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Review Article

Residual symptoms: Unmet needs for rheumatoid arthritis patients who achieved low clinical disease activity

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Abstract

Despite the advance in the treatment of rheumatoid arthritis (RA), a proportion of patients suffer from residual symptoms such as pain and functional disability, even after they achieve inflammatory remission or low disease activity (LDA), which is defined as criteria of difficult-to-RA. This review summarizes current knowledge on frequency, possible pathogenesis, risk factors, and treatment options of remaining pain/functional disability among patients in inflammatory remission or LDA to highlight the complexity and difficulty in managing this condition. As an increased number of patients are achieving clinical remission, the residual symptoms will become one of the most significant unmet needs in the treatment of RA.

Keywords: Rheumatoid arthritis, Low disease activity, Inflammatory remission, Pain

Introduction

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases characterized by inflammatory arthritis that may lead to destruction of bone and cartilage. While the primary manifestation of RA is swollen and tender joints, it is often associated with multiple coexisting conditions such as fibromyalgia, fatigue, and malaise. Recent advancement in the treatment of RA realized remission of inflammation in many patients and even more, structural remission in some cases [1,2].

Despite this progress, therapies for RA still seem to fall short of achieving sufficient patients' satisfaction levels. According to a web-based cross-sectional survey of RA patients who were enrolled in a patient research registry (Arthritis Power®) in the United States of America (USA), among adult RA patients with a history of ≥1 disease-modifying antirheumatic drugs (DMARDs) failure who continue their current DMARD(s) for ≥6 months, only 26% of the patients were satisfied with the treatment defined as treatment satisfaction questionnaire for medication (TSQM) global satisfaction score ≥8 [3]. TSQM consists of 11 questions and provides a validated score for effectiveness, side effects, convenience, and global satisfaction of the treatment [4]. Treatment satisfaction was measured using a cut-point of >8, which has been shown in past studies to be correlated with high medication adherence [5]. The patients who were unsatisfied with the current treatment were more likely to complain residual symptoms such as fatigue, sleep disturbance, and pain than those who were satisfied with the treatment. Another study showed increased pain without swollen joints led to a discrepancy toward worse patient perception than evaluator perception [6].

Such discrepancies between clinical indicators and subjective symptoms are observed even among patients who achieved remission [7] or low disease activity (LDA) [8,9] according to clinical indicators.

Clinical remission is defined as Simplified Disease Activity Index (SDAI) ≤3.3, Clinical Disease Activity Index (CDAI) ≤2.2 [10,11] or fulfilling Boolean-based definition [12]. LDA is defined as Disease Activity Score (DAS) <3.2 [13], 3.3 < SDAI ≤11, and 2.2 < CDAI ≤10 [10,11].

In a multicenter observational study in Japan, among 464 RA patients in SDAI remission or LDA, 35% showed moderate or high disease activity (M/HDA) by patient reported outcome (PRO) measured by RAPID3 [8]. Another study targeting 93 RA patients in Italy showed that about one fourth of patients in LDA and up to one fifth of patients in remission had residual functional impairment with a Health Assessment Questionnaire (HAQ) >0.5 [9]. A systematic review found that residual symptoms are observed in some patients despite their achieving LDA or remission, highlighting an unmet need in RA treatment [14].

This review summarizes the current understanding of residual pain and functional disability among RA patients who achieved clinical remission or LDA to highlight the importance and complexity of this unmet need.

Functional Disability and Pain among Patients Who Achieved LDA

Residual pain

Frequency in residual pain in patients with remission or LDA: Residual pain is not rare even among RA patients who achieved remission or LDA indicated by clinical indicators such as CDAI and DAS-28 [15].

