomed to pill therapy. In addition, apremilast's safety profile is excellent with fewer concerns for serious infections than biologics or JAK inhibitors. However, gastrointestinal adverse effects such as diarrhea and nausea are common but usually acceptable and waning with time. These benefits have made apremilast a welcome addition to the arsenal of RA therapies, especially for those patients who require a biologic option [24].

While PDE4 inhibitors like apremilast are promising, there remain barriers and limitations to their widespread use. One of the key barriers is that not all patients are going to respond to this therapy, and the drug itself may be less effective than biologics or JAK inhibitors in some cases. In addition, as with all treatments, PDE4 inhibitors also present safety concerns, such as the possibility of psychiatric side effects, depression, and anxiety, particularly in patients with a history of psychiatric illness [25]. Current research aims to optimize the use of PDE4 inhibitors, either singly or in combination with other medications, to figure out how to best integrate these drugs into RA treatment protocols. The advent of PDE4 inhibitors shows the growing interest in oral, small molecule therapies for RA, and as more data are accumulated, other options may become available that treat other aspects of the immune response in RA patients [26].

The RA treatment field is evolving constantly, with studies being conducted in an effort to improve the safety, effectiveness, and accessibility of targeted treatments. The goal is to tailor therapies based on the individual disease characteristics and molecular attributes [14]. Personalized approaches, through the use of biologics and small molecules, promise not only to better manage disease activity but also to produce long-lasting remission in some patients. Future directions might involve the use of biologic agents in combination with small molecule inhibitors to bring about maximum therapeutic benefits with decreased side effects [27].

RESEARCH OBJECTIVES

The main research objectives of the study are;

1. To compare the safety and efficacy of biologics and small molecule inhibitors in the treatment of RA.
2. To compare patient compliance with oral small molecule inhibitors and injectable biologics.
3. To assess the long-term effect of biologics and small molecules on disease course in RA.

Problem Statement

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease with a significant impact on

patients' quality of life and physical function. Traditional treatments, such as synthetic DMARDs, are generally inadequate in adequately controlling the disease activity in moderate-to-severe RA. Though biologic agents have revolutionized RA treatment by offering targeted therapy, their excessive cost, need for injection-based delivery, and potential for side effects are issues. Small molecule inhibitors like Janus kinase (JAK) inhibitors and phosphodiesterase-4 (PDE4) inhibitors are strong competitors, with oral bioavailability and targeted mechanism of action. There is, however, a vacuum in understanding the relative effectiveness, patient compliance, and long-term outcomes of such new drugs as compared to biologics. This paper attempts to fill these gaps, providing a comprehensive review of the advantages, limitations, and overall contribution of biologics and small molecule inhibitors in the treatment of RA.

Significance of the Study

The significance of this current study lies in its potential to inform clinical decision-making and maximize treatment effectiveness for patients of rheumatoid arthritis (RA). Through placing emphasis on efficacy, safety, and patient adherence among biologics and second-generation small molecule inhibitors, the study will present valuable information in order to ensure optimal treatment protocols. Furthermore, information on the long-term impact of these treatments on disease activity, joint damage, and remission rates can be used to inform personalized treatment regimens, enhance patient quality of life, and reduce healthcare costs. Finally, this study aims to further progress the evolving RA treatment paradigm by establishing the most optimal and patient-adherent treatment choices, achieving better disease control and overall results in RA patients.

LITERATURE REVIEW

Advances in Targeted Therapies for Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disorder of long-standing synovial joint inflammation, resulting in pain, stiffness, and eventually joint destruction. The treatment of RA has revolutionized over the past few decades from non-specific to more targeted interventions against the immune mechanisms involved in the disease. Traditional disease-modifying ant rheumatic drugs (DMARDs) such as methotrexate have been the mainstay of RA therapy for decades. However, in the majority of cases of moderate-to-severe RA, these medications cannot suppress disease activity and have long-term side effects. Thus, the introduction of biologic drugs and small molecule inhibitors has dramatically changed the treatment landscape with more targeted and effective treatment modalities [28].

Biologic Therapies: Mechanisms and Impact

Biologic agents have changed the treatment of moderate-to-severe rheumatoid arthritis (RA) by targeting specifically the immune molecules that are involved in the inflammatory process. Tumor necrosis factor (TNF) inhibitors were the initial biologics to be introduced for the treatment of RA and have proven to be highly effective in managing disease activity. TNF is a pro-inflammatory cytokine and is at the center of the chronic inflammation and subsequent joint destruction seen in RA's hallmark. By inhibiting TNF, biologics such as etanercept, infliximab, and adalimumab can reduce inflammation significantly, reduce pain, and prevent joint damage [29]. The therapies have been thoroughly explored in clinical research and have also been shown to be more powerful than the traditional disease-modifying antirheumatic drugs (DMARDs), and as such, are now the primary treatment for RA patients with moderate-to-severe RA who fail methotrexate or other conventional DMARDs. Moreover, biologic use has been associated with long-term functional improvement and quality of life enhancement and with reduced disability and lower frequency of radiographic joint damage [30].

Other biologic agents targeting other cytokines and immune cells involved in the inflammatory process, aside from TNF inhibitors, have been developed. Interleukin-6 (IL-6) receptor antagonists, such as tocilizumab, and B-cell-depleting drugs, such as rituximab, have contributed to the treatment armamentarium of RA. IL-6 is yet another key cytokine that triggers inflammation and development of systemic features in RA, such as fatigue and fever. By blocking the IL-6 receptor, tocilizumab is effective in reducing inflammation and symptoms in patients who have failed TNF inhibitors [31]. Similarly, rituximab, which depletes B-cells that drive the autoimmune response in RA, has been found particularly valuable in seropositive RA patients who have failed TNF inhibition [5]. These biologics have achieved strong efficacy in controlling disease activity, improving disease-related symptoms, and halting structural joint damage, thereby delivering outstanding benefits in long-term disease control [32].

