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Review

Integrating Primary Care and Specialized Therapies in Rheumatoid Arthritis: Optimizing Recognition, Management, and Referral Practices

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Abstract: Rheumatoid arthritis (RA) is an immune-mediated chronic and long-term condition that can lead to severe joint damage and disability. It has been shown that doctor–patient interaction and communication can have a significant impact on faster patient diagnosis and treatment outcomes. Primary care (PC) is the first level of patient contact with doctors and the health system. Communication between them is often ineffective, leading to delays in diagnosis, care, and the use of disease-modifying antirheumatic drugs (DMARDs). The protocols and standards for the treatment of RA are well established by all rheumatology organizations. All of them recommend early initiation of DMARDs, which leads to better long-term outcomes. There are some recommendations that would lead to better optimization of recognition, management, and referral practices. Early diagnosis, effective communication between general practitioners and specialists, and patient education about possible targeted therapies and biological products, as well as subsequent monitoring of therapies and screening for risk factors and comorbidities, will improve patient health and optimize costs. We aimed to offer strategies and possibilities for integrating and optimizing primary care and specialized therapies in RA because proper management will reduce the severity of the disease and even reduce mortality from chronic diseases such as RA.

Keywords: rheumatoid arthritis; primary care integration; disease management; early recognition; referral practices

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1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory symmetric polyarthritis that leads to progressive joint damage, periarticular erosion, and subsequent disability. RA constitutes the most frequently encountered inflammatory arthritis, affecting approximately

one in one hundred people worldwide. A female prevalence has been demonstrated (one male for every three females), with the peak onset reported to be between 30 and 50 years of age [1]. Commonly reported risk factors include smoking, positive family history, and carriage of the 'shared epitope' genetic factor, as well as other genetic regions (STAT4, IL6R, FCGR, etc.). To diagnose RA, the levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) also need to be determined when considering a patient with chronic inflammatory arthritis. At the same time, autoimmunity is proven by the presence of rheumatoid factor (RF) and/or anti-citrullinated protein antibody (ACPA) [2,3].

RA does not constitute a mere rheumatological diagnosis. Instead, it affects multiple organs and systems, leading to a variety of dermatologic, ocular, pulmonary, and cardiovascular complications, with the latter comprising the number-one predictor of mortality in RA patients [2,4]. The diagnosis of RA is based on the demonstration of chronic synovitis, requiring a minimum six-week interval of inflammatory joint involvement. However, "preclinical RA", as referred to by Cush, has an onset that can precede polyarthritis manifestations for months or even years [5].

It is well known that early diagnosis, when combined with early therapy onset, correlates with better prognosis and earlier remission in RA patients. Therefore, it is desirable that primary care providers, constituting the first point of contact for most patients, can correctly and efficiently diagnose and/or refer such cases to secondary care units. In this aspect, the identification of "preclinical RA" by general practitioners (GPs) is extremely beneficial for the patient.

As Chilton et al. advocate, the "therapeutic window of opportunity", spanning the 12-week interval between the onset of the first symptom and therapy initiation, is the optimal period for RA management to achieve disease remission, ameliorate joint damage and disability, prevent long-term complications, improve quality of life, and lessen the need for orthopedic surgery or hospitalization in the future [5,6]. Severe limitations in the management of RA in the primary care setting also arise from insufficient or lacking collaboration between GPs and specialists, inadequate availability of rheumatologic care units, difficulty in GPs utilizing disease-modifying antirheumatic drugs (DMARDs), and an absence of cardiovascular prevention/screening protocols [7].

This article seeks to identify factors in the collaboration between primary care providers and specialists that could enhance the prognosis of RA by enabling earlier diagnosis, ensuring effective management, and streamlining the referral process to secondary care units. Additionally, the role of primary care providers in RA treatment and diagnosis is thoroughly explored, and some key practices that could improve disease progression in RA patients are also outlined.

2. Search Strategy

A comprehensive literature search was conducted to explore the integration of primary care and specialized therapies in rheumatoid arthritis, focusing on optimizing recognition, management, and referral practices. The databases searched included PubMed, Scopus, Embase, and Web of Science. The search terms combined key concepts using Boolean operators, such as "rheumatoid arthritis" AND ("primary care" OR "general practitioners") AND ("specialized therapy" OR "targeted treatment") AND ("management" OR "referral practices"). The search was limited to peer-reviewed articles, systematic reviews, meta-analyses, and clinical trials published in English over recent years from 2010 (mostly the last five years: 2019–2024). The articles were screened for relevance, with inclusion criteria emphasizing interdisciplinary approaches and patient outcomes.

3. The Role of Primary Care in RA Recognition and Initial Management

Despite the rheumatologist being the leading specialist in the care of RA patients, the primary care physician (PCP) serves as the first contact for patients in most health systems. The PCP is responsible for recognizing the important features of recent-onset inflammatory arthritis and establishing joint deformities in patients whose disease was not previously recognized.

The three most important features that the PCP should recognize include morning stiffness, joint swelling, and the pattern of joint involvement. Morning stiffness is considered an important property of inflammatory arthritis, distinguishing it from the symptoms of osteoarthritis that become more prominent in the second half of the day [8,9]. Indeed, morning stiffness is more relevant in the context of the involvement of at least several joints, whereas its clinical relevance in the scenario of having one single painful/swollen large joint is not as clear.

Joint swelling is a necessary prerequisite for diagnosing a patient with RA, typically following a pattern of polyarthritis (affecting at least five joints). Tender joints without at least one swollen joint are still not sufficient to label a patient as RA according to the relatively sensitive 2010 classification criteria. In addition, RA has a typical pattern of symmetric joint synovitis, which is different from the "bony" enlargement of joints seen in osteoarthritis [10]. Furthermore, tenosynovitis may be the presenting feature in patients with RA. Despite its clinical relevance, it has not been included in classification criteria, possibly due to challenges in standardizing its assessment. While the 2010 classification criteria recognize joint swelling as a key feature, they do not differentiate between swelling caused by synovitis within the joint and tenosynovitis adjacent to the joint. However, it is important to note that tenosynovitis can be present even in the absence of visible swelling, and its identification does not necessarily rely on imaging alone [10].

