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REVIEW

Real-world evidence in rheumatic diseases: relevance and lessons learnt

Durga Prasanna Misra[1] · **Vikas Agarwal**[1]

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Abstract

An emerging trend in the medical literature, including the Rheumatology literature, is that of accumulating large, multicentric, multi-national data based on registries of patients seen in real life situations. Such real-world evidence (RWE) may help provide valuable insights into the long-term outcomes of disease in unselected patients seen in daily practice, including patients belonging to vulnerable populations such as extremes of age, during pregnancy and lactation. Evidences gathered from real life practice settings can help understand drug prescription patterns, including adherence to treatment guidelines, cost-effectiveness of therapy, and real-life long-term outcomes, and adverse effects of treatment with particular medications. Registry-based data also helps analyze comorbidities in patients with rheumatic diseases, and their impact on quality of life, morbidity and mortality. Traditionally, a randomized controlled trial (RCT), or systematic reviews of multiple, homogenous RCTs, have been considered the cornerstone of evidence-based medicine, and RWE does, at times, provide differing viewpoints from the results of particular drugs in clinical trial settings. Therefore, in the present day, it is prudent to consider the complementary nature of information derived from RWE to that obtained from rigorous, clinical trial settings. Future guidelines for disease management may consider it relevant to include information from RWE in addition to that available from clinical trials, to help devise management guidelines that are harmonious with routine practice settings.

Keywords Randomized controlled trial · Registries · Real-world data · Big data · Rheumatology

Abbreviations

AAV	ANCA-associated vasculitis
ANCA	Anti-neutrophil cytoplasmic antibody
Anti-MPO	Anti-myeloperoxidase
Anti-PR3	Anti-proteinase 3
AS	Ankylosing spondylitis
bDMARD	Biological disease-modifying antirheumatic drug
cDMARD	Conventional disease-modifying antirheumatic drug
BILAG	British Isles Lupus Assessment Group
BMI	Body mass index
DAS28-CRP	Disease activity score using 28 joints with C-reactive protein
DAS28-ESR	Disease activity score using 28 joints with erythrocyte sedimentation rate
DMARD	Disease-modifying anti-rheumatic drug
EBM	Evidence-based medicine
EMR	Electronic medical records
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis
GCA	Giant cell arteritis
GDPR	General data protection regulation
IIM	Idiopathic inflammatory myositis
ILD	Interstitial lung disease
LDA	Low disease activity
LFA-REAL	Lupus Foundation of America: rapid evaluation of activity in lupus
LTBI	Latent tuberculosis infection
MDA	Minimal disease activity
MMF	Mycophenolate mofetil
nrAxSpA	non-radiographic axial spondyloarthritis
NSAID	Non-steroidal anti-inflammatory drug
PAH	Pulmonary arterial hypertension

✉ Durga Prasanna Misra
durgapmisra@gmail.com; dpmisra@sgpgi.ac.in

Vikas Agarwal
vikasagr@yahoo.com; vikasagr@sgpgi.ac.in

[1] Department of Clinical Immunology and Rheumatology, Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow 226014, India

PET-CT	positron emission tomography computerized tomography
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
RWE	Real-world evidence
SDAI	Simplified disease activity index
SLE	Systemic lupus erythematosus
SLEDAI	Systemic lupus erythematosus disease activity index
SpA	Spondyloarthritis
TNF	Tumor necrosis factor alpha
UIP	Usual interstitial pneumonia
UK	United Kingdom
USA	United States of America
VERA	Very early rheumatoid arthritis

Introduction

In this era of evidence-based medicine, data driving healthcare and treatment decisions, including in the field of Rheumatology, is based on the literature published in this area. There are varying levels of evidence guiding decision making in therapeutics, with the highest level of evidence being a systematic review with meta-analysis of multiple randomized, controlled trials (RCT) with homogenous data. Traditionally, lesser weightage has been attributed to data derived from cohort studies [1, 2]. Information derived from RCTs and systematic reviews with meta-analyses traditionally forms the basis of the generation of management guidelines [3, 4]. Developments in the past couple of decades, such as the advent of electronic medical records, emphasis on multicentric collaborative research, and the emergence of big data, have necessitated a shift from this classical viewpoint of evidence-based medicine, with a need to maintain privacy of such data collected from routine care [5–7]. Considering the increasing amounts of real-world evidence (RWE) available in general, and specifically also in the field of Rheumatology of late, we have undertaken this narrative review to discuss the relevance of such RWE related to understanding of disease patterns as well as therapeutics, and attempt to understand the implications of this for Rheumatology practice. Insights derived from our review may help readers understand the need and relevance of RWE, as well as its complementary nature to the evidence drawn from RCT settings.

Search strategy

We adhered to a search strategy previously described for writing narrative reviews [8]. We searched the database Scopus (which includes the available data from Medline also) on the 17th of December, 2018, using the search terms "rheumatoid arthritis", "lupus", "osteoarthritis", "psoriatic arthritis", "spond*" (for articles related to spondyloarthritis), "scleroderma OR systemic sclerosis", "vasculitis" and "myositis", with the connector AND, and the terms "real world" or "real". The search results are depicted in Table 1. The titles and abstracts of these articles were screened to identify relevant articles. From this search, we excluded case reports and conference abstracts, including only original articles amongst those discussed in our review. Another search was conducted on Scopus on the 8th of January, 2019, to assess the trend of emerging registry-based data by using the same disease related search terms with the connector AND, along with "registry", restricting the search term to the abstract, title, and keywords, analysing publication numbers after 1990, and without any language restrictions. The items derived from the latter search were analyzed for the number of articles published in blocks of 5 years from 1990 onwards (1990–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2014, 2015 onwards), summarized in Fig. 1. Further general articles regarding real world evidence were identified by searching Scopus with the terms "real world evidence", "real world evidence", "electronic medical records" and "big data" on 17th December, 2018.

