



Rheumatology training and research in Iran

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Abstract

Rheumatology is one of the most important clinical subspecialties in Iran. In the past 2 decades, Iran has witnessed an immense progress in the field of rheumatology training and research, which has led to an increase in the number of rheumatologists and research performed in the field of musculoskeletal disorders. These advances have made way for greater access to subspecialty care for rheumatic disorders. To write this article, we performed a systematic literature search using PubMed/MEDLINE, Web of Science, SCOPUS, Google Scholar and SID databases. In the first part of the manuscript, we will provide information about the history of rheumatology, rheumatology practice, referral system, the rheumatology training in medical schools, training of rheumatology subspecialists and post-graduate program of continuing medical education for rheumatologists in Iran as well as the Iranian Rheumatology Society. We will then focus on rheumatology research, top researchers, research centers focused on rheumatic disorders, the characteristics of common rheumatic diseases and ultimately biologics and biosimilars in Iran.

Keywords Arthritis · Rheumatology · Iran · Teaching · Research · Publications

Introduction

Rheumatology is a clinical subspecialty that is rapidly evolving due to its links with sciences such as genetics, immunology and molecular biology. The prevalence of musculoskeletal problems in the population over the age of 15 in Iran is 42% [1, 2]. Osteoporosis (OP), osteoarthritis (OA), low back pain (LBP) and peri-articular disorders are the most common musculoskeletal problems in Iran, with frequencies of 17, 15.7, 15.5 and 4.6% in the population, respectively [2, 3]. A study on the burden of diseases and injuries in Iran carried out by the Ministry of Health and Medical Education (MOHME) in 2003 shows that musculoskeletal disorders with 900 per 100,000 Disability-Adjusted Life Years (DALY) are ranked 5th in Iran after accidents, psychiatric

disorders, heart diseases and prenatal disorders [4]. Due to the high frequency of musculoskeletal problems in Iran and the high costs and disabilities caused by these disorders, rheumatology is one of the most important clinical subspecialties in Iran. According to the policies of the MOHME, the number of rheumatologists in Iran should be increased to 1 per 150,000 people, and each university hospital should have at least two rheumatologists [5]. For this reason, education and research in the field of rheumatology has greatly improved in Iran over the past 2 decades. To the best of our knowledge, one article was only published in 2009 introducing rheumatology in Iran [6]. This article focuses on the history of rheumatology and rheumatology training [6]. In the last decade, the number of rheumatologists, rheumatologist training centers, research centers working on rheumatic disorders and researches in the field of rheumatology has grown dramatically and valuable data about rheumatic disorders in Iran have been obtained. This review focuses on the history of rheumatology, rheumatology training and research, the characteristics of common rheumatic diseases, and biologics and biosimilars in Iran.

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Search strategy

We used the recommended methods for a narrative literature review [7]. We performed a systematic literature search using PubMed/MEDLINE, Web of Science, SCOPUS, Google Scholar and SID databases in the English and Farsi language resources from 1960 to 2019. Search for the following words in the title, abstract and keyword was done: ankylosing spondylitis (AS), arthritis, Behcet's disease (BD), Behcet's syndrome, Churg–Strauss syndrome, dermatomyositis, eosinophilic granulomatosis with polyangiitis, familial Mediterranean fever (FMF), fibromyalgia, giant cell arteritis, granulomatosis with polyangiitis, Henoch–Schönlein purpura, idiopathic inflammatory myopathy (IIM), inclusion body myositis, Kawasaki syndrome, microscopic polyangiitis, myositis, osteoarthritis (OA), osteoporosis (OP), palindromic rheumatism (PR), polyarteritis nodosa, polymyalgia rheumatica, polymyositis, psoriatic arthritis (PsA), reactive arthritis, rheumatism, rheumatoid arthritis (RA), rheumatology, seronegative spondyloarthritis (SpA), seronegative spondyloarthropathy, systemic sclerosis (SSc), scleroderma, systemic lupus erythematosus (SLE), Takayasu arteritis, temporal arteritis, vasculitis, Wegener's granulomatosis. The search was limited to the articles published with the country affiliation of Iran. Only original research articles, review articles, brief reports and case reports were included. Letter to the editors, editorials, unpublished data and data presented in the form of abstracts of congresses were excluded. To write this article, we also used the information of the Ministry of Health and Medical Education (MOHME) [5], Iranian Rheumatology Association (IRA) [8], Rheumatology Research Center (RRC) [9], Continuing Medical Education (CME) office [10], Iranian Scientometric Information Database—ISID [11], Tehran University of Medical Sciences [12] and Food and Drug Administration of The Islamic Republic of Iran [13] websites.

History of rheumatology in Iran

Egyptian, Greek and Indian physicians knew about rheumatic diseases such as gout centuries ago [14]. Modern rheumatology began with advances in sciences such as biochemistry, genetics, immunology, epidemiology and pharmacotherapy of rheumatic diseases [14]. The first medical school in Iran was founded in 1934 at Tehran University in the capital (Tehran) [12]. The first journal of the Faculty of Medicine of Tehran University was published in Farsi language in 1942 [15]. The second and third medical schools were founded in 1946 and 1949 in Tabriz and

Mashad, respectively [16, 17]. In this period, rheumatic diseases were taught by internists [14, 16, 17]. Review of the journal publications of Tehran University's Faculty of Medicine shows that university professors such as Qasem Shafizadeh, Hasan Ahari, Sadeq Pirooz Azizi, Abutrab Nafisi and others knew rheumatic diseases such as SLE, RA, juvenile RA, Reiter's syndrome and Takayasu arteritis well [15]. Muhammad Hossein Ordoubadi was one of the most famous professors of medicine who used to teach rheumatology in Tehran University [14]. He was the chief editor of a textbook of medicine in Farsi language and the author of several chapters of this textbook on rheumatic disorders. He published several articles about systemic manifestations of RA [15].

