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REVIEW

Bulgarian rheumatology: science and practice in a cost-constrained environment

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Abstract

Our aim was to appraise publications from Bulgaria, to assess their global impact, and to describe features and challenges unique to the rheumatology practice in Bulgaria characterized by stringent cost constraints. The Scopus database was queried on 25th July 2018 and data on the number of published documents, their Hirsch-indices and citations number were extracted. Published Bulgarian guidelines for the management of rheumatic diseases and the presented data on Bulgarian Rheumatology Society were identified based on prior knowledge of the authors. From all the identified 1082 document the most extensively researched areas were rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), osteoporosis, and osteoarthritis (OA). For the last five years (from Jan 2013 to 25th July 2018) the number of publications was 293. We found that Bulgaria's international scientific collaboration in the field of rheumatology is focused on a handful of countries mainly from Europe. Although Bulgarian rheumatologists have access to costly biologic agents for treating their patients with rheumatic diseases, their funding may not be granted according to the current recommendations of European League against Rheumatism (EULAR) and national guidelines for the management of rheumatic diseases. Although the western world clearly dominates the production of scientific publications in rheumatology, Bulgarian rheumatology may present another perspective for diagnosis and management of patients with rheumatic diseases in a cost-stringent environment. Nevertheless, both rheumatology science and practice in Bulgaria still have a long way to go to take its deserved place among the other European countries.

Keywords Bulgaria · Rheumatology · Vasculitis · Osteoarthritis · Rheumatoid arthritis · Spondylitis · Systemic lupus erythematosus · Scleroderma · Myositis · Biologics

Abbreviations

AAV	ANCA-associated vasculitis
ACR	American College of Rheumatology
ANCA	Anti-neutrophil cytoplasmic antibody
BRS	Bulgarian Rheumatology Society
BS	Behçet's syndrome
CHCC	Chapel Hill Consensus Conference
COMP	Cartilage oligomeric matrix protein
csDMARDs	Conventional synthetic disease modifying anti-rheumatic drugs
DM	Dermatomyositis
DMARDs	Disease modifying anti-rheumatic drugs
EMA	European Medicine Agency
EULAR	European league against rheumatism
FDA	Food and Drug Administration
GCA	Giant cell arteritis
h	Hirsch
IIMs	Inflammatory idiopathic myopathies
LVV	Large vessel vasculitis
MMP-3	Matrix metalloproteinase 3
MPO	Myeloperoxidase
MSK	Musculoskeletal
NCPHA	National Center of Public Health and Analyses
NHIF	National Health Insurance Fund
nrAxSpA	Non-radiographic axial spondyloarthritis
OA	Osteoarthritis
PM	Polymyositis
PR3	Proteinase 3
RA	Rheumatoid arthritis
RNA	Ribonucleic acid
SLE	Systemic lupus erythematosus
SS	Sjogren's syndrome

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SSc	Systemic sclerosis
TA	Takayasu arteritis
tsDMARDS	Targeted synthetic disease modifying anti-rheumatic drugs
USA	United States of America

Introduction

Rheumatology, the science covering all non-surgical diseases potentially affecting the musculoskeletal (MSK) system [1], is one of the many subspecialties that evolved from general internal medicine during the course of the twentieth century. It is an interdisciplinary branch of internal medicine and paediatrics where the subject of study, diagnosis and treatment are rheumatic diseases [2]. The burden of rheumatic disorders, in terms of spectrum and extent, is likely to vary in different parts of the world [3]. Bulgaria has the highest rate of hospital beds in rheumatology departments in comparison to other Central and Eastern European countries [4] and according to data from the Bulgarian Rheumatology Society register, 150 rheumatologists are currently practicing in Bulgaria (2.13 per 100,000 inhabitants). Nevertheless, rheumatologic care is unevenly distributed across the territory of the country, leaving relatively large regions without or with difficult access to a specialist in rheumatology. A brief report of The National Center of Public Health and Analyses (NCPHA) of Bulgaria showed, that in 2016 hospitalized patients in rheumatologic, orthopedic and physiotherapy units of hospitals (discharged and deceased) due to diseases of the MSK system and connective tissue were 122,038 (1712.1 per 100,000 people) [5].

Located on the boundary between West and East, Bulgaria is a country with traditions in rheumatology practice [6]. However, rapid global progression rates in our cost-stringent environment hinder the delivery of high-quality care [7] and represent a huge challenge for the development of rheumatology science in Bulgaria. In this broad sense of the modern-day context, the management of the wide spectrum of MSK diseases is influenced by socioeconomics. Furthermore, numbers of publications and citations showed strongly significant correlations with population size and gross domestic product, as the USA and Western Europe clearly dominate the production of scientific publications in rheumatology [8]. This is the main reason why countries in Eastern Europe, and Bulgaria particularly, are lagging behind in terms of science productivity and practice organization.