Table 1 Search strategy. Search conducted on Scopus on 17th December, 2018, without language restrictions

Search term		Number of results	Number of selected articles
"Rheumatoid arthritis"	AND "real world"	350	17
	AND "real"	2942	
"Spond*"	AND "real world"	93	17
	AND "real"	778	
"Psoriatic arthritis"	AND "real world"	107	
	AND "real"	316	
"Osteoarthritis"	AND "real world"	115	7
	AND "real"	2488	
"Lupus"	AND "real world"	79	7
	AND "real"	1467	
"Scleroderma OR systemic sclerosis"	AND "real world"	20	5
	AND "real"	438	
"Myositis"	AND "real world"	20	6
	AND "real"	224	
"Vasculitis"	AND "real world"	27	8
	AND "real"	488	

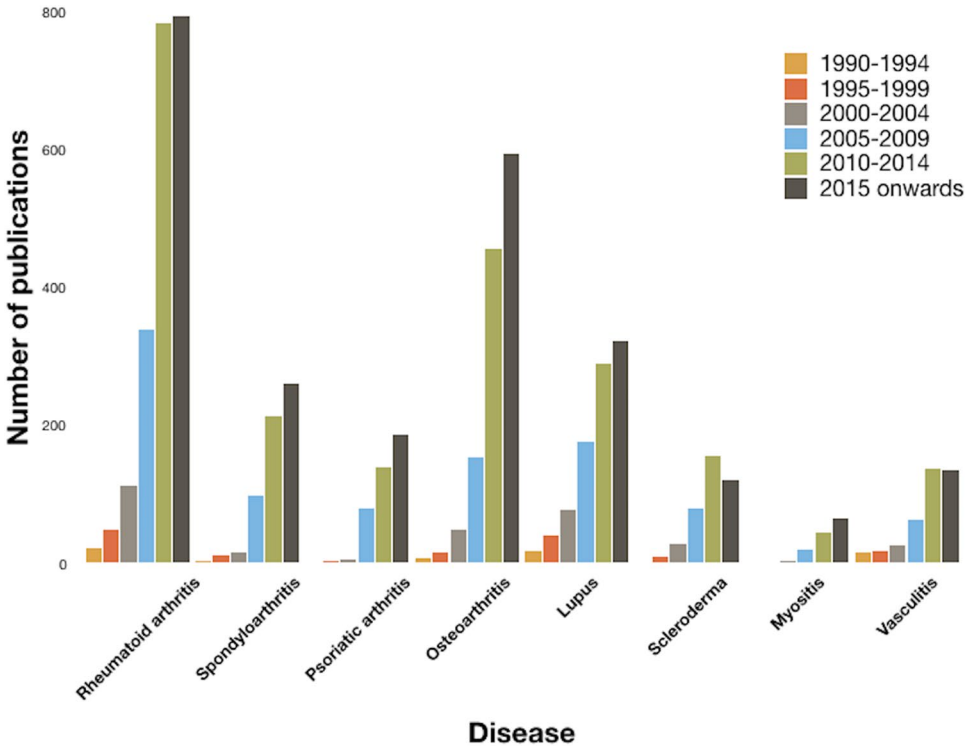

Fig. 1 Increase in the number of registry-based publication with time, derived from a Scopus search on the 8th of January, 2019

Real world evidence versus evidence from clinical trials

The comparison of RWE versus information gathered from RCTs has been exhaustively addressed in recent publications [9, 10], and is briefly discussed here. Whereas evidence derived from RCTs is given the highest weightage of all types of studies [1, 2], RWE generally is considered as a lesser form of evidence, prone to various types of bias, such as lack of complete follow up (attrition bias), recall bias (in retrospective studies), and physician bias (more severe disease may be treated more aggressively, thereby lending a possibility of better outcomes; positive findings may be recorded in notes, but not important negative findings). However, RCTs generally describe the outcomes in a relatively homogenous cohort of patients, selected to meet inclusion criteria for the particular study. An analysis of clinical trials in malignancies of the genitourinary tract revealed that an average of one-fourth patients were screened for inclusion, but eventually excluded [11]. Therefore, patients in clinical trials may not represent the entire spectrum of disease seen in clinical practice. Present standards require strict fulfillment of classification criteria for disease, in order to enroll a patient in a clinical trial. Classification criteria are inherently meant to be more specific, even at the cost of sensitivity [12], therefore, such strict requirements for fulfillment of classification criteria may again result in a proportion of patients actually seen in daily practice being excluded from clinical trials. In addition, it has been estimated that up to 20% of patients enrolled in clinical trials may not complete the follow up duration, or drop out due to adverse effects; therefore, the actual results in such patients may be missed in a per-protocol analysis of clinical trial results [13]. Information available from RWE may, therefore, provide valuable insights into such patients with a particular disease that may not either fulfill strict classification criteria, or do not fit into the particular disease pattern that clinical trials may address.

