Review

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Review

Frontiers in Rheumatoid Arthritis: Emerging Research and Unmet Needs in Pharmacologic Management

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Abstract

The management of rheumatoid arthritis (RA) has undergone several practice-defining evolutions, beginning with the approval of low dose methotrexate and continuing through the introduction of numerous disease-modifying antirheumatic drugs (DMARDs). With increasing capability to target pro-inflammatory pathways, successive therapeutics have carried the promise of improved disease control for patients with RA. Despite an expanding arsenal of therapeutics for RA, many patients fail to meet treatment objectives, leading to the recognition of several clinical phenotypes that remain therapeutically challenging under the current treat-to-target standard of care. These include both individuals with preclinical inflammatory arthritis as well as extensively treatment-experienced patients with refractory disease. Using precision medicine approaches to better characterize the pathogenesis of RA in such populations can help inform effective tailoring of DMARD therapy to individual patients. Simultaneously, observational data derived from clinical practice is increasingly being used to understand the risks and benefits of long-term DMARD therapy under real-world conditions of use. Together, these strategies offer opportunities to address unmet needs in the care of patients with RA. In this review, we identify several clinical RA phenotypes that demonstrate inadequate response to guideline-directed therapy and review frontiers in clinical research in RA, highlighting the use of precision medicine and real-world evidence-based approaches to advance individualized, patient-centered care.

Keywords: Rheumatoid arthritis; DMARD; treat-to-target; difficult-to-treat; phenotyping; precision medicine; biomarkers; long-term safety; real-world evidence; personalized medicine

1. Introduction

Rheumatoid arthritis (RA) is the most common type of autoimmune arthritis, with estimated prevalence of up to 1% of the global population [1]. Since the approval of low dose methotrexate for the treatment of RA in 1988, [2]. numerous disease-modifying antirheumatic drugs (DMARDs) have been approved for use in RA in the United States, including conventional synthetic DMARDs (csDMARDs), targeted synthetic DMARDs (tsDMARDs), and biological DMARDs (bDMARDs). The American College of Rheumatology (ACR) recently updated guidelines for the management of RA in 2021, [3] and consensus goals for pharmacotherapy have prioritized the reduction of disease activity. However, despite sustained research in RA management, a substantial proportion of patients with RA still do not achieve low disease activity or remission, and/or lack a durable response to DMARD therapy. Several clinical phenotypes have been described, most notably "difficult-to-treat" RA, for which ongoing research is aimed at improving therapeutic strategies.

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2. Current Treatment Paradigms in RA

2.1. Guideline-Directed Treatment

In the United States, standard of care for pharmacologic management in RA is largely informed by the 2021 ACR guidelines, developed by a voting panel comprising clinicians and patients, which strongly recommend initiation and optimization of methotrexate monotherapy for DMARD-naive patients with moderate or greater disease activity. Escalation of therapy by adding or switching to bDMARDs (e.g., tumor necrosis factor-alpha [TNF-a] inhibitor, T cell costimulatory inhibitor, interleukin [IL]-6 inhibitor, or anti-CD20 antibody therapy) or tsDMARDs (i.e., Janus kinase [JAK] inhibitors) is considered only if disease control is not achieved with methotrexate alone [3]. DMARD-naïve patients with low disease activity at diagnosis may alternatively be treated with hydroxychloroquine or sulfasalazine instead of methotrexate. TNF-a inhibitors are widely accepted as first-line bDMARD, although approximate therapeutic equivalence has been demonstrated across classes of United States Food and Drug Administration (FDA) approved bDMARDs and tsDMARDs [4–6]. Combination therapy with csDMARDs represent another therapeutic strategy, most commonly triple therapy with methotrexate (or leflunomide), hydroxychloroquine, and sulfasalazine; [7] given tradeoffs between benefits (e.g. low cost, less risk of adverse events) and drawbacks (e.g. high pill burden, longer lag time to take effect, poor retention), [8] guidelines conditionally recommend escalation to bDMARD/tsDMARD over triple therapy in prioritizing response to therapy as quickly as possible. Glucocorticoid avoidance is recommended for most patients.

International guidelines for RA treatment are similar to current ACR guidelines, with differences based largely on local availability of various DMARDs [9]. Amongst all guidelines, ongoing DMARD selection should be informed not only by disease activity, but also by taking into account patient preferences, comorbidity, and risk for adverse events, as well as clinician experience and cost.

