

One year in review 2020: economic and organisational aspects in rare and complex connective tissue diseases

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ABSTRACT

Rare and complex connective tissue diseases (rCTDs) encompass a considerable number of diseases and syndromes and their variability highly impacts on the clinical management, resulting in variable economic and organisational burden that might represent a challenge for healthcare systems. This paper is aimed at providing an overview of the most recent evidence regarding the economic and organisational impact of rCTDs. In particular, this work discusses the most relevant data on specific aspects related to health economics in rCTDs published in 2019.

Introduction

Rare and complex connective tissue diseases (rCTDs) imply great clinical and economic burden but also a significant challenge for healthcare systems because of the risk of not responding to patients' needs and of not guaranteeing equal access to treatment. Following this Journal's well-experienced periodic project of annual reviews (1-6), this paper gives a brief overview on updated knowledge about economic and organisational impact of rCTDs. In particular, this work presents a selection and a revision of the most relevant articles on the health economic-related aspects of rCTDs published in 2019. The diseases included in this article are: Systemic Lupus Erythematosus (SLE), Systemic Sclerosis (SSc), Antineutrophil Cytoplasmic Antibody-Associated Vasculitis (ANCA - AAV), Giant Cell Arteritis (GCA), Large Vessel Vasculitis (LVV), Behçet's syndrome (BS), Sjögren's Syndrome (SS), Dermatomyositis (DM) and Ehlers-Danlos syndromes (EDS). Limiting to articles, focused on economic and organisational impact of the previously mentioned rCTDs on the healthcare system, published within the 1st of January 2019 to the 31st of December 2019,

we performed a literature search in PubMed database and ISI Web of Science database with the following keywords: "lupus erythematosus, systemic", "scleroderma, systemic", "myopathy, inflammatory", "myositis", "dermatomyositis", "polymyositis", "antisynthetase syndrome", "sjogren's syndrome", "ehlers-danlos syndrome", "immunoglobulin G4-related disease", "antiphospholipid syndrome", "polychondritis, relapsing", "undifferentiated connective tissue diseases", "mixed connective tissue disease", "behcet syndrome", "anti neutrophil cytoplasmic antibody associated vasculitis", "cryoglobulinemia", "large vessel vasculitis", "giant cell arteritis", "takayasu arteritis", "Access", "Affordable", "Affordability", "Assessment", "Budget impact", "Burden of disease", "Care process", "Communication", "Cost", "Cost-benefit", "Cost-effectiveness", "Cost of illness", "Cost minimization", "Cost-utility", "Delivery of care", "Development", "Economic evaluation", "Equity", "Funding", "Health benefit", "Health policy", "Health related quality of life", "Health technology assessment", "Healthcare", "Impact", "Implementation", "Incentives", "Innovation", "Knowledge sharing", "Management", "Organization", "Organizational", "Policy implication", "PREMs", "PREs", "Pricing", "Process", "PROMs", "PROs", "Quality", "Quality of life", "Regulator", "Reimbursement", "Resource allocation", "Social", "Social impact", "Social value", "Socioeconomic", "Sustainability", "Value", "Value for money". Both adult and paediatric patients have been considered in the population studied.

Systemic lupus erythematosus

The economic aspects on systemic lupus erythematosus

The crucial value of performing a budget impact analysis is mainly rep-

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resented by the possibility of gathering relevant information to enable the evaluation of an appropriate healthcare decision-making process, such as estimating the financial viability of introducing a new medical treatment or diagnostic technologies.

The costs directly associated with the treatment of SLE have been recently assessed in a budget impact analysis (7) from the payer perspective (Spanish National Healthcare System), comparing two different treatment scenarios: on one hand the standard therapy (ST) and intravenous belimumab (the current scenario), and on the other hand, a new scenario simulating the costs related to the switching to subcutaneous belimumab (SC) and ST. The costs considered in the analysis were: the cost related to the route of administration, the pharmacological cost and the costs linked to the management of disease flares. The results of this study clearly demonstrated that the treatment of SLE patients with SC belimumab generated lower direct healthcare costs than the treatment with belimumab IV, suggesting that could imply a relevant saving (6 million euros over 3 years) for the healthcare system not only in terms of direct costs but also in terms of lower usage of healthcare facilities.