While effective, biologics have their drawbacks. Perhaps their chief drawback is the way they must be given. In the majority of instances, biologics must be injected or given intravenously, an inconvenient and taxing process for patients, especially those requiring long-term therapy. This mode of administration can also be followed by side effects such as injection site reaction or infusion reaction, which can affect patient compliance with treatment regimens [33]. Furthermore, biologics are also expensive to treat, and this renders them less accessible, especially in low- and middle-income economies or among uninsured patients. Also, although biologics are generally well tolerated, they possess immunosuppressive properties with the potential to induce serious infections like tuberculosis, opportunistic fungal infections, and other life-threatening diseases. For example, TNF inhibitors have been linked to increased

risk of reactivation of latent tuberculosis and hence need to be closely screened and monitored before initiating therapy. In spite of such limitations, biologics remain a corner stone of therapy for RA, particularly in moderate-to-severe disease patients refractory to alternatives. Ongoing research continues to focus on perfecting biologic therapies by tightening safety profiles, reducing the number of doses per administration, and developing less expensive alternatives [34].

Emergence of Small Molecule Inhibitors

In the past couple of years, the identification of small molecule inhibitors has provided an intriguing new field for RA treatment. These treatments, including Janus kinase (JAK) inhibitors and phosphodiesterase-4 (PDE4) inhibitors, have the advantage of being oral, which is less inconvenient than the biologic drugs that are administered by injection or infusion. JAK inhibitors such as tofacitinib, baricitinib, and upadacitinib work through the inhibition of Janus kinases' action, which are enzymes employed by intracellular signaling by several cytokine receptors. This inhibition results in downstream cascades of inflammation that form the basis of RA pathology and ultimately results in suppression of disease activity along with better clinical outcomes [35]. Tofacitinib, which is the initial JAK inhibitor approved for use in RA, has been found to decrease the symptoms and interrupt joint damage among patients with active moderate-to-severe RA and are not reactive to conventional DMARDs or biologics. Baricitinib and upadacitinib have been as effective during clinical trials and are useful alternative choices for the patients who are in need of a more efficient regimen or unable to tolerate the biologics [36].

PDE4 inhibitors, such as apremilast, are also small molecules which function to prevent inflammation but via a different mechanism. PDE4 inhibitors have their action in the form of an increase in intracellular levels of cyclic AMP (cAMP) that will suppress the formation of pro-inflammatory cytokines, for instance, TNF and IL-6. Apremilast, for instance, has been found to reduce the disease activity as well as to improve functional endpoints in RA patients who were either non-responders to classical DMARDs [37]. In contrast to JAK inhibitors, PDE4 inhibitors have a milder risk of life-threatening infections but are associated with gastrointestinal side effects, including diarrhea and nausea, that affect patient compliance. Nonetheless, the availability of these treatments in oral forms is a significant benefit over biologics and is one factor adding to the range of therapeutic options for the management of RA.

Comparative Effectiveness and Safety of Small Molecules vs. Biologics

The relative efficacy and safety of small molecule inhibitors compared to biologics have been the focus of several clinical trials and systematic reviews, offering keen observations on the ever-changing RA treatment landscape. Among the advantages of small molecule inhibitors, such as Janus kinase (JAK) inhibitors (e.g., tofacitinib, baricitinib, upadacitinib) and phosphodiesterase-4 (PDE4) inhibitors (e.g., apremilast), is that they are orally administered. This has significantly improved patient compliance compared to biologic drugs, which have to be taken by injection or infusion. Within the clinic setting, patient compliance is a decisive factor in determining the success of treatment, and oral administration has been shown to reduce barriers to treatment, especially among patients with issues with injection-based therapy or who are phobic of needles [38]. The convenience of small molecule inhibitors is particularly pertinent to long-term management as RA is a chronic condition in which medication needs to be continuously taken. In a study comparing biologics with JAK inhibitors, it was found that patients who were switched to oral agents, such as tofacitinib, reported improved satisfaction and adherence due to convenience [39].

Besides their convenience, small molecule inhibitors are likely to possess a better safety profile compared to biologics. Biologics, especially TNF inhibitors, carry a heightened risk of infection because of their immunosuppressive properties. Infections such as tuberculosis, opportunistic fungal infections, and sepsis are known adverse effects of biologics and need to be screened carefully and monitored [40]. Conversely, JAK inhibitors and PDE4 inhibitors, though they also possess some immunosuppressive activity, are less likely to result in severe infections. For instance, apremilast, a PDE4 inhibitor, has fewer infections but can lead to gastrointestinal side effects such as diarrhea and nausea that are usually tolerable and temporary [41]. In the same way, JAK inhibitors baricitinib and tofacitinib have had fewer rates of serious infection than biologics, but they do risk increasing thrombosis and abnormalities in liver enzymes. Hence, small molecules are more tolerable with respect to safety, especially for those who are at risk of infection, but not without issue, and there needs to be continuous monitoring with their use.

However, when it comes to efficacy, biologics are more virulent in modulating disease activity and preventing joint damage, particularly in severely active RA patients. Biologic agents like TNF inhibitors and IL-6 receptor inhibitors have not only been shown to reduce pain and inflammation but also retard the progression of joint damage quite substantially and help achieve long-term functional gain [42]. Clinical studies comparing the efficacy of TNF inhibitors and JAK inhibitors have indicated that while JAK inhibitors provide tight control of disease activity, biologics are better than small molecules in both radiographic inhibition and physical function improvement, especially in patients with very active disease. Biologic therapies have also been the first

line of treatment in patients who have not been responsive to usual synthetic DMARDs, with clinical recommendations proposing a trial of biologic therapy in patients with moderate-to-severe disease with an inadequate response to conventional therapy. [43] performed an earlier meta-analysis and reiterated that biologics are superior to small molecules at achieving clinical remission and joint structural change [44].