Given the scarce information on Bulgarian rheumatology practice and science, our aim was to sort out and appraise published rheumatology documents from Bulgaria and to assess their global impact, analyzing with respect to number of citations, h-index and collaborative efforts. Our second objective was to describe in details the specific features of rheumatology practice in Bulgaria under the conditions of cost-containment environment.

Search methodology

The search strategy adhered to previously published recommendations for conducting a narrative biomedical review [9]. The Scopus database was queried on 25th Jul 2018, limiting the search to affiliation country—Bulgaria. Initially, the search was carried out with no date restrictions to explore all the available documents on Scopus published by Bulgarian authors. We searched the Article title, Abstract, Keywords with each of the search terms (Table 1) covering all the main topics of rheumatology science: rheumatoid arthritis, spondyloarthritis, osteoarthritis, juvenile idiopathic arthritis, systemic lupus erythematosus, Sjogren's syndrome systemic sclerosis and mixed connective tissue disease, idiopathic inflammatory myositis, ANCA-associated vasculitides, other vasculitides, fibromyalgia and osteoporosis. Afterwards, information from the Scopus database was extracted in the last 5 years (from January 2013 to 25th July 2018) using the already mentioned search strategy. Additionally, data on Hirsch(h)-indices, citations number and international collaborations for the articles published with no date restriction and during the above mentioned time period were extracted from the Scopus database. Although we are aware that eponyms such as "Reiter's syndrome", "Wegener's disease" and others lack accuracy, lead to confusion, and hamper scientific discussion in a globalized world [10, 11], they were included as search terms, to extract a complete list of the available publications from Bulgaria. Data regarding the use of conventional synthetic, targeted synthetic and biologic disease modifying anti-rheumatic drugs (DMARDs) were derived from searches in the database and official correspondence with the National Health Insurance Fund (NHIF) of Bulgaria. Published Bulgarian guidelines for the management of rheumatic diseases and the presented data on Bulgarian Rheumatology Society (BRS) were identified based on prior knowledge of the authors.

Rheumatology science

All-time statistics for rheumatology science in Bulgaria

Overall, a total of 1082 documents related to rheumatology science and practice in Bulgaria were identified and published in journals indexed by Scopus database since 1968 (Fig. 1). All of them were filtered by affiliation country Bulgaria. In the late 1990s and in the beginning of the

Table 1 Pre-set search terms in Scopus database by topic and number of publications with no date restrictions

Topic	Search terms	No. of publications
Rheumatoid arthritis	"Rheumatoid arthritis"	320
Spondyloarthritis	"Spondyloarthropathy", "ankylosing spondylitis", "Psoriatic arthritis", "Reactive arthritis", "Reiter's syndrome", "spondyloarthritis"	103
Osteoarthritis	"Osteoarthritis", "degenerative joint disease", "osteoarthrosis"	160
Juvenile idiopathic arthritis	"Juvenile idiopathic arthritis", "juvenile arthritis", "juvenile chronic arthritis", "JIA", "enthesitis related arthritis"	47
Systemic lupus erythematosus	"Systemic lupus", "SLE"	236
Sjogren's syndrome	"Sjogren's syndrome", "Sjogren"	41
Systemic sclerosis and mixed connective tissue disease	"Systemic sclerosis", "Scleroderma", "mixed connective tissue disease", "Sharp's syndrome"	119
Idiopathic inflammatory myositis	"Idiopathic inflammatory myositis", "idiopathic inflammatory myopathy", "polymyositis", "dermatomyositis", "inclusion body myositis"	57
ANCA-associated vasculitides	"ANCA vasculitis", "ANCA associated vasculitis", "Granulomatosis with polyangiitis", "Wegener's disease", "Microscopic polyangiitis", "Eosinophilic granulomatosis", "Churg–Strauss disease"	15
Other vasculitides	"Polyarteritis nodosa", "Giant-cell arteritis", "Horton disease", "Takayasu arteritis", "Takayasu's arteritis", "Kawasaki disease", "Behcet's disease", "Behcet's syndrome"	47
Fibromyalgia	"Fibromyalgia"	26
Osteoporosis	"Osteoporosis"	170
Total		1082