Intensive follow-up protocols in RCTs may not necessarily reflect the realities of assessment of patients in busy hospital clinics, an issue which is addressable by RWE. Apart from RWEs, the emerging concept of pragmatic clinical trials also attempts to make the setting of RCTs more akin to real-life practice settings, in an attempt to improve the generalizability of their results [14]. RCTs also generally report findings at specific, pre-defined time periods, whereas, patients in real life will continue to have the disease and its treatment for much longer periods. Real world data may better reflect cultural sensitivities in treating disease in different parts of the world, compared to the strict, protocolized nature of RCTs. Considering the mandatory requirement for informed consent to keep up to the ethical standards expected of biomedical research, it is likely that subgroups of patients that are very sick, such as those requiring intensive care, on ventilatory or other vital organ support, will not be able to provide such consent. Indeed, sometimes, patients with milder disease may also be excluded from RCTs. Patients with comorbid conditions, such as chronic renal failure or chronic liver disease, may also not find inclusion

in RCTs, due to safety concerns of drug toxicity [15]. The conduct of RCTs, and therefore, their representativeness, may be limited to centers that are experienced in conducting such clinical trials. Rarer diseases in general practice, such as single gene disorders, may not have adequate patient numbers to conduct RCTs. Therefore, such patient groups would often be excluded from clinical trials, and RWE often remains the only mechanism of gathering scientific information about disease outcomes in such scenarios. Therefore, it is prudent to consider the information derived from RCTs and RWE as complementary to each other in the present day, rather than being at the opposite poles of the ladder of evidence-based medicine (EBM) (Fig. 2) [9, 10]. Table 2 summarizes areas where RWE provides valuable insights and may have an advantage compared to RCTs. In addition, there may be a need to consider devising strategies to use data on treatment outcomes generated from RWE, in systematic reviews and meta-analyses guiding management guidelines and healthcare decisions.

Electronic medical records and "big" data

Historically, patient records were maintained on medical charts or case files by the treating physician or health care worker. Over the past 3 decades, the emergence of computers, their widespread use and availability, the advent of the world wide web, as well as government regulation in certain parts of the world has led to the advent of electronic medical records (EMR). Even EMRs have evolved over time, from storing basic demographic details, to now possessing the capability to include all patient-related information, including calculation of outcome measures from routinely collected data using pre-designed algorithms.

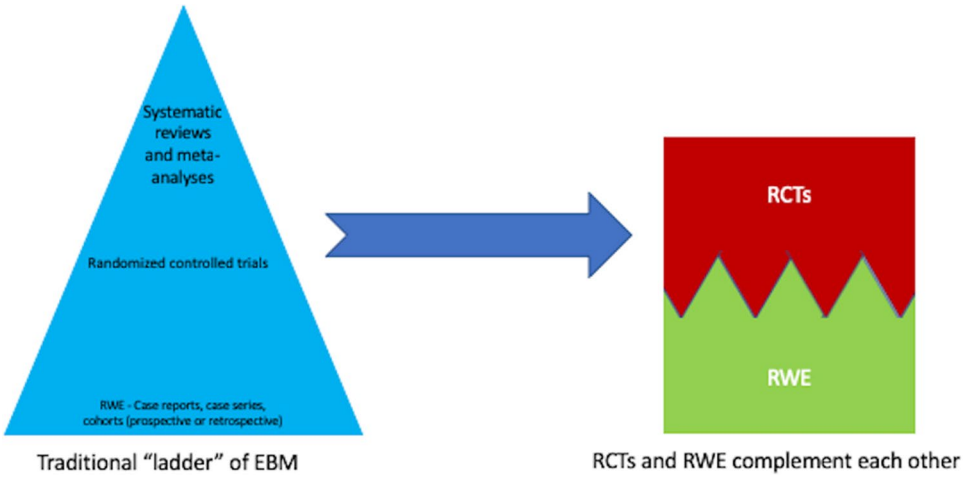

Fig. 2 Evolving concept regarding complementarity of real-world evidence (RWE) and randomized controlled trials (RCTs). *EBM* Evidence-based medicine

Table 2 Situations where RWE may be more feasible than RCTs

Disease outcomes over long duration, across countries, and ethnicities
Validation of simplified outcome measures for routine clinical use, rather than complex ones used in clinical trials
Patterns of real-life disease treatment, e.g., adherence to management guidelines, use of drugs (including biologic DMARDs)
Evolution of treatment patterns over time, and their implications
Cost effectiveness of newer drugs such as biologic or targeted synthetic DMARDs versus other drugs, or of biosimilar DMARDs versus innovator biologic DMARDs
Real-life prevalence and impact of comorbidities in rheumatic diseases
Real-life complications of drug treatment in rheumatic diseases, eg., Malignancy risk with long-term immunosuppressive therapy
Information about disease patterns and response to therapy in rarer diseases, such as some forms of systemic vasculitis, scleroderma, and idiopathic inflammatory myositis
Feasibility of translation of evidence derived from RCTs in real-life clinical practice, eg., rituximab and belimumab in lupus
Effectiveness of treatment regimens in critically sick patients in whom evidence from RCTs may not be feasible, such as patients with AAV or lupus with diffuse alveolar haemorrhage requiring ventilatory support, or in those with comorbidities such as chronic kidney disease or chronic liver failure
Effectiveness of treatment regimens in patients with disease who meet exclusion criteria for RCTs, including vulnerable patient groups such as the elderly, pregnant, or lactating patients