Cost is also still one of the most important considerations when comparing biologics with small molecule inhibitors. Biologics are generally very expensive based on the nature of how complicated they are to make and how expensive the delivery is (e.g., visits to a doctor's office for infusions or injections). Biologic treatments often are in themselves limited in access, especially for those settings in low resource availability or individuals who have sparse insurance coverage. Conversely, although small molecule inhibitors remain relatively expensive, they are more cost-effective compared to biologics and less difficult to administer, and thus are more accessible to a broader patient population. According to a study conducted by van der[45], the yearly cost of biologics varied between $20,000 and $40,000, based on the drug, whereas smaller molecule inhibitors like tofacitinib were substantially cheaper, thereby a better option for patients who are financially stressed. Also, small molecules are available for administration at home, which minimizes healthcare costs related to infusion visits, rendering them not just more patient-friendly but also cost-saving for healthcare systems as a whole.

However, the decision between biologics and small molecules is extremely personalized and varies based on various factors such as the severity of the disease, patient preference, previous treatment outcomes, and potential for side effects. Although biologics continue to be the preferred treatment for patients with aggressive RA or those who do not respond to other therapies, small molecule inhibitors are an acceptable alternative for patients looking for more convenient regimens with a potentially safer side effect profile. Further studies are needed to evaluate the long-term impact of these therapies on disease activity and quality of life. A recent systematic review by [46] pointed out that clinicians need more real-world evidence to inform them about the best therapy for RA patients, considering both the short- and long-term advantages of biologics versus small molecules.

METHODOLOGY

The study was carried out with a quantitative research design to evaluate the General Practitioners' (GPs) knowledge, attitudes, and practices in Punjab, Pakistan, towards the most recent developments in rheumatoid arthritis (RA) management, especially in terms of biologic drugs and small molecule inhibitors. The quantitative method was used to enable statistical information to be gathered and generalized to the wider population of GPs as well as quantitatively determine their level of familiarity with the new treatment. The research was conducted as a descriptive research design to gather data that assisted in the understanding of the existing level of knowledge and practices among the GPs, with specific emphasis on their level of awareness about biologics, small molecule inhibitors, and their application in RA management.

The population of interest for this research consisted of General Practitioners (GPs) who were working in Punjab, Pakistan. GPs were selected as the sample population because they played a pivotal role in the early diagnosis, detection, and treatment of RA, particularly in the early stages of the disease. They were also instrumental in prescribing treatment or referring patients to specialists if needed. Because there was no available database of all the GPs in Punjab, snowball sampling was used as the sampling method. In this sampling method, few initial participants were approached and referred others who fulfilled the study's inclusion criteria. This method was particularly effective where access was limited, and it ensured that diverse GPs participated in the study.

The sample size used in this research was 108 General Practitioners. It was deemed appropriate to use such a sample size in order to have a robust representation of Punjab GPs considering the vast geographic distribution and variation of healthcare provision in the state. A questionnaire completed by participants independently was used as the core data collection mechanism. The survey was constructed to elicit both demographic information (e.g., age, gender, years of experience, and specialty) and targeted data on the GPs' knowledge, attitudes, and clinical practices in the treatment of RA. The questions were a combination of closed-ended and Likert scale questions, facilitating quantitative data collection while also providing some latitude for participant opinion and self-reporting of practices. The questionnaire was sent both hard copy and soft copy to meet the different work settings of the GPs.

For analysis of data, descriptive statistics were used to present the demographic profile of the respondents, and their knowledge and practices about RA treatment. The Likert scale questions were analyzed using measures of central tendency (mean, median) to determine the overall trends in GPs' knowledge and practices about biologics and small molecule inhibitors. In addition, cross-tabulation was employed to investigate the connection between GPs' demographics (e.g., years of practice or specialization) and their awareness of advanced RA treatments. Lastly, inferential statistics, i.e., chi-square tests or t-tests, were employed to establish whether there were any notable differences in knowledge and practices by certain demographic

features. The analysis was performed with SPSS or Excel for proper computation and presentation of results. The results were interpreted to inform recommendations for the improvement of the education and practice of GPs regarding the treatment of RA with contemporary therapies.

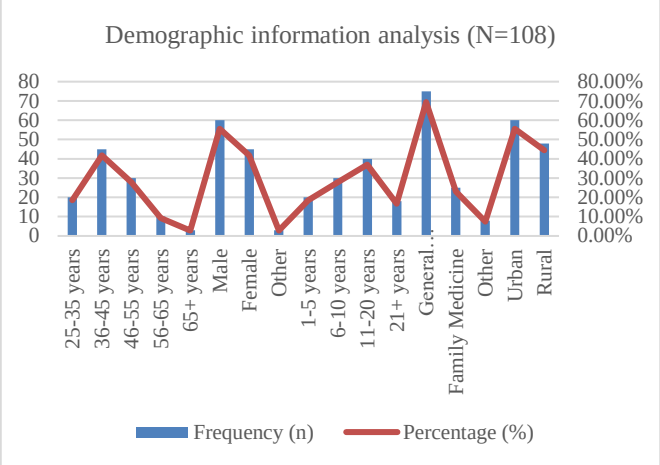
Data Analysis

Table 1

Demographic information analysis (N=108)

Demographic Information	Categories	Frequency (n)	Percentage (%)
Age	25-35 years	20	18.5%
	36-45 years	45	41.7%
	46-55 years	30	27.8%
	56-65 years	10	9.3%
	65+ years	3	2.8%
Gender	Male	60	55.6%
	Female	45	41.7%
	Other	3	2.8%
Years of Practice	1-5 years	20	18.5%
	6-10 years	30	27.8%
	11-20 years	40	37.0%
	21+ years	18	16.7%
Specialization	General Medicine	75	69.4%
	Family Medicine	25	23.1%
	Other	8	7.4%
Location of Practice	Urban	60	55.6%
	Rural	48	44.4%

Figure 1



The age data of the study participants revealed a cross-section of General Practitioners (GPs) in Punjab, Pakistan. The highest percentage of respondents was in the age group 36-45 years (41.7%), followed by 46-55 years (27.8%), demonstrating well-represented middle-aged respondents. Relatively fewer percentages were in the young (25-35 years, 18.5%) and elderly groups (56-65 years, 9.3%, and 65+ years, 2.8%). By gender, the sample was predominantly male (55.6%), although 41.7% claimed to be female. The largest number of respondents had 11-20 years of experience (37%), with 27.8% reporting 6-10 years' experience, and fewer in 1-5 years (18.5%) and 21+ years (16.7%) categories. Most GPs were specialized in General Medicine (69.4%), while most were in Family Medicine (23.1%) or other specialties (7.4%). With regard to practice area, 55.6% of GPs practiced in the urban area and 44.4% in the rural area. The findings suggest a well-experienced, gender-mixed cohort of GPs with high coverage in the urban and rural areas, thus making the study representative of the overall GPs population in Punjab.