2.2. Treat-to-Target

Current guidelines recommend adoption of a treat-to-target (TTT or T2T) strategy over usual care for RA management. This paradigm involves regular reassessment of disease activity with validated measures to guide adjustment and/or escalation of treatment, with the goal of achieving low disease activity or clinical remission [10]. Options for adjusting therapy include escalation of existing DMARD therapy (i.e. increasing dose or switching route of administration from oral to injection), combination therapy (i.e. adding DMARDs), or switching to a different class of DMARDs, with holistic reassessment of disease activity using composite measures of disease activity to drive treatment decisions. Although criteria for remission have been developed, an initial target of low disease activity may be preferred, as many patients may struggle to achieve these strict cutoffs due to comorbidities, treatment intolerance, or other patient-specific factors [11]. Overall, treatment goals should be individualized and based on clinical presentations as well as shared decision making between patients and clinicians, to ensure that the target is remission whenever feasible. There is substantial evidence supporting the T2T approach, which demonstrates improved likelihood of remission, radiographic stability, and function and quality of life as compared to usual care [12]. Longitudinal analysis of patients with RA demonstrated an association of T2T strategy with remission across disease activity indices, [13] although questions remain over what the optimal target is for individual patients [14]. While adherence is limited in real-world settings due to a variety of clinician, patient, and systemic factors, [15,16], and optimal treatment targets have not been established, [17] T2T remains the standard for care for RA.

3. Identifying Unmet Needs in the Management of RA

Despite the effectiveness of T2T as a treatment strategy for RA, many patients do not achieve remission in routine clinical practice, [18] with a substantial proportion of patients having suboptimal

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response to conventional guideline-directed therapies [19,20] Several clinical phenotypes have been identified in which existing therapeutic strategies may be insufficient to fully address patient needs.

3.1. Difficult-to-Treat RA

Recognition that a subset of patients fail to achieve treatment targets despite multiple lines of therapy led to the characterization of difficult-to-treat (D2T) RA, defined as: (1) failure of 2 or more bDMARDs or tsDMARDs after initial treatment with csDMARDs per guidelines, (2) signs suggesting active or progressive disease, and (3) management of signs and symptoms considered problematic by the patient and treating clinician, such as intolerable side effects of treatment or complications of chronic glucocorticoid use [21]. Prevalence estimates for D2T RA vary significantly, with recent review suggesting between 5.5% and 27.5% of patients may meet such criteria [22]. Numerous clinical features have been associated with D2T status, including younger age at diagnosis, female sex, seropositivity, and delayed treatment initiation [23]. Patients who progress to D2T status are more likely to have had high disease activity and radiographic damage at baseline [24,25]. Comorbidity relating to persistent inflammatory state, extra-articular disease, and the effects of long-term immunosuppressive therapy have also been described in D2T cohorts [26]. Pain and fatigue syndromes including fibromyalgia are more common amongst patients with D2T disease, and are posited to contribute to suboptimal treatment outcomes [27].

In addition, patients with D2T RA can be broadly characterized by inflammatory state. Patients with persistent inflammatory refractory RA (PIRRA) despite multiple lines of therapy may continue to present with polyarthritis, or may resolve to one or a few joints with refractory synovitis [28] In contrast, non-inflammatory refractory RA (NIRRA) is characterized by persistent arthralgia despite low swollen joint counts and inflammatory markers, and is associated with coincident obesity and fibromyalgia [29].

3.2. Late-Onset RA

Late-onset RA (LORA) refers to patients developing new inflammatory arthritis after the age of 60 years, with several distinctions between LORA and conventional presentations of RA such as acute onset of symptoms, approximately equal sex distribution, and more frequent involvement of large proximal joints (e.g., shoulders and knees) [30]. Presentations with prominent bursal involvement resembling polymyalgia rheumatica, or related remitting seronegative symmetrical synovitis with pitting edema (RS3PE) have also been described [31]. Patients with LORA are less likely to be seropositive than younger patients [32]. Comorbid musculoskeletal conditions including osteoarthritis and osteoporosis are common and may confound assessment.

Treatment of LORA requires consideration of aging-related comorbidities that may contribute to increased treatment toxicity. Although response rates are comparable to patients with earlier-onset disease, [33] LORA is associated with greater incidence of adverse events during treatment, including declining physical function [34]. For patients aged 75 years and older, targeting low-disease activity may be more appropriate than remission, as it is imperative to balance risks and benefits of treatment escalation in this population [35].