Previous researches reported that the frequency of residual pain among the patients with LDA is 12.5 - 60% [16,17]. A multi-center study in Belgium targeting early RA patients revealed that about a fifth of the patients who achieved clinical remission, defined by DAS-28CRP (<2.6) complained fatigue or pain after a year of the treatment [18]. In another study, 29% of early RA patients who exhibit a good response according to the definition by the European Alliance of Associations for Rheumatology (EULAR) [19]. As a result, pain levels remained significantly higher than that of healthy controls even among patients who achieved clinical remission [20].

The incidence of residual pain in patients in remission or LDA varies depending on the definition used. A study that measured clinical remission by DAS28-CRP (<2.6) reported 11.8% of the patients who achieved the remission showed MD-HAQ pain ≥4 (of 10) [16]. However, the same researcher reported that none of the patients who achieved remission by American College of Rheumatology (ACR)/EULAR Boolean criteria [≤1 swollen joint; ≤1 tender joint; CRP ≤1 mg/dL, and patient global assessment score ≤1 (of 10)] showed residual pain [16]. Another study reported that 5% of those in clinical remission according to the ACR/EULAR Boolean criteria showed pain Visual Analogue Scale (VAS) ≥30 mm [21].

Our multi-center inception cohort study targeted RA patients who initiated biological/targeted-synthetic disease modifying antirheumatic drug (b/tsDMARD) [22] also showed that among those who achieved clinical LDA by CDAI (≤ 10) within 6 months, only 38% showed significant reduction in pain VAS (≥ 40 mm). Ad-hoc analysis using the same database revealed that among those who achieved clinical remission (CDAI ≤2.8), proportion of pain VAS remission (≤30 mm) [23] was limited to 74%. In addition, among the patients who exhibited pain VAS ≥40 mm at the start of the treatment, 19% failed to show significant pain VAS reduction (≥40 mm). These results suggest about 20~25% of the patients in clinical remission still exhibit some residual pain (unpublished data).

Possible pathogenesis of residual pain: Mechanisms of pain in RA are complex and multifactorial, including inflammation, peripheral and central pain processing, and structural change within the joint [24-26]. Therefore, residual pain after achieving LDA or remission is closely related, but not fully dependent on residual inflammation. An analysis of an early RA cohort showed 64% of participants at the time of their first pain flare [worsening ≥4.8 points of non-normed 36-item short form of the Medical Outcome Study Questionnaire- body pain (SF36-BP) between consecutive measurements] did not concurrently fulfil criteria for a DAS28 flare (an increase in DAS28 ≥1.2; or an increase ≥0.6 if the first of the paired visits had DAS28 ≤3.2 between consecutive study visits) [27]. Other researchers reported the presence of histopathological synovitis in RA patients with remission was not associated with a higher pain VAS [28].

Pain without apparent synovitis is partly caused by direct interaction between proinflammatory cytokines with nociceptors like Aδ and C fibers. Cytokines like tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1β, chemokine, nerve growth factor and prostaglandin are reported to reduce the threshold of nociceptive neurons to the stimulation and thus cause chronic pain [29,30]. Other cytokines, including interferon (IFN)-γ, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-15, IL-17, IL-18 positively mediate pain through the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, while IL-4, IL-10 act as anti-nociceptive cytokine [31]. Cytokines also act directly on the central nerve system (CNS). Recent findings suggest that proinflammatory cytokines including IL-6, IFN-γ, IL-1β, TNF-α affect astrocytes and CNS-associated myeloid cells and ultimately cause neuroplastic pains [31-33].

In addition to inflammatory pain, RA patients sometimes show neuropathic pain (NP). NP often presents as secondary symptoms as a result of long-term or intensive inflammation, but it also occurs without inflammation or joint destruction [34], which is observed in about 20% of RA patient [35]. The causes of such NP include entrapment neuropathy (e.g. carpal canal syndrome), spinal cord compression (e.g. cervical spine disorders due to atlantoaxial dislocation), peripheral cord neuropathy (e.g. amyloidosis), and small-fiber neuropathy (e.g. neuropathy in Sjögren syndrome) [36].