However, rheumatology as a subspecialty in Iran started in the Tehran in the early 1960s by Amirkhan Shafizadeh, Farrokh Sarkari, Fereydoun Davatchi, Firroz Panahi, Ishaq Eshaghof, Mohammad Shafizadeh, Reza Mogtader and Saeed Bani Hashemi [8]. Rheumatology training from the perspective of a rheumatologist began in 1967 by Mohammad Shafizadeh at the Shahid Beheshti University and in 1969 by Fereydoun Davatchi at Tehran University [3]. Fereydoun Davatchi established the first outpatient clinic of rheumatology in 1970 at Emam Khomeini Hospital (previously Pahlavi Hospital) as well as the first department of rheumatology in 1974 at Shariati Hospital (previously Daryoush Kabir Medical Center) [6]. In 1970, Ali Asghar Egtedari at Shiraz University, in 1975, Ali Naseh at Mashhad University and in 1978, Jafar Forghanizadeh at Iran University of Medical Sciences began teaching rheumatology as rheumatologists [8]. The subspecialty of rheumatology was one of the first subspecialty groups that officially began rheumatology training according to the MOHME in 1985 in Tehran and Iran Medical Universities [6].

Rheumatology practice in Iran

Patients with rheumatic diseases in Iran are mainly treated by rheumatologists and sometimes general practitioners, internists, orthopedic surgeons, neurologists, neurosurgeons and rehabilitation specialists [6]. There are 245 rheumatologists in Iran (1 per 320,000 people) [8]. Most of them work in Tehran and provincial centers [8]. More than 50% of Iran's rheumatologists are practicing in the five largest cities of Iran, including Tehran, Isfahan, Shiraz, Mashhad, and Tabriz [8].

The referral system in rural and urban areas in Iran with a population below 20,000 started in 2005 [5]. In this system, a family physician responsible for a certain population refers patients to specialists or subspecialists [5]. Family physicians are staff members of the MOHME and refer patients to university clinics or hospitals [5]. Rheumatologists are in

the third level of the referral system [5]. This system causes patient and physician dissatisfaction due to factors such as the lack of appropriate teaching and culture-making in service recipients, inconsistency between different levels of the referral system and financial problems of the MOHME and insurance offices which delay the payment of financial claims of physicians. In urban areas with a population of more than 20,000, patients can refer directly to specialists and subspecialists [5]. One of the main problems in the treatment of rheumatic diseases in Iran is the lack of evidence-based guidelines. Although evidence-based medicine (EBM) has recently attracted the attention of the MOHME and EBM-oriented research centers and departments have been established in some of the medical schools and have started localization of guidelines, there are still no guidelines for the treatment of rheumatic diseases in Iran. It should be noted that public health, social security and army forces insurances have a guideline for paying for biological medication costs in the treatment of RA and SpAs.

The Iranian Rheumatology Society (IRA) has been established as a non-profit scientific association with activities in the field of rheumatology (joints, bones, muscles and immune systems) in the areas of counseling, education, information and research [8]. The IRA was founded in 1973 and has 280 members, 245 of which are rheumatologists [8]. This association is currently under the supervision of the MOHME [8]. IRA is a member of the Asia-Pacific Rheumatology League (APLAR) [8]. The *Journal of Rheumatology Research* is the official journal of the IRA published since 2016. This journal is a peer-reviewed, open-access, and quarterly journal publishing basic, epidemiological and clinical papers about rheumatic disorders in adult and children.

Rheumatology training in Iran

In Iran, 40 universities located in 36 cities have a department of rheumatology and 134 rheumatologists work as faculty members [5, 8]. Sixty-eight (51%) of these rheumatologists are women [5, 8]. In addition, 9 universities located in 7 cities have a department of pediatric rheumatology and 14 pediatric rheumatologists work as faculty members [5, 8].

Rheumatology training for medical students begins in the physiopathology course in the third year of medicine [5]. During rheumatology course, epidemiology, pathogenesis, clinical and laboratory manifestations and the principles of the diagnosis of rheumatic diseases are taught in 32–36 h [5]. Musculoskeletal examination is taught in the third year of medicine [5]. The course of physical examination is 64 h, during which the musculoskeletal system is taught in 4–8 h at bedside [5]. In the clinical course, rheumatology training is done in the rheumatology ward

of a university hospital for 4 weeks, 50–70% of which is inpatient and 30–50% is outpatient teaching [5].

Rheumatology is one of the main topics of internal medicine [5]. The duration of the internal medicine specialty course in Iran is 4 years [5]. Twenty-five months from this period is dedicated to inpatient care [5]. During this period, internal medicine residents are trained in the rheumatology ward for 2–3 months [5]. During the training in the rheumatology ward, residents learn the clinical and laboratory manifestations, diagnosis and treatment of rheumatic diseases, articular and peri-articular injections and interpretation of laboratory tests, musculoskeletal imaging and densitometry [5]. Residents of dermatology, cardiology, rehabilitation and infectious diseases also receive rheumatology training for 1 month [5].