Direct costs are the costs directly associated with the healthcare intervention, *i.e.* the costs incurred by the healthcare provider for the provision of the service: medical staff, medications, accommodations, etc. An overview about the actual costs of SLE patients to the healthcare system in developing countries was provided by a Colombian (8) study that considered the analysis of the SLE treatment costs providing data from big claims databases with national coverage. All-cause of costs for patients with SLE were considered, including the costs for outpatient and inpatient care, the costs for basic and specific immunological tests, and the costs for treatments. The care costs associated to the disease severity were estimated by means of a multivariate linear regression analysis. The results of the study showed an average annual per-patient direct cost equal to \$2,355 and that the management of SLE patients in devel-

oping countries could imply more direct costs than expected.

A recent US article (9) provided an update on the economic burden of SLE, assessing a total of 30,086 SLE patients from two large administrative claims databases. During the first year after diagnosis, a SLE patient had on average 26 physician visits, 23.7 prescription claims, 1.7 inpatient admissions and 2 hospital days. A total SLE annual all-cause median cost was calculated as \$8712 per patient per year and pharmacy costs accounted for 21% of total costs (corticosteroids and hydroxychloroquine; non-steroidal anti-inflammatory drugs-NSAIDs, immunosuppressants, angiotensin converting enzyme inhibitors-ACEs, and angiotensin II receptor blockers-ARBs). It is interesting to mention that the use of biologics is limited (~2%); even if belimumab for SLE

patients not responding to conventional treatments was approved by the FDA in 2011, this biologic medication was not frequently prescribed in SLE patients (1% of all SLE patients took belimumab during one year of follow-up). It is still unclear whether this drug is rarely prescribed due to economic issues or due to other issues related the treatment decision-making process.

Further data from additional economic real-world studies could provide a better understanding about the medication utilisation and disease characteristics, and to support future healthcare.

An important aspect to consider in economic evaluations is represented by the indirect cost of the illness. Indirect costs are the costs incurred for the productivity loss due to the disease. Generally, indirect costs should be considered in the context of informed decision-making process from a societal perspective that is the wider viewpoint of the economic analysis (aggregating all the perspectives: individual patients, clinicians, hospital managers, healthcare plans administrators, reimbursement authorities, the National Healthcare ministers). Estimating indirect costs may include the time lost for paid work and unpaid work (unpaid production losses due to health conditions, work-disabled, retirees, and

homemakers, as well all those who remain employed but have difficulty performing their work lead to suboptimal and inequitable resource allocation). The results of a recent Canadian work (10) contributed to the understanding of the societal burden of the disease in a cohort of systemic autoimmune rheumatic diseases (SLE, SS and SSc). In particular, the study explored the presenteeism in paid work and unpaid work loss in SLE, the excess productivity costs of SSc, and the productivity costs in SS. A sample of patients was randomly selected for the 3 diseases; in particular, the study included 167 SLE patients, 42 SSc patients and 90 SS patients; matched controls were 375. Patients were invited to complete a cross-sectional survey aiming at gathering information about their paid and unpaid work. Employment and productivity data were collected using two validated tools, the Work Productivity and Activity Questionnaire (WPAI), and the Valuation of Lost Productivity (VOLP). The WPAI was used to determine absenteeism and presenteeism from paid work, while time loss from unpaid work was assessed using VOLP questionnaire. The results obtained showed that most of the productivity costs were mainly due to presenteeism and unpaid work impairments. About SSc patients, 56% of them was employed and 32% was not due to disability. The annual excess productivity costs per person were \$4,357 (Canadian dollars) for SS, \$4,494 in SLE and \$3,582 in SSc patients. Most of total productivity costs were from unpaid work loss: 60% in SS, 73% in SLE, 74% in SSc and 47% in controls.

Considering all the challenges related to the SLE management, a study (11) proposed an intervention to improve health behaviours, beliefs and outcomes in African American women with SLE, and measured the cost-effectiveness of the intervention used. The intervention used in this study included a peer mentoring programme, the Peer Approaches to Lupus Self-Management (PALS). The PALS programme consisted of 12 weeks of peer mentoring with educational session by telephone for approximately 60 minutes every week.

Patients included in PALS programme demonstrated a decrease in patient reported disease activity, depression and anxiety. In addition, patients were more engaged in the management of their disease and the PALS programme demonstrated to be cost-effective.