ANCA anti-neutrophil cytoplasmic antibodies, *No* number

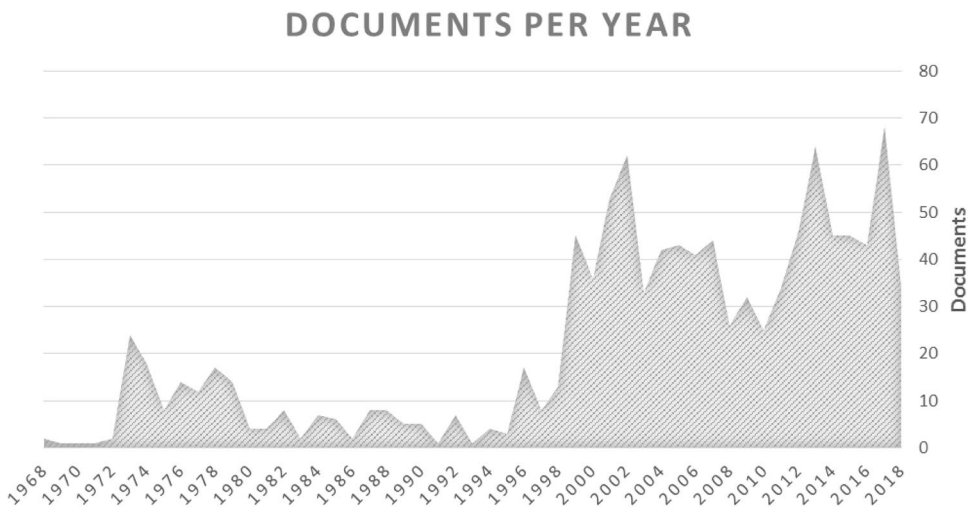

Fig. 1 Publications by year in the rheumatology field since 1968

new millennium we observed a sharp rise in the published papers, followed by a 15-year steady period until now. The most productive year according to statistics available by Scopus was 2017, when 67 publications from Bulgaria in the rheumatic field were published.

Logically, the top four of the most extensively researched areas were rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), osteoporosis, and osteoarthritis (OA). We found that Bulgaria's international scientific collaboration in the field of rheumatology is focused on a handful of countries mainly from Europe and more specifically from Germany (73 documents), Italy (52 documents), United Kingdom (44 documents), France (37 documents), United States (33 documents), Spain (35 documents), Netherlands (31 documents), Hungary (30 documents), Romania (29 documents) (Fig. 2).

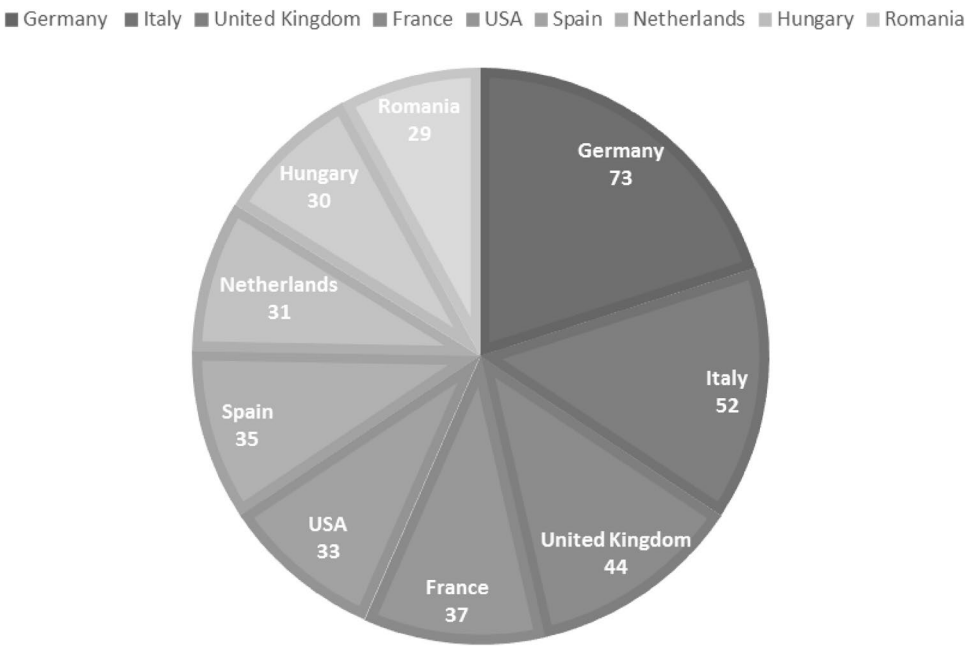

Fig. 2 International scientific collaboration according to number of publications

A 5-year analysis of publications from Bulgaria

293 documents were found published between Jan 2013 and 25th July 2018 from Bulgarian authors in the rheumatology field. Year by year analysis of published articles for the last 5 years is presented in Table 2. With 2716 citations the most cited publications in the last 5 years were clearly those which contained the term "rheumatoid arthritis" in their abstract, title or keywords. More detailed information about citation number and h-index of the articles published from Jan 2013 to 25th July 2018 is presented in Fig. 3.

An overview of citations for the selected documents showed that they were cited overall 6163 times and their median h-index according to Scopus database was 22 (range 0; 2460), whereas the article cited 2460 was a systematic analysis for the Global Burden of Disease Study [12].