3.3. Preclinical and Early RA

Over time, increasing attention has been focused on identifying patients at risk of developing RA and developing preventative strategies for those with preclinical disease. Circulating rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) precede the development of inflammatory arthritis, [36] with titers rising alongside increased systemic inflammation immediately prior to diagnosis [37]. Although genetic risk for RA may be conferred by factors such as the HLA-DRB1 shared epitope, several modifiable risk factors have also been associated with the development of pathogenic antibodies, including cigarette smoking, occupational exposures, obesity, and vitamin D deficiency [38]. Microbiome dysregulation, in particular overrepresentation of *P. gingivalis* and

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associated periodontitis, has also been identified as a risk factor for progression to RA in ACPA-positive individuals [39,40].

The association between palindromic rheumatism (PR) and RA has offered potential insights into the pathogenesis of RA. PR is an episodic arthritis characterized by flares of inflammatory arthritis that may last for days, resolving without incurring irreversible joint damage. Similarities in autoantibody profiles and patterns of joint involvement have been noted in PR and RA, [41] with imaging studies that suggest that PR flares are characterized by increased extracapsular inflammation, as opposed to the synovitis characteristic of RA [42]. Although the relationship of PR and RA remains unclear, historical reports note a high (>50%) rate of progression to RA, and PR is sometimes considered to exist on the spectrum of seropositive arthralgia with other precursors to clinical RA [41].

Numerous therapies have been evaluated for use in RA prevention, although the results have been inconsistent. A systematic review of clinical studies evaluating prevention strategies in individuals at high risk of developing RA, or with undifferentiated inflammatory arthritis, did not identify any DMARD-based strategies that successfully prevented the onset of disease, although treatment with abatacept or rituximab was associated with a delayed onset of RA by up to 18 months [43]. While early treatment with methotrexate does not prevent progression to clinical arthritis, long-term outcomes with regards to inflammation and functional status were improved [44]. Trials of glucocorticoids and other csDMARDs such as hydroxychloroquine have been less successful [45]. While RA prevention strategies have generally failed to prevent onset of disease thus far, data show promise for modifying disease trajectory, suggesting potential utility for specific cohorts such as patients at risk for developing severe disease.

4. RA Research Frontiers

Improved understanding of clinical phenotypes with suboptimal response to existing therapeutic strategies has fueled interest in developing precision medicine approaches to RA management. Molecular insights into the pathogenesis of the disease and evidence drawn from large real-world cohorts can aid in tailoring DMARD therapy at treatment initiation and/or at junctions when treatment escalation is being considered.

4.1. Biomarkers

Traditional laboratory evaluation in RA includes measurement of acute phase reactants (e.g. C-reactive protein, CRP, and sedimentation rate, ESR) for assessment of active inflammation, as well as characteristic autoantibodies associated with disease severity and extraarticular features. Only recently have additional biomarkers offered opportunities to further risk stratify individual patients and inform selection of therapy [46].

4.1.1. Autoantibodies

In addition to RF and ACPAs, patients with RA may present with additional autoantibodies against proteins that have undergone non-citrullination post-translational modifications, including anti-carbamylated protein, anti-acetylated protein, and malondialdehyde-acetaldehyde antibodies observed in early clinical disease [47]. Antibodies against native proteins, including PTX3, DUSP11, and PAD4 have also been identified [48]. These more recently described autoantibodies frequently correlate with the development of conventional ACPAs and can be associated with radiographic progression. Although highly specific, they are less sensitive, and not yet widely adopted in routine clinical practice.

Further serological testing may also enhance patient assessment. While up to 7.5% of patients with RA demonstrate clinical evidence of co-occurring (“secondary”) Sjogren’s disease, rates of positivity for antibodies to SS-A are substantially higher, being noted in up to 15% of patients [49]. Secondary Sjogren’s disease is associated with higher RA disease activity, [50–52] and more