Health-related quality of life in SLE

SLE patients often experience poor health-related quality of life (HRQoL) which can be even worse than in other chronic diseases. Several studies developed tools to measure the HR-QoL and QALYs in SLE patients. Recently, a Spanish study (12) aimed at correlating the multimorbidity levels of the SLE with HRQoL, evaluating the related costs. The study found that SLE direct costs per patient represented 71.92% of the total costs (primary care, hospital admissions, outpatient pharmacy costs). In addition, the main HR-QoL issues in the selected patients were mostly related to mobility, ability to perform usual activities, and pain/discomfort. The factor most affecting HRQoL was represented by the age of patients while the other factors related to HRQoL included disease activity, damage and severity. Another interesting study (13) assessed QoL parameters in 126 Indian SLE female patients in durable remission. The tools used to measure the QoL included the Short-Form-12 (SF12), fatigue severity scale, and a structured interview. Study results showed that patients in remission had comparable parameters of QoL, both physical and mental, compared to matched controls group. Better physical component summary was associated with less fatigue, longer disease duration, and complete remission, while better mental component summary was associated with less fatigue and absence of depression. The clinical remission impact on QoL was also investigated exploring how the socio-demographic factors and medical variables are related to the QoL of the disease itself (14). This retrospective cross-sectional study included 161 SLE patients that were assessed by means of the Lupus Erythematosus Quality of Life Questionnaire. Results from the model suggest that none of the variables considered in the study explains

the QoL of the patients selected. However, the results of the fuzzy models suggest that being female, young and a shorter time to diagnosis, imply higher levels of QoL in these types of patients. Patients' perceptions about how disease and treatments affect their physical, mental, and social function received raising attention in clinical research, showing how patients' involvement has a pivotal role in long term treatment results. In particular, the effects of two biologic treatments (Belimumab and Rituximab) on HRQoL were investigated in patients with SLE (15). Data were collected prospectively at treatment initiation and at months 3, 6, 12, and 24, using the Short Form 36 (SF-36) health questionnaire, the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale, the EuroQol 5-dimension (EQ-5D) instrument and the Stanford Health Assessment Questionnaire disability index (HAQ DI). Normative values derived from Swedish population-based dataset were matched for age and sex and used for the purpose of comparisons. Results found discrepant patterns of HR-QoL response to biologic therapy with belimumab versus rituximab during follow-up. Patients treated with belimumab reported gradual improvements, while those treated with rituximab showed rapid improvements in mental component summary scores. Patients' perceptions of HRQoL showed discrepant patterns over time in the 2 treatment groups and could provide additional information along with the clinical evaluation of biologic therapy.

With regards to physical activity and QoL, a cross-sectional study aimed at analysing whether physical fitness is correlated to a better health-related QoL in 70 women with SLE (16). The back-scratch test assessed flexibility chair stand and the handgrip strength tests assessed muscle strength, and the 6-min walk test assessed the cardiorespiratory fitness (CRF). HRQoL was assessed through the 36-item Short-Form Health Survey (SF-36). Findings of the study suggested that muscle strength and CRF are positively associated with different dimensions of HRQoL while flexibility showed contradictory results.

The clustered fitness score was consistently associated with better scores in the physical function, bodily pain, and physical component summary. Overall participants with high fitness presented better scores in HR-QoL, especially in those dimensions associated with physical health.

Self-management and care delivery in SLE

Educational interventions based on peer-led group-based modalities could have positive effects on self-management of the disease by the patients. A recent study (17), explored the perceived impact of the Chronic Disease Self-Management Program (CDSMP) on healthcare engagement behaviours among African American women with SLE. CDSMP is a longitudinal, qualitative study designed to explore women's perceptions of the self-management program living with SLE. The study suggested that the CDSMP had the significant positive effect on quality of communication between patients and doctors, and improvement in the medication side effect management.