Table 2 Number of publication in the last 5 years from Bulgaria

Topic/disease	No. of publications in the last 5 years						
	2013	2014	2015	2016	2017	2018	Overall
Rheumatoid arthritis	10	16	14	8	22	5	75
Spondyloarthritis	6	8	6	5	10	0	35
Osteoarthritis	12	4	8	8	13	5	50
Juvenile idiopathic arthritis	1	1	2	2	2	1	9
Systemic lupus erythematosus	15	15	11	6	7	4	58
Sjogren's syndrome	0	0	0	0	0	0	0
Systemic sclerosis and mixed connective tissue disease	10	5	5	7	4	6	37
Idiopathic inflammatory myositis	2	8	0	3	1	4	18
ANCA-associated vasculitides	1	2	3	2	2	0	10
Other vasculitides	1	6	2	2	3	1	15
Fibromyalgia	3	0	2	1	3	2	11
Osteoporosis	11	2	6	6	18	4	47
Total							293

ANCA anti-neutrophil cytoplasmic antibodies, *No* number

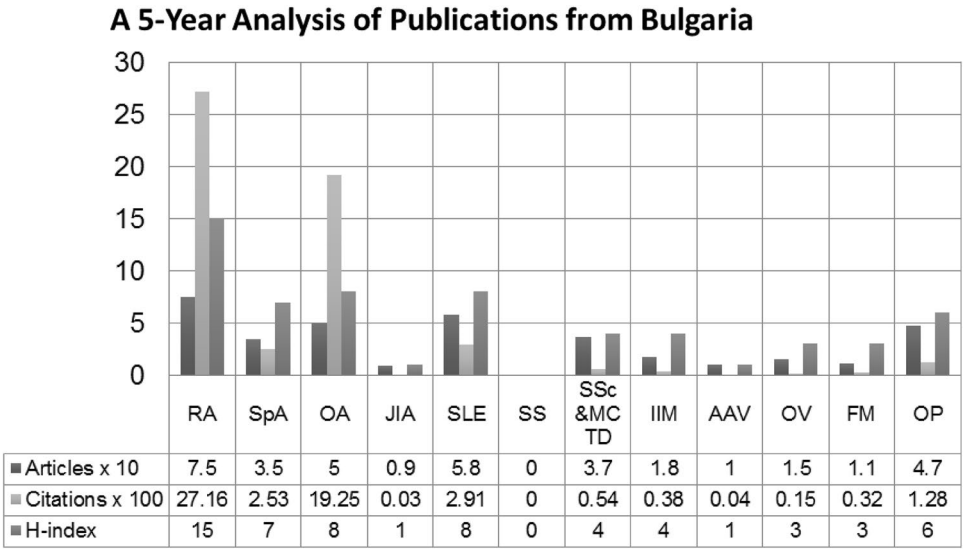

Fig. 3 A 5-year analysis of publications from Bulgaria including number of documents and citations and H-index. The shown H-index is only for articles published within the last 5 years (from Jan 2013 to 26th July 2018). *RA* rheumatoid arthritis, *SpA* spondyloarthritis, *OA* osteoarthritis, *JIA* juvenile idiopathic arthritis, *SLE* systemic lupus erythematosus, *SS* Sjogren's syndrome, *SSc&MCTD* systemic sclerosis and mixed connective tissue disease, *IIM* idiopathic inflammatory myositis, *AAV* ANCA-associated vasculitides, *OV* other vasculitides, *FM* fibromyalgia, *OP* osteoporosis

Rheumatology practice

Rheumatoid arthritis

Rheumatoid arthritis is the most common form of inflammatory arthritis dominating clinical rheumatology practice [13]. For the last 30 years, there has been a great gap in epidemiological data on the prevalence of RA in Bulgaria. A report prepared for the European Federation of Pharmaceutical Industry Associations estimated that 0.48% of the Bulgarian population older than 19 years is affected by RA. About half of the patients are at the age of 64 or older [14]. However, a study dating back from 1977 reported approximately twofold higher (0.98%) prevalence of RA [15]. Therefore, the actual number of adults in Bulgaria suffering from RA ranges from 28,000 to 56,000. Diagnostic decision making is often based on the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) RA criteria [16], despite being classification and not diagnostic criteria. Although we did not find any published data, regarding the initial treatment of RA in Bulgaria, in the authors' perspective, methotrexate monotherapy or methotrexate with low-dose "bridge" glucocorticoids are the most common initial treatment approaches. In mild cases or when methotrexate is contraindicated (hydroxy)chloroquine, sulfasalazine or leflunomide may be initiated. The most frequently used combination of conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) comprises methotrexate, sulfasalazine and (hydroxy)chloroquine. In recent years, however, combination therapy of csDMARDs is less commonly prescribed in clinical practice, due to the higher level of toxicity of these combinations in comparison with monotherapy [17] and the higher rate of profound responses with biologics [18]. The challenges in RA management lie when the treatment with csDMARDs failed. Out- and inpatient rheumatologists cannot initiate immediate treatment with biologics or targeted synthetic disease modifying anti-rheumatic drugs (tsDMARDS). They are obliged to send their patients with RA to centralized rheumatology centers with the proposal for treatment initiation with biologics or tsDMARDS. An expert medical decision for funding of biological and targeted synthetic DMARDS by Bulgarian NHIF is issued only in three specific standing committees in the country, located in specialized rheumatology centers of university hospitals in the three largest cities in Bulgaria. The NHIF criteria for funding are lagging behind the current EULAR recommendations [19] and guidelines for the management of RA at national level developed initially in 2008 and last updated in 2018 [20–22]. These are the main obstacles that hinder the treatment process of patients not only with RA, but also with other rheumatic diseases (Table 3).