On top of all that, nociplastic pain, hypersensitivity of neurons, is now attracting attention of physicians. Nociplastic pain is recently defined as 'pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain' [37]. Although the precise pathology is still to be elucidated, such pain is related to a variety of comorbidities like fibromyalgia, osteoarthritis, postoperative pain, and visceral pain hypersensitivity disorder [36].

Risk factors of residual pain: There are limited reports that describe direct risk factors of residual pain. In a 1-year follow-up of RA patients who achieved DAS-28 remission, higher Multi-Dimensional HAQ (MDHAQ) at 1 year was associated with patient global assessment, MDHAQ function, MDHAQ fatigue, MDHAQ

sleep, and arthritis self-efficacy [16]. Another study targeting early RA patients reported higher HAQ at baseline is associated with remaining pain in spite of a EULAR good response [19]. Comparison of RA patients with healthy controls identified several factors that are associated with a higher level of pain in RA, which include older age, longer disease duration, female sex, higher heat distribution index (HDI), continent (highest in Africa, lowest in Asia), and ethnicity (highest in native Americans and lowest in Asians), higher fatigue, poorer function, psychiatric comorbidity, basic multimorbidity, patients global physical and mental health [20]. Fibromyalgia among early RA patients were associated with pain at baseline and poor mental health [38].

Our previous study [22] identified age ≥80 years old compared with 20-29 years old, past history of fracture, failure of ≥2 classes of b/tsDMARDs, use of glucocorticoid, higher pain VAS and lower HAQ-disability index (HAQ-DI) at baseline as risk factors of less improvement in pain VAS within 6 months of the treatment, though this does not directly show VAS remission.

Interestingly, positivity of anti-citrullinated peptide antibody (ACPA) and rheumatoid factor (RF) seem to be a beneficial factor for fibromyalgia [38] and residual pain [22]. One possibility is that seropositive patients might be diagnosed as RA earlier than seronegative ones and thus more likely to receive intensive treatment in the early stage of the disease. However, further research is required to identify the underlying causes.

Treatments of residual pain: As proinflammatory cytokines directly act on peripheral and central nerves, direct inhibition of these cytokines such as TNF-α and IL-6 is expected to reduce nociplastic pains [32,39-41]. Especially, blocking IL-6 and JAK/STAT pathway is a promising treatment option. A recent study showed the effectiveness of anti-IL-6 antibody on disproportional pain [32] and unacceptable pain [39,40] among RA patients. Another study showed effectiveness of JAK inhibitor on residual pain of RA patients who achieved LDA [41]. Our study [22] also showed the use of JAK inhibitor significantly associated with reduction in pain VAS compared with TNF inhibitors. Even so, mechanisms of pain modulation are not sufficiently elucidated, and it is not clear whether it is reasonable to switch DMARDs of patients in remission just because of residual pain [42]. The current findings of residual pain are summarized in **Table 1**.

Functional disability

Frequency of functional disability in patients with remission or LDA: There is an accumulating evidence on the discrepancy between inflammatory remission or LDA either by clinical indicators [9] or ultrasonography [43] and functional improvement. Similar to residual pain, the incidence of functional disability in patients in remission or LDA varies depending on the definition used. A study found that 3% of the patients who achieved Boolean remission showed modified HAQ (mHAQ) >0.5 [21], while another study using SDAI reported 15% of the patients who achieved remission or LDA were categorized as moderate disease activity (MDA) or high disease activity (HDA) by Routine Assessment of Patient Index Data 3 (RAPID3) [8]. The proportion of functional disability increases with age, and thus a study targeting elderly RA patients showed 18% of patients at the age of ≥75 year old were HAQ >0.5 despite inflammatory remission by CDAI [44].

Table 1. Summary of current insights into residual pain.