AAV Anti-neutrophil cytoplasmic antibody associated vasculitis, *DMARD* disease-modifying anti-rheumatic drug, *RCT* Randomized controlled trial, *RWE* Real world evidence

Present-day, large, government-sponsored insurance databases provide invaluable real-life information about disease and its outcomes. Of late, the emergence of multi-national, cross-continental collaborations, coupled with the arrival of artificial intelligence, have resulted in the generation of enormous data sets of disease characteristics and outcomes. This so-called "big data", which is essentially RWE, can be analyzed at depth to provide novel insights into real-life behavior of disease in unselected patient groups, potentially representing the entire spectrum of its actual severity [5, 6, 16–18]. The limitations of such data, including the potential lack of completeness, and the requirement of manpower to feed such vast datasets into computers, also need to be acknowledged [19]. Speaking from personal experience, EMRs are still in a rudimentary phase of their development in many lesser economically developed areas of the world.

National and trans-national collaborations by clinical scientists have led to the growth of disease registries, and these provide valuable RWE on the spectrum of disease, associated comorbidities, and response to therapy in the actual practice setting, across ethnicities and age groups. We analyzed registry data in different rheumatic diseases published over time in Scopus, and could identify an exponential increase in the numbers of such publications over the last 3 decades (Fig. 1). There exist certain inherent limitations to registry data, including the quality and completeness of data, the use of coding to identify disease in national insurance databases (instead of actual diagnoses), the potential for bias and confounding, and the ability to determine association instead of causation, which must be recognized while drawing inferences from such data [20, 21].

Privacy protection considerations for RWE

Essentially, whenever patient data is shared across centers, there is a need to anonymize such data, so that the individual patient's personal details are not compromised. Furthermore, there is a need to seek informed consent of the individual patient before sharing such data. Existing [22] and recently implemented [7, 23] regulations regarding patient privacy merit discussion in this context. The General Data Protection Regulation (GPDR), which came into force a few months back, takes additional steps for the protection of the privacy of data of individuals, and prescribes measures wherein individuals can choose to withdraw their personal data from databases into which these have already been entered. These regulations have introduced an additional layer of complexity to the sharing of patient and registry data, wherein they recommend the need for explicit individual consent before such data is stored, as well as provide the onus for regulating the use of such data with the government. They also provision for the use of such data for the general advancement of society, including research for the greater benefit of society as a whole [7, 23]. Evolving registries and databases of patient health records should keep in mind such recent international regulations for the protection of privacy of the concerned individuals.

RWE in rheumatic diseases

In this section, we shall discuss some lessons that can be drawn from RWE in different major rheumatic diseases.

Insights from RWE in rheumatoid arthritis

Rheumatoid arthritis (RA) is the most common form of inflammatory arthritis seen in the clinic. Recent RWE evidence of large cohorts, mostly registry based, has helped enhance the understanding of intermediate and long-term outcomes in RA and their predictors. While traditionally cut-offs for disease activity score using 28 joints with erythrocyte sedimentation rate (DAS28-ESR) or C-reactive protein (DAS28-CRP) for low disease activity (LDA) and remission at taken as 2.6 and 3.2, a recent real-life analysis of 562 patients with RA from Italy proposed cutoffs of 2.4 for remission and 2.9 for LDA for DAS28-CRP, to have better concordance with DAS28-ESR [24]. A study of 538 patients with RA followed up over 12 years, showed that up to a fifth of such patients may never attain a state of low disease activity [25]. An analysis of a Norwegian registry of 1610 patients with RA revealed that the Simplified Disease Activity Index (SDAI) scored at 3 months could predict remission at 6 months, and those who were unable to attain SDAI remission at 3 months were unlikely to do so at 6 months also, suggesting the need for earlier intervention to reduce disease activity further at 3 months [26]. Another study of 711 Italian patients with RA identified early diagnosis (within 12 weeks of onset, i.e., very early RA or VERA), and institution of disease-modifying anti-rheumatic drugs (DMARDs) by 3 months of disease, predicted attainment of remission at 12 months. Also, those with VERA attaining disease remission had lesser associated costs, due to a two-third reduction in the use of anti-tumor necrosis factor alpha (anti-TNF) agents, compared to the rest of RA patients in remission [27].

The role of ultrasonography in the management of inflammatory arthritis, including RA, is an emerging area of interest, and real-world data has helped us understand this better. A recent study from Europe analyzed found the wrist or meta-carpophalangeal joints to be the most commonly scanned (> 60%), followed by the knee in a fourth, and the proximal interphalangeal joints in a fifth in daily clinical practice in 200 patients with RA. Such insights may help decision making in development of practice guidelines for

the use of ultrasound in clinical care of RA patients [28]. While a recent RCT (ARCTIC study) showed that attainment of ultrasonographic remission in RA, as opposed to clinical control of disease activity was associated with similar disease outcomes at 2 years, with increased biologic DMARD use if ultrasound synovitis was targeted [29], a recent real world study provided interesting complementary results. In this Swiss cohort of 318 patients with RA in remission (with 378 periods of remission during the study duration), the presence of ultrasonographic synovitis portended a higher risk of disease flare, and a shorter duration of sustenance of remission [30]. Thus, there may be a need to generate more real-world data before rejecting the role of ultrasound in assessment of remission in RA patients on treatment. In real-life also, ultrasonographic synovitis influences clinical treatment decisions on intensification of therapy in RA [31].