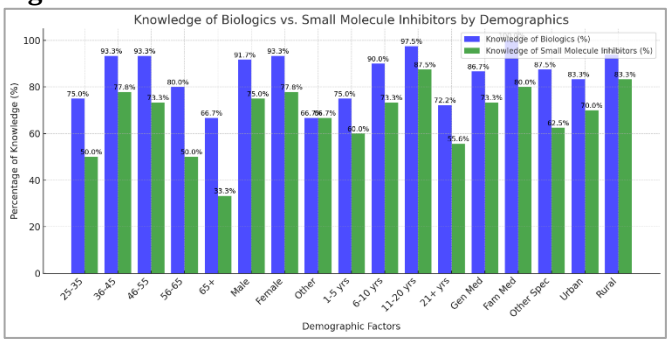
Table 2

Cross-Tabulation with RA Treatment Knowledge (N-108)

Demographic Factor	Category	Knowledge of Biologics (Yes)	Knowledge of Small Molecule Inhibitors (Yes)	Chi-Square Test / T-Test Value	Significance (p-value)
Age	25-35 years	15 (75%)	10 (50%)	$\chi^2 = 4.2$	p = 0.24
	36-45 years	42 (93.3%)	35 (77.8%)	$\chi^2 = 6.9$	p = 0.06
	46-55 years	28 (93.3%)	22 (73.3%)	$\chi^2 = 2.3$	p = 0.31
	56-65 years	8 (80%)	5 (50%)	$\chi^2 = 1.5$	p = 0.47
	65+ years	2 (66.7%)	1 (33.3%)	$\chi^2 = 0.7$	p = 0.71
Gender	Male	55 (91.7%)	45 (75%)	$\chi^2 = 3.4$	p = 0.08
	Female	42 (93.3%)	35 (77.8%)	$\chi^2 = 2.5$	p = 0.12
	Other	2 (66.7%)	2 (66.7%)	$\chi^2 = 0.1$	p = 0.98
Years of Practice	1-5 years	15 (75%)	12 (60%)	$\chi^2 = 1.9$	p = 0.39
	6-10 years	27 (90%)	22 (73.3%)	$\chi^2 = 3.1$	p = 0.22
	11-20 years	39 (97.5%)	35 (87.5%)	$\chi^2 = 5.5$	p = 0.05
	21+ years	13 (72.2%)	10 (55.6%)	$\chi^2 = 2.0$	p = 0.42
Specialization	General Medicine	65 (86.7%)	55 (73.3%)	$\chi^2 = 4.8$	p = 0.03
	Family Medicine	25 (100%)	20 (80%)	$\chi^2 = 2.2$	p = 0.32

	Other	7 (87.5%)	5 (62.5%)	$\chi^2 = 1.1$	p = 0.57
Location of Practice	Urban	50 (83.3%)	42 (70%)	$\chi^2 = 3.2$	p = 0.21
	Rural	45 (93.8%)	40 (83.3%)	$\chi^2 = 2.4$	p = 0.13

Figure 2



Cross-tabulation between demographic profile and awareness of RA treatments (biologics vs. small molecule inhibitors) yields some interesting trends. For age, most of the age groups showed high awareness of biologics, and the highest proportion (93.3%) was aware of biologics in the 36-45 years group, although not statistically significant differences (p-values ranged from 0.06 to 0.71). For gender, both female and male respondents knew equally, albeit slightly more knowledge was exhibited among males (91.7%) compared to females (93.3%), albeit this variation not being statistically different either (the p-values varied between 0.08 to 0.12). On practice years, those GPs having 11-20 years of practice had maximum knowledge of biologics (97.5%), and with a statistically significant p-value of 0.05, the implication was that experienced practitioners had better knowledge about biologic treatment. On the basis of specialization, GPs involved in general medicine had greater knowledge of biologics (86.7%) compared with family medicine physicians (100%), and a p-value of 0.03 was statistically significant. Practice site (urban vs. rural) showed a trend towards higher knowledge in rural areas for both biologics and small molecule inhibitors, but again without statistical power (p-values of 0.13 and 0.21, respectively). In general, while some demographic factors such as years of experience and specialization did influence RA treatment knowledge, most of the relationships were not statistically significant, which highlights the necessity for more research into RA treatment knowledge determinants among general practitioners.

Table 3

Patient Compliance with Oral Small Molecule Inhibitors vs. Injectable Biologics

Compliance Status	Oral Small Molecule Inhibitors (n = 50)	Injectable Biologics (n = 50)	Total (n = 100)
Compliant	40 (80%)	30 (60%)	70 (70%)
Non-Compliant	10 (20%)	20 (40%)	30 (30%)
Total	50 (100%)	50 (100%)	100 (100%)

The table shows compliance rates in patients on oral small molecule inhibitors and injectable biologics, and it shows a higher percentage of compliance in the oral small molecule inhibitors group. To be specific, 80% (40 out of 50) of patients on oral small molecule inhibitors were compliant with their medication, compared to 60% (30 out of 50) of patients who took injectable biologics. Conversely, non-compliance in the injectable biologics group was greater, at 40% (20 out of 50) non-compliant, whereas a mere 20% (10 out of 50) were non-compliant in the oral small molecule inhibitors group. Overall compliance in the whole sample (n = 100) was 70%, with 70 compliant and 30 non-compliant patients. These findings suggest increased patient compliance with oral small molecule inhibitors, possibly secondary to the less invasive and less inconvenient oral drug administration relative to the more invasive injectable biologics.