Rheumatology subspecialty course is 24 months [5]. The admission of the rheumatology subspecialty fellows is made up of internal medicine specialty board holders by written and Objective Structured Clinical Examination (OSCE) [5]. After the termination of the training period, rheumatology fellows must pass the examinations of the Subspecialty Board [5]. Eight universities in Iran train 19 rheumatology fellows annually [5]. These universities are Tehran University for Medical Sciences, Shahid Beheshti University for Medical Sciences, Iran University for Medical Sciences, Shiraz University for Medical Sciences, Mashhad University for Medical Sciences, Esfahan University for Medical Sciences, Tabriz University for Medical Sciences and Ahwaz Jundishapur University for Medical Sciences [5]. To eliminate the shortage of doctors in deprived areas of Iran, graduates have to work 48 months in areas designated by the MOHME [5].

Post-graduate program of continuing medical education (CME) for rheumatologists in Iran began in 1989 at the Rheumatology Research Center (RRC) of the Tehran University of Medical Sciences as weekly meetings introducing difficult or interesting cases [6]. Then the program was implemented at Iran University of Medical Sciences (since 1994) and Shahid Beheshti (since 1995) [6]. The CME for doctors officially started in 1990 [10]. The General Directorate of CME for physicians is part of the MOHME and its offices are based in medical science universities [10]. Under the CME act, physicians need to earn 25 retraining points for each year of their post-graduate medical practice to obtain a license to continue their medical practice [10]. The medical license must be renewed every 5 years [10]. This program is currently being implemented in the form of annual congresses and regional retraining programs at various universities [10]. Annual congresses for rheumatologists in Iran include the annual congress of the Rheumatology Research Center hosted by Tehran University of Medical Science since 1995; the annual congresses of Iranian Rheumatology Association hosted by IRA since 2007; the annual

seminar of rheumatology memorial of professor Mohammad Shafizadeh hosted by IRA since 2015 [8].

Research in rheumatology

Rheumatology research in Iran is mainly performed on common diseases, which are the main health problems [5]. These researches are in the field of genetics, epigenetics, immunology, epidemiology, clinical manifestations, prognosis and treatment of rheumatic diseases [5]. Researches are mainly conducted by professors from Medical Sciences Universities and research centers affiliated to these universities [5]. Fourteen research centers focus on musculo-skeletal, bone, autoimmune and rheumatic diseases in Iran [5]. The RRC of Tehran University of Medical Sciences is the pioneer of these centers. The core of this center was formed in 1974 [9]. Its initial members were six, but gradually it grew and became Iran's pole of rheumatology in 2001 [9]. The center has 480 international articles and 25 volumes of books on various rheumatic diseases

in Farsi [9]. The RRC has co-authored eight international books [9]. This center has BD, SLE, SSc, SpA, IIM and OP clinics, as well as the epidemiology unit and immuno-histochemistry lab [9]. The Community-Oriented Program for the Control of Rheumatic Diseases (COPCORD) study is the most significant research project of the center [1, 9, 18–20].

Rheumatology research in Iran has grown significantly over the past 10 years [11]. Figure 1 shows the chart of published articles in the field of rheumatic diseases based on Scopus search [21]. Among Iran's rheumatologists, Fereydoun Davatchi leads with 178 articles and h index = 29 in the first place [11]. Vahid Ziaee with 133 articles and H index = 20 has the most published articles among pediatric rheumatologists [11]. The article entitled "The International Criteria for Behcet's Disease (ICBD): A collaborative study of 27 countries on the sensitivity and specificity of the new criteria" with 312 citations is the most cited article with an Iran affiliation [11]. Figure 2 shows the ranking of Iranian universities based on the number of articles published in the field of rheumatic diseases [21].

Fig. 1 Number of published articles in the field of rheumatic diseases based on Scopus search

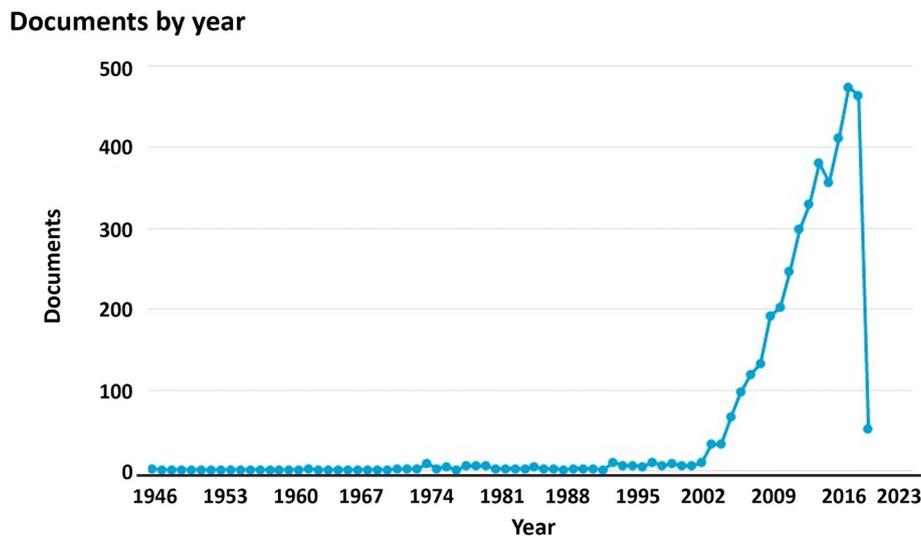
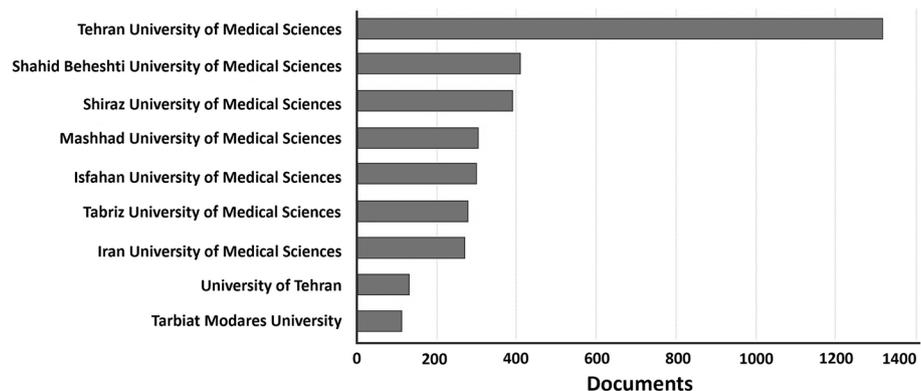