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commonly identified amongst patients with D2T-RA [53]. Anti-SS-A antibodies, even in the absence of sicca or other Sjogren's disease manifestations, are associated with reduced response to methotrexate and TNF inhibitors, [54,55] highlighting the potential need for alternative first-line DMARDs. Specifically, hydroxychloroquine and rituximab, both commonly used in the management of primary Sjogren's disease, may offer theoretical benefit for such patients, [49–51] although evidence from long-term studies in RA patients with positive anti-SS-A antibodies without overt Sjogren's disease are lacking. Small studies have also shown beneficial effects of tocilizumab and abatacept for patients with RA with positive anti-SS-A antibodies not responding to TNF inhibition, [50,56] with the latter also ameliorating symptoms of secondary Sjogren's disease [57] Given the known association between Sjogren's disease and lymphoma, careful consideration must be taken when selecting therapies to minimize malignancy risk. In the clinical development program for tofacitinib, incident lymphoma was observed among participants, with numerically greater rates of concomitant Sjogren's disease in those developing malignancy, underscoring the need for careful monitoring in this population [58]. Additional cardiovascular comorbidities and serologies (e.g., antiphospholipid antibodies) are not only associated with an increased risk of treatment complications, but may also give pause to consideration for treatment with JAK inhibitors. Overall, while the presence of anti-SS-A antibodies in RA patients may aid prognostication and inform early treatment with non-TNF bDMARDs, biological and clinical differences between patients with and without secondary Sjogren's disease remain incompletely understood.

4.1.2. Cytokine Profiles

Deconvolution of convergent pathways in the RA inflammatory cascade offers another approach to guide treatment decisions, with TNF-a, IL-1, IL-6, and other pro-inflammatory cytokines well-described as key drivers in the pathogenesis of RA [59]. Novel disease activity scores derived from cytokine profiling correlate with conventional measures and offer a more nuanced insight into inflammation than ESR or CRP [60] Despite the increased sensitivity of cytokine-based testing, their utility to disease management for individual patients is less understood. For example, treatment with methotrexate is associated with reductions in TNF-a, IL-17, and IFN gamma, [61] but bDMARD treatment results in less consistent cytokine responses [62] Discovering how to target dominant pro-inflammatory pathways remains a goal of cytokine-based molecular phenotyping, especially for patients with D2T. For a subset of patients, profiling may also support combination therapy; in small studies, the addition of rituximab or anti-IL-17 to TNF inhibitor therapy showed promise as a therapeutic strategy for treatment-refractory patients, although the safety of dual bDMARDs requires further investigation [63] In the future, cytokine profiling may offer clinicians additional insight into selecting between approved therapeutic mechanisms, with serial testing providing early evidence of secondary treatment failure to anticipate the need to change therapy.

4.2. Cellular Profiling

Characterization of cell types driving RA pathogenesis has focused on the synovium and peripheral blood, providing insights into disease mechanisms and potential differences in therapeutic response.

4.2.1. Synovium

Translational research indicates that features of the synovial microenvironment may predict disease trajectory. Spatial transcriptomics have revealed tissue-resident macrophages expressing the cell surface receptor LYVE1 as critical to synovial homeostasis; these macrophages are lost in early RA, but successful treatment with csDMARDs is associated with restoration of macrophage networks [64]. Their role in more advanced disease remains unknown. In addition to macrophages, the synovial cell repertoire includes substantial populations of T cells, fibroblasts, and myeloid cells, among which increased T cells, in conjunction with fibroblasts, are most commonly associated with

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seropositivity and higher baseline disease activity [65]. Composition of synovial cell populations varies independently of patient factors such as age and sex, but is correlated with current therapy, suggesting DMARDs may influence the synovial microenvironment. By describing cellular changes developing in the setting of therapy, such analyses suggest explanations for primary and secondary treatment failure, and potential therapeutic avenues based on dominant synovial phenotypes after initial treatment [66]. Through gene expression and histological analyses, four synovial phenotypes for RA have been characterized, each with distinct clinical implications. Patients with the myeloid phenotype were more likely to respond to TNF inhibitor therapy, whereas those with lymphoid phenotype had better responses to tocilizumab; low inflammatory (pauci-immune) and fibroid phenotypes, characterized by minimal or low evidence of pro-inflammatory pathway activation, tended to demonstrate lower response rates to DMARD therapy [67]. Fibroblast-like synoviocytes (FLS) are recognized as a key driver in chronic inflammation in RA and are often associated with seronegativity and D2T status; while there is interest in developing FLS-targeted medications, such therapeutic strategies remain an unmet need [68].