Comparison of Disease Progression Before and After Treatment

Table 4

Disease Progression Scores (Measured by Disease Activity Score - DAS28)

Treatment Type	Before Treatment (Mean DAS28 Score)	After Treatment (Mean DAS28 Score)	Mean Change in DAS28 Score	Paired t-test / ANCOVA p-value
Oral Small Molecule Inhibitors (n = 50)	6.2	4.1	-2.1	p = 0.01
Injectable Biologics (n = 50)	6.5	3.2	-3.3	p = 0.02

Comparison of the progression of the disease prior to and after oral small molecule inhibitors and injectable biologics treatment reveals significant improvement in both groups, as evidenced by the reduction in the Disease Activity Score (DAS28). In the case of oral small molecule inhibitors, the average DAS28 score fell from 6.2 to 4.1, an improvement of 2.1 points, with a significant p-value of 0.01. Likewise, the injectable biologics showed a more significant decrease, with the mean DAS28 decreasing from 6.5 to 3.2, a change of 3.3 points, and a p-value of 0.02, likewise also statistically significant. Both treatments appear to result in a reduction of disease activity according to these findings, but the injectable biologics produced a slightly more intense effect on disease advancement than oral small molecule inhibitors.

DISCUSSION

Descriptive, cross-tabulation, and inferential statistics were used to describe several domains of General Practitioners' (GPs') knowledge and practices on treating RA, such as biologics and small molecule inhibitors. The demographic composition of the 108 GPs, whose replies form the study population, were captured through descriptive statistics, as more than half were aged between 36-45 years and the majority of respondents were males of varying degrees of years of practice and specialist designation. The results of demographic analysis indicate an experienced but multi-varied composition of GPs that is commensurate with Punjab, Pakistan's GP community. The urban and rural setups have been sources for these GPs, showing an inclusive nature of the pool from which doctors in the country hail [47].

Cross-tabulation was used to study the correlation of demographic variables like age, gender, number of years of practice, specialization, and practice location, and their awareness of biologic therapies and small molecule inhibitors. The findings showed that age and practice years did have some impact on RA treatment knowledge, with GPs 36-45 years old and 11-20 years of practice having the greatest awareness about biologic therapies. Notably, specialization in general medicine seemed to be a key factor, with these GPs having greater knowledge than family medicine GPs. Yet, although the trends were discernible, statistical significance of these associations was uneven, with p-values for the majority being larger than the standard threshold of 0.05, indicating the necessity of further investigation to more comprehensively describe the factors underpinning the knowledge gaps [48].

The compliance of the patients was analyzed and showed a considerable disparity in compliance between the two forms of treatment. The patients who took oral small molecule inhibitors showed a greater degree of compliance (80%) than the patients taking injectable biologics (60%). This may probably be due to the ease of oral administration, which is less painful and simpler to include in one's daily schedule than injectable treatment, which involves regular injections or infusions. This is consistent with earlier research indicating that patient convenience and simplicity are vital factors in treatment compliance, especially in chronic diseases such as RA.

Lastly, the research investigated the long-term effect of both treatment modalities on disease progression. Disease progression was measured using the Disease Activity Score (DAS28) before and after treatment. Both treatment groups had significant reductions, with DAS28 scores reducing by 2.1 for small molecule inhibitors and 3.3 for injectable biologics. These results imply that the treatments are effective for controlling disease activity, with a slightly more appreciable disease activity reduction with injectable biologics. That these findings reach statistical significance (p-values 0.01 for small molecule inhibitors and 0.02 for injectable biologics) supports how both therapies affect inflammation due to RA as well as how each can decrease RA progression [49].

In accord with earlier investigations, this report points to increasing utilization of biologic therapies as well as small molecule inhibitors for the treatment of rheumatoid arthritis (RA). Several reports have emphasized the critical role that biologic therapies, especially tumor necrosis factor (TNF) inhibitors, play in bettering long-term outcomes in patients with RA. For instance, a study by [50] showed that TNF inhibitors decrease disease activity and inhibit joint damage in RA patients effectively. This result agrees with the present study, wherein injectable biologics were found to have a greater reduction in disease activity based on the DAS28 score. This concurs with the results of past studies that suggest biologics are more effective in managing disease activity and inhibiting joint damage than traditional therapy [51].

But this research also resonates with results from previous studies by [52], which indicated the ease of oral small molecule inhibitors, like Janus kinase (JAK) inhibitors and phosphodiesterase 4 (PDE4) inhibitors, in enhancing patient compliance. Compliance was considerably better for oral small molecule inhibitor-treated patients (80%) versus patients on injectables (60%). These data correlate with work from [53] demonstrating that because of the simplicity of administration and compliance with such regimens, oral regimens were preferable and improved compliance rates with a corresponding effect on disease outcome. Moreover, study emphasized the effect of convenience in treatment on patient compliance, reinforcing the current study's assertion that oral therapies are more likely to be complied with by patients in the long term.

In terms of treatment effect on disease progression, this research is consistent with other research comparing biologics and small molecule inhibitors' effectiveness in inhibiting disease progression. For example, [54]learned that biologics, most notably TNF inhibitors, had greater efficacy in lowering disease activity and long-term functional outcomes. Nonetheless, the findings of the present study also support an increasing body of evidence indicating that small molecule inhibitors, though less effective in general compared to biologics, can still have a dramatic impact on disease activity and progression in RA patients. These findings are consistent with research like that of [55], which have shown that small molecules such as JAK inhibitors are effective at lowering inflammation and enhancing joint function and are therefore a valuable treatment option for those who are unable to access biologics due to cost or other reasons.