Aspects	Findings	
Frequency	Literature review	Ad-hoc analysis of our inception cohort
	• 11-20% of patients in clinical remission by DAS-28CRP • 29% of early RA patients who exhibit good response by the EULAR definition • 0-5% of patients with clinical remission by ACR/EULAR Boolean criteria	Among those who achieved clinical remission (CDAI ≤2.8), 20-25% still exhibit some residual pain
Pathogenesis	• Residual inflammation • Direct interaction with nociceptors and cytokines • Neuropathic pain: entrapment neuropathy, spinal cord compression, peripheral cord • neuropathy, and small-fiber neuropathy • Nociplastic pain	
Risk factors	• Baseline condition: patient global assessment, higher HAQ at baseline, arthritis self-efficacy, higher level of pain, higher HDI, higher fatigue, psychiatric comorbidity, basic multimorbidity, mental health • Demographic factors: older age, longer disease duration, female sex, continent (highest in Africa, lowest in Asia), ethnicity (highest in Native Americans and lowest in Asians) • Medical condition: past-history of fracture, use of glucocorticoid	
Possible treatment options	Blocking proinflammatory cytokines, especially IL-6 and JAK/STAT pathway	

DAS: Disease Activity Score; RA: Rheumatoid Arthritis; EULAR: European Alliance of Associations for Rheumatology; ACR: American College of Rheumatology; CDAI: Clinical Disease Activity Index; HAQ: Health Assessment Questionnaire; IL: Interleukin; JAK/STAT: Janus Kinase/Signal Transducer and Activator of Transcription

Even with this evidence, quantitative studies of functional disability are still lacking. A systematic review of [15] identified 34 articles that measured versions of HAQ, but few showed quantitative data on the frequency.

Our inception cohort of b/ts DMARD [22] revealed that 51% of the patients who achieved remission or LDA by CDAI within 6 months failed to achieve HAQ-DI normalization (<0.5). We conducted ad-hoc analyses and found that among 635 patients who achieved remission within 6 months, 139 (22%) did not achieve HAQ normalization. As HAQ normalization is dependent on baseline HAQ, we further analyzed the degree of HAQ improvement. Among the patients with HAQ >0.22 at baseline, 19% did not show significant improvement in HAQ-DI (by >0.22). Even more, 2.7% showed a significant increase (by >0.22) in HAQ within the period (unpublished data).

Possible pathogenesis of residual functional disability: Although it is well-known that the proportion of functional disability among RA patients is higher than the healthy population [45], there is a paucity of literature that overviews its pathogenesis. Major causes of functional disability in the general elderly population are orthopedic diseases, dementia, and stroke [46], all of which are reported to be induced by RA. Orthopedic conditions are common in RA patients. Sometimes joint destruction and deformity cause a permanent reduction in HAQ (structural HAQ). Such impairment is observed even within a year from the onset [47].

Different from structural HAQ, stroke and cognitive impairment lead to reduction in HAQ without structural damage (functional HAQ). Although dementia risk in RA patients is still ambivalent [48], there are some evidence that inflammatory cytokines such as IL-1β, IL-6 and TNF-α cause cognitive deficit via synaptic plasticity, neurogenesis, and neuromodulation [49]. In addition, risks of cardiovascular diseases in RA patients are reported to be higher than healthy controls [50], partly due to chronic inflammation.

In addition to these common causes of functional disability, RA patients exhibit a variety of comorbidities associated with functional HAQ, including fatigue, malaise, depression, and sarcopenia [51]. Some cytokines related to the pathogenesis of RA are reported to be linked to symptoms of encephalomyelitis or chronic fatigue syndrome (ME/CFS) [52].

One mechanism that is common in a variety of fatigue, pain, and depression is stimulation of the hypothalamic-pituitary-adrenal (HPA) axis, which changes metabolism and catabolism of muscle and adipose tissues and reduces in physical activities as well [53]. The HPA axis seems to exert an ambivalent effect on fatigue. Stimulation of HPA axis may increase fatigue by upregulating catabolism and inflammation, while its hypofunction may also lead to fatigue via adrenal dysfunction [51].