Fig. 2 Rating of Iranian universities based on the number of articles issued in the field of rheumatology



Rheumatic disorders in Iran

Musculoskeletal diseases are one of the major health problems in Iran, and COPCORD study on a population of about 10,000 people in the Iranian capital (Tehran) showed that 42% of Iranians over the age of 15 experienced musculoskeletal problems last week [1]. LBP and knee OA were the most common [1]. Three other studies were carried out later in some other urban areas of Iran, which yielded different results. These studies in the northwest on the Azari population (Azar cohort) [22], in the west on the Kurdish population [18] and in the southeast of Iran on the Baluch population [19] revealed that the prevalence of musculoskeletal problems in the northwest, west and south of Iran was 33.4%, 43% and 54%, respectively [18, 19, 22]. All the studies included people over the age of 15 except the Azar cohort that was a pilot study in people over 35 [1, 18, 19, 22]. The prevalence of musculoskeletal problems in rural areas of Iran (67%) is higher [20].

Osteoarthritis

The prevalence of symptomatic OA in Iran is 16.6–20.7% [1]. Knee (15.3–19.3%), hand joints (2.3–3.9%) and neck (1.7–3.8%) OA are the most common [1]. Hip OA is rare in Iran, with a prevalence of 0.1–0.5% [1, 18–20]. OA is more common in the elderly and women, and 50% of women and 30% of men over the age of 50 have OA [1]. Female to male ratios for knee, hand and neck OA are 2.1:1, 3.6:1 and 2.4:1, respectively [1]. Dahaghin et al. in a case–control study considered the role of lifestyle in the development of knee OA [23]. They reported that prolonged squatting and cycling increase the risk of knee OA 1.5 and 2 times, respectively [23]. Traditionally, Iranians sit on the floor, and this method of sitting has always been a concern for physicians as a possible risk factor. Surprisingly, this study showed that sitting on the floor, carrying heavy objects and climbing the stairs after adjustment for weight are not risk factors for knee OA [23]. They showed that among different occupations, only being a housewife could increase the risk of knee OA [23].

Many instruments used for assessment of pain and function in OA have been translated to Farsi and validated, including Intermittent and Constant Osteoarthritis Pain (ICOAP) Measure for the knee [24], Arthritis Impact Measurement Scales 2-Short Form (AIMS2-SF) [25], Functional Index for Hand Osteoarthritis (FIHOA) [26], Knee injury and Osteoarthritis Outcome Score (KOOS) [27], Arthritis Impact Measurement Scales 2 (AIMS2) [28] and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [29].

In traditional Iranian medicine, herbal medicines are used extensively in the treatment of diseases. A lot of clinical trials have been done in Iran on the effects of herbal medications on the treatment of OA. Herbal remedies such as curcumin, Burdock root, chamomile, *Elaeagnus angustifolia* (EA), green tea, peganum, pomegranate juice have promising results [30–36]. These trials reported a significant improvement in the symptoms of OA and WOMAC. However, small sample size, short duration of follow-up and the lack of consideration of the effect of the herbal remedies in preventing structural changes are the main drawbacks of these trials. Panahi et al.'s study on the efficacy of EA extract in the treatment of knee OA is one of the largest clinical trials on this subject [33]. In this study, 99 patients with knee OA were randomized into three groups. The first group received EA 300 mg/day, the second group received EA 600 mg/day ($n=32$) and the third group received ibuprofen 800 mg/day for 7 weeks. The WOMAC-total decreased from 43 to 35 in the ibuprofen group. The WOMAC-total in the EA 300 mg/day and EA 600 mg/day groups decreased from 43 to 37 and from 43 to 36, respectively. The difference in the pre- and post-trial was significant in all the groups. No differences were observed between the groups. This study shows that EA is as effective as ibuprofen in reducing WOMAC.

Osteoporosis

OP is a common disease in Iran. According to the lumbar spine densitometry criteria, the prevalence of OP and osteopenia in Iranian people over the age of 30 is 17% and 35%, respectively [3]. OP and osteopenia in the northern provinces are more common than the southern provinces of Iran [3]. The best explanation for this difference is the difference in the prevalence of vitamin D deficiency in different geographical regions of Iran. Vitamin D deficiency is common in Iran. In a study conducted in Tehran in 2004, 80% of participants were vitamin D deficient [37]. Rahnavard et al. in a multicenter study showed a higher prevalence of vitamin D deficiency in the northern part of Iran [38]. Keramat et al. in a multicenter study assessed the risk factors of OP in post-menopausal women [39]. BMI ≤ 26 [odds ratio (OR) 3.9], education under 12 (OR 2.5), early menopause (before 45 years), post-menopausal duration of more than 5 years (OR 2.2), parity more than 3 (OR 1.9), lactation more than 2 years (OR 1.7), history of fracture during last 5 years (OR 2.2), bone and joint problems (OR 2.3), and tooth problems (OR 3.4) were the risk factors for spine osteoporosis [39]. Sunshine exposure more than 15 min per day, drinking seven or more cups of tea per day, and walking more than three times per week were protective [39]. Ahmadzadeh et al. compared the performance of three OP

risk assessment tools: osteoporosis risk assessment instrument (ORAI), simple calculated osteoporosis risk estimation (SCORE) and osteoporosis self-assessment tool (OST) in 211 post-menopausal women [40]. Twenty percent of the patients had OP [40]. Sensitivity of OST, ORAI and SCORE were 74, 83 and 95%, respectively [40]. Figures 71, 64 and 54% were obtained for the specificities of OST, ORAI and SCORE, respectively. SCORE had the highest accuracy rating of 59% [40].