Potential challenges in the recognition of RA at its early stages include a lack of confidence of the PCP in recognizing features of inflammatory arthritis. According to the results of a national cross-sectional survey of general practitioners (PCPs) in the UK, their confidence in diagnosing RA and detecting synovitis was only moderate: 7 (IQR 5 to 7) and 7 (IQR 6–8) on a 0–10 scale [11]. Indeed, PCPs may lack the required physical examination skills to recognize synovitis. Although the squeeze test has been described as a useful screening tool in detecting hand and foot polyarthritis, its properties are modest at best, according to the results of a cross-sectional analysis. At the metacarpophalangeal level, its sensitivity and specificity comprised 53% and 82%, respectively. At the metatarsophalangeal level, its sensitivity was 54%, with an even worse specificity of 74%, illustrating the difficulty of detecting synovitis of the foot joints [12]. Even rheumatologists may experience difficulty in detecting synovitis of the foot joints. Hence, the involvement of the feet has not even been included in the 28-joint count, which is a part of the most commonly used disease activity indices in RA, such as disease activity score 28 (DAS28) [13]. On the other hand, the detection of the synovitis of single joints may be associated with a level of uncertainty, as described in an analysis of 43 patients (1204 joints) from an academic rheumatological center, where doubtful swelling was noted in at least one joint in 40/43 patients (93%) [14].

Unnecessary referral of osteoarthritis patients with no signs of inflammatory arthritis may pose an additional burden to rheumatologists, prolonging the time to the first visit of RA patients. On the other hand, the late referral of newly diagnosed or suspected RA patients to rheumatologists has been associated with an increased likelihood of joint damage, given that the therapeutic "window of opportunity" may be missed. The therapeutic window of opportunity generally refers to the time frame of early RA, associated with the highest efficacy of disease-modifying drugs to achieve future drug-free remission and to prevent the development of joint erosions (joint damage, also termed radiographic

progression). Early disease recognition and referral to the rheumatologist within six weeks to a maximum of three months following presentation is of utmost importance, because the time to diagnosis is still inadequately prolonged in most settings, even those offering a fast referral system [15,16].

From a practical standpoint, at the beginning of the diagnostic process, it is more important to discern between inflammatory and non-inflammatory arthritis (osteoarthritis) than to distinguish between different types of inflammatory arthritides. Nevertheless, it should be noted that, in addition to RA, the typical pattern of polyarthritis can be seen in psoriatic arthritis, connective tissue diseases such as SLE, polyarticular gout, and calcium pyrophosphate dihydrate deposition disease (CPPD).

In rare cases where symmetric polyarthritis is recognized early, a self-limited viral infection (such as parvovirus B19) may be misdiagnosed as rheumatoid arthritis. However, this scenario should not pose an important public health burden due to the benign course of the viral disease in adults [17].

Laboratory tests may aid in the referral of patients with suspected RA. Acute phase reactants, including erythrocyte sedimentation (ESR) and C-reactive protein, are included both in the classification criteria and disease activity indices [10,18,19].

In addition, chronic disease anemia may serve as an additional clue to the presence of an inflammatory disease [20]. Furthermore, a patient presenting with inflammatory arthritis may benefit from testing for rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs), given that their positivity (especially exceeding three times above the upper level of normal) increases the likelihood of RA [18]. RF and/or ACPA positivity is associated with a higher risk of erosive disease (joint damage) [21].

Although conventional X-rays are not a necessary prerequisite for diagnosis or classification, the detection of erosions located at typical joint levels allows for diagnosing RA even without fulfilling other features. Conversely, a "normal" X-ray finding or finding suggestive of osteoarthritis does not exclude RA, given that conventional radiographs are not sensitive enough for detecting swollen joints without joint erosions [22]. Ultrasound may aid in diagnosing RA, especially in cases where the certainty of the clinical assessment is lower than expected, e.g., in pre-existent osteoarthritis. It helps in the differential diagnosis between osteoarthritis and inflammatory arthritis, and even between RA and other types of inflammatory arthritides such as psoriatic arthritis, gout, etc. Despite the fact that ultrasound examination is operator-dependent, it represents a relatively inexpensive imaging modality once an ultrasound machine is available [23].

Differential diagnosis of RA by GPs can be challenging due to the overlap of symptoms with other musculoskeletal conditions, particularly in the early stages of disease. The subtle nature of RA symptoms, such as joint pain and stiffness, can often be mistaken for other common conditions, which contributes to the difficulty in making a confident diagnosis. Additionally, GPs may experience reluctance to refer patients immediately to a specialist, especially if the nearest rheumatology center is located a significant distance away. This reluctance is often compounded by concerns about healthcare accessibility, delays in diagnosis, and the perceived burden on patients who would need to travel long distances for specialized care [24].

This raises an important question regarding the scope of this manuscript. While the focus has been on RA, it may be beneficial to broaden the discussion to include other major rheumatic disorders, particularly SLE, which can present with similar nonspecific symptoms. Expanding the manuscript to encompass these disorders provides a more comprehensive approach to the challenges faced by GPs in diagnosing and referring patients for specialized care, particularly in areas with limited access to rheumatology services. By addressing these issues, this manuscript can better highlight the need for

improved referral practices, better diagnostic tools, and enhanced education for primary care providers to ensure timely and accurate diagnosis of various rheumatic conditions.