4.2.2. Peripheral Blood

The accessibility of circulating immune cells has also facilitated investigation into their roles in systemic inflammation. Immunophenotyping of peripheral blood cells offers an alternative to clinical phenotyping or classical serologies to classify patients with RA. Notably, clustering patients by T cell and B cell abundance yields distinct clusters predicting differential responses to DMARD classes; treatment with the bDMARD or tsDMARD expected to provide the most benefit results in higher rates of low disease activity or remission than other agents [69]. Other studies have further characterized T cells in RA, with seropositive patients demonstrating increased dysregulation of Th17 and regulatory T (Treg) cells as compared to seronegative patients, a pathophysiologic process potentially mediated by IL-4 and associated with increased systemic inflammation [70]. T cell subsetting is under investigation for potential use in predicting response to specific therapies such as tocilizumab and abatacept [71]. In parallel, prognostic and therapeutic roles of autoreactive B cells, [72,73] NK cells, [74] circulating macrophages, [75] and additional cell types continue to emerge. Finally, clonal hematopoiesis is increasingly recognized as contributing to immune dysregulation, not only in aging but also in RA; a large Finnish cohort study identified unique clonal pathways for seropositive patients, characterized by *DNMT3A* mutations, as well as seronegative patients, who have increased presence of *TET2* mutations.

4.2.3. Chemokines and Other Proteins

Increased expression of the B cell signaling molecule CXCL13 has been observed in patients with early RA, regardless of seropositivity, who do not respond to methotrexate, suggesting that earlier treatment with bDMARD or tsDMARD therapy may be warranted [76]. Likewise, upregulation of the vascular homeostasis protein ANGPTL4 has also been identified as a moderator of erosive disease via TNF-related pathways, [77] and is being explored as a therapeutic target. However, not all efforts have led to the development of novel therapies. CCR5, a chemokine receptor expressed by synoviocytes, has been implicated in pro-inflammatory pathways via the activation of Th1 cells, [78] but antagonizing therapeutic antibodies failed to demonstrate benefit [79]. To date, hundreds of putative biomarkers have been described, although few have defined roles in the evaluation or management of RA [80]. As new molecular signatures are identified, their utility as RA biomarkers or therapeutic targets must be clarified.

4.3. Personalized DMARD Selection

A corollary of precision DMARD selection is the likelihood that patients may be exposed to therapeutics at earlier stages of disease, in novel combinations, and for prolonged periods of time. Currently, rates of DMARD discontinuation or switches are high, with median retention times of 25

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months or less across cohorts. As we approach 30 years since the FDA approved the first bDMARD (etanercept, in 1998), clinicians will increasingly face decisions regarding treatment strategies for patients who have been exposed to decades of immunosuppressive therapy. In addition to therapeutic safety monitoring, understanding the real-world effectiveness of b/tsDMARDs is essential to pharmacologic selection over long disease trajectories.

4.3.1. Real-World Safety of Biologic and Targeted Synthetic DMARDs

Clinicians seeking to escalate DMARD therapy beyond methotrexate must navigate safety profiles arising from randomized trials, observational studies, and analyses derived from administrative claims data and other sources. Over time, large registries and population-based studies have refined assessments of b/tsDMARD safety, with several themes arising under real-world conditions.

Although a serious consideration, infection risk is comparable for most approved RA therapies, with fewer than 10 serious infections per 100 treatment years [81,82]. For TNF inhibitor therapies, risk appears to decline after the initial 6-12 months of treatment, [83,84] a pattern that has been extrapolated for other therapeutic mechanisms, including rituximab [85]. While close monitoring for infection is warranted, evidence to date does not suggest infection risk precludes long-term treatment for most patients with RA.

Malignancy remains a concern for patients exposed to prolonged immunosuppression, especially when increased systemic inflammation and advancing age are considered as additional risk factors. Population-based studies have reassuringly demonstrated no increased risk of malignancy overall for long-term TNF inhibition, anti-IL-6, or anti-CD20 therapy as compared to b/tsDMARD-naïve patients or age-matched controls [86] Given the biological role of CTLA4, concern persists over abatacept's effects on anti-tumoral T cell immunity; in a recent meta-analysis, pooled data from observational studies supported increased risk of malignancy for abatacept, [87] although postmarketing safety data reveals no greater risk of malignancy for abatacept compared to other therapeutic mechanisms [88]. Studies on JAK inhibitors have inconsistently associated use with increased risk of malignancy, [89] notably non-melanoma skin cancer, [90] and decreased risk of other cancers including those of GI origin [91]. Given persistent uncertainty over malignancy risk, cautious use is recommended.