Large cohorts of real-world RA patients have also helped understand patterns of prescription and response to biological DMARDs (bDMARDs). A multicentric study of 802 RA patients from China treated with bDMARDs, showed that addition of a conventional synthetic DMARD to bDMARD was associated with lower disease activity, and those able to continue bDMARD for more than 12 months had greater proportions of LDA or remission, compared to those receiving the drug for less than 12 months [32]. An Italian study of 725 RA patients treated with bDMARDs over 16 years revealed a greater proportion of patients treated with bDMARDs in the first 2 years of disease, with bDMARD initiated at moderate disease activity (rather than high disease activity), in recent years compared to the period of study inception, reflecting a trend towards earlier use of bDMARDs in an attempt to control disease activity [33]. A study of 307 RA patients from Colombia showed similar responses at 3 years, irrespective of which anti-TNF agent was used; however, etanercept had lesser associated adverse events [34]. An analysis of multicentric data of 1910 patients with RA from Italy attempted to understand factors associated with prescription of bDMARDs. The investigators reported that those with greater age were more likely to be started on abatacept or tocilizumab rather than anti-TNF agents. Previous adverse events with bDMARD, prior latent tuberculosis infection (LTBI), or presence of comorbidities were associated with preference for abatacept, whereas, higher disease activity was associated with tocilizumab usage [35]. A recent systematic review of more than 20,000 patients with RA treated with anti-TNF agents from 27 different registry-based publications confirmed a decrease in mortality, and of incident cardiovascular events, an increase in the rate of infections, and no increased risk of developing malignancy, either de novo, or in those with a prior history of malignancy [36]. Registry-based data showed nearly 40% persistence of adalimumab use in 1695 RA patients at 3 years [37]. A report of 234 patients with RA treated with rituximab from Greece, followed up over a median of 27 months, reported continuation of the drug in 57%, with a greater risk of adverse events if the patients were elderly [38].

Real-world data on the use of biosimilar drugs in RA is also emerging. Two recent studies revealed real-life effectiveness of adalimumab [39] and infliximab biosimilar in RA and spondyloarthropathy (SpA) patients [40]. A recent French study reported retention in nearly three-fourth of 89 patients with RA, ankylosing spondylitis (AS) or psoriatic arthritis (PsA) switched over to infliximab biosimilar from the innovator molecule, at 33 weeks. A significant proportion of those switching back to the innovator molecule did so due to patient preference, rather than due to objective deterioration of disease activity [41]. With greater use of these drugs becoming more prevalent today, there is expected to be an increase in the available real world and registry data on the use of biosimilars in the next few years. Table 3 summarizes lessons learnt from RWE in RA.

Insights from RWE in spondyloarthritis and psoriatic arthritis

Spondyloarthropathies, including AS and PsA, are inflammatory arthritides also commonly encountered in clinical practice. Emerging data from registries of large number of patients has helped understand the long-term behavior of this group of diseases, and their subsets. Recently, a subset of axial SpA, who may not have radiographic features, i.e., non-radiographic axial SpA (nrAxSpA), has been identified. Registry data from a North American cohort compared 310 patients with AS with 97 nrAxSpa patients, and revealed that although the latter group had a younger age at diagnosis, the parameters of disease activity, functionality and quality of life were essentially similar in both groups [42].

Real-world data also helped better understand extra-articular features, comorbidities and outcomes in SpA. A study of 1250 patients with AS revealed an increased risk of developing inflammatory bowel disease by 20%, and of developing acute anterior uveitis by 30%, every 10 years [43]. One hundred and seven patients with axial SpA from a Danish cohort with stable disease activity over two separate visits 4 months apart, demonstrated fluctuations of pain, fatigue and patient global assessment, suggesting that these factors may need to be separately addressed in daily practice, apart from just assessing the disease activity status [44]. A cross-sectional analysis of 789 axial SpA patients from a registry in Korea revealed association of greater body mass index (BMI) with a higher prevalence of syndesmophytes in the spine, despite no obvious association of BMI with disease activity status [45]. Another analysis of 946 AS patients from Scotland with a mean duration of disease of 16 years, revealed worse disease outcomes in those who were current

Table 3 Lessons from real-world evidence in rheumatoid arthritis

Domain	Lesson learnt
Disease activity assessment	Potential to consider different cut-offs for DAS28-ESR and DAS28-CRP for LDA and remission [24]
	About 20% RA patients never attain LDA [25]
	Earlier attainment of remission, and early treatment institution, portend favourable longer term outcomes and less costs [26, 27]
Ultrasonography in clinical practice	Wrist and metacarpophalangeal joints most often scanned in clinical practice [28]
	Ultrasonographic synovitis may influence real-life clinical decision making on treatment intensification [31]
	Persistence of ultrasonographic diagnosis may predict earlier loss of disease activity control [30]
Real world use of bDMARDs	Lower disease activity when bDMARD combined with cDMARD (rather than bDMARD alone), and in those receiving bDMARD for longer duration [32]
	Similar effectiveness of different anti-TNF agents [34]
	Factors associated with individual bDMARD preferences [35]
	Long-term safety of anti-TNF agents [36]
	Persistence rates with different bDMARDs in real life [37, 38]
Use of biosimilars	Effectiveness of biosimilars in clinical practice [39, 40]
	Retention rates of biosimilars in clinical practice [41]

bDMARD Biological disease-modifying antirheumatic drug, *cDMARD* Conventional disease-modifying antirheumatic drug, *DAS28-CRP* disease activity score using 28 joints with C-reactive protein, *DAS28-ESR* disease activity score using 28 joints with erythrocyte sedimentation rate, *LDA* Low disease activity, *RA* Rheumatoid arthritis, *TNF* Tumor necrosis factor alpha

or ex-smokers. Those who had ever smoked had worse disease activity, functional status and quality of life; those who had stopped smoking had lower disease activity and better quality of life than current smokers [46].