Risk factors for functional disabilities: Joint damage, especially among elderly RA patients [45], is a major risk factor of functional disability in RA patients in general. It accounts for about 20% of HAQ scores among recent-onset RA patients [54]. Long-term high HAQ-DI is also associated with baseline or 1-year HAQ score, older age, female sex, disease activity, RF/ACPA positivity, co-morbidities, low education and low socio-economic status (SES) [55,56], patient's global health, physician's global assessment, depression score [57], myalgia, and fatigue [58]. Interestingly, disability index progress more slowly when patients were treated by a rheumatologist regularly than intermittently [59], presumably due to more intensive use of second-line antirheumatic medications, and more frequent joint surgeries when appropriate.

Nevertheless, risk factors of functional disability among patients in inflammatory remission or LDA are still to be elucidated. Komiya *et al.* targeted elderly RA patients (55-84 years old) with LDA and identified higher age, higher SDAI at baseline, concomitant use of glucocorticoid, nonuse of MTX as risk factors for HAQ >0.5 within 1-year observation period [44]. Another research on early RA patients found that patients in the "low inflammation - high HAQ" group identified by latent class analysis were on average older, were more often female, had more comorbidity and had more severe pain, fatigue, anxiety and depressive symptoms at baseline compared with patients in the "low inflammation - low HAQ" group [60]. Our previous research [22] found that longer disease duration, female sex, higher HAQ-DI at baseline, failure of ≥2 classes of b/tsDMARDs, and use of glucocorticoids are associated with less likelihood of the HAQ-DI normalization, while JAK inhibitor compared with TNF-α related to more likelihood of the normalization.

As functional disabilities are multifaceted and interrelated conditions, there might be a need to identify risk factors for each different condition.

Treatment of functional disability: As functional disability and pain are closely related, the treatments of residual pain listed in **Table 1** will be effective for functional disability as well. Moreover, given that inflammatory cytokines cause not only pain, but also fatigue [51], depression [61], and cognitive disfunction [49], anti-cytokine strategies may ameliorate residual symptoms closely related to functional disability independent of inflammation.

Our research [22] showed that JAK inhibitors use was associated with more frequent HAQ-DI normalization (<0.5) compared with TNF inhibitors use among patients in CDAI remission or LDA, which is consistent with a systematic review that showed advantage of JAK inhibitors to other bDMARDs in the improvement of SF-36 physical component score and functional assessment of chronic illness therapy – fatigue (FACIT-F) [62]. This preferable outcome of JAK inhibitors may partly reflect the rapid-acting nature [63-65] of these agents as well as direct effect. Given that long-lasting pain may cause decline in physical activity and thus worsen functional disability, and that patients prefer rapid onset of action of their treatment [66], time-to-response is an important aspect to be considered in the treatment choice.

One remaining question is whether to start or switch b/tsDMARD when patients achieved inflammatory remission but not satisfied with the treatment. As relief of symptom are leading treatment expectation of RA patients [66], it would be reasonable to switch DMARD to achieve treat-to-target (T2T). Even so, physicians may hesitate to escalate treatment just because of symptoms, from concern about adverse events such as malignancies. Therefore, further research about the benefit of treatment modifications among patients with high HAQ but low inflammation is required.

As well as modifications of b/tsDMARDs, de-escalation of glucocorticoid might be another treatment option for functional disfunction. Glucocorticoid increases risks of osteoporosis in a dose-dependent manner [67] and reduction of the agent improved

bone metabolism independent of disease activity [68]. In addition, long-term use of glucocorticoid suppresses HPA axis and cause adrenal atrophy, which can exacerbate fatigue and malaise among RA patients [51]. For these reasons, early reduction or cessation of glucocorticoid will be effective on functional HAQ among patients who achieved LDA.