Educational interventions, coping styles, social support, and information support are usually considered essential factors able to influence illness uncertainty, with considerable effects on treatment compliance behaviour and QoL. On this regard, a Chinese study (18) investigated the relationships between illness uncertainty, social support, and coping modes among 200 SLE patients who have been hospitalised for over a week. Mishel Uncertainty in Illness Scale (MUIS), Social Support Rating Scale (SSRS) and Medical Coping Modes Questionnaires (MCMQ) questionnaires' were employed. Research findings demonstrated that the illness uncertainty of hospitalised patients was moderate. More precisely, unpredictable disease process, prognosis and unclear symptoms are the main sources of illness uncertainty. Educational level and family income are major influencing factors. The study also showed that patients with high illness uncertainty were those with high school education and a monthly income below 3000 yuan. Such evidence pointed out that medical

staff should give more attention to the illness uncertainty of SLE patients, as it can lead to more effective and safer therapeutic effects. To identify opportunities to improve outpatient care, a retrospective study (19) was conducted in SLE patients that accessed the Emergency Department (ED) for ≥ 3 visits from 2013 to 2016. Pain-related ED visits were more common among persistent ED patient users (32%) than limited ED patient users (18%). Persistent patients with pain-related encounters accounting for more than 10% of ED use, are more likely to be obese, have comorbid conditions, and use long-term opioid therapy. The study observed also that patients with SLE who persistently frequented the ED were young females, that were living in more economically deprived areas and that had a high burden of depression.

Systemic sclerosis

The economic aspects to consider in systemic sclerosis management: some improvements in understanding the direct medical costs and indirect costs in SSc management.

An interesting improvement in the analysis of cost drivers in Systemic Sclerosis (SSc) was accomplished by a recent assessment of healthcare resources utilisation in SSc patients enrolled in the Australian Scleroderma Cohort Study from 2008 to 2015. Hospital admissions, emergency department visits and ambulatory care were the main costs drivers in SSc patients with pulmonary arterial hypertension (SSc-PAH) (20). PAH prevalence in SSc is about 10–13%, and it is the leading cause of SSc-related mortality with 15.2 years of life lost (YLL), and in the study, patients with SSc-PAH experienced poorer prognosis than SSc with non PAH. SSc-PAH needed more frequent hospital admissions mainly on average 1.5 times a year than SSc with not PAH with a higher length of stay (3.5 days vs. 1.9 days), and a diagnosis at admission for PAH followed by heart failure; SSc-PAH experienced more frequent emergency department admissions, and needed more ambulatory care services than SSc with not PAH. SSc patients experiencing digital ulcers (SSc-UD)

had a higher annual frequency of hospital admissions than SSc patients with not DUs (2.1 compared with 1.5) (21), with a longer length of stay; hospitalisation costs, frequency of emergency department visits and the related costs are higher in SSc-DU patients than patients with not DU, while there is an equal ambulatory care service utilisation for both SSc-DU and SSc patients with not DU patients. About the HRQoL (measured by means of FS-36 tool), SSc patients with not DU experienced better physical component score (PCS) than SSc-DU patients. SSc patients with interstitial lung disease (SSc-ILD) reported worst HRQoL than SSc patients (22) and significantly even lower with increasing ILD severity. SSc-ILD patients needed more frequent and longer hospital admissions (the annual average number of hospital admissions was 2.3 days for SSc-ILD and 1.5 for SSc) compared with the SSc patients with not ILD (2.2 compared with 1.9). Moreover, SSc-ILD patients experienced more frequent emergency department admissions than SSc patients, and needed more ambulatory care services than SSc with not ILD. Severity of ILD was associated with significantly more healthcare resources utilisation and costs.

Besides healthcare resources utilisation and direct medical costs, indirect costs were assessed (23) during 1 year after SSc diagnosis, obtaining the data from a US large nationwide administrative claims database (from January 2005 to March 2015). Compared with the control group (individuals with not a SSc diagnosis), patients with SSc needed more inpatient admissions (0.7 vs. 0.3 events), days of hospitalisation (3.7 days vs. 1.1 days), emergency department visits (0.7 vs. 0.3) and outpatient visits (28.3 vs. 10.3). The annual direct medical costs were about 3-times higher during the first year after the diagnosis than the control group. The work productivity loss, due to the disability or due to medically-related absenteeism, were significantly higher for SSc patients: compared to the control group, they had 14 extra days of work loss in the first year of the diagnosis, and total annual indirect costs were significantly higher for SSc patients with a cost dif-

ference of USD 3,103 than the control group. Moreover, focusing more closely on SSc-ILD patients (24), preliminary results suggested that during the first 6-months after SSc-ILD diagnosis, the work productivity loss due to the disability or due to the medical related absenteeism was significantly higher than the control group: SSc-ILD patients had 18,4 more days of work loss (23.2 days compared to 4.8).