Treatment of OP starts with bisphosphonates [8]. Most Iranian rheumatologists use teriparatide or denosumab in refractory cases, severe OP (OP with fracture) or when *T* score is lower than -3.5 [8]. Ebadi Fard Azar et al. analyzed the cost-effectiveness of teriparatide in comparison with bisphosphonates, for the prevention of hip, vertebral and wrist fractures in patients with post-menopausal OP [41]. They calculated cost per QALY for three treatment strategies (alendronate, risedronate and teriparatide) for 2 years. Considering risedronate as the base treatment, incremental cost-effectiveness ratios of (ICER) of US\$-2178 and US\$483,784 per QALY were obtained for alendronate and teriparatide, respectively [41].

Rheumatoid arthritis

The prevalence of RA in the urban and rural areas of Iran is 0.33% and 0.19%, respectively [1, 18–20, 22]. The prevalence of RA in the relatives of affected people is 0.83% [42]. The mean age of patients with RA in Iran is 46 and the ratio of female to male is 4:1 [1].

Genetic factors play a crucial role in the pathogenesis of RA [43]. However, researches conducted on the Iranian RA patients did not show a significant association between most genetic factors identified in other populations and the risk of RA [43]. These genes include protein tyrosine phosphatase non-receptor type 22 (PTPN22), protein-arginine deiminase type-4 (PADI4), signal transducer and activator of transcription 4 (STAT4), TNF-receptor-associated Factor 1 (TRAF1), C-C motif chemokine receptor 6 (CCR6), major histocompatibility complex (HLA-G), transcription regulator protein BACH2, Fc receptor-like (FCRL), dipeptidyl peptidase 4 (DPP4), CDK5 regulatory subunit-associated protein (CDK5RAP2), interleukin-1 receptor-associated kinase1 (IRAK1). Hormonal factors have an important role in the pathogenesis of RA. In a case–control study in the Azari population of Iran, Ghamarzad Shishavan et al. showed that being menopause, premature menarche (age at menarche < 13), maternal age ≥ 21 at first delivery increase the risk of RA development with odds ratios (ORs) of 3, 1.7, 1.9, respectively [44].

In Iran, RA is diagnosed 6 months after the onset of the disease on average [45]. The ACR/EULAR 2010 sensitivity

for the diagnosis of RA in Iran is 69% [45]. To start RA treatment, some rheumatologists use the combination therapy strategy using methotrexate (MTX) and another conventional synthetic disease-modifying antirheumatic drug (csDMARD), which is usually hydroxychloroquine (HCQ) or sulfasalazine (SSZ) [8, 46]. Others start monotherapy with MTX on the basis of the American College of Rheumatology (ACR) guideline and use combination therapy only for poor prognosis patients [8]. At the start of RA treatment, almost all Iranian rheumatologists use low-dose steroids [8, 46]. In cases that the goal of treatment is not achieved after 3 months, another csDMARD (usually HCQ, SSZ and leflunomide) or a biological medication, usually a tumor necrosis factor inhibitor (TNFi), is added to the treatment regimen [8]. For resistant cases, another TNFi or rituximab (RTX) is used [8]. In refractory cases that the patient is unable to pay for a biological medication, combination therapy with three and then four DMARDs is prescribed [8, 46]. The usual combinations for three csDMARD are combinations of MTX, HCQ and SSZ or leflunomide, HCQ and SSZ [8, 46]. For combination therapy with four csDMARD, the usual combinations are MTX, HCQ, SSZ and a calcineurin inhibitor; MTX, HCQ, SSZ and azathioprine; MTX, HCQ, SSZ and leflunomide [8, 46]. Davatchi et al. in a retrospective study showed that treatment with a combination of csDMARDs and low-dose prednisolone leads to ACR70 response in 70% of patients [46]. MTX is the most widely prescribed DMARD [8, 13]. Liver toxicity is a major concern in patients treated with MTX. We showed that MTX is well tolerated by Iranians and the likelihood of stopping MTX usage for liver complications during 5 years of treatment is 1.5% [47].

Few studies have been performed on the systemic manifestations of RA in Iran. Secondary Sjogren's syndrome develops in 6% of RA patients [48]. RA is a known risk factor for atherosclerosis. Shakeri et al. in a cross-sectional study reported a higher common carotid intima-media thickness in RA patients (0.72 mm) compared with controls (0.62 mm) [49].