In addition to the choice of drugs, other pharmacological, nutritional, psychological, and behavioral intervention is important to treat non-inflammatory comorbidities. Physical exercise [69,70], intake of vitamin D and omega-3 [70] as well as social support [71] are effective to improve physical activities of RA patients with depressive status and fatigue. For patients with fibromyalgia, anti-depressant and naltrexone, physiotherapy like acupuncture, repetitive transcranial magnetic stimulation (rTMS) or direct current stimulation (DCS), education, and other physical and psychological therapies should be considered [72]. Nevertheless, such an integrated way of care requires time and cost and may lead to an "RA paradox", in which specialized care may compete with a general plan of care [73]. As intervention on depression and fatigue is also affected by cultural sensitivity and social support [69,71,74], the management may require a holistic approach involving a variety of stakeholders in the community (**Figure 1**).

The current findings of functional disabilities among RA patients in remission or LDA are summarized in **Table 2**.

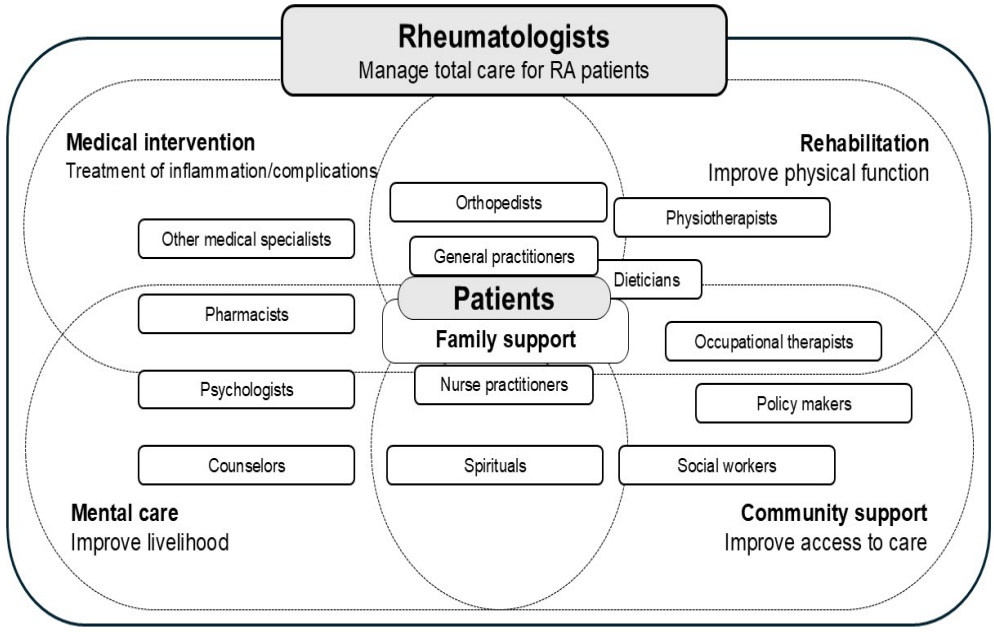

Figure 1. An example of patient-centered multidisciplinary approach for residual symptoms.

Table 2. Summary of current findings of functional disability of RA patients in remission or LDA.

Aspects	Findings	
Frequency	Literature review	Ad-hoc analysis of our inception cohort
	• 3% of patients in remission by Boolean criteria were with mHAQ >0.5 • 15% of patients in remission or LDA by SDAI are in MDA/HDA by RAPID3. • 18% of patients at the age of ≥75 y.o. in remission by CDAI were with HAQ >0.5	Among those with clinical remission (CDAI ≤2.8), about 20% did not achieve HAQ-DI improvement (by ≥0.22)
Pathogenesis	• Common causes of disfunction: orthopaedic diseases, dementia, and stroke • Inflammatory cytokines: IL-1β, IL-6, TNF-α cause cognitive deficit, chronic fatigue syndrome, and sarcopenia • Both stimulation and suppression of the HPA axis	
Risk factors	• Baseline conditions: higher SDAI, higher HAQ, comorbidities, pain, fatigue, anxiety and depressive symptoms at baseline • Demographic factors: higher age, female, longer disease duration • Medical condition: glucocorticoid use, failure of ≥ 2 classes of b/tsDMARDs	