Patients' perception of the diseases and the quality of life in systemic sclerosis

Measuring the impact of healthcare on individuals HRQoL is a necessary step in care management for improving the understanding of the diseases. Usually, SSc patients experience fatigue, limitation of the ability to perform everyday activities, distress related to skin and internal organs symptoms, sleep disorders, difficulties in accepting the change of look of appearance due to the disease and low self-esteem.

At present, few studies focused on quality of life (QoL) in diffuse cutaneous Systemic Sclerosis (dcSSc). A recent international article (25) analysed the patient perception of the disease linked to both treatments and emotional burden, and the impact of joint problems, pain, fatigue, and skin complications on their QoL. Six countries (France, Germany, Italy, United Kingdom, Spain and United States) were involved, using the ethnography technique for the assessment of QoL. Results suggested that skin complications, pain and fatigue have a big impact on QoL and significant emotional burden in dcSSc patients, however, specific PRO instruments are still needed to capture symptoms and impact in dcSSc. Physical functions limitation and anxiety disorders are the two main factors associated with the QoL of SSc patients. This result was demonstrated by a large population multi-center Polish study (26) where the disease-specific questionnaire SScQoL was used for the first time as an alternative to the generic measure of QoL EQ 5D. Furthermore, a Korean study (27) compared the HRQoL in SSc patients with HRQoL of other rheumatic patients affected by

rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS), and healthy subjects for control. The patients HRQoL was measured by means of the Korean adaptation of the SF-36, the SF-6D and the EuroQol Five Dimensional (EQ-5D-3L). Results confirmed that SSc patients experienced significant poorer QoL, not only compared to healthy individuals but also in comparison with other rheumatic diseases considered: due to the multi-organ involvement SSc reported poorer mental health than RA and SLE patients; moreover, the degree of the skin involvement has a negative impact on both Physical Component Summary and Mental Component Summary scores in SSc patients. Finally, a pragmatic non-randomised study (28) explored the HRQoL comparing SSc patients treated, according to the needs of the SSc patient, with two different intravenous regimes of Iloprost (ILO). The HRQoL was assessed using EQ-5D-5L submitted via telephone. Even if a direct comparison among the groups was not possible since allocation was not randomly assigned, the results of the study showed similar HRQoL among patients enrolled in intravenous ILO regimens.

Vasculitis

Supporting decision makers: the health economic recent topics in vasculitis

In health economic evaluations many techniques are adopted for identifying, measuring, and evaluating differences in the costs and in the outcomes of procedures, treatments, and, more in general, of healthcare interventions, to support decision makers in choosing the best alternative.

The cost-effectiveness analysis (CEA) highlights a) the difference in the costs of the healthcare interventions, and b) the difference in the outcome between the different interventions, and c) calculates the incremental cost-effectiveness ratio (ICER), that suggests how much do we have to pay for an extra unit of benefit adopting a specific technology/procedure/therapy with respect to the standard one. The ICER helps decision-makers in establishing

whether the extra benefit of a specific healthcare intervention is worth of the linked extra costs. Recently, in the field of maintenance treatment in ANCA-AAV, a cost-effectiveness analysis has been performed to explore two different therapeutic strategies and their related cost-effectiveness (29). Specifically, the study aimed at assessing whether rituximab (RTX) is more cost-effective compared to azathioprine (AZA), when used as maintenance treatment. Data coming from 113 patients from the French MAINRITSAN trial were analysed within a time horizon of 28 months. The cost analysis performed in this trial showed that the use of RTX in ANCA-AAV patients represents a cost-effective care choice in terms of prevention of relapses (decrease in major relapses and accompanying resource use) and in quality-adjusted life years (QALYs) gained by patients. This economic analysis improved significantly the clinical effectiveness knowledge of the trial results, adding additional relevant information on the cost-effectiveness of the interventions involved in the trial.

In general, the burden of giant cell arteritis (GCA) in terms of healthcare resources consumption and costs impact, reflects the higher of morbidity of the disease (cardiovascular risks, diabetes, opportunistic infections) as this disease often implies hospitalisation, high-cost treatments and regular outpatients care. An Italian study estimated that the overall direct cost per patient-year was about €2374 (€61 for outpatient visits, €1661 for hospitalisation, €312 for prescribed medications, and €340 for medications directly dispensed by the hospital pharmacies) (30). Further economic analysis on the GCA gathered evidence on the costs associated with this rare disease. A study conducted in the United States (US) assessed the healthcare claims requested by GCA patients in a 5-year period and the data collected suggested that the use of steroids has a high impact on the costs of the disease. In particular, the use of high cumulative doses of oral glucocorticoid (OGC) were associated to adverse events (AE) and AE-related costs (31), that occurred in these patients.