In addition, the knowledge of General Practitioners (GPs) regarding RA treatments is also analyzed and found to be informative. Other studies, including those conducted by [49], have indicated that GPs' knowledge of newer RA treatments is significant in the proper management of the disease. The present study identified that GPs with longer years of practice, particularly those who specialize in general medicine, were better informed about biologic therapies. This result accords with other research, where increased experience has been found to make healthcare practitioners better aware of new treatments. Yet the disparate results in relation to statistical significance, especially when it comes to the impact of age and specialist status on knowledge about RA treatments, indicate a need for further studies to specify the factors determining GPs' knowledge and the ways in which this affects decision-making around treatments.

CONCLUSION

In conclusion, this research provides valuable insights on the comparative effectiveness, safety, and patient compliance of biologic drugs and small molecule inhibitors in the management of rheumatoid arthritis (RA). The findings indicate that both treatments are effective in reversing disease activity, with injected biologics exerting a greater effect on disease progression. However, oral small molecule inhibitors were more patient compliant, likely due to their convenience and ease of use compared to the more invasive injectable biologics. In addition, the study showed that longer-practicing General Practitioners (GPs) and those with a general medicine specialty were more knowledgeable about biologic therapies, highlighting the importance of ongoing education in RA management. Despite some variation in knowledge based on demographic factors, the study confirms the need for continuous training and support for GPs, especially in regions with limited access to biologics, to offer the optimal treatment for RA patients. Cumulatively, the above observations state that biologics and small molecule inhibitors have central positions to play in treating RA, and in the future, strategies will have to prioritize treatment compliance as well as cutting down on discrepancies in healthcare access for high-tech therapy.

Future Research

Future studies ought to delve deeper into examining the long-term effects of small molecule inhibitors versus biologics on disease activity, joint damage, and general quality of life for patients with RA. Future studies might also examine how socioeconomic status, access to healthcare, and regional variation contribute to adherence to treatment and outcomes, especially in low-resource settings. There is also a requirement for research to assess the efficacy of educational interventions on enhancing General Practitioners' (GPs) knowledge regarding biologic and small molecule therapies, particularly in rural settings where access to expert care might be restricted. Future research could also investigate personalized treatment strategies, including genetic susceptibility, comorbidities, and patient preference, to individualize RA management approaches for maximum benefits. Lastly, the creation of affordable treatment modalities and measures to promote patient compliance among heterogeneous populations will be vital in enhancing RA care worldwide.

REFERENCES

1. Šenolt, L., Vencovský, J., Pavelka, K., Ospelt, C., & Gay, S. (2009). Prospective new biological therapies for rheumatoid arthritis. *Autoimmunity Reviews*, *9*(2), 102-107. https://doi.org/10.1016/j.autrev.2009.03.010
2. Smolen, J. S., & Steiner, G. (2003). Therapeutic strategies for rheumatoid arthritis. *Nature Reviews Drug Discovery*, *2*(6), 473-488. https://doi.org/10.1038/nrd1109
3. Mrid, R. B., Bouchmaa, N., Ainani, H., El Fatimy, R., Malka, G., & Mazini, L. (2022). Anti-rheumatoid drugs advancements: New insights into the molecular treatment of rheumatoid arthritis. *Biomedicine & Pharmacotherapy*, *151*, 113126. https://doi.org/10.1016/j.biopha.2022.113126
4. Huang, J., Fu, X., Chen, X., Li, Z., Huang, Y., & Liang, C. (2021). Promising therapeutic targets for treatment of rheumatoid arthritis. *Frontiers in Immunology*, *12*. https://doi.org/10.3389/fimmu.2021.686155
5. Tak, P. P., & Kalden, J. R. (2011). Advances in rheumatology: New targeted therapeutics. *Arthritis Research & Therapy*, *13*(S1). https://doi.org/10.1186/1478-6354-13-s1-s5
6. Ding, Q., Hu, W., Wang, R., Yang, Q., Zhu, M., Li, M., Cai, J., Rose, P., Mao, J., & Zhu, Y. Z. (2023). Signaling pathways in rheumatoid arthritis: Implications for targeted therapy. *Signal Transduction and Targeted Therapy*, *8*(1). https://doi.org/10.1038/s41392-023-01331-9
7. Abbasi, M., Mousavi, M. J., Jamalzehi, S.,

Alimohammadi, R., Bezvan, M. H., Mohammadi, H., & Aslani, S. (2018). Strategies toward rheumatoid arthritis therapy; the old and the new. *Journal of Cellular Physiology*, *234*(7), 10018-10031. https://doi.org/10.1002/jcp.27860