Possible treatment options	• Anti-cytokine strategies, especially use of JAK inhibitor • De-escalation of glucocorticoid • Physical exercise, intake of vitamin D and omega-3, and social support for depressive status and fatigue • Physiotherapies like acupuncture, rTMS or DCS, education, and other physical and psychological therapies for fibromyalgia

RA: Rheumatoid Arthritis; mHAQ: Minimal Health Assessment Questionnaire; SDAI: Simplified Disease Activity Index; LDA: Low Disease Activity; MDA: Moderate Disease Activity; HDA: High Disease Activity; CDAI: Clinical Disease Activity Index; HAQ-DI; HAQ-Disability Index; IL: Interleukin; TNF: Tumor Necrosis Factor; HPA axis: Hypothalamic-Pituitary-Adrenal axis; b/tsDMARD: biological/Targeted-Synthetic Disease Modifying Antirheumatic Drug; JAK: Janus Kinase; rTMS: Repetitive Transcranial Magnetic Stimulation; DCS: Direct Current Stimulation

Discussion

In 2022, EULAR and ACR defined difficult-to-treat RA (D2T RA) as a group of patients who remain symptomatic despite recommended treatment changes [75]. D2T RA includes heterogeneous conditions that are categorized into 3 main criteria: 1) Treatment failure history; 2) characterization of active/symptomatic disease, and 3) clinical perceptions. Among these definitions, Criteria 3, described as "The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient", weigh much on subjective complaint of the patients and thus lacks tools of objective evaluation. Recent advancement in DMARDs remarkably decreases D2T RA patients of criteria 1 and 2. On the other hand, D2T RA of criteria 3 seems to become a major unmet need in RA patients who achieved inflammatory remission or LDA.

Ageing of RA patients and increased importance in residual symptoms in Japan

The needs in the management of such residual symptoms will increase with the ageing of the population. Asian countries, especially Japan, are facing rapid ageing of the population. Moreover, the proportion of the patients with RA is aging far more rapidly than the general population for two reasons. First is improvement of treatment outcome due to the advancement of DMARDs, which slowed down organ dysfunction such as amyloidosis and joint destruction. As a result, patients with comorbidities can live to advanced age. Second, the age at onset is also increasing from unknown reasons [76]. In the 1960s, the proportion of elderly-onset RA in Japan was less than 10% and increased to more than 20% in the late 1980s [77], and >50% in 2012 [76]. Even among those who receive b/tsDMARDs, the age at the initiation or switching of b/tsDMARDs increased from 51.9 years in 2003 to 64.3 years in 2023. Partly due to this aging population, an increasing number of RA patients have comorbidity, which may affect residual symptoms. Our registry data revealed that the prevalence of comorbidities of the patients who receive b/tsDMARDs such as chronic kidney disease, lung disease, history of fragility fractures, history of pneumonia, history of malignancy, major adverse cardiovascular events, and thrombosis increased by 2-5 times in these two decades (unpublished data), highlighting the increasing complexity of the management of RA. Because of the increase in elderly RA patients and decrease in the proportion of drug-resistant patients, management of residual symptoms of the patient who achieved inflammatory remission or LDA is becoming increasingly important (**Figure 2**).