A United Kingdom (UK) registry of more than 1500 axial SpA patients on bDMARDs identified the presence of fibromyalgia in nearly a fifth of such subjects. Those with fibromyalgia were more likely to have worse disease activity, and worse quality of life; hence, it may be essential to address and treat the fibromyalgia separately in such individuals [47]. An insurance database analysis of more than 180,000 patients with PsA from the USA, identified comorbidities in about a half of such patients, including those associated with cardiovascular morbidity (diabetes, hypertension, dyslipidemia), fibromyalgia, and depression, suggesting a need to carefully identify and address such comorbid conditions in these individuals in daily practice [48]. Recently, a clinical trial in PsA introduced the concept of treat-to-target in PsA, with description of a target of minimal disease activity (MDA), which considers low disease activity in seven domains, including the skin, joints, entheses, and extent of disability [49]. This MDA index was recently validated in a real-life scenario, wherein 223 PsA patients in a Canadian registry, who were on anti-TNF agents, were analyzed for attainment of MDA. About one-half attained MDA at 1 year; lower disability, and a lesser number of tender joints at baseline, predicted attainment of MDA [50].

Registry-based data has also helped understand the therapeutics of SpA and PsA better, especially with the increasing use of bDMARDs in these conditions. A Canadian database of 467 patients receiving anti-TNF agents (about a third with SpA or PsA, remaining had RA) identified the number needed to treat to attain a minimal clinically significant difference in the health assessment questionnaire of 0.2, as approximately 2 in each disease [51]. Five Scandinavian databases of a total of more than 4000 AS patients, analyzed from 2010 to 2016, revealed increasing number of patients on bDMARDs during this period. However, the baseline disease severity at which bDMARD was started differed from country to country, reflecting a need for greater uniformity in treatment guidelines for AS followed in these countries [52]. Real life data has also enhanced understanding of retention rates of bDMARDs used over time. In a registry of 97 AS and 41 PsA patients from Thailand, nearly 60% retained the anti-TNF agent they were initiated on at 3 years follow-up [53]. A UK-based cohort of 125 patients with AS and 83 patients with PsA on anti-TNF agents identified 48 patients with disease stable enough to attempt dose reduction. About 60% of such patients could successfully reduce the dose of the drug by a third over the next 1 year [54]. With the advent of interleukin-17 targeted therapies in AS, real-life data from a Finnish database of more than 2600 patients with AS revealed nearly one-fourth reduction in costs of therapy with secukinumab compared to adalimumab [55].

The advent of biosimilars and their increasing use in SpA and PsA also needs analysis in the real world. A recent Italian real-life series of 41 patients with SpA, who were switched to infliximab biosimilar, revealed similar stable disease activity at 6 months of the switch of drug, with no increase in adverse events compared to the innovator

molecule [56]. Another large database of 2061 patients in a Danish registry (including more than 800 patients with SpA or PsA), of whom 79% were switched to etanercept biosimilar, revealed nearly 80% drug retention rate at 1 year, irrespective of whether the innovator molecule or biosimilar was used, with no objective evidence of any difference in control of disease activity [57].

Patients treated with bDMARDs are at increased risk of opportunistic infections, including tuberculosis. Recent real-life data from Taiwan, including more than 12,000 patient-years of drug exposure, has shown increased risk of developing tuberculosis with adalimumab compared to etanercept [58]. A recent real-life experience of more than 730 patients (400 SpA) from India (a high endemic zone for tuberculosis) treated with bDMARDs utilized a screening technique for LTBI with augmented tuberculin testing with ten tuberculin units, along with interferon gamma release assay, and reported LTBI in 37% patients, who were then treated with anti-tubercular drugs before instituting bDMARD. The authors compared these patients to a large cohort of 2930 patients not treated with bDMARDs, and reported a similar incidence of clinical tuberculosis infection (about 0.7%) in both groups, suggesting the effectiveness of this screening strategy to minimize the incidence of tuberculosis despite bDMARD use [59]. Thus, RWE has provided valuable insights into actual disease and treatment-related issues in SpA and PsA.