Therapeutic options available in the primary care setting are aimed at symptom relief and preservation of joint function, especially before a firm diagnosis of inflammatory arthritis such as RA has been made by the rheumatologist. Analgesic therapy includes paracetamol as the first analgesic of choice (up to 3 g daily) and nonsteroidal anti-inflammatory drugs (NSAIDs). Of note, these drugs do not affect inflammation and prevent joint damage. Therefore, even a good response to these symptomatic treatment options should not be an argument for prolonging referral to the rheumatologist. Furthermore, NSAIDs should be prescribed at a minimum effective dose given their potential gastrointestinal, cardiovascular, and renal risks. Non-pharmacological interventions should also be offered depending on their availability in the primary care setting. They include physical and occupational therapy, smoking cessation, and patient education [23].

In Bulgaria, primary care for patients with RA is primarily managed by general practitioners (GPs), who serve as the first point of contact for individuals seeking medical care. GPs play a crucial role in the early detection and referral of patients with suspected rheumatoid arthritis to specialized care [25]. However, the initial diagnosis and management of RA typically occur in specialized settings, such as rheumatology clinics or hospitals, where patients are referred for further assessment, including laboratory tests and imaging studies [15].

Once diagnosed, the ongoing management of rheumatoid arthritis often involves a multidisciplinary approach, with patients continuing care under the supervision of a rheumatologist. The primary care physician remains involved in monitoring the patient's overall health, managing comorbid conditions, and providing routine follow-up care, including monitoring for medication side effects [26]. In some cases, patients with complex or advanced disease may require hospitalization for more intensive treatment, such as biological therapies or joint surgery. Coordination between primary care providers and specialists is essential to ensure that patients with rheumatoid arthritis receive comprehensive care. Despite the strengths of the system, challenges such as limited access to specialized care in rural areas and delays in early diagnosis still exist, which can impact the timely initiation of appropriate treatment.

4. Specialized Therapies and Their Impact on RA Progression

Medical management of RA can aim at different outcomes, ranging from disease remission, reduction in disease activity, and the alleviation of joint pain and swelling to the prevention of mortality, disability, and cardiovascular complications. While the therapeutic outcome might differ, it is widely recommended that aggressive therapy should be started as soon as possible since, at the time of diagnosis, pre-existing radiologic changes are irreversible [1,27,28]. These radiological changes referred to in this context primarily involve joint damage, particularly in the small joints (e.g., the hands and feet), which are commonly detected through modalities such as plain radiographs, ultrasound, or advanced MRI. These changes are considered irreversible at the time of diagnosis, highlighting the importance of initiating aggressive therapy as early as possible.

A meta-analysis involving 12 studies has verified that patients who receive delayed treatment with DMARDs face an increased risk of radiographic joint space narrowing and bony erosions. In this respect, it is agreed that every recently diagnosed patient should be placed immediately on treatment, and even in cases of specific drug shortage/unavailability, other options should be offered [29]. Another point that supports the early initiation of treatment is the delay in the therapeutic result observed with the use of DMARDs, which can vary from 6 weeks to 6 months [1,27,28]. This variation in response time may be

influenced by several factors, including the type of DMARD used, the severity of the disease at diagnosis, the presence of comorbidities, and patient-specific characteristics such as age and overall health. Additionally, different subgroups of patients, such as those with early versus established disease or those with a higher baseline inflammatory burden, may experience different response times. Understanding these variations is crucial for tailoring treatment strategies and managing patient expectations regarding the time to therapeutic benefit.

The role of primary care providers, especially the GP, can differ significantly based on geographic location. For example, in areas with good organization and availability of secondary specialized centers with fast turnover, a GP is mainly responsible for the initial diagnosis/referral of the patient. Conversely, in areas with long waiting times and a shortage of specialized rheumatologic units, the GP might have to assume a more involved role by monitoring the therapeutic response and, in conjunction with a specialist, adjusting the treatment strategy. Other parameters affecting the level of involvement of primary care providers are limited resources, low availability of newer biologic treatments, and disparities in accessing a secondary care facility. Subsequently, primary care physicians must possess sufficient knowledge regarding the standard therapeutic options, be aware of the most common adverse effects and their potential drug interactions, closely monitor disease progress and response to therapy, and make suitable adjustments when needed [30]. While primary care physicians play a key role in managing general aspects of patient care, the monitoring of therapeutic effects and adjustments to treatment regimens may require close collaboration with specialists in rheumatology. This ensures that appropriate tools, such as imaging studies, laboratory tests, and disease activity measures (e.g., DAS28), are used to accurately assess treatment efficacy and make necessary adjustments. The role of primary care providers is crucial in the early detection and management of RA, particularly in remote areas with limited access to specialized care. However, it is important to acknowledge that GPs must balance their responsibilities for a wide range of diseases and may not have the extensive experience necessary to manage complex rheumatic disorders effectively. Given the high patient load and the need to maintain expertise in various medical conditions, it may be unrealistic to expect GPs to develop and sustain specialized skills in rheumatology. A more feasible approach would involve enhancing GPs' ability to recognize early symptoms and refer patients to rheumatologists when appropriate. Additionally, improving communication and coordination between primary care providers and specialists, possibly through telemedicine or referral networks, could help ensure timely diagnosis and treatment, especially in underserved areas with limited healthcare resources [30]. However, some skills in rheumatology are necessary—physical examination and recognition of inflammation and possibility of a multi-system disease. Furthermore, the consultant rheumatologist must have confidence in the accuracy of information transmitted by the PCP; thus, they need to be able to identify inflammation. Nevertheless, they must establish credibility with the consultant, and not be known for simply referring the patient who complains the most.

In the coming paragraphs, we summarize the current data to guide the evidence-based practice of primary care providers in treating RA with DMARDs.