Spondyloarthritis

The spondyloarthritis (SpA) is an inter-related group of inflammatory rheumatic diseases characterized by axial and peripheral arthritis, enthesitis, and dactylitis [23]. Extraarticular manifestations includes uveitis, psoriasis, and inflammatory bowel disease (in order of decreasing prevalence) are also characteristic for SpA [24, 25]. Although the modified 1984 New York criteria for classification of ankylosing spondylitis [26] are still being intensively used for diagnosis and are currently a required criterion for funding the treatment with biologics by Bulgarian NHIF [21, 22], Bulgarian rheumatologists more and more often relies on the Assessment of SpondyloArthritis international Society (ASAS) criteria [27, 28], using modern imaging modalities such as magnetic resonance aiming for the earliest diagnosis of spondyloarthritis. In pursuit of new diagnostic approaches, Ivanova et al. found

Table 3 Comparison of the local and EULAR recommendations and criteria for funding of Bulgarian NHIF for the use of biologic and targeted synthetic disease modifying anti-rheumatic drugs in rheumatoid arthritis

	Disease activity level for starting of bDMARD/tsDMARD	X-ray stage	Previous use of csDMARDs	Predicted first-choice bDMARD/tsDMARD	Switch of bDMARD/tsDMARD	Index used for assessing response	X-ray monitoring	Time to assess response	Topics of special interests		
									PG&BF	Surgical treatment	TBC
NHIF, 2018	DAS28 > 5.1	Stage II or higher	At least 2 csDMARDs, one of which MTX for a total 6 months	IFXb, ADA, or ETN*	Not specified	DAS28	Not specified	3 months	CI	Not specified	CI
BRS, 2018	DAS28 > 5.1	Not specified	At least 2 csDMARDs, one of which MTX or LEF, for a total 6 months	IFXb, ADA, ETN, CERT, GOL, TOC, RTX, or TFB**	Not specified	DAS28	After 1 year	3 months	Addressed	Addressed	Addressed
EULAR, 2016	T2T approach: moderate or high disease activity (after 6 months) or no improvement (after 3 months)	Not specified	1 csDMARD, preferably MTX	IFX, ADA, ETN, CERT, GOL, ABA, IL6i, RTX ***, or JAKi	T2T approach: moderate or high disease activity (after 6 months) or no improvement (after 3 months)	Preferably CDAI or SDAI	Not specified	3 months	Not specified	Not specified	Not specified

ABA abatacept, *ADA* adalimumab, *bDMARD* biological disease modifying anti-rheumatic drugs, *BRS* Bulgarian Rheumatology Society, *CDAI* Clinical Disease Activity Index, *CERT* certolizumab, *CI* contraindication, *csDMARDs* conventional synthetic disease modifying anti-rheumatic drugs, *DAS28* Disease Activity Score 28, *GOL* golimumab, *ETN* etanercept, *EULAR* European League Against Rheumatism, *JAKi* jak-inhibitors, *IFX* infliximab, *IFXb* infliximab biosimilar, *IL6i* interleukin6-inhibitors, *LEF* leflunomide, *MTX* methotrexate, *NHIF* National Health Insurance Fund, *PG&BF* pregnancy and breastfeeding, *RTX* rituximab, *SDAI* Simple Disease Activity Index, *T2T* treat-to-target, *TBC* tuberculosis, *TFB* tofacitinib, *tsDMARD* targeted synthetic disease modifying anti-rheumatic drugs

*The predicted first-choice bDMARD/tsDMARD is based on a requirement of Bulgarian NHIF for initiating treatment in patients without prior bDMARD or tsDMARD use: The therapeutic course with the highest cost-effectiveness should be chosen first