Insights from RWE in osteoarthritis

Osteoarthritis is the commonest form of arthritis seen in daily practice. Real world data of nearly 1200 patients with knee osteoarthritis suggested lack of adequate pain relief in greater than one-half of patients [60]. In this context, it is relevant to discuss a recent treatment recommendation from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) for the management of knee osteoarthritis. These recommendations have considered both RCT evidence, as well as RWE, before putting forth their recommendations. The ESCEO osteoarthritis guidelines suggest initial therapy with a potential disease-modifying agent, such as chondroitin sulfate or glucosamine, singly or in combination. While RCT evidence for the use of these agents is equivocal or negative, real life studies have shown some efficacy with respect to improvement of pain and function with the crystalline form of chondroitin sulfate. In addition, registry data from the Osteoarthritis Initiative in the USA demonstrated the potential for retardation of cartilage loss with either chondroitin sulfate alone, or with a combination of glucosamine and chondroitin sulfate. These guidelines further recommend the use of topical non-steroidal anti-inflammatory drugs (NSAIDs) should the above drugs fail, with the use of oral NSAIDs reserved for use for the shortest duration, and in the smallest dose feasible, while addressing prevalent cardiovascular and gastrointestinal risk factors. In those with a predisposition towards, or history of cardiovascular events, naproxen may be relatively safe, due to its property to inhibit cyclooxygenase 1 in preference to cyclooxygenase 2, coupled with its longer half-life in comparison to other NSAIDs, resulting in inhibition of platelet aggregation, an event which is favourable from the viewpoint of atherothrombotic events [61]. Alongside NSAID use, concomitant gastroprotective measures should be followed. Further, intra-articular viscosupplementation, although equivocal in RCTs, may have some role in symptomatic relief, based on RWE. Sustained release opiates are reserved for those with intractable pain [62–66].

Surgical replacement of the joint with osteoarthritis (commonly, the knee or the hip) is recommended if intractable pain persists despite conventional measures (including pharmacotherapy and physical therapy), or if there is severe functional limitation, restriction of mobility, or presence of significant deformities [67–69]. Little importance is recommended to be given to the actual severity of cartilage loss, without considering the symptomatology of patients. However, a recent real-life study provided evidence of actual medical practice being contrary to this. In this study, the decision-making process of orthopedic surgeons regarding more than 500 patients with hip osteoarthritis was analyzed. It was surprising that one of the major factors determining the need for surgery was the extent of radiographic cartilage loss [70]. This is an example of RWE providing insights into how to improve the prevailing standards of medical care.

Insights from RWE in systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a common autoimmune disease seen in the clinic. A recent study revealed the effectiveness of a simple disease activity scoring system, the Lupus Foundation of America—Rapid Evaluation of Activity in Lupus (LFA-REAL), when compared with established measures often used on clinical trials, such as the British Isles Lupus Assessment Group (BILAG) index, and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). The LFA-REAL utilizes a physician global assessment overall as well as in seven different domains, to provide a composite score. In 99 patients with lupus seen in routine clinical practice, the LFA-REAL scores correlated well with BILAG and SLEDAI scores, and showed acceptable intra-observer and inter-observer variation, therefore, was a reasonable alternative to more extensive disease activity scores for use in routine lupus care [71]. Registry data from a multinational lupus registry of 1227 patients revealed that physicians could potentially erroneously label patients with lupus as being in remission, when in fact their disease was active. The study revealed that patients with features

such as arthralgias, arthritis, fatigue, and even hematological and renal abnormalities had been erroneously labelled as having inactive disease. Therefore, such RWE suggested the need for treating physicians to demonstrate greater vigilance before labelling lupus patients in daily clinical practice as being in "remission" [72].

Interesting divergence between RCTs and RWE has been demonstrated in patients with lupus, and their response to B cell targeted therapies. The emergence of rituximab was met with much enthusiasm, however, two randomized controlled trials, the LUNAR trial [73] and the EXPLORER trial [74], which included patients with moderately to severely active disease, failed to show additional benefit of rituximab when compared with placebo. Both these studies were limited by the fact that they had high levels of background immunosuppression, with mycophenolate mofetil (MMF) in the LUNAR trial [73], and about a third each being on azathioprine, MMF, or methotrexate in the EXPLORER trial [74], along with corticosteroids. Hence, an additional benefit could not be demonstrated with rituximab versus placebo. This is in stark contrast to real-world data, wherein two large longitudinal studies of rituximab use in refractory lupus demonstrated a partial or complete response in greater than three-fourths of 128 patients at a mean of 20 months, and in greater than 80% of 134 patients over a mean follow-up of 27 months [75, 76]. Therefore, in clinical practice, rituximab continues to be used as an option in refractory lupus. This is quite contrary to the status of belimumab, another agent that targets B lymphocytes. This drug was proven to be effective in controlling disease activity in lupus based on RCTs, however, these were limited by not including patients with severe renal or central nervous system disease [77–79]. In this instance, RWE was helpful in reiterating the efficacy of belimumab in active systemic lupus [80, 81]. Despite favourable evidences for belimumab, it has yet to fascinate clinicians as much in day-to-day clinical practice, and more real-world data on its use may help better delineate its role. Emerging RWE suggests that a strategy of combining belimumab with rituximab may hold promise in refractory lupus [82].