4.1. Disease-Modifying Antirheumatic Drugs (DMARDs)

Both the EULAR and the American College of Rheumatology (ACR) guidelines have adopted a treat-to-target approach to RA, which includes a plethora of DMARDs, including conventional synthetic DMARDs (csDMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs). Table 1 provides a list of the most commonly used DMARDs, describing their main therapeutic effects and adverse reactions.

Table 1. Advances and limitations of integrating primary care and specialized therapies in RA, focusing on optimizing recognition, management, and referral practices.

Approach	Successes	Limitations
Early Diagnosis and Intervention	Earlier initiation of disease-modifying antirheumatic drugs (DMARDs) improves long-term outcomes.	Primary care providers may lack specialized training to recognize early symptoms of RA.
	Early referral to rheumatologists prevents joint damage and improves quality of life.	Diagnostic delay due to overlap with other inflammatory diseases.
Collaborative Care Models	Integrated care involving both primary care and specialists leads to comprehensive disease management.	Communication barriers between primary care and specialists can delay referrals.
	Shared care results in better management of comorbidities like cardiovascular disease.	Differences in management strategies and clinical priorities between primary care and rheumatology.
Patient Education and Self-Management	Encourages patients to actively participate in their care, leading to improved disease control.	Variability in patient adherence to treatment regimens and self-management strategies.
	Increased awareness of early signs of flare-ups and proper management techniques.	Lack of time and resources to educate patients thoroughly during routine visits.
Telemedicine and Digital Tools	Improved access to specialist care, particularly for patients in remote areas.	Limited digital literacy and access to technology in certain patient populations.
	Facilitates regular monitoring and disease activity assessment, enhancing disease control.	Telemedicine may not provide the same quality of assessment as in-person visits for complex cases.
Multidisciplinary Teams	Collaboration among rheumatologists, primary care physicians, physiotherapists, and nurses improves patient outcomes.	Coordination challenges and need for standardized protocols for team-based care in RA management.
	Multidisciplinary teams can address both medical and psychosocial aspects of RA care.	Resource constraints and inadequate funding for interdisciplinary team models in certain settings.
Medical Schools and Continuing Medical Education (CME) Programs	Provide essential knowledge and skills to physicians and specialists, ensuring they are well equipped to use new technologies and methods in patient care to improve recognition and management of rheumatic diseases.	Current curricula and CME programs may lack sufficient emphasis on training healthcare providers in the use of advanced EHR systems, leading to gaps in proficiency and delayed adoption in clinical practice.
Referral Pathways and Coordination	Timely referrals lead to better disease control and prevent unnecessary complications.	Inconsistent referral practices, leading to delays in specialized care.
	Streamlined referral pathways improve patient satisfaction and treatment outcomes.	Over-referrals or under-referrals due to a need for more awareness of referral criteria and guidelines.
Personalized Treatment Plans	Tailored therapies based on genetic, environmental, and comorbid factors lead to more effective management.	Difficulty in personalizing treatment due to diverse patient profiles and evolving disease characteristics.
	Precision medicine can improve efficacy and reduce side effects for patients.	High cost of personalized treatments, limiting their widespread application.

The first-line treatment strategy for treatment-naive RA patients endorses the use of cs-DMARDs, including methotrexate (MTX), hydroxychloroquine (HCQ), sulfasalazine (SSZ), and leflunomide (LEF) [27,31]. Once sustained remission is achieved, the primary care provider may consider a dose reduction in DMARDs (bDMARDs/tsDMARDs and/or csD-

MARDs) [21]. According to the EULAR 2022 recommendations, MTX should be the initial therapeutic option unless contraindicated, in which case, provided that no poor prognostic factors exist, an alternative csDMARD (LEF, SSZ) should be contemplated. Conversely, the presence of poor prognostic factors mandates the adjustment of the csDMARD plan to include a bDMARD [21]. The preference of MTX over other csDMASRDs can be partially explained by its superior safety profile and efficacy rates, evidenced by a systematic review involving 73 clinical trials [27].

To further support the suggested preference for MTX, the OPTIMA trial demonstrated that early treatment in RA with methotrexate and adjuvant glucocorticoids was sufficient when compared with a combination of MTX with a bDMARD (adalimumab). This allows for a delay in adding a bDMARD without significant damage to the patient's health, which is very important for areas with shortages of specialized rheumatological facilities [29].

While MTX can be administered through various routes, oral administration is associated with less serious adverse effects [28], which can prove advantageous in cases where the GP oversees the therapeutic regimen. Despite this, regular monitoring (once a month) of hepatic function and the immune system is required to optimize initial dosing at the start of therapy. Alfaro et al. studied leflunomide, used as the induction csDMARD in RA. LEF demonstrated a similar efficacy to MTX, whereas its effect on joint swelling reduction was lower. It was associated with greater hepatic enzyme rise but fewer gastrointestinal disturbances [32]. It is worth noting that the EULAR 2022 guidelines neither support nor discount the use of combination csDMARD therapy [21]. bDMARDs comprise a group of proteins manufactured to target specific molecular pathways contributing to the inflammation observed in RA, including, but not limited to, TNF, IL-6, and IL-1 inhibition [27].

A detailed list is provided in Table 1, but we will briefly describe a few examples of the most commonly used medications for treating RA. Adalimumab (ADA) is an example of a TNF-inhibitor (TNFi) administered subcutaneously with less toxicity than other medications within the same class [28]. As per the EULAR guidelines, a bDMARD is added as a second-line treatment to a csDMARD protocol for patients who are non-responsive to or intolerant of csDMARD monotherapy. Generally, bDMARDs are preferred over tsDMARDs when poor disease predictors exist: the failure of two csDMARDs, presence of autoantibodies, high disease activity, or early erosions. In case of failure to respond to the first bDMARD, a second one should be tried, either from the same or another class [21]. According to the EULAR guidelines, it has been suggested that patients not tolerant to csDMARDs for combination therapy with bDMARDs can preferentially use IL-6 inhibitors over other bDMARDs for combination therapy with tsDMARDs [21].