Seronegative spondyloarthritides

The prevalence of AS and other SpAs in the urban and rural populations in Iran is 25 and 23 per 10,000, respectively [1, 18–20, 22]. The mean age of AS patients in Iran at the time of diagnosis is 36–38 years, the ratio of male to female is 4:1 and 73% are HLAB-27 positive [50, 51]. The most prevalent HLAB-27 subtypes are 2702, 2704, 2705 and 2707, respectively [50, 51]. Delay in diagnosis is 6–8 years [50, 51]. Family history of SpA is found in 30% of patients [51]. Uveitis with the frequency of 15% is the most common extra-articular manifestation of AS [51]. Gastrointestinal

involvement (7.5%), skin lesions (4.4%) and pulmonary involvement (1.9%) are in the next ranks [51]. The first line of treatment is non-steroidal anti-inflammatory drugs (NSAIDs). In patients with peripheral joints involvement, a csDMARD, most commonly SSZ or MTX, is prescribed. Jamshidi et al. reported that 80% of AS patients were treated with NSAIDs [51]. SSZ (55%), MTX (25%) and prednisolone (22%) were the other commonly used medications [51]. Biologics were used for resistant cases [51]. Ten percent of AS patients who are managed by rheumatologists are treated with biological drugs [51].

Although there is no exact data on the incidence of arthritis in psoriasis patients, prevalence of PsA in a cohort of psoriasis patients was 9.1% [52]. In Moghaddassi et al.'s report on a cohort of PsA patients, the mean age of PsA patients at the time of diagnosis was 33, the female to male ratio was 1.1:1 [53]. The most common type of PsA in Iran is the asymmetric oligoarthritis form (46%) (54). The other types are classic PsA confined to DIP joints (23%), PsA with axial involvement (16%), polyarticular form (5%) and mutilating arthritis (2.2%) [53]. The most common extra-articular manifestation of PsA after skin and nail diseases is eye involvement (2.7%) [53].

Systemic lupus erythematosus

The prevalence of SLE in the urban and rural populations of Iran is 4–5 and 6 per 10,000, respectively [1, 18–21]. Data of the largest cohort of SLE in Iran with 2280 patients showed that the mean age of the patients was 24 ± 10 and the ratio of female to male was 10:1 [54]. The most common manifestations were musculoskeletal (83%), cutaneous (81%) hematologic (66%) and renal (65%) [54]. In another study in Fars province, kidney involvement frequency was lower (48%) [55]. The most common type of kidney involvement was type 4 (49%) [55].

Anti-malarial medications are the cornerstone of SLE treatment in Iran [8]. However, retinal toxicity of these medications in Iranians is higher than those reported in other countries. Espandar et al. in a study on 59 RA and SLE patients treated with HCQ for a mean period of 46 months reported 30.5% retinal toxicity by the fundoscopic, spectral domain optical coherence tomography and perimetry [56]. Hajjalilo et al. in a study showed that 49% of SLE patients are nasal carriers of *Staphylococcus aureus* and the rate of relapse in carriers is 2.5 times more than non-carriers [57].

The treatment of lupus nephritis (LN) is one of the main problems in the treatment of SLE patients. Mycophenolate mofetil (MMF) or cyclophosphamide (CYC) monthly pulse is used for remission induction in proliferative LN [8]. In a retrospective study on SLE patients with proliferative LN, Gadakchi et al. showed that there was no significant difference

in the rate of complete and partial remission in therapy with MMF and CYC [58]. Various methods were used for the treatment of resistant proliferative LN, including switching of MMF to CYC or vice versa, calcineurin inhibitors and combination therapy with cytotoxic drugs or rituximab [8]. In a retrospective study, Sheikholeslami et al. showed that a low-dose cyclosporine could result in a complete and partial remission in 67% and 26% of Iranians with MMF- or CYC-resistant LN [59]. Pakfetrat et al. in a 5-year follow-up showed that 14.2% of patients with LN suffered from chronic renal failure and 7.8% had end-stage renal disease (ESRD) [60]. The result of kidney transplantation in SLE patients in Iran is good. In a study by Ghafari et al. on 1350 transplanted kidneys, 10-year survival of graft in SLE patients (69%) was similar to non-SLE patients (73%) [61].

Systemic sclerosis

No information is available on the prevalence of SSc in Iran. No cases of SSc have been reported in COPCORD studies in Tehran, Sanandaj, Zahedan and Tuysarkan, and Azar cohort in populations of 10,000, 5800, 2100, 1500 and 1000 people, respectively [1, 18–20, 22]. The association of several genes with SSc has been shown in Iran, which include killer immunoglobulin-like receptors (KIRs)/HLA compounds such as activating KIR genotype 3 and HLA-BW4-A1 [62], HLA-DRB1*11: 04 [62], interferon regulatory factor 5-transcript 3 (IRF5-TNPO3) [62], Nuclear Factor Kappa B Subunit 1 (NFKB1) [62], Aquaporin 3 (AQP3) [63], and Integrin subunit beta 2 (ITGB2) [64].

The first symptoms of SSc often begin in the 3rd–4th decades [65]. Female to male ratio is 7:1 [65]. On average, the disease is diagnosed 3 years after the onset [66]. Approximately, 38% of patients have a diffuse form, 37% have a limited form, and 17% have overlap syndrome [67]. The most common symptom of the disease at the onset is phenomena of Raynaud's (41%) and the most common symptom is skin stiffness (97%) [66]; anti-nuclear antibodies, anti-topoisomerase, and anti-centromere are positive in 91%, 70% and 8%, respectively [66]. 5- and 10-year survival of SSc patients in Iran is 92.6% and 82.3%, respectively [66]. The leading causes of death in these patients are pulmonary involvement and cardiac events [66]. Age more than 50 at diagnosis and severe pulmonary involvement (DLCO < 60% and FVC < 60%) are the most important risk factors for death [66].