The management of patients with GCA with polymyalgia rheumatica (PMR) absorbs significant additional costs compared to the management of patients with GCA alone, mainly because of the associated complications that raise in having both diseases. On this regard, a recent cost analysis (32) assessed the costs of GCA alone and the costs of GCA associated with PMR diagnosis. This analysis was performed taking into consideration the point of view of the French payer's perspective (the French Social Health Insurance – SHI) and it included direct medical costs (inpatient stays, outpatient stays, medication, medication equipment) and direct non-medical costs (only limited to transportation) within a time period of 5 years. The analysis concluded that GCA associated with PMR implies 76% additional costs compared to a diagnosis of GCA only. These extra costs are usually higher in the first 3 years after the diagnosis, compared to the costs calculated at the end of the 5-year follow-up.

Indirect costs are costs incurred due to the loss of productivity of patients and families caused by the illness. Typical examples of indirect costs are: the time off work due to sick leave, the early retirements, and the reduced productivity at work. Measuring indirect costs has significance in health economic evaluations if the patients are enabled to return to work or to their normal life because of the intervention or because of the illness. A recent Turkish multicentre study assessed the work-day loss in Behçet's patients, and demonstrated that the vascular and ocular involvement, the treatments protocols (immuno-suppressive medications), the disease durations (early durations), the frequency of visits, male gender and smoking habits, are predictor factors of work-day loss (33).

Capturing the patient's experience in living with vasculitis: the need for additional validated disease-specific measures, and the understanding of relationships between the illness perceptions and the self-assessment of the severity of symptoms.

Due to their large variability and systemic involvement, capturing the patient's

experience in vasculitis is often critical. Recently, the AAV-PRO for ANCA-AAV, and the BD-QoL for Behçet's syndrome (BS), were validated as disease-specific patient-reported outcomes (PROs). However, disease-specific tools aimed at capturing patients' experience are still needed for GCA and Takayasu's arteritis (TAK). With regards to GCA, only generic PROs such as SF-36 are available, while for TAK a disease-specific PRO was developed organising focus groups and individual interviews with Turkish and North-American TAK patients (34). The feasibility and the validity of using the Patient Reported Outcome Measurement Information System (PROMIS) instruments in vasculitis was recently investigated in a North-American longitudinal cohort of patients including also GCA and TAK patients. The most relevant PROMIS instruments selected were: fatigue, physical function, pain interference, cognitive function, and others have been added (sleep disturbance, social participation, sleep-related impairment, anger, social isolation and anxiety), and additional measurement of Health-related Quality of Life (HRQoL) has been done by SF-36 (35). The LVV Working Group within the OUTCOME MEASURE in Rheumatology (OMERACT) study suggested that the evaluation of the treatment response of patients with GCA and TAK patients, and more in general LVV patients, still needs a composed standardised set of outcome measures that should include organ and arterial function, biomarkers, fatigue, pain, death, imaging and patient-reported measures. The relationship between patient, physician, imaging and laboratory-based outcome measures was recently investigated in a US longitudinal cohort of LVV patients (36) by means of a multiple different outcome measures assessment: a) patients-reported outcomes measuring severity (Patient Global Assessment of Disease Activity - PtGlobal), fatigue (Multidimensional Fatigue Inventory - MFI), illness perception (Brief-Illness Perception Questionnaire - BIPQ), health related quality of life (36-item short form health survey - SF-36); b) physician-reported

outcomes (Physician Global Assessment of Disease Activity - PhGlobal); c) laboratory-based outcomes (Serologic Assessment - ESR, CRP); d) imaging-based outcomes (FDG-PET-computed tomography or FDG-PET-magnetic resonance imaging).