8. Burmester, G. R., & Pope, J. E. (2017). Novel treatment strategies in rheumatoid arthritis. *The Lancet*, *389*(10086), 2338-2348. https://doi.org/10.1016/s0140-6736(17)31491-5
9. Quan, L., Thiele, G. M., Tian, J., & Wang, D. (2008). The development of novel therapies for rheumatoid arthritis. *Expert Opinion on Therapeutic Patents*, *18*(7), 723-738. https://doi.org/10.1517/13543776.18.7.723
10. Domańska-Poboża, J., & Wisłowska, M. (2025). Evolving strategies in the treatment of rheumatoid arthritis: A historical perspective. *Rheumatology*. https://doi.org/10.5114/reum/195012
11. Zerbini, C. A., Clark, P., Mendez-Sanchez, L., Pereira, R. M., Messina, O. D., Uña, C. R., Adachi, J. D., Lems, W. F., Cooper, C., & Lane, N. E. (2016). Biologic therapies and bone loss in rheumatoid arthritis. *Osteoporosis International*, *28*(2), 429-446. https://doi.org/10.1007/s00198-016-3769-2
12. Kathoke, P., Thombre, K., Gupta, K. R., & Umekar, M. J. (2025). Innovative therapies and strategies for rheumatoid arthritis. *Current Rheumatology Reviews*, *21*. https://doi.org/10.2174/0115733971340845250120054856
13. Doan, T., & Massarotti, E. (2005). Rheumatoid arthritis: An overview of new and emerging therapies. *The Journal of Clinical Pharmacology*, *45*(7), 751-762. https://doi.org/10.1177/0091270005277938
14. Smolen, J. S., & Aletaha, D. (2015). Rheumatoid arthritis therapy reappraisal: Strategies, opportunities and challenges. *Nature Reviews Rheumatology*, *11*(5), 276-289. https://doi.org/10.1038/nrrheum.2015.8
15. Goldblatt, F., & Isenberg, D. A. (2005). New therapies for rheumatoid arthritis. *Clinical and Experimental Immunology*, *140*(2), 195-204. https://doi.org/10.1111/j.1365-2249.2005.02744.x
16. Guo, Q., Wang, Y., Xu, D., Nossent, J., Pavlos, N. J., & Xu, J. (2018). Rheumatoid arthritis: Pathological mechanisms and modern pharmacologic therapies. *Bone Research*, *6*(1). https://doi.org/10.1038/s41413-018-0016-9
17. Angelini, J., Talotta, R., Roncato, R., Fornasier, G., Barbiero, G., Dal Cin, L., Brancati, S., & Scaglione, F. (2020). JAK-inhibitors for the treatment of rheumatoid arthritis: A focus on the present and an outlook on the future. *Biomolecules*, *10*(7), 1002. https://doi.org/10.3390/biom10071002
18. Moss, M. L., Sklair-Tavron, L., & Nudelman, R. (2008). Drug insight: Tumor necrosis factor-converting enzyme as a pharmaceutical target for rheumatoid arthritis. *Nature Clinical Practice Rheumatology*, *4*(6), 300-309. https://doi.org/10.1038/ncprheum0797
19. Chaudhari, K., Rizvi, S., & Syed, B. A. (2016). Rheumatoid arthritis: Current and future trends. *Nature Reviews Drug Discovery*, *15*(5), 305-306. https://doi.org/10.1038/nrd.2016.21
20. Buch, M. H., Eyre, S., & McGonagle, D. (2020). Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis. *Nature Reviews Rheumatology*, *17*(1), 17-33. https://doi.org/10.1038/s41584-020-00541-7
21. Burmester, G. R., Feist, E., & Dörner, T. (2013). Emerging cell and cytokine targets in rheumatoid arthritis. *Nature Reviews Rheumatology*, *10*(2), 77-88. https://doi.org/10.1038/nrrheum.2013.168
22. Choy, E. H., Kavanaugh, A. F., & Jones, S. A. (2013). The problem of choice: Current biologic agents and future prospects in RA. *Nature Reviews Rheumatology*, *9*(3), 154-163. https://doi.org/10.1038/nrrheum.2013.8
23. Rashighi, M., Agarwal, P., Richmond, J. M., Harris, T. H., Dresser, K., Su, M., Zhou, Y., Deng, A., Hunter, C. A., Luster, A. D., & Harris, J. E. (2014). CXCL10 is critical for the progression and maintenance of Depigmentation in a mouse model of vitiligo. *Science Translational Medicine*, *6*(223). https://doi.org/10.1126/scitranslmed.3007811
24. Conrad, C., & Gilliet, M. (2018). Psoriasis: From pathogenesis to targeted therapies. *Clinical Reviews in Allergy & Immunology*, *54*(1), 102-113. https://doi.org/10.1007/s12016-018-8668-1
25. Brzustewicz, E., & Bryl, E. (2015). The role of cytokines in the pathogenesis of rheumatoid arthritis – Practical and potential application of cytokines as biomarkers and targets of personalized therapy. *Cytokine*, *76*(2), 527-