Idiopathic inflammatory myopathies

No data exist on the prevalence of IIMs in Iran. The female to male ratio is 5:1 [67]. Mean age at diagnosis is 45 [68]. Most Iranian rheumatologists start treatment for IIMs with

high doses of steroids and a DMARD [MTX or azathioprine (AZA)] [67, 68]. Hajjalilo et al. in a study on 47 polymyositis and 29 dermatomyositis patients treated with MTX or AZA reported complete and partial response in 43% and 45% of patients [67]. A 10-year survival of patients was 92% [67]. Dysphagia and cancer were associated with poor response to treatment [67]. Naji et al. in a case–control study on 185 IIM patients showed the importance of early treatment [68]. In their study, the rate of remission and relapse within 1 year in patients treated in 3 months after the disease onset was 80% and 5%, respectively [68]; while these figures for patients in which treatment started after 3 months were 46% and 25%, respectively [68].

Behcet's disease

Iran is located in the middle of the Silk Road, but the disease was unknown in Iran until Professor Fereydoun Davatchi presented the first case series of BD in Iran at an International Congress in 1982 [9]. The prevalence of BD in Iran was estimated to be 16 per 100,000, but later the COPCORD study showed that this figure is 80 in 100,000 [69]. In different ethnic groups of Iran, the prevalence of BD is higher in Azaris [69]. The role of environmental factors, genetics and epigenetics in the pathogenesis of this disease has been introduced [70]. Having HLA-B*51 increases the risk of BD in Iranians by four times [71]. Genome-wide association studies (GWAS) on the interleukin-10 gene (IL10) and the IL23 receptor-IL12 receptor β 2 (IL23R-IL12RB2) locus showed the association between rs1518111 in IL10 and rs17375018, rs7517847, and rs924080 in IL23R-IL12RB2 locus and BD [72]. Esmaeili et al. reported a higher mutation of familial Mediterranean fever (FMF) gene in the Azari population of Iran [73]. An association has been reported between rs3761547 polymorphism in the FOXP3 gene [74] and rs1800872 polymorphism in the IL10 gene [75] with BD in the Azari population of Iran. In the last 2 years, several studies reported the association between epigenetic factors and BD including hypomethylation of IL6 gene [76], hypermethylation of IL10 gene [77] and upregulation of microRNA (mir)-155, miR-25, miR-106b, miR-326 and miR-93 [78, 79]. Vitamin D deficiency and the FokI polymorphism of vitamin D receptor gene have been proved to increase the risk of BD in the Azari population of Iran [80, 81]. Despite the role of cigarette smoking in the pathogenesis of RA and other autoimmune diseases, a case–control study did not show an increased risk of BD in smokers or an association between clinical manifestations of the disease and cigarette smoking [82].

Data from BD registry of RRC show that the mean age of patients in Iran is 25.6 years, male to female ratio is 1.3:1 and the most frequent manifestations are oral aphthosis

ulceration (98%), genital ulceration (64%), skin lesions (62%) and uveitis (56%) [83]. Despite the high frequency of vascular involvement in Turkey and central nervous system involvement in Japan, these figures in Iran are 9% and 4%, respectively [83]. Data of a cohort of BD of Connective Tissue Diseases Research Center (CTDRC) showed that although BD in males is more common than females, no difference exists in the age of disease onset and the clinical manifestations of BD between males and females [84]. However, disease activity in males is higher than females [84].

Measurement of BD activity is a challenge. Iranian Behcet's disease dynamic activity measure (IBDDAM) was created in RRC and presented in the 12th European congress of rheumatology in 1991 [9]. Shahram et al. in a study on 117 BD patients detected the cutoff points 0.45 and 3.5 for non-ocular IBDDAM and ocular IBDDAM, respectively [85]. Professor Davatchi was the representative of Iran at the International Team for the Revision of the International Criteria for Behcet's Disease (ITR-ICBD) [86]. Revised ICBD (rICBD) was validated in Iran with a sensitivity of 96.8% and specificity of 97.2% [87]. We compared the performance of the rICBD and international study group (ISG) criteria in the Azari population of Iran [88]. In this study, which was carried out on 211 BD patients and 648 controls, sensitivity, specificity and accuracy of rICBD criteria were 94.7%, 99.6% and 98.5%, respectively [88]. These figures for ISG criteria were 64.9%, 100%, and 91.4%, respectively [88].

The eye involvement is the main BD problem in Iran. Uveitis is one of the most common clinical manifestations of BD in Iran and leads to severe loss of vision (limited to light perception or perception of hand motion) in 11% of the eyes in patients with panuveitis and/or retinitis [89]. Most rheumatologists in Iran treat posterior uveitis and/or retinal vasculitis of BD aggressively with cytotoxic medications, most commonly CYC and AZA in combination with moderate- to high-dose glucocorticoids [8, 9, 90, 91]. Davatchi et al. in a cohort of BD patients treated with monthly pulse of CYC and AZA reported improvement in visual acuity (VA) and ophthalmic disease activity index in 44% and 72% of eyes, respectively [90]. In another study, Davatchi et al. showed that a delay of more than 1 year after the start of uveitis in aggressive therapy leads to a lesser improvement in VA [91]. TNFs or interferon- α was used for the treatment of resistant cases [8, 92]. We reported a decrease in eye inflammation in 87%, eye remission in 58% and cure in macular edema in 57% of BD patients with severe eye involvement treated with interferon- α [92]. Treatment compliance is an important constituent of the effectiveness of therapy in chronic diseases. We showed that more than 50% of BD patients are non-compliant and being male (OR 4.2), being unemployed (OR 5.1), having low income (OR 2.5) and unawareness about BD complications (OR 3) are the main risk factors [93].