Per this, tocilizumab (TCZ)—an IL-6 inhibitor—was employed in the U-ACT-Early trial, a multi-center, randomized, double-blind trial that involved newly diagnosed RA patients. The subjects were randomly allocated to three treatment groups: a TCZ group, a TCZ + MTX group, and a MTX group. Over the next 2 years, 88% of the patients in the TCZ arm achieved sustained remission, compared to 86% in the combination arm and 77% in the methotrexate arm [33]. Therefore, the results of TCZ efficacy can justify the EULAR, as mentioned earlier. Interestingly, the HIT HARD trial, an earlier investigator-initiated trial, attempted to compare an induction maintenance approach (induction with MTX and ADA for 6 months, then discontinuation of ADA and MTX monotherapy for another 6 months) with an MTX single induction protocol. The results were consistent with better responses during the first 6 months, with better radiological effects in the combination protocol [34]. The combination protocol was associated with better radiological outcomes. The radiological effects refer to improvements in joint damage and structural changes (reduced joint damage and erosion progression), assessed through standard radiological tests such as plain radiographs and/or advanced imaging modalities like MRI or ultrasound. These tests were

used to monitor disease progression and the effects of therapy longitudinally during this study. Time zero was determined as the baseline at the initiation of treatment, before any therapeutic intervention, and subsequent follow-up imaging allowed for the assessment of changes over time.

Olofsson et al. described the effectiveness of TNFi in helping RA patients regain previously lost workability. Indeed, patients initiated on TNFi therapy within 5 years of symptom onset had a doubled probability of regaining workability in the coming 3 years compared to controls [35]. Another interesting effect of TNFi is their inverse association with the occurrence of myocardial infarction in RA [36]. This is especially beneficial when contemplating the high cardiovascular risk encountered in RA patients and can potentially guide treatment in high-risk groups. A similar effect was demonstrated with the IL-1 inhibitor, anakinra, which improved myocardial deformation, endothelial function, and nitro-oxidative stress [37]. In a case report described by Schatz et al., anakinra also proved beneficial in the resolution of constrictive pericarditis in a patient refractory to corticosteroid administration [38].

Denosumab, a RANKL inhibitor, was demonstrated to repair erosions in RA partially. It is thus postulated that combination therapy with DMARDs might be of benefit for RA with progressive bone erosions. The results, however, were not reproducible with alendronate utilization [39]. An older study described the superiority of rituximab (RTX), a B cell depleter, plus MTX over MTX monotherapy regarding joint damage progression in patients with RA with previous unsatisfactory responses to TNFi [40].

Interesting results were obtained using a network meta-analysis of randomized control trials that compared the benefits and safety of six commonly used biologics (abatacept, rituximab, adalimumab, anakinra, infliximab, and etanercept) in patients with rheumatoid arthritis. Etanercept was described as the safest option compared to adalimumab, anakinra, and infliximab, while etanercept and adalimumab proved to be more effective than anakinra [41]. In the same vein, the ADACTA study concluded the superiority of TCZ when compared to ADA in reducing DAS28 in MTX-intolerant patients by 24 weeks (-3.3 vs. -1.8). Still, TCZ has a slightly higher rate of adverse reactions (12% vs. 10%) [42].

In conclusion, the choice of DMARD, including conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs), should be tailored based on disease severity, patient response, and the presence of poor prognostic factors. Early treatment with MTX and a treat-to-target approach are emphasized for optimal disease control. It is important to note that any use of MTX requires concomitant use of folic acid. While MTX remains a first-line therapy due to its proven safety and efficacy, biologics such as TNF inhibitors and IL-6 inhibitors offer additional benefits, particularly for patients with inadequate responses to csDMARDs. The evidence supports the notion that a combination of DMARDs, including MTX and biologics, provides superior therapeutic outcomes, including better radiological effects, when compared to monotherapy. Ultimately, timely initiation and individualized treatment strategies are key to achieving sustained remission and preventing long-term joint damage.

4.2. Targeted Therapies and Biologics

As an alternative to bDMARDs for second-line therapy in combination with csDMARD, we can also offer tsDMARDs. This class includes the orally administered Janus kinase inhibitor (JAKi) [27]. JAKi constitutes a small molecule targeted therapy that inhibits signal transduction through the JAK molecule, thereby suppressing interleukins and interferon expression [43]. Tofacitinib is a preferential JAK1/3 inhibitor but retains some minor activity on JAK2 and TYK2, whereas baricitinib mainly exerts its action on JAK1/JAK2 with only moderate and minor activity against TYK2 and JAK3, respectively. Upadacitinib is

only active against JAK1, whereas filgotinib is selective for JAK-1 while inhibiting the other receptors as well [44]. Their efficacy rates are comparable to TNFi in terms of ACR response rates and disease activity scores (DAS28) [45]. However, higher malignancy rates, major adverse cardiovascular effects, and severe infections, including hospital-treated herpes zoster infection, have been described in comparison to TNFi [21,46,47].

Data extracted from the worldwide 3-year post-marketing surveillance (PMS) of tofacitinib in the Pfizer safety database demonstrated an increased incidence of infections (RR = 2.57), gastrointestinal disorders (RR = 0.91), respiratory disorders (RR = 0.60), neoplasms (RR = 0.45), cardiac disorders (RR = 0.43), and hepatobiliary disorders (0.12) [48]. It is worth mentioning that the elevated venous thromboembolism risk associated with tofacitinib seems to be dose-dependent (especially high at 10 mg twice daily) [49].