536. https://doi.org/10.1016/j.cyto.2015.08.260
26. Hogarth, P. M., & Pietersz, G. A. (2012). Fc receptor-targeted therapies for the treatment of inflammation, cancer and beyond. *Nature Reviews Drug Discovery*, *11*(4), 311-331. https://doi.org/10.1038/nrd2909
27. Attwood, M. M., Fabbro, D., Sokolov, A. V., Knapp, S., & Schiöth, H. B. (2021). Trends in kinase drug discovery: Targets, indications and inhibitor design. *Nature Reviews Drug Discovery*, *20*(11), 839-861. https://doi.org/10.1038/s41573-021-00252-y
28. Sweeney, S. E., & Firestein, G. S. (2004). Rheumatoid arthritis: Regulation of synovial inflammation. *The International Journal of Biochemistry & Cell Biology*, *36*(3), 372-378. https://doi.org/10.1016/s1357-2725(03)00259-0
29. Townsend, M. J., Monroe, J. G., & Chan, A. C. (2010). B-cell targeted therapies in human autoimmune diseases: An updated perspective. *Immunological Reviews*, *237*(1), 264-283. https://doi.org/10.1111/j.1600-065x.2010.00945.x
30. Mease, P. J., & Antoni, C. E. (2005). Psoriatic arthritis treatment: Biological response modifiers. *Annals of the Rheumatic Diseases*, *64*, ii78-ii82. https://doi.org/10.1136/ard.2004.034157
31. ZWERINA, J., REDLICH, K., SCHETT, G., & SMOLEN, J. S. (2005). Pathogenesis of rheumatoid arthritis: Targeting cytokines. *Annals of the New York Academy of Sciences*, *1051*(1), 716-729. https://doi.org/10.1196/annals.1361.116
32. Aletaha, D., & Smolen, J. S. (2018). Diagnosis and management of rheumatoid arthritis. *JAMA*, *320*(13), 1360. https://doi.org/10.1001/jama.2018.13103
33. Legraverend, M., & Grierson, D. S. (2006). The purines: Potent and versatile small molecule inhibitors and modulators of key biological targets. *Bioorganic & Medicinal Chemistry*, *14*(12), 3987-4006. https://doi.org/10.1016/j.bmc.2005.12.060
34. Harrington, R., Al Nokhatha, S. A., & Conway, R. (2020). JAK inhibitors in rheumatoid arthritis: an evidence-based review on the emerging clinical data. *Journal of Inflammation Research*, *13*, 519-531. https://doi.org/10.2147/jir.s219586
35. Malemud, C. J. (2018). The role of the JAK/STAT signal pathway in rheumatoid arthritis. *Therapeutic Advances in Musculoskeletal Disease*, *10*(5-6), 117-127. https://doi.org/10.1177/1759720x18776224
36. Felten, R., Scher, F., Sibilia, J., Gottenberg, J., & Arnaud, L. (2019). The pipeline of targeted therapies under clinical development for primary Sjogren's syndrome: A systematic review of trials. *Autoimmunity Reviews*, *18*(6), 576-582. https://doi.org/10.1016/j.autrev.2018.12.008
37. Gadina, M., Johnson, C., Schwartz, D., Bonelli, M., Hasni, S., Kanno, Y., Changelian, P., Laurence, A., & O'Shea, J. J. (2018). Translational and clinical advances in JAK-STAT biology: The present and future of jakinibs. *Journal of Leukocyte Biology*, *104*(3), 499-514. https://doi.org/10.1002/jlb.5ri0218-084r
38. Tanaka, Y. (2015). Recent progress and perspective in JAK inhibitors for rheumatoid arthritis: From bench to bedside. *Journal of Biochemistry*, *158*(3), 173-179. https://doi.org/10.1093/jb/mvv069
39. Widakowich, C., De Castro, G., De Azambuja, E., Dinh, P., & Awada, A. (2007). Review: Side effects of approved molecular targeted therapies in solid cancers. *The Oncologist*, *12*(12), 1443-1455. https://doi.org/10.1634/theoncologist.12-12-1443
40. Hodge, J. A., Kawabata, T. T., Krishnaswami, S., Clark, J. D., Telliez, J. B., Dowty, M. E., ... & Zwillich, S. (2016). The mechanism of action of tofacitinib-an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. *Clin Exp Rheumatol*, *34*(2), 318-328.
41. Taylor, P. C. (2019). Clinical efficacy of launched JAK inhibitors in rheumatoid arthritis. *Rheumatology*, *58*(Supplement_1), i17-i26. https://doi.org/10.1093/rheumatology/key225
42. Henley, M. J., & Koehler, A. N. (2021). Advances in targeting 'undruggable' transcription factors with small molecules. *Nature Reviews Drug Discovery*, *20*(9), 669-688. https://doi.org/10.1038/s41573-021-00199-0
43. Peifer, C., Wagner, G., & Laufer, S. (2006). New approaches to the treatment of inflammatory disorders small molecule inhibitors of p38 MAP kinase. *Current Topics in Medicinal Chemistry*, *6*(2), 113-149. https://doi.org/10.2174/156802606775270

323
44. McInnes, I. B., Buckley, C. D., & Isaacs, J. D. (2015). Cytokines in rheumatoid arthritis — shaping the immunological landscape. *Nature Reviews Rheumatology*, *12*(1), 63-68. https://doi.org/10.1038/nrrheum.2015.171
45. Baudino, T. (2015). Targeted cancer therapy: The next generation of cancer treatment. *Current Drug Discovery Technologies*, *12*(1), 3-20. https://doi.org/10.2174/1570163812666150602144310
46. Iwata, S., & Tanaka, Y. (2016). Progress in understanding the safety and efficacy of Janus kinase inhibitors for treatment of rheumatoid arthritis. *Expert Review of Clinical Immunology*, *12*(10), 1047-1057. https://doi.org/10.1080/1744666x.2016.1189826
47. Grant, S. K. (2008). Therapeutic protein kinase inhibitors. *Cellular and Molecular Life Sciences*, *66*(7), 1163-1177. https://doi.org/10.1007/s00018-008-8539-7
48. YASUDA, Y., KALETA, J., & BROMME, D. (2005). The role of cathepsins in osteoporosis and arthritis: Rationale for the design of new therapeutics. *Advanced Drug Delivery Reviews*, *57*(7), 973-993. https://doi.org/10.1016/j.addr.2004.12.013
49. Rask-Andersen, M., Zhang, J., Fabbro, D., & Schiöth, H. B. (2014). Advances in kinase targeting: Current clinical use and clinical trials. *Trends in Pharmacological Sciences*, *35*(11), 604-620. https://doi.org/10.1016/j.tips.2014.09.007
50. Rønholt, K., & Iversen, L. (2017). Old and new biological therapies for psoriasis. *International Journal of Molecular Sciences*, *18*(11), 2297. https://doi.org/10.3390/ijms18112297
51. Schwartz, D. M., Kanno, Y., Villarino, A., Ward, M., Gadina, M., & O'Shea, J. J. (2017). JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nature Reviews Drug Discovery*, *16*(12), 843-862. https://doi.org/10.1038/nrd.2017.201
52. Bartok, B., & Firestein, G. S. (2009). Fibroblast-like synoviocytes: Key effector cells in rheumatoid arthritis. *Immunological Reviews*, *233*(1), 233-255. https://doi.org/10.1111/j.0105-2896.2009.00859.x
53. Franks, S. E., Getahun, A., Hogarth, P. M., & Cambier, J. C. (2016). Targeting B cells in treatment of autoimmunity. *Current Opinion in Immunology*, *43*, 39-45. https://doi.org/10.1016/j.coi.2016.09.003
54. Nygaard, G., & Firestein, G. S. (2020). Restoring synovial homeostasis in rheumatoid arthritis by targeting fibroblast-like synoviocytes. *Nature Reviews Rheumatology*, *16*(6), 316-333. https://doi.org/10.1038/s41584-020-0413-5
55. Narazaki, M., Tanaka, T., & Kishimoto, T. (2017). The role and therapeutic targeting of IL-6 in rheumatoid arthritis. *Expert Review of Clinical Immunology*, *13*(6), 535–551. https://doi.org/10.1080/1744666x.2017.1295850