Familial Mediterranean fever

Iran is close to the Mediterranean, so FMF is not a rare disease. Most reports of FMF in Iran are in northwest where Azari Turks live [94–98]. The prevalence of FMF in the Azari population of Iran is 8 in 1000 [22]. M694V, V726A, E148Q and M680I are the most common MEFV alleles that cause FMF in Iran [94, 95]. These mutations are compound heterozygote in 40%, heterozygote in 26% and homozygote in 13% [95]. In 21% of patients no mutations can be found [95]. Abdominal pain (93%) and fever (88%) are the most common symptoms [96]. In 72% of the cases, the disease starts before age 10 [94]. However, in 8.5% of the patients, the disease presents after age 20 [94]. For a start a dose of 1 mg/day of colchicine is prescribed and the dose is gradually increased to 3 if the symptoms are not controlled [95]. Forty-seven percent of patients are non-adherent to therapy [97]. However, a complete control of attacks and partial response (more than 50% decrease in frequency of attacks) were reported in 77 and 23% of patients, respectively [97].

Palindromic rheumatism

The exact prevalence of PR in Iran is unclear. In the COPCORD studies, PR was not reported, but in the Azar cohort, it was reported as 4 in 1000 [1, 18–21]. In a cohort of inflammatory arthritis in the CTDR, the prevalence of PR was 2.8% [99]. The ratio of RA to PR frequency was 16:1 [99]. The mean ages of PR patients at the time of diagnosis was 38.5 years; male to female ratio was 1:1 [100]. PR in average was diagnosed 4 years after onset. Knee (68%), metacarpophalangeal (51%), wrist (43%) and proximal interphalangeal (41%) joints were most commonly involved joints [100]. Rheumatoid factor and anti-cyclic citrullinated peptide were positive in 46.4% and 42% of the PR patients, respectively [100]. We showed that treatment of PR with a tight control strategy reduces the attacks of the disease and the risk of RA development [101]. In a retrospective study, we included 92 patients with PR who were treated with HCQ and low-dose prednisolone [101]. In refractory cases, MTX was added or replaced [101]. In the absence of therapeutic response, other csDMARDs were added sequentially [101]. PR attacks were controlled in 83% of the patients, and in a follow-up period of 33 months, RA only developed in 8.7% of the patients [101].

Biologics and biosimilars

Etanercept (Enbrel) was the first biological medication introduced in the Iranian market in 1998 to treat rheumatic diseases [13]. Subsequently, other original biological medications including Infliximab (Remicade®), Adalimumab

(Humira®), Rituximab (MabThera®), Denosumab (Prolia®) and Teriparatide (Forteo®) were available to patients [13]. Since the last decade, two Pharmaceutical Companies, Cinnagen [102] and Aryogen [103], established in 1994 and 2009, began producing biosimilars for the treatment of rheumatic diseases in Iran. These companies received EULAR Good Manufacturing Practice or EU-GMP approval [102, 103]. Production and use of biologics and biosimilars in Iran are under the supervision of the Biological Unit of the Food and Drug Administration of the Islamic Republic of Iran [13]. Biosimilar products for the treatment of rheumatic diseases manufactured in Iran include the following: CinnoRA®-Adalimumab, Altebrel™-Etanercept, CinnoPar®-Teriparatide and Zytux™-Rituximab [13]. The efficacy and safety of these medications have been shown in Phase III. Clinical trials and articles have been published on the three medications of CinnoRA® [104], CinnoPar® [105] and Zytux™ [106]. In the initial years of the availability of biologics and biosimilars, the purchase of these drugs was difficult or impossible for most patients because of their high cost and lack of insured coverage; but now insurers pay 90% of their costs. Based on a raw estimation of 243,000 RA patients and 97,200 AS patients in Iran, 15,900 patients with RA and 13,200 AS patients need a treatment with biologics, and 6800 RA patients (2.8%) and 4200 AS patients (3.4%) are treated with these drugs [1, 8, 13]. Table 1 shows the rate of the use of biologics and biosimilars in the field of rheumatology and the share of pharmaceutical companies in their market in 2018 based on the Food and Drug Administration of the Islamic Republic of Iran report [13].

Future perspectives

Although rheumatologist training in Iran has been established, research in rheumatology is in early stages. There is a pressing need for evidence-based guidelines for the management of rheumatic diseases in Iran. Creation of registries

Table 1 Biologics and biosimilars marketing in the field of rheumatology in Iran

Generic name	Brand name	Number of patients
Denosumab	Prolia®	15,713
Adalimumab	CinnoRA®	11,016
Adalimumab	Humira®	54
Etanercept	Altebrel™	2545
Etanercept	Enbrel®	126
Teriparatide	CinnoPar®	2440
Teriparatide	Forteo®	236
Infliximab	Remicade®	2287

and performing multicentric studies, RCTs and community-based studies for common rheumatic diseases, especially for diseases common in Iran (e.g., FMF, BD) would give rheumatologists more relevant data and would help them adopt the right strategy for the management of rheumatic diseases. More collaboration with basic science researchers (e.g., immunologists and molecular biologists), finding financial resources and collaboration with international research centers will open new horizons for rheumatology in Iran.

Conclusion

Rheumatology is a growing science in Iran, and the number of rheumatologists has multiplied over the past 2 decades. Although there are increasing number of publications on rheumatic diseases in Iran, there is a pressing need for more multicenter studies, community-based studies, RCTs, internationally collaborative researches and the establishment of registries for rheumatic diseases and the development of native guidelines for the treatment of common rheumatic diseases.

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Compliance with ethical standards

Conflict of interest None of the authors of this paper have a conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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