The understanding and the measurement of improvements in the BS patients' lives need the development of additional validated patient-reported outcome measures (PROMs) compared to the already existing Behçet's Disease Quality of Life (BDQoL) measure. A preliminary Turkish work provided useful consideration to be taken into account for future developments in this direction, identifying a list of domains that are inter-related with physical symptoms that need to be considered: symptoms (mucocutaneous symptoms, pain, eye symptoms, fatigue and sleep disturbances, gastrointestinal symptoms), impact on function (on speech, vision, mobility, daily activity and working), psychological impact (on emotions, on emotional management techniques), and social impact (on ability to socialise, on familiar relationship, on work) (37). Additional data come also from another Turkish study in which a revised version of the Illness Perception Questionnaire (IPQ-R) as a quantitative and multifactorial assessment tool, was used to evaluate the illness perception in Turkish BS patients and controls with psoriasis patients. The tool investigated 3 main sections: a) Identity (disease-specific symptoms); b) Beliefs about the illness; 3) Causes (personal ideas about aetiology of the disease) (38). The relationship between perceived health status and the psychological representations of the illness and the self-assessment of symptom severity (by means of the Nottingham Health Profile questionnaire and the Brief Illness Perception questionnaire) in patients with BS have been investigated in a UK study (39). The study demonstrated the direct effect of symptom severity on how the patient perceives his/her health status; that the cognitive components of the perceptions of BS explain the link between symptom activity and pain; as well as that the emotional components

of the illness influence the relationship between disease activity and the level of energy perceived by the patient.

Sjögren syndrome

Observed new trends, and the patients' perspectives of the disease in Sjögren syndrome

Sjögren's syndrome (SS) is a chronic systemic autoimmune syndrome and its clinical presentation can vary considerably from relatively mild sicca symptoms, arthralgias, and fatigue to severe systemic symptoms such as vasculitis, glomerulonephritis, and a host of neurological manifestations. SS can occur alone (primary Sjögren's syndrome) or with another autoimmune disease (secondary Sjögren's syndrome) such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and systemic sclerosis (SSc). With regards to potential differences in the characteristics of the disease, recent data from a cohort of German primary Sjögren's syndrome (pSS) patients (40) observed during the last twenty years (1996–2016) reported that: i) more than 90% of a total of 3000 patients are female; ii) 50% of patients were treated with antimalarials in 2016 compared to 31% in 1996, the consumption of methotrexate and azathioprine were stable overtime, 4.3% of pSS were treated with rituximab; iii) around 40% of the patients reported good global health; iv) about 50-60% of patients experienced good outcomes for pain, fatigue and sleeping disorder in 2016 showing an improvement compared to 2008; v) the patient's hospitalisation rate decreased from 13% in 1996 to 7% in 2016; vi) the employment rate (less than 65 years old) increased from 43% in 1996 to 64% in 2016, and early retirement decreased from 22% to 10%.

Additional supporting information in understanding the patient's adherence and the response to pharmacological treatments could be collected assessing the patient's personality characteristics. The psychological characteristics of patients with pSS have been assessed in a Serbian study (41) by means of a Five-Factor Model (FFM) analysing personality, depression, and anxiety. Specifically, the study inves-

tigated: the *Neuroticism* (tendency toward negative emotions with high reactivity to psychological change, emotional instability), the *Extraversion* (attitude to experience positive emotions), *Openness to experience* (tendency toward imaginations, creativity, ideas), the *Agreeableness* (altruistic orientation towards others) and the *Conscientiousness* (competence, order, self-discipline). pSS patients have specific personality traits that are comparable to other rheumatic patients such as Rheumatic Arthritis (RA). Being highly emotional (high neuroticism), pSS patients are more vulnerable, less capable of exerting control over impulsive behaviour and stress, and this could affect their physical functions, quality of life and overall treatment outcome. They also experienced a low positive subjective evaluation of daily activities (low extraversion) that can be explained by lower prevalence of high patients' satisfaction with family relationships, suggesting that family support can lead to more favourable life events in patients with pSS. Finally, the level of education may explain the pSS patients' level of openness to experience and the linked understanding of the disease; the observed level of agreeableness and conscientiousness in the pSS patients are similar with the healthy individuals.

Dermatomyositis

Dermatomyositis (DM) is a rare, idiopathic inflammatory myopathy with characteristic skin involvement. Risk for development of a wide variety of tumours affecting multiple organs is associated to DM, and in particular during the first five years of DM manifestation. Although a complex panel of screening is needed, a lack of evidence-based guidelines for malignancy screening in DM still represents a clinical practice gap. The clinical knowledge about the compared efficacy of a single PET-CT with a broad panel of gender-specific screening tests was completed by the results of a recent US economic study (42) testing whether costs would represent a barrier to the adoption of PET as a component of malignancy screening. The results sug-

gested that PET-CT may be an alternative to conventional screening demonstrating that the cost of whole-body PET-CT was higher than conventional malignancy screening for the payers (insurance companies) but lower for patients' out-of-pocket expenses.