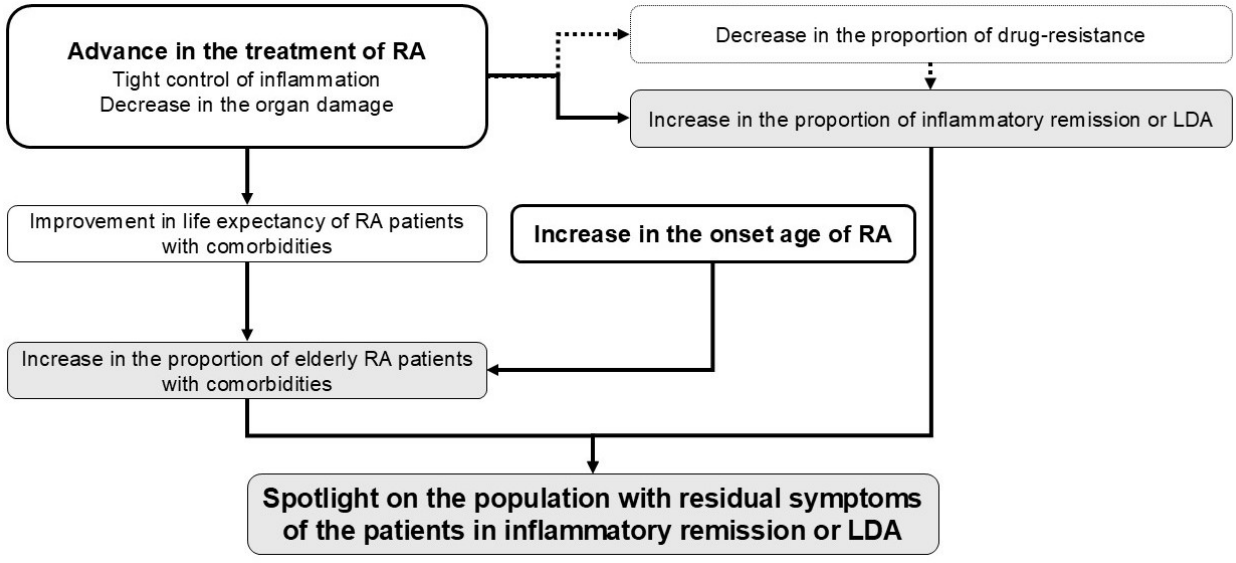

Figure 2. Scheme of the increased importance in the management of residual symptom of RA patients who achieved remission and low disease activity (LDA).

Challenges in the management of residual symptoms

Recent studies have revealed that worse functional disability is associated with cardiovascular and all-cause mortality [78], joint damage, work disability [55], and employment rate [58]. However, there still exist several challenges to overcome in the management of the disability among patients in inflammatory remission or LDA. First, there is lack of assessment tools and there are no validated consensus tools to evaluate and monitor residual symptoms [51]. Lack of either imaging or laboratory tests make an impartial assessment of residual symptoms difficult. Currently, some outcome indicators such as subjective pain, HAQ-DI, Euro QoL-5 Dimensional questionnaire (EQ-5D), and SF-36 are used, but they cannot distinguish non-inflammatory symptoms from inflammatory ones. To establish effective treatment strategies, tools that can discern whether the symptoms arise from inflammation, structural damages, nociceptive and/or nociplastic mechanisms, or psychological factors.

Second, research methods on residual symptoms are not standardized, which makes it difficult to synthesize evidence generated all over the world. We may need to establish global consensus in the timing of evaluation, collection of clinical variables such as comorbidity and SES, inclusion criteria of the patients, and outcome measurement.

Third, treatment options for residual symptoms of patients in remission or LDA. Intervention on depressive status may improve disease management and daily functioning of the patients [69], but the size of the impact is still to be elucidated. Effective intervention for fatigue is still an unmet need for RA patients [70]. Further research on non-drug treatment including self-management, rehabilitation, and physiotherapy is also required.

Conclusion

Residual symptoms of patients in remission or LDA are becoming a major unmet need in RA treatment. Elucidating molecular mechanisms of each symptom such as pain, fatigue, sleep disorder, and malaise, and standardized methods that enable synthesis of evidence are required to overcome the dearth of evidence in this field. Rheumatologists should involve a variety of stakeholders in their community to improve patients' well-being and functioning as a whole.

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