**The predicted first-choice bDMARD/tsDMARD is based on the current availability of the drugs in Bulgaria

***The EULAR recommendations also includes EMA/FDA approved biosimilars

that serum cytokines such as tumor necrosis factor-alpha and interleukin-18 in ankylosing spondylitis were associated with disease activity [29]. Although, to date, NHIF funded biologics only in patients with radiographic sacroiliitis [21, 22], in the authors' perspective, Bulgarian rheumatologists try to adhere to the recent management recommendations for axial and peripheral SpA, which advocated individualization of the treatment target and achievement of clinical remission/inactive disease of musculoskeletal and extra-articular manifestations [25, 30]. Guidelines for the management of psoriatic arthritis and axial SpA at national level were initially developed in 2008 and were a subject to an update in 2018 [31, 32]. The treatment of non-radiographic axial spondyloarthritis (nrAxSpA) was also addressed in the latest version of Bulgarian guidelines for axial SpA, since patients with nrAxSpA share the same clinical characteristics and the same burden of disease and are also characterized with the same response to anti-inflammatory medication as patients with radiographic axial SpA [33].

Osteoarthritis

Osteoarthritis is the most common cause of joint pain associated with different degree of physical disability, decreased quality of life and life expectancy [34–36]. Historically, the term "osteoarthritis" was initially introduced to describe a common clinical finding: painful and deformed joints in elderly people. Although more than 60 years have passed from the radiographic characterization given by Kellgren and Lawrence [37], the modern Bulgarian rheumatologist still relies on the radiographic features of OA to establish the diagnosis and track disease progression: joint space narrowing, subchondral osteosclerosis, subchondral cysts and osteophytosis [38]. However, the current trend is to avoid unnecessary tests, particularly radiographs, when the patient presents with typical signs and symptoms of OA [39]. Unfortunately, the symptomatic and radiographic stages of the disease often occur relatively late into the progression of OA. Furthermore, significant evidence has been recently accumulated that there are early, pre-symptomatic and pre-radiographic biomarkers, which if detected, may allow for earliest possible treatment [40]. This created the need for further search, identification and verification of novel diagnostic modalities in patients with OA reflecting the process of joint remodeling. The circulating serum biomarkers cartilage oligomeric matrix protein (COMP), matrix metalloproteinase-3 (MMP-3) and Coll2-1 have recently been investigated in Bulgarian population, establishing the relationship between MMP-3 and OA generalization and COMP and structural changes [41]. Although, to date, greater understanding of the pathogenetic mechanisms in OA has accrued, the applied in clinical practice conservative treatment approaches are still aiming at relieving symptoms rather than influencing the biochemical environment of the joint and the disease progression [42]. Commonly prescribed medications include analgesics, non-steroidal anti-inflammatory drugs, and symptomatic slow-acting drugs for OA. Local injections of glucocorticoids, hyaluronans, and platelet-rich plasma are often applied in refractory cases [43].

Systemic lupus erythematosus

Systemic lupus erythematosus is a complex polygenic autoimmune disease characterized by a variety of clinical manifestations and a wide profile of autoantibodies [44]. Genetic polymorphisms in cytokine genes, which influence gene expression and cytokine production, may have an important impact on SLE susceptibility and severity [45]. Although the updated SLICC criteria are designed to be more inclusive in identifying patients with SLE (at the price of reduced specificity) [46, 47], in the authors' perspective, the set of classification criteria, proposed by ACR and modified in 1997 [48], are still widely applied and used even for diagnostic purposes among rheumatologists in Bulgaria because of their easier implementation in the routine workflow of clinicians. However, at the very early stage of the disease, when an inadequate number of features are met, the ACR criteria may have suboptimal sensitivity [49]. Treatment may vary widely depending on the involved organ(s) or system(s) and is usually initiated with antimalarials in uncomplicated cases. In renal, central nervous system and severe vascular involvement we adhere to the current EULAR recommendations [50–52], using potent immunosuppressive therapy such as pulse regimen of intravenous cyclophosphamide in combination with high-dose glucocorticoids. Lately, new treatment options, represented mainly by novel biologic agents, are emerging and Bulgarian researchers are actively taking part in their investigation [53–55].

Sjogren's syndrome

Sjogren's syndrome (SS) is a chronic slowly progressive autoimmune disorder characterized by lymphocytic infiltration of the exocrine glands, mainly the lacrimal and salivary glands, resulting in impaired secretory function [56]. It may present either alone, primary SS, or in the context of an underlying autoimmune disease, most commonly RA, or SLE (secondary SS) [57]. The lack of any published and indexed by Scopus articles in the last 5 years (Table 2) presents the great "gap" of rheumatology science in Bulgaria in terms of SS. From practical point of view, Bulgarian rheumatologists adhere to the treatment goals set by Sjögren's Syndrome Foundation: symptom palliation, prevention of complications and proper selection of patients for immunosuppressive therapy [58]. If patients are complaining of inflammatory musculoskeletal pain, in addition to sicca

symptoms, antimalarials and other csDMARDS are used as first-line therapy. In case of serious organ manifestations, more potent immunosuppressants such as azathioprine, cyclophosphamide, mofetil mycophenolate, and cyclosporine A in combination with glucocorticoids are applied.