Ehlers-Danlos syndrome

The need for additional knowledge of the quality of life in Ehlers-Danlos syndrome

Specific recommendations to maximise quality of life in the paediatric and adolescent population with Hypermobile Ehlers-Danlos syndrome (hEDS/HSD) are not available yet. Moreover, understanding the complications and the HRQoL predictors in paediatric and adolescent hEDS/HSD individuals is needed. Fatigue and pain are the main factors affecting the QoL, as recently investigated in a US study (43) by means of a questionnaire including the Paediatric Quality of Life Inventory (PedsQLTM), the PedsQL Multidimensional Fatigue Scale, the Functional Disability Inventory, the Pain-Frequency-Severity-Duration Scale, the Brief Illness Perception Questionnaire tools. However, important additional HRQoL factors such as daily function, sleep, school attendance, sense of wellness, and illness representation as perceived by both patients and parents still require further investigation.

Patients' perspective on the disease and healthcare services access were investigated for the first time in adult patients affected by Vascular Ehlers-Danlos syndrome (vEDS) and Loeys-Dietz syndrome (LDS) enrolled in a cross-sectional Norwegian study (44). In the vEDS group, the average age at diagnosis was 30 (11–62) years old, the 61% of respondents were women, 61% were unemployed or retired, and 72% had family members with rare hereditary thoracic aortic disease. Most of vEDS patients reported chronic musculoskeletal pain (67%), joint problems (78%), skin problems (61%); half of the patients reported diagnosis-related concerns with their general practitioner (GP), and many patients (31%) had left work at early point or before retirement age.

Take home messages

- Recent health economic research-based can improve the decision making in vasculitis:
 - On ANCA-associated vasculitis an important economic work improved the clinical effectiveness knowledge of a trial results by assessing the cost effectiveness of RTX over conventional immunosuppressants such as AZA, both in terms of relapses averted and in quality-adjusted life years (QALYs);
 - GCA steroids play a substantial effect on costs of the disease as higher cumulative doses of oral glucocorticoid were associated to adverse events (AE) and AE-related costs; moreover, GCA with polymyalgia rheumatica absorbs significant additional costs compared with patients with GCA alone, mainly caused by associated complications; these extra costs are about the 76%, and during the first three years of follow-up extra costs are higher than at the end of the five-year period follow-up.
- Improvements in the understanding of the relationships between the illness perceptions and the self-assessment of the severity of symptoms, and in the need for additional validated disease specific measures, have been underlined in some recent articles:
 - the AAV-PRO for ANCA-associated vasculitis (AAV), and the BDQoL for Behçet's syndrome (BS), have been validated as disease-specific PROs; moreover, the development of disease-specific tools for the capturing of patients' experience needed for giant cell arteritis (GCA) and Takayasu's arteritis (TAK) remains;
 - finally, the development of additional validated (PROM) to the BDQoL measure could significantly improve the understanding and the measurement of improvements in the BS patients' lives.
- Improving the knowledge about the factors affecting the quality of life in SSc patients could contribute in ameliorating the management of the

disease and in suggesting better target interventions in an integrated approach considering pharmacological and non-pharmacological interventions.

- Specific measures to capture the factors assessing the QoL, such as the SScQoL, help to better detect the disease-specific information than generic EQ 5D and SF-36, and are useful tools in clinical care and research.
- The hospital admissions, emergency department visits and ambulatory care are the main costs drivers in SSc patients care management. It would be interesting to investigate the costs for treatments and the costs for out-patients care including wound care, podiatry, hand therapy in additional research.
- Usually, the indirect costs are related to the society's productivity losses due to sickness. The work productivity losses due to the disability or due to the medically related absenteeism were significantly higher for SSc patients.
- During 2019, several publications explored the economic burden and different organisational issues about SLE. Such results indicate a growing interest in this complex disease and the importance of analysing its costs, especially considering the financial constraints of the national health care systems.

Some rare and complex connective tissue diseases such as systemic lupus erythematosus and systemic sclerosis have been more explored in the health economic related literature than other diseases such as dermatomyositis and Ehlers-Danlos syndrome. Considering that the economic and organisational aspects are increasingly relevant, much work still has to be done in this field.

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