Real-world data also informs estimates of risk for characteristic adverse events first observed in the development of b/tsDMARDs. TNF inhibitor therapies remain contraindicated for patients with symptomatic heart failure, [92] as well for those who have or are at risk of developing multiple sclerosis, [93,94] but are otherwise comparatively safe [95]. Although abatacept was initially suspected to exacerbate chronic obstructive pulmonary disease (COPD), this signal has not been observed in analyses of administrative data [96] IL-6 inhibitors increase lipid levels, but their use has not been associated with increased risk of cardiovascular disease as compared to tsDMARDs [97,98]. Previous diverticulitis, on the other hand, remains a contraindication, with higher intestinal perforation rates than any other DMARD class corroborated in a large RA registry [99] Despite findings in postapproval clinical trials that JAK inhibitors are associated with increased risk of major adverse cardiovascular events (MACE) and venous thromboembolism (VTE), [100] only a class-wide increased risk of VTE has been consistently identified in subsequent analyses [101]. Notably, rates of MACE have proven comparable to those of TNF inhibitors, [102] even for patients with history of cardiovascular disease [103,104]. Finally, other than rare reports of progressive multifocal leukoencephalopathy associated with rituximab, estimated to occur at a rate of 2.6 cases per 100,000 treated patients with RA, [105] long-term use is generally well-tolerated and is not associated with increased risk of infection [106,107].

Despite early safety signals, real-word analyses have largely confirmed the tolerability of b/tsDMARDs. However, clinicians must weigh individual patient factors against continuously evolving clinical data when making treatment decisions.

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4.3.2. Anticipating Clinical Trajectories for Patients Treated with b/tsDMARDs

As conventional clinical trials only provide information on the outcomes of treatment over relatively short time periods, additional sources of clinical evidence are critical to understanding responses to treatment over intervals that more accurately reflect the natural course of RA. Clinical data derived from multiple observational sources now provide opportunities to evaluate b/tsDMARD performance in real-world settings.

Rheumatology registries have existed since the mid-twentieth century, yielding invaluable insights into the epidemiology of RA, comorbidities, and treatment outcomes [108]. Their presence at the forefront of computerized health information systems has allowed registries to capture increasingly granular data, facilitating therapeutic assessment via target trials and other novel designs. Registry-based research efforts continue globally to this day. For example, the "JAK-pot" collaboration leverages data from tens of thousands of b/tsDMARD treatment courses, to explore the safety and comparative effectiveness of JAK inhibitors across clinical settings, [109,110] including for patients with D2T disease. Although registry analyses require careful consideration of the generalizability of findings beyond enrolled populations, these curated sources of real-world data can provide insights into the selection and sequencing of DMARD therapy [111].

In addition to registries, large-scale observational studies increasingly answer clinical questions in RA, driven by the availability of clinical documentation and expanded testing for secondary analyses [112]. Efforts such as The Rheumatoid Arthritis Real-world Cohort Study in China (ReALSA) aim to collect data on patients longitudinally, correlating clinical, laboratory, imaging, and pathological data to facilitate evolving analyses of real-world patients with RA [113]. Observational studies can also support therapeutic strategies, such as improved response rates with combined bDMARDs and csDMARDs, [114] although few studies have demonstrated a consistent superior benefit of one therapeutic strategy over others [115]. In one notable exception, the Kyoto University Rheumatoid Arthritis Management Alliance (KURAMA) cohort documented improvement in functional outcomes associated with increasing b/tsDMARD use over 10 years of follow-up; researchers observed more rapid improvement in disease activity with TNF inhibitors, but greater sustained responses to IL-6 inhibitors, addressing a knowledge gap left by the absence of comparative efficacy trials with the potential to inform clinical decision making [116]. The development of biobanks can extend the reach of such studies, enabling reanalysis of biological specimens in light of future technologies and validating translational insights into RA pathophysiology [65,117].