A trial led by Rubbert-Roth et al. compared upadacitinib to abatacept. Although it proved to be superior to abatacept with regard to the DAS28 score, it was also associated with more severe adverse effects, including one death, one nonfatal stroke, and two venous thromboembolic events [50]. Consequently, JAKi is currently offered to patients not at risk of venous thromboembolism. An advantage of JAKi, when considering primary care, is that it can be administered as monotherapy for patients not complying with/unwilling to follow a combination scheme with similar radiologic effects [51]. Potential new therapeutic targets for novel therapeutic approaches in RA are under investigation, including Toll-like receptors, Bruton's tyrosine kinase, transforming growth factor β (TGF-β), and the phosphoinositide-3-kinase pathway [28].

To sum up, while targeted therapies and biologics, including JAKi, offer effective treatment alternatives for rheumatoid arthritis, their use must be carefully considered due to the associated risks, such as increased incidence of infections, cardiovascular events, and malignancies. Despite these concerns, JAKi provides an option for patients who are unable or unwilling to follow combination therapy, with the potential for similar radiological effects as biologics. Ongoing research into new therapeutic targets continues to expand treatment options, with the aim of improving outcomes while minimizing adverse effects.

4.3. Patient Monitoring and Adjustment of Therapies

EULAR guidelines call for frequent and early monitoring of RA. Specifically, during the active phase of the disease, monitoring should occur every 1–3 months, and, depending on the results, further action may be needed [21]. If the GP notices no improvement by the 3-month point, or if the treatment target has not been reached by the 6th month, they should consider consulting a specialist for therapy adjustment. GPs need to be aware and actively monitor patients for the presence of active inflammation in RA, evidenced by morning stiffness. In areas of low resources, in collaboration with secondary care physicians, they should be able to perform more specialized tests, e.g., compression testing [7]. Most agents require individual monitoring practices. For example, MTX requires monitoring of its hepatotoxic and immunosuppressive effects, ideally every month at the beginning of treatment [21]. Some known drug interactions exist for MTX, including with AZP and LEF, resulting in liver and lung adverse effects, as well as with cotrimoxazole, leading to pancytopenia [28]. Primary care providers must be aware of such events when multiple agents are used to avoid potential severe complications. For LEF, it is also advised to monitor liver function and look for signs of alopecia, allergy, or gastrointestinal disturbance [28].

With SSZ use, serial monitoring of albumins, creatinine, and calculated eGFR (estimated glomerular filtration rate) is desirable. Initially, it should be performed every 2 weeks until the dose remains unchanged for 6 weeks, then every month for 3 months, and thereafter, every 3 months [52]. Prolonged use and high doses of HCQ are associated with retinal toxicity, even after cessation of therapy. Therefore, periodic screening for early de-

tection is recommended [28]. Patients treated with bDMARDs, especially TNFi, should be regularly screened for infections [53], malignancies [54], and potentially the development of antidrug antibodies in case of non-response [55]. Lastly, patients using JAKi should be routinely screened for malignancies, while regular monitoring for infection, cardiovascular disorders, and thrombosis is necessary [56]. A potential tool in monitoring DMARDs, especially useful in primary care settings, could be the utilization of machine learning prediction models to identify responses to therapy. A similar study was performed to predict responses to bDMARDs through DAS28 score quantification, although the methods require further refinement before they can be implemented in clinical practice [57].

5. Enhancing Communication and Collaboration Between Primary Care and Rheumatology Specialists

Effective management of RA requires seamless communication and collaboration between PCPs and rheumatology specialists. Early diagnosis and timely initiation of treatment are critical for preventing joint damage and improving patient outcomes. However, more communication and care coordination can be needed to ensure optimal treatment. This section explores key strategies for enhancing collaboration, including developing standardized referral pathways, improved information sharing through electronic health records (EHRs), and co-management approaches that optimize primary care and rheumatology roles.

One of the most important steps in improving collaboration is the establishment of standardized referral pathways. Clear referral criteria help PCPs identify the early signs of RA and ensure timely referral to rheumatology specialists. Evidence shows that early specialist involvement within the first 12 weeks of symptom onset—the "window of opportunity"—significantly improves long-term outcomes by reducing disease progression and improving quality of life [58].

Referral pathways should include the following: (1) early identification criteria such as persistent joint pain, morning stiffness lasting longer than an hour, and elevated inflammatory markers; (2) streamlined processes that minimize administrative barriers, ensuring rapid access to rheumatology care; and (3) feedback mechanisms where rheumatologists provide timely updates on diagnosis and treatment plans, enabling PCPs to understand the rationale for specific interventions. Moreover, implementing triage systems where urgent cases are prioritized can further optimize patient flow, ensuring that those with early RA or aggressive disease are seen promptly.

Effective communication between PCPs and rheumatologists hinges on robust information-sharing systems. Shared EHRs are essential for facilitating real-time data exchange and enhancing collaborative care. EHRs should be interoperable, allowing primary and specialty care providers to access comprehensive patient histories, lab results, imaging studies, and treatment plans [59].

The benefits of shared EHRs consist of the following: (1) improved continuity of care by ensuring that both PCPs and rheumatologists are aware of the patient's clinical status, treatment milestones, and any adjustments to the care plan; (2) reduction in duplicate testing, which minimizes unnecessary costs and enhances patient convenience; and (3) enhanced patient safety through the integration of alerts for potential drug interactions, which is especially important in RA management, where immunosuppressive therapies are common [59].

However, to maximize the utility of EHRs, healthcare systems should invest in user-friendly platforms that facilitate seamless documentation and communication. Regular EHR use training for PCPs and rheumatologists can also improve adoption rates and data accuracy. This system facilitates real-time data monitoring, enabling seamless commu-

nication between healthcare providers and ensuring that patient information is readily available for both specialists and PCPs. Additionally, patients will have secure access to their health data through portable devices, which enhances patient engagement and fosters better management of their care.