Systemic sclerosis

Systemic sclerosis (SSc) is a multisystem progressive autoimmune disease characterized by impairment of microcirculation and deposition of connective tissue in the skin and internal organs, accompanied by immunological events [59, 60]. Three times more common in women [61], systemic sclerosis has a prevalence ranging from 7/million to 489/million, associated with geographical variations [62]. The 2013 ACR/EULAR classification criteria validated the routine testing of anti-centromere, anti-topoisomerase I, anti-RNA polymerase III autoantibodies but also encouraged the development and validation of wider panel biomarkers for diagnostic and monitoring purposes [63]. Following these recommendations, Krasimirova et al. examined a wide panel of specific autoantibodies in Bulgarian population and introduce them for routine clinical practice [64]. Considering the significant complexity and heterogeneity of systemic sclerosis and the limited evidence for available treatments, [65] we, as clinicians, remain debtors to patients with scleroderma. Current treatment strategies for systemic sclerosis are aimed at managing complications and providing symptomatic relief [66].

Idiopathic inflammatory myopathy

Idiopathic inflammatory myopathies (IIMs) are a group of heterogeneous, systemic diseases, characterized by muscle weakness, muscle enzyme elevations, inflammation on muscle biopsy, and extra muscular manifestations [67, 68]. IIMs can be differentiated into several major and distinct subsets: polymyositis (PM), dermatomyositis (DM), myositis associated with another connective tissue disease or cancer, juvenile myositis (juvenile DM and juvenile PM) and inclusion body myositis. Despite the great number of diagnostic modalities we already use, including an immunological panel detecting myositis-associated and -specific antibodies, the diagnosis of IIMs still remains a challenge for the clinician. This is due to the fact that IIMs may be associated with another connective tissue disease and most importantly—with cancer. Muscle biopsies from Bulgarian patients with PM or DM revealed the following characteristic histopathological changes: infiltrates of small mononuclear cells (57% of all muscle biopsies), necrotic fibers (50%), interstitial fibrosis (60%), atrophy (40%). Important histopathologic differences were described among dermatomyositis and polymyositis [69]. In the authors' opinion, glucocorticoids remain the mainstay of initial treatment of IIMs. First-line conventional immunosuppressive drugs include either azathioprine or methotrexate. When they fail, cyclophosphamide or mofetil mycophenolate are taken into consideration. The application of intravenous immunoglobulins is also a valuable alternative for treating therapy-resistant patients with IIMs [70].

Vasculitides

Reflecting the evolvement of disease names and definitions over time as medical knowledge and understanding advance, in 2012 the Chapel Hill Consensus Conference (CHCC) defined the disease nomenclature system currently used by clinicians. It specified the name that should be used for a specifically defined disease process according to the predominant vessel involvement and distinctive features. It is neither a classification system that specifies what findings must be observed in a specific patient to classify that patient for clinical research nor a diagnostic system that directs clinical management [71]. Nevertheless, it provides an irreplaceable guidance in the proper naming of individual vasculitides and provides a prerequisite for their proper diagnosis and management.

Takayasu arteritis (TA) and giant cell arteritis (GCA) are defined as large vessel vasculitis (LVV) affecting large arteries more often than other vasculitides [71]. While TA affects predominantly the aorta and primary branches and occurs more common in reproductive age, GCA damages mainly the cranial arteries and is characteristic of elderly population [72, 73]. Bulgarian contribution in the scientific field of LVV mainly consists of case reports and case–control studies [74, 75] due to the relatively low prevalence of both diseases (especially TA) and the lack of multicenter cooperation among specialized hospitals. In the authors' perspective, glucocorticoids remain the mainstay of therapy in LVV. Several steroid-sparing agents such as azathioprine, methotrexate, cyclophosphamide, and mycophenolate mofetil are also used in clinical practice. Anti-interleukin-6 agents are discussed as an alternative to conventional immunosuppressive treatments in refractory cases and represent an effective glucocorticoid sparing treatment option after the approval of tocilizumab by the US FDA and EMA for the indication GCA in 2017 [76, 77]. However, the Bulgarian NHIF is currently not funding it for this indication and most of the patients cannot afford it. In the past few years, Bulgarian rheumatologists have established a successful partnership with cardiovascular centers specialized in endovascular procedures—a critical part of the comprehensive management of TA [75].