4.3.3. Outcome Measures

As observational studies have propagated, standardization of rheumatology outcomes assessments spurred by groups including ACR and the International Consortium for Health Outcomes Measurement (ICHOM) can facilitate meta-analysis of clinical outcomes across practice settings [118,119]. Others, including Outcome Measures in Rheumatology (OMERACT), have sought to describe and standardize outcomes measures used in observational studies directly [120]. Given the marked heterogeneity of RA, no consensus has been reached on ideal outcome measures for the evaluation of RA, although the Clinical and Simplified Disease Activity Indices (CDAI/SDAI) and Disease Activity Score-28 (DAS28) are commonly used. Patient-reported outcome measures such as the Health Assessment Questionnaire (HAQ), Patient-Reported Outcomes Measurement Information System (PROMIS) score, and others also inform assessment by providing patient perspectives on function and disability [119]. As observational sources of data continue to develop, standardized outcomes assessments are necessary to extend clinical trial findings and inform RA management beyond conventional drug development timelines.

4.3.4. Shared Decision Making

While significant emphasis has been placed on translational breakthroughs in the management of RA, research findings should be viewed in terms of their potential to support shared decision

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making between patients and clinicians. One of the overarching principles of RA management under the T2T framework is the prioritization of patient preference in treatment decisions [10]. Management decisions must be made with respect for patients' expectations for treatment, risk tolerance for adverse events, medication burden, willingness to escalate or change therapy, and other personalized considerations. Shared decision making should continue to be prioritized under precision medicine approaches, with clinicians providing decision support to patients by helping interpret the increasingly granular data available at the point of care. This approach ensures that care is truly individualized, and that personal health information is used to inform patient choices, rather than preempt them.

5. Conclusions

In this review, we discuss several unmet needs in RA management and recent developments in precision medicine approaches to RA. Additional research is needed to develop effective strategies across the clinical spectrum, from prevention in individuals at risk of developing RA to management of longstanding and difficult-to-treat disease. While current and upcoming strategies may not sufficiently control RA for all patients, the emerging roles of neuromodulation, nanomedicines, cellular therapy, and other technologies remain under active investigation. As we mark 75 years since the Nobel Prize was awarded for the discovery of cortisone, first used for the treatment of RA, advances in biomedical science continue to offer promise for individuals living with RA whose needs are not fully met by the standard of care.

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Abbreviations

The following abbreviations are used in this manuscript:

RA	Rheumatoid arthritis
DMARD	Disease-modifying antirheumatic drug
ACR	American College of Rheumatology
TNF-a	Tumor necrosis factor-alpha
IL	Interleukin
CD20	Cluster of differentiation 20
JAK	Janus kinase
FDA	(United States) Food and Drug Administration
TTT or T2T	Treat-to-target
D2T	Difficult-to-treat
PIRRA	Persistent inflammatory refractory rheumatoid arthritis
NIRRA	Non-inflammatory refractory rheumatoid arthritis
LORA	Late-onset rheumatoid arthritis

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RS3PE	Remitting seronegative symmetrical synovitis with pitting edema
RF	Rheumatoid factor
ACPA	Anti-citrullinated protein antibody
HLA	Human leukocyte antigen
PR	Palindromic rheumatism
PTX3	Pentraxin 3
DUSP11	Dual specificity phosphatase 11
PAD4	Peptidyl arginine deiminase type 4
SS-A	Sjögren syndrome–related antigen A
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
IFN	Interferon
LYVE1	Lymphatic vessel endothelial hyaluronan receptor 1
FLS	Fibroblast-like synoviocyte
NK	Natural killer
DNMT3	DNA methyltransferase 3
TET2	Tet methylcytosine dioxygenase 2
CXCL13	C-X-C motif chemokine ligand 13
ANGPTL4	Angiopoietin-like 4
CCR5	C-C chemokine receptor type 5
CTLA4	Cytotoxic T-lymphocyte–associated protein 4
GI	Gastrointestinal
COPD	Chronic obstructive pulmonary disease
MACE	Major adverse cardiovascular events
VTE	Venous thromboembolism
ReALSA	Rheumatoid Arthritis Real-world Cohort Study in China
KURAMA	Kyoto University Rheumatoid Arthritis Management Alliance
ICHOM	International Consortium for Health Outcomes Measurement
OMERACT	Outcome Measures in Rheumatology
CDAI	Clinical Disease Activity Index
SDAI	Simplified Disease Activity Index
DAS28	Disease Activity Score-28
HAQ	Health Assessment Questionnaire
PROMIS	Patient-Reported Outcomes Measurement Information System

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