To ensure the protection of sensitive patient information, the system will incorporate robust data safety measures, including encryption protocols, secure authentication processes, and compliance with privacy regulations (e.g., HIPAA, GDPR). Further details on the system's architecture, data storage, access, and sharing protocols will be provided. Additionally, a graphic abstract will be included to visually illustrate the system's components, data flow, and its key functions, along with an outline of the data safety programs employed to safeguard patient data.

Co-management strategies are vital in optimizing care for patients with RA, allowing PCPs and rheumatologists to share responsibilities based on their expertise. In this model, PCPs handle general health maintenance, while rheumatologists focus on disease-specific management. The key components of co-management include (1) vaccination and preventive care: PCPs are well positioned to administer vaccines, such as influenza, pneumococcal, and COVID-19 vaccines, which are essential for RA patients on immunosuppressive therapies [60].

PCPs also monitor for comorbidities like cardiovascular disease, diabetes, and osteoporosis, which are more prevalent in RA patients. (2) Routine Monitoring: While rheumatologists monitor disease activity through specific biomarkers and imaging, PCPs can manage routine lab tests, such as liver and kidney function, to assess the safety of disease-modifying antirheumatic drugs (DMARDs) and biologics. (3) Patient Education and Lifestyle Counseling: PCPs can provide guidance on smoking cessation, diet, exercise, and stress management, which are important adjuncts to RA treatment [61,62].

Clear communication channels must be established for successful co-management. Regular case reviews and joint consultations, whether in person or via telemedicine, can ensure alignment in care plans. Developing co-management agreements that outline specific roles, responsibilities, and expectations can minimize confusion and enhance collaboration. Enhancing communication and collaboration between primary care providers and rheumatology specialists is essential for optimizing RA management. Standardized referral pathways ensure early specialist involvement, shared EHRs facilitate efficient information exchange, and co-management strategies leverage the strengths of both primary care and specialty care providers. By implementing these strategies, healthcare systems can improve early diagnosis, ensure comprehensive care, and ultimately enhance outcomes for patients with RA. Strengthening the partnership between primary care and rheumatology will improve patient experiences and contribute to more efficient and effective healthcare delivery.

Table 1 summarizes the advances and limitations of integrating primary care and specialized therapies in RA, focusing on optimizing recognition, management, and referral practices.

6. Optimizing Patient Education and Self-Management

6.1. Education on Medication Adherence and Self-Management

PCPs play a crucial role in educating patients with RA about medication adherence and lifestyle modifications, which are fundamental in managing this chronic condition [63]. RA treatment typically involves long-term use of disease-modifying antirheumatic drugs or biologic agents. Ensuring adherence to prescribed medications is critical for achieving these therapeutic goals. PCPs are positioned to address common barriers to adherence, such as misunderstanding the importance of long-term therapy, concerns over side effects, or the complexity of drug regimens. Educating patients about the benefits of consistent medication

use, potential adverse effects, and the long-term management of RA can significantly enhance patient compliance [64].

Furthermore, PCPs should provide guidance on complementary lifestyle modifications—such as weight management, smoking cessation, and regular physical activity—that can help reduce disease activity and improve patient outcomes. These discussions, coupled with tailored educational resources and regular follow-ups, enable patients to engage more actively in their treatment plans, contributing to better disease control and quality of life [65].

6.2. Supporting Symptom Self-Management

Beyond pharmacologic treatment, self-management strategies are essential in optimizing the overall management of RA [27]. PCPs should emphasize the importance of physical therapy (PT) to patients as part of a comprehensive self-management approach. Regular PT aids in maintaining joint flexibility, building muscle strength, and improving functional capacity, which is crucial for minimizing disability in RA patients. Tailored exercise regimens can help prevent joint deformities and enhance mobility [66]. Additionally, dietary modifications may play a supportive role in managing inflammation. Evidence suggests that diets rich in omega-3 fatty acids, antioxidants, and other anti-inflammatory components may contribute to reducing RA symptoms and complement pharmacologic therapies. PCPs should educate patients on these dietary adjustments and refer them to nutritionists when necessary to ensure an individualized approach [67]. Incorporating these lifestyle modifications into daily routines, alongside other techniques such as stress management and adequate rest, empowers patients to take an active role in managing their disease. This holistic approach not only reduces symptom burden, but also fosters a sense of control, ultimately improving patients' physical and emotional well-being. By providing the necessary education and support, PCPs can significantly enhance the efficacy of RA management and improve patient outcomes [68].

The timely presentation of patients with RA is often delayed due to the subtle or underestimated nature of its early symptoms, particularly in younger individuals. This delay in seeking medical care can lead to missed opportunities for early intervention, which is crucial for improving long-term outcomes. To address this issue, national campaigns focused on raising awareness about the early signs and symptoms of RA could play a vital role in promoting earlier recognition of the disease. These campaigns would aim to educate both the general public and healthcare professionals about the importance of early detection, particularly for individuals who may be at higher risk, such as younger populations where symptoms can often be overlooked or attributed to other conditions. By integrating primary care and specialized therapies, we can optimize the recognition and management of, and referral practices for, RA, ensuring that patients are promptly referred to rheumatology specialists for further evaluation and treatment. Such initiatives could help bridge the gap between primary care and specialized care, facilitating earlier diagnosis, reducing disease progression, and ultimately improving patient outcomes.

7. Challenges and Barriers in Integrated RA Care

There are major structural and systemic obstacles to integrated RA care that prevent prompt diagnosis and efficient treatment. One major healthcare gap is the lack of access to rheumatologists [69]. Rheumatologists are scarce in many rural or isolated areas of some nations, forcing patients to travel great distances and wait long periods for visits. This creates a serious healthcare gap [70]. The median time between the onset of symptoms and the rheumatologist's evaluation was 24 weeks, according to a study comparing medical centers around Europe [71]. Timely intervention is critical, as irreversible complications

may result from rheumatic illness diagnosis and treatment delays [72]. One important factor in managing this problem is telemedicine—or telerheumatology, in the case of rheumatological disorders [73].