Behçet's syndrome (BS) is another systemic vasculitis that is characterized by variable vessel involvement and may affect the skin, mucosa, joints, eyes, arteries, veins, nervous

system and the gastrointestinal system [78]. The disease shows significant geographic differences in its prevalence and clinical features [79]. Located near the "Silk Road", Bulgaria may have a higher prevalence of BS than most of the European countries. However, this hypothesis remains speculative, as, to our knowledge, no published data are available for our country. Management of patients with BS mainly depends on the particular organ(s) and system involved [78]. However, in the authors' point of view, the most commonly prescribed first-line treatment remains colchicine in patients with mucocutaneous and/or joint involvement in a combination with low-dose glucocorticoids. In line with the latest EULAR recommendations, high-dose glucocorticoids followed by slow tapering and more potent immunosuppressants, including azathioprine, cyclosporine A, cyclophosphamide, are reserved for severe cases. An off-label prescription of monoclonal anti-TNF antibodies could be considered in refractory patients [78], although funding of the treatment course may present a difficult task.

According to the CHCC nomenclature ANCA-associated vasculitis (AAV) are "necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries), associated with myeloperoxidase (MPO) ANCA or proteinase 3 (PR3) ANCA" [71]. A small, single-center study comparing the prevalence and the clinical features of the MPO-ANCA and the PR-3-ANCA positive AAV showed that the Granulomatosis with polyangiitis was the most common AAV in Bulgaria, microscopic polyangiitis was the second most common and Churg–Strauss syndrome took the last third place [80] which is in consistence with the published data. According to the same study, the vasculitis in the ANCA-negative patients had milder course, usually involved the upper respiratory tract and the lungs and does not lead to organ insufficiency. First-line treatment of AAV is pulse therapy with cyclophosphamide and glucocorticoids. In refractory to treatment with conventional immunosuppressants cases Bulgarian NHIF is currently funding treatment with anti-CD20 monoclonal antibodies.

Bulgarian Rheumatology Society (BRS)

With 150 members, the BRS is the national scientific society of rheumatologists in Bulgaria. BRS is a member of EULAR. The society was founded in 1983 when the Union of Medical Societies in Bulgaria unanimously decided to separate the Rheumatology Section of the Scientific Medical Society of Cardiology and Rheumatology to form an independent organization called initially Scientific Medical Society of Rheumatology. In 1986, at the national conference level, the newly transformed society adopted its first statutes. In 2000 it has been renamed to its modern name Bulgarian Rheumatology Society (BRS) [6]. For 26 years, BRS publishes a scientific medical journal with four printed issues annually called "Revmatologiia", indexed currently by Scopus. Its main goals are to develop a national program for diagnosis, prevention and treatment of rheumatic diseases, to take part in solving specific scientific tasks in the field of rheumatology, to initiate and participate in the development of recommendations, guidelines and other materials concerning rheumatic diseases.

Conclusion

Although the western world clearly dominates the production of scientific publications in rheumatology [8], Bulgarian rheumatology may present another perspective for diagnosis and management of patients with rheumatic diseases in a cost-constrained environment. Nevertheless, from the long list of challenges that are awaiting us as a society (Table 4), rheumatology science and practice in Bulgaria has still a long way to go to take its deserved place among the other European countries. In this broad sense of the modern-day context, the management of the wide spectrum of MSK diseases and the scientific contribution in the field of rheumatology are strongly influenced by socioeconomics. Bulgarian rheumatologists have no choice but to adhere to the world-renowned recommendations and guidelines for good clinical practice and management of patients with rheumatic diseases protecting them from experimenting at the expense of the patients with rheumatic diseases. Therefore, a unique to the needs of the Bulgarian population, cost-effective model for the management of rheumatic diseases should be developed.

Table 4 Future challenges of Bulgarian rheumatology science and practice

Future challenges	Goals
Development of a unified Bulgarian national register for rheumatic diseases	To improve the treatment and follow-up of patients with rheumatic diseases To create a source of valuable information with practical and scientific value
Gathering epidemiological data of rheumatic diseases	To gather, analyze and publish epidemiological data regarding the prevalence and distribution of rheumatic diseases in Bulgaria
Development and management of screening programs for early identification of rheumatic diseases	To identify patients with early and "very" early rheumatic diseases, so that first-line treatment can be initiated before significant disability or joint destruction occur
Implementation of new diagnostic modalities specific for rheumatic diseases	To implement new diagnostic technics and most importantly, to train adequately the medical staff through international exchange programs to apply them in clinical practice
Development of cost-effective models in rheumatology practice	To identify and manage larger numbers of patients with rheumatic diseases in our stringent cost control setting
Balanced distribution of rheumatologic care in Bulgaria	To grant equal access of patients to rheumatologic care
Multicentre collaboration	To establish and develop the collaboration among rheumatology centers and clinics in Bulgaria and among different medical specialties participating in rheumatic patients' management

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Compliance with ethical standards

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

Conflict of interest Tsvetoslav Georgiev declares that he has no conflict of interest. Rumen Stoilov declares that he has no conflict of interest.

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