Insights from RWE in scleroderma

Scleroderma or systemic sclerosis is an uncommon autoimmune disease, and recently published registry-based data have greatly enhanced our understanding of the course of this disease. An analysis of more than 1600 patients with scleroderma in a multicentric Spanish registry revealed that those with a non-Raynaud's symptom at onset had worse survival over long-term follow up (up to 30 years), compared to those with Raynaud's phenomenon as a first symptom. Further, the investigators identified male gender, diffuse scleroderma, and major organ involvement, such as interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), renal or cardiac involvement at initial presentation, as factors predisposing to higher risk of mortality in these patients [83]. Another Spanish registry of nearly 1400 scleroderma patients revealed ILD in 43%, and this was a major predictor of adverse outcomes in diffuse scleroderma, as opposed to PAH in limited scleroderma [84]. Data of 160 patients from a North American database of scleroderma with PAH showed nearly 50% mortality at 8 years, with the degree of PAH, and the limitation of functionality due to PAH, being predictors of a worse eventual outcome [85]. A multicentric European registry of 342 patients with scleroderma-associated renal involvement revealed that, whereas they had a greater chance of becoming dialysis-independent when compared with patients with renal involvement of other etiologies, they also had a greater risk of death once they had been initiated on dialysis. The same registry data showed similar results post-renal transplantation in those with renal failure due to scleroderma or with other etiologies [86]. Another analysis of greater than 9000 in-patient admissions in patients with scleroderma from a North American database revealed infections, acute kidney injury, and aspiration to be associated with a greater risk of mortality [87]. Such information on large numbers of scleroderma patients, including those with rarer manifestations such as renal involvement, was scarce before the advent of multicentric registries.

Insights from RWE in idiopathic inflammatory myositis

The idiopathic inflammatory myositis (IIM) are another rare group of diseases, and registry-based data had helped us understand them better. Data of more than 3000 patients from a European multicentric registry revealed ILD in nearly a third, and malignancy in nearly a seventh of such patients. Smoking was associated with more severe systemic manifestations of ILD, malignancy, and cardiac involvement in such individuals [88]. Two recent analyses of 370 Australian patients and 479 Spanish patients with inflammatory myositis enrolled in multicentric national registries revealed infections, neoplasia, and cardiovascular events as factors associated with a greater risk of mortality [89, 90]. A registry-based analysis of 81 patients with usual interstitial pneumonia (UIP) pattern of ILD with idiopathic pulmonary fibrosis, compared to 43 patients with UIP associated with IIM, revealed greater probability of long-term survival in those with IIM [91]. Real life data has also shown intriguing comparisons with clinical trial data in IIM. In a large multicentric trial of rituximab in refractory inflammatory myositis, there were no demonstrable differences between the two groups, randomized to receive rituximab either at trial initiation or a month after trial initiation. This might

have been due to the high baseline level of immunosuppression with corticosteroids in both groups. However, a deeper analysis of the data showed that greater than 80% patients had overall improvement [92]. In real life studies too, rituximab was found to be an effective agent with demonstrable clinical improvement in refractory IIM [93, 94]. Thus, RWE has provided valuable information on long term outcomes and real-life improvements in refractory IIM.

Insights from RWE in vasculitis

Recent literature derived from real world studies has significantly enriched our understanding of systemic vasculitis. Giant Cell Arteritis (GCA) is one of the commonest forms of large vessel vasculitis seen in clinical practice. A real life studied demonstrated the potential non-invasive role of positron emission tomography computerized tomography (PET-CT) in diagnosing GCA, when compared with temporal artery biopsies [95]. Generally, there is an excellent response to corticosteroids in a majority of patients with GCA. However, two recent analyses of 2497 patients and 8777 patients with GCA enrolled in health care databases demonstrated a higher risk of developing adverse events, such as diabetes, hypertension, cataract, and osteoporosis, in patients with GCA receiving corticosteroids, with a dose-dependent increase in such adverse effects [96, 97]. These findings reiterated the need for seeking corticosteroid-sparing or reducing regimens in such patients [96, 97]. Another real life study reiterated the effectiveness of tocilizumab as a steroid-sparing treatment in GCA [98], complementing the information available from RCTs [99].

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a devastating, yet relatively rare condition. Recent RWE has enriched our understanding of this disease and its treatment. A comparison of 437 AAV patients in cohort studies with 657 in clinical trials reported that those enrolled in trials were older, had more severe disease (including more severe renal impairment), and lesser upper airway involvement. Those with granulomatosis with polyangiitis, but not microscopic polyangiitis in clinical trials had greater risk of disease relapse, and more likely to die than patients in cohort studies [100]. An analysis of greater than 14,000 results on ANCA in a single laboratory revealed borderline positivity for either antibodies to proteinase 3 (anti-PR3) or myeloperoxidase (anti-MPO) in 137 patients. However, it was concerning that even these patients with borderline ANCA positivity had a higher rate of developing renal failure on long-term follow-up, suggesting the need for continued surveillance [101]. Another Canadian database analysis of nearly 3000 patients with glomerulonephritis requiring immunosuppression, including nearly 350 patients with AAV, reflected the changing practice over the past 3 decades, with a significant increase in both the cost as well as the use of immunosuppressive therapy during this period [102]. An analysis of an American database of nearly 2800 patients with AAV followed up over 12 months revealed that nearly a fifth experienced disease flares in this period, and there were significantly increased costs in those individuals with disease flares compared to without [103].

Conclusion

Real world data has provided insights into the actual behavior of rheumatic diseases in the clinic, at times varying from that seen in RCTs. Present-day guidelines for the management of rheumatic and other diseases greatly prioritize the evidence from RCTs compared to other forms of evidence, including RWE. However, there may be a need to modify such guidelines in the future to also consider real-life evidence in the published literature, in order to improve the acceptability and applicability of such guidelines for clinical care. In addition, it may be prudent to consider the feasibility of using information derived from RWE in systematic reviews guiding healthcare management decisions.

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Compliance with ethical standards

Conflict of interest Durga Prasanna Misra declares that he has no conflict of interest. Vikas Agarwal declares that he has no conflict of interest.

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