There are several care approaches, such as online video calls for remote evaluations and assistance with rural consultations. In recent years, telerheumatology has been increasingly used for preliminary assessment and appointment prioritization, as well as for patient education, rehabilitation, and the gathering of patient-reported outcomes (PROs). Compared to paper-based PROs, electronic PROs provide long-term advantages for illness monitoring [74].

Moreover, inadequate collaboration between multidisciplinary teams, including rheumatologists and psychologists, can result in missed opportunities for comprehensive, patient-centered care, poor data sharing, and duplication of diagnostic efforts. According to Knittle et al., cognitive behavioral therapy (CBT) has the strongest evidence for effectiveness in managing pain in RA patients [75]. However, CBT is most effective when delivered early in the course of the disease, within the first 2 years [76]. So, intervening early can prevent long-term physical and psychological morbidity.

Good communication between all factors of the management team can boost efficacy and trust, but limited contact time with patients also presents challenges [63]. Patients themselves encounter a number of barriers that affect how they participate in integrated RA therapy. Lack of knowledge about how RA progresses frequently leads to unwillingness to follow recommended treatments or delays in seeking medical help [77]. Adherence concerns are also widespread, sometimes caused by a fear of adverse effects from prescriptions, misinformation, or distrust of healthcare providers. Psychosocial problems, such as depression and anxiety, are common among RA patients and impair adherence and follow-up [78].

Moreover, studies show that patients with RA and low socioeconomic levels experience financial and appointment-keeping issues. Cultural and linguistic obstacles—as seen in ethnic minorities and those with lesser education, respectively—may also impede good communication, preventing patients from completely understanding the significance of their treatment plan or navigating healthcare systems efficiently [79,80]. Addressing these challenges requires systemic reforms, enhanced communication technologies, and targeted patient education to build a more accessible, patient-centered RA management model.

8. Policy and Healthcare System Improvements

Enhancing the integration of primary care and specialized therapies for RA requires systemic changes in healthcare policy and funding. Integrating care models—such as patient-centered medical homes (PCMHs) or collaborative care networks—can improve coordination between general practitioners (GPs) and rheumatologists. Increased funding is essential to support RA-specific programs, including early detection initiatives, multidisciplinary teams, and community-based care. Policymakers should incentivize collaboration by providing financial support for innovative care models and ensuring equitable access to specialized treatments. Creating standardized referral pathways can also streamline patient transitions between primary and specialty care, reducing delays in diagnosis and treatment.

8.1. Training Programs and Continuous Education

Continuous education and training for primary care providers are crucial in enhancing early detection and management of RA. Comprehensive programs should focus on recognizing early signs of RA, understanding the latest therapeutic advances, and implementing evidence-based treatment guidelines. Regular workshops, online courses, and

collaborative case reviews with rheumatologists can ensure that PCPs remain updated on emerging therapies and diagnostic criteria. In addition to formal training, establishing mentorship networks where PCPs can consult with specialists will foster a culture of continuous learning and improve patient outcomes [81].

Yet, the PCPs' training in rheumatology remains inadequate. Limited exposure during medical education, insufficient musculoskeletal assessment training, and a lack of rheumatology-focused continuing medical education (CME) contribute to delayed diagnoses and suboptimal early management. To address this gap, integrating rheumatology modules into medical curricula, offering structured musculoskeletal examination training, and expanding access to CME programs tailored for PCPs are essential. Additionally, implementing point-of-care screening tools, enhancing collaboration with rheumatologists through telemedicine, and utilizing AI-driven decision support systems in electronic health records can facilitate timely referrals and improve outcomes. Strengthening PCP education and support systems will enhance early RA recognition, optimize management, and ultimately improve patient care.

8.2. Enhanced Use of Digital Health and Telemedicine

Integrating digital health technologies and telemedicine holds significant potential for improving RA care. Remote monitoring tools, such as mobile apps and wearable devices, can facilitate the real-time tracking of symptoms and medication adherence, enabling early intervention when disease activity increases. Telemedicine can bridge the gap between primary care and rheumatology by providing patients in remote or underserved areas with timely access to expert consultations. Developing secure, interoperable EHRs will ensure seamless provider communication, allowing for shared decision-making and comprehensive care planning. Future initiatives should prioritize the development of user-friendly platforms that enhance patient engagement and empower individuals to participate in their care actively [82].

Optimizing integrated care for RA demands a multifaceted approach that combines policy reforms, continuous education, and innovative digital health solutions. By enhancing collaboration between primary care and specialty providers, leveraging technology, and ensuring adequate funding, healthcare systems can improve early diagnosis, management, and long-term outcomes for RA patients.

9. Conclusions

Patients with RA usually first present to their primary care doctor, who should refer them to a rheumatologist. Delay in accurate diagnosis leads to rapid progression, significant joint pain, and deformity if not treated aggressively. All guidelines recommend early treatment with DMARDs and the use of specialized therapies. Communication between patients, specialists, and GPs needs to be improved. Proper management of the disease also requires contact with physiotherapists and nurses. Improving patient education and awareness is also critical for the proper management of RA. Thus, the early diagnosis, possible targeted therapies, the monitoring of therapies, screening for risk factors and comorbidities, will improve patient health and optimize costs.

If an interdisciplinary approach is included, it can help optimize the promptitude and effectiveness of RA management and improve the quality of life of patients. These approaches can also be applied to other chronic inflammatory diseases that lead to disability. These approaches, which focus on early diagnosis, integrated care, and targeted treatment strategies, can also be applied to other chronic inflammatory diseases that lead to disability, such as SLE, ankylosing spondylitis, and psoriatic arthritis. Given that the differential

diagnosis is a critical aspect at presentation for many rheumatic disorders, the principles outlined in this analysis are not limited to RA alone.

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